National Toxicology Program
U.S. Department of Health and Human Services

NTP Cancer Hazard Assessment Report on Night Shift Work and Light at Night

April 2021

National Toxicology Program Cancer Hazard Assessment Report on Night Shift Work and Light at Night

Running title: Night Shift Work and Light at Night and Cancer

National Toxicology Program
Public Health Service
U.S. Department of Health and Human Services

Foreword

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

Preface

The National Toxicology Program (NTP) conducted cancer hazard assessments of night shift work and light at night for possible listing in the Report on Carcinogens (RoC) because of important potential health concerns associated with these two exposure scenarios.

For night shift work and light at night, the RoC review process proceeded through development of a draft RoC monograph, public comment, and external peer review. Following additional internal deliberation and agency input, it was determined that the cancer hazard conclusions for these two exposure scenarios would be published as a cancer hazard assessment report. To avoid confusion with traditional RoC listings, NTP has used descriptors in this report other than the RoC listing categories to communicate the cancer hazard conclusions for night shift work and light at night.

The substance profiles (from the draft RoC monograph) for these two exposure scenarios have been used to inform the summary of the scientific evidence supporting NTP's cancer hazard assessment conclusions for the two exposure scenarios that can lead to circadian disruption—persistent night shift work and certain lighting conditions.

About This Report

National Toxicology Program[1]

[1]Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Collaborators

Ruth M. Lunn, Pamela J. Schwingl, Stanley T. Atwood, Suril S. Mehta, Gloria D. Jahnke, Sanford C. Garner

Role	Collaborator	Affiliation
Co-project leads Responsible for execution and coordination of project activities, including conception, design, planning, conduct, or technical review of the cancer hazard evaluations.	Ruth M. Lunn, DrPH Pamela J. Schwingl, PhD	NIEHS, DNTP, ORoC ILS
Evaluation Team Contributed to design, conduct, technical review, and interpretation of studies for the cancer hazard evaluation	Stanley T. Atwood, MS Sanford C. Garner, PhD Gloria D. Jahnke, DVM Suril S. Mehta, DrPH	ILS ILS NIEHS, DNTP, ORoC NIEHS, DNTP, ORoC

Contributors

Role	Contributor	Affiliation
Provided technical assistance for report preparation	Whitney Arroyave, PhD Andrew Ewens, PhD Alton Peters, MS	ILS ILS ILS
Technical Advisors Provided critical review of specific sections of the report	David Blask, PhD, MD Mariana Figueiro, PhD Johnni Hansen, PhD	Tulane University School of Medicine, New Orleans, LA Rensselaer Polytechnic Institute, Troy, New York Danish Cancer Society Copenhagen, Denmark
NIEHS Internal Review Committee Provided critical review of scientific and technical elements of the cancer hazard evaluations	John Bucher, PhD (Chair) Windy A. Boyd, PhD Tania Carreón-Valencia, PhD Claire Caruso, PhD, RN Suzanne Fenton, PhD Gopi Gadupudi, PhD	NIEHS, DNTP NIEHS, DNTP NIOSH NIOSH NIEHS, DNTP NIEHS, DNTP

Role	Contributor	Affiliation
	Stephanie Holmgren, MSLS, MBA	NIEHS, DNTP
	Christina Lawson, PhD	NIOSH
	Scott Masten, PhD	NIEHS, DNTP
	Arun Pandiri, PhD	NIEHS, DNTP
	Leslie Reinlib, PhD	NIEHS, DERT
	Amy Wang, PhD, BVM	NIEHS, DNTP
	Alexandra White, PhD	NIEHS, DIR

Acknowledgements

Role	Participant	Affiliation
Administrative assistance	Ella J. Darden, BS	ILS
	Tracy L. Saunders, BS	ILS
Editorial assistance	Susan Dakin, PhD	Independent consultant
Web-based database developer	Andy J. Shapiro, MS	NIEHS (formerly)
Literature searches	Jessica A. Geter, MSLS	ILS (formerly)
	Lara Handler, MSLS	ILS
Organized the peer review meeting	Mary Wolfe, PhD	NIEHS
Logistical support for the peer review meeting	Susan S. Blaine, BA	ICF
	Katherine R. Helmick, MPH	ICF
	Jeanne Luh, PhD	ICF
	Kelly A. Shipkowski, PhD	ICF
	River B. Williams, BS	ICF

ICF = ICF Incorporated, LLC.
DIR = Division of Intramural Research.
ILS = Integrated Laboratory Systems, Inc.
DNTP = Division of the National Toxicology Program.
NIEHS = National Institute of Environmental Health Sciences.
NIOSH = National Institute of Occupational Safety and Health.
ORoC = Office of the Report on Carcinogens, DNTP, NIEHS.

Funding

The cancer hazard evaluations were funded by the DNTP of NIEHS. ICF support was provided through NIEHS contract number GS00Q14OADU417/HHSN273201600015U and ILS provided support through subcontract number 16EDBO0078 with ICF.

Peer Review

Peer review of the "Draft Report on Carcinogens Monograph on Night Shift Work and Light at Night" was conducted by an *ad hoc* expert panel at a public meeting on October 5, 2018, in the Rodbell Auditorium at the National Institute of Environmental Health Sciences, David P. Rall Building, Research Triangle Park, NC (see NTP 2019a for materials, minutes, and panel recommendations from meeting). The selection of panel members and conduct of the peer review were performed in accordance with the Federal Advisory Committee Act and implementing federal policies and regulations.

The panel members served as independent scientists, not as representatives of any institution, company, or governmental agency.

The charge to the peer-review panel was as follows:

1. Comment on whether the "Draft Report on Carcinogens Monograph on Night Shift Work and Light at Night" is technically correct, clearly stated, and objectively presented.
2. Provide opinion on whether a significant number of U.S. residents (a) work (or formerly worked) night shifts and (b) are (or were in the past) exposed to light at night.

The panel was asked to vote on the following:

1. Whether the scientific evidence supports the level of evidence conclusions regarding carcinogenicity from cancer studies in humans.
2. Whether the scientific evidence supports NTP's preliminary policy decision on the listing status in the Report on Carcinogens (RoC) of persistent night shift work that causes circadian disruption and certain lighting conditions that cause circadian disruption.

The peer-review report is available on the NTP website (NTP 2019b). Following peer review, a decision was made not to submit night shift work and light at night for RoC listing. The peer-review report was then used to revise the assessments and inform the final cancer hazard assessment conclusions for night shift work and light at night (see Introduction).

Peer-Review Panel Members

Laura Beane Freeman, Ph.D. (Chair)
Senior Investigator
Occupational and Environmental Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Rockville, Maryland, USA

Massimo Bracci, M.D., Ph.D.
Researcher
Department of Clinical and Molecular Sciences
Università Politecnica delle Marche
Ancona, Italy

Loning Fu, Ph.D.
Associate Professor
Baylor College of Medicine
Houston, Texas, USA

Steven Hill, Ph.D.
Professor
Department of Structural and Cellular Biology
Tulane University School of Medicine
New Orleans, Louisiana

Francis Lévi, M.D., Ph.D.
Professor, Biomedicine
Warwick Medical School
Warwick University
Coventry, United Kingdom

Florence Menegaux, M.D., Ph.D.
Researcher
Epidemiology Cancer and Environment Team
Research Center on Epidemiology and Population Health (CESP)
Institut National de la Santé et de la Recherche Médicale (INSERM)
Villejuif, France

Marie-Elise Parent, Ph.D.
Professor, Epidemiology
Institut National de la Recherche Scientifique – Institut Armand-Frappier Research Center
Quebec, Canada

Eva Schernhammer, M.D., Dr.P.H., M.P.H., M.Sc.
Adjunct Professor
Department of Epidemiology
Harvard T.H. Chan School of Public Health
Boston, Massachusetts, USA

Summary of NTP Cancer Hazard Conclusions
Exposure Circumstances That Cause Circadian Disruption:

Persistent Night Shift Work
Certain Lighting Conditions

Running title: NTP Cancer Hazard Conclusions on Persistent Night Shift Work and Certain Lighting Conditions

Introduction

The invention of electric light brought about the transformation of a culture in which people's activities and sleep patterns were limited by the natural light-dark cycle to one in which people work, sleep, eat, and receive goods and services throughout the 24-hour day. Thus, people in their daily lives — through lifestyle choices, location of residence, and work schedule — are exposed to new patterns and types of light including electric light at night (LAN). Exposure to LAN and activities enabled by LAN can potentially result in daily physiological and behavioral oscillations (known as "circadian rhythms") becoming misaligned with external stimuli (a phenomenon known as "external desynchronization") or with each other (referred to as "internal desynchronization") leading to circadian disruption, which is the misalignment of the circadian timing system. Night shift work includes exposure to electric LAN, sleep disturbances, or changes in meal timing, as well as other potential factors (e.g., social stressors, lifestyle behaviors, decreased exposure to sunlight, and lower vitamin D levels). Most, but not all, of these factors can lead to circadian disruption.

The National Toxicology Program (NTP) conducted cancer hazard assessments for two exposure scenarios: night shift work and exposure to LAN. We used systematic review methods to identify studies, to evaluate study quality, and to integrate evidence across studies. Detailed information on the systematic review methods are described in the Report on Carcinogen (RoC) Protocol (NTP 2018a) and RoC Handbook (NTP 2015). Using established criteria, level of evidence conclusions from cancer epidemiology studies were reached for night shift work, exposure to outdoor and indoor LAN and transmeridian travel. Because circadian disruption is a key intermediate in the pathway between exposure and potential cancer, for each exposure scenario, we used a triangulation approach to integrate the evidence from the cancer studies with evidence from studies of exposure and circadian disruption and studies of circadian disruption and cancer. Other mechanistic data included in the assessment were studies of each exposure scenario and key characteristics of carcinogens, which could be mediated in part by circadian disruption. Lastly, based on the totality of the evidence, we contextualized the cancer hazards, i.e., specifically defined the circumstances by which night shift work or light at night may cause cancer.

This document provides a brief summary of the scientific evidence supporting NTP's cancer hazard assessments conclusions for two exposure scenarios that can lead to circadian disruption: persistent night shift work and certain lighting conditions (for the full report, see NTP 2019[1]). Part 1 discusses circadian rhythms, circadian disruption and cancer, which is common to both cancer hazard assessments. Part 2 (persistent night shift work) and Part 3 (certain lighting conditions) summarize the assessments specific for each exposure scenario.

[1] The full report is title NTP Cancer hazard Assessment on Night Shift Work and Light at Night. The title has been changed in this summary to reflect the contextualization of the cancer hazards.

Part 1: Circadian Rhythms, Circadian Disruption, and Cancer

The Biology of Circadian Rhythms and Their Disruption

Daily oscillations or circadian rhythms of physiological and behavioral processes occur in humans and almost all other species. Examples include reaction time and alertness, body temperature, as well as some regulators of the circadian timing system (e.g., cortisol and melatonin) (see Figure 1). A complex network of internal clocks is responsible for coordinating circadian rhythms with each other and with the solar day. Because the natural period of the internal clock is slightly longer than 24 hours, an environmental stimulus (i.e., the natural light-dark cycle) is needed to make the internal master clock match the 24-hour day (i.e., to "entrain" the clock). Light that is effective in entraining the master clock is known as "circadian light". A protein photoreceptor (melanopsin) in specialized cells of the eye (retinal ganglion cells) detects the light and relays the light signal to the master clock located in the suprachiasmatic nucleus (SCN) of the brain, which then sends signals to a large network of peripheral clocks, located in almost every cell of the body, to keep daily rhythms synchronized. These SCN signals may be sent both directly via the autonomic nervous system and indirectly through neuroendocrine signals (e.g., glucocorticoids from the adrenal gland, melatonin from the pineal gland) (Honma 2018, Brown and Azzi 2013). Exposures, such as meal timing, can also provide external time cues for coordinating physiological cycles and are important for regulating peripheral clocks. A small number of core clock genes, which are expressed in both the SCN and peripheral tissues, regulate the internal clock and are responsible for generating the circadian rhythms of thousands of clock-controlled genes (Fu and Kettner 2013).

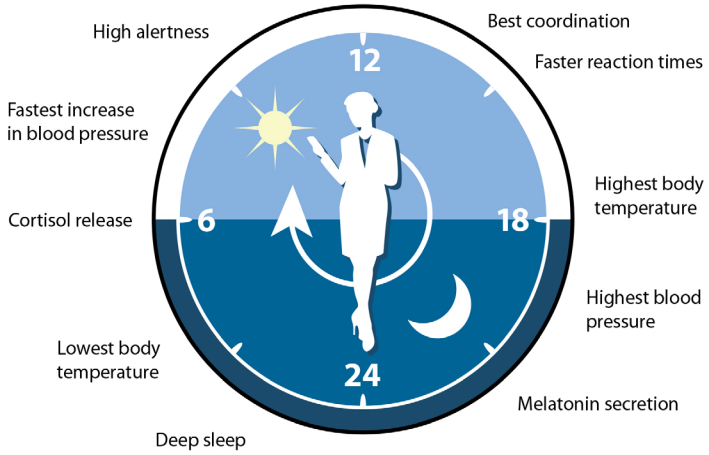

Figure 1. The circadian clock
Peaks in selected circadian rhythms and body temperature are shown across the 24-hour day.
Figure adapted from Nobel Prize 2017, with permission.

Circadian disruption occurs when the body's regular rhythmic patterns (i.e., timing system) become disorganized. The daily circadian rhythms are no longer coordinated with each other or the 24-hour day. This can occur when people are exposed to light at the "wrong time", such as during the night when people typically are asleep; when work schedules change from daytime activity and nighttime sleep to nighttime activity and daytime sleep; during rapid travel across several time zones; or from changes in sleep schedule on weekdays from that on the weekends (i.e., social jet lag) (McMahon *et al.* 2018). Exposure to light affects the circadian system by changing the levels and timing of nighttime melatonin (circadian signaling hormone) production and by shifting (advancing or delaying) the timing of circadian rhythms ("phase shifting"). "Phase advances" in circadian rhythms occur when people are exposed to light in the latter part

of the biological night (when people typically are asleep), travel east across several time zones, or work on a schedule that rotates from night to evening to day shifts. Conversely, "phase delays" in circadian rhythms occur when people are exposed to light in the early part of the evening, travel west across several time zones, or work on a schedule that rotates from day to evening to night shifts. Other characteristics of shift work, such as changes in meal timing and sleep disturbances, can also contribute to circadian disruption, and result in adverse health effects, including cancer (Smolensky *et al.* 2016).

Circadian Disruption and Cancer

Circadian disruption has strong links to cancer and is proposed to be the major mechanism by which night shift work and exposure to electric LAN increase the risk of certain cancers. Key biological steps that affect cancer-relevant pathways include disruption of the circadian timing system leading to altered output signals from the SCN (e.g., sympathetic nervous system, suppression and alteration of melatonin patterns) and desynchronization of peripheral clock gene expression. The sympathetic nervous system mediates chronic stress pathways leading to adverse biological effects related to tumor development, growth, and metastasis (Buijs *et al.* 2001, Furness *et al.* 2006, McCory 2007).

Exposure to light at a sufficient level, for a sufficient duration, with appropriate timing, and at the appropriate wavelength can reduce and alter the timing of melatonin secretion by the pineal gland during the night .There is strong evidence that melatonin inhibits tumor growth in experimental animals (Mirick and Davis 2008) by protecting against biological events related to cancer (Erren 2005, Hill *et al.* 2015). Studies in experimental animals and human cancer tissues and cell lines have shown that these protective effects, which affect all stages of cancer development and progression (for review see NTP 2019) are especially important for hormone-related cancers such as breast cancer. Melatonin's anti-cancer effects are thought to be due, in part, to its regulation of the expression of clock genes and other genes involved in the development of breast and other types of cancer via epigenetic and other mechanisms.

Exposure to excessive LAN, jet lag, or night shift work causes phase shifts and alters the expression of master and peripheral clock genes and the circadian rhythms controlled by these genes. A properly functioning circadian system plays an important role in preventing cancer formation and suppressing tumor growth based on the several lines of evidence.

- Altered expression of some clock genes has been linked to tumor prognosis of some cancers in humans (Altman 2016, Reszka and Przybek 2016).
- Inactivation or alteration of clock genes increases tumor growth or susceptibility to carcinogens in animals (Fu *et al.* 2002, Zeng *et al.* 2010, Mteyrek *et al.* 2017).
- Clock genes regulate many genes related to carcinogenicity.
- Polymorphisms in clock genes (i.e., alternative gene products that may be less active) have been reported to be associated with increased female breast-cancer risk in humans (reviewed by Benna *et al.* 2017, Reszka *et al.* 2017).

Part 2: Persistent Night Shift Work

Characteristics of Night Shift Work

Shift work generally means any arrangement of daily working hours other than standard daylight hours (7:00 AM or 8:00 AM to 5:00 PM or 6:00 PM) (IARC 2010). Night shift work is typically defined as working at least 3 hours between midnight and 5:00 AM (Stevens *et al.* 2011). Night shift workers may work only nights (i.e., permanent night shift workers) or alternate between night, day, and evening shifts (i.e., rotating night shift workers). Forward-rotating schedules go from day to evening to night shifts, whereas backward rotating schedules go from night to evening to day shifts. Schedules can also vary in the number of consecutive days before a shift changes; fast schedules change every 2, 3, or 4 days (IARC 2010, Stevens *et al.* 2011, Vermeulen 2016).

Night shift work is a complex exposure scenario that includes exposure to electric LAN, sleep disturbances, or changes in meal timing, as well as other potential factors (e.g., social stressors, lifestyle behaviors, decreased exposure to sunlight, and lower vitamin D levels).

Over 10 million adults in the United States (7% of the working population) frequently work night shifts, according to a 2015 survey of 2,782 U.S. adults (CDC 2015). Frequent night shift work is more common among men, African-Americans, and non-Hispanics; is slightly more common among workers with a high school education than those with either less or more education; and decreases with increasing age. The occupations with the highest prevalence of adults who frequently work nights include the following: (1) protective services, (2) transportation and material moving, (3) healthcare practitioners and technical occupations, (4) production and manufacturing, and (5) healthcare support (as shown in Figure).

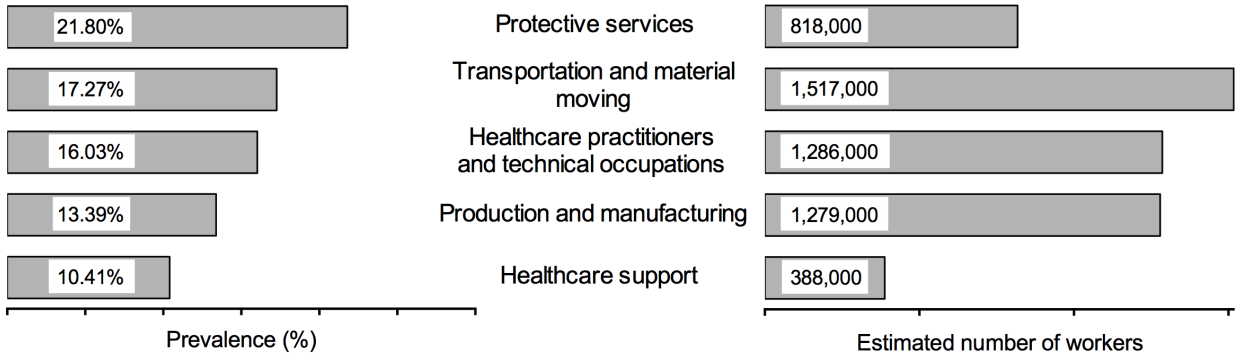

Figure 2. Prevalence and estimated numbers of U.S. workers who frequently work night shifts

Frequent night shifts were defined as at least 6 of the past 30 days with any time worked between 1:00 AM and 5:00 AM in 2015. The percentage of U.S. workers for each occupation was adjusted for age, sex, and race using the projected 2000 U.S. population as the standard population.
Source: CDC 2015.

Cancer Hazard Assessment Conclusions

There is high confidence for a causal relationship between human cancer and persistent night shift work — i.e., frequent and long-term night shift work, especially beginning in early

adulthood — that causes circadian disruption. This conclusion is based on sufficient evidence of carcinogenicity from the collective body of cancer epidemiological and mechanistic studies in humans and mechanistic studies in experimental animals.

- Human epidemiological studies provide strong (but not sufficient) evidence that persistent night shift work is associated with an increased risk of female breast cancer, and mechanistic and other related studies provide evidence that circadian disruption plays a major role in cancer-relevant pathways.
- A large pooled analysis of five epidemiological studies found that female night shift workers who have an elevated risk of breast cancer are those who started working night shifts before age 30 and worked at least 3 times/week for 10 or more years; however, the exact conditions cannot be defined, as duration and frequency may depend on the specific combination of these metrics (e.g., duration may be longer if frequency is less).

Epidemiological Cancer Studies in Humans

There is strong but not quite sufficient evidence from epidemiological studies that persistent night work (e.g., frequent and long-term night shift work, or working a large number of night shifts over a lifetime, especially in early adulthood) causes female breast cancer. There is also limited evidence from epidemiological studies that night shift work causes prostate cancer. The literature databases on other types of cancer are inadequate to evaluate a relationship with night shift work because of the small total numbers of studies or numbers of informative studies (e.g., well-designed and well-conducted studies capable of detecting an effect) for each type of cancer.

The data from the night shift work studies are inadequate to evaluate the roles of LAN, sleep disturbances, or other factors in causing breast cancer. In general, lifestyle behaviors, such as smoking and alcohol consumption, body mass index, parity or age at first full-term pregnancy, breast cancer screening, as well as demographic factors such as age, socioeconomic status, or education were considered in the night shift work studies and these factors did not explain the excess risk. Therefore, the exposure scenario that best fits the available epidemiological evidence is “persistent night shift work”.

Female breast cancer

The conclusion that persistent night shift work increases the risk of female breast cancer (hereinafter referred to as breast cancer) was based on an assessment of 21 studies including 9 cohort studies and 12 case-control studies (see Table 1). Although a few of these studies were of women from specific populations (e.g., nurses, textile workers, etc.), most studies were of women from general populations with mixed occupations. In general, studies that had complete and accurate occupational histories, evaluated different types of work-practice metrics, included workers who had started shift work at earlier ages, and adjusted for potential confounders (discussed below) were considered to be the most informative (i.e., studies with high or moderate utility to inform the cancer hazard evaluation). Cohort studies that included only older workers were not considered as informative, because they (1) may have included larger numbers of women who were able to adapt to night shift work and (2) would not have included women who started working night shift in early adulthood and who developed breast cancer before the cohort enrollment date.

Night shift work was associated with an increased risk of breast cancer in 11 of the 13 most informative studies and in 6 of 8 studies that were considered less informative due to study limitations (see Table 1). Moreover, the excess risk was observed in studies that controlled for potential confounders (such as age, reproductive history, lifestyle factors, body mass index, and socioeconomic status) in different or mixed occupations and geographical locations, which helps to minimize concerns that chance, bias, or confounding may have explained the positive findings. In most studies, an excess risk of breast cancer was found mainly among women who had worked night shifts for many years or at a high frequency, or who had worked a large number of night shifts over their lifetimes.

The most convincing evidence for a positive association between night shift work and breast cancer was among women who started working nights at an early age and worked nights frequently or for many years from the following studies:

- a pooled analysis of 5 case-control studies that were conducted in Australia, Canada, and Europe using the same definition of night shift work (Cordina-Duverger *et al.* 2018) and stratified by findings for menopausal status, and
- two Nurses' Health Study (NHS/NHS2) cohorts, which used somewhat similar study designs and methods but which differed in their age requirement at enrollment (i.e., NHS enrolled mostly "older" women and NHS2 enrolled mostly "younger" women) (Wegrzyn *et al.* 2017).

Both studies found a doubling of risk among younger women but not older women performing persistent night shift work. Breast cancer risk in these studies was higher for more recent exposure (e.g., occurring in women still working or who recently worked night shifts), which may suggest that night shift work acts to promote tumor growth, a finding consistent with the results of studies in experimental animals. Finally, the evidence from human cancer studies is stronger for estrogen-receptor-positive, progesterone-receptor-positive, and human-epidermal-growth-factor-receptor 2-positive subtypes of breast cancer than for hormone- or growth-factor-negative tumors, which is congruent with the proposed mechanisms of carcinogenicity and with findings of increased hormone levels, such as estrogen, in night shift workers compared to day shift workers.

Limitations include low sensitivity of most cohort studies for assessing metrics of persistent night shift work conditions, the lack of studies evaluating racial groups other than white or Asians, and the retrospective nature of the exposure assessment in the case-control studies. In addition, two informative cohort studies did not find an association between night shift work and breast cancer risk (Li *et al.* 2015, Vistisen *et al.* 2017).

Table 1. Summary of epidemiological studies of night shift work and breast cancer[a]

Reference	Study design	Ever worked	Duration	Frequency/ cumulative	Younger age[a]	Receptor positive
Moderate to strong evidence for a positive association — informative studies						
Wegrzyn *et al.* 2017	Cohort (NHS2)[b]		+++		+++	++
Davis *et al.* 2001	Case-control	++	+++ *	+++ *		
Grundy *et al.* 2013	Case-control		+	+++[c] *	I	+++
Hansen and Lassen 2012	Case-control	+	+++*	+++[c,d]*		
Hansen and Stevens 2012	Case-control	+++	+++*	+++		
Lie *et al.* 2011, Lie *et al.* 2013	Case-control			+++[c]*		+++
Menegaux *et al.* 2013, Cordina-Duverger *et al.* 2016	Case-control	++	+	++[c,e]	+++	+++
Some evidence for a positive association — informative studies						
Knutsson *et al.* 2013	Cohort	+++			+	
Fritschi *et al.* 2013	Case-control	++[f]	+[g]		+	
Papantoniou *et al.* 2015a	Case-control	+	+	+[d]	++	++
Pesch *et al.* 2010, Rabstein *et al.* 2013	Case-control	Null	+	+	++	I
Some evidence for a positive association — lower-utility studies						
Åkerstedt *et al.* 2015	Cohort	Null	++		+	
Travis *et al.* 2016 UK EPIC Oxford	Cohort	Null	++[e]			
Travis *et al.* 2016 Million Women Study	Cohort	Null	++[e]			
Tynes *et al.* 1996	Cohort		+++*		++	
Hansen 2001	Case-control	++	++		–	
Wang *et al.* 2015	Case-control	++			+	++
No evidence for a positive association						
Li *et al.* 2015	Cohort (informative)		Null	Null	Null	
Vistisen *et al.* 2017	Cohort (informative)	Null				+
Pronk *et al.* 2010	Cohort (low-utility)	Null	Null	Null	Null	
O'Leary *et al.* 2006	Case-control (low-utility)	–	–			

Studies are grouped by the level of evidence (e.g., moderate, some), which is based on the findings for different exposure metrics (e.g., ever worked night shifts, duration, frequency, or timing), and by study quality (e.g., informative, low utility). The shades of blue and number of pluses indicate the strength of the association; tan indicates a null or negative association.

– = RR < 1; * = significant exposure-response relationship. I = inconclusive results; NHS2 = Nurses' Health Study 2; blank space = not reported.

[a]Analyses based on collective information (including direct and indirect measures of age) suggesting that breast cancer risk is higher in women starting work at a younger age or pre-menopause.

[b]Findings specific for the NHS (older cohort) not included in table as the collective findings from the two cohorts were considered as one study.

[c]Combined analyses of metrics related to frequency and duration of work.

[d]Cumulative number of night shifts.

[e]Increased risk for an intermediate category of duration (e.g., at least 10 years), but not for the longest category of duration.

[f]Ever exposed to phase-shift work.

[g]Increased risk for duration category of ≤ 10 years but not for longer duration categories.

Prostate cancer

There is limited evidence that night shift work causes prostate cancer, based on consistently positive findings across epidemiological studies with varying study designs, located in different geographical areas, and in workers of mixed occupations. Seven of 10 studies (5 of which were considered to be of moderate to high quality) included in the evaluation found that either ever working night shifts (Kubo *et al.* 2006, Conlon *et al.* 2007, Parent *et al.* 2012, Papantoniou *et al.* 2015b, Behrens *et al.* 2017, Tse *et al.* 2017) or working night shifts for a long duration (Conlon *et al.* 2007, Parent *et al.* 2012, Papantoniou *et al.* 2015b, Behrens *et al.* 2017, Wendeu-Foyet *et al.* 2018 as shown in Figure 3 below) were associated with an increased, although imprecise, risk of prostate cancer (Note: Kubo *et al.* 2006, Kubo *et al.* 2011, Hammer *et al.* 2015 and Tse *et al.* 2017 did not report effect estimates on study duration). Two studies found that prostate cancer risk increased with increasing years of working night shifts (Papantoniou *et al.* 2015b, Behrens *et al.* 2017). A population-based case-control study (Wendeu-Foyet *et al.* 2018) found increased prostate-cancer risk with extensive permanent night shift work. Findings from three studies that had methodologic limitations were either inconclusive (Kubo *et al.* 2011) or null (Hammer *et al.* 2015, Åkerstedt *et al.* 2017). Overall, the database is limited by the small number of informative studies, potential misclassification of work-shift status, and the limited number of exposure metrics (such as frequency) that could be evaluated.

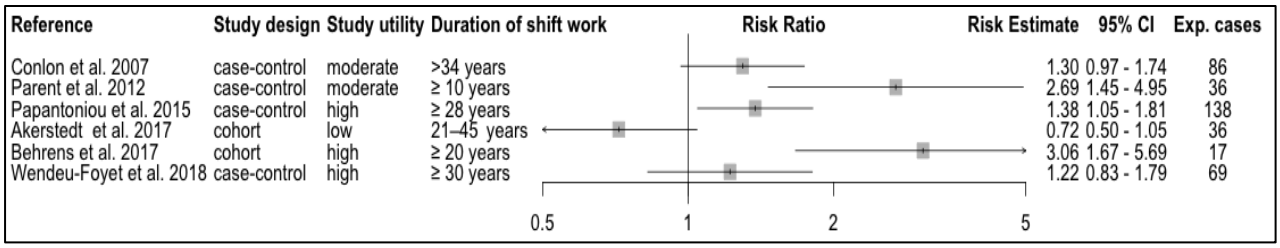

Figure 3. Forest plot of human studies on the risk of prostate cancer by cumulative duration of night shift work

A positive association between duration of shift work and prostate cancer is one that is to the right of a risk ratio of 1. The forest plot shows an overall increased risk of prostate cancer for individuals working night shifts for longer durations over a lifetime.

Studies on Mechanisms of Carcinogenesis and Other Relevant Data

Overall, the mechanistic and other relevant data indicate that the increased risk of cancer found in night shift workers is mediated, in part, by circadian disruption. This evidence comes from (1) studies of simulated shift work in experimental animals, (2) studies of night shift work and circadian disruption or biological effects that are linked to cancer, and (3) studies of circadian disruption and cancer (see Circadian Disruption and Cancer). Because of the complex interactions and overlapping effects of LAN-induced melatonin suppression, circadian disruption, sleep deprivation, change in meal-timing, potential vitamin D deficiency, and other factors, it is not possible to separate their relative individual contributions to the development and progression of cancer.

Studies in experimental animals

Studies in experimental animals provide strong evidence that exposure to LAN, simulated shift work or chronic jet lag (e.g., mimicking travel across several time zones) promotes tumor growth primarily in animals receiving transplanted tumor cells or initiated with carcinogens and supports the findings from the human epidemiological studies. Shift work was simulated in studies in experimental animals through weekly inversion of the light-dark cycle (e.g., exposing the animals to light during the day for one week and during the night for the next week) or by shifting the times when lights were switched on and off (either forward or backward shifts). Three studies found that simulated shift work or chronic jet lag promoted mammary tumor growth in mice (Van Dycke *et al.* 2015, Fang *et al.* 2017) or rats (Logan *et al.* 2012). Studies in mice and rats found that simulated shift work or chronic jet lag also enhanced the growth of other types of cancer — abdominal fluid (Ehrlich carcinoma or sarcoma 180), bone (osteosarcoma), liver, lung, lymphoma, plasmacytoma (immune tumors), and pancreas — in animals co-exposed to chemical carcinogens or radiation, injected with transplanted cells, or animal models that are susceptible to carcinogens (see Table 2 below). Another study found that mice exposed to lighting conditions simulating chronic jet lag had a higher incidence of liver tumors than did control-group mice (Kettner *et al.* 2016).

Table 2. Summary of carcinogenicity studies of simulated shift work or chronic jet lag in experimental animals

Tumor type	Simulated shift work	Chronic jet lag	References
Abdominal fluid (Ehrlich carcinoma or sarcoma 180): Implants	↑ mice		Li and Xu 1997
Bone: Implants		↑ mice	Filipski *et al.* 2004, Filipski *et al.* 2005, Filipski *et al.* 2006
Liver tumors:			
Spontaneous		↑ mice	Kettner *et al.* 2016
Promotion		↑ mice	Filipski *et al.* 2009
Lung tumors:			
Promotion (genes)		↑ mice	Papagiannakopoulos *et al.* 2016
Implants		↑ mice	Wu *et al.* 2012
Lymphoma: Promotion (radiation)			Lee *et al.* 2010
Mammary gland:			
Spontaneous	↑ mice		Van Dycke *et al.* 2015
Promotion (chemical)		↑ mice	Fang *et al.* 2017
Implants		↑ rats	Logan *et al.* 2012
Plasmacytoma (immune tumor):		↑ rats	Wu *et al.* 1988
Implants			
Pancreas: Implanted cells		↑ mice	Filipski *et al.* 2006

↑ = statistically significant increase; empty cells = not tested.
Implant = increased tumor size or growth rate or decreased time for tumor development (latency) of transplanted cells or tissue.
Promotion = increased incidence, multiplicity, or size or decreased latency of tumors initiated by chemical carcinogens.

Spontaneous = increased multiplicity or incidence or decreased latency of tumors in studies not using co-exposure to chemicals or implantation with cancerous cells or tissues.

Studies of night shift work and cancer related to circadian disruption

Circadian disruption, night shift work, and cancer risk have not been adequately evaluated together within individual studies. However, there is evidence that night shift work is associated with circadian disruption (discussed below) and that circadian disruption is linked to cancer of the breast and other tissues (as discussed in Circadian Disruption and Cancer). There is also evidence that shift work (in humans and animals) causes biological effects that are characteristic of known human carcinogens.

Overall, most shift workers, including those working permanent shift schedules, do not appear to adapt their circadian rhythms to their sleep schedule (i.e., melatonin continues to peak at night instead of during their daytime sleep) (Boivin and Boudreau 2014, Jensen *et al.* 2016). In addition, many workers do not tolerate shift work as evidenced by symptoms that include persistent fatigue, sleep-medication dependence, and mood disturbances such as depression. Many of these symptoms (such as heart rate, stress behaviors) are regulated by the sympathetic nervous system and provide evidence for sympathetic nervous system-mediated circadian disruption in humans (Mohawk *et al.* 2012, Brown and Azzi 2013, Honma 2018). Some studies have found that individual workers who were able to alter the timing of their melatonin production so it paralleled their sleep time had better shift work tolerance and improved sleep quality compared to workers who did not alter their timing; however, there were individual differences (reviewed by Burch *et al.* 2005).

Numerous studies conducted in different populations of both men and women have reported that night shift workers had lower nighttime (Davis *et al.* 2012, Ji *et al.* 2012, Bracci *et al.* 2013, Mirick *et al.* 2013, Song *et al.* 2016) or average (Papantoniou *et al.* 2014, Gómez-Acebo *et al.* 2015, Leung *et al.* 2016) levels of melatonin (usually measured as a metabolite in the urine) than day workers. Moreover, the effects of nighttime melatonin suppression may be related to persistent shift work, measured, for example, as total number of night shifts (Schernhammer *et al.* 2004), number of consecutive night shifts (Leung *et al.* 2016), or number of years working night shifts (Papantoniou *et al.* 2014). Although there is strong evidence that night shift work is associated with melatonin suppression, it is not clear that the suppression is caused directly by exposure to LAN. A few studies have found an association between light levels and urinary melatonin levels in night shift workers (Grundy *et al.* 2009, Grundy *et al.* 2011, Papantoniou *et al.* 2014); however, only a few studies have measured both light and melatonin and they used different measurement methods, study designs, and analyses.

Studies of night shift workers and simulated shift work in experimental animals suggest that shift work may be associated with altered clock gene expression (Fu and Kettner 2013, Kettner *et al.* 2014, Stevens and Zhu 2015), deregulation of sympathetic nervous system (SNS) signaling (Adams *et al.* 1998), or desynchronization of the central clock–SNS–peripheral clock axis (Lee *et al.* 2010).

There is also evidence that night shift work is with biological effects that are related to carcinogenicity (collective evidence across the characteristics with the strongest associations with altered circulating levels of estrogen, and epigenetic changes that modify the expression of

core clock genes or clock-controlled genes). A strength of the database is that these effects were also observed in the animal carcinogenicity studies of modeled LAN, chronic jet lag, or simulated shift work, thus providing direct links of these biological effects to cancer. In addition, some of these biological effects have been observed in studies of night shift workers and are similar to those mediated by low melatonin levels or deregulation of clock genes, which supports the role of circadian disruption in shift work-related carcinogenicity.

Part 3: Certain Lighting Conditions

Characteristics of Certain Lighting Conditions

Modern electric lighting practices, beginning with the invention of incandescent lights in the late 19th century, have led to ill-timed exposure to unnatural light, typically to electric light during the day and night combined with insufficient exposure to daylight. For most of human history, people were exposed to bright light from natural sources during the daytime and to a very dark environment at night, whereas modern practices have led to exposure to some level of dim light throughout the 24-hour day. As the light-dark cycle is the major stimulus for coordinating the circadian system, certain lighting conditions can lead to circadian disruption and adverse health effects.

"Circadian light" is defined as the light received at the eye that stimulates the circadian system, as measured by nighttime melatonin suppression, and it is a biomarker of circadian disruption. The characteristics related to electric light that are most likely to cause circadian disruption include a combination of shorter wavelengths, longer duration, exposure to light during the biological night, and higher light intensity or levels. Light regulating the circadian system is received by specialized non-visual photoreceptors in the retina of the human eye; these receptors are especially sensitive to short wavelengths that are perceived as blue light by the human eye (Figure 4 presents the spectra of circadian light). As all of these characteristics are related, the exact specifications (such as duration) depend on other light characteristics. In addition to exposure to electric LAN, total light exposure (e.g., insufficient exposure to daylight) is also important in circadian regulation.

Beginning with the patenting of Edison's incandescent light bulb, primary light sources for homes and workplaces have evolved through fluorescent lights to light-emitting diodes (LEDs) and more recently to the organic LEDs (OLED) and active-matrix organic LEDs (AMOLED) used in mobile devices, laptops, and televisions. Technological advances have generally increased the energy efficiency of lighting sources for both indoor (e.g., home and office) and outdoor (e.g., streets and parking lots) lighting, but these light sources emit a larger proportion of total light in wavelengths perceived as blue by the human eye (see Figure 4).

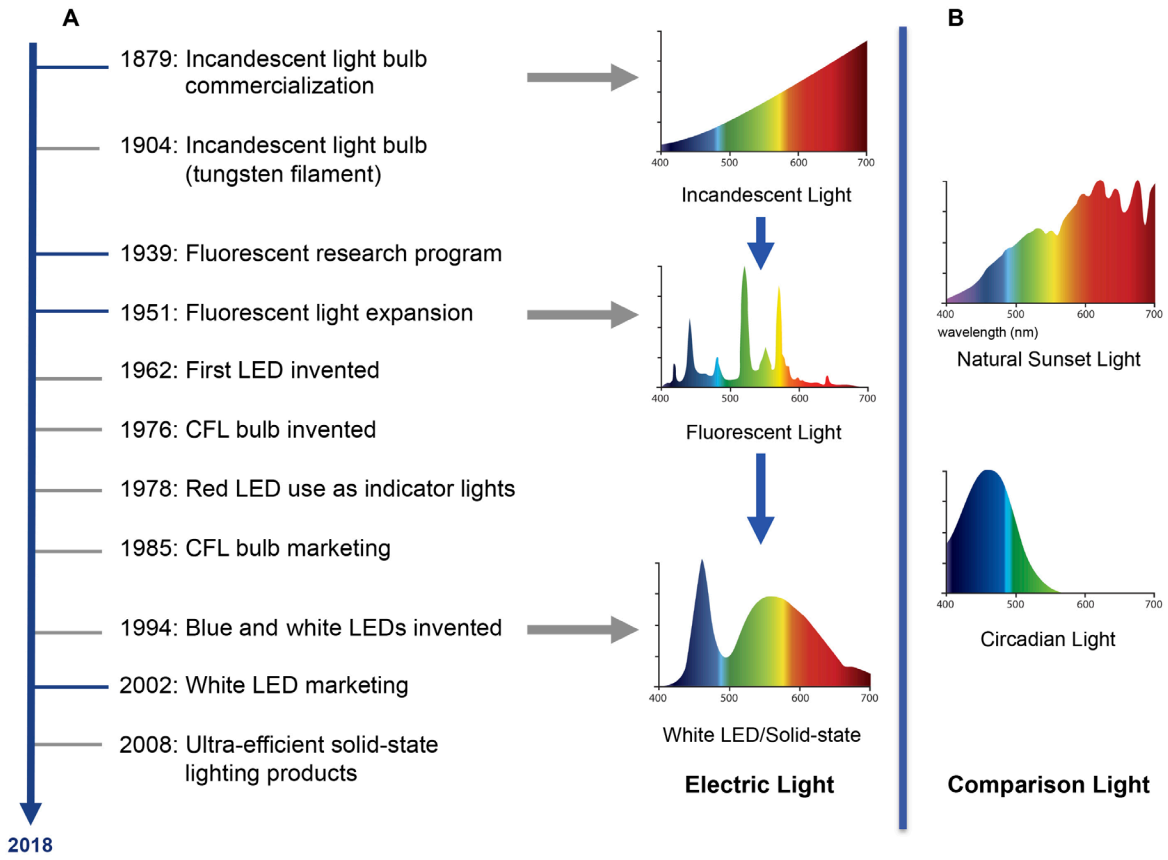

Figure 4. Technological advances in lighting over time have led to lighting with higher levels of short wavelengths

Panel A shows the timeline of key historical events related to the major types of electric lighting and the corresponding spectra. Panel B depicts spectra for comparison light: natural sunset light and circadian light. Incandescent light has little short wavelength light (i.e., blue light, wavelength 400 to 490 nm) similar to natural sunset light whereas white LED light has higher amounts of shorter wavelength light similar to circadian light.
Sources Adapted from Brainard *et al.* 2001, Matulka and Wood 2013, Zielinska-Dabkowska 2018.

LED = light emitting diodes; CFL = compact fluorescent lights.

Exposure to aberrant lighting conditions may include excess electric LAN from outdoor lights, indoor lighting at home and at work, and use of self-luminous electronic devices, as well as insufficient natural light during the day.

Exposure to indoor electric lighting is nearly ubiquitous in our society. The level of light from electric lights or self-luminous displays, e.g., TVs, computers, or smartphones, generally ranges from 5 to 200 lux. Types of indoor lights include incandescent, halogen, fluorescent, compact fluorescent, and LEDs (DOE 2018, NOAO 2018). Sources of blue light exposure at night include LED and fluorescent lamps, and video displays, such as OLEDs and liquid crystal displays (LCDs) (Oh *et al.* 2015). Many Americans, especially adolescents and teens, use electronic devices before sleeping. Findings from the 2011 Sleep in America Poll (N = 1,508 participants, ages 13 to 64 years) indicate that an estimated 90% of Americans use some type of electronic device a few nights per week within 1 hour of bedtime with 60% (regardless of age) watching television and a greater percentage of adolescents (72%) and young adults (67%) using cell

phones compared to middle-aged (36%) and older adults (16%) (Gradisar *et al.* 2013, Smolensky *et al.* 2015).

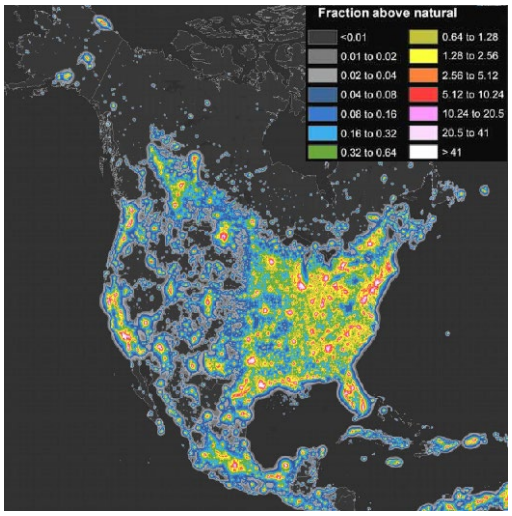

Figure 5. Map of North America's artificial sky brightness, in twofold increasing steps, as a ratio to the natural sky brightness

Many outdoor areas, such as roadways, shopping centers, stadiums, etc. are lighted at night, and the propagation of stray light due to the lighting demands of urban development is often referred to as "light pollution" (Pauley 2004, Navara and Nelson 2007). The use of LED lights outdoors is increasing rapidly (NOAO 2018). In 2016, satellite imaging data of the Earth at night (see Figure 5) indicated that more than 99% of the U.S. population lived under light-polluted skies at night (i.e., artificial sky brightness was increased by at least 8% above the natural background at the zenith, which is the darkest part of the sky hemisphere), and celestial objects like the Milky Way are no longer visible from most locations on the earth (Falchi *et al.* 2016). Outdoor light is brightest in metropolitan areas especially in the eastern United States and in California.

Cancer Hazard Assessment Conclusions

There is moderate confidence for a causal relationship between human cancer and certain lighting conditions — i.e., excessive LAN exposure combined with insufficient daylight exposure — that cause circadian disruption. This conclusion is based on strong evidence that LAN acts through mechanisms that are likely to cause cancer in humans.

- Toxicological and mechanistic data indicate that exposure to LAN causes melatonin suppression and other types of circadian disruption, which lead to the proliferation and growth of breast or mammary-gland cancer in experimental animals.
- LAN causes biological effects that are characteristics of recognized carcinogens.
- Studies in humans show that LAN causes melatonin suppression.
- Other studies suggest that total light, including the type of light received during the day, is important in circadian regulation, nighttime melatonin secretion, and carcinogenicity.
- The available studies from humans are inadequate to evaluate the relationship between exposure to LAN and cancer.

The characteristics related to electric light that are most likely to cause circadian disruption include a combination of shorter wavelengths (e.g., blue light), longer exposure duration, higher light intensity or levels, and exposure to electric light during the biological night. The exact conditions leading to circadian disruption (e.g., duration) depend on the combination of these metrics. In addition to exposure to electric LAN, total light exposure (i.e., having insufficient exposure to daylight) is also important in circadian regulation and thus is part of certain lighting conditions.

Studies on Mechanisms of Carcinogenesis and Other Relevant Data

Overall, mechanistic and other relevant data indicate that circadian disruption plays a role in LAN carcinogenicity. This evidence comes from (1) cancer studies of LAN in experimental animals, (2) studies of LAN or total light exposure and circadian disruption or biological effects that are linked to cancer, and (3) studies of circadian disruption and cancer (see Circadian Disruption and Cancer).

Cancer studies in experimental animals

Studies in experimental animals provide evidence that LAN can enhance growth of breast and other types of tumors and that melatonin plays a key role in LAN-related carcinogenicity. Exposure to continuous bright light, dim LAN, or altered light patterns (i.e., other than 12 hours dark, 12 hours light) promoted mammary-gland tumors initiated by chemical carcinogens in several strains of rats, increased the rate of growth of human breast cancer cells transplanted into rats and of mouse mammary-gland cells transplanted into mice, and increased the numbers of mammary-gland tumors per animal (tumor multiplicity) in a mouse model of human breast cancer. In addition, exposure of rats to seasonal lighting for Northern latitudes (i.e., a maximum of 4.5 hours of light in winter and 24 hours of light in summer) resulted in an increase in benign mammary-gland tumors (See Table 3 for references and details of the studies.)

In almost all studies, LAN also promoted the growth of other types of cancer — of the brain, cervix (implanted human cells), liver, lung, kidney, peripheral nervous system, prostate, and skin — in studies that either co-exposed the animals to chemical carcinogens or transplanted cancer cells into LAN-exposed animals (as summarized in Table 3). Exposure of rats to continuous LAN increased the incidences of leukemia and lung tumors and the total incidence of tumors (Anisimov *et al.* 2004). Three of the over 25 studies found no association with LAN exposure and tumor growth (Anderson *et al.* 2000, Travlos *et al.* 2001, Popovich *et al.* 2013), one study found a decrease in tumor growth with LAN exposure (Isobe *et al.* 2008), and findings from another study were not clear (Waldrop *et al.* 1989).

These carcinogenic effects were mediated, in part, by melatonin. LAN exposure caused dose-related suppression of melatonin levels (Blask *et al.* 2005, Blask *et al.* 2009), and co-exposure to melatonin (usually administered in drinking water) partly reversed tumor growth promoted by LAN (Kothari 1987, Blask *et al.* 2014, Dauchy *et al.* 2014, Schwimmer *et al.* 2014). Other studies found that in nude rats (immunodeficient) perfused (*in situ*) with melatonin-depleted blood from pre-menopausal women exposed to bright LAN, transplanted human breast tumors or rat liver tumors showed high proliferative activity, whereas perfusion with melatonin-rich blood from women collected during nighttime without light exposure suppressed tumor growth (Blask *et al.* 2005, Blask *et al.* 2009). These findings support the relevance of the LAN animal models to carcinogenicity in humans.

Table 3. Summary of carcinogenicity studies of lighting conditions in experimental animals

Tumor type	Constant light	Dim LAN	Altered L-D cycle	References
Brain (glioma cells): Implant	↑ rats			Guerrero-Vargas *et al.* 2017
Breast Human xenograft	↑ rats	↑ rats		Blask *et al.* 2003, Blask *et al.* 2005, Blask *et al.* 2014, Dauchy *et al.* 2014
Mammary gland				
Promotion	↑ rats			Hamilton 1969, Kothari *et al.* 1982, Anisimov *et al.* 1994, Cos *et al.* 2006,
Implant		↑ mice		Schwimmer *et al.* 2014
Spontaneous	↑ mice		↑ rats	Baturin *et al.* 2001, Vinogradova *et al.* 2009
Cervix: Human xenograft	↑ mice			Yasuniwa *et al.* 2010
Kidney	↑ rats			Beniashvili *et al.* 2001
Liver				
Promotion	↑ rats			van den Heiligenberg *et al.* 1999
Implant	↑ rats	↑ rats		Dauchy *et al.* 1997, Dauchy *et al.* 1999, Blask *et al.* 2005, Dauchy *et al.* 2011
Lung				
Promotion			↑ mice	Nakajima *et al.* 1994
Spontaneous	↑ mice			Anisimov *et al.* 2004
Leukemia: Spontaneous	↑ mice			Anisimov *et al.* 2004
PNS: Promotion	↑ rats			Beniashvili *et al.* 2001
Prostate: Implant			↑ mice	Haim *et al.* 2010
Skin				
Promotion			↑ mice	Nelson and Blom 1994
Xenograft	↑ mice		↑ mice	Lang *et al.* 2003, Otálora *et al.* 2008

L-D = light-dark; ↑ = statistically significant increase; empty cells = not tested; PNS = peripheral nervous system.
Statistically significant increases are defined for each experimental model as follows:
Implant = increased tumor size or growth rate or decreased time for tumor development (latency) of transplanted cells or tissue.
Promotion = increased incidence, multiplicity, or size or decreased latency of tumors initiated by chemical carcinogens.
Spontaneous = increased multiplicity or incidence or decreased latency of tumors in studies not using co-exposure to chemicals or implanted cancerous cells or tissues.

In contrast to the studies of modelled LAN, exposure to blue-enriched light during the daytime increased nighttime melatonin levels, decreased plasma or blood levels of metabolism biomarkers, changed levels of tumor growth biomarkers, and decreased growth of prostate and liver xenografts in rats compared to animals exposed to white light during the day (Dauchy *et al.* 2013, Dauchy *et al.* 2015, Dauchy *et al.* 2016, Dauchy *et al.* 2018).

Studies of LAN or total light exposure and circadian-disruption-related cancer

In addition to the evidence from cancer studies in experimental animals that melatonin suppression plays a role in LAN-induced carcinogenicity, there is also evidence that LAN causes circadian disruption in humans and evidence that circadian disruption is linked to cancer (see Circadian Disruption and Cancer).

Experimental studies in humans provide evidence that electric LAN exposure occurring in people's everyday lives can cause melatonin suppression, depending on the wavelength, level, duration, timing, and total light exposure (Figueiro 2017, Lunn *et al.* 2017). Although short, blue light wavelengths (446 to 475 nm) are more effective than longer wavelengths in reducing nighttime melatonin production (Brainard *et al.* 2001, Figueiro *et al.* 2017), the human circadian system is sensitive to levels of ordinary room light. The duration of LAN exposure needed to induce circadian disruption depends on other characteristics of light such as wavelength, timing, and level. For example, Nagare *et al.* (2018) reported that exposure duration was a significant factor in inducing melatonin suppression in subjects exposed to two different types of white light (with equivalent ability to suppress melatonin secretion) for one to four hours. Some experimental studies suggest that blue light exposure during the daytime or morning can help reduce LAN-induced melatonin suppression (Kozaki *et al.* 2015, 2016, Nagashima *et al.* 2018) and improve measures of sleep quality and mood (Viola *et al.* 2008). In addition, night-time sensitivity to light-induced circadian disruption (usually measured by melatonin suppression) is influenced by light exposure during the day (reviewed by Figueiro 2017 and Lunn *et al.* 2017). Individual sensitivities related to age, sex, chronotype (preferences for sleep times during a 24-hour period), and polymorphisms in clock genes can affect sensitivity to LAN. Children have been shown to be more sensitive to LAN-induced melatonin suppression than adults, and sensitivity to LAN decreases with age. For example, exposure to luminous displays (~87 lux) induced a greater degree of melatonin suppression (~25%) in teens (aged 15 to 17 years) than in college students or middle-aged adults (Figueiro and Overington 2016).

The database of field studies is inadequate to evaluate the effects of bedroom lighting (such as from turning on lights or from outdoor lights, as measured by satellite) because of the small number of studies, low levels of light, or insensitivity of exposure assessment methods (Davis *et al.* 2001, Levallois *et al.* 2001, Hurley *et al.* 2013).

LAN exposure also has been shown to alter clock-gene expression in the SCN and peripheral tissues of experimental animals; the results varied according to light source, tissue, and the specific genes studied. Two studies found some evidence in humans that exposure to blue light alters clock-gene expression (Chen *et al.* 2005, Cajochen *et al.* 2006). Studies of biomarkers of circadian disruption in humans as well as cancer studies in animals indicate that the total light experience, including LAN and light during the daytime, impacts circadian disruption and cancer risk (Dauchy *et al.* 2015, Dauchy *et al.* 2018).

LAN causes some biological effects in experimental animals that are characteristics of carcinogens (collective evidence across the characteristics with the strongest associations for metabolic). A strength of the database is that these effects were also observed in the carcinogenicity studies of LAN or simulated shift work, thus providing direct links between the biological effects and cancer. In addition, some of these biological effects have been observed in studies of night shift workers who were exposed to LAN, supporting the conclusion that exposure to certain lighting conditions may cause cancer in humans.

Epidemiological Cancer Studies in Humans

The database is inadequate to evaluate the risk of breast cancer due to LAN exposure. The database consists of studies that measured outdoor LAN using satellite imagery and studies that assessed indoor LAN exposure in the sleeping area.

Two cohort studies in the United States (Hurley *et al.* 2014, James *et al.* 2017), a case-referent study (using lung cancer cases as the comparison group) (Bauer *et al.* 2013) and a population-based case-control study in Spain (Garcia-Saenz *et al.* 2018) found an increased risk of breast cancer among women in the highest category of outdoor LAN exposure or blue-light LAN exposure (Garcia-Saenz *et al.* 2018). The increased risk was observed mainly in premenopausal women in two studies (Hurley *et al.* 2014, James *et al.* 2017). These findings are supported by a case-control study which found that Israeli women living near strong artificial LAN sources had a 50% increased risk of breast cancer; however, no information was provided on the sources or proximity of the LAN (Keshet-Sitton *et al.* 2016). A major limitation of the literature is the uncertainty as to whether the studies using satellite images were assessing the direct effects of LAN or the effects of activities (such as changes in eating behaviors or lifestyles) related to or enabled by LAN exposure.

The studies of LAN in the sleeping area used a wide variety of metrics for evaluating indoor LAN exposure, such as the number of times lights were turned on and the subjective level of light in the room. Although some studies found positive associations between specific metrics of LAN and increased breast cancer risk, overall the evidence across studies was inconsistent.

The database was inadequate to evaluate exposure to LAN and other types of cancer because of a small number of informative studies.

References

Adams SL, Roxe DM, Weiss J, Zhang F, Rosenthal JE. 1998. Ambulatory blood pressure and Holter monitoring of emergency physicians before, during, and after a night shift. *Acad Emerg Med* 5(9): 871-877.

Åkerstedt T, Knutsson A, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. 2015. Night work and breast cancer in women: a Swedish cohort study. *BMJ Open* 5(4): e008127.

Åkerstedt T, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. 2017. Night work and prostate cancer in men: a Swedish prospective cohort study. *BMJ Open* 7(6): e015751.

Altman BJ. 2016. Cancer clocks out for lunch: Disruption of circadian rhythm and metabolic oscillation in cancer. *Front Cell Dev Biol* 4: 62.

Anderson LE, Morris JE, Sasser LB, Stevens RG. 2000. Effect of constant light on DMBA mammary tumorigenesis in rats. *Cancer Lett* 148(2): 121-126.

Anisimov VN, Zhukova OV, Beniashvili DS, Bilanishvili VG, Menabde MZ. 1994. Light deprivation, electromagnetic fields and mammary carcinogenesis. *Adv Pineal Res* 7: 229-234.

Anisimov VN, Baturin DA, Popovich IG, Zabezhinski MA, Manton KG, Semenchenko AV, Yashin AI. 2004. Effect of exposure to light-at-night on life span and spontaneous carcinogenesis in female CBA mice. *Int J Cancer* 111(4): 475-479.

Baturin DA, Alimova IN, Anisimov VN, Popovich IG, Zabezhinski MA, Provinciali M, Mancini R, Franceschi C. 2001. The effect of light regimen and melatonin on the development of spontaneous mammary tumors in HER-2/neu transgenic mice is related to a downregulation of HER-2/neu gene expression. *Neuro Endocrinol Lett* 22(6): 441-447.

Bauer SE, Wagner SE, Burch J, Bayakly R, Vena JE. 2013. A case-referent study: light at night and breast cancer risk in Georgia. *Int J Health Geogr* 12: 23.

Behrens T, Rabstein S, Wichert K, Erbel R, Eisele L, Arendt M, Dragano N, Brüning T, Jöckel KH. 2017. Shift work and the incidence of prostate cancer: a 10-year follow-up of a German population-based cohort study. *Scand J Work Environ Health* 43(6): 560-568.

Beniashvili DS, Benjamin S, Baturin DA, Anisimov VN. 2001. Effect of light/dark regimen on *N*-nitrosoethylurea-induced transplacental carcinogenesis in rats. *Cancer Lett* 163(1): 51-57.

Benna C, Helfrich-Förster C, Rajendran S, Monticelli H, Pilati P, Nitti D, Mocellin S. 2017. Genetic variation of clock genes and cancer risk: a field synopsis and meta-analysis. *Oncotarget* 8(14): 23978-23995.

Blask DE, Dauchy RT, Sauer LA, Krause JA, Brainard GC. 2003. Growth and fatty acid metabolism of human breast cancer (MCF-7) xenografts in nude rats: impact of constant light-induced nocturnal melatonin suppression. *Breast Cancer Res Treat* 79(3): 313-320.

Blask DE, Brainard GC, Dauchy RT, Hanifin JP, Davidson LK, Krause JA, Sauer LA, Rivera-Bermudez MA, Dubocovich ML, Jasser SA, Lynch DT, Rollag MD, Zalatan F. 2005. Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res* 65(23): 11174-11184.

Blask DE, Dauchy RT, Brainard GC, Hanifin JP. 2009. Circadian stage-dependent inhibition of human breast cancer metabolism and growth by the nocturnal melatonin signal: consequences of its disruption by light at night in rats and women. *Integr Cancer Ther* 8(4): 347-353.

Blask DE, Dauchy RT, Dauchy EM, Mao L, Hill SM, Greene MW, Belancio VP, Sauer LA, Davidson L. 2014. Light exposure at night disrupts host/cancer circadian regulatory dynamics: impact on the Warburg effect, lipid signaling and tumor growth prevention. *PLoS One* 9(8): e102776.

BLS. 2004. *Current Population Survey, May 2004: Work Schedules and Work at Home Supplement File*. Technical Documentation CPS—04. Washington, D.C.: Bureau of Labor Statistics, US Department of Labor. 221 pp.

BLS. 2005. *Workers on Flexible and Shift Schedules in May 2004*. USDL 05-1198. U.S. Department of Labor, Bureau of Labor Statistics. 14 pp. https://www.bls.gov/news.release/flex.nr0.htm.

Boivin DB, Boudreau P. 2014. Impacts of shift work on sleep and circadian rhythms. *Pathol Biol (Paris)* 62(5): 292-301.

Bracci M, Copertaro A, Manzella N, Staffolani S, Strafella E, Nocchi L, Barbaresi M, Copertaro B, Rapisarda V, Valentino M, Santarelli L. 2013. Influence of night-shift and napping at work on urinary melatonin, 17-beta-estradiol and clock gene expression in pre-menopausal nurses. *J Biol Regul Homeost Agents* 27(1): 267-274.

Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, Rollag MD. 2001. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* 21(16): 6405-6412.

Brown SA, Azzi A. 2013. Peripheral circadian oscillators in mammals. In *Circadian Clocks*. 2013/04/23. Kramer A, Merrow M, eds. Berlin: Springer. pp. 45-66.

Buijs RM, Kalsbeek A. 2001. Hypothalamic integration of central and peripheral clocks. *Nat Rev Neurosci* 2(7): 521-526.

Burch JB, Yost MG, Johnson W, Allen E. 2005. Melatonin, sleep, and shift work adaptation. *J Occup Environ Med* 47(9): 893-901.

Cajochen C, Jud C, Münch M, Kobialka S, Wirz-Justice A, Albrecht U. 2006. Evening exposure to blue light stimulates the expression of the clock gene *PER2* in humans. *Eur J Neurosci* 23(4): 1082-1086.

CDC. 2015. *CDC-NIOSH Worker Health Charts. Work Organization*. Centers for Disease Control and Prevention. https://wwwn.cdc.gov/Niosh-whc/chart/ohs-workorg/work and select "All Work Organization" from drop-down menu for work organization and "adjusted prevalence" from drop-down menu for value to chart to find adjusted prevalence of frequent night work and shift work (with estimates of numbers of workers exposed). See PDF cover page for other query instructions. Accessed on 3/21/18.

Chen ST, Choo KB, Hou MF, Yeh KT, Kuo SJ, Chang JG. 2005. Deregulated expression of the *PER1, PER2* and *PER3* genes in breast cancers. *Carcinogenesis* 26(7): 1241-1246.

Conlon M, Lightfoot N, Kreiger N. 2007. Rotating shift work and risk of prostate cancer. *Epidemiology* 18(1): 182-183.

Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, Guénel P. 2016. Night work and breast cancer risk defined by human epidermal growth factor receptor-2 (HER2) and hormone receptor status: A population-based case-control study in France. *Chronobiol Int* 33(6): 783-787.

Cordina-Duverger E, Menegaux F, Popa A, Rabstein S, Harth V, Pesch B, Brüning T, Fritschi L, Glass DC, Heyworth JS, Erren TC, Castaño-Vinyals G, Papantoniou K, Espinosa A, Kogevinas M, Grundy A, Spinelli JJ, Aronson KJ, Guénel P. 2018. Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol*.

Cos S, Mediavilla D, Martínez-Campa C, González A, Alonso-González C, Sanchez-Barceló EJ. 2006. Exposure to light-at-night increases the growth of DMBA-induced mammary adenocarcinomas in rats. *Cancer Lett* 235(2): 266-271.

Dauchy RT, Sauer LA, Blask DE, Vaughan GM. 1997. Light contamination during the dark phase in "photoperiodically controlled" animal rooms: effect on tumor growth and metabolism in rats. *Lab Anim Sci* 47(5): 511-518.

Dauchy RT, Blask DE, Sauer LA, Brainard GC, Krause JA. 1999. Dim light during darkness stimulates tumor progression by enhancing tumor fatty acid uptake and metabolism. *Cancer Lett* 144(2): 131-136.

Dauchy RT, Cecil KS, Dauchy EM, Hanifin JP, Mao LL, Slakey LM, Belancio VP, Hill SM, Brainard GC, Blask DE. 2011. Melatonin-depleted blood from healthy adult men exposed to environmental light at night stimulates growth, signal transduction and metabolic activity of tissue-isolated human prostate cancer xenografts in nude rats. *Cancer Res* 71: 2.

Dauchy RT, Dauchy EM, Hanifin JP, Gauthreaux SL, Mao L, Belancio VP, Ooms TG, Dupepe LM, Jablonski MR, Warfield B, Wren MA, Brainard GC, Hill SM, Blask DE. 2013. Effects of spectral transmittance through standard laboratory cages on circadian metabolism and physiology in nude rats. *J Am Assoc Lab Anim Sci* 52(2): 146-156.

Dauchy RT, Xiang S, Mao L, Brimer S, Wren MA, Yuan L, Anbalagan M, Hauch A, Frasch T, Rowan BG, Blask DE, Hill SM. 2014. Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer. *Cancer Res* 74(15): 4099-4110.

Dauchy RT, Hoffman AE, Wren-Dail MA, Hanifin JP, Warfield B, Brainard GC, Xiang S, Yuan L, Hill SM, Belancio VP, Dauchy EM, Smith K, Blask DE. 2015. Daytime blue light enhances the nighttime circadian melatonin inhibition of human prostate cancer growth. *Comp Med* 65(6): 473-485.

Dauchy RT, Wren-Dail MA, Hoffman AE, Hanifin JP, Warfield B, Brainard GC, Hill SM, Belancio VP, Dauchy EM, Blask DE. 2016. Effects of daytime exposure to light from blue-enriched light-emitting diodes on the nighttime melatonin amplitude and circadian regulation of rodent metabolism and physiology. *Comp Med* 66(5): 373-383.

Dauchy RT, Wren-Dail MA, Dupepe LM, Hill SM, Xiang S, Anbalagan M, Belancio VP, Dauchy EM, Blask DE. 2018. Effect of daytime blue-enriched LED light on the nighttime circadian melatonin inhibition of hepatoma 7288CTC Warburg effect and progression. *Comp Med* 68(4): 1-11.

Davis S, Mirick DK, Stevens RG. 2001. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 93(20): 1557-1562.

Davis S, Mirick DK, Chen C, Stanczyk FZ. 2012. Night shift work and hormone levels in women. *Cancer Epidemiol Biomarkers Prev* 21(4): 609-618.

DOE. 2018. *Fluorescent Lighting and LED Lighting*. U.S. Department of Energy. https://www.energy.gov/energysaver/save-electricity-and-fuel/lighting-choices-save-you-money/fluorescent-lighting and https://www.energy.gov/energysaver/save-electricity-and-fuel/lighting-choices-save-you-money/led-lighting. Accessed on 5/31/18.

Erren TC. 2005. Could visible light contribute to the development of leukaemia and other cancers in children? *Med Hypotheses* 64(4): 864-871.

Falchi F, Cinzano P, Duriscoe D, Kyba CC, Elvidge CD, Baugh K, Portnov BA, Rybnikova NA, Furgoni R. 2016. The new world atlas of artificial night sky brightness. *Sci Adv* 2(6): e1600377.

Fang M, Ohman Strickland PA, Kang HG, Zarbl H. 2017. Uncoupling genotoxic stress responses from circadian control increases susceptibility to mammary carcinogenesis. *Oncotarget* 8(20): 32752-32768.

Figueiro M, Overington D. 2016. Self-luminous devices and melatonin suppression in adolescents. *Light Res Technol* 48(8): 966-975.

Figueiro MG. 2017. Disruption of circadian rhythms by light during day and night. *Curr Sleep Med Rep* 3(2): 76-84.

Figueiro MG, Steverson B, Heerwagen J, Kampschroer K, Hunter CM, Gonzales K, Plitnick B, Rea MS. 2017. The impact of daytime light exposures on sleep and mood in office workers. *Sleep Health* 3(3): 204-215.

Filipski E, Delaunay F, King VM, Wu MW, Claustrat B, Gréchez-Cassiau A, Guettier C, Hastings MH, Francis L. 2004. Effects of chronic jet lag on tumor progression in mice. *Cancer Res* 64(21): 7879-7885.

Filipski E, Innominato PF, Wu M, Li XM, Iacobelli S, Xian LJ, Lévi F. 2005. Effects of light and food schedules on liver and tumor molecular clocks in mice. *J Natl Cancer Inst* 97(7): 507-517.

Filipski E, Li XM, Levi F. 2006. Disruption of circadian coordination and malignant growth. *Cancer Causes Control* 17(4): 509-514.

Filipski E, Subramanian P, Carriere J, Guettier C, Barbason H, Lévi F. 2009. Circadian disruption accelerates liver carcinogenesis in mice. *Mutat Res* 680(1-2): 95-105.

Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, Boyle T, El-Zaemey S, Rogers P, Peters S, Slevin T, D'Orsogna A, de Vocht F, Vermeulen R, Heyworth JS. 2013. The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer* 109(9): 2472-2480.

Fu L, Pelicano H, Liu J, Huang P, Lee C. 2002. The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response in vivo. *Cell* 111(1): 41-50.

Fu L, Kettner NM. 2013. The circadian clock in cancer development and therapy. *Prog Mol Biol Transl Sci* 119: 221-282.

Furness JB. 2006. The organisation of the autonomic nervous system: peripheral connections. *Auton Neurosci* 130(1-2): 1-5.

Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, Amiano P, Martín Sánchez V, Guevara M, Capelo R, Tardón A, Peiró-Perez R, Jiménez-Moleón JJ, Roca-Barceló A, Pérez-Gómez B, Dierssen-Sotos T, Fernández-Villa T, Moreno-Iribas C, Moreno V, García-Pérez J, Castaño-Vinyals G, Pollán M, Aubé M, Kogevinas M. 2018. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain Study). *Environ Health Perspect* 126(4): 047011.

Gómez-Acebo I, Dierssen-Sotos T, Papantoniou K, García-Unzueta MT, Santos-Benito MF, Llorca J. 2015. Association between exposure to rotating night shift versus day shift using levels of 6-sulfatoxymelatonin and cortisol and other sex hormones in women. *Chronobiol Int* 32(1): 128-135.

Gradisar M, Wolfson AR, Harvey AG, Hale L, Rosenberg R, Czeisler CA. 2013. The sleep and technology use of Americans: findings from the National Sleep Foundation's 2011 Sleep in America poll. *J Clin Sleep Med* 9(12): 1291-1299.

Grundy A, Sanchez M, Richardson H, Tranmer J, Borugian M, Graham CH, Aronson KJ. 2009. Light intensity exposure, sleep duration, physical activity, and biomarkers of melatonin among rotating shift nurses. *Chronobiol Int* 26(7): 1443-1461.

Grundy A, Tranmer J, Richardson H, Graham CH, Aronson KJ. 2011. The influence of light at night exposure on melatonin levels among Canadian rotating shift nurses. *Cancer Epidemiol Biomarkers Prev* 20(11): 2404-2412.

Grundy A, Richardson H, Burstyn I, Lohrisch C, SenGupta SK, Lai AS, Lee D, Spinelli JJ, Aronson KJ. 2013. Increased risk of breast cancer associated with long-term shift work in Canada. *Occup Environ Med* 70(12): 831-838.

Guerrero-Vargas NN, Navarro-Espíndola R, Guzmán-Ruíz MA, Basualdo MDC, Espitia-Bautista E, López-Bago A, Lascurain R, Córdoba-Manilla C, Buijs RM, Escobar C. 2017. Circadian disruption promotes tumor growth by anabolic host metabolism; experimental evidence in a rat model. *BMC Cancer* 17(1): 625.

Haim A, Yukler A, Harel O, Schwimmer H, Fares F. 2010. Effects of chronobiology on prostate cancer cells growth in vivo. *Sleep Sci* 3(1): 32-35.

Hamilton T. 1969. Influence of environmental light and melatonin upon mammary tumour induction. *Br J Surg* 56(10): 764-766.

Hammer GP, Emrich K, Nasterlack M, Blettner M, Yong M. 2015. Shift work and prostate cancer incidence in industrial workers: A historical cohort study in a German chemical company. *Dtsch Arztebl Int* 112(27-28): 463-470.

Hansen J. 2001. Increased breast cancer risk among women who work predominantly at night. *Epidemiology* 12(1): 74-77.

Hansen J, Lassen CF. 2012. Nested case-control study of night shift work and breast cancer risk among women in the Danish military. *Occup Environ Med* 69(8): 551-556.

Hansen J, Stevens RG. 2012. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. *Eur J Cancer* 48(11): 1722-1729.

Hill SM, Belancio VP, Dauchy RT, Xiang S, Brimer S, Mao L, Hauch A, Lundberg PW, Summers W, Yuan L, Frasch T, Blask DE. 2015. Melatonin: an inhibitor of breast cancer. *Endocr Relat Cancer* 22(3): R183-204.

Honma S. 2018. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. *J Physiol Sci* 68(3): 207-219.

Hurley S, Nelson DO, Garcia E, Gunier R, Hertz A, Reynolds P. 2013. A cross-sectional analysis of light at night, neighborhood sociodemographics and urinary 6-sulfatoxymelatonin concentrations: implications for the conduct of health studies. *Int J Health Geogr* 12: 39.

Hurley S, Goldberg D, Nelson D, Hertz A, Horn-Ross PL, Bernstein L, Reynolds P. 2014. Light at night and breast cancer risk among California teachers. *Epidemiology* 25(5): 697-706.

IARC. 2010. Shift work. In *Painting, Firefighting, and Shiftwork*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, vol. 98. Lyon, France: International Agency for Research on Cancer. p. 563-764.

Isobe Y, Fukamachi K, Hida H, Tsuda H, Nishino H. 2008. Diethylnitrosamine-induced hepatic lesions are greater in rats maintained under a light-dark cycle than under constant light, related to the locomotor activity rhythm. *Asian Pac J Cancer Prev* 9(4): 619-624.

James P, Bertrand KA, Hart JE, Schernhammer ES, Tamimi RM, Laden F. 2017. Outdoor light at night and breast cancer incidence in the Nurses' Health Study II. *Environ Health Perspect* 125(8): 087010.

Jensen MA, Garde AH, Kristiansen J, Nabe-Nielsen K, Hansen AM. 2016. The effect of the number of consecutive night shifts on diurnal rhythms in cortisol, melatonin and heart rate variability (HRV): a systematic review of field studies. *Int Arch Occup Environ Health* 89(4): 531-545.

Ji BT, Gao YT, Shu XO, Yang G, Yu K, Xue SZ, Li HL, Liao LM, Blair A, Rothman N, Zheng W, Chow WH. 2012. Nightshift work job exposure matrices and urinary 6-sulfatoxymelatonin levels among healthy Chinese women. *Scand J Work Environ Health* 38(6): 553-559.

Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A. 2016. Can avoiding light at night reduce the risk of breast cancer? *Integr Cancer Ther* 15(2): 145-152.

Kettner NM, Katchy CA, Fu L. 2014. Circadian gene variants in cancer. *Ann Med* 46(4): 208-220.

Kettner NM, Voicu H, Finegold MJ, Coarfa C, Sreekumar A, Putluri N, Katchy CA, Lee C, Moore DD, Fu L. 2016. Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. *Cancer Cell* 30(6): 909-924.

Knutsson A, Alfredsson L, Karlsson B, Åkerstedt T, Fransson EI, Westerholm P, Westerlund H. 2013. Breast cancer among shift workers: results of the WOLF longitudinal cohort study. *Scand J Work Environ Health* 39(2): 170-177.

Koopman A, Rauh S, van't Riet E, Groeneveld L, van der Heijden A, Elders PJ, Dekker JM, Nijpels G, Beulens J, Rutters F. 2017. The association between social jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population. *J Biol Rhythms* 32(4): 359-368.

Kothari LS, Shah PN, Mhatre MC. 1982. Effect of continuous light on the incidence of 9,10-dimethyl-1,2-benzanthracene induced mammary tumors in female Holtzman rats. *Cancer Lett* 16(3): 313-317.

Kothari LS. 1987. Influence of chronic melatonin on 9,10-dimethyl-1,2-benzanthracene-induced mammary tumors in female Holtzman rats exposed to continuous light. *Oncology* 44(1): 64-66.

Kozaki T, Kubokawa A, Taketomi R, Hatae K. 2015. Effects of day-time exposure to different light intensities on light-induced melatonin suppression at night. *J Physiol Anthropol* 34: 27.

Kozaki T, Kubokawa A, Taketomi R, Hatae K. 2016. Light-induced melatonin suppression at night after exposure to different wavelength composition of morning light. *Neurosci Lett* 616: 1-4.

Kubo T, Ozasa K, Mikami K, Wakai K, Fujino Y, Watanabe Y, Miki T, Nakao M, Hayashi K, Suzuki K, Mori M, Washio M, Sakauchi F, Ito Y, Yoshimura T, Tamakoshi A. 2006. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. *Am J Epidemiol* 164(6): 549-555.

Kubo T, Oyama I, Nakamura T, Kunimoto M, Kadowaki K, Otomo H, Fujino Y, Fujimoto N, Matsumoto T, Matsuda S. 2011. Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. *Int J Urol* 18(3): 206-211.

Lang R, Hintner H, Hermann A, Brandstaetter R. 2003. Photoperiod modulates melanoma growth in C57BL/6 mice. *Exp Dermatol* 12(4): 510-513.

Lee S, Donehower LA, Herron AJ, Moore DD, Fu L. 2010. Disrupting circadian homeostasis of sympathetic signaling promotes tumor development in mice. *PLoS ONE* 5(6).

Leung M, Tranmer J, Hung E, Korsiak J, Day AG, Aronson KJ. 2016. Shift work, chronotype, and melatonin patterns among female hospital employees on day and night shifts. *Cancer Epidemiol Biomarkers Prev* 25(5): 830-838.

Levallois P, Dumont M, Touitou Y, Gingras S, Masse B, Gauvin D, Kroger E, Bourdages M, Douville P. 2001. Effects of electric and magnetic fields from high-power lines on female urinary excretion of 6-sulfatoxymelatonin. *Am J Epidemiol* 154(7): 601-609.

Li JC, Xu F. 1997. Influences of light-dark shifting on the immune system, tumor growth and life span of rats, mice and fruit flies as well as on the counteraction of melatonin. *Biol Signals* 6(2): 77-89.

Li W, Ray RM, Thomas DB, Davis S, Yost M, Breslow N, Gao DL, Fitzgibbons ED, Camp JE, Wong E, Wernli KJ, Checkoway H. 2015. Shift work and breast cancer among women textile workers in Shanghai, China. *Cancer Causes Control* 26(1): 143-150.

Lie JA, Kjuus H, Zienolddiny S, Haugen A, Stevens RG, Kjaerheim K. 2011. Night work and breast cancer risk among Norwegian nurses: assessment by different exposure metrics. *Am J Epidemiol* 173(11): 1272-1279.

Lie JA, Kjuus H, Zienolddiny S, Haugen A, Kjaerheim K. 2013. Breast cancer among nurses: is the intensity of night work related to hormone receptor status? *Am J Epidemiol* 178(1): 110-117.

Logan RW, Zhang C, Murugan S, O'Connell S, Levitt D, Rosenwasser AM, Sarkar DK. 2012. Chronic shift-lag alters the circadian clock of NK cells and promotes lung cancer growth in rats. *J Immunol* 188(6): 2583-2591.

Lunn RM, Blask DE, Coogan AN, Figueiro MG, Gorman MR, Hall JE, Hansen J, Nelson RJ, Panda S, Smolensky MH, Stevens RG, Turek FW, Vermeulen R, Carreon T, Caruso CC, Lawson CC, Thayer KA, Twery MJ, Ewens AD, Garner SC, Schwingl PJ, Boyd WA. 2017. Health consequences of electric lighting practices in the modern world: A report on the National Toxicology Program's workshop on shift work at night, artificial light at night, and circadian disruption. *Sci Total Environ* 607-608: 1073-1084.

Malone SK, Zemel B, Compher C, Souders M, Chittams J, Thompson AL, Lipman TH. 2016. Characteristics associated with sleep duration, chronotype, and social jet lag in adolescents. *J Sch Nurs* 32(2): 120-131.

Matulka R, Wood D. 2013. *The History of the Light Bulb*. Energy.gov. Updated on 11/22/13. https://energy.gov/articles/history-light-bulb. Accessed on 10/24/17.

McCorry LK. 2007. Physiology of the autonomic nervous system. *Am J Pharm Educ* 71(4): 78.

McMahon DM, Burch JB, Wirth MD, Youngstedt SD, Hardin JW, Hurley TG, Blair SN, Hand GA, Shook RP, Drenowatz C, Burgess S, Hebert JR. 2018. Persistence of social jetlag and sleep disruption in healthy young adults. *Chronobiol Int* 35(3): 312-328.

McMenamin T. 2007. A time to work: recent trends in shift work and flexible schedules. *Mon Labor Rev* December: 3-15.

Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, Kerbrat P, Fevotte J, Guenel P. 2013. Night work and breast cancer: a population-based case-control study in France (the CECILE study). *Int J Cancer* 132(4): 924-931.

Mirick DK, Davis S. 2008. Melatonin as a biomarker of circadian dysregulation. *Cancer Epidemiol Biomarkers Prev* 17(12): 3306-3313.

Mirick DK, Bhatti P, Chen C, Nordt F, Stanczyk FZ, Davis S. 2013. Night shift work and levels of 6-sulfatoxymelatonin and cortisol in men. *Cancer Epidemiol Biomarkers Prev* 22(6): 1079-1087.

Mteyrek A, Filipski E, Guettier C, Oklejewicz M, van der Horst GT, Okyar A, Lévi F. 2017. Critical cholangiocarcinogenesis control by cryptochrome clock genes. *Int J Cancer* 140(11): 2473-2483.

Nagare R, Plitnick B, Figueiro M. 2018. Effect of exposure duration and light spectra on nighttime melatonin suppression in adolescents and adults. *Lighting Res Technol*.

Nagashima S, Osawa M, Matsuyama H, Ohoka W, Ahn A, Wakamura T. 2018. Bright-light exposure during daytime sleeping affects nocturnal melatonin secretion after simulated night work. *Chronobiol Int* 35(2): 229-239.

Nakajima H, Narama I, Matsuura T, Nomura T. 1994. Enhancement of tumor growth under short light/dark cycle in mouse lung. *Cancer Lett* 78(1-3): 127-131.

Navara KJ, Nelson RJ. 2007. The dark side of light at night: physiological, epidemiological, and ecological consequences. *J Pineal Res* 43(3): 215-224.

Nelson RJ, Blom JM. 1994. Photoperiodic effects on tumor development and immune function. *J Biol Rhythms* 9(3-4): 233-249.

NOAO. 2018. *Types of Light*. National Optical Astronomy Observatory. 6 pp. https://www.noao.edu/education/QLTkit/ACTIVITY_Documents/Energy/Types_of_Lights.pdf.

Nobel Prize. 2017. *Press Release on The Nobel Prize in Physiology or Medicine 2017*. Updated on 10/2/17. https://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/press.html. Accessed on 7/5/18.

NTP. 2015. *Handbook for Preparing Report on Carcinogens Monographs*. Research Triangle Park, NC: National Toxicology Program. 89 pp. https://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf.

NTP. 2018a. *Night Shift Work and Light at Night (LAN): Human cancer studies*. Research Triangle Park, NC: National Toxicology Program. 46 pp. https://ntp.niehs.nih.gov/ntp/roc/protocols/electric-light_508.pdf.

NTP. 2019. *National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night*. National Toxicology Program. Updated on 9/30/19. https://ntp.niehs.nih.gov/go/717273.

O'Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, Gammon MD, Leske MC, for the Electromagnetic Fields Breast Cancer on Long Island Study Group. 2006. Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol* 164(4): 358-366.

Oh JH, Yoo H, Park HK, Do YR. 2015. Analysis of circadian properties and healthy levels of blue light from smartphones at night. *Sci Rep* 5: 11325.

Otálora BB, Madrid JA, Alvarez N, Vicente V, Rol MA. 2008. Effects of exogenous melatonin and circadian synchronization on tumor progression in melanoma-bearing C57BL6 mice. *J Pineal Res* 44(3): 307-315.

Papagiannakopoulos T, Bauer MR, Davidson SM, Heimann M, Subbaraj L, Bhutkar A, Bartlebaugh J, Vander Heiden MG, Jacks T. 2016. Circadian rhythm disruption promotes lung tumorigenesis. *Cell Metab* 24(2): 324-331.

Papantoniou K, Pozo OJ, Espinosa A, Marcos J, Castano-Vinyals G, Basagana X, Ribas FC, Mirabent J, Martin J, Carenys G, Martin CR, Middleton B, Skene DJ, Kogevinas M. 2014. Circadian variation of melatonin, light exposure, and diurnal preference in day and night shift workers of both sexes. *Cancer Epidemiol Biomarkers Prev* 23(7): 1176-1186.

Papantoniou K, Castaño-Vinyals G, Espinosa A, Aragonés N, Pérez-Gómez B, Ardanaz E, Altzibar JM, Sanchez VM, Gómez-Acebo I, Llorca J, Muñoz D, Tardón A, Peiró R, Marcos-Gragera R, Pollan M, Kogevinas M. 2015a. Breast cancer risk and night shift work in a case-control study in a Spanish population. *Eur J Epidemiol* 31(9): 867-878.

Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Burgos J, Gomez-Acebo I, Llorca J, Peiro R, Jimenez-Moleon JJ, Arredondo F, Tardon A, Pollan M, Kogevinas M. 2015b. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. *Int J Cancer* 137(5): 1147-1157.

Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. 2012. Night work and the risk of cancer among men. *Am J Epidemiol* 176(9): 751-759.

Pauley SM. 2004. Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. *Med Hypotheses* 63(4): 588-596.

Pesch B, Harth V, Rabstein S, Baisch C, Schiffermann M, Pallapies D, Bonberg N, Heinze E, Spickenheuer A, Justenhoven C, Brauch H, Hamann U, Ko Y, Straif K, Brüning T. 2010. Night work and breast cancer - results from the German GENICA study. *Scand J Work Environ Health* 36(2): 134-141.

Popovich IG, Zabezhinski MA, Panchenko AV, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Anisimov VN. 2013. Exposure to light at night accelerates aging and spontaneous uterine carcinogenesis in female 129/Sv mice. *Cell Cycle* 12(11): 1785-1790.

Pronk A, Ji BT, Shu XO, Xue S, Yang G, Li HL, Rothman N, Gao YT, Zheng W, Chow WH. 2010. Night-shift work and breast cancer risk in a cohort of Chinese women. *Am J Epidemiol* 171(9): 953-959.

Rabstein S, Harth V, Pesch B, Pallapies D, Lotz A, Justenhoven C, Baisch C, Schiffermann M, Haas S, Fischer HP, Heinze E, Pierl C, Brauch H, Hamann U, Ko Y, Bruning T, Consortium G.

2013. Night work and breast cancer estrogen receptor status--results from the German GENICA study. *Scand J Work Environ Health* 39(5): 448-455.

Reszka E, Przybek M. 2016. Circadian genes in breast cancer. *Adv Clin Chem* 75: 53-70.

Reszka E, Przybek M, Muurlink O, Peplonska B. 2017. Circadian gene variants and breast cancer. *Cancer Lett*.

Roenneberg T, Allebrandt KV, Merrow M, Vetter C. 2012. Social jetlag and obesity. *Curr Biol* 22(10): 939-943.

Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, Dekker JM. 2014. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? *J Biol Rhythms* 29(5): 377-383.

Schernhammer ES, Rosner B, Willett WC, Laden F, Colditz GA, Hankinson SE. 2004. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. *Cancer Epidemiol Biomarkers Prev* 13(6): 936-943.

Schwimmer H, Metzer A, Pilosof Y, Szyf M, Machnes ZM, Fares F, Harel O, Haim A. 2014. Light at night and melatonin have opposite effects on breast cancer tumors in mice assessed by growth rates and global DNA methylation. *Chronobiol Int* 31(1): 144-150.

Smolensky MH, Sackett-Lundeen LL, Portaluppi F. 2015. Nocturnal light pollution and underexposure to daytime sunlight: Complementary mechanisms of circadian disruption and related diseases. *Chronobiol Int* 32(8): 1029-1048.

Smolensky MH, Hermida RC, Reinberg A, Sackett-Lundeen L, Portaluppi F. 2016. Circadian disruption: New clinical perspective of disease pathology and basis for chronotherapeutic intervention. *Chronobiol Int*: 1-19.

Song G, Yoon KA, Chi H, Roh J, Kim JH. 2016. Decreased concentration of serum melatonin in nighttime compared with daytime female medical technologists in South Korea. *Chronobiol Int* 33(9): 1305-1310.

Stevens RG, Davis S, Thomas DB, Anderson LE, Wilson BW. 1992. Electric power, pineal function, and the risk of breast cancer. *FASEB J* 6(3): 853-860.

Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, Castaño-Vinyals G, Davis S, Frings-Dresen MH, Fritschi L, Kogevinas M, Kogi K, Lie JA, Lowden A, Peplonska B, Pesch B, Pukkala E, Schernhammer E, Travis RC, Vermeulen R, Zheng T, Cogliano V, Straif K. 2011. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 68(2): 154-162.

Stevens RG, Zhu Y. 2015. Electric light, particularly at night, disrupts human circadian rhythmicity: is that a problem? *Philos Trans R Soc Lond B Biol Sci* 370(1667).

Travis RC, Balkwill A, Fensom GK, Appleby PN, Reeves GK, Wang XS, Roddam AW, Gathani T, Peto R, Green J, Key TJ, Beral V. 2016. Night shift work and breast cancer incidence: Three prospective studies and meta-analysis of published studies. *J Natl Cancer Inst* 108(12): djw169.

Travlos GS, Wilson RE, Murrell JA, Chignell CF, Boorman GA. 2001. The effect of short intermittent light exposures on the melatonin circadian rhythm and NMU-induced breast cancer in female F344/N rats. *Toxicol Pathol* 29(1): 126-136.

Tse LA, Lee PMY, Ho WM, Lam AT, Lee MK, Ng SSM, He Y, Leung KS, Hartle JC, Hu H, Kan H, Wang F, Ng CF. 2017. Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. *Environ Int* 107: 1-7.

Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. 1996. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control* 7(2): 197-204.

Uzoigwe CE, Sanchez Franco LC. 2018. Night shifts: chronotype and social jetlag. *BMJ* 361: k1666.

van den Heiligenberg S, Deprés-Brummer P, Barbason H, Claustrat B, Reynes M, Lévi F. 1999. The tumor promoting effect of constant light exposure on diethylnitrosamine-induced hepatocarcinogenesis in rats. *Life Sci* 64(26): 2523-2534.

Van Dycke KC, Rodenburg W, van Oostrom CT, van Kerkhof LW, Pennings JL, Roenneberg T, van Steeg H, van der Horst GT. 2015. Chronically alternating light cycles increase breast cancer risk in mice. *Curr Biol* 25(14): 1932-1937.

Vermeulen R. 2016. *Types and Characteristics of Shift Work and the Concept of Shift Work as a Complex Exposure Scenario*. Universitat Utrecht, Institute for Risk Assessment Science. 26 pp.

Vinogradova IA, Anisimov VN, Bukalev AV, Semenchenko AV, Zabezhinski MA. 2009. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats. *Aging (Albany NY)* 1(10): 855-865.

Viola AU, James LM, Schlangen LJ, Dijk DJ. 2008. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand J Work Environ Health* 34(4): 297-306.

Vistisen HT, Garde AH, Frydenberg M, Christiansen P, Hansen AM, Andersen J, Bonde JP, Kolstad HA. 2017. Short-term effects of night shift work on breast cancer risk: a cohort study of payroll data. *Scand J Work Environ Health* 43(1): 59-67.

Waldrop RD, Saydjari R, Rubin NH, Rayford PL, Townsend CM, Jr., Thompson JC. 1989. Photoperiod influences the growth of colon cancer in mice. *Life Sci* 45(8): 737-744.

Wang P, Ren FM, Lin Y, Su FX, Jia WH, Su XF, Tang LY, Ren ZF. 2015. Night-shift work, sleep duration, daytime napping, and breast cancer risk. *Sleep Med* 16(4): 462-468.

Wegrzyn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, Laden F, Willett WC, Hankinson SE, Schernhammer ES. 2017. Rotating night shift work and risk of breast cancer in the nurses' health studies. *Am J Epidemiol*.

Wendeu-Foyet MG, Bayon V, Cénée S, Trétarre B, Rébillard X, Cancel-Tassin G, Cussenot O, Lamy PJ, Faraut B, Kheder SB, Léger D, Menegaux F. 2018. Night work and prostate cancer risk: Results from the EPICAP study. *OEM* 75(8): 573-581.

Wu J, Sánchez de la Peña S, Halberg F, Cornélissen G, Wetterberg L, Halberg E, Lakatua D, Bingham C, Harvey J, Bazin H, Zheng T, Leung B, Tran B. 1988. Chronosynergistic effects of lighting schedule-shift and cefodizime on plasmacytoma growth and host survival time. *Chronobiologia* 15(1-2): 105-128.

Wu M, Zeng J, Chen Y, Zeng Z, Zhang J, Cai Y, Ye Y, Fu L, Xian L, Chen Z. 2012. Experimental chronic jet lag promotes growth and lung metastasis of Lewis lung carcinoma in C57BL/6 mice. *Oncol Rep* 27(5): 1417-1428.

Yasuniwa Y, Izumi H, Wang K-Y, Shimajiri S, Sasaguri Y, Kawai K, Kasai H, Shimada T, Miyake K, Kashiwagi E, Hirano G, Kidani A, Akiyama M, Han B, Wu Y, Ieiri I, Higuchi S, Kohno K. 2010. Circadian disruption accelerates tumor growth and angio/stromagenesis through a wnt signaling pathway. *PLoS One* 5(12): e15330.

Zeng ZL, Wu MW, Sun J, Sun YL, Cai YC, Huang YJ, Xian LJ. 2010. Effects of the biological clock gene *Bmal1* on tumour growth and anti-cancer drug activity. *J Biochem* 148(3): 319-326.

Zielinska-Dabkowska KM. 2018. Make lighting healthier. *Nature* 553(7688): 274-276.

Zubidat AE, Haim A. 2017. Artificial light-at-night - a novel lifestyle risk factor for metabolic disorder and cancer morbidity. *J Basic Clin Physiol Pharmacol* 28(4): 295-313.

Table of Contents

List of Tables

List of Figures

Abstract

Introduction

Modern electric lighting practices have facilitated a society in which people may work, sleep, and receive goods and services at any time of the day. People are exposed to ill-timed, unnatural, electric light (such as light at night, or "LAN") through lifestyle choices, necessity, the locations of their residences, and employment during the night shift. As light is the critical regulator for circadian rhythms, exposure to LAN can cause circadian disruption, which can be associated with potential adverse health effects such as cancer. Night shift work includes exposure to electric LAN, sleep disturbances, or changes in meal timing, as well as other potential factors (e.g., social stressors, lifestyle behaviors, decreased exposure to sunlight, and lower vitamin D levels). Most, but not all, of these factors can lead to circadian disruption.

Methods

The National Toxicology Program (NTP) conducted cancer hazard assessments for two exposure scenarios: night shift work and exposure to LAN. We used systematic review methods to identify studies, evaluate study quality, and integrate evidence across studies. Using established criteria, we reached conclusions regarding the strength of the evidence from cancer epidemiology studies for night shift work, exposure to outdoor and indoor LAN, and transmeridian travel. Because circadian disruption is a key intermediate in the pathway between exposure and potential cancer, for each exposure scenario, we used a triangulation approach to integrate the evidence from the cancer studies with evidence from studies of exposure and circadian disruption and studies of circadian disruption and cancer. Our assessment also included mechanistic studies of each exposure scenario and key characteristics of carcinogens. Lastly, based on the totality of the evidence, we placed the cancer hazards into context by specifically defining the circumstances by which night shift work or LAN may cause cancer.

Results and Discussion

Night Shift Work: Human epidemiology studies provide strong (but not sufficient) evidence that persistent night work (i.e., frequent and long-term night shift work, or working a large number of night shifts over a lifetime, especially in early adulthood) causes female breast cancer. Evidence that persistent night shift work causes prostate cancer is considered limited. Cancer studies in experimental animals found that simulated shift work or chronic jet lag promotes the growth of mammary-gland and other types of tumors in experimental animals. Finally, mechanistic studies in humans and non-humans demonstrated that (1) circadian disruption plays a role in shift-work-mediated carcinogenicity, and (2) night shift work is associated with biological effects that are recognized as key characteristics of carcinogens. A strength of the database is that several animal cancer studies also measured biological effects that are associated with circadian disruption or are characteristics of carcinogens, thus providing a link between exposure, intermediate biological effects, and cancer. Some biological effects observed in experimental animals were also observed in night shift workers. NTP concludes overall that there is sufficient evidence for the carcinogenicity for breast cancer based on the collective body of cancer epidemiology and mechanistic studies in humans.

LAN: Evidence to evaluate the relationship between outdoor LAN exposure, indoor LAN exposure, and transmeridian travel and human cancer from epidemiology studies alone was considered inadequate. However, toxicological and mechanistic studies in experimental animals

of modeled LAN provide strong evidence that LAN promotes proliferation and growth of human breast cancer implants, promotes proliferation of other types of cancer, causes biological effects (collective evidence) that are identified as characteristics of carcinogens and that the effects are mediated in part by circadian disruption. The animal studies demonstrate that melatonin suppression (a biomarker of circadian disruption) plays a direct role in LAN-mediated mammary tumor or breast carcinogenicity. Studies in humans demonstrate that exposure to LAN causes melatonin suppression.

NTP Final Cancer Hazard Conclusions

There is high confidence for a causal relationship between human cancer (breast and less so prostate) and persistent night shift work — i.e., frequent and long-term night shift work, especially beginning in early adulthood — that causes circadian disruption. This conclusion is based on sufficient evidence of carcinogenicity from the collective body of evidence from cancer epidemiological studies and mechanistic studies in humans and in experimental animals. The strongest evidence is for breast cancer.

There is moderate confidence for a causal relationship between human cancer and certain lighting conditions — i.e., excessive LAN exposure combined with insufficient daylight exposure — that cause circadian disruption. This conclusion is based on strong evidence that LAN acts through mechanisms that are likely to cause cancer in humans.

Introduction

Modern electric lighting practices have facilitated a society in which people may work, sleep, and receive goods and services at any time of the day. People are exposed to ill-timed, unnatural, electric light (such as light at night, or "LAN") through lifestyle choice, necessity, the locations of their residences, and employment during the night shift. As light is the critical regulator for circadian rhythms, exposure to LAN can cause circadian disruption, which can be linked to potential adverse health effects such as cancer.

The objective of this report is to conduct cancer hazard assessments for night shift work and exposure to LAN and to adequately define these two exposure scenarios based on the cancer hazard assessment.

- Night shift work is defined as typically working at least 3 hours between midnight and 5:00 AM, which is the time period most likely to be associated with circadian disruption. It is a complex exposure scenario that includes exposure to electric LAN, sleep disturbances, or changes in meal timing, as well as other potential exposures (e.g., decreased exposure to sunlight, and lower vitamin D levels). Sleep disturbances and changes in meal timing are also related to circadian disruption.
- LAN refers to exposure to light during the biological night which is the time when the circadian clock promotes sleep.

Cancer Hazard Assessments

NTP proposed review of the two exposure circumstances—night shift work and light at night—because of ubiquitous exposure and concern for potential health effects. After obtaining input from the public and the NTP Board of Scientific Counselors, NTP selected these two exposure circumstances for review. Because of the complexity of this topic, the NTP convened a public workshop on March 10-11, 2016, to obtain external scientific input on topics important for informing the literature-based cancer hazard assessments, including strategies for integrating data across evidence streams (for more information see, https://ntp.niehs.nih.gov/go/workshop_ALAN). The panel recommended that the topic could be viewed as modern electric lighting practices and several of these experts also provided input on the development of the document. This information was used to develop the protocol for preparing the draft report. The Draft RoC Monograph[2] was developed to support the scientific assessment to determine whether night shift work and light at night should be listed in the RoC. As noted in the Preface, following peer review (see "Peer Review"), a decision was made not to move forward with these two exposure scenarios for listing in the RoC and the RoC listing category recommendations were changed to cancer hazard assessment conclusions to avoid confusion.

[1]Available at https://ntp.niehs.nih.gov/go/717273.

Methods

This report evaluates the available, relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends an overall cancer hazard assessment conclusion for night shift work and light at night. The scientific information came from publicly available sources.

This section outlines the framework for the report, the report contents, and key questions; it also provides a brief overview of the draft report's methods.

Framework and contents

As circadian disruption is a key intermediate in the pathway between exposure and potential cancer, this monograph uses a triangulation approach to review studies evaluating (1) exposure (night shift work and light at night) and circadian disruption, (2) studies on circadian disruption and cancer, and (3) studies of the exposure scenarios and cancer. Studies of exposure and biological effects (e.g., key characteristics of carcinogens) which may result from circadian disruption were also included in the evidence integration. The table below summarizes the evidence streams, exposures of interest, and outcomes. This is somewhat analogous to a "population, exposure, comparator, outcome" statement except that population has been replaced by evidence stream (e.g., humans, experimental animals, *in vitro* studies).

Report Framework

Evidence stream	Exposure (intermediate)	Comparison group	Cancer outcome or effect
Main effects			
Human epidemiology studies	Night shift work	Day shift workers	Breast cancer, prostate cancer, colorectal cancer, lung cancer, hormonal cancers
Human epidemiology studies	LAN Outdoor LAN LAN in the sleeping area	Low exposure to LAN	Breast cancer
Human epidemiology studies	Transmeridian travel	Large number of trips vs. lower number of trips	Breast cancer
Supporting evidence			
Experimental animals	LAN proxies: continuous light, dim light at night, interrupted light	Standard lighting, usually 12 hr light and 12 hr dark	Total neoplasms (usually combined) Primarily tumor proliferation, promotion, or latency Cancer site is dependent on type of initiator and xenograft Mammary gland or human breast (xenografts) is most studied site

Evidence stream	Exposure (intermediate)	Comparison group	Cancer outcome or effect
Experimental animals	Shift work proxies Simulated shift work Chronic jet lag	Standard lighting, usually 12 hr light and 12 hr dark	Spontaneous tumors in cancer-prone mouse model Primarily tumor proliferation, growth or latency; cancer site is dependent on type of initiator and xenograft Mammary gland or human breast (xenografts) is one of the studied sites
Intermediate effects[a]			
Human molecular epidemiology	Night shift workers Night shift among rotating shift workers	Day shift workers Day shift among rotating shift workers	Circadian disruption: primarily melatonin and clock gene expression
Human experimental studies	Different types of light (e.g., wavelength, level, duration, timing)	Same individuals or comparisons of other subjects exposed to "control" lighting conditions	Circadian disruption: primarily melatonin and clock gene expression
Experimental animal studies	LAN proxies	Standard lighting, usually 12 hr light and 12 hr dark	Circadian disruption: primarily melatonin and clock gene expression
Experimental animal studies	Simulated shift work or chronic jet lag	Standard lighting, usually 12 hr light and 12 hr dark	Clock gene expression
Molecular epidemiology studies	Night shift work	Day shift workers	Biological effects related to cancer (e.g., 10 characteristics of carcinogens)
Experimental animal studies	LAN proxies Simulated shift work or jet lag	Standard lighting, usually 12 hr light and 12 hr dark	Biological effects related to cancer
Human epidemiology studies	Circadian disruption Melatonin or melatonin proxies (blind people)	General population (for blind people) or sighted people Low vs. high levels	Breast cancer
Human epidemiology studies	Circadian disruption Clock gene polymorphisms	Clock gene polymorphisms	Breast cancer susceptibility
Human, animal, & *in vitro* (reviews)	Melatonin, clock gene expression	Not relevant	Cancer and biological effects related to cancer

Evidence stream replaces population.
Blue = exposure; green = cancer outcome; purple = circadian disruption.
[a]Includes (1) studies of "exposure" and intermediates (circadian disruption or biological effects related to cancer) and (2) studies of the intermediate and cancer or biological effects related to cancer.

The process of reaching the cancer hazard assessment conclusions for night shift work and LAN included assessing the level of evidence from cancer studies of night shift work and LAN in humans. Human cancer studies of transmeridian travel were also reviewed as this involves exposure to both LAN and shift work; however, no overall cancer hazard conclusion was made for this exposure scenario. Most of the studies in experimental animals were mechanistic studies that examined growth of tumors after chemical or genetic initiation or after injection of tumor cells or implantation of tissue and were not designed to evaluate incidences of specific tumors as would be reported in chronic cancer studies. The assessment of circadian disruption as an intermediate between exposure and cancer included a review of (1) studies of LAN and shift work and biomarkers of circadian disruption and (2) studies of circadian disruption (primarily melatonin and clock gene desynchrony) and cancer (see Table above). The latter body of evidence is included in the discussion of mechanistic data. This approach informed the organization of the monograph (provided below). The overall cancer hazard evaluation is informed by an integration of the totality of the evidence. The sections of the monograph are as follows:

- Circadian Regulation and Disruption, Night Shift Work and Light at Night: Characterization and Exposure (Section 1)
- Light at Night and Night Shift Work: Circadian Disruption Studies (Section 2)
- Human Breast Cancer Studies (Night Shift Work, LAN, Transmeridian Travel) (Section 3)
- Other Human Cancer Studies (Night Shift Work) (Section 4)
- Studies of Cancer in Experimental Animals (Section 5)
- Mechanistic and Other Relevant Data (Section 6)
- Evidence Integration and Cancer Hazard Assessment Conclusions (Section 7)

The appendices in the report contain supplementary information, including the literature search strategy and the tables on the findings from human cancer studies.

Key scientific questions for each type of evidence stream

The report provides information relevant to the following questions for each type of evidence stream or section topic.

Overall questions

- Do a significant number of people residing in the United States work night shifts?
- Are a significant number of people residing in the United States exposed to LAN?
- Does night shift work pose a cancer hazard to humans?
    - If so, how should it be defined?
    - Can we define the underlying exposures related to circadian disruption?
- Does LAN pose a cancer hazard to humans?
    - If so, how should it be defined?

Questions related to the evaluation of human cancer studies

- What are the methodological strengths and limitations of these studies?
- What are the potential confounding factors for cancer risk at the tumor sites of interest?
- Is there a credible association between exposure to LAN or working the night shift and cancer?
    - If so, can the relationship between cancer outcomes and exposure to LAN or working nights be explained by chance, bias, or confounding?

Questions related to the evaluation of mechanistic data and other relevant data

- Do the animal cancer studies provide support for the findings in studies in humans?
- Are the animal studies informative for evaluating the potential carcinogenicity of LAN and night shift work?
- Do the mechanistic data provide support for a role of circadian disruption in the potential carcinogenicity of LAN or night shift work?
- Do the mechanistic data provide convincing relevant information that LAN and night shift work act through mechanisms indicating they would likely cause cancer in humans?

Report preparation methods

The methods for preparing the NTP cancer hazard assessments for night shift work and LAN are described in the "Report on Carcinogens Protocol: Night Shift Work and Light at Night" (NTP 2018) (hereinafter referred to as "Protocol"), which incorporated a systematic review approach for identification and selection of the literature (see Appendix A), using inclusion/exclusion criteria, extraction of data and evaluation of study quality according to specific guidelines, and assessment of the level of evidence for carcinogenicity according to established criteria. Links are provided to the appendices within the document, and specific tables or sections can be selected from the table of contents.

General procedures

The "Handbook for Preparing Report on Carcinogens Monographs" (hereinafter referred to as "Handbook") provides a detailed description of the methods that were used (NTP 2015).

Selection of the literature

Preparation of the monograph began with development of a literature search strategy to obtain information relevant to the topics listed above for Sections 1 through 6 using search terms outlined in the Protocol. Approximately 6,500 citations were identified from these searches and uploaded to web-based systematic review software for separate evaluation by two reviewers applying the inclusion/exclusion criteria. Based on these criteria, 722 references were selected for final inclusion in the cancer hazard assessment. Literature searches were updated on a monthly basis prior to posting the peer-review draft on August 24, 2018. References recommended by the peer reviewers were also considered for the final version. NTP has monitored the literature through September 2019 and did not identify any studies that would affect the overall cancer hazard conclusions. No studies from the updated monitoring have been included in this final assessment because these studies would not have been peer reviewed.

Data extraction and quality assurance procedures

Information for the relevant cancer and mechanistic studies was systematically extracted in tabular format and/or summarized in the text from studies selected for inclusion in the monograph. All sections of the monograph underwent scientific review and quality assurance (i.e., assuring that all the relevant data and factual information extracted from the publications had been reported accurately) by a separate reviewer. Any discrepancies were resolved by the writer and the reviewer through discussion and reference to the original data source.

Evaluation of studies on circadian disruption

This section used reviews as well as individual studies. It briefly reviews circadian disruption, and studies of night shift work and exposure to LAN and markers of circadian disruption. The literature is considered to be representative but not necessarily comprehensive. Data from key individual studies were extracted into tables. Although a formal quality assessment was not conducted, key limitations of studies were noted.

Evaluation of human cancer studies

Two reviewers evaluated the quality of each study using a series of questions (and guidelines for answering the questions) related to risk of bias and to study sensitivity (as described in the Protocol). Any disagreements between the two reviewers were resolved through discussion or by consultation with a third reviewer and reference to the original data source. The approach to synthesizing the evidence across studies and reaching a conclusion on the level of evidence for carcinogenicity is also outlined in the Protocol. Level-of-evidence conclusions (inadequate, limited, or sufficient) were made by applying the RoC listing criteria (see below) to the body of evidence.

Evaluation of cancer studies in experimental animals

As mentioned previously, most of the studies in experimental animals were mechanistic studies that examined growth of tumors after chemical or genetic initiation or after injection of tumor cells or implantation of tissue and were not designed to evaluate incidences of specific tumors as would be reported in chronic cancer studies. Thus, a systematic review of the studies was not conducted. The section provides an overview of the relevant findings and conclusions of the evidence across studies for LAN and night shift work.

Evaluation of mechanistic and other relevant data

This section provides an overview of the key findings from studies of circadian disruption (primarily melatonin suppression and altered clock gene expression) and possible mechanisms of carcinogenicity. Due to the extensive literature and general acceptance of the oncostatic effects of melatonin, this information primarily comes from reviews. This section also reviews individual studies measuring exposure to LAN and shift work and biological effects related to cancer as well as key information related to the melatonin hypothesis. The purpose of the section is to integrate the relevant information to reach conclusions that inform the hazard evaluation.

Overall cancer hazard assessment conclusions

The cancer hazard assessment involved integration of the relevant evidence from studies evaluating the pathway from exposure to circadian disruption to cancer. The level of evidence conclusions from studies in humans and overall NTP cancer hazard assessment were reached by

applying the RoC listing criteria to these assessments. The section uses a series of evidence-based tables and figures that summarize the assessments from the entire report to provide transparency for the decision-making process for reaching the cancer hazard assessment conclusions for LAN and night shift work. The cancer hazard assessment conclusions are based on the RoC listing categories although different cancer hazard conclusions are used in order to avoid confusion with RoC listings as follows: (1) high confidence for a causal relationship with human cancer meets the criteria for *known to be a human carcinogen* and (2) moderate confidence for a causal relationship with human cancer meets the criteria for *reasonably anticipated to be a human carcinogen*.

RoC Listing Criteria

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

1 Circadian Regulation and Disruption, Night Shift, and Light at Night: Characterization and Exposure

The invention of the electric light in the late 1800s resulted in a change in the lighted environment as industrialized and developing societies switched from a sun-based system, supplemented by fire/candle light and gas lamps, to an electricity-based system (Stevens and Rea 2001). Furthermore, technological advances in the 20th and 21st centuries have added other sources of light exposure, including television, computers, cell phones, and other electronic devices. The United Nations proclaimed 2015 the International Year of Light and Light-Based Technologies in recognition of how light "has revolutionized medicine, opened up international communication via the Internet, and continues to be central to linking cultural, economic, and political aspects of the global economy" (UNESCO 2015). In conjunction with these advances, modern electric lighting practices and electronic devices (1) have led to ill-timed, unnatural exposure to light resulting from too little exposure to daylight together with too much exposure to electrical light at night (LAN) and (2) have enabled a dramatic shift in daily activity (including work, play, meal times) and sleep patterns compared to the typical patterns prior to the introduction of electricity. These changes are associated with disruption of the circadian system and potential adverse health effects, including certain cancers (Lunn *et al.* 2017). In 2016, the American Medical Association Council on Science and Public Health (AMA 2016) noted that the organization supported conversion of community (i.e., primarily street) lighting to light-emitting diodes (LEDs) because of the associated savings in energy, but they recommended that communities consider potential impacts of conversion on human health, including potential melatonin suppression.

The objective of this cancer hazard assessment is to evaluate the relationship between two exposures related to modern electric lighting practices — LAN and night shift work — and cancer. In order to understand the relationship between exposure to ill-timed, unnatural light and adverse biological effects or outcomes, this section presents a brief introduction to circadian regulation and disruption (Section 1.1). It also provides information on the sources and extent of exposure to LAN (Section 1.2), jet lag and social jet lag (Section 1.3), and night shift work (Section 1.4) among U.S. residents. These topics provide a foundation for understanding the relationship between exposures related to modern electric lighting practices (LAN and night shift work) and (1) circadian disruption (Section 2), (2) human cancer (Sections 3 and 4), and (3) cancer in experimental animals (Section 5), as well as potential mechanisms of carcinogenicity of LAN and night shift work, which are thought to be mediated by circadian disruption (Section 6).

1.1 Circadian timing system and its disruption

Virtually all forms of life, from cyanobacteria to humans, exhibit daily oscillations or rhythms of physiological and behavioral processes, and almost all cells in the body contain a molecular circadian clock that regulates the timing of cellular functions, gene expression, and signaling pathways (Arellanes-Licea *et al.* 2014, Stevens *et al.* 2014, Turek 2016). Circadian timing systems in all life forms have in common three core characteristics: (1) an endogenous and self-sustaining ~24-hour physiological oscillator, (2) an input mechanism to signal environmental time of day, and (3) an output mechanism to synchronize circadian-controlled behavior, physiology, and metabolism (Lowrey and Takahashi 2004, Stevens *et al.* 2014, Kiss and Ghosh

2016). These characteristics are illustrated in Figure 1-1. Some of the critical components and factors for maintaining robust circadian rhythms include the daily light-dark cycle, the master circadian clock in the suprachiasmatic nucleus (SCN), clock genes in the SCN and peripheral tissues, neural and neuroendocrine output signals from the SCN, body temperature, feeding-fasting cycles, and sleep-activity patterns (Takahashi *et al.* 2008, Dibner *et al.* 2010, Honma 2018). These are briefly discussed below.

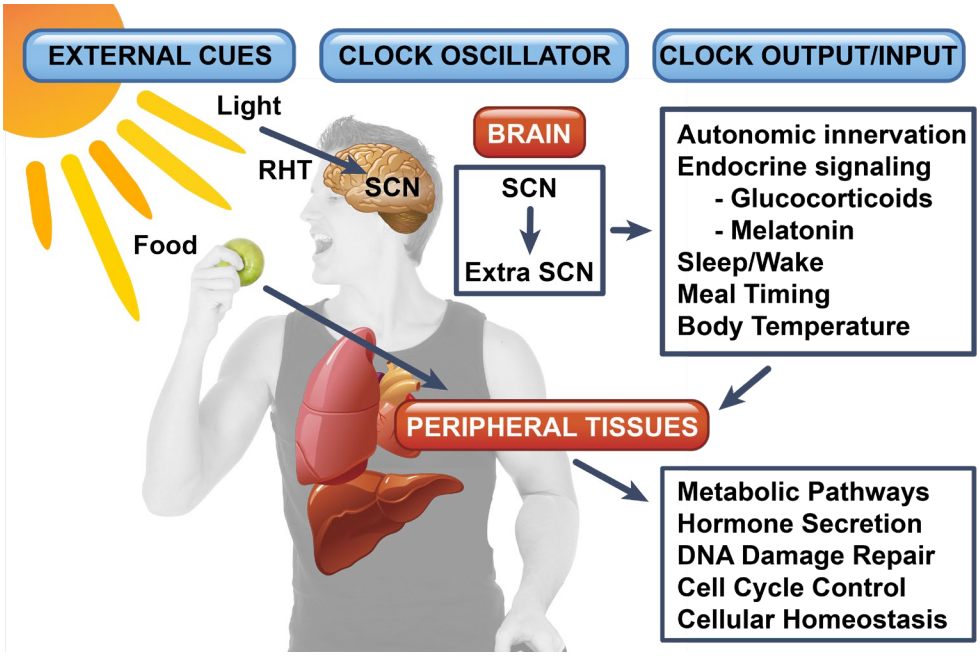

Figure 1-1. Regulation of the circadian timing system by internal and external cues

The master circadian clock found in the suprachiasmatic nucleus (SCN) of the brain receives information about the daily light cycle via the retinohypothalamic tract (RHT). The SCN sends temporal information to other regions of the brain and peripheral clocks through various output pathways that are not completely understood. These include autonomic innervation, endocrine signals (e.g., glucocorticoids and melatonin), sleep-wake cycle, meal timing, and body temperature. Melatonin also conveys signals back to the SCN and other parts of the brain. Collectively, these external and internal cues work together to ensure alignment of the various physiological and behavioral rhythms with the daily and seasonal light-dark cycle and to maintain internal synchronization of the central and peripheral clocks. Adapted from Lunn *et al.* (2017) (used with permission, license number 4260831046002).

As illustrated in Figure 1-1, the circadian timing system is organized in a hierarchical manner consisting of a master oscillator, the bilaterally paired SCN in the anterior hypothalamus (located just above the optic chiasm), and downstream peripheral oscillators in the brain and other tissues (Lunn *et al.* 2017, Honma 2018). In humans, the SCN maintains a self-sustaining, free-running period, in the absence of any environmental cues, that is slightly longer than 24 hours; however, environmental cues reset and resynchronize the SCN each day to maintain synchrony among behavioral, physiological, and environmental rhythms (Buhr and Takahashi 2013, Figueiro 2017).

The term zeitgeber (German word for time giver) is used in circadian biology to describe any daily environmental cue that synchronizes or entrains the circadian timing system (Lowrey and Takahashi 2004). The light-dark cycle is the primary zeitgeber that synchronizes and resets the SCN to the 24-hour solar day. Input from the light-dark cycle is received by specialized non-

visual photoreceptors called intrinsically photosensitive retinal ganglion cells that are anatomically and functionally distinct from the rods and cones used for vision, which play a comparatively minor role in light detection for the circadian system (Berson *et al.* 2002, Hattar *et al.* 2002, Schmidt *et al.* 2011, Figueiro 2017). The non-visual photoreceptors are spread across the retina and transmit photic information to the SCN regarding both time of day (i.e., day versus night) and season (i.e., duration of night) via the retinohypothalamic tract (Takahashi *et al.* 2008, Lowrey and Takahashi 2011, Stevens *et al.* 2014). Thus, the natural 24-hour light-dark cycle provides necessary temporal cues to the SCN to achieve and maintain internal synchronization of the period (τ) and phasing (ϕ) of the circadian time structure to support activity during the day and restoration and repair during sleep at night in humans and other diurnal species (Smolensky *et al.* 2015).

A fundamental difference between the central clock and peripheral clocks lies in their susceptibility to various synchronization pathways or entrainment signals (Brown and Azzi 2013, Schibler *et al.* 2015). Whereas the SCN primarily responds to light and is largely insensitive to its own output signals, peripheral clocks respond to a complex network of SCN-driven timing signals. Phase information transmitted from the SCN to the rest of the brain and body allows organisms to control proper timing of diverse behavioral and physiological functions including hormone release, sleep-wake cycles, feeding-fasting schedules, thermoregulation, and metabolism in anticipation of cyclic changes in their environment (Takahashi *et al.* 2008, Mohawk *et al.* 2012, Buhr and Takahashi 2013).

Although the mechanisms are not fully understood, the SCN synchronizes cellular oscillators or clocks in the brain and peripheral organs and tissues by directly relaying temporal information via autonomic innervation, and indirectly through neuroendocrine signals (e.g., glucocorticoids from the adrenal gland, melatonin from the pineal gland) and activity-directed signals (Balsalobre *et al.* 2000, Mohawk *et al.* 2012, Brown and Azzi 2013, Honma 2018). Activity-directed timing cues for peripheral tissues, including food intake and body temperature, are also important (Buhr *et al.* 2010, Asher and Sassone-Corsi 2015, Wehrens *et al.* 2017). In particular, feeding-fasting rhythms are recognized as a dominant zeitgeber for most peripheral clocks (Schibler *et al.* 2015). There is also evidence that local cellular signaling pathways can affect peripheral clocks and gene expression patterns independently from the SCN (Mohawk *et al.* 2012, Husse *et al.* 2015). Although each cell is governed by its own independent clock, these clocks are coupled together to maintain a single rhythm within the tissue, and the hierarchical architecture allows peripheral functions to maintain coordination via cues from the SCN (Dibner *et al.* 2010, Honma 2018). Thus, peripheral clocks are entrained by multiple and redundant direct and indirect signaling pathways (Brown and Azzi 2013).

The following sections briefly discuss the roles of endocrine signals (melatonin from the pineal gland and glucocorticoids/cortisol from the adrenal gland) and the genetic clock in maintaining circadian rhythms. This is followed by a brief discussion of circadian disruption and exposures that contribute to circadian disruption.

1.1.1 Role of melatonin and glucocorticoids

The SCN conveys timing cues to the pineal gland and adrenal glands via the paraventricular nucleus of the hypothalamus (an important control center of the autonomic nervous system) (Takahashi *et al.* 2008). The pineal gland produces melatonin while the adrenal gland releases

glucocorticoids (cortisol in humans and corticosterone in rodents) (Sollars and Pickard 2015). Both melatonin and glucocorticoids exhibit robust circadian rhythms in humans and laboratory rodents and exert receptor-mediated effects in peripheral tissues. However, some strains of mice (e.g., C57BL/6) produce low levels of melatonin due to a spontaneous mutation in a gene encoding a key enzyme in the melatonin biosynthesis pathway (Pfeffer *et al.* 2018). Studies using melatonin-deficient strains show that altered light-dark cycles can disrupt the circadian timing system in the absence of a "normal" melatonin secretion pattern and that circadian disruption can affect carcinogenic pathways without causing melatonin suppression or disrupting melatonin rhythms (Filipski *et al.* 2002, Filipski *et al.* 2005, Mteyrek *et al.* 2016). The studies show that melatonin is not the only output signal of the SCN to peripheral tissues and that there are multiple mechanisms and pathways that contribute to internal and external synchronization (Schibler *et al.* 2015, Pfeffer *et al.* 2018). Balsalobre *et al.* (2000) also demonstrated that glucocorticoids were not the only signal involved in resetting the phase of peripheral clocks as mutant mice lacking glucocorticoid receptors in the liver still expressed genes in a circadian manner in this organ.

Melatonin and melatonin-binding receptors. Melatonin (*N*-acetyl-5-methoxytryptamine) is a tryptophan derivative that is primarily synthesized in the pineal gland, a small endocrine gland located near the center of the brain, that serves as both an output and input factor to the circadian system (Chowdhury *et al.* 2008, Hardeland 2013). The SCN transfers circadian signals to the pineal gland via a neural pathway, thus driving the rhythmic synthesis of melatonin (i.e., low during the day and high during the night) regardless of whether the animal is diurnal or nocturnal. Melatonin also provides input to the SCN and peripheral clocks and thus functions as an internal synchronizer of circadian rhythms (Figueiro 2017). Although melatonin is primarily produced in the pineal gland, it is also produced in other tissues such as the gastrointestinal tract, skin, retina, and bone marrow (Chowdhury *et al.* 2008, Slominski *et al.* 2008, Talib 2018). However, extra-pineal production of melatonin functions locally as an autocrine or paracrine signal and is not released to the blood in significant amounts (Srinivasan *et al.* 2008).

Three melatonin-binding receptor subtypes have been identified in vertebrates. These include two membrane G protein-coupled receptors (MT1, MT2) that have been identified in all vertebrates so far investigated, and one cytosolic receptor (MT3) that has been found only in non-mammalian species (Reiter *et al.* 2014, Trivedi and Kumar 2014). Although melatonin does not directly bind to nuclear receptors, it may carry out some of its functions by indirectly stimulating nuclear receptor (e.g., RORα, RORγ) gene transcription, modulating translation/processing, or by interacting with ROR proteins (Slominski *et al.* 2016). MT1 and MT2 are expressed in most cells in peripheral, immune system, and central nervous system tissues (Giannoulia-Karantana *et al.* 2006, Hardeland 2013, Reiter *et al.* 2014). However, as a small lipophilic molecule, melatonin can also enter cells directly (Haus and Smolensky 2013, Reiter *et al.* 2014). Thus, melatonin has numerous receptor-mediated, as well as receptor-independent, actions and plays an important chronobiological role by directing the temporal organization of almost all organs (without necessarily involving feedback to the SCN), regulating expression of circadian oscillator genes (core clock genes) in central and peripheral tissues, steering expression of melatonin-regulated genes not controlled by self-sustained oscillators, and modulating the secretion of other hormones (e.g., growth hormone, pituitary gonadotropins, adrenocorticotropins, estrogen, glucocorticoids, etc.) (Chowdhury *et al.* 2008,

Slominski *et al.* 2012, Reiter *et al.* 2014, Smolensky *et al.* 2015). Melatonin is also a biomarker of circadian regulation.

Glucocorticoids and glucocorticoid receptors. Glucocorticoids are secreted by the adrenal glands and are regulated by the SCN via the hypothalamic-pituitary-adrenal axis (Faraut *et al.* 2013, Sollars and Pickard 2015). Glucocorticoid receptors are expressed in most peripheral cell types, but not in the SCN (Brown and Azzi 2013). Thus, glucocorticoid rhythms are potent transcriptional regulators that play an important role in synchronizing peripheral clocks (Sollars and Pickard 2015). A study using the glucocorticoid analog dexamethasone demonstrated that glucocorticoids efficiently synchronized the phase of circadian gene expression in cultured rat fibroblasts and transiently reset the phase of circadian gene expression in peripheral tissues (liver, kidney, and heart) *in vivo* but not in the SCN (Balsalobre *et al.* 2000).

1.1.2 Clock genes and circadian rhythms

The clock mechanism in the SCN and the peripheral oscillators are similar at the molecular level and involve a small number of core clock genes (Table 1-1) that generate circadian oscillations in cell-autonomous transcriptional-translational feedback loops (Figure 1-2) (Kettner *et al.* 2014). The core clock genes are defined as those whose protein products are essential for the generation and regulation of circadian rhythms (Ko and Takahashi 2006). The driving elements of the primary feedback loop include the transcription factors circadian locomotor output cycles kaput (CLOCK) or its homologue — neuronal PAS domain protein 2 (NPAS2) — and brain and muscle aryl hydrocarbon receptor nuclear translocator [ARNT]-like (BMAL1) (Ko and Takahashi 2006, Haus and Smolensky 2013). During the day, the transcription factors CLOCK/NPAS2 and BMAL1 combine to form a heterodimer that binds to E-box regulatory elements in target promoter regions and initiates transcription of *Period* (*Per1*, *Per2*, and *Per3*), *Cryptochrome* (*Cry1* and *Cry2*), and other genes. The negative feedback loop component occurs when PER and CRY form heterodimers and translocate back to the nucleus to repress their own transcription by inhibiting CLOCK:BMAL1 heterodimers. During the night, the PER:CRY heterodimer is degraded, thus enabling CLOCK:BMAL1 to initiate a new transcription cycle. The entire cycle is completed in approximately 24 hours (Takahashi *et al.* 2008). CLOCK:BMAL1 heterodimers also induce another regulatory loop by activating transcription of retinoic acid-related orphan nuclear receptors *Rev-erbα* and *RORα* which, respectively, repress and activate transcription of BMAL1. In addition, data indicate that the circadian clock is also regulated by multiple post-translational modifications including phosphorylation, ubiquitination, acetylation, and SUMOylation (Mehra *et al.* 2009, Hirano *et al.* 2016, Honma 2018). These modifications of core clock proteins affect most aspects of clock biology and interact with the molecular clock feedback loops to fine-tune the precision of the circadian clock and to enhance its stability and adaptability.

This small number of core clock genes regulates the expression of thousands of genes including cell-cycle regulation, DNA damage response, and energy metabolism cycles (Haus and Smolensky 2013, Stevens *et al.* 2014, Panda 2016). Estimates for the percentage of transcription regulated by clock genes range from 2% to 10% in given tissues (Haus and Smolensky 2013, Stevens *et al.* 2014) and up to as much as 40% to 50% in other estimates (Huisman *et al.* 2016, Mure *et al.* 2018, Ruben *et al.* 2018). However, the expression patterns of clock genes in peripheral tissues are tissue specific and optimized to accommodate the particular tissue's

function throughout the circadian cycle (Storch *et al.* 2002, Buhr and Takahashi 2013, Haus and Smolensky 2013). Further, there is considerable variation among tissues in both the genes involved as well as the timing of their activation in relation to oscillator function, and in some cases, homologous genes have different tissue-specific functions (Brown and Azzi 2013, Buhr and Takahashi 2013).

Table 1-1. Selected mammalian circadian core clock genes, gene products, and primary functions

Gene name	Gene(s)	Protein	Function
Circadian locomotor output cycles kaput Brain and muscle ARNT-like protein 1	*Clock* *Bmal1*	CLOCK BMAL1	Positive component of the feedback loop: CLOCK/BMAL1 complex initiates transcription of *Per, Cry*, *Rev-erbα*, and numerous other genes
Period Cryptochrome	*Per1, 2, and 3* *Cry 1 and 2*	PER1, 2, and 3 CRY1 and 2	Negative component of the feedback loop: PER/CRY complex translocates to the nucleus and inhibits CLOCK:BMAL1
Reverse viral erythroblastosis oncogene or nuclear receptor subfamily 1, group D, member 1	*Rev-erbα or NR1D1*	REV-ERBα and ß	Forms accessary feedback loop that links core negative and positive feedback loops. Inhibits BMAL1 expression
Retinoic acid receptor-related orphan receptor A	*RORA*	RORα, ß, and γ	Part of accessory feedback loop that activates BMAL1 expression
Neuronal PAS domain protein 2	*Npas2*	NPAS2	Transcription factor: Clock paralog in the forebrain
Casein kinase 1	*Csnk1*	CK1ε and δ	Post-translational modification: phosphorylates PER, CRY, and BMALl; regulates their sub-cellular localization, activity, and/or stability
Deleted in esophageal cancer	*Dec1 and 2*	DEC1 and 2	Transcription factor: suppresses *Per* and *Cry* transcription, activated by BMAL1/CLOCK
Timeless	*Tim*	TIM	Part of negative transcription-translation feedback loop interacting with Cry1, involved in cell-cycle progression, determination of period length and maintenance of genome stability

Sources: Lowrey and Takahashi 2011, Kettner *et al.* 2014, Benna *et al.* 2017.

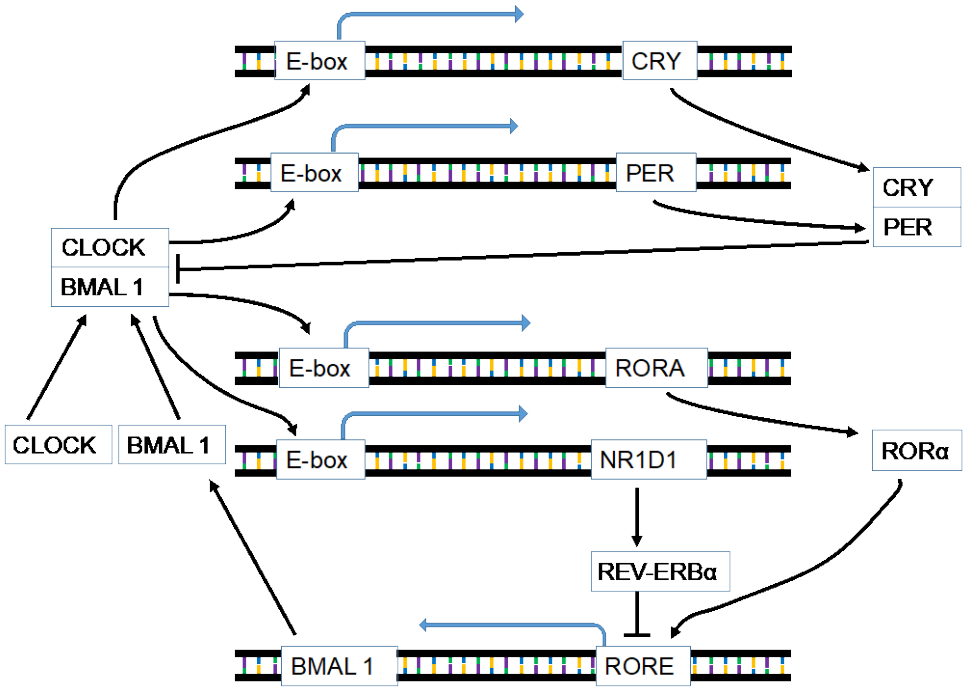

Figure 1-2. Core circadian machinery transcription-translation regulatory feedback loops

Adapted from Salavaty 2015, licensed under CC BY4.0.

1.1.3 Circadian disruption

Circadian disruption occurs when the daily circadian rhythms of some biomarkers are suppressed (Filipski *et al.* 2005, Filipski and Levi 2009, Filipski *et al.* 2009) or are no longer coordinated with each other or the 24-hour day and can be defined as internally or externally induced, acute or chronic temporal disorganization including, but not limited to, misalignment of the time structure in living systems potentially leading to adverse health outcomes (Lunn *et al.* 2017). Several exposure circumstances can cause circadian disruption such as excessive exposure to LAN, certain practices of night shift work (permanent or rotating shifts involving night work), transmeridian travel or a misalignment between social demands and biological time (i.e., social jet lag), and sleep deprivation (Zubidat and Haim 2017).

Exposure to light can affect the circadian system by changing the levels and timing of nighttime melatonin production and by inducing phase shifts (advances or delays) in melatonin or other rhythms. Phase advances (e.g., shortening the period of endogenous rhythms or day) in circadian rhythms occur when people are exposed to light in the latter part of the biological night (when people typically are asleep), travel east across several time zones, or work on a schedule that rotates backwards from night to evening to day shift. Conversely, phase delays in circadian rhythms (e.g., lengthening the period of endogenous rhythms or day) occur when people are exposed to light in the early part of the evening, travel west across several time zones, or work on a schedule that rotates forwards from day to evening to night shift (Stevens *et al.* 2011). Shift workers are slow to adapt (or may never adapt) to changes in light and sleep schedule. Furthermore, during the process of adapting, and during the adaptation period, endogenous rhythms are not synchronized with the external environment and/or with each other (Arendt 2010).

1.2 Light at night

Modern electric lighting practices involve exposure to ill-timed unnatural light, typically including exposure to electrical dim light during the night or day (e.g., offices and schools) and insufficient exposure to daylight. For most of human history, people were exposed to bright light from natural sources during the daytime and to a very dark environment at night, whereas modern practices have led to exposure to some level of dim light throughout the 24-hour day.

1.2.1 Characteristics and sources of light exposure

Visible light reaching the eye can be either monochromatic (light of a single wavelength or limited range of wavelengths interpreted by the human eye as a single color, such as violet, blue, green, yellow, orange, or red) or polychromatic (light composed of more than one wavelength, including white light, which includes all wavelengths of visible light from 380 to about 780 nm).

Light produced by different sources can be measured in terms of its brightness (generally expressed in units called lumen), but a more useful measurement for exposure to light is the amount of light illuminating a surface, which is measured in units of lux or lumen/m^2.

Natural light, which includes all wavelengths of white light, comes directly from the sun, and can be scattered and reflected by the atmosphere, or reflected by the moon. On a clear day, the outdoor light level is about 10,000 lux, but bright sunlight can be as much as 10 times higher at 100,000 lux (NOAO 2015). The daily cycle of exposure to the blue wavelengths in the spectrum of sunlight is most important for synchronizing circadian rhythms (Smolensky *et al.* 2015). Natural indoor light is generally in the range of 200 lux to 400 lux while the outdoor light level for a full moon is about 0.1 lux (NOAO 2015, Lighting Research Center 2018).

Electric light can be produced by (1) incandescence (light emitted from heating of matter, e.g., a wire filament in an incandescent or halogen light bulb) or (2) luminescence (light emitted when a material absorbs energy from an external stimulus and then releases it as light; e.g., discharge, fluorescent, and light-emitting diode [LED] lamps) (Elert 2018).

Since the patenting of Edison's incandescent light bulb in the late 19th century, primary light sources for homes and workplaces have evolved through fluorescent lights to light-emitting diodes (LEDs) and more recently to the organic LEDs (OLED) and active-matrix organic LEDs (AMOLED) used in mobile devices, laptops, and televisions (see Figure 1-3). While technological advances have generally increased the energy efficiency of lighting sources for both indoor (e.g., homes and offices) and outdoor (e.g., streets and parking lots) lighting, these light sources emit a larger proportion of total light in wavelengths perceived as blue by the human eye. The spectrum of incandescent light is similar to that of light at sunset, whereas LEDs emit a greater proportion of shorter wavelengths that is more similar to circadian light. These light sources include those used both indoors and outdoors (incandescent, fluorescent, and LED). Newer technologies such as OLEDs and AMOLEDs are not illustrated but these generally use sets of red, green, and blue pixels to produce a mixture of wavelengths that can be perceived by the human eye as white or other colors and thus would be expected to include wavelengths in the blue region of the spectrum.

Circadian light (CL_A) is defined as light that impacts the circadian system, which is measured by the light that causes suppression of melatonin synthesis (see Section 2.1), and circadian

stimulus (CS) is the relative effectiveness of CL_A for producing melatonin suppression under specific conditions. No standardized function (i.e., sanctioned by national or international standard-setting bodies) characterizing the spectral sensitivity of the human circadian system is currently available, but circadian system spectral sensitivity functions (Gall and Bieske 2004, Andersen *et al.* 2012, Lucas *et al.* 2014) and one mathematical model have been proposed (Rea *et al.* 2005).

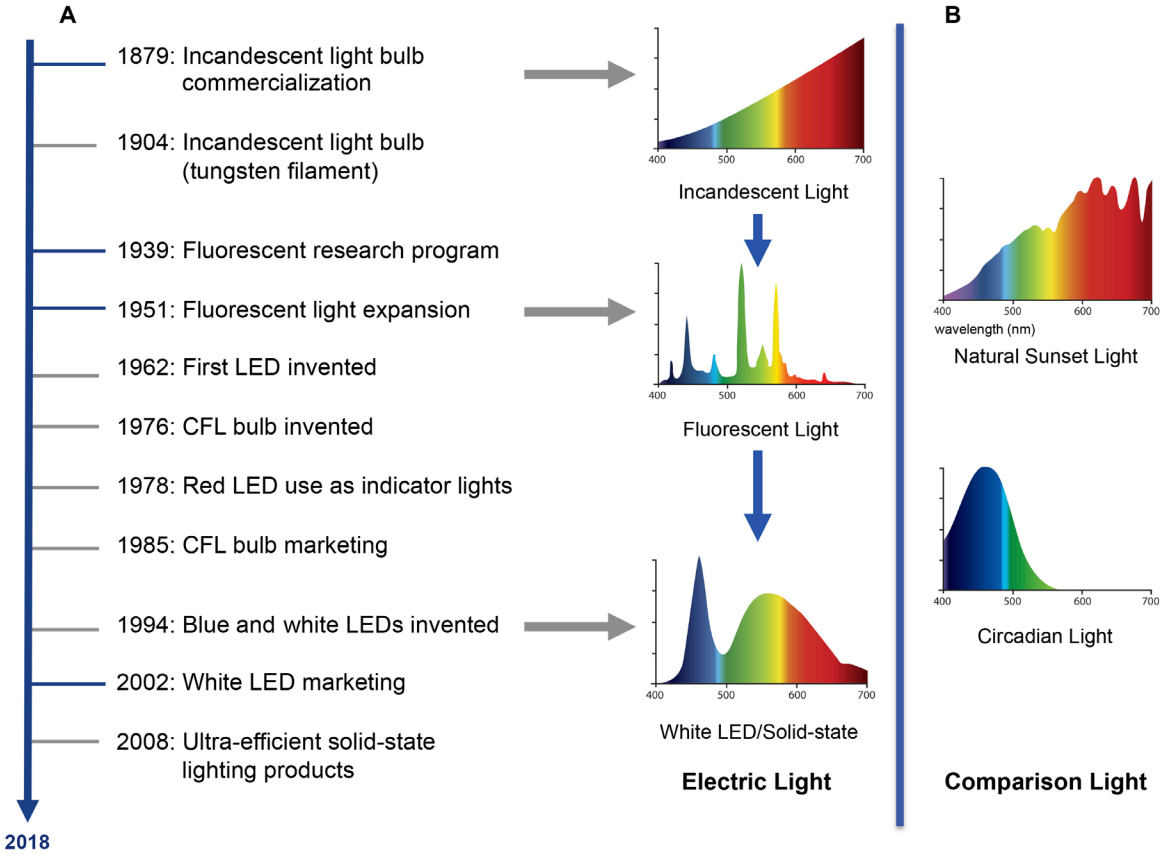

Figure 1-3. Technology advances in lighting over time have led to lighting with higher levels of short wavelengths

Panel A shows the timeline of key historical events related to the major types of electric lighting and the corresponding spectra. Panel B depicts spectra for comparison light: natural sunset light and circadian light. Incandescent light has little short wavelengths (blue light) similar to natural sunset light whereas white LED light has higher amounts of shorter wavelengths similar to circadian light.
Sources: Adapted from Brainard *et al.* 2001, Matulka and Wood 2013, Zielinska-Dabkowska 2018.
LED = light emitting diodes; CFL = compact fluorescent lights.

Methods for measuring circadian light are still being developed as this is a relatively new area for research. The traditional instrument for measuring visual light, the photometer, is designed to quantify the response of an average human observer, which is based on a peak effect around 555 nm (Thapan *et al.* 2001). As a result, measurement of personal circadian light exposure for epidemiological studies of circadian stimulus requires development of new instruments that can reflect the critical role that light within the blue range of the spectrum plays in circadian stimulus. One such instrument is the Daysimeter, which measures personal circadian light

exposures as well as rest and activity levels (Bierman *et al.* 2005, Rea *et al.* 2005, Rea *et al.* 2008, Miller *et al.* 2010). Miller *et al.* (2010) have proposed use of phasor magnitude as a metric for circadian disruption with a higher value indicating greater synchrony between activity and the light-dark cycle and a lower value indicating less synchrony. Noting that currently there is no standardized model of the spectral sensitivity of the human circadian system, Lucas *et al.* (2014) recommended that researchers record the spectral power distributions (SPDs) of light exposures in human circadian system response experiments because the SPDs can be used with units of measurement that are currently available or developed in the future.

1.2.2 Human exposure to LAN

A significant number of people in the United States are directly exposed to ill-timed, unnatural electrical light at night from outdoor lighting, indoor lighting at home and at work, lighting from self-luminous electronic devices, and insufficient natural light during the day. Light also can enable other activities that can lead to circadian disruption, including shift work involving night shifts (see Section 1.3) and irregular sleep-wake cycles that can lead to "social jet lag." Other disruptions of circadian rhythms result from jet lag caused by transmeridian travel across multiple time zones.

Natural light

Median exposure to daylight ≥ 1,000 lux for middle-aged adults (N = 106 study subjects recruited by random telephone dialing) in San Diego, CA was only about 58 min/day (Espiritu *et al.* 1994, Smolensky *et al.* 2015). Exposure to outdoor sunlight (5,000 to 100,000 lux) is orders of magnitude higher than exposure to indoor light. Exposure duration is higher in the summer and varies somewhat by geographical location. Median summer exposure to natural daylight ≥ 1,000 lux in different parts of the United States ranged from 2.2 hours/day (San Diego, CA) to 2.4 hours/day (Rochester, MN), and median winter exposure ranged from 0.4 hours/day (Rochester, MN) to 1.3 hours/day (San Diego, CA) (Cole *et al.* 1995).

Indoor light and electronic use

Indoor electrical lighting exposure is nearly ubiquitous in our society. The light level from indoor electric lights are generally in the range of 20 to 40 lux for residential incandescent/halogen lights and 100 to 200 lux for office fluorescent lights (Figueiro 2018). By comparison, natural indoor light is approximately 200 to 400 lux. The types of lighting used have changed in recent years; traditional incandescent and halogen bulbs have largely been replaced by newer types (DOE 2018, NOAO 2018). The United States Energy Information Administration's (EIA) Commercial Buildings Energy Consumption Survey data indicated that standard fluorescent lights were used in 78% of all lighted floor space in commercial buildings (e.g., general office space, retirement homes, hospitals) in 2012, while another 13% used compact fluorescent lights (EIA 2017, 2018). Due to their increased efficiency and lower operating costs, use of LED lights for indoor commercial and residential applications (e.g., recessed downlights in offices and kitchens) is rapidly increasing; the Department of Energy (DOE) estimated that from 2014 to 2016, approximately 812 million indoor LED lighting systems have been installed (a market penetration of 12.3%) (DOE 2017, 2018). As mentioned above, these electric light sources generally have different wavelength ranges that include higher amounts of blue light. In addition to LEDs and CFLs, other sources of blue light exposure at

night include video displays, which are often based on organic LEDs (OLEDs) or liquid crystal displays (LCDs) (Oh *et al.* 2015).

Information on normal light levels in the home and from outside light sources are limited. A pilot study by Pacific Northwest National Laboratory collected information on light levels reaching the eye (in lux) for 30 lighting professionals who reported on specific areas within their homes and on outside light visible in the interior (Miller and Kinzey 2018). The results of this study are presented in Table 1-2, with median values as well as minimum and maximum values of illuminance; the light sources associated with those levels are identified in the footnotes. The highest illuminances (347 to 485 lux) were reported for several different light sources, including LEDs, CFLs, and halogen bulbs. The level of exposure to outside light did not exceed 20 lux in this pilot study.

Table 1-2. Summary of illuminances measured at the eye in the homes of 30 lighting professionals

	Illuminance at eye (lux)		
Space or task	**Minimum**	**Median**	**Maximum**
Kitchen – normal evening lighting	6[a]	104	485[b]
Living/family room – normal evening lighting	3[a]	23	410[a,c]
Living/family room – TV only	0[f]	2	139[f]
Living or dining room – brightest light outside with no interior lighting	0[d]	0.5	20[a]
Bedroom – pre-bedtime room lighting and task (reading) light	1[e]	15	347[a,c]
Bedroom – pre-bedtime room lighting plus light from reading cell phone or tablet	1[f]	14	86[f]
Bedroom – light from reading cell phone or tablet only	0[f]	0.6	13[f]
Bedroom – all lights off, drapes/blinds closed	0[f]	0	2[f]
Bedroom – brightest light outside with no interior lighting	0[d]	0.1	5[a]

Source: Miller and Kinzey 2018.
[a]Light emitting diode; [b]compact fluorescent; [c]halogen; [d]high pressure sodium; [e]incandescent; [f]not reported.

Many Americans (especially adolescents and teens) use electronic devices with self-luminous displays (e.g., cell phones, computers, e-readers, or tablets) before sleeping. Findings from the 2011 Sleep in America Poll (N = 1,508 participants, ages 13 to 64 years) indicate that an estimated 90% of Americans use some type of electronic device a few nights per week within 1 hour of bedtime with 60% (regardless of age) watching television and a greater percentage of adolescents (72%) and young adults (67%) using cell phones compared to middle-aged (36%) and older adults (16%) (Gradisar *et al.* 2013, Smolensky *et al.* 2015).

Parents of newborns (0 to 6 months old) have increased exposure to LAN because they spend approximately 2 hours awake each night performing nocturnal caretaking (McBean and Montgomery-Downs 2015). The same study found that mothers of infants were exposed to

estimated light intensity of 90 to 180 lux when using room level light (13.6% of the mothers) or a floor lamp (11.1%) but to less than 20 lux when using a night light (35.4%), leaving a door to another lighted room slightly open (28.3%), using a desk lamp (25.3%), or using light from electronic devices (19.2%); other sources of light were reported by less than 10% of the women. The fathers of the infants were also potentially affected by increased exposure to LAN since the authors noted that fathers provided care 29% of the time; however, no data were collected for the types of light exposure experienced by the fathers in this study.

Outdoor light

Light trespass is light being cast where it is not wanted or needed (Rensselaer Polytechnic Institute 2018), and can be made worse by lighting demands of urban development, e.g., roadways, shopping centers, stadiums, etc. (Pauley 2004, Navara and Nelson 2007). Major sources of light for these applications include halogen lamps (stadium lights), high- and low-pressure sodium lamps (street lights), metal halide lamps (street lights, parking lot lights, and stadium lights) and LED street lamps (NOAO 2018). Further, the use of LED lights outdoors is increasing rapidly; DOE estimated that from 2014 to 2016, approximately 46.1 million outdoor LED lighting systems have been installed (a market penetration of 29.7%) (DOE 2017, NOAO 2018). In 2016, satellite imaging data of the Earth at night indicated that more than 99% of the U.S. population were exposed to sky glow at night (i.e., electric sky brightness was increased at least 8% above the natural background at the zenith, which is the darkest part of the sky hemisphere) (Falchi *et al.* 2016). Figure 1-4 shows a map of North America's electric sky brightness as a ratio to the natural sky brightness. The urban areas of the United States with the highest levels of sky glow are the areas in the Northeast megalopolis, including Washington, D.C., Baltimore, Philadelphia, New York, and Boston (Kane 2016). Additionally, the eastern half of the United States from approximately the midline near the eastern edge of Mexico and running north to the Canadian border shows many other intense areas of sky glow. In the Western United States, San Francisco and Los Angeles also have very high levels, but with the exception of a few major cities, the rest of the West has minimal sky glow. Sky glow describes the brightening of the sky caused by outdoor lighting and natural atmospheric and celestial factors (Rensselaer Polytechnic Institute 2018). Light trespass and sky glow are often referred to by the less specific term of "light pollution."

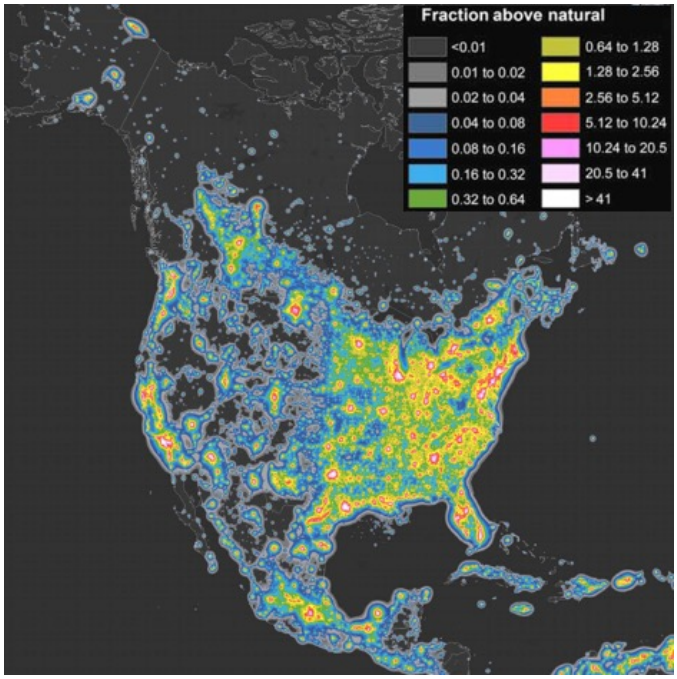

Figure 1-4. Map of North America's artificial sky brightness as a ratio to the natural sky brightness

Source: Falchi *et al.* 2016, licensed under CC BY 4.0.

1.3 Shift work

1.3.1 Types of shift work

"Shift work" can be defined at the organizational or the individual worker level. For example, the International Labour Organization defines shift work as "a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers" at different day and night hours (ILO 2004). Table 1-3 summarizes general types of shift work and related shift scheduling criteria.

At the individual level, shift work generally means any arrangement of daily working hours other than standard daylight hours (7:00 AM or 8:00 AM to 5:00 PM or 6:00 PM) such as night or evening (IARC 2010). Night shift work is typically defined as working at least 3 hours between midnight and 5:00 AM (Stevens *et al.* 2011). Night shift workers work only nights (i.e., permanent night shift workers) or alternate between night, day, and evening shifts (i.e., rotating night shift workers). Forward-rotating schedules are those that go from day to evening to night shifts, whereas backward-rotating schedules go from night to evening to day shifts. (IARC 2010, Stevens *et al.* 2011, Vermeulen 2016). Schedules can also vary in the number of consecutive days before shift changes. Schedules with increased rotation speeds (e.g., changing daily or every 2 or 3 days) vs. slower-rotating shift schedules can foster higher phase shifts and circadian disruption (Costa *et al.* 2010, Neil-Sztramko *et al.* 2014). Many different schedules are possible, but a schedule in common use for more than 20 years is a fast-rotating schedule consisting of 2 day shifts, 2 afternoon or evening shifts, 2 night shifts, and 2 days off over a period of 8 days (Costa *et al.* 1994, Tucker and Folkard 2012, Business Management Systems 2017). This schedule typically employs 4 teams and three 8-hour shifts with each team rotating through a sequence of 2 day shifts, 2 afternoon or evening shifts, 2 night shifts, and 2 days off over a cycle of 8 days. Intermediate rotating schedules (changing weekly) or slow rotating schedules (changing every 15 to 30 days) are other types of rotating schedules.

Table 1-3. General types of shift work and related shift scheduling criteria

Shift work system parameter	Description
Type of shift work	
Permanent	People work regularly on one shift (i.e., morning, afternoon, or night only)
Rotating	People alternate working on different shifts
Continuous	Work covers all days of the week
Discontinuous	Work is interrupted on weekends
With or without night work	Working time can extend into the night (e.g., at least 3 hours worked between midnight and 5:00 AM)
Related shift scheduling criteria	
Duration of shift	Generally 8 hours (although other durations are possible)
Speed of rotation	Number of consecutive days worked before changing shift • Fast (e.g., changes daily; changes every 2, 3, or 4 days) • Intermediate (e.g., weekly change)

Shift work system parameter	Description
	• Slow (e.g., changes every 15, 20, or 30 days)
Direction of rotation	Forward rotation (i.e., morning → afternoon/evening → night) Backward rotation (i.e., night → afternoon/evening → morning)
Length of shift cycle	A cycle is a series of shift and rest days lasting until the series re-starts at the same point • Short (6–9 days) • Intermediate (20–30 days) • Long (up to 6 months or more)
Rest periods after shift	Number and arrangement of rest days between shifts
Regularity or irregularity of shift schedule	Consistency of timing or occurrence of work; can be based on special employer arrangements
Shift intensity	Number of non-day shifts (including night, evening, or afternoon shifts) worked per week, per month, or per year

Sources: IARC 2010, Stevens *et al.* 2011, Vermeulen 2016.

Other types of shift work schedules include (1) split shifts, in which working time consists of two distinct periods each day (e.g., 4 hours in the morning and 4 hours at night) (McMenamin 2007), and (2) compressed week schedules, in which the standard work week is reduced to fewer than 5 days and the employee makes up the full number of weekly hours by working more hours each day (e.g., four 10-hour days; three 12-hour days; or a week of five 9-hour days followed by a week of four 9-hour days) (WebFinance 2018).

1.3.2 Exposure

Multiple lines of evidence indicate that tens of millions of people in the United States work schedules outside normal daylight hours (i.e., approximately 7:00 AM or 8:00 AM to 5:00 PM or 6:00 PM) either consistently or as part of flexible or rotating work shifts (BLS 2004, 2005, McMenamin 2007, IARC 2010, Presser and Ward 2011, Alterman *et al.* 2013, CDC 2015). Data from two relatively recent surveys, each of more than 17,000 adults (17,524 adults in a 2010 NHIS-OHS survey [Alterman *et al.* 2013] and 19,456 adults in the 2015 NHIS–OHS survey [CDC 2015]) indicated that ~27% of employees are estimated to work alternative shifts involving non-day hours (e.g., night, evening, or rotating shifts). The percentages from these data are higher than the prevalence of shift work of 14.8% estimated by the 2004 Bureau of Labor Statistics (BLS) data (based on sampling of 10,189 workers) (BLS 2004, 2005, McMenamin 2007) suggesting a possible increase over time. Definitions of shift work in the 2015 CDC data, the 2010 CDC data (night, evening, or rotating shift), and the 2004 BLS data (evening, night, rotating, or split shift, or employer-arranged irregular schedule) were similar. No comparable data for frequency of night work were reported by BLS.

Approximately 7% of all employed adults (10,834,000 people ≥ 18 years of age) worked frequent nights (i.e., working any amount of time between 1:00 AM and 5:00 AM for 6 to 30 days over the previous 30-day period) according to the 2015 NHIS-OHS survey (based on sampling data for 2,782 adults). Frequent night work was more common in men, African-Americans, and non-Hispanics; was slightly more common in workers having high school education versus having less or more than high school education; and decreased with increasing

age. The 3 industries with the highest prevalence of frequent night work were mining (18.08%, an estimated 111,000 people); transportation, warehousing, and utilities (15.48%, an estimated 1,141,000 people); and healthcare and social assistance (11.84%, an estimated 2,021,000 people) (CDC 2015). People engaged in frequent night work in the mining industry tended to be older (≥ 65 years), male, white, and non-Hispanic (NHIS-OHS survey, CDC 2015).

The 5 occupations with the highest prevalence of frequent night work were the following: (1) protective services, (2) transportation and material moving, (3) healthcare practitioners and technical occupations, (4) production, and (5) healthcare support. These five accounted for an estimated 5,288,000 people, or approximately 50% of workers engaged in frequent night work. Figure 1-5 presents prevalence rates and estimated numbers of workers in these occupations with the highest prevalence of night work based on the 2015 NHIS-OHS dataset (CDC 2015). Estimated numbers of workers for these individual occupations ranged from 388,000 people to 1,517,000 people (NHIS-OHS survey, CDC 2015). Data from the American Time Use Survey (using BLS data) found that ~7% to 20% of workers (≥ 15 years old) worked their main job from 11:00 PM to 3:00 AM in similar occupations (protective services, healthcare, production, and transportation), with the highest percentage in protective services (Torpey 2015).

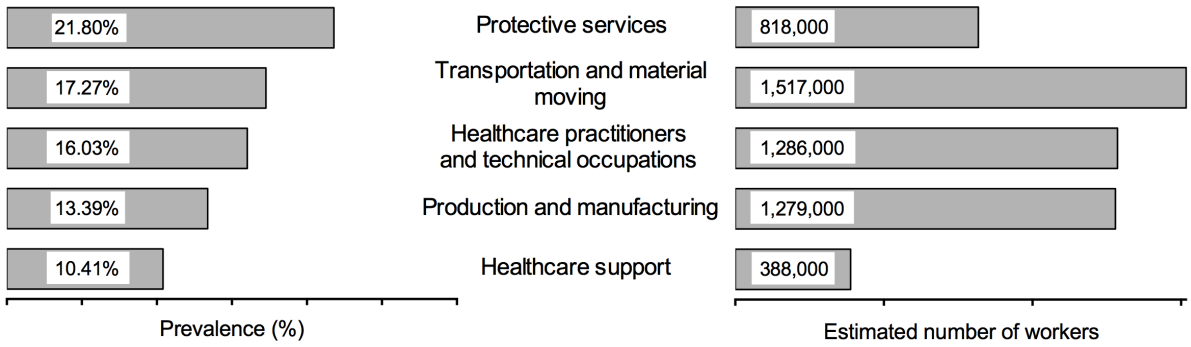

Figure 1-5. Prevalence and estimated numbers of U.S. workers who frequently work night shifts

Frequent night shifts were defined as at least 6 of the past 30 days with any time worked between 1:00 AM and 5:00 AM in 2015. The percentage of U.S. workers for each occupation was adjusted for age, sex, and race using the projected 2000 U.S. population as the standard population.
Source: CDC 2015.

Shift work as a complex exposure scenario

Night shift work includes exposure to electric LAN, sleep disturbances, or changes in meal timing, as well as other potential factors (e.g., social stressors, lifestyle behaviors, decreased exposure to sunlight, and lower vitamin D levels). Shift workers are also affected by social jet lag. One study of 1,829 shift workers estimated average social jet lag of 1.37 hours for day workers and 4.61 hours for night workers (Yong *et al.* 2016). The direction and speed of shift work rotations does not seem to impact the extent of social jet lag since fast clockwise shift changes were associated with 2.8 hours of social jet lag and slow counterclockwise shift changes with 2.7 hours; social jet lag for day workers was 0.9 hours (Kantermann *et al.* 2014).

Direct exposure to LAN among shift workers

Typical natural indoor light is in the range of 200 to 400 lux, and an office lit by fluorescent light is in the range of 100 to 200 lux. Only a very limited number of studies have measured personal

light exposures at night in shift workers working indoors, and average levels were mostly below 100 lux (see Table 1-4). In all studies, LAN exposures were measured using either (1) light intensity data loggers worn around the neck or at shoulder level to approximate eye-level or (2) a light exposure/activity monitor on the non-dominant wrist. Only Burch *et al.* (2005), who compared light exposures in workers across three shifts, reported a 24-hour time-weighted light exposure measure which did not account for LAN specifically; however, night shift workers had the lowest light exposure.

Table 1-4. Measurements of personal light exposure in shift workers

Reference	Study population (N)	Measure Timing of light[a]	Light exposure (lux)[a]
Burch *et al.* 2005 United States	Permanent night shift workers Medical device manufacturing facility (N = 32)	24-hour time weighted average 10:00 PM to 6:00 AM	427
Dumont *et al.* 2012 Canada	Canadian rotating shift workers Telecommunications center (N = 10)	Median during night shift	72.5
Grundy *et al.* 2009 Canada	Rotating shift nurses (N = 31)	Mean during night shift Midnight to 5:00 AM	7.02
Grundy *et al.* 2011 Canada	Rotating shift nurses (N = 123)	Maximum during night shift Midnight to 5:00 AM	37.2
Papantoniou *et al.* 2014 Spain	Permanent night shift workers Various occupations (N = 72)	Median for Midnight to 5:00 AM	38

[a]Light measured using light intensity loggers around neck, shoulder, or wrist.

Other exposures enabled by light among shift workers

LAN enables changes in the timing of what would normally be considered "daytime activities" among shift workers, in particular sleep disturbances, meal timing, dietary patterns, and physical activity. However, these changes vary across populations. Meal timing and dietary patterns have been shown to differ between day and night workers and between flight attendants and the general population (Esquirol *et al.* 2009, Winter *et al.* 2014, Wirth *et al.* 2014a, Hemiö *et al.* 2015) (see Section 6).

Physical activity has been shown generally to be higher among night workers than day workers in a number of studies, although it is not clear if this is due to more activity at night or activity during the day. For example, Wegrzyn *et al.* (2017) reported that participants in the younger cohort, i.e., the Nurse's Health Study 2 (NHS2), reported more physical activity than participants in the older cohort, i.e., the Nurse's Health Study(NHS), and in both cohorts, activity levels in

rotating workers were higher than in day workers. Neil-Sztramko *et al.* (2016) reported that although shift workers had less sedentary time than day workers, they were more likely to have poor body composition, and lower aerobic capacity. In a study of shift workers and metabolic syndrome, Esquirol *et al.* (2009) reported that shift workers had increased job strain and higher total and at-work physical activity.

1.4 Transmeridian travel and social jet lag

Another category of shift workers is employees working in the airline industry, who in addition to working multiple shifts may travel frequently across multiple time zones. Long distance flights with rapid time zone shifts of more than 3 hours can produce desynchronization between an individual's circadian rhythms and destination day-night cycles (Rose *et al.* 1999). Symptoms of this desynchrony, including fatigue, loss of concentration and appetite, indigestion, and irritability, are commonly known as "jet lag." In 2016, there were over 124,000 airline and commercial pilots and over 116,000 flight attendants in the United States (BLS 2017a, b). The U.S. Department of Transportation reported that approximately 117 million total passengers traveled on transmeridian flights in 2017 (destinations in Europe [65 million], Far East [34 million], Middle East [10 million], Africa [2 million], and Australasia [6 million]) (DOT 2018); further, assuming that the number of flights from these locations to the United States would carry a similar number of passengers, an estimated 234 million passenger flights included transmeridian travel exceeding 3 hours in 2017. One report (Sharma and Shrivastava 2004) estimated that 90% or more of airline crew members experience symptoms of jet lag. Similar data for the general flying public was not identified, but most people crossing more than 3 time zones likely experience it as well.

Social jet lag is misalignment between one's circadian timing system and sleep-wake cycle based on social clocks, e.g., waking to an alarm clock on weekdays for work or school and then sleeping and waking without an alarm on the weekend (i.e., "sleeping in") (Roenneberg *et al.* 2012, Rutters *et al.* 2014, McMahon *et al.* 2018, Uzoigwe and Sanchez Franco 2018). Social jet lag symptoms are similar to jet lag symptoms except they are more chronic in nature. For jet lag, upon arrival at a different location, one's circadian clock can be re-set to local sunrise and sunset times, thereby limiting jet lag symptoms to a transitory experience. For social jet lag, misalignment is chronic as it is continuously experienced on a weekly (or other time unit) basis, usually for long periods of time. Over two-thirds of the general population could be affected by social jet lag (up to 2 hours shift between weekdays and weekends), and adolescents can have even higher social jet lag (≥ 2 hours) (see Table 1-5) (Roenneberg *et al.* 2012, Rutters *et al.* 2014, Malone *et al.* 2016, Koopman *et al.* 2017, McMahon *et al.* 2018).

Table 1-5. Social jet lag in various populations

Population	Number of participants (N)	Social jet lag estimate (%)			Reference
		≤ 1 hr	> 1 hr but < 2 hr	≥ 2 hr	
Apparently healthy participants	145	74	–	26	Rutters *et al.* 2014
Healthy young adults[a]	390	50	33	17	McMahon *et al.* 2018
9th and 10th grade students	182	–	–	40–68	Malone *et al.* 2016
Primarily central European participants	64,110	NR	NR	~ 33[c]	Roenneberg 2012
General Dutch population	1,585	61	31	8	Koopman *et al.* 2017

[a]Absolute value of social jet lag.
[b]NR = not reported.
[c]Roenneberg *et al.* (2012) also noted that 69% reported at least 1 hour of social jet lag.

1.5 Summary

Circadian regulation, i.e., daily oscillations or rhythms of physiological and behavioral processes, occurs in humans and almost all other species. Circadian rhythms in humans are controlled by the master circadian clock in the SCN which communicates with the brain and peripheral organs and tissues directly via neural signals and indirectly via neuroendocrine (e.g., melatonin and glucocorticoids) and activity-related (e.g., feeding-fasting, body temperature) signals. Melatonin, a tryptophan derivative primarily synthesized in the pineal gland, serves as both an output and input factor to the circadian system and is an important biomarker of circadian disruption. Experimental models show that melatonin can modulate expression of circadian clock genes in central and some peripheral tissues. The core clock genes include *Clock*, *Bmal1*, *Npas2*, *Per1, 2,* and *3, Cry1* and *2, Rev-erbα,* and *RORs*. These and a few other core clock genes regulate expression of thousands of other genes, estimated to make up 50% of the transcriptome with tissue specificities in mammals. The clock genes control cell-cycle regulation, DNA damage response, energy metabolism, and numerous other physiological processes.

The transformation of modern society to an electricity-based sociocultural and work organization system together with technological advances in the 20th and 21st centuries has resulted in widespread exposure to electric light and to light from a multitude of electronic devices. The resulting ill-timed, unnatural light includes light at night (LAN), which enables activities to be performed at any time of the day or night including night shift work. These changes are associated with disruption of the circadian system, which may lead to potential adverse long-term health effects such as cancer. Circadian disruption occurs when the daily circadian rhythms are no longer coordinated or are suppressed and can be defined as internally or externally induced, acute or chronic temporal disorganization including, but not limited to, misalignment of the time structure in living systems. Furthermore, the lack of coordination between sleep-wake, feeding-fasting, and other cycles within the 24-hour day can cause acute or chronic temporal disorganization that potentially leads to many adverse health outcomes.

Since the patenting of Edison's incandescent light bulb in the late 19th century, primary light sources for homes and workplaces have evolved through fluorescent lights to light-emitting diodes (LEDs) and more recently to the organic LEDs (OLED) and active-matrix organic LEDs

(AMOLED) used in mobile devices, laptops, and televisions. While technological advances have generally increased the energy efficiency of lighting sources for both indoor (e.g., homes and offices) and outdoor (e.g., streets and parking lots) lighting, these light sources emit a larger proportion of total light in wavelengths perceived as blue by the human eye. Circadian light (CL_A) is defined as light that impacts the circadian system, which is measured by the light that causes suppression of melatonin synthesis, an effect that is more sensitive to blue light.

A significant number of people living in the United States are exposed to LAN because of work schedules outside normal hours (i.e., shift work, including work at night) and from ill-timed, unnatural electric light exposure, which includes "light pollution" at night (a phenomenon that affects more than 99% of the U.S. population), and adolescent and teen use of self-luminous displays from a variety of electronic devices (e.g., cell phones, computer screens, e-readers, or tablets) before sleeping. Mothers caring for infants during the night also are exposed to light at night from various light sources, including the use of electronic devices such as cell phones, lighted tablets, and televisions.

A significant number of US residents – greater than 10.8 million people – have performed frequent night work with various types of permanent or rotating and continuous or discontinuous shift schedules. Industries and occupations with the highest prevalence of night work include protective services, healthcare and social assistance, production and manufacturing, and transportation.

2 Light at Night and Night Shift Work: Circadian Disruption Studies

This section provides an overview of the literature on LAN and night shift work and circadian disruption, primarily as assessed by melatonin suppression and altered clock gene expression as these are primary factors in the proposed mechanisms of carcinogenicity. Studies on potential effects on cancer are discussed in Sections 3, 4, and 5, and studies on biological effects related to cancer are discussed in Section 6. Studies of offshore shift workers were not included in the review as these workers may have additional stresses (such as absence of family and social contact) that may affect circadian rhythms (Folkard 2008).

2.1 Biomarkers and characteristics of circadian disruption

As mentioned in Section 1, daily oscillations or rhythms of physiological and behavioral processes occur in humans and almost all other species. Figure 2-1 depicts the timing of some of the major circadian rhythms. These include melatonin, cortisol, body temperature, and clock gene expression, which have been used as biomarkers to measure the extent of circadian disruption among shift workers or people exposed to LAN. Ideally, these biomarkers should be physiological rhythmic variables, reproducible, and reliable (Touitou *et al.* 2017). Altered sleep due to LAN and shiftwork is related to circadian disruption, and thus is briefly reviewed, as well as behavioral (i.e., non-photic zeitgebers) models of circadian disruption. A limitation is that few studies measured multiple markers of circadian disruption and thus could not evaluate uncoupling of biomarkers.

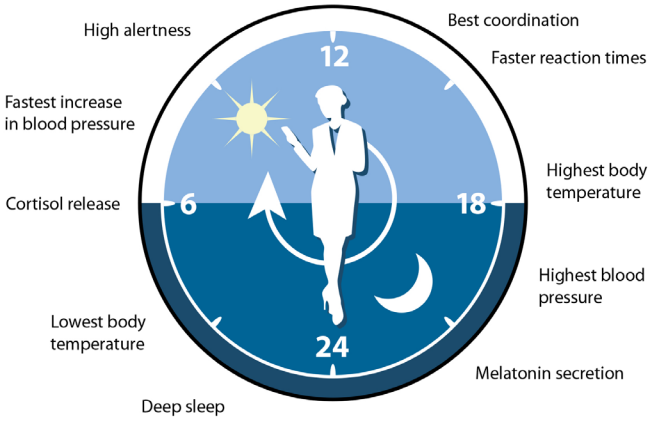

Figure 2-1. The circadian clock
Figure adapted from Nobel Prize 2017, with permission.

2.1.1 Melatonin

As discussed in Section 1.1, melatonin secretion and rhythms are controlled by the SCN and are suppressed or shifted by exposure to LAN. It is a modulator (albeit not the only modulator) of the central and peripheral circadian clocks as well as an important regulator of numerous biological processes in tissues and organ systems, including the breast (Slominski *et al.* 2012, Reiter *et al.* 2014, Hill *et al.* 2015, Smolensky *et al.* 2015). In humans, melatonin also regulates the sleep-wake cycle by chemically causing drowsiness and lowering the body temperature by fine-tuning vascular tone in the skin (Brown 1994, Kräuchi *et al.* 2006). Melatonin production (e.g., changes in amplitude, duration, and timing) is considered to be a useful biomarker of circadian dysregulation. Compared to other circadian biomarkers, it is less influenced by external factors. It is also a regulator of the hypothalamic-pituitary gonadal axis and gonadal function

(Mirick and Davis 2008, Bonde *et al.* 2012). In normally entrained individuals, plasma melatonin levels are low during the day and start to increase in the evening (~2 hours before bedtime), peak in the middle of the biological night (midnight to 5:00 AM), and then decrease rapidly. The peak of melatonin levels is approximately 2 hours before the nadir of the core body temperature rhythm (~5:00 AM) and approximately 4 to 6 hours before the crest of the cortisol rhythm (Dijk *et al.* 2012, Touitou *et al.* 2017).

Melatonin can be measured in the saliva, urine (as its major metabolite, 6-sulfatoxymelatonin [aMT6s]), plasma, or blood. Morning urinary aMT6s accounts for 70% of the previous night total plasma melatonin and thus is related to peak nocturnal melatonin production (Schernhammer *et al.* 2004). Several studies have found that a single morning urinary melatonin sample or serum melatonin is a reliable marker for assessing melatonin levels over time (6 months to up to 5 years) (Schernhammer *et al.* 2004, Nogueira *et al.* 2013). Serum or plasma melatonin has a short half-life and its measurement reflects the amount of melatonin circulating at the time of sample collection (Nogueira *et al.* 2013). Measurement of plasma melatonin at multiple time intervals can be useful for determining time of melatonin onset or peak melatonin, duration of melatonin secretion, and total amount of melatonin secretion (see below); however, multiple blood draws are impractical for epidemiological studies. Salivary melatonin levels and time of peak melatonin highly correlate with serum melatonin levels except in people with low melatonin levels. Similar to plasma melatonin, multiple sampling is required; however, a major advantage is that the testing is non-invasive and participants can collect their own samples (Mirick and Davis 2008). However, there is considerable interindividual variability in both the peak and total levels and circadian rhythm of melatonin (Slawik *et al.* 2016). Potential sources of variation of melatonin levels include season or length of day (usually higher in the winter), age, sex, menstrual cycle phase, smoking, alcohol consumption, socioeconomic status, and body mass index (Davis *et al.* 2001b, Hurley *et al.* 2013, Nogueira *et al.* 2013, Wada *et al.* 2013).

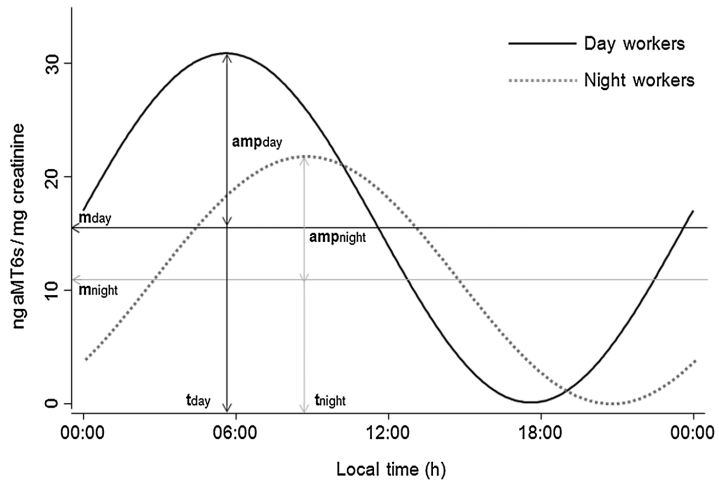

Figure 2-2. Cosinor modeling of melatonin metabolite (aMT6s) production over time for day and night workers

Source: Papantoniou *et al.* 2014, used with permission under license number 4318840942132

amp = amplitude or the distance between the maximum and mesor; aMT6s = 6-sulfatoxymelatonin; h = hour; m = mesor or the circadian mean; t = peak time (for day and night workers).

The circadian rhythm production of melatonin over time can be modeled as a cosine wave in which the mesor is the average level of melatonin (see Figure 2-2). The amplitude is the difference between the lowest and highest level of melatonin (e.g., fluctuation) over time, and the acrophase is the time of the highest or peak melatonin levels (Gómez-Acebo *et al.* 2015). The circadian phase of melatonin rhythms can also be assessed via dim light melatonin onset (DLMO), which is the timing of the onset of melatonin secretion above a threshold level (prior to bedtime) when collected under dim light conditions (Lewy 1999) and is the most sensitive and direct index for identifying an individual's

biorhythm. Studies using cosinor modeling have an advantage over those using single void samples in that the latter have the potential for confounding due to circadian phase differences in individuals (e.g., if night shift workers adapt to their shift schedule, a single void sample would come at a different point in their cycle compared with day workers) (Papantoniou *et al.* 2014).

2.1.2 Clock and clock-controlled gene expression

Clock gene expression can also be used to evaluate circadian disruption. In human blood leukocytes, mRNA levels of the negative regulators of the peripheral clock — *PER, CRY1* and *CRY2* — peak in the morning whereas the mRNA levels of the positive regulator, BMAL1, peak in the evening or midnight; CLOCK (also a positive regulator) has not been found to have rhythmicity in blood leukocytes in most population studies (reviewed by Reszka *et al.* 2013). One study of normally synchronized healthy humans found interindividual variability of clock gene expression profiles in peripheral blood lymphocytes (Teboul *et al.* 2005).

Two recent studies report methods to accurately estimate internal circadian time based on the rhythmic expression of clock and clock-associated genes from a single blood sample (Wittenbrink *et al.* 2018) or a single skin sample (Wu *et al.* 2018). These studies identified partially overlapping sets of blood- and skin-based transcript biomarkers (CRISPLD2, CRY1, ELMO2, FKBP4, HSPH1, KLF9, LGALS3, NR1D1, 2, and PER1, 2, 3, were selected by Wittenbrink *et al.* and ARNTL, HLF, NPAS2, NR1D2, and PER2 by Wu *et al.*) that were as accurate as the dim-light melatonin onset (the current gold standard method) and much more practical and economical.

2.1.3 Other circadian biomarkers: Cortisol, core body temperature

Cortisol is a hormone that is regulated by the hypothalamus-pituitary-adrenal axis, and has anti-inflammatory, metabolic (gluconeogenesis), and immunosuppressive effects (Ulhôa *et al.* 2015). Under normal conditions, cortisol levels peak in the early morning around awakening (cortisol awaking response) and decline throughout the day; they are lowest at the beginning of nocturnal sleep (Boivin and Boudreau 2014). Cortisol is also a putative endogenous circadian entrainer of peripheral clocks along with other glucocorticoids (Mavroudis *et al.* 2012). Glucocorticoids induce the expression of clock genes by binding to the glucocorticoid receptor element in these genes, which can lead to downstream regulation of the peripheral clock network. Cortisol levels can be influenced by stress, and chronically elevated cortisol levels have been associated with adverse health outcomes such as cardiovascular disease (as reviewed by Griefahn *et al.* 2006).

Core body temperature is at its highest one to two hours before bedtime; afterwards it decreases, reaching its lowest temperature approximately two hours prior to waking, and then steadily increases during the day (Boivin and Boudreau 2014). Although mammals maintain a generally constant body temperature and normally do not entrain to external environmental temperature cycles, the SCN drives subtle circadian rhythms in body temperature (Buhr *et al.* 2010). Peripheral clocks in mammals are sensitive to these subtle changes such that body temperature is recognized as an important timing cue for peripheral but not central clocks (see Section 1.1).

2.1.4 Sleep

Sleep is regulated by an interaction between (1) the homeostatic process, which corresponds to the rhythms of sleep pressure (which increases during the wake period and decreases during the sleep period), and (2) the circadian process, which corresponds to rhythms of sleep propensity during the biological day. These two systems are linked and changes in one system affect the other. Sleep parameters such as sleep onset latency, sleep efficiency, sleep duration, and REM sleep latency vary with the circadian phase and depend on the timing of sleep relative to core body temperature and melatonin rhythms (Boivin and Boudreau 2014, Samuelsson *et al.* 2018). As mentioned previously, melatonin production peaks in the evening (prior to bedtime). Although melatonin production, which starts to increase in the evening prior to bedtime, is not required to sleep, in experimental studies, elevated melatonin production has been associated with increased sleepiness (Burch *et al.* 2005).

2.2 Light at night and circadian disruption biomarkers

This section focuses primarily on studies of acute melatonin suppression and chronic circadian disruption (as measured by altered or desynchronized clock gene expression) in humans and experimental animals since these effects are linked with tumor growth (see Section 6).

2.2.1 Human studies of melatonin suppression and clock gene expression

LAN at an applicable wavelength, sufficient level and duration, and appropriate timing can acutely suppress melatonin, which can be measured by the timing and amount of nocturnal melatonin production. In addition, the total light experience (or photic history) as well as individual sensitivities to light can modify how light will affect the circadian system, including melatonin suppression and clock gene expression (Figueiro 2017, Lunn *et al.* 2017). Sleep disruption is also an important downstream effect of exposure to LAN (Smolensky *et al.* 2015).

Light characteristics related to circadian disruption

Nighttime melatonin suppression can occur after exposure to light with wavelengths from 420 to 600 nm (Brainard *et al.* 2001); however, short-wavelength light or “blue” light wavelengths are more effective than longer wavelengths in reducing daily melatonin production (Brainard *et al.* 2001, Figueiro *et al.* 2017). For example, one experimental study in humans found that exposure to narrowband short-wavelength light (peak wavelength = 460 nm) induced a two-fold greater melatonin suppression and two-fold greater phase delay compared to exposure to narrowband middle-wavelength light (555 nm) of equal photon density (Lockley *et al.* 2003). Peak sensitivity for melatonin suppression occurs at 446 to 474 nm, with a peak sensitivity (i.e., lowest irradiance required to elicit a constant criterion response) occurring at 460 nm (Brainard *et al.* 2001, Figueiro *et al.* 2017).

Although short-wavelength light is more effective in inducing circadian disruption, the human circadian system is also sensitive to ordinary room light levels. Based on a model developed by Rea and colleagues (as reviewed by Figueiro *et al.* 2006) using experimental data, a potential threshold for melatonin suppression (~10% melatonin suppression) would be ~30 lux of warm white light at the cornea after 60-minute exposure (see Figure 2-3). This model is somewhat consistent with three studies of volunteers which reported that evening exposure to indoor lighting conditions typically found at the workplace or home can cause acute melatonin suppression. A study by Gooley *et al.* (2011) reported that exposure to electric light (range 60 lux to 130 lux at the eye) before bedtime induced a delay in melatonin onset, resulting in shortened nighttime melatonin duration and decreased nighttime melatonin levels.

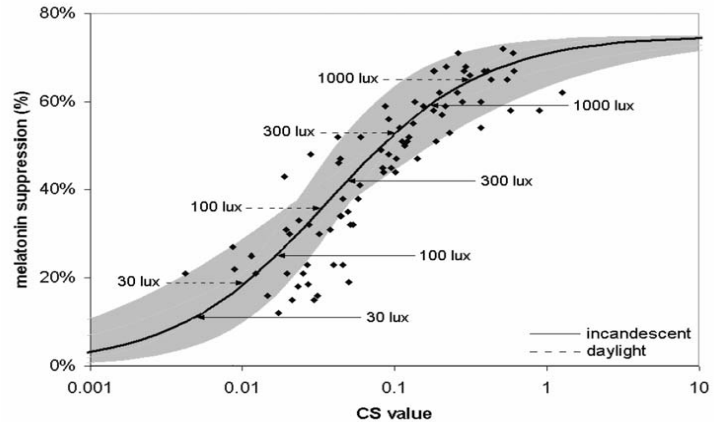

Figure 2-3. Human nocturnal melatonin suppression as a function of circadian light stimulus

Source: Figueiro *et al.* 2006, licensed under Creative Commons 2.0.

Logistic models using plasma melatonin data from volunteers exposed to 6.5 hours of light (ranging from 3 to 9,100 lux at the eye) during the early biological night predicted that half-maximal melatonin suppression occurs in the range of indoor light intensity (~50 to 130 lux at the eye) (Zeitzer *et al.* 2000). This study also found that circadian phase shifting occurred in a dose-dependent manner with light exposure of 15 lux and 500 lux (at the eye). Wahnscaffe *et al.* (2013) reported that 30 minutes of exposure to different types of normal lighting conditions containing varying amounts of blue light – office daylight white (500 lux), bathroom daylight white (130 lux), hall daylight white (500 lux), and "Planon" (an experimental light prototype) warm white (500 lux) – one hour before bedtime reduced salivary melatonin both during and after exposure to light in healthy men and women. Melatonin levels were not reduced after exposure to bedroom yellow light (130 lux). The comparison in this study was melatonin levels from constant exposure to dim light (less than 10 lux) from 7:00 PM to midnight. In contrast to polychromatic light, under controlled conditions (dilated pupils while subjects' heads rested in an apparatus that provided a uniform, patternless stimulus that encompassed the entire visual field) exposure to 0.4 to 3.3 lux of monochromatic blue light (440 to 480 nm) for 1.5 hours suppressed melatonin by 50% in healthy humans (Brainard *et al.* 2001, Glickman *et al.* 2002).

The duration of LAN exposure needed to induce circadian disruption depends on other characteristics of light such as wavelength, timing, and level. For example, Nagare *et al.* (2018) reported that exposure duration was a significant factor in inducing melatonin suppression in subjects exposed to two different types of white light (circadian stimulus of 0.25 at the eye level) for one to four hours.

The timing of light can influence whether light advances (i.e., shortens the 24-hour cycle) or delays the biological clock. Exposure to light in the morning (after the nadir for core body

temperature) causes a phase advance (i.e., melatonin peaks earlier than normal) whereas exposure to light at the end of the afternoon and early evening (prior to the nadir for core body temperature) causes a phase delay (Touitou *et al.* 2017).

The circadian clock is sensitive to the entire 24-hour pattern of light exposure, and recent studies show that the amount of daylight exposure is also important in regulating circadian rhythms. Light levels in indoor offices are typically below what is needed for activation of the circadian system. Some experimental studies suggest that blue light exposure during the daytime or morning can help reduce LAN-induced melatonin suppression (Kozaki *et al.* 2015, 2016, Nagashima *et al.* 2018) and improve measures of sleep quality and mood (Viola *et al.* 2008). In addition, night-time sensitivity to light-induced circadian disruption (usually measured by melatonin suppression) is influenced by light exposure during the day (reviewed by Figueiro 2017 and Lunn *et al.* 2017).

Individual sensitivities to LAN

Individual sensitivities related to age, sex, chronotype, and polymorphisms in clock genes can affect sensitivity to LAN. Circadian photoreception decreases as a result of aging; middle-aged adults have only 50% of circadian photoreception compared with children. Loss of circadian photoreception is due to age-related increases in crystalline lens light absorption and decreases in pupil area (Turner and Mainster 2008). Several experimental studies have shown that children are more sensitive (approximately two-fold) to LAN-induced melatonin suppression than middle-aged adults after exposure to similar light conditions (reviewed by Turner and Mainster 2008, Higuchi *et al.* 2014). Self-luminous displays induced a greater degree of melatonin suppression (23%) in teens (aged 15 years to 17 years) after 1 hour of exposure than college students or middle-aged adults (Figueiro and Overington 2016). Moreover, some studies suggest that children may be more sensitive to lower light conditions and that the youngest children have the greatest circadian sensitivity. Higuchi *et al.* (2014) reported that melatonin secretion was significantly suppressed in school-aged children but not adults (mean age ~42 years) exposed to room light conditions (140 ± 82.7 lux). To ascertain the effect of LAN on puberty, male adolescents were grouped by Tanner staging as pre- to mid-pubertal children (age 9.1 to 14.7 years) and late to post-pubertal adolescents (age 11.5 to 15.7 years); the pre- to mid-pubertal group experienced greater melatonin suppression from evening light exposure at 15, 150, and 500 lux than late to post-pubertal adolescents (Crowley *et al.* 2015).

Chronotype describes people as being “morning types,” who have an earlier sleep schedule and usually earlier circadian phase and “evening types,” who have a later sleep cycle and usually later circadian phase. It can be measured using questionnaires such as the Munich ChronoType Questionnaire and Horne-Østberg morningness-eveningness questionnaire (Roenneberg *et al.* 2007, Roenneberg and Merrow 2007). Some studies suggest that morning types and evening types experience different light profiles; morning types may spend more time exposed to sunlight (bright light) with less exposure to light in the evening than evening types; exposure to bright light during the day may increase the amplitude of the light-dark cycle (difference between daylight and nighttime light intensity). There is also a spectrum of responses within the morning and evening type chronotypes with some individuals having more extreme circadian phases. Morning types with very early circadian phases are thought to have a shorter endogenous period than 24 hours; therefore, without proper entrainment, these subjects will continue to advance

their circadian phase progressively each day. When these subjects were exposed to light close to the DLMO, it produced a phase delay and might prevent further advancement of their circadian phase. The converse was found for evening types with very late circadian phases with endogenous periods longer than 24 hours. In this case, light exposure 10 to 12 hours after the DLMO produced a phase advance and may prevent further delay of their circadian phase. Other morning and evening types have intermediate circadian phases, and differences in sleep patterns may not be related to circadian phases and could be related to homeostatic sleep regulation (Goulet *et al.* 2007 and studies reviewed by Goulet *et al.* 2007).

Sources of light exposure potentially associated with circadian disruption

Several randomized cross-over studies of teens or young adults have shown that the use of electronics with self-luminous displays (such as computers or tablets) prior to bedtime can acutely suppress melatonin onset, disrupt sleep, or decrease morning alertness (Cajochen *et al.* 2011, Figueiro *et al.* 2011, Wood *et al.* 2013, Chang *et al.* 2015, van der Lely *et al.* 2015, Figueiro and Overington 2016, Green *et al.* 2017, Chinoy *et al.* 2018) (see Table 2-1 for a description of these studies). These studies suggest that blue light is a main factor in suppressing melatonin since a stronger association with exposure to LAN was observed when subjects were exposed to electronics using blue light goggles (Figueiro *et al.* 2011, Wood *et al.* 2013) or computer screens with short wavelengths (Green *et al.* 2017). In addition, the use of goggles that blocked blue light attenuated the melatonin suppression (van der Lely *et al.* 2015). A study of middle-aged adults found that subjects using smart phones emitting blue light had delayed melatonin onset but similar melatonin levels as subjects using smart phones with non-blue light (Heo *et al.* 2017). In addition to wavelength, the amount of circadian disruption from self-luminous electronics may depend on the duration of the exposure and prior light exposure. Tablet use prior to bedtime for two hours but not one hour induced melatonin suppression in a small study of teens and young adults (Wood *et al.* 2013). Teenagers exposed to bright light (for 6.5 hours) during the daytime and who used tablets prior to bedtime had similar salivary melatonin levels as those reading a physical book, suggesting that bright light during the daytime can attenuate induction of nocturnal melatonin suppression by short-wavelengths emitted from electronic devices during evening exposure (Rångtell *et al.* 2016). Findings from a cross-sectional study found that young adults with delayed sleep schedules had a later DLMO and reported more time using light-emitting devices (cell phones, tablets, TVs, computers) before bedtime than control subjects (Van der Maren *et al.* 2018).

Table 2-1. Studies of melatonin suppression and exposure to electronics with self-luminous displays

Study	Study design/population	Exposure	Results
Cajochen *et al.* 2011 Switzerland	Randomized cross-over Young adult males Aged 19–35 yr	5-hr exposure White LED backlit Non-LED screen LED screen with more than twice as much 464 nm light emission than a white non-LED-backlit screen	LED vs. non-LED ↓ nighttime salivary melatonin

Study	Study design/population	Exposure	Results
Chang *et al.* 2015 United States	Randomized cross-over 12 healthy young adults 25 ± 2.9 yr	Reading 4 hr before bedtime for 5 consecutive nights with fixed sleep times Light-emitting eBook Printed book	eBook reader vs. printed book ↓ nighttime plasma melatonin & phase shift sleep problems: ↑ time to fall asleep, ↓ evening sleepiness, & ↓ morning alertness
Chinoy *et al.* 2018 United States Follow up of Chang *et al.* 2015	Randomized cross-over 9 young healthy adults 25.7 ± 3.0 yr	Reading 4 hr before bedtime for 5 consecutive nights with self-selected sleep times Light-emitting eBook Printed book	eBook reader vs. printed book ↓ nighttime plasma melatonin & delayed onset sleep problems: later self-selected bedtime ↓ evening sleepiness, and ↓ morning alertness
Figueiro *et al.* 2011 United States	Cross-over 21 subjects age 28 ± 9.9 yr	1 hr at midnight to computer monitor Alone (33 lux at eye) + blue goggles (short wavelength 470 nm, 40 lux) + orange goggles ("dark" control)	LAN vs. dark control ↓ melatonin blue-light goggles ↓ (not significant) melatonin computer monitor only
Figueiro and Overington 2016	20 adolescents Aged 15 to 17 yr	Self-luminous devices starting 3 hr prior to bedtime 1st night: orange goggles ("dark") 2nd night: 1 hr orange goggles + 2 hr without goggles Melatonin collected at 1 (T1), 2 (T2), and 3 hr (T3) from start of study	LAN vs. T1 ↓ melatonin at T2 and T3; highest suppression T3
Green *et al.* 2017 Israel	Random cross-over 19 subjects Aged 24.3 ± 2.8 yr	Exposure for 2 hours at night to computer screen; 3 days rest between exposures Light intensity: low (LI): vs. high (HI) Wavelength: short (SWL) vs. Long (LWL) Four conditions LI/SWL, HI/SLW, LI/LWL, HL/LSW	Melatonin measured at 3 time points SWL: Greatest melatonin suppression irrespective of intensity

Study	Study design/population	Exposure	Results
Heo *et al.* 2017 South Korea	Randomized, cross-over 22 middle-aged adult males	Smart phones with and without blue light Played smart phone video games from 7:30 PM to 10:00 PM	Blue vs. non-blue light Later onset of serum melatonin (phase delay) but no difference in melatonin levels Blue light also affected sleep, body temperature, and performance
Rångtell *et al.* 2016 Switzerland	Randomized, cross-over 14 healthy adults	Reading for 2 hr (before bedtime) following 6.5 hr exposure to constant bright light (~569 lux) Light-emitting eBook Printed book	LED tablet vs. printed book No difference in salivary melatonin or sleep parameters
van der Lely *et al.* 2015	Randomized cross-over 13 male high school students Aged 15–17 yr	LED computer screen with clear lens (CL) glasses (control) LED computer screen + blue light blocking glasses (BB)	CL vs. BB glasses during late evening ↓ melatonin levels prior to sleep and attenuated evening rise in melatonin ↑ subjective sleepiness but no effect on sleep measures ↓ psychomotor performance Significant interaction of sampling time & glasses for melatonin and borderline interaction of sampling time & glasses for subjective sleepiness
Van der Maren *et al.* 2018	Cross sectional 28 subjects Aged 18–28 yr 14 with delayed sleep schedule (later than midnights, complaints) 14 matched controls	Observational measured light recordings, circadian phase (salivary DLMO) and sleep	Delayed vs. control Later wake time and shorter sleep duration 2 hr later than DLMO ↑ exposure to blue light at night and greater use of light-emitting devices (mainly computers) 3 hr prior to bedtime ↓ exposure to blue light during the day
Wood *et al.* 2013	Randomized cross-over 13 volunteers	1–2 hr exposure to tablets at night	Tablets vs. dark control

Study	Study design/population	Exposure	Results
	Aged 18.9 ± 5.2 yr	Highest brightness + blue light goggles + orange light goggles	↓ melatonin levels for tablet + blue light at 1 and 2 hr ↓ melatonin levels for tablet at highest brightness at 2 hr but not 1 hr No effect with tablets + orange light

BB = blue-light blocking; CL = clear lenses; DLMO = dim light melatonin onset; HI = high light intensity; hr = hour; LED = light emitting diode; LI = low light intensity; LWL = long wavelength light; SWL = short wavelength light; yr = year.

Most studies on bedroom lighting did not find an association between indoor LAN and melatonin suppression; however, the few available studies may not have had the power to detect an association and light exposure during the day was not measured or controlled in these studies. A cross-sectional study of adolescents with self-reported behaviors on sleep patterns and exposure to bedroom lighting found that urinary melatonin metabolite levels were lower among participants who experienced sleep interruption and turned on lights but not among participants who did not turn on lights (Hersh *et al.* 2015). However, self-reported measures of bedroom light (e.g., light outside the bedroom, electronic or TV use) did not affect metabolite levels. Levallois *et al.* (2001) reported that nocturnal urinary melatonin levels were somewhat lower, but not significantly so, among individuals reporting light use at night compared to those not using light; no differences in nocturnal melatonin levels were found for those exposed to nocturnal bedroom light greater than and less than 50 lux (measured using a light meter; details on whether this was at the eye were not provided). No association was found between melatonin suppression and turning lights on during the night or ambient light in the bedroom ≥ 10 lux; however, the studies might not have had enough statistical power to detect an effect as the levels of ambient light were low (median = 2.1 lux), the proportion of nights with light ≥ 10 lux was low, and the number of times light was turned on at night was low (median = 0, range = 0 to 6) (Davis *et al.* 2001a). A study of Japanese children also did not find an association between bedroom lighting and morning urinary melatonin levels (Wada *et al.* 2013). An experimental study found that eight-hour exposure to bedroom light intensity (50 lux at the eye) prior to bedtime caused melatonin suppression compared to exposure to dim light (< 3 lux); suppression was reduced using a LED light with selective reduction in short wavelengths (Rahman *et al.* 2017).

The California Teacher Study found a small, non-statistically significant inverse relationship between outdoor LAN (measured using satellite imagery data obtained from the U.S. Defense Meteorological Satellite Program [DMSP]) and 24 hour urinary aMT6s levels (Hurley *et al.* 2013); a limitation of the study was that they did not directly measure nocturnal melatonin suppression (e.g., the investigators did not measure first urine void). Studies of light entering sleeping areas after residential lights have been turned off (i.e., light trespass) generally indicate that, due to low light levels received at the cornea through closed curtains and further through closed eyelids, light trespassing into bedrooms is likely ineffective for melatonin suppression during sleep (Figueiro *et al.* 2006).

Clock gene expression studies

Blue light has been reported to alter clock gene expression. Non-ocular exposure to blue light phototherapy (total irradiance including room light at 5,500 lux to 7,200 lux) decreased the expression of *BMAL1* and increased the expression of *CRY1* in jaundiced full-term neonates (aged 12 days to 27 days) after 24 hours of treatment with eyes covered compared to levels before treatment (Chen *et al.* 2005). Plasma melatonin levels were also decreased; however, this study could not evaluate whether there is a relationship between decreased melatonin levels and altered clock gene expression because samples were only taken one time before and one time after exposure. No change in clock gene expression was observed in infants not given phototherapy after covering their eyes for 24 hours (total irradiance from room lights was 72 lux to 84 lux). A study in adult volunteers using lower doses and shorter duration of monochromatic light (12.1 $\mu W/cm^2$ for 460 nm and 10.05 $\mu W/cm^2$ for 550 nm, which is in the range of 70 lux to 85 lux for 2 hours) found that exposure to blue light (460 nm) in the evening significantly increased *PER2* expression in oral mucosa samples measured 24 hours after exposure; exposure to green light (550 nm) caused a lower non-significant increase in *PER2* gene expression (Cajochen *et al.* 2006).

2.2.2 Experimental animal studies on melatonin suppression and clock gene expression

The circadian systems of nocturnal rodents and diurnal humans differ in both their spectral and absolute sensitivities to light (Bullough *et al.* 2006). In terms of absolute sensitivities, nocturnal rodents are 3,000 to 10,000 times more sensitive to LAN-induced circadian disruption than humans, as measured by the ratio of the thresholds for melatonin suppression and for circadian phase shifting (Bullough *et al.* 2006, Figueiro 2017). Although diurnal rodents (e.g., ground squirrels, Eastern chipmunks) have similar sensitivities to light as humans, they are rarely used as models to investigate the health consequences of LAN. Nevertheless, when the difference in sensitivity is accounted for, nocturnal rodents and humans show similar levels of light-dependent circadian disruption as measured by the cross correlation between light and dark and activity and rest patterns (Radetsky *et al.* 2013, Rea and Figueiro 2014).

Most studies of circadian disruption in animals used constant dim LAN (< 1 lux) or constant bright LAN (≥ 300 lux), while a few studies investigated the effects of exposure to a 30-minute bright LAN pulse during the middle of the night (see Sections 5 and 6). These studies show a wide range of psychological effects and physiological biomarkers of LAN-induced circadian disruption including melatonin suppression, altered clock gene expression, and biological effects related to both cancer and non-cancer outcomes (see Section 6 for mechanistic studies related to carcinogenicity; non-cancer outcomes are beyond the scope of this evaluation).

Melatonin suppression

The relationship between LAN exposure and melatonin in experimental animals appears to be particularly complex and is influenced by the pattern and intensity of LAN exposure as well as the spectrum of light exposure during the day (Travlos *et al.* 2001, Cos *et al.* 2006, Blask *et al.* 2009, Dauchy *et al.* 2014, Dauchy *et al.* 2016). These studies show that melatonin suppression is dose-dependent but exposure to dim LAN (0.2 lux) can reduce melatonin secretion by 65%. Exposure to dim indoor lighting during the day is also associated with greater circadian phase shift responses to LAN. Travlos *et al.* (2001) reported that female F344 rats exposed to

intermittent light pulses every two hours for one night showed an average melatonin suppression of 65% compared to controls. When exposure to light pulses continued for 2 or 10 weeks, the overall suppression was reduced to 35% and 25%, respectively, with a slight phase advance in the melatonin rhythm. However, rats exposed to light pulses every two hours at night for 26 weeks had serum melatonin levels that were three-fold higher than controls, which suggests an adaptive process that is consistent with the diminishing effect observed in the first 10 weeks. This study also reported evidence that pinealectomized rats were able to reestablish a melatonin cycle, suggesting that melatonin was produced by organs or tissues other than the pineal gland.

Exposure to bright sunlight affects nocturnal melatonin synthesis by increasing nocturnal melatonin secretion and decreasing vulnerability to suppression and circadian disruption by LAN (Dauchy *et al.* 2013, Smolensky *et al.* 2015). Studies in male albino Buffalo rats or nude rats demonstrated that daytime exposure to broad-spectrum cool white fluorescent lighting filtered through blue-tinted cages or to LED lights enriched in the blue portion of the visible spectrum (465 to 485 nm) resulted in a 6- to 7-fold increase in nighttime peak plasma melatonin levels and increased the duration of the nighttime melatonin signal compared to rats held in clear cages and exposed to cool white fluorescent lights during the day (Dauchy *et al.* 2013, Dauchy *et al.* 2015, Dauchy *et al.* 2016, Dauchy *et al.* 2018). Moreover, mean or total plasma or blood levels (over 24-hr day) of total fatty acids, linoleic acid, acid-gas levels, glucose, corticosterone, and leptin were lower in rats exposed to daytime blue light compared to the controls, suggesting that daytime blue light affects circadian regulation of rodent metabolism. These data, in combination with the studies of LAN, suggest that the totality of the daily light environment includes complementary exposures that contribute to circadian disruption (i.e., too little sunlight during the day and too much LAN).

Clock gene expression

LAN exposure also altered clock gene expression in the SCN and peripheral tissues of experimental animals (Table 2-2). Most studies used mice, and *Clock*, *Bmal1*, *Per1*, *Per2*, and *Cry1* were the most frequently studied genes. Several studies also investigated clock proteins. Although all of the studies show that LAN exposure clearly affects expression of some clock genes and proteins in peripheral tissues and the central clock, not all genes investigated were altered in all tissues. These studies used different designs and results varied by light source and intensity, tissues, species, and the specific genes or proteins studied. These data may also reflect the functional redundancies and complexity built into the molecular clockwork circuitry, which include at least two functionally redundant isoforms for all clock genes except *Bmal* (Schibler *et al.* 2015).

Table 2-2. Effects of LAN exposure on clock gene expression

Reference	Species (sex)	Light exposure day:night hr (day:night lux)	Endpoint Clock genes and proteins Tissue(s)	Results (gene/protein expression)
Gubareva *et al.* 2016	SHR mice	12:12: C 24:0[a]	Proteins: CLOCK, BMAL1, CRY1 Skin	CLOCK, CRY1: no effect BMAL1: increased

Reference	Species (sex)	Light exposure day:night hr (day:night lux)	Endpoint Clock genes and proteins Tissue(s)	Results (gene/protein expression)
Fonken *et al.* 2013a	Swiss Weber mice (M)	14:10 (150:0): C 14:10 (150:5)	Genes: *Clock, Bmal1, Per1, Per2, Cry1, Cry2, Rev-erbα* Proteins: CLOCK, BMAL1, PER1, PER2 Hypothalamus/SCN, hippocampus, liver, fat	Hypothalamus/SCN *Clock, Bmal1, Cry1, Rev-erbα*: no effect *Per1, Per2, Cry2*: reduced CLOCK, BMAL: no effect PER1, PER2: reduced Liver *Clock, Rev-erbα:* no effect Bmal1, Per1, Per2, Cry1, Cry2: reduced Hippocampus and fat: no effect
Shuboni and Yan 2010	CD1 mice (M)	12:12 (300:1): C 12:12 (300:20): dim light with/without 30 min LAN pulse (300)	Genes*: Per1, Per2* Proteins: PER1 SCN	Dim LAN PER1: increased at baseline but not at peak (overall decrease in amplitude of PER1 rhythm) *Per1* and *Per2:* increased LAN pulse *Per1* and *Per2:* increased in control and dim LAN treatment groups but lower in the dim LAN group
Bedrosian *et al.* 2013	Siberian hamsters (F)	16:8 (150:0): C 16:8 (150:5)	Proteins: BMAL1, PER1, PER2 SCN, hippocampus	SCN BMAL1: no effect PER1, PER2: abolished peak expression Hippocampus BMAL1, PER1: no effect PER2: reduced peak expression
Honda *et al.* 2017	Broiler chicks (M)	12:12: C 12:12: white:blue light 24:0[a] white light	Genes: *Bmal1, Cry1, Per3* Diencephalon, liver, skeletal muscle	Continuous white light *Bmal1*, *Cry1*, *Per3:* altered mRNA levels in all three tissues White:blue light: no effect

C = control; F = female; M = male.
[a]Continuous light.

2.3 Shift-work and circadian disruption biomarkers

This section reviews studies of night shift workers and melatonin suppression, clock gene expression, and shift work tolerance or adaptation.

2.3.1 Studies of night shift workers

Night shift work includes permanent and rotating night shift work, which are discussed in Section 1, and can include many different types of scheduling patterns including consecutive shifts in either forward (i.e., clockwise or day to evening to night shifts) or backward (i.e., counterclockwise or night to evening to day shifts) directions, consecutive nights on a specific shift (e.g., morning, evening, or night), and variations in the number of days off between shifts. Most biomonitoring studies have not compared effects for different types of rotating shifts; however, a few studies suggest that effects on circadian disruption are more pronounced in backward (or counterclockwise) working schedules than forward (or clockwise) schedules (Nesthus *et al.* 2001, Boquet *et al.* 2004, Vangelova 2008).

People working at night and sleeping during the day are continuously exposed to external synchronizers promoting a day-oriented schedule and thus experience circadian desynchrony, as evidenced by changes in levels and timing of peak melatonin production and other biomarkers of circadian disruption, such as changes in the rhythms of core body temperature. In addition, night and rotating shiftwork may alter cortisol levels and the cortisol awaking response (reviewed by Ulhôa *et al.* 2015). One study found young shift workers (under age 40) had higher long-term cortisol levels as measured in hair samples than day workers (Manenschijn *et al.* 2011). However, findings are somewhat conflicting across studies; some studies found no effect, others found differences in the direction of the effects (e.g., lower or higher levels among night workers, increased or decreased cortisol activation), or found a flattened or blunted cortisol profile (reviewed by Fekedulegn *et al.* 2012, Niu *et al.* 2015, Hung *et al.* 2016).

Night shift workers also complain about reduced sleep quality, shortened sleep periods, and insomnia, especially following a night shift. Duration of daytime sleep in night shift workers usually ranges from four to seven hours, and workers sleep longer on rest days. Night shift workers are usually awake during their nocturnal melatonin peak periods, which may also contribute to night-time sleepiness as melatonin plays an important role in regulating sleep (reviewed by Boivin and Boudreau 2014 and Kim *et al.* 2015).

Adaptation to shift work

Overall, most shift workers do not appear to tolerate shift work or adapt their circadian rhythms to their sleep schedule (i.e., melatonin continues to peak at night instead of during their daytime sleep) (Boivin and Boudreau 2014). Some studies have found that individual workers who are able to alter the timing of their melatonin production to parallel their sleep time had better shift work tolerance and improved sleep quality compared to workers who did not alter their timing; however, there are individual differences (reviewed by Burch *et al.* 2005). A review of six studies of permanent shift workers found that only a small minority of permanent night shift workers (< 3%) underwent a complete phase adjustment and only 21% showed substantial adjustment so as to derive any benefit from it (Folkard 2008). Furthermore, there was no difference in results regardless if shiftwork occurred in dim or normal lighting. The review concluded that only a small minority of permanent night workers undergo complete phase adjustment of endogenous melatonin.

A more recent review found that circadian rhythms of melatonin, cortisol, and heart rate are not adapted to night work after one to three consecutive night shifts (Jensen *et al.* 2016). A meta-

analysis of studies of experimental shift work tolerance found that circadian desynchronization (as measured by oral temperature circadian rhythms) still occurred among male workers classified as shift work tolerant (based on lack of medical complaints such as sleep alteration, fatigue, changes in behavior, or digestive problems) although at a lower rate (16.7%) than non-tolerant shift workers (55.8%) (Reinberg and Ashkenazi 2008). Circadian desynchronization occurred in 11% to 17% of former shift workers who were currently symptom free but had been discharged from shift work due to poor tolerance. A study of 48 shift workers found that tolerant shift workers were older and worked longer durations than non-tolerant workers (Reinberg and Ashkenazi 2008).

Sleep strategy, age, chronotype, and genetic susceptibility may influence adaptation to night shift work. A review of 60 studies on shift work tolerance found conflicting findings for age, gender, and chronotype (Saksvik *et al.* 2011). In general, studies have found that individuals at younger age are better at adapting to shift work as measured by cognitive skills or sleep, while older workers had better health outcomes, which may be influenced by the healthy shift worker effect. Most studies found that morning (or earlier) chronotypes have more difficulties adapting to night shift work than evening types as measured by problems with sleep; some studies found evening chronotypes did better as measured by their perception of work performance and perceived shift work tolerance (Saksvik *et al.* 2011). Gamble *et al.* (2011) reported that rotating night shift workers who used sleep deprivation to switch to and from night shift work and diurnal sleep during days off were the most poorly adapted (based on self-reported adaptation and questions related to sleep) to shift work. There was some suggestion that clock gene polymorphisms were associated with sleep behavior and might contribute to shift work adaptation (Gamble *et al.* 2011).

The effect of race on adaptation to shift work remains an important research gap although some studies have suggested that the period of endogenous circadian rhythms differs between European Americans and African Americans. African Americans were predicted to be less likely to delay circadian rhythms when working nights and sleeping during the day, and adapted less readily to night work than European Americans (Eastman *et al.* 2016). These results may also have implications for African-American shift workers in the United States, who are disproportionately represented in night work (see Section 1.3.2).

Studies of melatonin suppression

There is strong evidence that night shift work suppresses or disrupts nighttime melatonin production (see Table 2-3). As most night shift workers do not adapt their circadian rhythms to their sleep:wake cycle, the most informative studies are those that compared melatonin levels at multiple time periods, such as those using cosinor analysis of mesor (average levels), amplitude (fluctuation), and acrophase (timing of peak melatonin production) in night shift vs. day shift workers. Studies comparing nighttime melatonin in night shift workers after night work to levels in day shift workers after nighttime sleep were also informative. Several studies in different geographical locations and of different types of workers found that night shift workers (permanent and rotating) had lower morning urinary aMT6s after night work compared to day shift workers after sleep (Schernhammer *et al.* 2003, Burch *et al.* 2005, Davis *et al.* 2012, Ji *et al.* 2012, Bracci *et al.* 2013, Mirick *et al.* 2013). Compared to day shift workers on a work day, night shift workers also had lower total (Borugian *et al.* 2005, Daugaard *et al.* 2017) or mean

melatonin levels (Hansen 2006, Papantoniou *et al.* 2014, Gómez-Acebo *et al.* 2015, Leung *et al.* 2016, Song *et al.* 2016), or amplitude (Gómez-Acebo *et al.* 2015), or a later acrophase (Papantoniou *et al.* 2014, Gómez-Acebo *et al.* 2015) on a work night.

Findings regarding the suppression of melatonin levels in night shift workers after nighttime sleep on a day off are conflicting, however. Urinary aMT6s levels were lower after night sleep on a non-work day for night workers compared to levels in day workers after night sleep in Seattle health care workers (Davis *et al.* 2012, Mirick *et al.* 2013), but not in Italian health workers (Bracci *et al.* 2014).

The studies indicate that persistent night shift work (i.e., frequent or long-term) was associated with nighttime melatonin suppression; however, findings for specific exposure metrics across studies are somewhat difficult to compare due to differences in the type of shift worker (e.g., permanent or rotating), gender, melatonin measurements, or analyses. Three studies of female rotating night shift workers found that a high frequency of shift work or several consecutive shifts was associated with decreased nighttime (measured in the morning) or average melatonin levels. The following are key findings from these studies:

- A significant ($P = 0.008$) inverse association between morning urinary aMT6s levels and increasing number of working nights in the two weeks prior to collection of the urine samples was found among premenopausal nurses in the Nurses' Health Study (Schernhammer *et al.* 2004).
- A study of Polish midwives and nurses who currently worked night shifts found decreased morning UaMT6s for working ≥ 8 night shifts/month in all women and in premenopausal women (Peplonska *et al.* 2012).
- Compared to day workers, a Canadian study (Leung *et al.* 2016) found a greater reduction in average aMT6s levels between hospital workers who worked ≥ 3 consecutive nights and women who worked < 3 consecutive nights.

However, a Spanish study of permanent male and female night workers from various occupations (Papantoniou *et al.* 2014) found the most pronounced reduction of average urinary aMT6s levels in subjects who worked ≤ 4 consecutive nights (compared to day workers) in the two weeks prior to urine collection. Permanent night shift workers had a delay in the time of peak melatonin production compared to day workers, which was most pronounced among men who worked the most nights in the railroad industry, suggesting partial adaptation of circadian timing with sleep:wake cycle (Papantoniou *et al.* 2014). Three studies also found an inverse relationship between long-term shift work and average melatonin levels (Papantoniou *et al.* 2014, Leung *et al.* 2016 — nurses only analyses) or peak melatonin level (Grundy *et al.* 2011). No significant trend was found for morning melatonin levels and shift work duration or cumulative number of night shifts among Polish nurses and midwives (Peplonska *et al.* 2012); however, this analysis was limited because it combined the current and former rotating Polish nurses and midwives.

Studies that compared melatonin levels in rotating shift workers or current night shift workers after working day and night shifts were not considered as informative since there may be more chronic effects on melatonin suppression due to shift work (as discussed above). Analyses of melatonin levels during day and night sleep time in night workers may be evaluating differences

in melatonin due to circadian timing rather than from night work *per se,* as indicated in a study of Canadian rotating nurses. Grundy *et al.* (2009) reported lower melatonin levels during nighttime sleep after working days and during daytime sleep after working nights, but not in nighttime melatonin levels after working night shift or during nighttime sleep after working days (Grundy *et al.* 2011). Anjum *et al.* (2013) reported that melatonin levels were lower in nurses after working nights than days when within-subject comparisons were made. In contrast, a small study of telecommunication rotating night workers (Dumont *et al.* 2012) using within-subject comparisons found that melatonin levels were similar between the night and day shifts.

The relationship between shift work and melatonin levels may be modified by race/ethnicity, age, and chronotype (Bhatti *et al.* 2014, Papantoniou *et al.* 2014, Leung *et al.* 2016), although findings for these potential modifiers are somewhat inconsistent across studies, and the database is limited in its ability to evaluate whether race is an effect modifier, as Asians are the only group that has been specifically evaluated. Bhatti *et al.* (2013b) reported that Asian-American night shift workers had urinary aMT6s levels closer to their day shift levels compared to white workers (female health workers in Seattle), suggesting they may be able to adapt better to shift work than whites. In contrast, the Shanghai Women's Health Study found some evidence to suggest that night shift work causes melatonin suppression in middle-aged Chinese women based on the findings of a significant inverse relationship between morning urinary aMT6s levels (not first void) and job exposure matrix scores for night shift work (Ji *et al.* 2012). Of note, urinary aMT6s levels were low in this study, which could be due to the fact that first void samples were not collected and the study may not have directly measured nocturnal melatonin suppression. Two studies of postmenopausal Japanese workers (Nagata *et al.* 2008, Nagata *et al.* 2017) were considered to be uninformative because of low numbers of night shift workers and because biological samples were not collected after night work.

Some support for the findings comes from an experiment which suggested that sensitivity of melatonin to light suppression is influenced by eye pigmentation and/or ethnicity. Caucasian and Asian males were exposed to 1,000 lux light two hours prior to their salivary melatonin peak. The percentage of suppression of melatonin secretion was significantly larger in light-eyed Caucasians (88.9%) than in dark-eyed Asians (73.4%) ($P = 0.01$) (Higuchi *et al.* 2007). No studies were identified for other races.

LAN during shift work and melatonin suppression

There is some evidence from six field studies (two in overlapping populations) (Table 2-3) and one experimental study to suggest that LAN contributes, in some part, to melatonin suppression observed in night shift workers; however, few studies measured melatonin and light in the same study. It is difficult to compare findings across studies because of differences in study design, sample type, type of workers, and light levels. Daugaard *et al.* (2017) reported that LAN at > 80 lux during the night mediated ~5.9% of 16.5% melatonin suppression in night shift workers. Two overlapping Canadian studies of rotating nurses found an inverse relationship between urinary or salivary melatonin levels and average LAN (Grundy *et al.* 2009, Grundy *et al.* 2011), and a Spanish study found that permanent night workers with the highest LAN exposure had greater melatonin suppression (38% vs. 27% suppression) and more pronounced shifts in the timing of peak melatonin than workers with the lowest LAN exposure, albeit levels of light at night were low in this study (Papantoniou *et al.* 2014). A small study of rotating night workers

found an inverse relationship between light exposure and total 24-hour urinary melatonin secretion but not melatonin levels secreted during the work night (Dumont *et al.* 2012). To determine the direct effect of night work on nighttime melatonin production in moderate intensity light exposure and to assess the effect of consecutive night shifts on melatonin production, an experimental study of healthy volunteers subjected to three nights of simulated shift work (50 lux at the eye level) was conducted. The authors reported that nighttime melatonin production based on 24-hour urine collections significantly decreased after the third consecutive night, and the decrease was progressive over the three nights. The authors suggested that decreases in melatonin levels, however, were mainly the result of circadian disruption associated with the process of re-entrainment rather than the direct effect of low intensity light (< 100 lux) (Dumont and Paquet 2014).

Table 2-3. Field studies of night shift work and melatonin levels in shift workers

Study Country (year or years of exposure)	Population	Methods: timing	Results	Comments
Night shift workers vs. day shift workers				
Davis *et al.* 2012 Mirick *et al.* 2013 Bhatti *et al.* 2013b, 2014 USA Women: 2003–2008 Men: 2007–2011	Seattle healthcare workers — at least 20 hr/wk nights or days Women — pre-menopausal ages 20–49 yr Men — ages 20–55 yr Davis (women) 172 NSW; 151 DSW Mirick (men) Bhatti 2014 (women & men) 354 NSW; 310 DSW Bhatti 2013 (white & Asian women) NSW: 110 white and 19 Asian DTW: 115 white and 32 Asian	UaMT6s After sleep NSW: Daytime sleep following 1st night shift NSW: Nighttime sleep on night off after ≥ 2 consecutive night shifts DSW: nighttime sleep after ≥ 1 day shifts After work NSW: 2nd night shift DSW: day shift	All studies ↓ UaMT6s NSW compared to DTW Nocturnal (NSW night work, DTW night sleep) Nighttime sleep Day sleep (NSW) vs. night sleep (DSW) ↓ UaMT6s within NSW Day sleep vs. night sleep Night work vs. night sleep	Bhatti 2014: chronotype Morning-type night workers had levels closer to day shift workers compared to evening-type night shift workers Bhatti 2013: race Asians suffered less disruption than whites (UaMT6s closer to DSW than whites) Adjusted for potential confounders
Borugian *et al.* 2005 Canada	Convenience sample ages ≥ 19 yr, working ≥ 20 hr/wk 14 rotating NSW nurses 3 DSW nurses 5 DSW office (2 men, 3 women)	Salivary melatonin 3 times in 24 hours (awaking, midday, and mid sleep relative to night or day work schedule)	NSW vs. DSW ↓ Total melatonin on work nights than day workers on work days	Light measured using light logger Rotating shift workers had two times higher light exposure during night shifts than on their day off or day-shift work (not statistically significant) Small numbers of participants limit the utility of the study

Study Country (year or years of exposure)	Population	Methods: timing	Results	Comments
Bracci *et al.* 2013 Italy (2011)	National Health Service hospital wards – 184 nurses (premenopausal) 31 rotating NSW; 31 DSW ≥ 48 night-shifts/yr	UaMT6s 7:00 AM; end of night shift or beginning of morning shift	↓ UaMT6s NSW compared to DSW regardless of nap	Rapid rotating clockwise: day, evening, night, off, off No association with clock gene expression Adjusted for potential confounders
Bracci *et al.* 2014 Italy (2012)	National Health Service hospital wards; 184 nurses (premenopausal) 60 rotating NSW; 56 DSW 56 permanent daytime nurses Assigned for ≥ 2 yr for ≥ 60 night-shifts/yr with no schedule breaks in last 6 months	UaMT6s Beginning of morning shift after a regular night sleep on a day off	UaMT6s similar in night shift workers & permanent day workers	Rapid rotating clockwise Alterations in clock gene expression Adjusted for potential confounders
Burch *et al.* 2005 United States (2001–2002)	Medical device manufacturing unit; 171 workers 3 non-rotating shifts: day (6:00 AM–2:00 PM) swing (2:00 PM–10:00 PM) night (10:00 PM–6:00 AM)	UaMT6s (creatinine adjusted) Post work and post sleep (including all voids during sleep)	NSW vs. DSW ↓ UaMT6s total sleep period ↑ UaMT6s post work ↓ Sleep:work ratio	Light exposure measured using light logger; NSW non-significantly lower 24-hr light exposure than DSW Ratio of post sleep and post work —potential indicator of circadian disruption Comparing post work and sleep may not be informative for workers who do not adapt to night shift work since it will not capture peak melatonin levels for each shift type Adjusted for potential confounders
Daugaard *et al.* 2017 Denmark	87 NSW 254 DSW	Salivary melatonin	NSW vs. DWS	Light measured using a light logger. On work days, LAN higher for NSW than DWS; light during

Study Country (year or years of exposure)	Population	Methods: timing	Results	Comments
	322 work days and 301 off days	Samples every four hours on a work day and a day off with initial sample after waking (morning for DSW and afternoon for NSW) and a sample before bedtime	↓ 16.5% on work nights; similar on day off LAN > 80 lux during night ↓ melatonin after ≥ 10 minute exposure ↓ 5.9% melatonin mediated by LAN (> 80 lux)	the day higher for DSW than NSW. Light levels similar for DSW and NSW on off days Limitation: Participants decided on which day to take sample in a 7-day week
Dumont *et al.* 2012	13 rotating NSW telecommunication (aged 23–50)	24-hr UaMT6s Two 48-hour periods (once when working day/evening shift and the other for night shift) beginning of 2nd work shift	Day vs. night shift No difference in melatonin levels Light & melatonin Inverse association between light exposure during night and 24-hr melatonin but not melatonin during work time	Light measured using a light logger; no difference in median light exposure between day and night periods over 24 hr or during work time
Hansen *et al.* 2006 Denmark	170 nurses (volunteers) 81 rotating 89 fixed: 50 fixed night; 27 fixed day; 12 fixed evening	UaMT6s Spot urine samples over 24 hours at various times on a workday and on a day off: the 2nd workday of a shift and 2nd day off	↓ UaMT6s NSW (rotating or fixed) vs. DSW on a workday Workday vs. day off for NSW (fixed or rotating) but not DSW	Adjusted for sampling time and potential confounders
Ji *et al.* 2012 China (1997–2000)	Shanghai Women Health Study (aged 40–70) 296 women/night shift work measured by JEM	UaMT6s (creatinine adjusted) Early morning, middle morning, late morning, and afternoon	↓ UaMT6s with ↑ JEM scores for night shiftwork for early morning samples only	Adjusted for potential confounders Samples not based on first void

Study Country (year or years of exposure)	Population	Methods: timing	Results	Comments
Nagata *et al.* 2017 Japan (2008–2009)	Follow-up of women attending breast cancer screenings; 617 participants 10 current night shift workers 532 not currently working shift work	UaMT6s (creatinine adjusted) Following a night's sleep on a day off	No differences in UaMT6s levels between current shift workers and workers not currently working shifts	Uninformative study: only 10 workers, measured on a day off Current shift work without information about previous shift work duration Adjusted for potential confounders
Schernhammer *et al.* 2004, Schernhammer *et al.* 2006a United States NHS (1989–1990); NHS II (1996–1999)	Nurse's Health Study II (NHS II) 2004: 80 randomly selected cancer-free participants (premenopausal) 2006: 459 rotating NSW from NHS II, primarily pre-menopausal nurses (ages 33–50), includes 80 nurses from 2004 study	UaMT6s (creatinine adjusted) 2004: repeated measurements 2006: one measurement	2004 NSW: inverse association with increasing numbers of nights worked within 2 weeks of urine collection and urinary melatonin level 2006: ↓ UaMT6s (NS) NSW vs. DSW > 4 nights in 2 weeks of urine collection	Same study population as cancer studies 2004: Repeat melatonin measure (3 samples per woman, 80 women): ICC = 0.72 Adjusted for potential confounders
Song *et al.* 2016 Korea (NR)	100 female medical technologists (≥ 40 hr/wk) 50 permanent NSW; 50 DSW NSW – no earlier than 6:00 PM – at least 8 hr	Serum melatonin blood samples collected between 8:00 AM and 9:00 PM	NSW compared to DSW ↓ mean melatonin levels ↓ melatonin receptor expression	No difference in p53 expression in NSW vs. DSW
Cosinor analyses				
Gómez-Acebo *et al.* 2015 Spain (2012–2013)	Health care workers (aged 20–65) or teachers (aged 20–30) 63 rotating NSW (health care workers) 73 DSW (health care workers & teachers)	UaMT6s Collected over a 24-hr period following the 2nd day or 2nd night shift	NSW compared to DSW ↓ average UaMT6s (mesor) ↓ UaMT6s fluctuation (amplitude)	Forward rotating: 2 or 4 morning shifts, 2 afternoon shifts, 2 night shifts, 2 off days

Study Country (year or years of exposure)	Population	Methods: timing	Results	Comments
			Later time of peak UaMT6s (acrophase)	
Leung *et al.* 2016 Canada (NR)	261 female hospital workers 114 rotating NSW; 147 DSW	UaMT6s 48-hr time period Fixed: 2 workdays Rotating: 1 day, 1 night shift	NSW (night shift) vs. DSW ↓ average UaMT6s (mesor) Earlier time of peak UaMT6s (acrophase) Within participant comparison of rotating workers: night vs. day shift ↓ average UaMT6s (mesor) Earlier time of peak UaMT6s (acrophase)	Chronotype Differences in UaMT6s (mesor) between NSW and DSW were more pronounced among later chronotypes and among shift workers working ≥ 3 consecutive nights Among nurses, cumulative shift work (duration) was associated with ↓ mesor Mesor or acrophase not associated with duration of past shift work Adjusted for potential confounders
Papantoniou *et al.* 2014 Spain (2011)	Workers at 2 hospitals, a car industry, and railroad company 63 men and 54 women 75 permanent NSW 42 DSW	UaMT6s 24-hour time period on work day	NSW (night shift) vs. DSW ↓ average UaMT6s (mesor) Later peak time UaMT6s (acrophase) Exposure response Lower average UaMT6s among those with longest lifetime duration and lower frequency in a 2-week period Phase shift was related to # of hours worked NSW with highest LAN exposure vs. DSW	Light exposure measured using a data logger; mean light on overnight shift ranged from 15 to 246 lux Chronotype Morning preference chronotype had lower melatonin levels but chronotype did not affect acrophase Adjusted for potential confounders

Study Country (year or years of exposure)	Population	Methods: timing	Results	Comments
			Greatest ↓ melatonin levels Greatest phase shift	
Night shift vs. day shift in rotating night shift worker				
Anjum *et al.* 2013 India	62 rotating men and women health professionals (aged 20–40): working 9 continuous shifts that alternated between day and night	UaMT6s Every 8 hours (afternoon, night, morning)	Within person comparison NSW vs. DSW ↓ mean UaMT6s for afternoon, night, and morning with greatest difference at night and in the morning	Within person comparisons
Grundy *et al.* 2009 Canada (2006)	61 rotating night nurses (aged 30–65 yr); DD, NN, 5 days off 29 sampled on day shift 32 sampled on night shift	UaMT6s NSW: after awakening from daytime sleep for those working 2nd consecutive night shift and nighttime sleep for those working 2nd consecutive day shift Salivary melatonin 4 samples over 24 hr	UaMT6s ↓ after night shift than day shift Salivary melatonin No alteration in timing of peak salivary melatonin levels (peak still occurred at night regardless of shift) Light intensity (average between midnight and 5:00 AM): inverse relationship with UaMT6s All subjects combined ($P = 0.002$) NSW ($P = 0.06$) Lower levels during day sleep and peak at night during work (midnight to 5:00 AM)	Light measured using light meter; higher light during sleep and during night hours for those working night compared to those working the day shift Study limitation: not comparing peak UaMT6s levels in both groups since peak after night shift is during the night and UaMT6s were measured after daytime sleep in the night workers Adjusted for potential confounders
Grundy *et al.* 2011	123 rotating nurses aged 30–65 yr); DD, NN, 5 days off	UaMT6s	UaMT6s	Same population sources as Grundy *et al.* 2009

Study Country (year or years of exposure)	Population	Methods: timing	Results	Comments
Canada (2008–2009)	Participated in the study twice (after night and day) in summer and winter 1st season:118 both shifts 2nd season: 96 night, 103 day	Two samples: Early morning (after night shift for night or nighttime shift for day) and midday (after daytime sleep for night and mid shift for day) Salivary melatonin 4 samples over 24 hr	No differences between night and day shift ≥ 20 yr shift work associated with increase in peak and possibly change in melatonin levels Light intensity: small inverse relationship Peak (P = 0.07) and change (P = 0.04) in melatonin levels and light observed in night work group	Measured light using light meter, maximum levels at night 37.2 lux Session and chronotype no effect Adjusted for potential confounders
Peplonska *et al.* 2012 Poland	1,117 nurses and mid-wives selected from national registries (aged 40–60 yr); 724 provided morning samples 354 currently rotating NSW 370 currently DSW	UaMT6s Morning samples for analysis of NSW Evening samples used for between subject variability	Current NSW vs. DSW Similar morning UaMT6s ↓ morning UaMT6s for working ≥ 8 night shifts/month in total (P = 0.019) and in premenopausal women *(P* = 0.011) ↓ morning UaMT6s for working ≥ 10 hr/night *(P* = 0.06) Combined DSW and NSW No trend with duration, total hours, or cumulative number of night shifts	No association with subjective type of light at night at work Sensitivity analysis excluding 10 women who moved to day jobs in last year before study start Study limitation: women currently working days had previously worked rotating NSW for an average of 12 yr (most ≥ 5 yr before study start). Analysis of cumulative history of shiftwork included melatonin measurement from current DSW after sleeping Adjusted for potential confounders

D = day; DSW = day shift workers; hr = hour; ICC = intraclass correlation coefficient; JEM = job exposure matrix; N = night; NSW = night shift workers; UaMT6s = urinary 6-sulphatoxymelatonin; yr = year.

Studies of clock gene expression

There is some evidence from field studies (Table 2-4) and one experimental study that expression of peripheral clock genes (primarily measured in blood) is altered in night shift workers compared to day shift workers; however, the database is limited by small numbers of studies, differences in the genes evaluated, and types of samples collected across studies (see Table 2-4). Sample timing and methodology appear to be key factors in interpreting the findings. A series of studies of overlapping populations of Italian nurses found that several clock genes had altered expression in night rotating workers compared to day workers when RNA was measured in blood samples taken after a day off work (Bracci *et al.* 2014) but not when measured in blood samples taken immediately after working night shift (Bracci *et al.* 2013); the degree of overlap in the studies is not known. The third study of this population found that *PER2* expression (as measured in pubic hair) was decreased in night shift workers compared to day shift workers in samples taken in the morning but not at other times (Bracci *et al.* 2016). Fang *et al.* (2015a) reported that *PER2* expression was affected by both types of shift work and sampling time in a crossover studies of interns working day and night shifts. After night work, *PER2* expression was higher in the evenings than the mornings whereas the opposite pattern (higher *PER2* expression in the morning than the night) was observed after day shift; therefore, when *PER2* was measured in the evening, its expression was increased after night shift compared to day shift. A small experimental study using polychromatic white light to simulate 8 hours of night shift work for 9 days (10-hour shift in the sleep/wake cycle) found that expression of *PER1* and *PER2* adapted to the shifted sleep/wake schedule within 3 days on the shifted sleep/wake schedule (James *et al.* 2007). Increased *PER1* expression was found to be related to lifetime exposure to working nights among current night shift workers compared to current day shift workers who previously worked nights, suggesting that persistent night shift work may be associated with circadian desynchrony (Reszka *et al.* 2013). Epigenetic mechanisms may be responsible for changes in clock gene expression; several studies found that long-term shift work was associated with epigenetic changes in clock genes (Zhu *et al.* 2011, Bhatti *et al.* 2015, Samulin Erdem *et al.* 2017b, see Section 6.3.2, Table 6-2).

Table 2-4. Field studies of clock gene expression in shift workers

Study	Population	Methods: timing	Results	Comments
Bracci *et al.* 2013 Italy (2011)	National Health Service hospital wards; 184 nurses Premenopausal ≥ 2 yr 31 rotating NSW; 31 DSW ≥ 48 night-shifts/yr	*BMAL1, NPAS2, CRY1, CRY2, PER2, PER3,* and *REVERBa* Blood 7:00 AM at the beginning of the day shift or end of night shift	No association in adjusted analyses; ↑ *PER2* and *PER3* in NSW vs. DSW in crude analyses	Rapid rotating clockwise: day, evening, night, off, off Adjusted for potential confounders
Bracci *et al.* 2014 Italy (2012)	National Health Service hospital wards; 184 nurses 60 rotating NSW; 56 DSW Premenopausal; ≥ 2 yr Assigned for ≥ 2 yr for ≥ 60 night-shifts/yr with no schedule breaks in last 6 months	*BMAL1, CLOCK, NPAS2, CRY1, CRY2, PER1, PER2, PER3,* and *REVERBα* mRNA Blood Beginning of morning shift after a regular night sleep on a day off	NSW vs. DSW ↑ *BMAL1, CLOCK, NPAS2, PER1* and *PER2, REVERBα* ↓ *CRY1, CRY2,* and *PER3*	Rapid rotating clockwise: day, evening, night, off, off Adjusted for potential confounders
Bracci *et al.* 2016 Italy (2012)	National Health Service hospital wards; 184 nurses 23 rotating NSW; 25 DSW Premenopausal; ≥ 2 yr Assigned for ≥ 2 yr for ≥ 60 night-shifts/yr with no schedule breaks in last 6 months	*PER2* mRNA Saliva and pubic hair follicle cells Working day after a day off 6:00 AM, 9:00 AM, 3:00 PM, 8:00 PM, 4:00 AM	NSW vs. DSW ↓ *PER2* at 8:00 AM (maximum value); no significant differences at other times ↓ 24-hr variations of *PER2* expression	Rapid rotating clockwise: day, evening, night, off, off Significant differences in cortisol and temperature profiles but not melatonin level
Reszka *et al.* 2013 Poland (2008–2010)	184 nurses and midwives who currently work day or rotating shift (aged 40–60 yr) 92 current NSW and 92 current DSW	*BMAL1, CLOCK, CRY1, CRY2, PER1, PER2,* and *PER3* Blood morning after night work (average	↑ *PER1* Current NSW vs. DSW > 15-yr NSW vs. DSW	38% of DSW had worked nights for ≥ 15 yr; average 7.3 yr since quitting DSW Large inter-individual differences *PER2* and *PER 3* down regulated in late vs. early morning

Study	Population	Methods: timing	Results	Comments
	All workers had previously worked rotating NSW	7:15 AM) or before day work (average 8:30 AM)	Lifetime duration of night shift work among NSW but not DSW	Adjusted for potential confounders and sample time
Fang *et al.* 2015b	Crossover study 15 shift workers (aged 21–34 yr) ≥ 7 days on floating night shift rotation	*PER2, NR1D* mRNA Blood: Before (6:00 PM) and after (8:00 AM) night shift Blood: Before (8:00 AM), during (1:00 PM), and after (6:00 PM) day shift	NSW vs. DSW ↑ *PER2* in evening	Shifts effects Day shift: *PER2* higher in the morning than in the evening Night shift: *PER2* higher in the evening than the morning

DSW = day shift worker; hr = hour; NSW = night shift worker; yr = year.

2.3.2 Experimental animal studies of simulated jet lag/simulated shift work and melatonin suppression and clock gene expression

This section reviews the principal findings from simulated jet lag, simulated shift work, and circadian disruption in experimental animals. Similar to studies of LAN exposure, simulated jet lag and shift work animal models indicate that these exposures show altered patterns of clock gene and hormone expression patterns that contribute to circadian disruption.

Jet lag is simulated by exposing experimental animals to an advance or delay in the daily timing of light followed by re-entrainment to the new light/dark cycle (Arble *et al.* 2010, Evans and Davidson 2013, LeGates *et al.* 2014). The magnitude and direction of the phase shift affects the rate and probability of re-entrainment and takes longer following phase advances than phase delays (Illnerová *et al.* 1989, Ruby *et al.* 1998, Reddy *et al.* 2002). Simulated shift work studies with experimental animals are highly variable in both protocol and measured endpoints.

The effect of jet lag on melatonin levels in animal models is not clear. Most studies used mice that are melatonin deficient, or melatonin levels were not measured (Filipski *et al.* 2004, Filipski *et al.* 2005, Filipski *et al.* 2006, Davidson *et al.* 2009, Lee *et al.* 2010, Wu *et al.* 2010, Wu *et al.* 2012, Kettner *et al.* 2015, Van Dycke *et al.* 2015, Kettner *et al.* 2016, Papagiannakopoulos *et al.* 2016). One study reported that jet-lagged mice showed altered temporal profiles of melatonin and corticosterone levels, although their overall levels throughout the day did not reach statistical significance (Iwamoto *et al.* 2014). No shift work models were identified that measured melatonin secretion patterns.

Clock gene expression rhythms in the SCN and peripheral tissues were altered in most experimental animal studies of acute or chronic jet lag or simulated shift work (Table 2-5). As with LAN studies, the genes most frequently studied were *Clock*, *Bmal1*, *Per1*, *Per2*, and *Cry1*. These studies show that clock genes in the SCN and peripheral tissues are differentially affected, re-entrain to the altered light-dark cycle at different rates, and re-entrainment is generally more difficult after phase advance than phase delay (Haus and Smolensky 2013). Thus, circadian disruption results in differential re-entrainment times of clock genes in the SCN and peripheral tissues following jet lag leads to transient desynchronization during periods where some tissues are re-entrained while others are not (Arble *et al.* 2010, Haus and Smolensky 2013). Some cells and tissues may take several weeks to fully re-entrain (Haus and Smolensky 2013). One study also reported that chronic jet lag altered clock gene expression in mouse lung in a sexually dimorphic manner (Hadden *et al.* 2012). Another study in rats reported that chronic shift-lag altered *Bmal1* and *Per2* gene and protein expression patterns in natural killer (NK) cells and that these alterations were correlated with suppressed NK cytolytic activity (Logan *et al.* 2012).

Studies of simulated shift work in male Wistar rats reported that PER1 and PER2 protein expression was not altered in the SCN (Table 2-5) (Salgado-Delgado *et al.* 2008, Salgado-Delgado *et al.* 2010). However, forced activity during the normal rest phase induced internal circadian gene desynchrony within the hypothalamus and liver and uncoupled metabolic functions from the SCN (Salgado-Delgado *et al.* 2010, Salgado-Delgado *et al.* 2013). Female Copenhagen rats exposed to a chronic jet lag protocol showed disrupted expression of *Per2* and DNA damage-response genes (Fang *et al.* 2017). Other studies showed that simulated chronic jet lag efficiently suppressed expression of *Bmal1* and *Per2* mRNAs in brown adipose tissue (Lee *et*

al. 2010), PER2, CRY1, and BMAL1 proteins in white adipose tissue (Kettner *et al.* 2015), and *Bmal1*, *Per1*, *Per2*, *Clock*, *Cry1*, and *Rev-erbα* mRNAs and BMAL1, CRY1, and PER2 proteins in livers of wild-type C57BL6/J mice (Kettner *et al.* 2016).

Table 2-5. Effects of simulated shift work or jet lag exposure on clock gene expression in experimental animals

Reference	Species (sex)	Exposure	Clock gene(s)/ proteins Tissue(s)	Results
Reddy *et al.* 2002	CD1 mice (M)	12:12 LD: C 6-hr phase advance 6-hr phase delay	*Per1, Per2, Cry1* SCN	Phase advance *Per1, Per2*: increased rapidly day 1, then declined to control levels after 2–3 hr *Cry1*: Not acutely affected Days 3–8: dissociation of *Per* and *Cry1* gene expression due to rapid entrainment of *Per* to the new photoschedule and slower entrainment of *Cry* Phase delay *Per* and *Cry* rhythms entrain rapidly (within 2 cycles in parallel with activity-rest cycle)
Yamazaki *et al.* 2000	Transgenic rat (mouse *Per1* promoter linked to luciferase reporter)	12:12 LD: C 6- and 9-hr phase advance 6- and 9-hr phase delay (Only SCN and skeletal muscle examined after 9-hr shifts)	*mPer1* transgene SCN, liver, skeletal muscle, lung	Phase advance (6 hr) SCN: entrained after first cycle Muscle, lung: arrhythmic or disrupted after first cycle, entrained after sixth cycle Liver: Shifted 2 hr after first cycle, entrained by sixth cycle Phase delay (6 hr) SCN: entrained after first cycle Muscle, lung: shifted 4 hr after first cycle, entrained after sixth cycle Liver: arrhythmic or unshifted after first cycle, shifted 3.5 hr after sixth cycle Phase advance (9 hr) SCN: entrained after first cycle Muscle: arrhythmic after first cycle Phase delay (9 hr) SCN: entrained after first cycle Muscle: shifted 3 hr after first cycle

Reference	Species (sex)	Exposure	Clock gene(s)/ proteins Tissue(s)	Results
Davidson *et al.* 2009	*mPer2*^{LUC} knock-in mice (M/F)	12:12 LD: C 6-hr phase advance	*mPer2*	SCN: partial shift on day 1 and entrained by day 3; however, varies by subregion. SCN shown to have population of fast-shifting cells that are more prevalent in the ventral aspect Thymus, lung: entrained by day 3 Esophagus: partial shift by day 3, entrained by day 5–8 Spleen: No shift by day 3, entrained by day 5 Full resynchronization of the SCN and peripheral tissues after 8 days
Iwamoto *et al.* 2014	CBA/N mice (M)	12:12 LD: C 8-hr phase advance every 2 days for 10 days All mice transferred to continuous dark schedule for 3 days prior to sacrifice	*Clock, Bmal1, Per1, Per2, Cry1* SCN, liver	SCN: temporal profiles of all clock genes were altered, acrophases delayed by 5.5 to 9 hr, and peak levels of *Per1* and *Per2* were 65% of controls Liver: significant interaction between lighting conditions and time in expression of all clock genes, acrophases delayed by 7 to 11.2 hr, *Per1* and *Per2* increased, *Clock* suppressed
Hadden *et al.* 2012	C57BL6J mice (M/F)	12:12 LD: C 8-hr phase advance every 2 days for 4 wk	*Clock, Bmal1, Per1, Per2, Cry1, Rev-erbα* Lung	Males: *Clock* decreased, *Per2* and *Rev-erbα* increased Females: *Bmal1* and *Rev-erbα* decreased, *Per2* and *Cry2* increased. *Per2* expression was higher in females than in males Overall, all clock genes showed a higher coefficient of variation in chronic jet lag groups of both sexes
Lee *et al.* 2010	C57BL6J mice (M/F)	12:12 LD: C 8-hr phase advance every Monday followed by 8-hr phase delay every Thursday for 8 wk	*Bmal1*, *Per2* Brown adipose tissue	Complete suppression for both *Bmal1* and *Per2* mRNAs
Kettner *et al.* 2015	C57BL6J mice (M)	12:12 LD: C 8-hr phase advance every Monday followed by 8-hr phase delay every Thursday for 8 wk	BMAL1, PER2, CRY1 White adipose tissue	Complete suppression of both PER2 and BMAL1 protein expression and significantly decreased CRY1 protein expression and abolished rhythmic expression

Reference	Species (sex)	Exposure	Clock gene(s)/ proteins Tissue(s)	Results
Kettner *et al.* 2016	C57BL6J mice (M)	12:12 LD: C 8-hr phase advance every Monday followed by 8 hr phase delay every Thursday for 8 or 26 wk	*Clock, Bmal1, Per1, Per2, Cry1, Rev-erbα* BMAL1, PER2, CRY1 Liver	Decreased and arrhythmic expression of Bmal1, Clock, Cry1, Rev-erbα expression. Decreased and shifted Per1 and Per2 expression rhythm. Completely suppressed PER2 and BMAL1 protein expression and significantly decreased CRY1 protein expression and abolished rhythmic expression
Logan *et al.* 2012	F344 rats (M)	12L:12D: C 6-hr phase advance every 2 days for 10 shifts	*Bmal1, Per2* BMAL1, PER2 Natural killer cells (spleen)	Circadian expression patterns of both clock genes and proteins altered, acrophases shifted for all except PER2
Salgado-Delgado *et al.* 2008	Wistar rats (M)	12:12 LD: C Simulated night work (forced activity for 8 hr during the light phase/normal sleep phase)	PER1, PER2 SCN	PER1 and PER2 proteins remained in phase with the LD cycle
Salgado-Delgado *et al.* 2010	Wistar rats (M)	12:12 LD: C Simulated night work (forced activity for 8 hr during the light phase)	PER1 SCN, arcuate and dorsomedial nuclei of hypothalamus	SCN: no effect Arcuate and dorsomedial nuclei: PER1 rhythms were shifted and uncoupled from the SCN
Salgado-Delgado *et al.* 2013	Wistar rats (M)	12:12 LD: C Simulated night work (active for 8 r during the light phase)	*Clock, Bmal1, Per1, Per2* Liver	*Clock, Bmal1,* and *Per1*: acrophase inverted *Per2*: lost rhythm
Fang *et al.* 2017	Copenhagen rats (F)	12:12 LD: C Simulated jet lag (advanced light onset by 12 hr for 7 days; day of shift, 24-hr L and day of shift back to regular LD cycle, 24-hr D	Per2 Mammary glands	Disrupted rhythmic expression of Per2 and reduced rhythmic expression of most DNA-damage response genes

C = control; F = female; M = male.

2.3.3 Behavioral modifications: non-photic zeitgebers

Overall, behavioral modification studies show that feeding schedules are potent zeitgebers that uncouple the daily metabolic and clock gene oscillations in peripheral tissues from the SCN and can override the influence of the SCN on the peripheral oscillators (Damiola *et al.* 2000, Escobar

et al. 2007, Hoogerwerf *et al.* 2007, Asher and Sassone-Corsi 2015). High-fat diets also modified circadian synchronization to light after a simulated jet-lag test (Mendoza *et al.* 2008). Nocturnal rats that were trained to perform a task requiring sustained attention during the day produced a powerful and reversible diurnal activity pattern that was maintained after a six-hour phase advance in the light cycle (Gritton *et al.* 2009). The SCN, in turn, influences attentional processing via modulation of circadian sleep/wake/arousal states. These data suggest that the forebrain structures involved in attention and the SCN likely interact in a bi-directional manner. Finally, rat models of night shift work show an altered temporal pattern of food intake and a shift in the diurnal rhythms in the hypothalamic structures associated with metabolic functions and sleep regulation (Salgado-Delgado *et al.* 2008, Salgado-Delgado *et al.* 2010). However, SCN activity remained in phase with the light-dark cycle. The physiological and behavioral consequences observed in rats are similar to those observed in night shift workers (Salgado-Delgado *et al.* 2008), thus, these data suggest that the combination of working and eating at night are important factors leading to internal circadian desynchronization observed in shift workers (see Section 6 for a discussion of meal timing as a potential mechanism for shift work carcinogenicity).

2.4 Summary

Although modern electric lighting practices have clearly benefited humankind, electricity also has facilitated a shift in the natural diurnal human activity patterns towards a more nocturnal lifestyle, thus effectively forcing a misalignment with individual's internal circadian clocks (i.e., circadian disruption). The extent of circadian disruption among night shift workers or people exposed to LAN can be evaluated using biomarkers such as melatonin, cortisol, body temperature, and clock gene expression. In normally entrained individuals, plasma melatonin levels are low during the day and start to increase in the evening, peak in the middle of the biological night, and then decrease rapidly. The peak of melatonin levels is before the nadir of the core body temperature rhythm (early morning) and approximately 4 to 6 hours before the crest of the cortisol rhythm.

LAN of sufficient intensity, duration, applicable wavelength, and appropriate timing can affect the circadian system. Circadian disruption is often measured by the timing and amount of nocturnal melatonin. Nighttime melatonin suppression can occur after exposure to light with wavelengths from 420 to 600 nm; however, short-wavelength or "blue" light wavelengths are more effective than longer wavelengths in reducing daily melatonin production. Modeling studies suggest that a potential threshold for melatonin suppression would be ~30 lux of white light at the cornea for 60 minutes. In contrast to polychromatic light, under controlled conditions exposure to less than 1 lux of monochromatic blue light has been shown to suppress melatonin. In addition, the total light experience and light exposure during the daytime as well as individual sensitivities can modify the circadian response to light. Children have been shown to be more sensitive to LAN-induced melatonin suppression than adults.

Studies of shift workers provide strong evidence that night shift work suppresses or disrupts nocturnal melatonin production and thus is associated with circadian disruption. Some studies have found that more "extensive" night work (i.e., higher frequency or longer duration) has a greater effect on suppressing melatonin levels. Studies evaluating the relationship between measured light and melatonin levels among shift workers or in simulated shift work experiments

provide some evidence that light may contribute but is probably not the only factor related to melatonin suppression. Night shift workers also complain about reduced sleep quality, shortened sleep periods, and insomnia, especially following a night shift. Overall, the majority of permanent shift workers do not appear to tolerate shift work or adapt to shift work as evidenced by lack of entrainment of core body temperature, cortisol levels, and melatonin to a night schedule (i.e., cortisol continues to peak in the early morning and melatonin continues to peak at night regardless of the chronological sleep time). Sleep strategy, age, chronotype, and genetic susceptibility may influence adaptation to night shift work.

Studies in shift workers and experimental studies in humans provide some evidence that shift work and exposure to LAN can alter clock gene expression; however, the database is limited by small numbers of studies, differences in the genes evaluated and types of samples collected across studies. Sample timing and methodology appear to be key factors in interpreting the findings. Epigenetic mechanisms may be responsible for changes in clock gene expression; several studies found that long-term shift work was associated with epigenetic changes in clock genes.

Many studies of circadian disruption in animals used dim LAN, intermittent LAN, or constant light protocols as surrogates for LAN. These studies show a wide range of psychological effects and physiological biomarkers of LAN-induced circadian disruption including melatonin suppression, and altered clock gene expression. Similar to studies of LAN exposure, simulated jet lag and shift work animal models indicate that these exposures show altered patterns of clock gene that contribute to circadian disruption. Overall, behavioral modification studies show that feeding schedules are potent zeitgebers that uncouple the daily metabolic and clock gene oscillations in peripheral tissues from the SCN and can override the influence of the SCN on the peripheral oscillators.

3 Human Female Breast Cancer Studies

Introduction

The cancer hazard evaluation of electric lighting focused primarily on two exposure scenarios involving electric lighting practices that may cause circadian disruption: (1) night shift work, including permanent night shifts or rotating night and day shifts, and (2) exposure to LAN, such as indoor light in the sleeping area or outdoor environmental lighting. Also evaluated were studies of travel across time zones (transmeridian travel), which can cause circadian disruption as well. All three of these scenarios were evaluated with respect to the risk of breast cancer, the major tissue site of interest. Studies of the relationship between night shift work and cancer at other tissue sites are described in Section 4.

Details of the procedures (such as databases and literature search terms and screening methods) used to identify and select the primary studies and supporting literature for the evaluation of human female breast cancer (hereinafter referred to as "breast cancer") in relation to these exposure scenarios are provided in Appendix A (literature search strings) and the RoC protocol (NTP 2018). Primary epidemiology studies were considered for the cancer evaluation if the study (1) was peer reviewed, (2) provided risk estimates (or sufficient information to calculate risk estimates) specifically for night work, exposure to indoor or outdoor environmental LAN, or transmeridian flights, and (3) provided exposure-specific analyses for night work, indoor or outdoor environmental LAN, or transmeridian flights at an individual level. Studies of workers that provided job title alone and no further specification of shifts worked (e.g., nurses) were not included. Outdoor LAN studies had to provide individual-level exposure (address-linked exposure data) and outcome data. Flight studies were chosen based upon whether they provided risk estimates for proxy measures of circadian disruption, such as numbers of transatlantic flights or computed numbers of time zones crossed.

This section begins with a brief overview of the epidemiology of breast cancer (Section 3.1) and a discussion of the key issues regarding each exposure scenario. Sections 3.2 through 3.4 assess the available epidemiologic literature for night work, light at night, and transmeridian travel in relation to breast cancer. Each of these sections begins with a discussion of the key issues to be addressed in the evaluation for that exposure scenario.

- Overview of the study methods and characteristics
- Evaluation of study quality
- Breast cancer hazard assessment: Synthesis of the evidence across studies

Section 3.5 concludes with NTP's preliminary level of evidence conclusion.

3.1 Overview of breast cancer epidemiology

Breast cancer rates have been rising in the United States since 1975, when rates were 103 per 100,000 women. In the past 10 years rates increased by 0.3% per year and in 2018, the age-adjusted annual breast cancer rate was reported to be 126/100,000 women (SEER 2018 data for 2011 to 2015). Now, female breast cancer is the most common cancer in the United States, and accounts for 15% of all new U.S. cancer cases. The mortality rate is lower — 20.9/100,000 women — than the incidence rate and the five-year survival rate is 89.7%. Rates in U.S. young

women vary according to race and ethnicity, with black women under the age of 35 having twice the incidence of invasive breast cancer and three times the breast cancer mortality of young white women (Shavers *et al.* 2003, Anders *et al.* 2009).

Incidence rates in European countries, where most of the cohort studies were conducted, were somewhat lower (IARC 2012), and mortality rates were similar. For example, in the European Union, breast cancer incidence per 100,000 women was 106.6, and mortality was 22.4.

Early-onset breast cancer and postmenopausal breast cancer differ with respect to risk factors and types of tumors. Breast tissue may be more susceptible to environmental exposures before the first full-term pregnancy or at younger ages; one explanation is that full-term pregnancy causes terminal differentiation of many cells, thereby reducing the number of stem cells at risk for malignant transformation (Institute of Medicine 2012).

3.2 Night shift work

None of the shift-work studies measured circadian disruption directly; however, certain working practices such as working night shifts for longer durations or more frequency may be surrogates for night work related to circadian disruption. Another issue to consider was the age at which women started night shift work as timing of exposure during susceptible hormonal stages has been shown to be important in breast cancer etiology. In general, the adequacy to evaluate different surrogates was reflected in the ratings of study utility and was systematically considered in the assessments of the evidence from the individual studies and across studies. Other key issues that were systematically evaluated were potential effect modifiers, such as chronotype (individual sleep-propensity rhythm). In addition, the type of breast cancer as defined by receptor status (e.g., positive or negative estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]) was evaluated.

Twenty-six studies of breast cancer and shift work in independent populations satisfying the inclusion criteria were identified. These included twelve independent cohort studies (Jørgensen *et al.* 2017, Vistisen *et al.* 2017, Wegrzyn *et al.* 2017 [two separate cohorts using somewhat similar methods — NHS and NHS2], Travis *et al.* 2016 [three separate cohorts — U.K. Biobank, Epic Oxford, and Million Women], Schwartzbaum *et al.* 2007, Pronk *et al.* 2010, Knutsson *et al.* 2013, Koppes *et al.* 2014, Åkerstedt *et al.* 2015); five nested case-control studies (Tynes *et al.* 1996, Lie *et al.* 2011, Hansen and Lassen 2012, Hansen and Stevens 2012, Li *et al.* 2015); and eight population-based case-control studies (Davis *et al.* 2001b, Hansen 2001, O'Leary *et al.* 2006, Pesch *et al.* 2010, Fritschi *et al.* 2013, Grundy *et al.* 2013a, Menegaux *et al.* 2013, Papantoniou *et al.* 2015a); and one hospital-based case-control study (Wang *et al.* 2015a). Gu *et al.* (2015) reported on breast cancer mortality within the NHS cohort and thus is not counted as a separate study. In addition, a separate analysis pooling recoded data from five of the case-control studies was included in this assessment, as this analysis provided additional information beyond that reported in the individual studies (Cordina-Duverger *et al.* 2018). Nested case-control studies that were based on data recorded independently in administrative records about individuals who were later classified as cases and controls were grouped with the cohort studies (i.e., Tynes *et al.* 1996, Li *et al.* 2015), whereas those that collected data retrospectively from persons with known cancer diagnoses were grouped with the case-control studies (i.e., Lie *et al.* 2011, Hansen and Lassen 2012, Hansen and Stevens 2012). A pilot case-control study of working at night and breast cancer risk in India was not included in the evaluation because of

inadequate reporting of study methods especially for assessment of night shift work (Datta *et al.* 2014). Studies are listed in Tables 3-1 (cohort studies) and 3-3 (case-control studies) from most recent to oldest publication.

3.2.1 Cohort studies and relevant nested case-control

Overview of study methods and characteristics

Twelve independent cohort studies of breast cancer and shift work and two nested case-control studies (Tynes *et al.* 1996, Li *et al.* 2015) for which data were collected on exposure prior to breast cancer diagnosis (Table 3-1, listed in reverse chronological order) are available for evaluation. The NHS and NHS2 cohorts, though independent, were considered together as one cohort in the quality evaluation, because the methods were similar, although not identical, and because considered together, they allowed analysis by age starting night work as the two cohorts differ by age of participants at baseline. Any differences in the quality assessment for a specific type of bias or sensitivity are noted below. Table 3-1 includes details only from the latest update of a study population or the most comprehensive report on a population, along with citations of related previous publications. Detailed data on study design, methods, and findings were systematically extracted as described in the study protocol. Seven additional publications on these populations were identified that contained relevant analyses or information used in the evaluation.

Table 3-1. Cohort studies of breast cancer and shift work

Reference	Population	Outcome and sources(s)	Exposure assessment and information
Jørgensen *et al.* 2017	**Danish Nurses Organization** 28,731 currently working nurses Baseline 1993; members added in 1999 Older age: ≥ 44 yr at baseline	Breast cancer mortality Danish Register of Causes of Death	Self-administered questionnaire Metrics: currently working rotating shifts, fixed nights, fixed evenings 22% worked rotating shifts and 5.4% fixed nights
Vistisen *et al.* 2017	**Danish Payroll Data Cohort** 55,381 women 2007–2013 enrolled Younger age: 39.4/35.5 yr average age total/inception	Breast cancer incidence; receptor status Danish Cancer Registry	Danish Working Hour payroll data Metrics: ever/never, timing of night work Night work: workers with ≥ 1 yr for ≥ 3 hr of work only between midnight and 5:00 AM 41.3% ever night work

Reference	Population	Outcome and sources(s)	Exposure assessment and information
Wegrzyn *et al.* 2017 preceded by (Schernhammer *et al.* 2001, Schernhammer *et al.* 2006b)	**U.S. Nurses Health Study Cohorts (NHS and NHS2)** 78,516 (NHS) 114,559 (NHS2) Enrolled 1976 (NHS) 1989 (NHS2) Older age: 28% premenopausal (NHS) Younger age: 82% premenopausal (NHS2)	Breast cancer incidence; receptor status Self-report, proxy, postal system, or National Death Index (NDI), 93% validated with pathology reports	Self-administered mailed questionnaire Metrics: ever, duration of rotating night work; for NHS2, both baseline and follow-up cumulative duration Night work: no. years working rotating shifts ≥ 3/mo 60%/62% ever rotating shifts (NHS/NHS2)
Gu *et al.* 2015	**Nurses Health Study (NHS)** 74,862 nurses, 17 locations Enrolled 1976, questionnaire in 1988 Older age: 6% premenopausal in 1988	Breast cancer deaths Next of kin and postal authorities, NDI; physician review of medical records and death certificates	Self-administered mailed questionnaire Metrics: ever, duration of rotating night work Night work: worked rotating shifts ≥ 3/mo 59% rotating shift work
Travis *et al.* 2016	**U.K. Million Women Study** 522,246 women (general population) Enrolled 1996–2001 Older age: average 68 yr	Breast cancer incidence NHS Central Registers incidence or death	Self-administered mailed questionnaire Metrics: ever/never, duration, recency, latency, and timing of night work Night work: midnight–6:00 AM, for ≥ 3 nights/mo 14% ever night work
Travis *et al.* 2016	**U.K. EPIC Oxford** 22,274 women (general population) Enrolled 1993–1999 Older age: median 58 yr at exposure assessment	Breast cancer incidence National Health Service (NHS) Central Registers invasive breast cancer incidence or death	Self-administered mailed questionnaire Metrics: ever/never, duration Night work: ≥ 1 yr and ≥ 1 night/mo or 12 nights/yr 14% ever night work
Travis *et al.* 2016	**U.K. Biobank Study** 251,045 women (general population) Enrolled 2006–2010 Older age: average 51 yr	Breast cancer incidence NHS Central Registers invasive breast cancer or death	In office touch-screen computerized questionnaire Metrics: current work at night; usually or always Night work: midnight–6:00 AM 3.6% current night work

Reference	Population	Outcome and sources(s)	Exposure assessment and information
Åkerstedt *et al.* 2015	**Swedish Twin Registry Cohort** 13,656 women (general population) Enrolled 1998–2003 Older age: 41–60 yr at enrollment	Breast cancer incidence Swedish Cancer Registry and Cause of Death Register	Computerized telephone interview Metrics: ever/never nights, duration of night work Night work: working hours that meant working nights "at least now and then" Overall: 25% ever worked nights; 2.4% worked nights ≥ 21 yr
Li *et al.* 2015	**Shanghai Textile Worker Cohort (nested case-control)** 267,400 active and retired textile employees at 551 companies 1,709 cases, 4,780 controls Enrolled 1989–1991 Older age: average 53.4 yr	Breast cancer incidence Factory, occupational and government records, Shanghai Cancer Registry; histologically confirmed by review of pathology reports or tissue slides	Trained interviewers researched company records (80%), interviewed supervisors (12%) or participant (8%); all jobs held in factory/textile industry Metrics: Frequency/intensity, duration, rotating nights, cumulative frequency; no permanent nights in population Night work: midnight–5:00 AM 67% ever nights; 33% ≥ 20 yr; 85% worked only 1–2 jobs during their tenure
Koppes *et al.* 2014	**Netherlands Labor Force Survey Cohort** 285,723 women (general population) Enrolled 1996–2009 Younger age: 85% < 50 yr	Breast cancer incidence Hospital admission	Labor force survey data questionnaire and computerized in-person interview Metrics: for current job, none, occasional, or regular; plus hr/wk worked within "occasional" and "regular" categories Night work: midnight–6:00 AM for paid jobs held ≥ 12 hours, current job only 10.4% occasional or regular night work
Knutsson *et al.* 2013	**Work, Lipids, and Fibrinogen Occupational Cohort** 4,036 women Enrolled 1992–1995, 1996–1997, 2000–2003 Younger age: 82% premenopausal	Breast cancer incidence Swedish Cancer Registry and cause of death registry	Self-administered mailed questionnaire Metrics: ever worked nights ascertained over 3 time periods Night work: 10:00 PM–6:00 AM or 6:00 PM–6:00 AM on ≥ 1 follow-up questionnaire 13.6% night shift work
Pronk *et al.* 2010	**Shanghai Women's Health Study** 73,049 women (general population) Enrolled 1996–2000 Older age: 26% premenopausal	Breast cancer incidence Shanghai Cancer Registry and Shanghai vital statistics database	JEM and in-person interview, all jobs held ≥ 1 yr Metrics: ever/never, frequency/intensity, duration Self report: ≥ 1 yr night work ≥ 3 nights/mo starting at 10:00 PM 44% JEM; 26% self-report

Reference	Population	Outcome and sources(s)	Exposure assessment and information
Schwartzbaum *et al.* 2007	**Swedish working women, register-based** 1,148,661 (general population) Working in 1960 and 1970 Younger age: 73% < 50 yr	Breast cancer incidence Swedish Cancer Registry and Cause of Death Register	JEM for industries considered shift work based on jobs worked ≥ 20 hr/wk held in 1960 and 1970 Metrics: ever worked in occupation-industry combination with 70% shift workers or worked in occupational-industry combo. with ≤ 30% shift workers 0.06% exposed
Tynes *et al.* 1996	**Norwegian radio and telegraph operators** 2,616 operators certified to work 1920–1980, working at sea 50 cases/259 controls Younger age: 58% < 50 yr	Breast cancer incidence Norway Cancer Registry	Company records: job histories for each ship NOS Metrics: duration, intensity Night work: "frequent presence in the radio room both at night and during the day" 63.7% ever night; 34% long duration of night work

JEM = job exposure matrix; NDI = National Death Index; NOS = not otherwise specified.

The cohorts were located in the United States, the United Kingdom, Sweden, Denmark, Norway, the Netherlands, and China. Eight studies were drawn from general populations (including seven studies of working women) selected from different geographical locations for the purpose of studying various environmental factors (Schwartzbaum *et al.* 2007, Pronk *et al.* 2010, Knutsson *et al.* 2013, Koppes *et al.* 2014, Åkerstedt *et al.* 2015, Travis *et al.* 2016). Four cohorts consisted of nurses or health professionals: NHS, NHS2 (Gu *et al.* 2015, Wegrzyn *et al.* 2017), the Danish nurses cohort (Jørgensen *et al.* 2017), and the Danish Payroll Data cohort (Vistisen *et al.* 2017). Other cohorts included members of specific occupations, such as textile workers (Li *et al.* 2015) and radio and telegraph workers (Tynes *et al.* 1996).

While the earliest study enrollment began in 1961 (Tynes *et al.* 1996), women may have reported night work three or more decades earlier, dating this exposure as early as the 1930's. Typical shift-work schedules have changed considerably over this period (see Section 1). The proportion of the female population exposed to night work varied considerably, from 0.06% (Schwartzbaum *et al.* 2007) to 67% of women ever working nights (Li *et al.* 2015); general cohort studies of specific occupations (e.g., Tynes *et al.* 1996, Pronk *et al.* 2010, Li *et al.* 2015) had a higher proportion of night shift workers compared to population-based cohorts or case-control studies.

Evaluation of study quality

A detailed evaluation of the quality of the shift work cohort studies is provided in Appendix B, Table B-1. The most important issues bearing on the overall quality of the cohort studies were the potential for selection bias, exposure misclassification, and sensitivity.

Selection bias

The potential for selection bias in these studies ranged from low to high, with concerns focused mainly on potential healthy-worker survivor bias, completeness of follow-up, or left-truncation

bias. In general, incomplete follow-up, if related to shift work, can introduce bias in either direction; left truncation is likely to bias results towards the null. In studies of shift work, the age range of the population can indicate the severity of survivor bias, with studies having the oldest populations at enrollment being most susceptible. Individuals who can adapt to night work are more likely to stay longer in jobs requiring night work, while those who cannot adapt or who become ill from night work may die, leave employment, or change to day shifts. In many occupations, night work is common early during a career (e.g., nurses) and less common as people continue to work and graduate to day shifts. Gu *et al.* (2015), reporting on breast cancer and night work in the NHS cohort, indicated that much of the follow-up of the older NHS cohort of surviving nurses was accrued at midlife or around retirement of these nurses; the percentage of nurses working rotating night shifts declined from 40% in their early 20s to less than 5% after age 45, with only very few women (< 2%) starting night shifts at midlife or later.

The age ranges represented in the cohort studies varied, with implications for consideration of left-truncation. The oldest cohorts included primarily postmenopausal women (Pronk *et al.* 2010, Travis *et al.* 2016, Wegrzyn *et al.* 2017 [NHS], Jørgensen *et al.* 2017) and the youngest cohorts included primarily premenopausal women (Tynes *et al.* 1996, Knutsson *et al.* 2013, Koppes *et al.* 2014, Vistisen *et al.* 2017, Wegrzyn *et al.* 2017, [NHS2]. While the older NHS cohort would likely be subject to left-truncation, the younger NHS cohort would not; considered together they highlight issues of how this selection bias can operate. Thus, for this latter reason we considered the studies together. The Shanghai textile workers, not an older cohort *per se*, could be considered a "survivor cohort," as the population consisted of a high percentage of ever night workers (67%), with 33% having worked nights for at least 20 years (Li *et al.* 2015). The remaining populations fell into an intermediate age range. The Vistisen *et al.* (2017) study of a relatively young population of health professionals likely suffered from left-truncation bias, as well as potentially from other selection biases. Past data on this cohort were not available, so an inception cohort was formed to address the potential magnitude of this bias; however, the latter subcohort was on average 35.5 years of age, suggesting that these women would have worked prior to the specified analytic washout period. Differences in education and parity between the overall and inception cohorts suggested that other selection factors also might have been operating. The Knutsson *et al.* (2013) study was created from two subcohorts of workers with very low follow-up rates. Insufficient information was presented to determine whether selection factors might have been operating in ways that could have biased the results from this study. In addition, the Knutsson study reported 47% loss to follow-up over three follow-up periods.

Exposure misclassification

In general, the potential for bias in exposure assessment was rated by integrating three factors: (1) how night work was initially defined, (2) the quality of the measurements, and (3) whether the study included one or more metrics that could differentiate between the subjects with the more persistent night shift working history from those who had less intense night shift working history. In general, concern was greater about non-differential exposure classification than about differential exposure misclassification, with the bias most likely in the direction of underestimating the risk of breast cancer due to night shift work. The risk of exposure assessment bias was considered to be moderate or low in six studies and high in three studies; in four studies, the exposure assessment was considered to be inadequate.

Definitions of night work. Definitions of "exposed" and "unexposed" varied across the cohort studies making exposure difficult to compare across studies. Based on the conditions in Denmark, where hospital nurses have a tradition of working very regular shifts (7:00 AM to 3:00 PM, 3:00 PM to 11:00 PM, or 11:00 PM to 7:00 AM), Garde *et al.* (2016) found the most agreement and least potential misclassification among studies by using a definition of night work that specified a minimum number of hours of work during biological night (e.g., between midnight and 5:00 AM) or limited the definition of biological night to a narrow range of hours (e.g., any time between 1:00 AM and 4:00 AM). Half of the cohort studies defined night work using a minimum number of hours during the biological night (Schwartzbaum *et al.* 2007, Koppes *et al.* 2014, Li *et al.* 2015, Travis *et al.* 2016 [Million Women Study and UK Biobank Cohort], Vistisen *et al.* 2017), whereas two studies required respondents to provide start and end times for work periods (Pronk *et al.* 2010, Knutsson *et al.* 2013). The remaining three studies did not specify which hours in the night were worked (Åkerstedt *et al.* 2015, Travis *et al.* 2016 [UK EPIC Oxford], Wegrzyn *et al.* 2017). Some of the definitions required that the "exposed" women work a minimum number of nights or rotating shifts in a given time period, e.g., at least 3 nights per month in Pronk *et al.* (2010), Travis *et al*. (2016), and Wegrzyn *et al.* 2017) Million Women Study or at least 1 night per month in the Travis *et al.* (2016) EPIC Oxford Cohort. These differences affected the meaning of the estimates derived from these studies, as women working 3 or more nights per month could be more "exposed" than those working only 1 or more nights per month. In five of the cohort studies reporting a minimum exposure time, at least one year of night work was required for a woman to be considered "exposed." Three studies (Koppes *et al.* 2014, Åkerstedt *et al.* 2015, and the Travis *et al.* 2016 EPIC Oxford Study) used vague definitions with respect to both the hours worked during night shift and how often night shifts were worked (e.g., "occasionally," "worked nights at least now and then," or "regularly"), which would tend to bias the findings towards the null, underestimating the risk of breast cancer.

In studies with large proportions of women ever performing night work, the definition of "unexposed" is important. In particular, most nurses begin their careers working nights, as night shifts are often routinely assigned during training. Therefore, the small numbers of "unexposed" women in studies of nurses might not have been completely unexposed, which would tend to bias the results towards the null. Studies having the highest overall proportion of women ever performing night work or performing night work for many years included Tynes *et al.* (1996) (radio and telegraph operators, 63.7% exposed), Li *et al.* (2015) (textile workers, 67% exposed), and Wegzryn *et al.* (2017) (nurses, 60% exposed in NHS and 62% exposed in NHS2).

Quality of exposure measurements. Correct classification of exposure depends upon having night-work metrics based on information that allows night work to be linked to specific jobs during specific periods of time. Studies based on self-reported lifetime occupational histories or complete individual histories from administrative records were considered the most informative. Self-reported data can be susceptible to non-differential memory bias; questions about job-by-job histories that provide multiple prompts to help respondents remember, however, are superior to those asking more general questions. Furthermore, collection of such complete job-by-job data enables the examination of multiple exposure windows, including the earliest exposures to night work. Two studies reported on the adequacy of memory of shift work, using information from repeated surveys. Knutsson *et al.* (2013) found, based on an overall question about lifetime night

work, that night work was remembered well, whereas shifts without night work were remembered less well among those completing a baseline and two follow-up questionnaires. Travis *et al.* (2016) reported good agreement among a subset of participants who answered questions about shift work on two occasions, two months apart; 97.5% agreement was reported for ever shift work, and 96.2% agreement for duration of shift work.

Four of the cohort studies assessed exposure with a lifetime history method using questionnaires or interviews, querying all women who worked at least 1 or 3 nights per month (Pronk *et al.* 2010, Travis *et al.* 2016 [UK EPIC Oxford and Million Women Study], Wegrzyn *et al.* 2017). An advantage of the NHS2 cohort compared to the NHS cohort (Wegrzyn *et al.* 2017) was that rotating night shift was assessed at subsequent follow-up periods in addition to baseline.

Three studies (Koppes *et al.* 2014, Travis *et al.* 2016, [UK Biobank Study], Jørgensen *et al.* 2017) assessed exposure based exclusively on the current job and did not collect data on prior history of shift-work exposure, leading to the possibility that many "unexposed" women had actually been exposed. The exposure assessment for these three studies was considered uninformative, and they were excluded from the overall hazard evaluation.

Although administrative records (used in Tynes *et al.* 1996, Li *et al.* 2015, Vistisen *et al.* 2017) avoid memory bias associated with self-reported data, they are not without problems. In Li *et al.* (2015), factory-level shift-work information was linked to each study subject's work history data, but data on lifetime exposure in non-textile industry jobs were not available. In Tynes *et al.* (1996), the definition of "night work" was vague and did not provide sufficient detail for understanding how exposed and unexposed women differed from one another. Vistisen *et al.* (2017) based their exposure assessment on a database of complete administrative payroll records; however, the definition of the unexposed "day workers" (at least 3 hours of work between 6:00 AM and 8:00 PM) might have misclassified a small number of women into categories that were not consistent with biological day or night (Kolstad *et al.* 2017, Stevens 2017).

Three studies used a job exposure matrix (JEM) that classified occupations by percentage of work performed at night or day based on an external survey (Schwartzbaum *et al.* 2007, Pronk *et al.* 2010, Koppes *et al.* 2014). As JEMs used in these studies did not assess exposure on an individual level, but rather used external data sources that estimated night work based primarily on job titles, exposure misclassification was likely introduced. Pronk *et al.* (2010) also collected data on lifetime history of night work and reported that while the JEM classified 44% of the women as potentially working night shifts, self-reported questionnaire data classified only 26% of women as night workers, suggesting substantial exposure misclassification (overestimation of exposure) by the JEM method. In the national study of working women in Sweden (Schwartzbaum *et al.* 2007), only 0.06% of women were reported to be night workers, an extremely low estimate in a country with an estimated 10% to 20% female night workers, suggesting that this JEM severely misclassified (underestimated) night work.

Multiple exposure metrics and effect modifiers. Studies that included one or more metrics (e.g., duration, number of night shifts per time period, or timing of exposure) differentiating the most highly exposed from those with inconsequential exposure have the potential to elucidate the type of exposure with the most impact on risk; these studies therefore received higher exposure assessment ratings. Nine of the studies included metrics on the duration of shift work, and two

studies reported on number of night shifts per time-period (Pronk *et al.* 2010, Li *et al.* 2015). Schwartzbaum *et al.* (2007) reported night work at two censuses taken ten years apart.

Outcome misclassification

Gu *et al.* (2015) and Jorgensen *et al.* (2017) were studies of breast cancer mortality. Because breast cancer mortality is relatively low and survival high (as discussed above), it is unlikely to adequately reflect incidence, and such an analysis is likely to miss about 90% of cases having longer survival and later death, likely resulting in loss of statistical power to detect an effect. All other studies included incident breast cancer cases and with one exception had low or moderate risk of bias. Koppes *et al.* (2014) used hospital admission data which may lead to bias in estimates of incidence given differential access to medical treatment; in addition, their methods did not differentiate between prevalent and incident cases.

Potential confounding

As the presence of confounding can be assessed only after consideration of the results, the potential for bias resulting from inadequate inclusion of potential confounders in the analysis was assessed as part of the utility evaluation. The primary potential confounders specified in the protocol included occupational co-exposures, age, socioeconomic status or education, parity or age at first full-term pregnancy, and alcohol use. In the general population studies, occupational co-exposures were likely not of concern, as the numbers of participants across co-exposure categories were likely to be small. In the study of textile workers (Li *et al.* 2015) magnetic field exposure, which had been identified as a risk factor in a previous analysis of this cohort, was evaluated. Occupational co-exposures, such as ethylene oxide, were not considered in the NHS and NHS2 studies of nurses (Wegrzyn *et al.* 2017); however, such exposures could bias the effect away from the null if large numbers of nurses were exposed to such carcinogens in the course of their duties, as has been described in studies of exposures among nurses (e.g., EWG 2007). Meal timing was not measured and not controlled in any of the studies.

Another concern was the practice of adding variables to the models that were unrelated to night work or were in the causal pathway — e.g., age at menarche, body mass index (BMI), family history of breast cancer, and benign breast disease (Travis *et al.* 2017, Wegrzyn *et al.* 2017) — which could have the effect of biasing estimates towards the null; however, most studies included family history, BMI, and age at menarche in their analysis, with some studies including these in the final models. Studies that did not control for key potential confounding factors that could bias estimates away from the null included Koppes *et al.* (2014), who did not measure alcohol consumption, measured occupation as a proxy for socioeconomic status and education, and used the number of children in household as a proxy for parity, and Tynes *et al.* (1996) and Schwartzbaum *et al.* (2007), neither of which measured relevant potential confounders such as parity and alcohol use.

Sensitivity

Sensitivity to detect an effect was generally of major concern in the cohort studies due to a number of issues: (1) small numbers of cases among women with high exposure (level, duration, or number of night shifts per time-period) (Schwartzbaum *et al.* 2007, Pronk *et al.* 2010, Knutsson *et al.* 2013, Åkerstedt *et al.* 2015, Travis *et al.* 2016 [EPIC Oxford Study and UK Biobank Study]), (2) inadequate range in exposure levels or duration to allow evaluation of

exposure-response relationships (Schwartzbaum *et al.* 2007, Knutsson *et al.* 2013, Åkerstedt *et al.* 2015, Travis *et al.* 2016), (3) inadequate length of follow-up (Pronk *et al.* 2010, Åkerstedt *et al.* 2015, Travis *et al.* 2016, Vistisen *et al.* 2017), or (4) older populations with potentially inappropriate windows of exposure (Pronk *et al.* 2010, Åkerstedt *et al.* 2015 [NHS], Travis *et al.* 2016 [Million Women Study]).

Studies with larger numbers of cases in the highest exposure category, and therefore greater sensitivity, included the NHS cohort (Wegrzyn *et al.* 2017), the Million Women study (Travis *et al.* 2016), and the Shanghai Women's Health Study (Pronk *et al.* 2010). However, lower sensitivity was associated with the studies by Åkerstedt *et al.* (2015), Pronk *et al.* (2010), Travis *et al.* (2016) (all cohorts) and Vistisen *et al.* (2017) which had short mean follow-up times of 3.1 to 10 years. Only three of the cohorts (Schwartzbaum *et al.* 2007, Knutsson *et al.* 2013, Wegrzyn *et al.* 2017) had longer mean follow-up times (12.4, 19, and 24 years, respectively).

Overall utility of the cohort studies

Table 3-2 summarizes the results of the bias and quality evaluation of cohort studies of breast cancer and shift work. Overall, nine of the cohort studies had some utility for the cancer hazard assessment. Wegrzyn *et al.* (2017) was the most informative cohort study. Including data from the older and younger NHS cohorts (NHS and NHS2), together with the information provided by Gu *et al.* regarding attrition of older night workers in the NHS cohort, illustrates the bias from left truncation that can arise in older cohorts followed at late ages in studies of shiftwork, a bias that may be present in several of the other cohort studies. Three cohort studies had moderate utility for the evaluation (Knutsson *et al.* 2013, Li *et al.* 2015, Vistisen *et al.* 2017). The remaining six cohort studies had low utility to inform the cancer hazard evaluation, primarily because of limited exposure assessments, potential left-truncation bias due to older age at recruitment, and/or lower sensitivity.

Table 3-2. Summary of bias and quality evaluation: Cohort studies of shift work and breast cancer

Citation	Selection[a]	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility[b]
Vistisen *et al.* 2017	+	+	+++	++	+++	++	+	++
Wegrzyn *et al.* 2017 (NHS and NHS2)	+++	++	+++	++	+++	+++	++	+++
Jørgensen *et al.* 2017	+	0	++	++	++	+++	+	0
Travis *et al.* 2016								
Million Women Study	+	++	+++	++	++	++	+	+
Epic Oxford Study	++	++	+++	++	++	+	+	+
UK Biobank Study	+	0	+++	++	++	+	0	0
Åkerstedt *et al.* 2015	++	+	+++	++	+++	+++	+	+
Li *et al.* 2015 (nested)	++	++	+++	+	+++	+++	+	++
Koppes *et al.* 2014	+++	0	+	+	+++	+++	0	0
Knutsson *et al.* 2013	+	++	+++	+++	++	++	++	++
Pronk *et al.* 2010	++	++	+++	+++	++	++	+	+
Schwartzbaum *et al.* 2007	++	0	+++	+	++	+++	0	0
Tynes *et al.* 1996 (nested)	+++	+	+++	+	++	++	+	+

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

The studies by Jørgensen *et al.* (2017), Koppes *et al.* (2014), and Travis *et al.* (2016) (UK Biobank Study) were judged to have inadequate utility based on their exposure assessments, which were limited to the current job, with no prior history of night work exposure. That the cohorts investigated by Jørgensen *et al.* (2017) and Travis *et al.* (2016 UK Biobank Study) consisted mostly of older women made the omission of past jobs particularly problematic, as it is likely that many "unexposed" women had previous night work. In addition, the UK Biobank Study (Travis *et al.* 2016) and Koppes *et al.* (2014) used very short follow-up times, decreasing the studies' sensitivity to detect an effect. The study by Schwartzbaum *et al.* (2007) also was judged to have inadequate utility because of its poor exposure assessment, an underestimate of the proportion of the population exposed, lack of metrics other than night work at two time periods, and inadequate control for confounding. Therefore, these four studies were not included in the full hazard evaluation, which considered only the remaining nine cohort studies.

3.2.2 Case-control studies including relevant nested case-control studies

Overview of study methods and characteristics

Twelve case-control studies were included in the evaluation: nine case-control studies and three nested case-control studies assessing exposure after diagnosis (Lie *et al.* 2011, Hansen and Lassen 2012, Hansen and Stevens 2012) (Table 3-3). Most studies were conducted in Europe (Denmark, France, Spain, and Germany), and the rest were conducted in Canada, the United States, Western Australia, and Guangzhou, China. Eight of the twelve studies were general population studies, and one study was hospital based (Wang *et al.* 2015a). Two studies included only nurses (Lie *et al.* 2011, [the Norwegian Nurses cohort] , Hansen and Stevens 2012 [the Danish Nurses cohort), and one was a study of women in the military (Hansen and Lassen 2012). The numbers of case]s in these studies ranged from 141 (Hansen and Lassen 2012) to 7,035 (Hansen 2001), with most having between 660 and 1,700 cases. The proportion of control subjects working nights ranged from 4.6% (Hansen 2001) to 84.3% (Lie *et al.* 2011). The ages of the populations varied; the percentages of premenopausal case subjects ranged from 63% (Wang *et al.* 2015a) to 26% (Pesch *et al.* 2010) or 33% under the age of 50 (Hansen and Stevens 2012). Cordina-Duverger *et al.* (2018) pooled the results of five of these case-control studies (Pesch *et al.* 2010, Fritschi *et al.* 2013, Grundy *et al.* 2013a, Menegaux *et al.* 2013, Papantoniou *et al.* 2015a). Relevant highlights of the pooled analysis are mentioned in this section.

Table 3-3. Case-control studies of breast cancer and shift work

Reference	Population	Breast cancer incidence source(s)	Exposure assessment and information
Cordina-Duverger *et al.* 2018	**Pooled analysis of 5 case-control studies** Western Australia (BCEES), Canada (CBCS), France (CECILE), Germany (GENICA), and Spain (MCC-Spain)	Regional cancer registries (Canada, Australia) or major hospitals in study areas (France, Canada, Germany, Spain) Receptor status	In-person interview, all jobs held ≥ 6 mo (≥ 12 mo in Spain) Metrics: ever/never, duration of night work, night shift length, no. shifts/wk, no. night hours/wk, cumulative no. lifetime night shifts, years since last night shift, intensity by duration, intensity by night shift length, intensity by years since last night shift Night shift: working nights midnight–5:00 AM, and most extreme value for each metric 11.9% ever nights; 2.2% highest intensity of night work
Papantoniou *et al.* 2015a	**MCC-Spain study** Population-based study Enrolled 2008–2013 30% < 50 yr of age 1,708 cases 1,778 controls	Catchment-area hospitals Receptor status	In-person interview, all jobs held ≥ 1 yr Metrics: ever/never, frequency, duration, rotating, permanent night work Night shift: ≥ 1 year, midnight–6:00 AM for ≥ 3 times/mo (overnight, late evening [ending after midnight] and early morning [starting before 6:00 AM]) 13.3% ever nights; 5.9% ≥ 15 yr

Reference	Population	Breast cancer incidence source(s)	Exposure assessment and information
Wang *et al.* 2015a	**Guangzhou, China** Hospital-based study Enrolled 2010 and 2012 63% premenopausal 661 cases; 714 controls	Consecutively recruited recent cancer cases in two hospitals Receptor status	In-person interview, ever worked nights ≥ 6 mo ≥ 1 time/wk Metrics: ever/never; night work + sleep duration + daytime napping Night shift: ≥ 6 mo ≥ 1 time/wk, midnight–6:00 AM 37.6% ever nights
Fritschi *et al.* 2013, Fritschi *et al.* 2018	**BCEES study** Population-based Enrolled 2009–2011 30% premenopausal 1,202 cases; 1,785 controls	Western Australia Cancer Registry	Mailed questionnaire, and in-person interview for occupational questions, all jobs held ≥ 6 mo Metrics: ever/never, duration, phase shift Night shift: ≥ 6 mo, midnight–5:00 AM 21.3% ever nights among controls; 5.6% 20+ yr
Grundy *et al.* 2013a	**CBCS study** Population based Enrolled 2005–2010 35% premenopausal 1,134 cases; 1,179 controls	Vancouver BC - British Columbia Cancer Registry; Kingston, ON - Breast Assessment Program Receptor status	Self-administered questionnaire or telephone interview, all jobs ≥ 6 mo Metrics: duration, % evenings/nights (20%, 40%, 60%, 80%, 100% (permanent night shift work), receptor status Night shift: jobs with shifts from 11:00 PM–7:00 AM 34.4% ever nights; 2.5% 30+ yr
Menegaux *et al.* 2013 Cordina-Duverger *et al.* 2016 (receptor status)	**CECILE study** Population based Enrolled 2005–2007 31% < 50 yr of age 1,232 cases; 1,317 controls	Catchment-area hospitals Receptor status	In-person interview, all jobs ≥ 1 yr Metrics: ever/never, frequency/intensity, duration Night shift: ≥ 6 mo for ≥ 6 hr between 11:00 PM–5:00 AM 11.2% ever nights 3.6% ≥ 4+ yr for ≥ 3 nights/wk
Hansen and Lassen 2012	**Danish military workers** Nested case-control study Occupational cohort Enrolled 2005–2006 45%/56% premenopausal (day/night workers) (intermediate age) Cohort = 18,551 141 cases; 551 controls	Danish Cancer Registry	Self-administered mailed questionnaire, all jobs ≥ 1 yr Metrics: ever/never, duration, frequency, cumulative exposure. Night shift: respondents working 5:00 PM–9:00 AM for ≥ 1 yr (rotating and permanent nights) 29.4% ever worked nights; 8.4% worked ≥ 15 yr

Reference	Population	Breast cancer incidence source(s)	Exposure assessment and information
Hansen and Stevens 2012	**Danish female nurse study** Nested case-control study Enrolled 2002–2005 Older age: 33% < 50 yr Cohort = 58,091 267 cases; 1,035 controls	Danish Cancer Registry	Telephone interview, all jobs ≥ 1 yr Metrics: cumulative frequency, duration, rotating, permanent nights Night shift: respondents working after midnight for 8 hr for ≥ 1 yr (rotating and permanent nights) 77.8% ever nights; 12.5% 20+ yr
Lie *et al.* 2011 Lie *et al.* 2013 – *receptor status*	**Norwegian Nurses Study** Nested case-control study Assembled 2004 for cases diagnosed 1990–2007 Older age: 33% premenopausal Cohort = 49,402 699 cases; 895 controls	Norwegian Cancer Registry Receptor status	Telephone interview, all jobs ≥ 1 yr after graduation Metrics: duration of any night work; duration of work in hospitals; duration of work in schedules with ≥ 3 consecutive nights/mo, cumulative no. lifetime night shifts, lifetime average no. night shifts/mo Night shift: respondents working ≥ 1 yr midnight–6:00 AM 84.3% ever nights
Pesch *et al.* 2010 Rabstein *et al.* 2013 – *receptor status*	**GENICA study** Population based Enrolled 2000–2004 26% premenopausal 857 cases; 892 controls	Catchment area hospitals Receptor status	In-person interview followed by a telephone interview, all jobs ≥ 1 yr Night shift: ≥ 1 yr full-time work between midnight–5:00 AM Metrics: ever/never, frequency, duration night work 7% ever nights among controls; 1.2% 20+ years
O'Leary *et al.* 2006	**EBCLIS study** Selected general population Enrolled 1996–1997 39% premenopausal 487 cases; 509 controls	First primary, *in situ*, or invasive breast cancers Catchment area hospitals	Staff-administered in-home interview, all jobs ≥ 6 mo in past 15 yr Metrics: ever/never, duration, frequency of nights Night shift: ≥ 6 mo working nights = 7:00 PM–following morning or afternoon to 2:00 AM during past 15 yr 9.8% ever nights in 15 yr prior to reference date for controls

Reference	Population	Breast cancer incidence source(s)	Exposure assessment and information
Davis *et al.* 2001b	**Seattle, WA, U.S.A.** Population based Enrolled 1992–1995 33% premenopausal 813 cases; 793 controls	Cancer Surveillance System of the Fred Hutchinson Cancer Research Center of Seattle cancer registry	In-person interview, all jobs held ≥ 6 mo Metrics: frequency, duration of night work, hours per week Night shift: ≥ 6 mo working 7:00 PM–9:00 AM 10 yr prior to diagnosis 5% ever worked nights
Hansen 2001	**Danish study of working women** Population based Registry study conducted prior to 2001 72% < 60 yr of age 7,035 cases; 7,035 controls	Danish Cancer Registry	JEM: Record linkage to pension fund records; classification of jobs held ≥ 6 mo based on % night work from separate nationwide survey Metrics: frequency, duration of night work Night shift: ≥ 6 mo in trades where ≥ 60% of workers worked at night Jobs with ≥ 60% night work 4.6% for ≥ 6 mo 1.4% for ≥ 6 yr

BCEES = Breast Cancer Employment and Environment Study, Australia; CBCS = Canadian Breast Cancer Study, Vancouver BC and Kingston, ON; CECILE Study = Cote d'Or and Ille-et-Vilaine, France; EBCLIS = Electromagnetic Fields and Breast Cancer on Long Island Study; GENICA = German Gene–Environment Interaction and Breast Cancer, Bonn, Germany; MCC-Spain = Multi-Case-Control-Study, Spain.

Evaluation of study quality

A detailed description of the quality of the shift work case-control studies is provided in Appendix B, Table B-2. The most important issues bearing on the overall quality of these studies were selection bias, exposure misclassification, and sensitivity.

Selection bias

Most studies showed low or moderate potential for selection bias. In three of the four studies with the lowest control participation rates and other methodologic differences that could potentially bias results (Pesch *et al.* 2010, Fritschi *et al.* 2013, Grundy *et al.* 2013a), the authors conducted sensitivity analyses to address these issues and reported no evidence to suggest the presence of selection bias. The O'Leary *et al.* study raised the most serious concern regarding selection bias. The subset of cases and controls in this study were selected from a larger case-control study based on long-term residential stability, and the low proportion of pre-menopausal women in the night work study (39%) differed from the full set of cases and controls by age, menopausal status, race, parity, education, BMI, and alcohol and hormone replacement therapy use, suggesting that some selection bias may have been introduced. No further information was available to assess bias due to differences in shift work, as these questions were asked during a second interview.

In the nested case-control studies, the healthy worker effect was also likely to have been present and to have biased estimates of effect toward the null if women who did shift work early in their careers and were diagnosed with cancer were not included in the cohort. In the Danish Military workers study (Hansen and Lassen 2012), 66% of case subjects diagnosed in the relevant time period were alive at the time of the interview, and only 40% of all case subjects completed the interview. Hansen and Stevens (2012) reported that data were not available to assess the impact of this loss from the original cohort, but in this study of somewhat older survivors, some selection bias was also likely.

Exposure misclassification

As with the cohort studies, the potential for bias in exposure assessment in the case-control studies was rated by (1) how night work was initially defined, (2) the quality of the measurements, and (3) whether the study included metrics that differentiated between subjects with more persistent night shift working history and those who had less intense night shift working history. Again, concern was greater about non-differential classification than differential misclassification, with the bias most likely to underestimate the risk of breast cancer due to shift work. The risk of exposure assessment bias was considered moderate or low in nine studies and high in three studies.

Definitions of night work. As with the cohort studies, the case-control studies of night work varied in their definitions of "exposed" and "unexposed," with some definitions likely to result in a higher risk of misclassification than others. All the case-control studies except one (Grundy *et al.* 2013a) required a minimum exposure period, with about half requiring at least six months of night work and the rest requiring at least one year. Six studies defined night work as occurring within a specific time period, reducing the likelihood of misclassification (Pesch *et al.* 2010, Lie *et al.* 2011, Hansen and Lassen 2012, Fritschi *et al.* 2013, Papantoniou *et al.* 2015a, Wang *et al.* 2015a). Five studies required respondents to provide start and end times for work periods (Davis *et al.* 2001b, O'Leary *et al.* 2006, Hansen and Stevens 2012, Grundy *et al.* 2013a, Menegaux *et al.* 2013). Two studies required that the "exposed" women work a minimum number of nights in a given time period (e.g., at least 3 nights per month in Papantoniou *et al.* 2015a and at least 1 night per week in Wang *et al.* 2015a). Grundy *et al.* (2013a) allowed the definition of night work to vary from 20% to 100% of all jobs being spent on evening and/or night shifts, capturing both rotating and permanent (100%) night shift schedules. A more restricted night work variable (11:00 PM to 7:00 AM) was reported on, but in very little detail. That the main analyses included evenings reduced the value of these estimates. Cordina-Duverger *et al.* (2018) recoded individual-level data on night work from job-by-job detailed histories collected in five of these case-control studies (Pesch *et al.* 2010, Fritschi *et al.* 2013, Grundy *et al.* 2013a, Menegaux *et al.* 2013, Papantoniou *et al.* 2015a) to allow a common characterization of exposure to night work during the biological night (midnight to 5:00 AM). This new definition of exposure reduced the proportion of the exposed controls in each study by small amounts (1% to 4%) compared with the usually broader definitions used in the original studies. However, the reduction in the estimate of exposed controls was 17.7% for the Grundy *et al.* (2013a) study, indicating more serious exposure misclassification.

Quality of exposure measurements. All except one study used self-reported questionnaires or interviews to determine night work using answers to questions on a job-by-job basis. Two

studies used different methods. Hansen (2001) used a JEM that classified occupations by percentage of workers likely to perform night work estimated from an external survey. Individuals working in trades in which at least 60% of workers were night workers were considered "exposed," and those working in trades with fewer than 40% night workers were considered "unexposed." This study did not collect additional self-reported data to compare with the JEM. While about 20% of females work nights in Denmark, only about 6% of this population was considered exposed by their methods.

Overall, recall bias was not considered to be a major concern in most of the case-control studies. Eight of the twelve studies collected data before 2007, when IARC classified shift work as a probable human carcinogen (IARC 2010), reducing the potential for recall bias, as issues of shift work in relation to cancer were not previously widely publicized. In addition, Hansen and Stevens (2012) and Hansen and Lassen (2012) did not find an association of breast cancer with reported exposure to electromagnetic fields (an exposure with no known association with breast cancer included in the questionnaire to test for recall bias), which suggests that recall bias was unlikely. Three studies collected all data after 2007 (Fritschi *et al.* 2013, Papantoniou *et al.* 2015a, Wang *et al.* 2015a), and one study collected data before and after 2007 (Grundy *et al.* 2013a); however, these studies did not uniformly report elevated risks of breast cancer among night workers. Lizama *et al.* (2017) conducted a study using memory prompts and questions about the participant's belief that shift work causes breast cancer. Depending on the sequence of administration of these questions, they concluded that any observed association between shift work and breast cancer was unlikely to have been influenced by recall bias.

Finally, studies collecting night work histories on a job-by-job basis were less likely to be subject to recall bias than those asking more general questions about lifetime exposure to night work. Härma *et al.* (2017) used payroll data to evaluate the quality of self-reported shift work questions; they found that questions on "shift work with night shifts" and "permanent night work" showed high sensitivity (96% and 90%) and specificity (92% and 97%), while those asking about "regular day work" showed moderate sensitivity (73%) and high specificity (99%), and "shift work without night shifts" showed low sensitivity (62%) and moderate specificity (87%). The authors concluded that the validity of self-reported assessment of shift work varies among work schedules and is likely to contribute to bias towards the null when the question "shift work without night shifts" is used in the questionnaire.

Multiple exposure metrics. A strength of the case-control study database was that multiple metrics in several studies were evaluated with respect to duration, frequency, and timing of exposure. Some studies conducted more in-depth analysis using metrics such as consecutive nights (Lie *et al.* 2011), type of shift, and length of night shift (Cordina-Duverger *et al.* 2018). In addition, several studies reported on combined metrics of duration and frequency to classify those with the most persistent night shift work history (Davis *et al.* 2001b, Lie *et al.* 2011, Hansen and Lassen 2012, Hansen and Stevens 2012, Grundy *et al.* 2013a, Menegaux *et al.* 2013, Papantoniou *et al.* 2015a). Only one case-control study limited its exposure assessment to "ever/never" night work (Wang *et al.* 2015a). Hansen (2001) included an estimate of shift work duration which improved the quality of his exposure assessment, thus this study was retained in the database.

Beyond these metrics, Fritschi *et al.* (2013, 2018) defined an additional three-level metric, "phase shift." This variable was based on individual data on shift schedules and the work by Haus and Smolensky (2013) indicating that forward rotations cause less circadian disruption than do backward rotations. Exposure was classified as "high" if the job involved 44 nights forward rotation or 46 nights backward rotation; "medium" with 3 to 4 nights forward or 4 to 6 nights backward rotation; and "low" with 3 nights backward rotation. If night shift was worked for ≥ 4 week block, phase shift was downgraded by one level assuming that peripheral rhythms would synchronize with central rhythms over this time. Fritschi *et al.* (2018) later incorporated chronotype into this metric, such that "late circadian disruption" occurred if one hour or more of the evening work day was after the start of the woman's biological night, and "early circadian disruption" occurred if the start of the morning work day was before the end of the woman's biological night.

Potential confounding

The potential for confounding bias across the case-control studies was generally of minimal concern; no study found any substantial difference between adjusted and unadjusted models. Overall, co-exposures were not controlled for, which is generally not an issue in population-based studies, as the numbers of people with similar co-exposures across a variety of jobs are typically small. As with the cohort studies, the practice of adding variables unrelated to night work or in the pathway to breast cancer when they were unrelated to exposure may have had the effect of biasing estimates towards the null (Menegaux *et al.* 2013). One study did not control for socioeconomic status (Davis *et al.* 2001b), and in two studies, alcohol use was not controlled for or data on alcohol use were derived from non-individual-level external sources (Hansen 2001, Pesch *et al.* 2010).

Sensitivity

The studies by Hansen and Lassen (2012) and Lie *et al.* (2011) had the highest ratings for sensitivity to detect an effect. In many studies, the numbers of case subjects working nights for long durations or at high frequencies was low, reducing the potential for these studies to find an effect (O'Leary *et al.* 2006, Pesch *et al.* 2010, Grundy *et al.* 2013a, Papantoniou *et al.* 2015a). Two case-control studies with older populations (Davis *et al.* 2001b, O'Leary *et al.* 2006) elicited exposure information only for the past 15 years prior to diagnosis or 10 prior to the reference date. The older age of these populations along with the restricted exposure period made these studies the least sensitive for finding an effect, particularly one based on long durations of night work at an early age. Although the Cordina-Duverger *et al.* (2018) pooled analysis was not separately rated for quality, this analysis was more sensitive than the individual studies, in that more cases of night shift work were included, and multiple levels of various exposure metrics across night workers enabled better differentiation of those with persistent night shift work.

Overall utility of the case-control studies

Table 3-4 summarizes the results of the bias and quality evaluation of case-control studies of breast cancer and shift work. Overall, a larger number of the case-control studies than the cohort studies were considered to have high or moderate utility for the cancer hazard evaluation. In general, these studies had detailed exposure assessments on lifetime history of shift work and included metrics of duration, intensity, and timing to evaluate persistent practices of night work. In contrast, the cohort studies often had little information on exposure metrics or complete

occupational history. Because of their cross-sectional nature and the use of lifetime job histories, the case-control studies mostly avoided the complex issues of selection that plagued cohort studies (e.g., left truncation). Recall was likely to suffer at least from some non-differential misclassification; however, such questions as job-by-job start and stop times and length of employment in each job tend to increase the quality of recall, compared with more general questions about night work, decreasing concern about differential recall bias. Finally, more of the case-control studies were conducted before the 2007 onset of public and media interest in the relationship between shift work and cancer, which may also have lowered the chance of differential recall bias. Three studies (Hansen 2001, O'Leary *et al.* 2006, Wang *et al.* 2015a) were judged to have low utility to inform the evaluation because of concerns about exposure assessment and sensitivity to detect an effect. The overall quality of the case-control studies was improved by the inclusion of the pooled analysis using a uniform definition of night work and night work metrics across five studies.

Table 3-4. Summary of study quality evaluation: Case-control studies of shift work and breast cancer

Citation	Selection[a]	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility[b]
Papantoniou *et al.* 2015a	++	+++	+++	+++	+++	+++	++	+++
Wang *et al.* 2015a	++	+	++	++	++	+++	+	+
Fritschi *et al.* 2013	++	+++	+++	+++	+++	+++	++	+++
Grundy *et al.* 2013a	+++	++	++	+++	+++	+++	++	++
Menegaux *et al.* 2013	+++	++	+++	+++	+++	+++	++	+++
Hansen and Lassen 2012 (nested)	++	+++	+++	+++	+++	+++	+++	+++
Hansen and Stevens 2012 (nested)	++	+++	+++	+++	+++	+++	++	+++
Lie *et al.* 2011 (nested)	++	++	+++	++	+++	+++	+++	++
Pesch *et al.* 2010	+++	++	+++	++	+++	+++	+	++
O'Leary *et al.* 2006	++	+	+++	+++	+++	+++	+	+
Davis *et al.* 2001b	+++	++	+++	+++	++	++	+	++
Hansen 2001	+++	+	+++	++	+++	+++	+	+

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

3.2.3 Breast cancer hazard assessment: Night shift work

The goal of the cancer hazard assessment was to determine the level of evidence (sufficient, limited, or inadequate, as defined by the RoC listing criteria) for the relationship between breast cancer risk and night shift work related to circadian disruption.

Findings of all the individual studies included in the shift work analysis are provided in Appendix B, Tables B-3 (cohort studies) and B-4 (case-control studies), and selected findings are shown in forest plots below.

Overview of methods

The first step in the cancer hazard assessment was to determine the confidence in the evidence from each study. This step was followed by synthesis of the level of evidence across studies, considering the key issues and the RoC listing criteria to reach a level-of-evidence conclusion. The cancer hazard assessment included consideration of the following factors:

- How consistent is the evidence across studies and what sources of heterogeneity might explain differences in results?
- Key issues: What exposure metrics predict breast cancer risk and/or breast cancer subtype? How does any consideration of latency or recency of exposure in these analyses affect the results? Does chronotype modify the association between night work and breast cancer?
- Can the findings be explained by chance, bias, or confounding?

The level of confidence in the evidence from the individual studies (rated as "evidence," "some evidence," "null," or "inconclusive") was reached by considering the strength of the association, the potential for specific biases or confounding, the expected directions and distortions of those potential biases or confounding, and the sensitivity of the study to detect an effect. Guidelines for evaluating the confidence of the evidence in each study are as follows:

Moderate to strong evidence: Elevated risk estimates of night shift work found for several analyses of different exposure metrics, exposure-response relationships, or effect modification reported usually in moderate to high utility studies. At least one of the estimates is statistically significant. Low utility studies can provide evidence of an association if the potential for bias is towards the null.

Some evidence: Statistically significant risk estimates found for at least one exposure metric of night shift work or multiple non-statistically significant estimates with at least moderate precision from multiple analyses. The evidence can come from high or moderate utility studies or studies with low utility if the potential for bias is towards the null, or if the study has low sensitivity.

Null: Studies which are considered "null" show effect estimates ≤ 1.0.

Inconclusive: Findings vary; the overall direction of potential biases is unknown; potential confounding may explain the findings; or studies have very low precision and the findings may be due to chance.

NTP did not consider the meta-analysis approach informative and thus did not include its own meta-analysis nor include the published meta-analyses in the cancer hazard assessment. The 2016 NTP Workshop on Shift Work at Night, Artificial Light at Night, and Circadian Disruption noted limitations in the utility of meta-analysis because of significant heterogeneity in definitions of "shift or night work." For example, some studies defined shift work as working at specific

hours, others defined it as working a certain number of rotating days per month or week. Thus, differences in the definitions of shift work across studies result in different meanings for "ever exposed" and for duration of exposure. In addition, breast cancer is a heterogenous disease, which also complicates pooling risk estimates. Finally, most meta-analyses did not conduct study quality evaluations, evaluate young age starting night work, or explore combinations of exposure metrics.

Seven meta-analyses have been published since 2013 (Ijaz *et al.* 2013, Jia *et al.* 2013, Kamdar *et al.* 2013, Wang *et al.* 2013, He *et al.* 2015, Lin *et al.* 2015, Travis *et al.* 2016), as well as a qualitative review of seven of these (Pahwa *et al.* 2018). Three of the four analyses found a statistically significant positive risk of breast cancer risk among women ever working night shifts; three of four analyses reported statistically significantly elevated risks for long duration; two of three analyses reported statistically significantly elevated estimates for a fixed number of years (e.g., risk for every 5 years); and both of the analyses reporting on fixed frequency of night shifts and/or cumulative nights reported statistically elevated estimates. Of note, the only meta-analysis finding no excess risk of breast cancer in shift workers (ever or long duration) was the study by Travis *et al.* (2016), who limited their analysis to cohort studies, which NTP considered to be less informative than the case-control studies.

Consistency of the evidence across studies

Overall, there is consistent evidence for a relationship between persistent metrics of night shift work and breast cancer risk across studies (as summarized in Table 3-5).

Of the twenty-one studies considered to have utility for the evaluation, seven provided "moderate to strong evidence," and ten provided "some evidence" of an association between breast cancer risk and a metric associated with extreme or persistent night work. (Note that the two cohorts of the Nurse's Health Study were counted as one study because they used similar methods to evaluate cancer risk in cohorts that differ by age at baseline, see Table 3-7). Moreover, consistent findings of increased risk of breast cancer in women exposed to night shift work were found across different occupational groups and different geographical populations.

The available data provide strong evidence that metrics associated with persistent night work — frequent, long-term, and night work starting in early adulthood — best predict risk of breast cancer. Although, in general, no linear exposure-response effects were seen in these data, the women with the highest levels of exposure had the highest risks. Some evidence also supports the hormonal pathway by which shift work is hypothesized to affect breast cancer risk. Statistically significantly elevated risks of breast cancer among night workers with receptor-positive cancer subtypes (e.g., ER+, PR+, or HER2+) were consistently observed, although most studies did not have large enough samples to find significant interaction; and some elevated but not statistically significant risks were also reported for receptor-negative subtypes. The studies that could investigate this risk by menopausal status also found that premenopausal night workers were at the highest risk of breast cancer of these breast cancer subtypes.

Across the four studies that had data to investigate chronotype as a potential effect modifier, chronotype was not clearly related to breast cancer risk. The evidence supporting these conclusions is discussed below.

The database is inadequate to determine the contribution of specific exposures contributing to night shift work – such as LAN, sleep, or meal timing – to the excess risk of breast cancer (see Section 6 for a discussion of sleep and altered meal timing). In these studies, confounding bias was generally of minimal concern. Risk estimates generally were no lower in models fully adjusted for confounding factors than in unadjusted models or models adjusted only for age. In some cases, the risk estimates were elevated in the fully adjusted models.

Table 3-5. Summary of levels of evidence from human studies of night shift work and breast cancer

Reference	Study design	Ever worked	Duration	Frequency/ cumulative	Younger age[a]	Receptor positive
Moderate to strong evidence of a positive association - informative studies						
Wegrzyn (NHS2) 2017	Cohort[b]	–	↑↑	–	Pre	↑
Davis 2001	Case-control	↑	↑↑ *	↑↑*	–	–
Grundy 2013	Case-control	–	(↑)	↑↑[c,*]	I	↑↑
Hansen & Lassen 2012	Case-control	(↑)	↑↑ *	↑↑[c,d,*]	–	–
Hansen & Stevens 2012	Case-control	↑↑	↑↑ *	↑↑	–	–
Lie 2011, 2013	Case-control	–	–	↑↑[c,*]	–	↑↑
Menegaux 2013; Cordina-Duverger 2016	Case-control	↑	(↑)	↑[c,e]	YA	↑↑
Some evidence for a positive association - informative studies						
Knutsson 2013	Cohort	↑↑	–	–	YA	–
Fritschi 2013, 2017	Case-control	↑[f]	↑[g]	–	YA	–
Papantoniou 2015	Case-control	(↑)	(↑)	(↑)[d]	Pre	↑
Pesch 2010; Rabstein 2013	Case-control	Null	(↑)	(↑)	YA	I
Some evidence for a positive association - lower utility studies						
Akerstedt 2015	Cohort	Null	↑	–	YA	–
UK EPIC Oxford, Travis 2016	Cohort	Null	↑[e]	–	–	–
Million Women, Travis 2016	Cohort	Null	↑[e]	–	–	–
Tynes 1996	Cohort	–	↑↑ *	–	YA	–
Hansen 2001	Case-control	↑	↑	–	–	–
Wang 2015	Case-control	↑	–	–	Pre	↑
No evidence of a positive association						
Li 2015	Cohort, informative	–	Null	Null	Null	–
Vistisen 2017	Cohort, informative	Null	–	–	–	(↑)
Pronk 2010	Cohort, low utility	Null	Null	Null	Null	–
O'Leary 2006	Case-control, low utility	↓	↓	–	–	–

↑↑ = RR ≥ 1.8 and/or highest exposure metric or exposure response; ↑ = RR ≥ 1.2 or not the highest exposure metric; (↑) = RR ≥ 1.2, CI includes 1; ↓ = RR < 1; * = significant exposure response relationship; – = not reported; I = inconclusive; NHS2 = Nurses' Health Study 2.

Shade of blue indicates the strength of the evidence with darkest color indicating the strongest relationship.

[a]Analyses based on collective information (including direct and indirect measures of age) suggesting breast cancer risk is higher in women starting work at a younger age (YA), among premenopausal women (Pre).

[b]Findings specific for the NHS (older cohort) not included in table as the collective findings from the two cohorts were considered as one study.
[c]Combined analyses of metrics frequency-related measures and duration of work.
[d]Cumulative number of night shifts.
[e]↑ for an intermediate category of duration (e.g., at least 10 years), but not for the longest category of duration.
[f]Ever exposed to phase shift work.
[g]↑ for ≤ 10 years duration category but not for longer duration categories.

Metrics of exposure

Several different types of exposure metrics were used in the studies, as summarized in Table 3-6.

Table 3-6. Summary of night shift work exposure metrics and potential effect modifiers

Citation	Ever/never	Duration	Permanent	Follow-up data	Frequency	Receptor status	Menopausal status	Age started	Last worked	Chronotype	Health workers*
Case-control studies											
Danish Military Workers	X	X			X					X	
Danish Female Nurse Cohort	X	X	X		X						X
Norwegian Nurses Cohort[a]					X	X	X				X
Fred Hutchinson Cancer Center Study	X	X			X						
Western Australia Study	X	X					X			X	
Canada Study[b]		X				X	X				X
Danish Female Workers	X	X									
CECILE Study, France[c]	X	X			X	X	X	X			
MCC/Spain Study	X	X	X		X	X		X		X	
GENICA Study[d]	X	X			X	X		X	X		
EBCLIS study	X				X						
Guangzhou, China Study	X					X					
Cohort studies											
Danish Payroll Data Cohort	X					X					X
Swedish Twin Registry	X	X									
WOLF cohort				X				X			
Shanghai Textile Worker Cohort					X		X				
Shanghai Women's Health Study	X	X			X			X			
Million Women Study	X	X		X					X	X	X
Epic Oxford Study	X	X								X	
Norwegian radio and telegraph operators		X[e]						x			
Nurses Health Cohorts		X		X		X	X	X	X		X

See Tables 3-1 and 3-3 for citations.
EBCLIS = Electromagnetic Fields and Breast Cancer on Long Island Study; WOLF = Work, Lipids, and Fibrinogen.
*Population or subanalysis.

[a]Reported in two publications: Lie *et al.* 2011, Lie *et al.* 2013.
[b]Grundy *et al.* reported results by the percentage of all nights worked, but the definition of night work included nights and/or evenings.
[c]Reported in 3 publications: Menegaux *et al.* 2013 , Truong *et al.* 2014, Cordina-Duverger *et al.* 2016 .
[d]Reported in 3 publications: Pesch *et al.* 2010, Rabstein *et al.* 2013, Rabstein *et al.* 2014.
[e]Age-specific metric only.

Ever night work

As mentioned in the discussion of exposure misclassification, the metrics used to measure "night work" varied from study to study, complicating the comparison across studies. "Ever night work," while used in 10 of the 12 studies, is perhaps the least sensitive metric of night work that may be involved in circadian disruption. Using "ever night work" or "ever phase shift" (Fritschi *et al.* 2013) as the exposure metric and stratifying by study design, Figure 3-1 shows that eight of ten case-control studies reporting on this metric observed a positive association between breast cancer and ever night work, one study found no relationship (Pesch *et al.* 2010), and one study reported an inverse association (O'Leary *et al.* 2006). Fritschi *et al.* (2013) reported a statistically significant dose-response relationship for phase shift ($P = 0.04$). In contrast, only one cohort study reported a positive association between breast cancer and ever night work (Knutsson *et al.* 2013). However, the heterogeneity was largely explained by study quality (Figure 3-2). The four highest-utility studies (Hansen and Lassen 2012, Hansen and Stevens 2012, Fritschi *et al.* 2013, Menegaux *et al.* 2013) reported 16% to 80% increased risk of breast cancer among those ever working nights, compared with the seven lowest-utility studies, four of which reported risk estimates close to 1.0 and one reporting an estimate below 1.0. The pooled analysis of five case-control studies (Cordina-Duverger *et al.* 2018) reported a risk estimate of 1.12 (95% confidence interval [CI] = 1.0 to 1.25) for ever working nights.

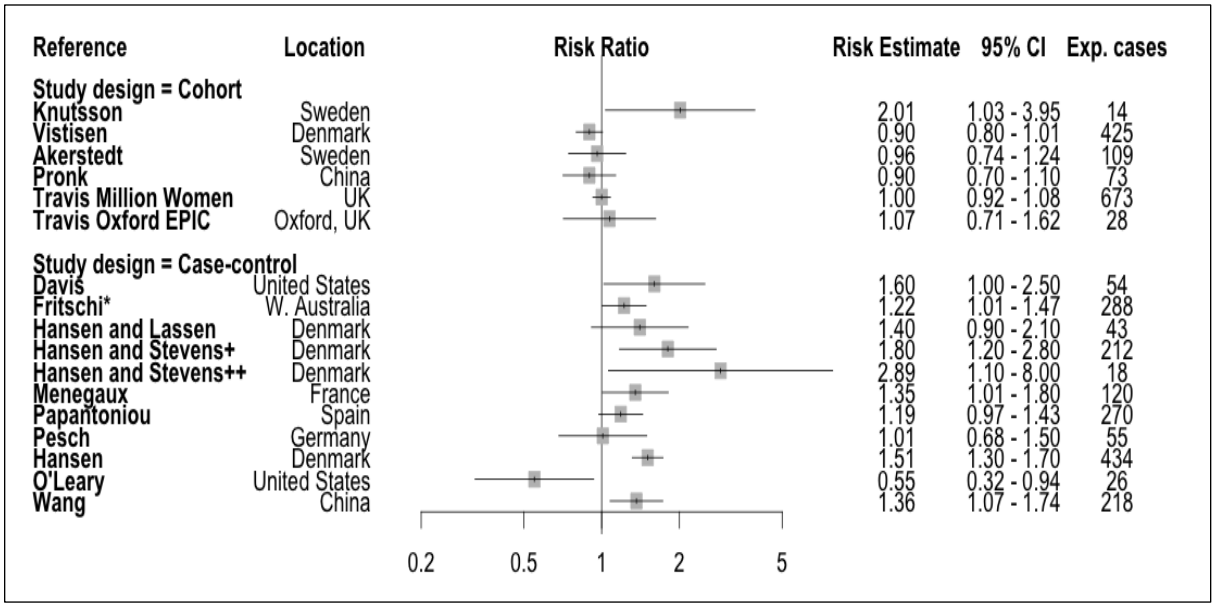

Figure 3-1. Breast cancer risk by "ever night work" by study design

Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates.
*Trend $P = 0.04$ for phase shift.
+Rotating night shifts without permanent nightwork.
++Rotating night shifts with permanent nightwork.

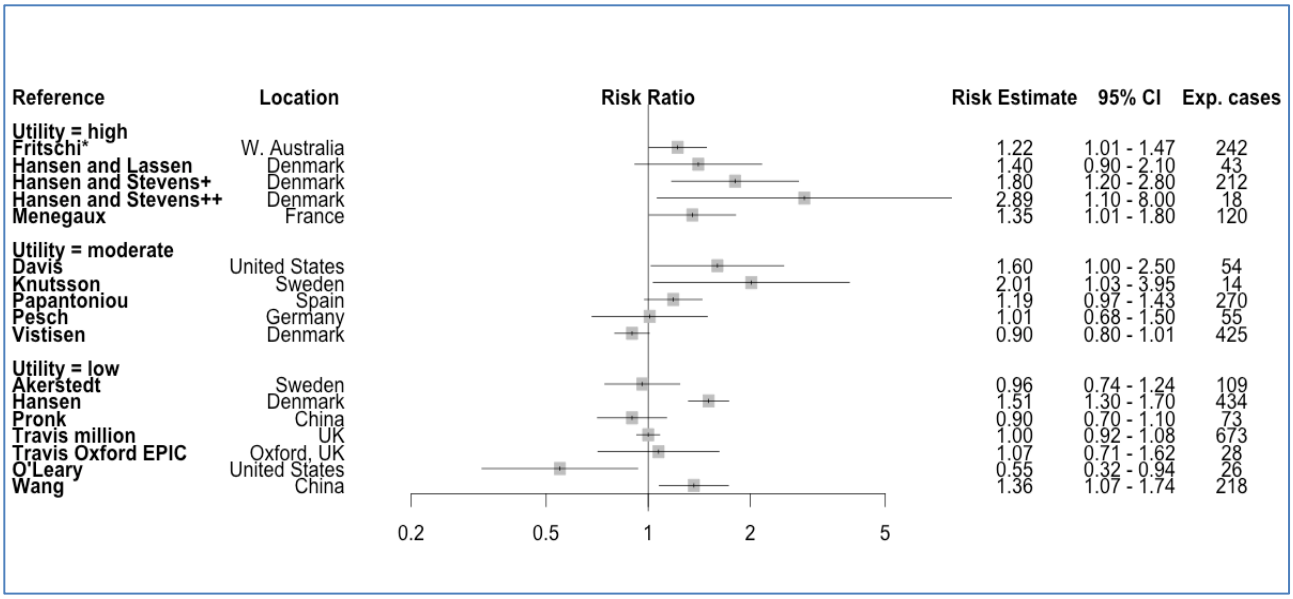

Figure 3-2. Breast cancer risk by "ever night work" by study utility

CI = confidence interval.
Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates.
*Trend $P = 0.04$ for phase shift.
+Rotating night shifts without permanent nightwork.
++Rotating night shifts with permanent nightwork.

Duration of working the night shift

Across studies, categories of duration and frequency varied considerably, and some studies included frequency of nights within their definition of night work, thus duration of night work represented a somewhat combined measurement of frequency and duration. In general, the most extensive duration reported by each study tended to be associated with an increased risk of breast cancer. Eleven moderate- and high-utility studies reported on duration of night work, using various categories to classify years of work. Seven studies reported excess risks of 54% to 248% for the longest reported duration of night work, and three of these studies reported statistically significant results for durations of at least 15 years (Hansen and Lassen 2012) or at least 20 years (Hansen and Stevens 2012, Wegrzyn *et al.* 2017 [NHS2]). Hansen and Lassen reported a significant exposure response trend for duration and breast cancer risk ($P = 0.03$). Night work for at least 15, 20, or 30 years showed non-statistically significant associations with increased risks of 22% (Papantoniou *et al.* 2015a), 248% (Pesch *et al.* 2010), and 68% (Grundy *et al.* 2013a). Menegaux *et al.* (2013) and Davis *et al.* (2001b) reported non-statistically significant excess risks of 54% for at least 4.5 years and 60% for at least 3 years for at least one night per week. Davis also reported a statistically significant continuous exposure-response relationship ($P = 0.04$) between breast cancer risk and number of years working at least one night shift per week (odds ratio [OR] = 1.13, 95% CI = 1.01 to 1.27). Estimates close to 1.0 were reported for at least 20 years by Fritschi *et al.* (2013) and at least 27.67 years by Li *et al.* (2015) (see Figure 3-3).

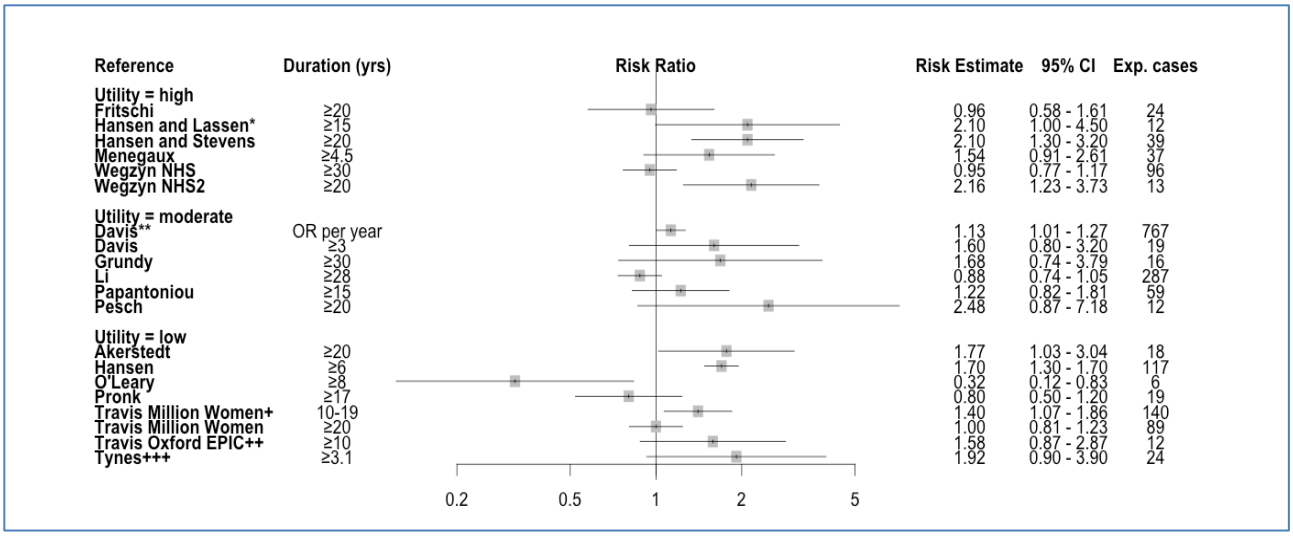

Figure 3-3. Breast cancer risk by longest reported duration of night work by study utility

CI = confidence interval.
Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates.
*Trend is P = 0.03.
**Trend is P = 0.04 for continuous duration.
+Travis Million Women study OR refers to total years worked among those who last worked nights within the past 10 years.
++Travis Oxford EPIC study OR was estimated by a fixed-effects model combining the categories of 10–19 years and ≥ 20 years duration (NTP).
+++A combined estimate for duration for all women in the Tynes *et al.* study was calculated using reported frequencies for women < 50 and ≥ 50 years of age.

Among studies with low utility, excess risks of 77% were reported for night work duration of at least 21 years (Åkerstedt *et al.* 2015), 70% for at least 6 years (Hansen 2001), and 92% for at least 3.1 years (Tynes *et al.* 1996, based on a calculated estimate of the age-specific estimates provided). In the U.K. EPIC Oxford study (Travis *et al.* 2016) only one exposed case subject had at least 20 years of exposure; combining estimates for 10 to 19 years and at least 20 years resulted in a calculated estimate of 58% increased risk for at least 10 years. The Vistisen *et al.* (2017) study of payroll workers did not support a short-term effect of night shift work in this young population (about two thirds of whom were aged 50 or younger).

No clear exposure-response pattern for duration was observed in these studies. However, six studies found statistically significant or borderline significant elevated risks of breast cancer in the range of 9% to over twofold for shorter durations of night work (Hansen and Stevens 2012), 1 to 5, 5 to 10, and 10 to 20 years; Grundy *et al.* (2013a) < 15 years; Papantoniou *et al.* (2015a) < 5 years; Wegrzyn *et al.* 2017), NHS < 15 years among women with ≤ 10 years of follow-up; Li *et al.* (2015) < 15 years among postmenopausal women; and Fritschi *et al.* (2013) for < 10 years duration of phase shift and graveyard shifts.

Frequency or cumulative (lifetime) number of night shifts

Results from nine high- and moderate-utility studies suggested that breast cancer risk was associated with a high frequency (average number of shifts per unit time) or cumulative number of night shifts over a lifetime (Figure 3-4).

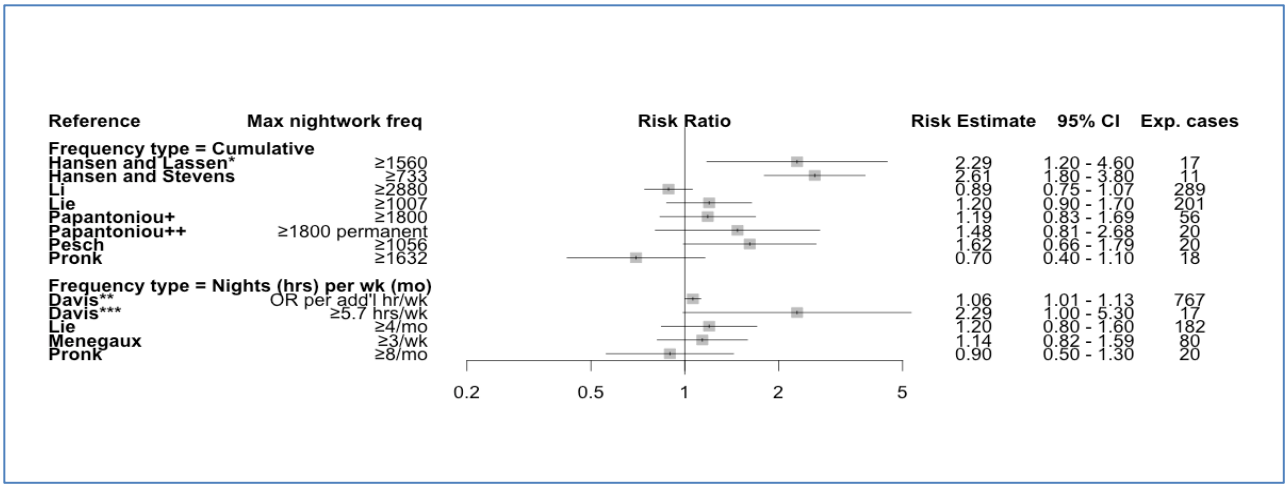

Figure 3-4. Breast cancer risk by cumulative (lifetime) # night shifts or frequency

CI = confidence interval.
Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates.
*Trend is $P = 0.02$.
**Trend is $P = 0.03$.
***Trend is $P = 0.04$.
+Refers to lifetime cumulative number of night shifts.
++Refers to lifetime cumulative number of permanent night shifts only.

Among the six high- or moderate-utility studies reporting on the cumulative (lifetime) number of night shifts, two studies reported statistically significant twofold excess risks among workers with the highest number of cumulative night shifts (Hansen and Lassen 2012, [229%], Hansen and Stevens 2012, [261%]). Hansen and Lassen observed a significant exposure response trend in risk with increasing cumulative night shift work, with an adjusted OR of 2.3 (95% CI = 1.2 to 4.6) in the highest tertile of exposure (*P* for trend = 0.02). Three studies (Pesch *et al.* 2010, Lie *et al.* 2011, Papantoniou *et al.* 2015a) reported a non-significant excess risk among those with the highest number of lifetime night shifts. Risk estimates (non-significant) less than one were reported from the Li *et al.* (2015) and the Pronk *et al.* (2010) study (a low-utility study); neither study found an association with breast cancer and any metric of shift work.

Two high-utility studies reported increased risks of breast cancer for fixed night work or permanent night schedules. Hansen and Stevens (2012) reported threefold excess risks of breast cancer among those ever working "ever fixed nights" in combination with rotating nights; and Papantoniou *et al.* (2015a) reported that a larger cumulative number of permanent night shifts was associated with a non-significant higher risk of breast cancer.

Among the three high- or moderate-utility studies reporting on the average number of nights or hours per week or month worked, only Davis *et al.* (2001b) reported a statistically significant exposure-response trend of increasing risk with more hours per week of night work; in this study women working at least 5.7 hours per week had more than a twofold increase in the risk of breast cancer. Also, the risk of breast cancer significantly increased with each additional hour per week (10-year weighted average) of night work (OR = 1.06 for each hour, 95% CI = 1.01 to 1.13). Menegaux *et al.* (2013) reported the highest intensity (≥ 3 nights per week) with an excess non-

statistically significant risk of 14%. Lie *et al.* reported a non-significantly elevated risk of 20% for working ≥ 4 nights/month.

Combined measures of night shift work

Four high- or moderate-utility studies reported measures of duration of shift work combined with different measures of frequency, i.e., percentage of night shifts worked, consecutive nights worked, or average number of night shifts worked per week (Figure 3-5). Risks were elevated for all measures of long duration and frequent night shifts with one exception (Menegaux *et al.* 2013). Grundy *et al.* (2013a) reported non-significant doubling of risk among women working 15 to 30 years and ≥ 30 years for 100% evenings or nights; and 2- to 3-fold excess risks among women working ≥ 30 years at 50% or 80% evening/nights (Figure 3-5); however, evenings and night shifts were not differentiated. Lie *et al.* (2011) found elevated risks of breast cancer among nurses working 5 to 7 consecutive night shifts for at least 5 years. Hansen and Lassen reported a statistically significant doubling of risk for women with at least three night shifts per week for ≥ 15 years (P_{trend} = 0.02). Menegaux *et al.* (2013) reported a statistically significant elevated risk of breast cancer in women working < 3 nights per week for ≥ 4.5 years (OR = 2.1, 95% CI = 1.26 to 3.45), but not for ≥ 3 nights among per week for ≥ 4.5 years.

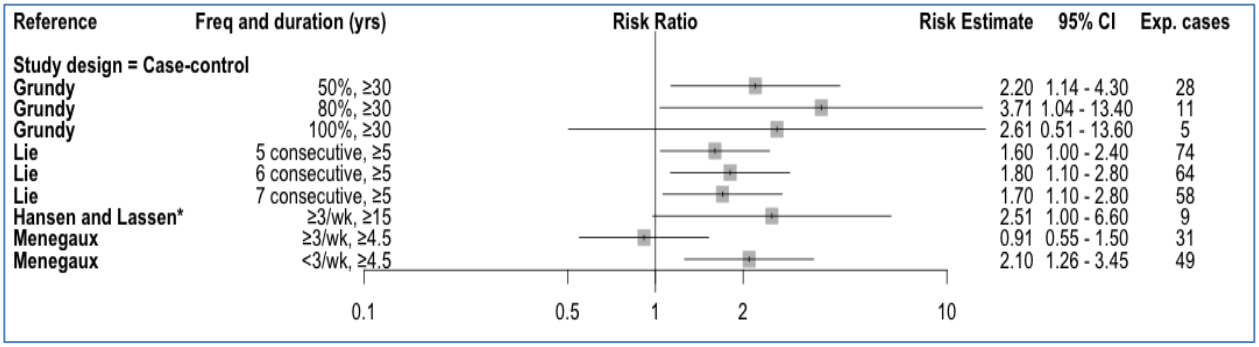

Figure 3-5. Breast cancer risk by percentage of all shifts worked, average consecutive number of shifts or average number of night shifts per week and duration of shift work (yrs)

CI = confidence interval.
Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates.
*Trend is P = 0.02.

Timing of exposure

Based on several lines of evidence related to the timing of night work, night work early in life appears to be related to an excess risk of breast cancer. The strongest evidence comes from studies of premenopausal vs. postmenopausal women with long duration of exposure, suggesting that shift work started in early adulthood. This evidence is supported by studies evaluating risk by age at starting work or analyses of younger populations. In addition to age starting work, recency of night work may also be an important determinant of breast cancer risk.

Analyses of premenopausal and postmenopausal women

The strongest evidence that breast cancer risk is related to shift work in early life comes from the pooled analysis (Cordina-Duverger *et al.* 2018) of five case-control studies (Pesch *et al.* 2010, Fritschi *et al.* 2013, Grundy *et al.* 2013a, Menegaux *et al.* 2013, Papantoniou *et al.* 2015a) which

had the most statistical power to evaluate various metrics of exposure and stratify analyses by menopausal status. This analysis found that risk estimates for all metrics among premenopausal women were higher than among postmenopausal women or all women combined and most were statistically significant. In general, the highest risk of breast cancer occurred among women with persistent night shift work — those working the most nights or most night hours per week, most hours on a night shift, or higher frequency with more recent exposure. Similar elevated risks were observed among women working < 10 years and working ≥ 20 years. Moreover, risks were greater than two-fold among premenopausal women with the most persistent working conditions, that is, those who worked at least 3 nights per week for ≥ 10 years or ≥ 10-hour shifts. Persistent night shift work was not associated with postmenopausal breast cancer regardless of duration of exposure to night work or length of night shift with the possible exception of postmenopausal women working ≥ 3 nights/week within the past two years (see Table 3-7).

Among the individual case-control studies, the Spanish study (Papantoniou *et al.* 2015a) found a stronger association between breast cancer and night shift work in premenopausal women than in postmenopausal women, whereas increased risks of breast cancer among night workers (for some exposure metrics) were reported among both pre- and post-menopausal women in three other studies (Fritschi *et al.* 2013, Grundy *et al.* 2013a, Menegaux *et al.* 2013); the German study (Pesch *et al.* 2010) provided analyses of post-menopausal women only. In addition to the fact that the definitions of exposure differed across the individual studies and thus were difficult to compare, they each lacked the statistical power to clearly determine whether risk varied by menopausal status, and thus, detailed analyses of combined exposure metrics were limited.

Further evidence regarding shift work in early life comes from the Nurses' Health Study. This study measured only one metric, duration of rotating work (defined as working ≥ 3 nights/month), in an older cohort of primarily postmenopausal women (NHS), and a younger cohort of primarily premenopausal women (NHS2). The results of these analyses are summarized in Table 3-7. In the NHS2 cohort a 2-fold statistically significant higher risk of breast cancer was observed among those working ≥ 20 years. However, in analyses stratified by length of follow-up, this effect was seen primarily among participants during the first 10 years of follow-up. In the older NHS cohort, no effect was observed even among those working rotating nights for ≥ 30 years, although a small, non-significant elevated risk was observed during the first 10 years of follow-up. These findings suggest that the effect of rotating work is stronger in younger women working long durations at an early age. In addition, in the NHS2 cohort, while nightwork for at least 20 years was significantly elevated by 116% among women reporting at baseline, the cumulative risk of breast cancer which incorporated follow-up data on shiftwork after the baseline showed only a borderline elevated risk of 40% (reported in Appendix B-3). This reduction may have been due to the addition of women with different patterns of shiftwork accumulated after baseline (e.g., women first starting shift work during later years), and illustrates the higher risk among women reporting shiftwork at early ages.

Table 3-7. Breast cancer risks among women in the NHS studies and pooled analysis of 5 case-control studies

NHS and NHS2 cohorts Wegrzyn *et al.* 2017		Pooled analysis of 5 studies[a] Cordina-Duverger *et al.* 2018	
Exposure group	**HR (95% CI)**	**Exposure group**	**OR (95% CI)**
NHS2 (younger)		**Pre-menopausal**	
Duration (yr)[b] & follow-up		≥ 3 nights/wk and	
≥ 20 (all)	2.15 (1.23–3.73)	≥ 10 yr	2.55 (1.03–6.30)
≥ 20 & ≤ 10 yr	2.35 (1.04–5.31)	≥ 10-hr shift	2.15 (1.21–3.84)
		≤ 2 yr[c]	2.21 (1.30–3.76)
NHS (older)		**Post-menopausal**	
Duration (yr)[b] & follow-up		≥ 3 nights/wk and	
≥ 30 (all)	0.95 (0.77–1.17)	≥ 10 yr	1.00 (0.56–1.77)
≥ 30 & ≤ 10 yr	1.26 (0.97–1.64)	≥ 10-hr shift	0.90 (0.55–1.48)
		≤ 2 yr[c]	1.58 (0.68–3.64)

CI = confidence interval; HR = hazard ratio; OR = odds ratio.
[a]Includes Pesch *et al.* 2010, Fritschi *et al.* 2013, Grundy *et al.* 2013a, Menegaux *et al.* 2013, Papantoniou *et al.* 2015a.
[b]Since baseline.
[c]Last exposure.

The Guangzhou, China hospital-based case-control study by Wang *et al.* (2015a) provides further evidence based on an overall statistically significant positive relationship between "ever" night shift work and breast cancer risk (OR = 1.34, 95% CI = 1.05 to 1.72) which was due primarily to the effect in premenopausal women (OR = 1.47, 95% CI = 1.07 to 2.01) who made up over 60% of the study population. In contrast, the Shanghai Women's Health Study (Pronk *et al.* 2010) which included primarily postmenopausal women reported no effect of night work on breast cancer risk.

Analyses related to young age

Increased risk of breast cancer among women working nights at early ages or before the first full-term pregnancy is moderately supported across the six studies reporting on this exposure, particularly in the two studies combining night work at an early age with the longest reported durations (Tynes *et al.* 1996, Menegaux *et al.* 2013). Both studies reported doubling of risks among women working ≥ 3 years before the age of 50 (not statistically significant) (Tynes *et al.* 1996) or for ≥ 4 years before the first full-term pregnancy (statistically significant) (Menegaux *et al.* 2013). Two of four studies reporting on night work prior to age 30 or first full-term pregnancy reported non-significant 25% increased risk (Papantoniou *et al.* 2015a) or 50% increased risk (Pesch *et al.* 2010), but did not report on duration of night work. Because it is common to work nights for short periods of time early in one's career or during training, when analyses do not consider duration of night employment, many women are included who worked only for very short time periods, potentially diluting the estimates.

Two cohort studies that enrolled younger women found some increases in risk among women working long durations in subanalyses of the populations under the age of 60 compared to the entire population (Akerstedt *et al.* 2015, Knutsson *et al.* 2013).

No associations between breast cancer and exposure to night work before the birth of the first child were reported by Fritschi *et al.* (2013), nor by Wegrzyn *et al.* (2017), in the NHS2 cohort. Wegrzyn *et al.* explained that this null result in the NHS2 study might have been due to the exclusion of parous women at baseline (70%) in this analysis, because reported shift work at baseline could not be attributed to either the pre- or post-pregnancy period. Thus, only nulliparous women were included in this analysis, and the relevant time window in this secondary analysis may have been missed. Reporting on a younger cohort, Vistisen *et al.* (2017) found no evidence of a short-term effect of night work during a very short follow-up period; however, this study was likely biased by left-truncation, which likely biased the estimation of the effect towards the null.

Recency of night work

These data suggested that the risk of breast cancer was higher among women with recent night work. Pesch *et al.* (2010), the Travis *et al.* (2016) the Million Women Study, and Wegzryn *et al.* (2017) reported on recency of night work (years since women stopped working nights). In the NHS2 cohort (Wegzryn *et al.* 2017), a statistically significant interaction was found between rotating shift work and the follow-up time period ($P = 0.03$). Among women with at least 20 years of rotating shift work, the risk of breast cancer was significantly increased (HR = 2.35, 95% CI = 1.04 to 5.31) in the first 10 years of follow-up, but no association was observed during the second 10 years of follow-up. In the older NHS cohort, a 26% excess non-statistically significant risk was found in the first 10 years of follow-up (HR = 1.26, 95% CI = 0.97 to 1.64), but no association was found during the second ten years of follow-up. In an analysis restricted only to postmenopausal women, Pesch *et al.* found a 76% non-significant increase in the risk of breast cancer among those currently working night shifts, but a non-significant reduced risk of breast cancer among those with more than 20 years since their last night work. In the Million Women Study (Travis *et al.* 2016), among women working night shifts within the past 10 years, the risk of breast cancer was significantly increased (RR = 1.41, 95% CI = 1.07 to 1.86) among those working 10 to 19 years; no increase was observed for those working more than 20 years. The pooled analysis of case-control studies (Cordina-Duverger *et al.* 2018) found a statistically significant 26% excess risk of breast cancer among women whose last shift was within 2 years, but an excess risk of only 7% to 9% for longer times since last night work, with risk declining as time since the last night shift increased (no trend test was reported). This finding may help explain the observed higher risk of breast cancer in premenopausal compared to postmenopausal women, as mostly younger, premenopausal women work night shifts and older postmenopausal women work day shifts.

Type of tumor

Six high- or moderate-utility studies reported on effect modification by breast-cancer receptor status (Grundy *et al.* 2013a, Lie *et al.* 2013, Papantoniou *et al.* 2015a, Wang *et al.* 2015a, Vistisen *et al.* 2017, Wegrzyn *et al.* 2017, Cordina-Duverger *et al.* 2018), along with one low-utility study (Rabstein *et al.* 2013). Results across the studies, except for the low-utility study, consistently found significantly elevated risks of receptor-positive breast cancer subtypes (e.g., ER+, PR+, or HER2+) (Figure 3-6). The risk of HER2+ was elevated in two studies that investigated it (Vistisen *et al.* 2017, Cordina-Duverger *et al.* 2018), and the risk of HER2– subtypes also was elevated in Wang *et al.* (2015a). No study had large enough samples to detect significant interactions. The studies that could investigate risk by menopausal status

(Papantoniou *et al.* 2015a, Cordina-Duverger *et al.* 2016) also found that premenopausal night workers were at highest risk of positive receptor subtypes of breast cancer, supporting the hormonal pathway by which shift work is hypothesized to affect breast cancer risk (Figure 3-7). In the pooled analysis (Cordina-Duverger *et al.* 2018), premenopausal women who had ever worked night shifts had statistically significant excess risks of ER+ breast cancer, with higher risk for ER+/HER2+ subtypes (77%) than ER+/HER2– (35%) breast cancer. Postmenopausal women who had ever worked night shifts also showed a statistically significant excess risk of ER+/HER2+ breast cancer (OR = 1.59, 95% CI = 1.11 to 2.28). Regarding receptor-negative subtypes, one statistically significant elevated risk was reported for ER– breast cancer among women with the longest duration of night work (Rabstein *et al.* 2013), with the remaining elevated estimates for receptor-negative subtypes based on small numbers of exposed cases, and aggregated within two studies (Lie *et al.* 2013, Rabstein *et al.* 2013) (Figure 3-8).

Three studies reported on shift work in relation to *in situ* and invasive cancers with conflicting findings (O'Leary *et al.* 2006, Grundy *et al.* 2013a, Papantoniou *et al.* 2015a). Papantoniou *et al.* (2015a) found a higher risk for invasive cancers; however, no difference in risk was reported by Grundy *et al.* (2013a) nor O'Leary *et al.* (2006). Wang *et al.* (2015a), however, reported a statistically significant elevated risk among women with localized tumors, but not in women with regional or distant breast cancer.

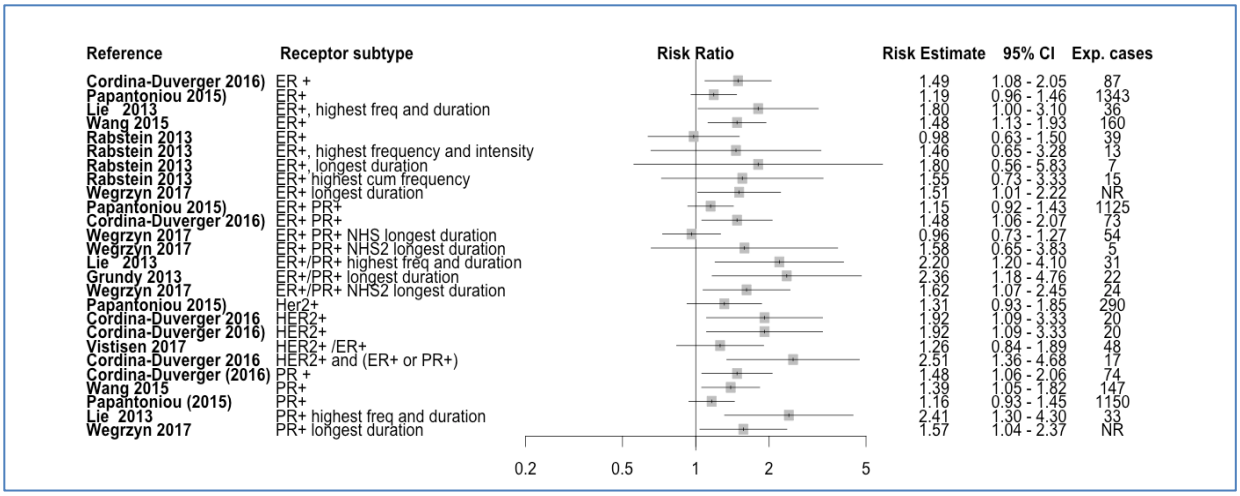

Figure 3-6. Risk of receptor-positive breast cancer and night work, all women

CI = confidence interval.

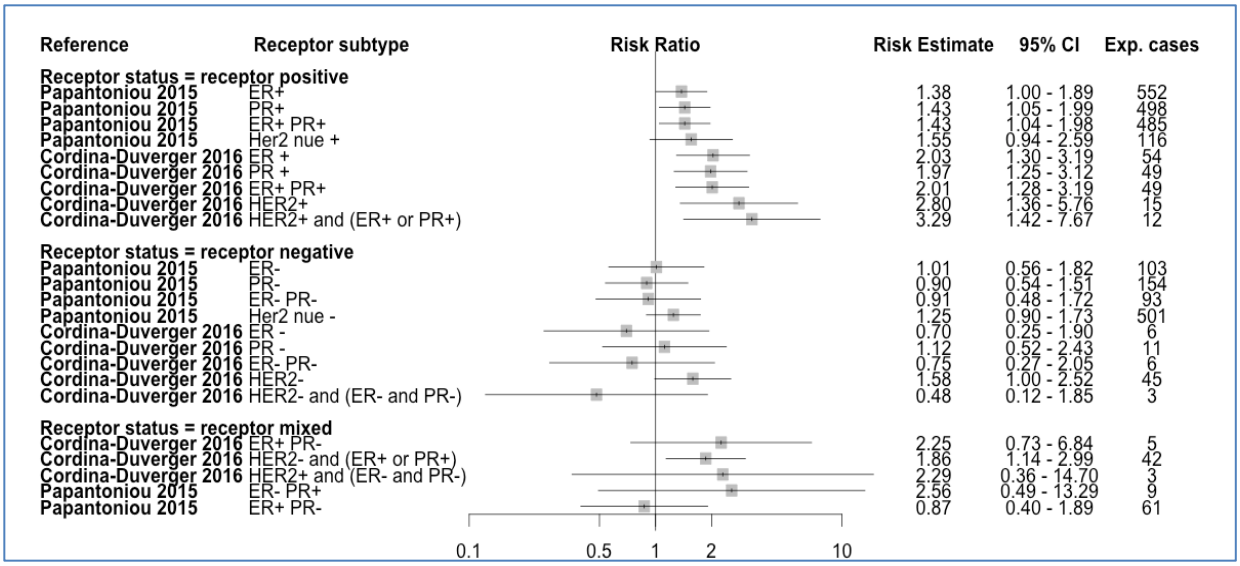

Figure 3-7. Risk of breast-cancer and night work by receptor subtypes, premenopausal women

CI = confidence interval.

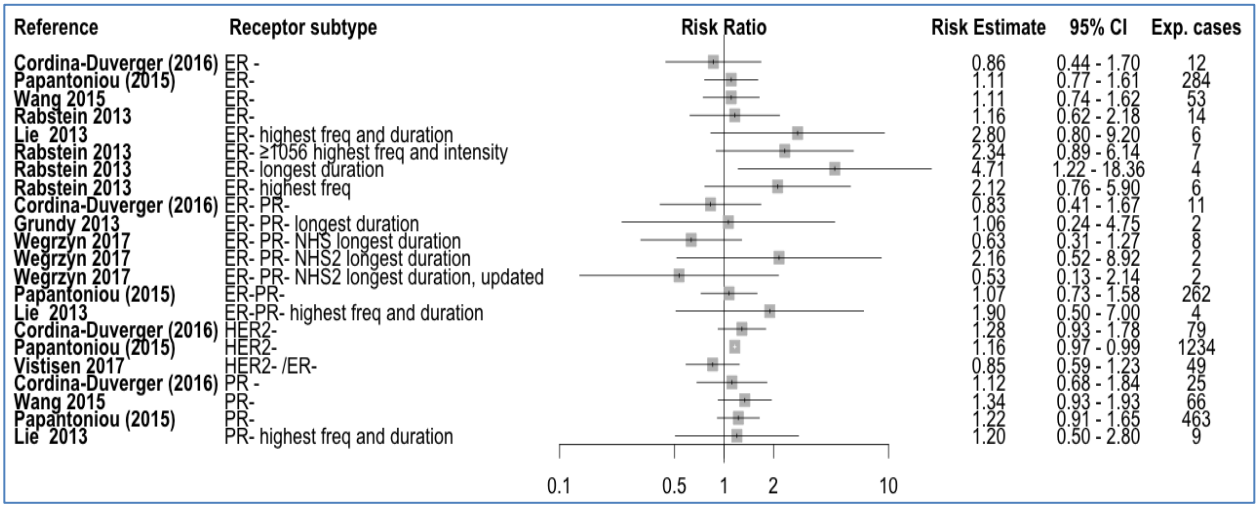

Figure 3-8. Risk of receptor-negative breast cancer subtypes and night work, all women

CI = confidence interval.

Effect modifiers: patient characteristics

Chronotype

Results from four studies reporting on chronotype suggest that chronotype was not clearly associated with the risk of breast cancer. Two studies reported that morning types may have a higher risk of breast cancer associated with night work (Hansen and Lassen 2012, Papantoniou *et al.* 2015a), and two studies reported no association (Fritschi *et al.* 2013, Travis *et al.* 2016 Million Women Study). Studies varied in how chronotype was assessed; some asked one question, while others used instruments developed for this purpose. The extent to which differences in assessment explain some of the heterogeneity is not clear. In each of these studies,

the percentage of evening types tended to be highest among women with the longest durations of night work (either 10 to 20 years or at least 20 years) and lowest among women with no night work.

Occupation and race

Four studies included either nurses or health professionals exclusively (Lie *et al.* 2011, Hansen and Stevens 2012, Vistisen *et al.* 2017, Wegrzyn *et al.* 2017), and three others included them as a smaller analytic subpopulation (Grundy *et al.* 2013a, Travis *et al.* 2016 Million Women Cohort). Thus, the evidence for the association of night work with breast cancer was not restricted to nurses or health professionals. Increased risks were found for nurses and health-care workers (Lie *et al.* 2011, Hansen and Stevens 2012, Wegrzyn *et al.* 2017, [NHS2 cohort]), for other occupations, including textile workers, and in studies of mixed occupations. Similar patterns of risk were reported for both health-related and non-health-related occupations (Grundy *et al.* 2013a, Travis *et al.* 2016).

Race and ethnicity were also not specifically controlled for in any of the studies. All of the night work studies with the exception of the Wegryzn *et al.* (2017) U.S. NHS/NHS2 study were conducted in European or Asian populations, and none controlled for race. The NHS/NHS2 study would potentially be most informative for the U.S. population concerning the risk of night work among African-American women. However, only a small number of these women are part of the study population, and results are not reported by race. Although it has been hypothesized that the effect of light at night on breast cancer may vary by race, in particular, that Asian or brown-eyed individuals should be less sensitive to light at night than blue- or green-eyed individuals, findings on melatonin suppression are unclear (see Section 2). While the Pronk *et al.* (2010) study of Asian women in Shanghai found no effect of night work on breast cancer, the Chinese case-control study by Wang *et al.* (2015a) found an overall positive relationship between "ever" night shift work and breast cancer risk. However, the Pronk *et al.* (2010) cohort was older and primarily postmenopausal, and had a very short follow-up period, whereas over 60% of women in Wang *et al.* (2015a) were premenopausal. Thus, it is not clear whether race/ethnicity was the source of heterogeneity in these Chinese studies.

Chance, bias, or confounding

Alternative explanations for the evidence in these studies cannot be completely ruled out. Findings of elevated breast cancer risk among night workers in case-control studies have been discounted because of the probability of recall bias (Travis *et al.* 2016). Most of these studies collected data before 2007, when shift work first became widely publicized as a potential risk factor for breast cancer. In addition, two studies reporting elevated breast-cancer risks did not find an association of breast cancer with electromagnetic fields, an exposure with no known association with breast cancer included in questionnaires, which helps to alleviate concerns for differential recall bias. Furthermore, questions about lifetime job-by-job work schedules in most of the case-control studies reduced the likelihood of recall bias, and memory of night work in the past appeared to agree well with records of night work in populations where these data were available.

Studies were conducted in the United States, Europe, and Asia and included populations of shift workers that differed widely with respect to their reproductive history (e.g., parity, age at first

full-term pregnancy), lifestyle factors (e.g., alcohol, smoking, physical activity, and hormone use), body mass index, and socioeconomic background, all factors related to breast cancer risk. However, almost all studies considered these risk factors as well as physical activity and BMI, and adjustments for potential confounders made no material difference in any of the studies reporting both crude and adjusted estimates. None of the nurses' studies took into account co-exposures to carcinogens in the workplace; however, nurse cohorts only accounted for 3 of the 17 studies finding evidence of an association and the remaining positive studies were population-based studies in which specific occupational co-exposures are less of a concern.

Shift workers in the United States tend to have lower adherence to breast cancer screening guidelines and have lower income, education, and use of health insurance (Tsai *et al.* 2014). However, such a difference in breast cancer screening between day and night workers is not likely to explain the elevated risks among night workers found across the studies in this review. Such a difference would likely bias the relative risks toward the null, with fewer breast cancer cases detected in the exposed group. Tsai *et al.* (2014) also noted that shift workers in particular industries and occupations (e.g., manufacturing, food service and preparation, personal care services, and production) were least likely to get regular mammographies. Four studies controlled for mammography use or number of mammograms. In a study of nurses (Wegrzyn *et al.* 2017), an additional model was run to determine evidence of bias due to differential screening in shift workers and day workers but none was found. One additional population-based study (O'Leary *et al.* 2006) found that shift workers reported a lower number of mammograms but this variable did not reach the criteria for inclusion in the final model. Finally, as most studies controlled for socioeconomic status it is likely that confounding from screening would be somewhat controlled.

3.3 LAN

In general, the adequacy of the proxies used to define and measure LAN in relation to their likelihood to cause circadian disruption was considered in evaluating the studies. For example, brighter light, the color spectrum of light, and more frequent exposures to light during biological night may be more likely to cause circadian disruption. The key issues applicable specifically to outdoor environmental LAN and indoor LAN are discussed in detail below.

3.3.1 Overview of study methods and characteristics

The environmental LAN studies are listed in Table 3-8.

Table 3-8. Studies of breast cancer and environmental (outdoor and indoor) LAN

Reference	Population	Breast cancer incidence sources	Exposure information and assessment
Outdoor LAN			
Garcia-Saenz *et al.* 2018	**MCC-Spain study** Population-based case-control study Enrolled 2008–2013 380 cases; 490 controls 0% shift workers	Major hospitals in study area Receptor status	In-person interviews for covariates and residential history Outdoor LAN: images from International Space Station for Barcelona and Madrid for 2012–2013 with remotely sensed upward light intensity and blue light spectrum for each geocoded longest residence Metrics: (1) outdoor visual ALAN as a proxy for luminance - visual light; and (2) melatonin suppression index (MSI) blue light
James *et al.* 2017	**U.S. Nurses Health Study 2 (NHS2)** Cohort study 109,672 registered nurses Enrolled 1989–2013 3,549 cases 82% premenopausal at baseline 42% of person-years from shift workers	Self-report, proxy, postal system, or NDI Validated by medical record review, by state cancer registries, next of kin, or death records	Self-administered mail questionnaire for covariates and residential history Outdoor LAN, satellite imagery data (DMSP) high-dynamic-range data 2006–2010 Metrics: cumulative average outdoor LAN Cumulative average outdoor LAN: 29.7 $nW \cdot sr^{-1}/cm^2$ Broad national range of outdoor LAN levels 0.39 to 248.1 $nW \cdot sr^{-1}/cm^2$
Hurley *et al.* 2014	**U.S. California Teacher Study** Cohort study 106,731 active and retired female enrollees Enrolled 1995–1996 5,095 cases 46% < 50 yr % shift workers NR	California Cancer Registry	Self-administered mailed questionnaire for covariates and residential history Outdoor LAN, satellite imagery data (DMSP) 2006 high-dynamic-range data Metrics: average annual nighttime radiance value assigned to residence at baseline 17% with highest outdoor light exposure by DMSP LAN range = 0–175 $nW \cdot sr^{-1}/cm^2$ Mean LAN = 35 $nW \cdot sr^{-1}/cm^2$ Median LAN = 32 $nW \cdot sr^{-1}/cm^2$
Bauer *et al.* 2013	**Georgia U.S.A.** Case-referent study Enrolled 2000–2007 33,503 cases 14,314 lung cancer referents 29% < 54 yr % shift workers NR	Georgia Comprehensive Cancer Registry	Georgia Comprehensive Cancer Registry and U.S. Census Data. Outdoor LAN, satellite imagery data, DMSP-OLS Metrics: low (0–20 $nW \cdot sr{-}1/cm^2$) medium (21–41 $nW \cdot sr{-}1/cm^2$ high (> 41 $nW \cdot sr{-}1/cm^2$) 59.7% with high LAN levels LAN range = 0 to 63 $nW \cdot sr{-}1/cm^2$

Reference	Population	Breast cancer incidence sources	Exposure information and assessment
Indoor LAN			
Garcia-Saenz *et al.* 2018	**MCC-Spain study** Population-based case control study Enrolled 2008–2013 1,219 cases; 1,385 controls 30% < 50 yr of age	Major hospitals in study area Receptor status	Indoor LAN In-person interviews Metrics: Self-reported level of light in sleeping area at age 40; or at diagnosis/interview for those < 40 78% controls exposed to some light
Johns *et al.* 2018	**Generations Study U.K.** Cohort study Enrolled 2003–2012 105,866 women 1,775 cases Average age = 46.5 yr 16.9% shiftwork in past 10 yr	Self-report and NHS Central Registers Verified against medical records	Indoor LAN; self-administered mailed or online questionnaire Metrics: At recruitment and at age 20 read easily at night at work or see across the room (high); see hand in front of you, but not across the room (medium); too dark to see hand, or wear a mask (low); Yes/No night waking and exposure to light Exposed: 79.1% reported medium or high LAN
White *et al.* 2017	**Sister Study, U.S.A.** Cohort study Enrolled 2003–2009 50,884 women 2,736 cases Average age = 55.6 yr 0% shift workers	Annual health updates and follow-up questionnaires 81.1% of cases verified by medical records	Indoor LAN, computerized telephone questionnaire Metrics: Type of light on when sleeping; turning light on upon awaking during the night 82.3% exposed to some indoor LAN
Keshet-Sitton *et al.* 2016	**Israeli Jewish workers** Population-based case-control study Enrolled 2010–2014 93 cases, 185 controls Average age = 54.5 yr in controls 0% shift workers	Comprehensive Cancer Center in Soroka Medical Center, Beer-Sheva, and the Baruch Padeh, Poria Medical Center in Tiberius	Indoor LAN, self-administered questionnaire Metrics: subjective light level in bedroom at night, falling asleep or sleeping with TV on, light penetrating the room from outside, dim light on during the night, closed shutters; turning lights on when waking in the night; type of bedroom and bed light illumination (long or short wavelength); residing near strong ALAN sources during five years prior to diagnosis or reference date % exposed NR
Hurley *et al.* 2014	**U.S. California Teacher Study cohort** See outdoor light	See outdoor light	Indoor LAN, self-administered mailed questionnaire Metrics: non-users, heavy, light, and medium based on frequency of using bright light per week, months used, and hours per night 5% used bright light during sleeping 17% of bright light users had the highest level of frequency and duration

Reference	Population	Breast cancer incidence sources	Exposure information and assessment
Fritschi *et al.* 2013	**BCEES Western Australia case** Population-based case-control study Enrolled 2009–2011 253 cases; 335 controls 100% shift workers	Western Australia Cancer Registry	Indoor LAN at work, mailed questionnaire with follow-up telephone interview for shift work Metrics: reading easily at night at work (high), able to see but not well enough to read at work (medium), enough light to read in bedroom when sleeping during the day (low) 51% controls reported high LAN
Kloog *et al.* 2011	**Northern Israel** Population-based case-control study Enrolled 2000 794 cases; 885 controls Mean age = 64.6 yr % shift workers NR	Residents of northern Israel at time of diagnosis identified from all hospitals in Israel	Indoor LAN, in-person interview Metrics: bedroom light levels, light coming from outside the bedroom, availability of shutters in the bedroom, and sleeping with the television on 22.6% of controls reported high ambient light levels
Li *et al.* 2010	**Connecticut, U.S.A.** Population-based case-control study Enrolled 1994–1997 363 cases; 356 controls 20.4%/35.7% of cases/controls premenopausal % shift workers NR	Yale-New Haven Hospital system and Comprehensive Cancer Center; Connecticut Tumor Registry	Indoor LAN, in-person interview Metrics: lights on while sleeping, presence of various types of exterior light affecting the sleeping area, use of shades while sleeping, radio/TV/hall LAN on while sleeping during 10 years prior to diagnosis or reference date 7.2% controls kept light on while sleeping
O'Leary *et al.* 2006	**EBCLIS, NY, U.S.A.** Population-based case-control study Selected population Enrolled 1996–1997 487 cases; 509 controls 39% premenopausal	Hospitals in Nassau and Suffolk Counties, NY	Indoor LAN, staff-administered in-home interview Metrics: frequency of turning on lights during sleep hours in 5 yr prior to diagnosis 7.6% worked nights in 15 yr prior to diagnosis/reference 5.6% of controls turned lights on ≥ 2 times/night and ≥ 2 nights/wk
Davis *et al.* 2001b	**Fred Hutchinson Cancer Research Center, WA, U.S.A.** Population-based case-control study 1992–1995 enrollment 808 cases; 708 controls 33% premenopausal	Cancer surveillance system of the Fred Hutchinson Cancer Research Center, Seattle, WA	Indoor LAN, in-person interview Metrics: turning on lights at night; % of time light on at night, ambient light levels at night, turning off lights to sleep in 10 years prior to diagnosis or reference date 6.0% ever nights in 10 yr prior to diagnosis 3.4% of controls had brightest ambient lights in bedroom

ALAN = artificial light at night; BCEES = Breast Cancer Employment and Environment Study; Australia; DMSP = U.S. Defense Meteorological Satellite Program; EBCLIS = Electromagnetic Fields and Breast Cancer on Long Island Study; LAN = light at night: MCC = Multi Center Case-Control- Study, Spain.

Five studies included measures of outdoor LAN: two cohort studies (Hurley *et al.* 2014, James *et al.* 2017), two case-control studies (Keshet-Sitton *et al.* 2016, Garcia-Saenz *et al.* 2018), and one case-referent study (Bauer *et al.* 2013). Ten studies (two cohort studies and eight case-control studies) included measures of indoor LAN, specifically LAN in the sleeping area; three of these reported on both indoor and outdoor LAN (Hurley *et al.* 2014, Keshet-Sitton *et al.* 2016, Garcia-Saenz *et al.* 2018). The studies of LAN in the sleeping area varied by the inclusion and treatment of night workers: three studies limited analyses to non-shift workers (Keshet-Sitton *et al.* 2016, White *et al.* 2017, Garcia-Saenz *et al.* 2018); two studies asked questions about shift work but did not integrate this information into the analyses (Davis *et al.* 2001b, O'Leary *et al.* 2006); one study incorporated information on shift work during the past 10 years into the analysis (James *et al.* 2017); three studies made no mention of shift work (Li *et al.* 2010, Kloog *et al.* 2011, Hurley *et al.* 2014); and one study restricted data on LAN to shift workers when they were working nights (Fritschi *et al.* 2013).

3.3.2 Evaluation of study quality

Studies measuring outdoor and indoor LAN were evaluated separately for their utility. A detailed evaluation of study quality for the LAN studies is provided in Appendix C, Table C-1. The most important issues bearing on the overall quality in these studies were the potential for selection bias and study attrition, exposure misclassification, confounding, and study sensitivity.

Outdoor LAN

Selection

The Bauer *et al.* (2013) study raised concerns regarding selection bias based on the removal of approximately 20% of addresses because they were not geocoded; these occurred particularly in rural areas, where LAN is low. Although the authors stated that rural Georgia has a higher proportion of white than black residents, there are notable exceptions — in many Georgia counties, the proportion of black residents is 50% to 78%, and these are largely rural areas in the southwest of the state, where addresses are likely to be too nonspecific to geocode, and LAN might be minimal. Being far from urban centers, these counties might also have had fewer diagnosed cases of breast cancer. Elimination of addresses in these counties may have biased the results away from the null. In the Garcia-Saenz *et al.* (2018) study, only 52% of potential controls participated, suggesting the possibility of attrition bias in an unknown direction. The Keshet-Sitton *et al.* (2016) study included only one question about residing near a strong source of LAN. Selection bias might have been operating in this study; case and control subjects might not have been selected from the same population, as the control subjects were friends or acquaintances of case subjects and women recruited through personal meetings in schools. Although home residence was matched, more control than case subjects lived in rural areas, defined as a settlement with fewer than 2,000 residents. In addition, significantly more control than case subjects were non-native born.

Exposure misclassification

Two separate issues were considered in evaluating exposure misclassification — first, whether an exposure surrogate was an acceptable proxy for the exposure of interest (i.e., the extent of the exposure to LAN to the individual is associated with circadian disruption, see Section 2 for studies on melatonin suppression), and second, how precisely the proxy was measured. In three

of four studies, outdoor LAN measurements based on geocoded addresses were measured using light levels from satellite imagery data from the U.S. Defense Meteorological Satellite Program (DMSP; NOAA 2015). A study in Georgia (unpublished data cited as part of the study by Bauer *et al.* 2013) found a significant correlation with satellite data and ground level outdoor circadian light readings as measured by the Daysimeter. However, a study of teachers in Albany, New York and Vermont (rural, suburban, and urban areas) found no correlation between sky brightness (superimposed on addresses but not geocoded) and indoor light (e.g., light levels in the bedroom or in the bedroom window) nor with personal light exposure measurements measured at the eye between twilight and night time using a Daysimeter (which were not location specific). Personal light levels were predicted to suppress melatonin by ~ 7%. In addition, information on the use of individual activities related to exposure to LAN (such as using blackout curtains) was not available in any of the cancer studies of exposure to outdoor light.

Regarding the precision of the proxy measurement, the particular DMSP datasets and methods used to create exposure variables differed among the three studies and had implications for misclassification bias. Bauer *et al.* (2013) used the DMSP low-dynamic-range data, whereas James *et al.* (2017) and Hurley *et al.* (2013) used the DMSP high-dynamic-range data, which includes a much broader range of radiance in urban areas, thus reducing potential exposure misclassification in urban areas. The low-dynamic-range data do not vary beyond 63 $nW \cdot sr^{-1}/cm^2$ in urban areas, which was the upper limit reported by Bauer *et al.* (2013); for James *et al.* (2017) and Hurley *et al.* (2013), the upper limits were 248 and 175 $nW \cdot sr^{-1}/cm^2$, respectively.

The Garcia-Saenz *et al.* (2018) study used a different methodology to calculate visual LAN and the melatonin suppression index (MSI), which attempted to address the limitations in the previous studies using only satellite images. Their method was based on images taken with commercial Digital Single-Lens Reflex (DSLR) cameras of two cities by astronauts aboard the International Space Station (ISS) in 2012 and 2013 provided by the Earth Science and Remote Sensing Unit, NASA Johnson Space Center (NASA 2018). Unlike satellite images, these images provided information in three spectral bands in the visual range (RGB: red [R], green [G], blue [B]) with spatial resolution of about 30 m. The estimate of visual light was reported as well as the estimate for the MSI. The MSI represents the degree to which the spectrum shape of different lights are effective in suppressing the melatonin production compared to a standard which corresponds approximately to the average midday sunlight in Western and Northern Europe.

Each study used a different approach for handling address changes, which might have affected exposure misclassification. Only James *et al.* (2017) incorporated time-varying information on LAN, using updated addresses and DMSP values. Hurley *et al.* (2014) used the baseline address to assign LAN values and conducted sensitivity analyses comparing the overall population with a subset of the population that resided at the same address throughout the study period; the results were similar. Bauer *et al.* (2013) extracted and averaged LAN values for the one known address at diagnosis (or referent date) for each year of exposure prior to diagnosis, which ranged from 9 to 16 years, assuming that the address at diagnosis had been stable over those years prior to diagnosis. The direction and magnitude of misclassification resulting from this assumption is unknown; it depends on the residential mobility of the population and other population

characteristics. The Garcia-Saenz study geocoded the longest residence, which in this low mobility population was greater than 30 years for 80.2% of the respondents.

Outcome misclassification

It is not clear whether the outcome methods in Bauer *et al.* (2013) clearly distinguished between relevant diseased and non-diseased participants, or whether lung-cancer cases were the appropriate comparison group, as it is unclear whether lung cancer is related to shift work or LAN (see Section 4). If LAN is related to lung cancer, then the estimate of effect in this study would be biased towards the null. Each of the other studies had low potential for bias due to outcome misclassification.

Sensitivity

If LAN exposure is most relevant at younger ages, all the outdoor studies have limited sensitivity to detect such an effect. Bauer *et al.* (2013) used different exposure windows, but none prior to 9 to 16 years before diagnosis in this older group of cases (mean age = 60, standard deviation = 14). In addition, the range of exposure levels was attenuated by use of low-dynamic-range DMSP data. In the Hurley *et al.* (2014) population, about 16% of women were under the age of 40 at baseline, when the current-year satellite image data were applied, meaning that LAN exposure data at young ages were not available for most women in the cohort. Data from an early exposure window were missing in James *et al.* (2017) as well, but because this cohort was younger at baseline and had a larger proportion of premenopausal women at the time of exposure measurement than either of the other studies, it has greater sensitivity to detect an effect of age at exposure. The Garcia-Saenz *et al.* (2018) population was somewhat older, and exposure to LAN was derived from recent LAN data (2013 to 2014); while this urban population was relatively stable, it is unknown how much LAN changed in the two cities over the decades when the population was younger, 30 to 40 years earlier. Finally, whether the LAN measurements from satellite data indicate results with levels high enough to cause circadian disruption was considered in the exposure-assessment section.

Potential confounding

Each of these studies raised some concern about confounding. In James *et al.* (2017), factors associated with outdoor LAN may not have been fully controlled for by factors included in the models; alternatively, factors unrelated to LAN but included in the model may have reduced the estimates of the effect. Regarding confounding from other sources of LAN that might influence the breast cancer and LAN relationship, only James *et al.* (2017) reported on the percentage of person-time that was rotating shift work and stratified analyses by shift work. The final models used by Hurley *et al.* (2014) included several variables unrelated to LAN, which might have lowered the risk estimates. Bauer *et al.* (2013) measured several relevant potential confounders on a county-wide, not individual, basis (parity, education, and smoking, but not race). Alcohol consumption was not controlled for in this analysis, and residual confounding was likely to remain because of the lack of individual-level data. As socioeconomic factors are associated with urban light, Garcia-Saenz *et al.* (2018) adjusted for socioeconomic status both at the individual and area level; however, adjusting for socioeconomic status may not resolve completely the potential bias introduced by high attrition in the controls.

Overall utility

Table 3-9 summarizes the bias and quality evaluation of the studies of breast cancer and environmental LAN. The Garcia-Saenz *et al.* (2018), James *et al.* (2017) and Hurley *et al.* (2014) studies each had moderate utility; Bauer *et al.* (2013) had low overall utility.

Table 3-9. Summary of study quality evaluation: LAN and breast cancer

Citation	Selection[a]	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility[b]
Outdoor LAN								
Garcia-Saenz *et al.* 2018	++	++	+++	+++	+++	+++	++	++
James *et al.* 2017	+++	+/++	+++	++	+++	+++	++	++
Hurley *et al.* 2014 (Outdoor)	+++	+/++	+++	++	+++	+++	+	++
Bauer *et al.* 2013	+	+	+++	+	+++	+++	+	+
Keshet-Sitton *et al.* 2016 (Outdoor)	+	+	+	++	+++	++	+	+
Indoor LAN								
Garcia-Saenz *et al.* 2018	++	++	+++	+++	+++	+++	++	++
Johns *et al.* 2018	+++	+	+++	++	+++	+++	+	+
White *et al.* 2017	+++	+	++	+++	+++	+++	+	+
Keshet-Sitton *et al.* 2016 (Indoor)	+	++	+	++	+++	++	++	++
Hurley *et al.* 2014 (Indoor)	+++	++	+++	++	+++	+++	++	++
Fritschi *et al.* 2013	++	+	+++	+++	++	+++	++	+
Kloog *et al.* 2011	++	++	++	++	++	++	++	++
Li *et al.* 2010	+++	+	+++	++	++	+++	+	+
O'Leary *et al.* 2006	++	+	+++	++	+++	+++	+	+
Davis *et al.* 2001b	+++	++	++	++	+++	+++	++	++

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

Indoor LAN studies

Selection

Attrition in the case-control studies (O'Leary *et al.* 2006, Kloog *et al.* 2011, Fritschi *et al.* 2013, Garcia-Saenz *et al.* 2018) might have introduced selection bias; issues regarding selection for the Keshet-Sitton *et al.* (2016) study addressed above are relevant for indoor lighting as well.

Exposure misclassification

These studies used several different metrics of exposure to light in the sleeping area. As with outdoor LAN, the relevant issues are how well these metrics corresponded to actual levels of LAN that could reduce melatonin levels and/or cause circadian disruption and how accurately they were measured.

Exposure metrics. The studies used several metrics that could be roughly associated with lux levels, as described in Section 2: (1) daylight or sleeping during the day (200 to 400 lux), (2) various self-reported levels and durations of light in the sleeping area at night or before sleep, (3) awakening at night with LAN (5 to 200 lux), and (4) light from outside the sleeping area or use of shades or shutters (< 1 lux) or residing near strong sources of artificial LAN. Section 2 describes results from several studies concluding that changes in melatonin levels can occur at levels of exposure to polychromatic white light as low as 30 lux. Therefore, LAN metrics that capture exposure to types of light corresponding to greater than 30 lux may be most relevant; such LAN would include light from room LAN, e-devices, and television. Another metric used that was not specifically associated with lux levels was "non-peak sleep," defined as not sleeping between 1:00 AM and 2:00 AM, when the melatonin peak occurs. None of these metrics represented measured light, specific types of LAN, or duration of LAN. In addition, alignment of the exposure categories and lux levels was imperfect, and several categories overlapped.

Ideally, specific information about the type, level, and duration of LAN that could differentiate individuals with high and low exposure would be available for each analysis; however, there was inadequate information available to assess the level of light exposure in the sleeping area or the conditions of LAN. Seven studies collected data on the subjective level of light in the sleeping area at night, the metric most likely to be useful for differentiating exposure levels (Davis *et al.* 2001b, Kloog *et al.* 2011, Fritschi *et al.* 2013, Hurley *et al.* 2014, Keshet-Sitton *et al.* 2016, Garcia-Saenz *et al.* 2018, Johns *et al.* 2018). However, none of these studies used methods that were precise enough to align a subjective level of light with specific lux levels, nor the light spectrum, and none were easily comparable with one another. For example, subjective levels considered to be "high" may vary within and across populations. Davis *et al.* (2001b) and Johns *et al.* (2018) asked participants to rate the level of ambient light in their bedroom on a scale of 1 to 5 or 6, with "night" being defined as the time between turning off the lights to go to sleep and waking up, the lowest light level defined by wearing a mask to keep light out, and level 6 defined as having enough light to be able to read comfortably.

Fritschi *et al.* (2013) assessed LAN by asking women whether they could read easily at night at work (high exposure) or could see but not well enough to read at work (medium exposure). Those women who did not fit either of these definitions but whose bedrooms were light enough to read in when they were sleeping during the day were assigned low exposure. Hurley *et al.* (2014) defined levels using categories of hours per night, days per week, and months per year

sleeping with a bright light. The criteria for "heavy" users were at least 10 months of use for at least 5 days per week and 7 hours per night; the criteria for "light" users were 0 to 3 months, 1 to 3 days per week, and 1 to 2 hours per night; and "medium" users were defined as those with all other combinations of duration and frequency. Garcia-Saenz *et al.* (2018) asked women to report on light in the sleeping area at the age of 40 using a four-digit Likert scale: a) total darkness, b) almost dark, c) dim light, and d) quite illuminated. No additional specification of the scale was provided. For subjects < 40 years of age, this level was reported for the time of diagnosis or interview; responses were similar for those ≥ 40 and those < 40 years of age (Pearson R = 0.90). Neither Keshet-Sitten *et al.* (2016) nor Kloog *et al.* (2011) provided definitions for subjectively reported levels of light, but rather reported on continuous, not categorical, levels.

Quality of the measurements. The ability of study subjects to correctly recall past light levels and LAN practices in the bedroom bears on the quality of the measurements and may vary according to the recency of the exposure being asked about. Studies asked about time just prior to diagnosis (Kloog *et al.* 2011, Garcia-Saenz *et al.* 2018 [cases < 40 years old at interview], one year prior to recruitment (Hurley *et al.* 2014, White *et al.* 2017, Johns *et al.* 2018), for awakening during the night with lights on 5 years prior to diagnosis (O'Leary *et al.* 2006), 10 years prior to diagnosis (Davis *et al.* 2001b, Li *et al.* 2010, Johns *et al.* 2018 for light level), or 10 to 15 years prior to diagnosis (Keshet-Sitton *et al.* 2016). Johns *et al.* (2018) and Garcia-Saenz *et al.* asked about light level in the sleeping area at age 20 and at age 40, respectively, but for women many years older than these ages, memory of this exposure is likely to be misclassified. Although the 10 to 15 years prior to diagnosis may be the most relevant time for cancer etiology, ability to adequately recall LAN conditions might have been low. Recall bias might be somewhat of a consideration, although the association of light in the sleeping area with breast cancer was not directly addressed in the IARC report on shift work in 2007, and it is unknown to what extent this association was recognized in any of these studies at the time of data collection.

Sensitivity

In all studies, only a small proportion of women reported exposure to high levels of LAN when asked to rate the level in the sleeping area; however, at least 30 women in each study were classified as highly exposed using their respective classifications. Finally, the exposure window was not sufficiently described in several studies (Kloog *et al.* 2011, Fritschi *et al.* 2013, White *et al.* 2017).

Potential confounding

Overall, these studies raised low to moderate concerns about potential confounding, as most controlled for potential confounding factors. However, some studies likely over-controlled for variables likely to be in the breast-cancer pathway (e.g., BMI, age at menarche), introducing a bias towards the null particularly when unrelated to exposure.

Overall utility

None of these studies were considered to have high utility for evaluating the relationship between breast cancer risk and exposure to light that caused circadian disruption. Five of the studies were considered to have moderate utility for this evaluation, based on their attempts to capture levels of LAN in the sleeping area (Davis *et al.* 2001b, Kloog *et al.* 2011, Hurley *et al.*

2014, Keshet-Sitton *et al.* 2016, Garcia-Saenz *et al.* 2018). The remaining five studies were considered to have low utility.

3.3.3 Breast cancer hazard assessment: Environmental LAN

Findings of the studies of outdoor and indoor environmental LAN included in the analysis are provided in Appendix C, Table C-2. The level of confidence in the evidence ("evidence," "some evidence," "null," or "inconclusive") from the individual studies of environmental LAN was reached by considering the strength of the association, the potential for specific biases or confounding, the quality of the exposure assessment, the expected directions and distortions of those potential biases or confounding, and the sensitivity of the study to detect an effect. The evidence is summarized in a heat map below (see the "Indoor LAN" section).

Outdoor environmental LAN

Overall, all four satellite studies of outdoor environmental LAN and the study by Keshet-Sitton (2016) found a positive association between outdoor LAN and increased breast cancer risk. However, there are concerns whether satellite data is measuring LAN or behaviors associated with LAN, and whether LAN from the outdoors is sufficiently high to disrupt circadian processes.

The four studies reported statistically significant excess risks of breast cancer among women in the highest LAN quintiles of exposure (14% in James *et al.* 2017, 12% in Hurley *et al.* 2014, 12% in Bauer *et al.* 2013, 47% for blue-light MSI in Garcia-Saenz *et al.* 2018, but no relationship between visual light and breast cancer). Hurley *et al.* (2014) and James *et al.* (2017) both reported statistically significant exposure-response relationships (*P*-values of 0.06 and 0.02, respectively), and suggested that the effect of outdoor LAN was seen primarily among premenopausal women in the highest quintile of exposure, reporting statistically significant excess risks of breast cancer of 34% and 20%, respectively, with virtually no excess risk among postmenopausal women (neither study reached statistically significant interaction). Garcia-Saenz *et al.* (2018) reported that exposure to the highest versus lowest tertile of blue light spectrum was slightly higher in postmenopausal women (OR = 1.31, 95% CI = 0.84 to 2.03) compared with premenopausal women (OR = 1.09, 95% CI = 0.57 to 2.09; *P* for interaction = 0.7).

The findings do not seem to be explained by shift worker status as no significant effect modification for night shift work was found in the NHS2 study (James *et al.* 2017) and the Spanish study excluded shift workers (Garcia-Saenz *et al.* 2018).

Results regarding the effect of outdoor LAN on subtypes of breast cancer varied across the three studies reporting on them: two studies found elevated risks among women with hormone receptor-positive tumors (ER+ tumors, James *et al.* 2017); ER+/PR + tumors, Garcia-Saenz *et al.* 2018); whereas in contrast, Hurley *et al.* (2014) reported a marginally higher risk among women with ER– and PR– tumors compared to hormone receptor-positive tumors but noted that analyses were limited by small numbers and no actual data were reported.

Additional results indicated statistically significant interaction between never, past, and current smokers (*P* = 0.008), such that past smokers had a 23% increased risk, and current smokers a statistically significant 54% increased risk of breast cancer (James *et al.* 2017).

Consistent with these findings, seven ecological studies of countries or communities reported that LAN, as measured by satellite images, was associated with breast cancer incidence (Kloog *et al.* 2008, Kloog *et al.* 2010, Kim *et al.* 2015, Rybnikova *et al.* 2015, Portnov *et al.* 2016, Keshet-Sitton *et al.* 2017, Rybnikova and Portnov 2018). All of these studies, however, were limited by the lack of individual-level data on exposure, confounding, and outcome. However, Rybnikova and Portnov (2018) reported on the effect of different subspectra using a multi-spectral year 2011 satellite image for Greater Haifa Metropolitan Area in Israel. They reported a positive association between breast cancer incidence and short-wavelength (blue) LAN subspectrum, and insignificant associations with green and red subspectra.

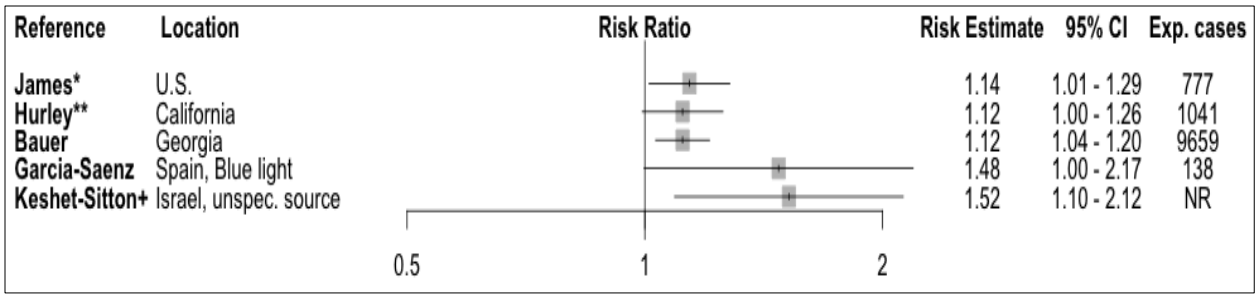

Figure 3-9. Risk of breast cancer and light at night (LAN)

CI = confidence interval.
*Trend test $P = 0.02$.
**Trend test $P = 0.06$.
+Unspecified outdoor source of LAN.

Indoor LAN

Of the indoor LAN studies, two of the five studies with moderate utility and one of the five low utility studies provided some evidence of an effect. The major predictor of heterogeneity across these indoor LAN studies was the variation in surrogates used to measure approximate LAN levels (lux) in the sleeping area and the lack of specificity regarding lux levels. The results are summarized in Table 3-10.

Table 3-10. Heat map of indoor LAN results (risk estimate by exposure metric)

Citation	Garcia-Saenz	Johns	White	Keshet-Sitton	Hurley	Fritschi	Kloog	Li	O'Leary	Davis
Highest ambient level in sleep area (~100–200 lux)		≤ 1		≤ 1	1.13 ns	1.25 ns				1.4 ns
Turns on light on during waking (~20–200 lux)		≤ 1	≤ 1	≤ 1				1.4[a] ns	1.65[b] sig	≤ 1
Room light on while reading before sleep (~200)				≤ 1						
Medium light in the sleeping area (~20–100 lux)		≤ 1	≤ 1	≤ 1	≤ 1	≤ 1				≤ 1
Low levels (5–80 lux)[c]		≤ 1	≤ 1	1.26[c]	1.17 ns	≤ 1	≤ 1	≤ 1		≤ 1
Low to high subjective light intensity[d], continuous	≤ 1			1.2[d] ns			1.22[d] sig			1.1 ns
Any use of LAN at night					≤ 1					
Bed light used for reading before sleep				≤ 1[e] sig						
Light from the outside (~< 1 lux)			≤ 1	≤ 1[f] sig			≤ 1	1.2 ns		
Frequency of non-peak sleep										1.7 sig
Daylight or sleeping during the day (~200–400 lux)			≤ 1			1.25 ns		1.4[a] ns		

ns = not statistically significant; sig = statistically significant.
[a]Postmenopausal.
[b]Frequency of waking and turning on lights ≥ 1/week and ≥ 2/night.
[c]Reported use of specific low sources such as dim light, TV, clock radio, hall light, nightlight in the sleeping area hall.
[d]Self-reported ordinal levels of subjective light intensity from low to high.
[e]Reported that participants used long wavelength incandescent/halogen illumination as bed lights in this study.
[f]Reported closed shutters in the sleeping area.

Among the five moderate-utility studies, two found some evidence of breast cancer being associated with the highest self-reported ambient light level (40% statistically significant excess risk; Davis *et al.* 2001b), or subjective light level (22% statistically significant excess risk [Kloog *et al.* 2011]). In addition, Davis *et al.* (2001b) reported a significant 70% excess risk of breast cancer associated with frequent non-peak sleep. Kloog *et al.*(2011) reported a modest, but statistically significant effect of increasing light levels.

Results from the Hurley *et al.* (2014) study were inconclusive as there was no clear pattern of risk, and results from the highest level of light were only weakly elevated. Garcia-Saenz *et al.* (2018) reported a non-statistically significant inverse relationship between the highest level of light and breast cancer. Results from Keshet-Sitton *et al.* (2016) for indoor light are inconclusive

as there is no effect with high reported levels of light, but a weak non-significant relationship between low light levels and breast cancer.

Among the five low-utility studies, only one study indicated some evidence of an effect (O'Leary *et al.* 2006), reporting a 65% increased risk of breast cancer among women who woke up at least once a week and turned on the lights at least twice per night.

Results from the four low utility studies were either inconclusive or null. The results from the studies by White *et al.* (2017) and Johns *et al.* (2018) were null; however, the Johns *et al.* (2018) study reported a significantly reduced risk of breast cancer among premenopausal women with ER+ breast cancer and elevated risks of postmenopausal ER– breast cancer among women with high and medium self-reported ambient light levels in the sleeping area. Fritschi *et al.* (2013) queried LAN only among shift workers, and observed a non-statistically significant 25% elevated risk of breast cancer among women who worked at night in light sufficient to read easily and among those who had slept with medium or high levels of light for up to 19 years, yielding inconclusive results. The results from the Li *et al.* (2010) study were also inconclusive.

Key issues and chance, bias, and confounders

Outdoor LAN

Whether satellite images are an appropriate proxy for LAN or proxies for other behaviors of daily living associated with LAN, or whether the LAN measurements from satellite data at the residence are sufficient to cause circadian disruption remain unanswered questions. The finding by Garcia-Saenz *et al.* (2018) that breast cancer risk was associated with the blue-light spectrum but not the full visual spectrum suggests that this measure of outdoor LAN may be more relevant. However, to understand the association between outdoor LAN and breast cancer, additional studies measuring exposure to all sources of light at night and their intensities and spectral characteristics are needed. Regarding confounding, while James *et al.* (2017) adjusted for air pollution and population density, other studies did not. Furthermore, other factors related to both breast cancer and LAN (Rybnikova *et al.* 2015) could potentially explain the associations observed in these studies.

Indoor LAN

Findings for indoor LAN were inconsistent across studies; the major predictor of heterogeneity across indoor LAN studies was the varied metrics used to measure indoor LAN, making it difficult to compare studies. The positive finding observed for some metrics in some studies may be due to chance, bias, or confounding. Whether the low light exposure levels and the light spectra used in the sleeping areas in indoor studies were sufficient to disrupt circadian rhythms remains a question. Furthermore, none of these studies considered LAN during the evening. Although some studies asked about shades or curtains to block light from outside, none presented such data by subjective levels of LAN. The use of incandescent vs. fluorescent or LED LAN varies across countries and time periods, and better representation of types of LAN could help with interpretation of these results. In addition, the average proportion of the night when LAN was used was measured only by Davis *et al.* (2001b); this metric could be used to stratify data on light levels. Overall, more precise measurements and a better understanding of the relationships of these various metrics to one another would strengthen this literature base.

3.4 Transmeridian travel

3.4.1 Overview of study methods and characteristics

Six publications of four independent cohort or nested case-control studies investigating the relationship between transmeridian travel and breast cancer in the United States and Scandinavian countries were identified (Reynolds *et al.* 2002, Linnersjö *et al.* 2003, Pinkerton *et al.* 2012, Pukkala *et al.* 2012, Schubauer-Berigan *et al.* 2015, Pinkerton *et al.* 2016). Three of these included analyses of the U.S. Pan American cohort (Pinkerton *et al.* 2012, Schubauer-Berigan *et al.* 2015, Pinkerton *et al.* 2016). The mortality study by Pinkerton *et al.* (2012) was not included in the assessment because of the high survival rates for breast cancer (as discussed above). The Pan Am cohort incidence studies were based on retrospectively collected exposure data from case and non-case subjects in the survival cohort. Other studies were based on administrative data, including both the retrospective cohorts (Reynolds *et al.* 2002, Pukkala *et al.* 2012) and a nested case-control study within a retrospective cohort (Linnersjö *et al.* 2003). Table 3-11 lists the five studies included in the cancer hazard evaluation.

Table 3-11. Studies of breast cancer and transmeridian travel

Reference	Population	Outcome assessment method	Exposure assessment and metrics
Pinkerton *et al.* 2016	Pan Am World Airways cohort, nested case-control in same cohort as Schubauer-Berigan 2015 344 cases and 5,749 controls in the cohort of 6,093 flight attendants	Same as Schubauer-Berigan *et al.* 2015	Retrospective telephone interview (2002–2005) and domicile records, 1930–1990 Metrics: standard sleep interval (SSI 10:00 PM–8:00 AM); cumulative travel hr; no. time zones crossed Exposed: > 933.9 time zones crossed; > 395 hours working during SSI; > 853 days employment duration Comparison: lower exposure and U.S. population rates Additional analyses for effect modification and confounding
Schubauer-Berigan *et al.* 2015	Pan Am World Airways cohort, nested case-control study 6,093 female flight attendants working at least 1 yr between 1953 and 1990	Invasive breast cancer incidence Self or proxy report and medical record review Registries in states with Pan Am domicile locations	Same as Pinkerton *et al.* 2016

Reference	Population	Outcome assessment method	Exposure assessment and metrics
Pukkala *et al.* 2012	Nordic Airlines Cohort (Finland, Iceland, Sweden) Retrospective cohort study of 8,507 female cabin crew employed at varying times per country generally between 1955 and 2005.	Breast cancer incidence Population-based registries in Finland, Iceland, Sweden, and Norway 577 cases	Historical airline timetables Metrics: flight duration, frequency, avg annual no. of 1-way flights crossing ≥ 6 time zones Exposed: 100+ flights crossing ≥ 6 time zones
Linnersjö *et al.* 2003	Swedish Scandinavian Airline System (SAS) Nested case-control study 2,324 female cabin crew employed between 1957 and 1994	Breast cancer incidence Swedish National Cancer Register and National Cause of Death Register 76 cases	Administrative records from SAS Metrics: employment duration, total block hr, block hr of high-altitude, long-distance flights Exposed: 10,000+ block hr; high-altitude, long-duration flight duty; ≥ 5,000 block hr of high-altitude long-distance flight
Reynolds *et al.* 2002	Association of Flight Attendants in California Retrospective cohort of 6,895 females diagnosed between 1988 and 1995	Breast cancer incidence California Cancer Registry 60 cases	Administrative records Metrics: international or domestic flights, duration of service, age at entry

3.4.2 Evaluation of study quality

A detailed evaluation of study quality of the transmeridian travel studies is provided in Appendix C, Table C-3, and the quality evaluation is summarized in Table 3-12. The most important issues bearing on the overall quality of these studies were the potential for exposure misclassification, confounding, and study sensitivity.

Table 3-12. Summary of study quality evaluation: transmeridian travel and breast cancer

Citation	Selection[a]	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility[b]
Linnersjö *et al.* 2003	++	+	+++	+	+++	+++	+	+
Pukkala *et al.* 2012	+++	++	+++	++	+++	++	++	++
Reynolds *et al.* 2002	++	+	+++	+	+++	+++	++	+
Pinkerton *et al.* 2016 *(update of Schubauer-Berigan et al. 2015)*	++	+++	++	+++	+++	+++	++	++
Schubauer-Berigan *et al.* 2015	++	+++	++	++	+++	+++	++	++

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

The studies with the highest utility for the evaluation were the nested case-control studies of the Pan Am cohort (Pinkerton *et al.* 2016 and Schubauer-Berigan *et al.* 2015), which were based on adequate exposure assessment, control of confounding factors, and study sensitivity. However, based on information provided by the studies together with the earlier mortality analysis, it is possible that these studies were limited by selection bias towards the null. The study sample consisted largely of survivors exposed to long durations of transmeridian flight at young ages, and surviving members of the incidence cohort had longer employment histories (based on flight records) than the full mortality cohort (Pinkerton *et al.* 2012). With respect to exposure assessment, the studies captured the number of time zones crossed, long-haul flights, and hours working during a standard sleep interval (10:00 PM to 6:00 AM), using self-reported data on employment duration and cumulative number of time zones crossed calculated with algorithms developed by Grajewski *et al.* (2003) and Waters *et al.* (2009). While this study captured working hours during the standard sleep interval and could conceivably be included with other night shift studies, it was not included in Section 3.2, as working on flights crossing time zones during the standard sleep interval can be considered to be a very different exposure scenario. That is, flying across time zones into daylight, with concomitant changes in the level and timing of lighting and meals is sufficiently different from working nights in one time zone. Although these studies were able to sufficiently differentiate between individuals with high and low exposure, the exposure metrics were highly correlated, and certain relevant analytic subsets included relatively few women. Pukkala *et al.* (2012) also attempted to quantify time zones crossed, using historical airline timetables to estimate flight durations and frequencies to which these women would have been exposed; women were classified as exposed if, based on their employment duration, they were estimated to have worked 100 or more flights crossing at least 4, 5, or 6 time zones. The calculations resulted in an estimate of at least 40% of flight crew being highly exposed.

Studies with less precise exposure metrics for circadian disruption used block hours and the number of high-altitude flights, with no further information about time zones crossed (Linnersjö *et al.* 2003), or whether flight assignments were considered to be primarily international or domestic (Reynolds *et al.* 2002), again with no additional information on time zones crossed or numbers of flights beyond years of employment.

Linnersjö *et al.* (2003) and Reynolds *et al.* (2002) did not have sufficient information to control for potential confounding. The remaining studies included potential confounding factors in their analytic models, and had either low or moderate risk of bias due to confounding. As with the shift-work studies, adjustment for potential confounding did not materially change the unadjusted estimates. The sensitivity of most of the studies was limited by their inability to differentiate the most highly exposed aircrew.

3.4.3 Breast cancer hazard assessment: Transmeridian travel

Findings of the studies of transmeridian travel included in the analysis are provided in Appendix C, Table C-4.

Overall, the studies provided inadequate evidence of an association between high levels of transmeridian travel and breast cancer risk. The results from studies of transmeridian travel were heterogenous, likely because of differences in exposure classification and low sensitivity of the studies to detect effects. The levels of evidence are summarized in Table 3-13.

Table 3-13. Summary of levels of evidence from studies of breast cancer and transmeridian travel

Study utility or informativeness	Level of evidence	Retrospective cohort studies	Retrospective nested case-control studies
Moderate: 2 studies	Some evidence		Schubauer-Berigan *et al.* 2015 Pinkerton *et al.* 2016 (in subgroup of women with parity ≥ 3)
	Null	Pukkala *et al.* 2012	
Low: 2 studies	Moderate to strong evidence	Reynolds *et al.* 2002	
	Some evidence	Linnersjö *et al.* 2003	

Among the moderate-utility studies, two studies found some evidence for an association between transmeridian flights and breast cancer (Schubauer-Berigan *et al.* 2015, Pinkerton *et al.* 2016), and the third study found no such evidence (Pukkala *et al.* 2012). In the Pan Am cohort overall, high levels of transmeridian flights did not increase the risk of breast cancer, but the authors could not exclude the possibility that high levels of transmeridian flight might increase breast cancer risk in a subgroup of women (Pinkerton *et al.* 2016). Among the approximately 15% of the Pan Am cohort with parity of 3 or more, a significant positive exposure-response trend was observed for cosmic radiation and number of time zones crossed that were robust to multiple model assumptions. In addition, among high-parity women a non-statistically significant positive trend was observed for hours spent traveling during the standard sleep interval. The high correlation among exposure metrics made it impossible to assess whether radiation and transmeridian travel (which may be a proxy for circadian disruption) were independently associated with breast cancer. Pukkala *et al.* (2012) found no association between breast cancer risk and number of flights crossing at least 4, 5, or 6 time zones.

Among the low-utility studies, Reynolds *et al.* (2002) reported statistically significant elevated risks of breast cancer for three exposure metrics (79% for flying on international vs. domestic flights, 57% for at least 15 years of employment vs. less than 15 years, and 72% for working as a flight attendant before the age of 25 vs. beginning work at age 25 or later). Linnersjö *et al.* (2003) reported a non-statistically significant 80% excess risk of breast cancer among those flying on high-altitude long-distance flights compared to those who did not; and a non-statistically significant threefold increased risk for flying more than 5,000 block hours (total time from flight departure to arrival, including time on the ground) in high-altitude long-distance flights, based on small numbers of exposed case subjects.

Key issues

The major issues in these studies were exposure assessment, study sensitivity, and potential confounding. Exposure to crossing time zones is difficult to study, as this specific information typically is not captured by airlines in administrative records. Furthermore, potential co-

exposures, such as cosmic radiation, are usually highly correlated with exposure to transmeridian travel. Exposure proxies used in these studies were less than satisfactory, as "international flights" can include flights within only one or two time zones; without more information, this proxy is difficult to interpret. Similarly, data on block hours might indicate years of service or flight intensity, but yield little information about time zones. Self-reported lifetime total number of time zones crossed is likely to be highly misclassified. Such uncertainty regarding exposure assessments resulted in low sensitivity to differentiate levels of exposure.

Chance, bias, or confounding

Alternative explanations for the reported increased risks of breast cancer from transmeridian travel cannot be completely ruled out. Neither of the low-utility studies that reported elevated risks (Reynolds *et al.* 2002, Linnersjö *et al.* 2003) had sufficient information to control for potential confounding. In Pinkerton *et al.* (2016), low cumulative exposure, potential exposure misclassification, and low participation in the nested study may have contributed to the finding of elevated risk in the small group of women with parity of at least 3. An evaluation of the final models among cohort members with at least 3 births revealed little confounding of the exposure estimates by any of the covariates.

3.5 NTP level-of-evidence conclusion

There is strong, but not sufficient evidence from cancer epidemiology studies that persistent night shift work (e.g., frequent and long-term, or working a large number of night shifts over a lifetime, especially in early adulthood) causes breast cancer in women.

In general, female night shift workers found to be at elevated risk for breast cancer are those who started working before age 30 and worked at least 3 times/week and for 10 or more years; however, the exact conditions (e.g., number of years worked) which put an individual at increased risk may depend on the specific combination of these metrics (e.g., duration may be longer if frequency is less) or other factors. Although the evidence is strong, it does not quite meet the criteria for "sufficient," as bias cannot be completely ruled out and two informative cohort studies did not find an association between night shift work and breast cancer risk (Li *et al.* 2015, Vistisen *et al.* 2017).

The epidemiology data from the night shift work studies are unable to evaluate the roles of LAN, sleep disturbances, or other factors related to shift work in breast cancer carcinogenicity. In general, behaviors of daily life related to stress, such as smoking or alcohol consumption, were considered in the night shift work studies and these factors did not explain the risk.

The data available from epidemiological studies are inadequate to evaluate the relationship between breast cancer and exposure to LAN (both indoor and outdoor).

Although some studies found positive associations for specific metrics of LAN and an increased breast cancer risk, overall, the evidence across studies for specific metrics of indoor light was inconsistent and there are concerns whether satellite data is measuring individual exposure to LAN or other behaviors of daily life that may correlate with the satellite data.

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and transmeridian travel.

4 Other Human Cancer Studies

Introduction

The objective of this section is to evaluate the level of evidence (sufficient, limited, or inadequate) of the carcinogenicity of night work for cancers other than breast cancer. The major cancers of interest include prostate (Section 4.1), colorectal cancer (Section 4.2), female hormonal cancers (i.e., ovarian and endometrial cancers, Section 4.3), and lung cancer (Section 4.4). The database was inadequate to conduct formal cancer hazard assessments for other cancer sites (e.g., malignant melanoma, other skin cancers, leukemia, non-Hodgkin lymphoma [NHL], stomach and pancreatic cancers) (Section 4.5) or other exposure scenarios (e.g., light at night [LAN], transmeridian travel, geographical coordinates) (Section 4.6).

Twenty-five studies of night work and hormonal, prostate, colorectal, or lung cancers satisfied the inclusion criteria, including twelve cohorts and seven population-based case-control studies of independent populations from the United States, Europe, the United Kingdom, Canada, China, and Australia. Although most studies examined exposure to night work and risk of one cancer type, a few cohort studies (Taylor and Pocock 1972, Schwartzbaum *et al.* 2007, Yong *et al.* 2014a, Jørgensen *et al.* 2017) and two case-control studies (Parent *et al.* 2012, studies on the Spanish multi-center case-control study by Papantoniou and colleagues) reported on night work and multiple primary cancer sites of interest. Nurses, workers in specific occupational settings, and general populations are represented in the studies; with one exception (Taylor and Pocock 1972), all were published since 2003. A Japanese cohort study by Fujino (2007) examined shift work and mortality from multiple incident cancer types, but was excluded due to insufficient information on population and methods. Studies of workers that provided job title alone and no further specification of shifts worked, e.g., radio and telegraph operators (Tynes *et al.* 1996), were not included.

Each cancer hazard assessment includes an evaluation of study quality followed by a synthesis of the evidence across cancer sites. Similar to the assessment of studies on breast cancer, the evaluation of potential selection and exposure misclassification bias and sensitivity played a major role in identifying the most informative studies. Methods for evaluating study quality and synthesizing the evidence across studies are described in Section 3 and the Shift Work at Night, Light at Night, and Circadian Disruption Protocol (NTP 2018).

Circadian disruption is not directly measured; thus, persistent practices of night shift work may be a surrogate for night shift work related to chronic circadian disruption (e.g., long duration, high frequency, or intensity of night work schedules). Other key issues that may modify the relationship of circadian disruption and cancer include participant's chronotype. Issues specific to particular cancers are prostate cancer severity, ovarian and lung cancer subtypes, smoking, and specific cancer subtypes and gender for colorectal cancer.

4.1 Prostate cancer

Prostate cancer is the most common non-skin cancer in men living in the United States, representing almost 10% of all incident cancers. Approximately 161,360 incident prostate cancer cases and 26,730 prostate cancer deaths were predicted for 2017 in the United States (Howlader *et al.* 2017). Prostate cancer has a high survival rate, with 98.2% of men living past five years

from diagnosis. Prostate cancer aggressiveness, however, is a critical component of disease progression and cancer severity. Evidence shows that tumor severity, classified as Gleason grade, is generally established early in tumor pathogenesis (VanderWeele *et al.* 2014) and that lower grade prostate cancer does not always progress to more severe grades (Penney *et al.* 2013), suggesting prostate cancer aggressiveness is an important factor to consider. Further, risk factors associated with aggressive prostate cancer, such as obesity, should be taken into consideration (Allott *et al.* 2013). As non-aggressive prostate cancer is not immediately fatal, the use of mortality data in studies may represent both new and prevalent cases of disease, and most of the incident cases in a given year would not be captured by mortality for that year, as deaths for any given year represent cases diagnosed years earlier.

4.1.1 Overview of study methods and characteristics

Eight cohort studies (Kubo *et al.* 2006, Schwartzbaum *et al.* 2007, Kubo *et al.* 2011, Gapstur *et al.* 2014, Hammer *et al.* 2015, Dickerman *et al.* 2016, Åkerstedt *et al.* 2017, Behrens *et al.* 2017) and five population-based case-control studies (Conlon *et al.* 2007, Parent *et al.* 2012, Papantoniou *et al.* 2015b, Tse *et al.* 2017, Wendeu-Foyet *et al.* 2018) of incident prostate cancer were eligible for review (Table 4-1). Studies by Yong *et al.* (2014a) and Yong *et al.* (Yong *et al.* 2014b) used the same study population of male chemical workers as Hammer *et al.* (2015) to examine multiple cancers, including prostate cancer; however, Hammer *et al.* (2015) provided a more in-depth analysis of prostate cancer incidence, and therefore, will be included. Tables include details only from the latest update of a study population or the most comprehensive report on a population. Detailed data on study design, methods, and findings were systematically extracted as described in the study protocol.

Table 4-1. Studies of prostate cancer and night work

Reference	Population	Outcome and source(s)	Exposure assessment and information
Cohort studies			
Kubo *et al.* 2006	**Japan Collaborative Cohort Study** 1988–1990 (enrollment) 14,052 working men (population based)	Incident prostate cancer Death certificates and linkage with cancer registries	Self-administered questionnaire *Night work:* fixed and rotating shift not defined *Metrics:* type of shift at longest job
Schwartzbaum *et al.* 2007	**Swedish workers, registry-based cohort** Registered in 1960 and 1970 census (enrollment) 1971–1989 (follow-up) 2,102,126 workers (population based)	Incident cancer using prostate and other cancers Swedish Cancer Registry or Cause of Death Register (SIR study)	Job exposure matrix (JEM) *Night work:* workplace had rotating schedule or work between 1:00 AM & 4:00 AM *Metrics:* ever worked in occupation–industry combinations
Kubo *et al.* 2011	**Japanese industry-based retrospective cohort** Records from 2006–2008	Incident prostate cancer Health insurance records	Company records *Night work:* continuous counter-clockwise 3-shift rotation system

Reference	Population	Outcome and source(s)	Exposure assessment and information
	4,995 working men (specific manufacturing corporation)		*Metrics:* ever worked a rotating shift for > 80% of career
Gapstur *et al.* 2014	**U.S. Cancer Prevention Study II cohort study** 1982–2010 (enrollment and follow-up) 305,057 employed men (population based)	Fatal prostate cancer Underlying cause of death Personal inquiries and verification using death certificates/national registry	Self-administered questionnaire *Night work:* not defined for rotating shifts, fixed night started work from 9:00 PM–midnight *Metric:* current type of shift work (fixed night or rotating shifts)
Hammer *et al.* 2015	**German Rhineland-Palatinate chemical workers** 1995–2005 (employment records) 2000–2009 (follow-up) 27,828 male production workers (specific chemical company)	Incident prostate cancer; type of cancer Rhineland-Palatinate Cancer Registry	Company records *Night work:* forward rotating system: one 12-hr shift (6:00 AM–6:00 PM), 24 hr off, 12-hr (6:00 PM–6:00 AM), and another 48 hr off) *Metric*: ever worked
Dickerman *et al.* 2016	**Older Finnish Twin Cohort** 1981–2012 (follow up period) 11,370 men who were twins born before 1958	Histologically confirmed incident and fatal prostate cancer National registries	Self-administered questionnaire Rotating shifts: rotated through morning, evening, or night shifts in a 2- or 3-shift pattern *Night work*: fixed or night shift not defined *Metrics*: type of shift, work at current or latest job, chronotype
Åkerstedt *et al.* 2017	**Swedish Twins Registry cohort study** 1998–2010 (enrollment and follow-up period) 12,322 men who were twins born before 1959	Incident prostate cancer Swedish cancer or death registries	Telephone-based questionnaire *Night work*: not defined *Metrics:* ever (1+ year), duration of night work
Behrens *et al.* 2017	**German Heinz-Noxdorf Recall cohort study** 2000–2011 (enrollment and follow-up period) 1,757 men residing in highly industrialized Ruhr area (population based)	Incident prostate cancer Medical or death records	Computerized baseline questionnaire (not known who administered it). Follow-up questionnaire by mail *Night work:* 12:00 AM–5:00 AM (night work), any hours from 6:00 PM–7:00 AM (shift work) *Metrics:* ever worked (1+ year), duration of night or shift work, preferred midpoint of sleep

Reference	Population	Outcome and source(s)	Exposure assessment and information
Case-control studies			
Conlon *et al.* 2007	**Northeastern Ontario case-control study** 1995–1998 (enrolled) 760 cases 1,632 population-based controls	Incident prostate cancer Ontario cancer registry 1995–1998	Self-administered questionnaire *Night work*: rotating full-time (not defined) *Metrics:* ever worked, duration, age at first shift work, and years since full-time rotating shiftwork
Parent *et al.* 2012	**Montreal multisite case-control cancer study** 18 hospitals 1979–1985 (enrolled) 400 male cases 512 male population-based controls	Incident, histologically confirmed prostate, colon, rectal, lung, and other cancers Cases from pathology departments in Montreal hospitals	In-person questionnaire *Night work*: included work between 1:00 AM–2:00 AM for ≥ 6 mo *Metrics:* Ever, cumulative duration, and night work ≤ 20 yr or ≥ 20 yr in the past
Papantoniou *et al.* 2015b	**MCC-Spain population-based case-control study** 11 hospitals, 7 regions 2008–2013 (enrolled) 1,095 cases 1,388 population-based controls	Histologically confirmed prostate cancer, including anatomical, pathological, and clinical stage, prostate-specific antigen (PSA) levels and Gleason score for most cases Medical records	In-person interviews with questionnaire *Night work*: any time between midnight & 6:00 AM for ≥ 3 nights/mo *Metrics*: Ever worked shifts (≥ 1 yr), type of shift (permanent and rotating), cumulative duration, cumulative frequency, duration, and frequency by chronotype
Tse *et al.* 2017	**Chinese hospital-based case-control study** 2011–2016 (enrollment period) 431 male cases 402 male hospital controls without cancer	Newly confirmed prostate cancer by histology Hospital-based cases and controls	In-person questionnaire *Night work:* 1+ hour between midnight & 5:00 AM *Metric:* ever worked (more than once a month for > 1 yr)
Wendeu-Foyet *et al.* 2018	**France EPICAP population-based case-control study** 2012–2013 (enrolled) 819 male cases 879 male population-based controls	Newly confirmed prostate cancer by histology, including Gleason score, PSA levels, and stage Medical records and cancer registry	In-person questionnaire *Night work:* 270 hr or 3 nights/mo for > 1 yr *Metrics:* ever worked, shift type (permanent or rotating), duration, number of consecutive nights worked, night shift length, cumulative frequency, shift timing, rotation type, shift rotation speed, sleep duration, chronotype

hr = hour(s); JEM = job-exposure matrix; mo = month(s); PSA = prostate-specific antigen; yr = year(s).

Studies were from a broad geographic range, including populations from the United States, Canada, Spain, Germany, Sweden, Finland, France, and Japan. Cohort studies comprised occupational chemical and manufacturing workers, as well as the general population, including a cohort of twins. Cancer incidence was determined through registry linkages, death certificates or registries, and company records. A cross-sectional study showing men ages 40 to 65 years old in the National Health and Nutritional Examination Survey (NHANES) who reported working shifts had significantly elevated prostate-specific antigen (PSA) levels at or above 4.00 ng/mL (Flynn-Evans *et al.* 2013). This study, however, was excluded because only the PSA screening test, but no incident cancer, was reported.

4.1.2 Evaluation of study quality

A detailed evaluation of study quality for all potential biases is available in Appendix D, Table D-1; an overview of the assessment is provided in Table 4-2. It should be noted that studies by Schwartzbaum *et al.* (2007) and the study design of Papantoniou *et al.* (2015b) have also been evaluated and described in detail in the breast cancer section (see Section 3 for details on study quality metrics), and thus, will not be discussed in detail in this section except for an overall study utility assessment; additional study findings are provided in Appendix D, Table D-2. Similar to the breast cancer evaluation, Schwartzbaum *et al.* (2007) was ultimately excluded from the hazard evaluation due to poor exposure assessment.

Table 4-2. Summary of study quality: Shift work and prostate cancer

Citation	Selection[a]	Exposure	Outcome	Confounding methods	Adequacy of analysis	Selective reporting	Sensitivity	Utility[b]
Cohort studies								
Kubo *et al.* 2006	++	+	++	+++	+++	+++	+	+
Schwartzbaum *et al.* 2007	++	0	+++	+++	++	+++	+	0
Kubo *et al.* 2011	+	++	+	+++	+	++	+	+
Gapstur *et al.* 2014	+++	0	++	++	+++	+++	+	0
Hammer *et al.* 2015	++	+	++	+++	+++	+++	+	+
Dickerman *et al.* 2016	+++	0	+++	+++	+++	+++	+	0
Åkerstedt *et al.* 2017	++	+	+++	+++	+++	+++	+	+
Behrens *et al.* 2017	++	+++	++	+++	+++	+++	++	+++
Case-control studies								
Conlon *et al.* 2007	++	++	++	+++	++	+++	++	++
Parent *et al.* 2012	+++	++	+++	++	+++	+++	++	++
Papantoniou *et al.* 2015b	++	++	+++	+++	+++	+++	++	+++
Tse *et al.* 2017	++	+	+++	+++	+++	+++	+	+
Wendeu-Foyet *et al.* 2018	+++	+++	+++	+++	+++	+++	+++	+++

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

Selection bias

Potential selection bias is a major concern for one study. The Japanese manufacturing study by Kubo *et al.* (2011) included a small, highly selected surviving sub-cohort of participants (ages 49 to 65) from a larger cohort. If persons not able to tolerate shift work left the cohort, died, or changed to day work, they would not have been identified in this sub-cohort of survivors. This suggests that the estimate of effect in this study might be biased towards the null.

Some studies were determined to have minimal (Parent *et al.* 2012, Gapstur *et al.* 2014, Dickerman *et al.* 2016, Wendeu-Foyet *et al.* 2018) or some concern (Kubo *et al.* 2006, Conlon *et al.* 2007, Kubo *et al.* 2011, Hammer *et al.* 2015, Papantoniou *et al.* 2015b, Åkerstedt *et al.* 2017, Behrens *et al.* 2017, Tse *et al.* 2017) for selection bias. For Behrens *et al.* (2017), eligible subjects who did not participate in follow-up had higher rates of prostate cancer which may attenuate the risk estimates if those participants were more likely to have engaged in shift work.

Concerns of selection bias are present in the German chemical industry (Yong *et al.* 2014a, Hammer *et al.* 2015), as employees of the chemical company were required to have a medical examination both prior to work and subsequently every three years. The authors considered that healthy worker survival bias may be induced through ongoing selection out of the shift-worker group based on health-related criteria, so a term for employment duration was included in regression models as a proxy for work-related effects. Both day and shift workers had a higher incidence of prostate carcinoma than the general population (standardized incidence rate [SIR] = 1.44, 95% confidence interval [CI] = 1.22 to 1.70 for daytime workers; SIR = 1.51, 95% CI = 1.30 to 1.74 for shift workers), indicating potential detection bias in this industry population with access to prostate screening. The study by Åkerstedt *et al.* (2017) may be subject to potential healthy-worker survivor effect (HWSE) as it did not have adequate information on lifetime history of shift work in a primarily older study population (41–60 years old) at baseline.

Attrition bias was possible in two case-control studies (Conlon *et al.* 2007, Papantoniou *et al.* 2015b) where non-participants differed from participants and fewer than 50% of the controls responded to the questionnaire, substantially fewer than among cases (74%). The use of hospital controls in Tse *et al.* (2017), which included patients with pancreatic and colorectal diseases, may not have been an ideal comparator group considering the potential impact of night work on pancreatic and colorectal cancers. It should be noted that the case-control studies by Parent *et al.* (2012) and Papantoniou *et al.* (2015b) used the same control population for multiple cancer case examinations. If the control population was not selected to be appropriate for all cancer cases, then the results may be subject to selection bias.

Exposure misclassification

Similar to studies on breast cancer, the ranking of the exposure assessment is determined by the integration of three factors: (1) how night work was initially defined, (2) the quality of the measurements, and (3) whether the study includes one or more metrics that can differentiate those with the most persistent night shift work practices from those with less extensive night shift work practices.

Definitions of night work exposure varied among prostate cancer studies, making for complex comparisons. Only six studies considered individuals exposed if they worked nights at least six months (Parent *et al.* 2012) or one year (Papantoniou *et al.* 2015b, Åkerstedt *et al.* 2017, Behrens

et al. 2017, Tse *et al.* 2017, Wendeu-Foyet *et al.* 2018). As mentioned in Section 3.2.1, studies characterizing night work as either a narrow range of nighttime hours or minimum number of night hours worked are subject to less exposure misclassification (Garde *et al.* 2016). Five studies defined exposure as working anytime between a range of night hours (Schwartzbaum *et al.* 2007, Gapstur *et al.* 2014, Papantoniou *et al.* 2015b, Behrens *et al.* 2017, Tse *et al.* 2017). Parent *et al.* (2012) defined night work that included working between 1:00 AM and 2:00 AM. Hammer *et al.* (2015) defined rotating shift work as working a 12-hour shift from 6:00 PM to 6:00 AM. Wendeu-Foyet *et al.* (2018) used the French definition of night shift work which involves night work for 270 hours/year or 3 nights/month. Other available studies are subject to exposure misclassification as explicit timings of night or rotating shift work were not captured.

Exposure information was assessed using questionnaire data, occupational records, or a job exposure matrix (JEM). Two cohort studies (Gapstur *et al.* 2014, Dickerman *et al.* 2016) based their exposure assessments on current employment at baseline only, with no data on lifetime exposure, and therefore were considered to be of critical concern. All other studies except for Behrens *et al.* (2017) and Wendeu-Foyet *et al.* (2018) were considered to have high or moderate concern for exposure misclassification. Most studies did not adequately assess lifetime history of shift work. Based on this limited information, if unexposed participants had actually engaged in shift work at a prior time period, exposure status will have been misclassified and therefore effect estimates may be biased toward the null.

In both cohorts described in Hammer *et al.* (2015) and Yong *et al.* (2014a), occupational exposure records were not available for the entire period of a worker's employment. To assess the extent of misclassification bias, the authors examined a random sample of workers and found that 5% of the day workers transferred at least once to shift work and 18% of the shift workers had transferred to day work. Regarding duration, the authors calculated an error rate of exposure duration of 2.2% for day workers and 11.6% for shift workers. For ever exposure to shift work, misclassification in individuals known to be shift workers after 1995 would be low, but day workers after 1995 may not be truly unexposed, leading to a bias away from the null.

The most common metrics in the studies were type of shift and duration of working night shift. Night work type was not consistently categorized across studies, with five studies differentiating fixed and a rotating night shift schedule (Kubo *et al.* 2006, Gapstur *et al.* 2014, Papantoniou *et al.* 2015b, Dickerman *et al.* 2016, Wendeu-Foyet *et al.* 2018), and four studies examining a rotating shift schedule only (Conlon *et al.* 2007, Schwartzbaum *et al.* 2007, Kubo *et al.* 2011, Hammer *et al.* 2015). Rotating shift patterns were detailed in few studies, including a three-shift counter-clockwise pattern (Kubo *et al.* 2011), a two- or three-shift pattern (Dickerman *et al.* 2016), a forward rotating pattern (Hammer *et al.* 2015), or only forward, only backward, or both pattern types (Wendeu-Foyet *et al.* 2018). A few studies may have defined rotating night work to include both night and evening shifts (Conlon *et al.* 2007, Hammer *et al.* 2015, Dickerman *et al.* 2016). Wendeu-Foyet *et al.* (2018) also examined differences by shift timings, as either early morning, late evening, or overnight shifts.

Three studies (Kubo *et al.* 2006, Åkerstedt *et al.* 2017, Tse *et al.* 2017) relied on an overall question on prior shift work history to attempt to characterize exposure but without further capturing total work history, and thus may be subject to misclassification.

Sensitivity

All of the cohort studies lacked sensitivity for a variety of reasons: small numbers of exposed cases (Kubo *et al.* 2011, Behrens *et al.* 2017), young cohort (Hammer *et al.* 2015), or very little information on exposure variability (Schwartzbaum *et al.* 2007, Gapstur *et al.* 2014, Dickerman *et al.* 2016).

Overall study utility

Four case-control studies (Conlon *et al.* 2007, Parent *et al.* 2012, Papantoniou *et al.* 2015b, Wendeu-Foyet *et al.* 2018) and one cohort study (Behrens *et al.* 2017) were considered to be of high or moderate utility, and therefore, were the most informative studies (Table 4-2). In general, these studies captured lifetime history of shift work, at least a moderate number of exposed prostate cancer cases, and, for the cohort study, an internal comparator analysis. Five studies were categorized as having low or moderate utility (Table 4-2). Lastly, three cohort studies (Schwartzbaum *et al.* 2007, Gapstur *et al.* 2014, Dickerman *et al.* 2016) were deemed as inadequate study utility either for measuring current shift work exposure only or very poorly characterizing shift work.

4.1.3 Prostate cancer hazard assessment

Findings for all the individual studies included in the analysis are available in Appendix D, Table D-2, and selected findings are graphed in the forest plots below.

As stated in Section 3.2.5, NTP did not consider the meta-analysis approach informative and thus did not include its own meta-analysis nor did it include the published meta-analyses in the cancer hazard assessment. Three meta-analyses (Rao *et al.* 2015, Gan *et al.* 2018, Mancio *et al.* 2018), published since 2013, found significant aggregate risk estimates greater than 1.00 with ever working shifts, but only for rotating shift types. Two of three analyses found an exposure-response trend with increasing duration of shift work exposure. One meta-analysis found elevated estimates for studies of Asian populations compared to Western populations. Limitations that weakened the utility of these meta-analyses for the purposes of this assessment were the inclusion of studies with poorly characterized shift work, including only concurrent shift work exposure and not including the most recent large case-control study of prostate cancer (Wendeu-Foyet *et al.* 2018)

Consistency of the evidence across studies

Overall, the identified prostate cancer studies provide consistent evidence of an association with prostate cancer risk. Moreover, prostate risk was associated with persistent night shift work (e.g., long duration, high cumulative frequency of night shifts over a lifetime, or combinations of frequency and duration).

Seven of the ten studies provided evidence that night shift work increases prostate cancer risk (Table 4-3 shows the studies grouped by level of evidence and study utility). As described in Section 3, the level of evidence for each study was reached by considering the findings across all metrics or analyses reported in the study as well as study quality, and the direction (if known) for any potential biases. Studies providing moderate to strong evidence found significant positive relationships, increased risk of prostate cancer in those working nights for the longer duration of exposure, and/or a significant positive trend of prostate cancer with night work duration (Parent

et al. 2012, Papantoniou *et al.* 2015b, Behrens *et al.* 2017). Studies providing some evidence found a significant association with night work and prostate cancer; however, the positive findings were restricted to limited analyses. Some studies did not have adequate information on duration of night work (Kubo *et al.* 2006, Tse *et al.* 2017). Wendeu-Foyet *et al.* (2018) saw evidence of a relationship only when persistent permanent shift work was performed, and Conlon *et al.* (2007) saw significantly increased prostate cancer risk only in certain younger age groups and durations of shift work but no clear exposure-duration patterns were observed.

Two studies (Hammer *et al.* 2015, Åkerstedt *et al.* 2017) did not find associations with prostate cancer risk and the evidence from the remaining study by Kubo *et al.* (2011) was considered inconclusive due to a small number of exposed cases and inadequate information on night work exposure.

The major predictor of heterogeneity across studies was study quality. All of the most informative studies (high or moderate quality) found an association between night work and prostate cancer risk. Of the lower quality studies, two were considered to offer some evidence of an effect (Kubo *et al.* 2006, Tse *et al.* 2017) and three were null or inconclusive (Kubo *et al.* 2011, Hammer *et al.* 2015, Åkerstedt *et al.* 2017).

The summary of the key metrics measured, study utility, and level of evidence of all studies is listed in Table 4-3. Details on the metrics of exposure and effect modifiers are discussed below.

Table 4-3. Evidence summary table and key metrics assessed for studies of night work and prostate cancer

			Key metrics measured in study			
Reference	**Study utility**	**Study design**	**Ever worked**	**Years worked**	**Cumulative frequency**	**Cancer severity**
Strong evidence or some evidence of prostate cancer risk						
Behrens	+++/++	Cohort	***	***		
Papantoniou	+++/++	Case-control	**	***	**	***
Wendeu-Foyet	+++/++	Case-control	Null	***	**	**
Conlon	+++/++	Case-control	***	**		
Parent	+++/++	Case-control	***	***		
Kubo 2006	+	Cohort	**			
Tse	+	Case-control	*			
Null or inconclusive evidence						
Kubo 2011	+	Cohort	*			
Hammer	+	Cohort	Null			Null
Åkerstedt	+	Cohort	Null	Null		

+++/++ = informative (dark yellow); + = low utility (light yellow); strength of association increases with number of * and darker shade of blue for key metrics.

Metrics of exposure

Most studies reported on ever exposure, five studies reported on exposure duration (Conlon *et al.* 2007, Parent *et al.* 2012, Åkerstedt *et al.* 2017, Behrens *et al.* 2017, Wendeu-Foyet *et al.* 2018),

and two studies reported on lifetime cumulative shifts (Papantoniou *et al.* 2015b, Wendeu-Foyet *et al.* 2018).

Ever night work

The evaluated studies differed in their approaches to classifying exposure to shift and/or night work, which may add to the heterogeneity in results (see Figure 4-1). Overall, four of the five moderate- and high-utility studies reported an elevated risk of prostate cancer in individuals who had ever worked night shifts (Conlon *et al.* 2007, Parent *et al.* 2012, Papantoniou *et al.* 2015b, Behrens *et al.* 2017), two of which were statistically significant (Parent *et al.* 2012, Behrens *et al.* 2017). Wendeu-Foyet *et al.* (2018) reported a null association with ever working night shifts.

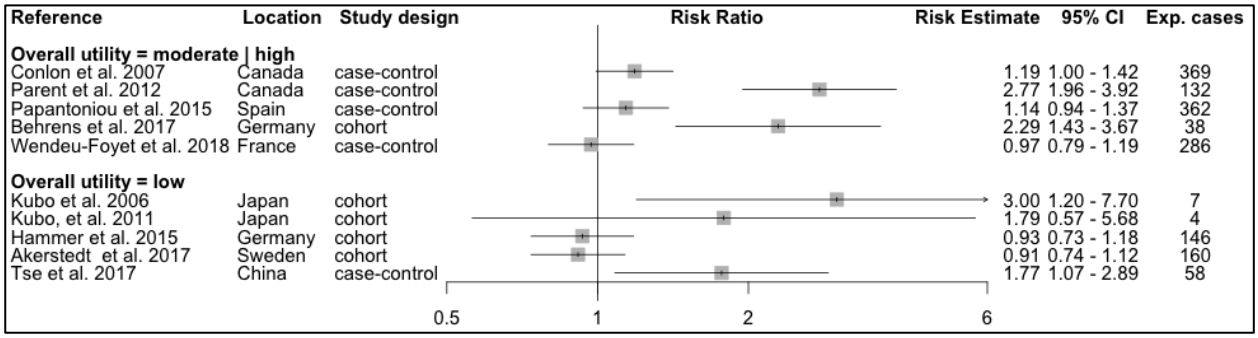

Figure 4-1. Forest plot of human studies on the risk of prostate cancer from ever exposure to night work; stratified by study utility

Note: Plotted confidence intervals (CI) are standardized and estimated based on software package, and therefore may differ slightly from study confidence intervals.

All remaining studies were determined to have low study utility. Hammer *et al.* (2015) reported a null association between night work in an occupational setting in Germany and risk of prostate cancer. Two studies (Kubo *et al.* 2006, Tse *et al.* 2017) reported elevated risks based on very small numbers of rotating shift worker cases. Another study reported a positive but non-significant relationship between night work and prostate cancer (Kubo *et al.* 2011). Although Åkerstedt *et al.* (2017) found a null association of night work and prostate cancer, a duration-stratified model showed a slight increased risk compared to unadjusted estimates for certain durations of night work exposure.

Exposure metrics

Although the definitions of duration and cumulative frequency of exposure differed across studies, long duration and greater cumulative frequency of night work suggest an overall increased risk of prostate cancer incidence, but with inconsistent dose-response patterns across studies. Five high-and moderate-utility studies and one low-utility study examined cumulative duration of shift or night work and risk of prostate cancer; the longest duration of night shift work reported by each study is presented in Figure 4-2. The studies varied in their categorization of shift work duration, with four studies involving subjects engaged in 20 or more years of night work. Five high- and moderate-utility studies reported increased risk of prostate cancer for the highest duration category, though only the estimates reported by Parent *et al.* (2012), Behrens *et al.* (2017), and Papantoniou *et al.* (2015b) were statistically significant. Two studies

(Papantoniou *et al.* 2015b, Behrens *et al.* 2017) reported a significant exposure-response trend of prostate cancer incidence by duration of night work whereas no clear exposure-duration response patterns were observed with the other studies (Conlon *et al.* 2007, Parent *et al.* 2012, Wendeu-Foyet *et al.* 2018). The low-utility prospective study reported null associations across all durations (Åkerstedt *et al.* 2017). Although Hammer *et al.* (2015) did not evaluate lifetime duration of shift work *per se,* the study found an increased risk of prostate cancer in chemical workers with increasing duration of employment who worked 30 years or more at the company (unreported hazard ratios).

Two studies provide evidence that other measures of persistent night shift work are related to increased prostate cancer risk. Papantoniou *et al.* (2015b) observed an increased risk of prostate cancer among those working rotating nights with the highest cumulative exposure (≥ 2,857 rotating night shifts; odds ratio [OR] = 1.32, 95% CI = 0.99 to 1.77). Wendeu-Foyet *et al.* (2018) did not see an association with prostate cancer and cumulative frequency of lifetime night shifts for overall, permanent, or rotating night shift work; however, a positive association was observed with combined exposure metrics. A significantly elevated risk of prostate cancer was seen, however, in all participants working ≥ 30 years and either ≥ 6 consecutive nights (OR = 1.71, 95% CI = 1.06 to 2.76), or greater than 10 hours shift length (OR = 2.49, 95% CI = 1.11 to 5.61), and in participants working greater than 10 hours shift length and either at least 1,314 cumulative nights (OR = 1.76, 95% CI = 1.03 to 3.03) or ≥ 6 consecutive nights (OR = 1.86, 95% CI = 1.05 to 3.27). These associations generally strengthened and remained significant when examining permanent night shift workers only. Wendeu-Foyet *et al.* (2018) found a significantly decreased risk of prostate cancer for shift lengths less than 8 hours (OR = 0.32, 95% CI = 0.16 to 0.34) and a significantly increased risk with greater than 10 hours shift length (OR = 1.88, 95% CI = 1.08 to 3.26). No relationship was found when examining direction or speed of shift rotation, or timing of night shift (i.e., early morning, late evening, and overnight shifts).

Although most studies examined rotating night shift work, three studies (Kubo *et al.* 2006, Papantoniou *et al.* 2015b, Wendeu-Foyet *et al.* 2018) examined rotating and fixed (permanent) night shift work separately. Generally, there were no major differences in risk of prostate cancer between rotating and permanent night shift work in the three studies. Wendeu-Foyet et al. (2018) also did not find an increased risk when examining direction and speed of shift rotation.

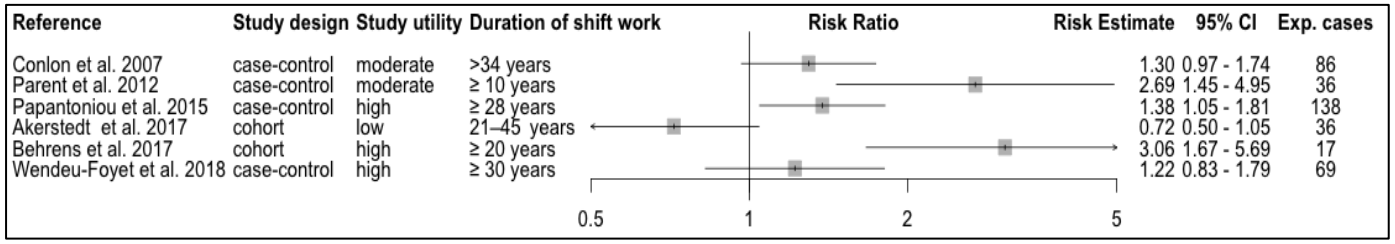

Figure 4-2. Forest plot of human studies on the risk of prostate cancer by longest cumulative duration of night work

Note: Plotted confidence intervals (CI) are standardized and estimated based on software package, and therefore may differ slightly from study confidence intervals.

Effect modification or outcome subtype

Prostate cancer severity

There is some evidence that night shift work is associated with more severe prostate cancer; however, this is limited to only three studies that examined prostate cancer severity and night work. Papantoniou *et al.* (2015b) found a statistically significant positive association between night work and high-risk prostate tumors (according to the D'Amico classification) (relative risk ratio [RR] = 1.40, 95% CI = 1.05 to 1.86), particularly among men working rotating nights for the longest duration (≥ 28 years; RR = 1.63, 95% CI = 1.08 to 2.45; P_{trend} = 0.027), and for those working the highest cumulative frequency of night shifts (≥ 2,857 shifts; RR = 1.78, 95% CI = 1.17 to 2.69; P_{trend} = 0.007). Men with a history of night work and Gleason score > 7 at diagnosis had a higher risk (RR = 1.43, 95% CI = 0.99 to 2.07), compared to those with a lower Gleason score (< 7; RR = 1.09, 95% CI = 0.85 to 1.38). Wendeu-Foyet *et al.* (2018) also found a borderline significant positive association between permanent, but not rotating, night work and aggressive prostate cancer (with Gleason scores 7+) (OR = 1.41, 95% CI = 0.98 to 2.04). Elevated risk of aggressive prostate cancer was significantly associated with working ≥ 20 years of permanent shifts (OR = 1.76, 95% CI = 1.13 to 2.75; P_{trend} = 0.003), ≥ 6 consecutive permanent nights (OR = 1.87, 95% CI = 1.13 to 3.11), > 10 hours permanent shift length (OR = 2.63, 95% CI = 1.23 to 5.63; P_{trend} = 0.04), and combined metrics of persistent permanent shift work.

In contrast, Hammer *et al.* (2015) found little evidence that the risk of prostate cancer differs by severity; however, risk estimates were imprecise, there were few exposed cases with advanced prostate cancer (T4), and this was a null study for all metrics. This study was conducted in a relatively young cohort of German chemical workers, and the detection of prostate cancer may be higher in this particular cohort considering screening was more frequent.

Chronotype, preferred midpoint of sleep

Although both chronotype and diurnal preference (measured by preferred midpoint of sleep) were examined in three studies, they do not substantially modify the association between shift work and risk of prostate cancer. The effect of chronotype on the risk of prostate cancer in night workers was evaluated in the Papantoniou *et al.* (2015b) and Wendeu-Foyet *et al.* (2018) studies, with all studies reporting elevated risks for evening chronotype. However, the Spanish study (Papantoniou *et al.* 2015b) also found that morning chronotype had an increasing risk with long-term exposure (≥ 28 years) (OR = 1.79, 95% CI = 1.16 to 2.76; P_{trend} = 0.017).

Behrens *et al.* (2017) reported that earlier sleep preference was associated with significantly higher risk of prostate cancer when compared to intermediate and late sleepers. Stratified analysis by vitamin D status did not reveal differences in risk of prostate cancer.

Chance, bias, and confounding

Study findings were unlikely to be explained by unmeasured confounding, although because there are no known causes of prostate cancer, there is always potential for unknown causes to confound results. However, positive associations were observed across different geographical locations or racial groups, populations, and study designs, which help to decrease concerns from unknown confounders. Potential confounders for prostate cancer and shift work studies included

age and occupational exposures, which were generally controlled for in statistical analyses. NTP thought that body mass index (BMI) could be the causal pathway of shift work and cancer, and therefore, was not included as a key confounder in the study quality assessment (e.g., consider it as some concern); however, NTP did note that BMI was controlled for in a few studies (Kubo *et al.* 2006, Kubo *et al.* 2011, Parent *et al.* 2012, Åkerstedt *et al.* 2017). Results from Åkerstedt *et al.* (2017) and Kubo *et al.* (2006) remained null and positive, respectively, after controlling for BMI. Kubo *et al.* (2011) saw an increased relative risk after controlling for BMI, but results remained non-significant. Parent *et al.* (2012) did not report unadjusted estimates, but a significantly increased risk of prostate cancer was present after controlling for BMI. No studies evaluating aggressive prostate cancer controlled for BMI, a potential risk factor. A few studies found significant differences in levels of physical activity by shift work status, which may be a result of decreased access to outdoor activities and greater sedentary duties in night workers. Controlling for physical activity, a potential but not established risk factor associated with shift work but not prostate cancer, was only considered in two studies (Parent *et al.* 2012, Papantoniou *et al.* 2015b), both of which found a positive association with prostate cancer. There is a greater likelihood that findings were biased due to exposure misclassification (primarily non-differential). Lifetime exposure to nighttime shift work was not fully captured in many studies measuring ever versus never exposure, and thus, there is a possibility that unexposed comparator groups had worked nights. The potential for exposure misclassification of unexposed participants would therefore attenuate risk estimates toward the null.

None of the occupational cohort studies controlled for frequency of prostate cancer screening. As mentioned earlier, the use of regular prostate cancer screening in certain occupational studies, including the use of more sensitive tests such as PSA, may increase the likelihood of disease detection. If day shift workers are more likely to be screened than night shift workers due to availability, then differential outcome misclassification may bias results.

4.2 Colorectal cancer

In 2017, an estimated 135,430 new colon and rectum cancer cases were predicted in the United States. Colorectal cancer is the second leading cause of cancer-related death in the United States (Howlader *et al.* 2017). There is a moderate chance of surviving five years after colorectal cancer diagnosis (64.9%, 2007 to 2013 age-adjusted SEER data). Based on SEER age-adjusted data from 2009 to 2013, about three-quarters (74%) of cases are diagnosed at the localized (39%) or regional stage (35%). The remaining fourth of cases are diagnosed at the distant stage or are unstaged and have much lower survival rates (13.9%, and 35.4%, respectively). Studies that rely on mortality data to represent incident colorectal cancer may not be capturing most incident cancers unless latency is sufficiently long or the cancer stage is aggressive.

4.2.1 Overview of study methods and characteristics

Five independent cohort studies of colorectal cancer (Schwartzbaum *et al.* 2007, Yong *et al.* 2014a, Jørgensen *et al.* 2017, Papantoniou *et al.* 2018, [Nurses' Health Study (NHS)]) were available for review, as well as three population-based studies (Parent *et al.* 2012, Papantoniou *et al.* 2017, Walasa *et al.* 2018). Study populations measuring shift work were from North America (United States, Canada), Europe (Sweden, Denmark, Germany, Spain), and Australia. Two cohort studies used the NHS cohort to examine shift work exposure and either colorectal cancer incidence (Papantoniou *et al.* 2018) or mortality (Gu *et al.* 2015; NHS cohort only), so the study

populations were likely to have overlapped. In this current review, only Papantoniou *et al.* (2018) was included and Gu *et al.* (2015) served as supplementary information (Table 4-4). Another previous NHS study (Schernhammer *et al.* 2003) has been superseded by the combined NHS/NHS2 study by Papantoniou *et al.* (2018), which contains a longer follow-up period. Similarly, two retrospective cohort studies used the cohort of German chemical workers to examine colorectal cancer incidence (Yong *et al.* 2014a) or mortality (Yong *et al.* 2014b). In this current review, only incident colorectal cancer was included (Yong *et al.* 2014a), and mortality information from Yong *et al.* (2014b) served as supplementary information (Table 4-4). Most studies combined colon and rectal cancers, with Parent *et al.* (2012), Schwartzbaum *et al.* (2007), Walasa *et al.* (2018), Papantoniou *et al.* (2017) and Papantoniou *et al.* (2018) examining colon and rectal cancers together and/or separately. Studies of men, women, and both men and women were included.

Table 4-4. Studies of colorectal cancer and night work

Reference	Population	Outcome and source(s)	Exposure assessment and information
Cohort studies			
Papantoniou *et al.* 2018 (Gu *et al.* 2015, supporting study)	**Nurses' Health Study (NHS) and NHS2 cohorts** NHS: 1976 (enrolled), 1988 (exposure collection), 1988–2012 (follow-up) NHS2: 1989 (enrolled), 1989–2013 (follow-up) NHS: 77,349 women NHS2: 113,371 women	Incident colon and rectum cancers Self-report, next of kin, postal service, death registry	Self-administered questionnaire *Night work*: undefined time for ≥ 3 rotating night shift/mo *Metrics*: Ever worked rotating night shifts (≥ 1 yr), duration of rotating night work; for NHS2, both baseline and follow-up cumulative duration
Schwartzbaum *et al.* 2007	**Swedish workers, registry-based cohort** See Table 4-1 1,148,661 female shift workers	Incident colon and rectum and other cancers. (See Table 4-1)	See Table 4-1
Yong *et al.* 2014a (Yong *et al.* 2014b, supporting study)	**German Rhineland-Palatinate chemical workers retrospective cohort** 1995–2005 (employment records) 2000–2009 (follow-up) 27,828 male production workers (specific chemical company)	Incident cancers; colon and rectum and other cancers Rhineland-Palatinate Cancer Registry	Company records *Night work:* forward rotating system with: one 12-hr shift (6:00 AM–6:00 PM), 24 hr off, 12-hr shift (6:00 PM–6:00 AM), and another 48 hr off) *Metric*: ever worked

Reference	Population	Outcome and source(s)	Exposure assessment and information
Jørgensen *et al.* 2017	**Danish Nurses Organization study** 1993 and 1999 (recruitment) 2012 (end of follow-up) 28,731 working nurses (population based)	Fatal colorectal and other cancers Underlying cause of death Danish Register of Causes of Death using underlying cause of death	Self-administered questionnaire *Night work*: fixed nights (11:00 PM–7:00 AM); rotating shifts include day (7:00 AM–3:00 PM) and evening (3:00 PM–midnight) *Metrics*: current type of shift work (fixed nights or rotating shifts)
Case-control studies			
Parent *et al.* 2012	**Montreal multisite case-control cancer study** See Table 4-1 400 male cases 512 male population controls	Incident, histologically confirmed colon, rectal, and other cancers (see Table 4-1)	See Table 4-1
Papantoniou *et al.* 2017	**MCC-Spain population-based case-control study** 23 hospitals in 12 regions 2008–2013 (enrolled) 1,626 cases 3,378 controls; men and women	Histologically confirmed colon and rectal cancers, including anatomical and histological stage Medical records	In-person interviews with questionnaire *Night work*: 1+ hour between midnight & 6:00 AM for ≥ 3 nights/mo Exposed: Worked night shifts ≥ 1 yr (at least 1 hour from midnight–6:00 AM for ≥ 3 nights/mo) *Metrics*: Ever worked shifts (≥ 1 yr), type of shift, cumulative duration, age at first shift work, shift work ≤ 15 yr or ≥ 15 yr in the past
Walasa *et al.* 2018	**Western Australia population-based case-control study** 2005–2007 (enrolled) 350 cases 410 controls; women only	Incident, histologically confirmed colorectal cancer Western Australian Cancer Registry	Job exposure matrix (JEM) *Night work*: any work between midnight & 5:00 AM *Metrics:* ever worked in occupation-industry combinations with ≥ 70% of participants as shift workers, cumulative duration, and exposure to LAN and phase shift

mo = month; yr = year.

4.2.2 Evaluation of study quality

A detailed evaluation of study quality for all potential biases is available in Appendix E, Table E-1 and an overview of the assessment is provided in Table 4-5. It should be noted that the breast cancer section (Section 3) evaluated Schwartzbaum *et al.* (2007), Jørgensen *et al.* (2017), and the study design of Papantoniou *et al.* (2017), and the prostate cancer section (Section 4.1) also evaluated Parent *et al.* (2012) and the study design of Yong *et al.* (2014a) (in Hammer *et al.*

2015); therefore, detailed discussions have been excluded in this section except for overall study utility and study findings in Appendix E, Table E-2. Similar to the breast cancer evaluation, Schwartzbaum *et al.* (2007) and Jørgensen *et al.* (2017) were ultimately excluded from the hazard evaluation due to poor exposure assessment.

Table 4-5. Summary of study quality: Shift work and colorectal cancer

Citation	Selection[a]	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility[b]
Cohort studies								
Papantoniou *et al.* 2018	++	++	+++	+++	+++	+++	+++	+++
Schwartzbaum *et al.* 2007	++	0	+++	+	++	+++	+	0
Yong *et al.* 2014a	++	+	++	+	+++	+++	+	+
Jørgensen *et al.* 2017	+	0	++	+++	++	+++	+	0
Case-control studies								
Parent *et al.* 2012	+++	++	+++	++	+++	+++	++	++
Papantoniou *et al.* 2017	++	++	+++	++	+++	+++	++	++
Walasa *et al.* 2018	++	+	+++	++	+++	+++	++	+

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

Selection bias

Some (Schwartzbaum *et al.* 2007, Yong *et al.* 2014a, Papantoniou *et al.* 2017, Papantoniou *et al.* 2018, Walasa *et al.* 2018) or major concerns (Jørgensen *et al.* 2017) of selection bias are due to lack of accounting for healthy worker survivor effect and low response rates. Additionally, selection bias can be an issue for both younger and older populations. Younger cohorts with an inadequate latency period may not have been engaged in shift work long enough to see an effect. For the NHS/NHS2 combined study, NTP evaluated both the combined NHS and NHS2 cohorts to allow for the examination of how left truncation may operate (similar to Section 3). There was some concern of selection bias for the NHS cohort given the potential for left truncation, and minimal concern for the NHS2 cohort.

Exposure misclassification

There were serious or critical concerns regarding exposure misclassification in four studies. Jørgensen *et al.* (2017) limited their assessment of night and rotating shift work to current job and thus was assessed as having a critical concern for exposure misclassification. Critical concern due to exposure misclassification issues with the JEM in Schwartzbaum *et al.* (2007) is explained in greater detail in Section 4.1. Walasa *et al.* (2018) also used a JEM that characterized shift work at an aggregate level; however, the JEM was considered to be stronger than that of Schwartzbaum *et al.* (2007), given it was based on detailed information of lifetime occupational

history. In the combined NHS/NHS2 study (Papantoniou *et al.* 2018), exposure misclassification is likely, given the survey question only asked for rotating, but not fixed, night shift work. The younger NHS2 cohort is less likely to be subject to exposure misclassification due to post-baseline follow-up questionnaires on shift-work status.

Outcome misclassification

The use of mortality data to approximate incidence of colorectal cancer in the supporting NHS study (Gu *et al.* 2015) and in Jørgensen *et al.* (2017) can result in a significant loss of cancer cases depending on survival and subsequent loss of power, and an underestimation of the risk estimate based on the high survival rate for this cancer.

Sensitivity

Schwartzbaum *et al.* (2007), Yong *et al.* (2014a), and Jørgensen *et al.* (2017) had low study sensitivity due to little or no information on duration or other metrics of shift work exposure. Other studies had moderate or high study sensitivity. Compared to the older NHS cohort, the younger NHS2 cohort had a lower number of exposed cases who worked shifts 15 or more years, and did not have information on tumor anatomical site.

Overall study utility

The study of the U.S.-based NHS and NHS2 cohorts (Papantoniou *et al.* 2018) and case-control studies in Canada (Parent *et al.* 2012) and Spain (Papantoniou *et al.* 2017) were considered to be informative for the evaluation (high or moderate utility). The NHS/NHS2 combined study (Papantoniou *et al.* 2018) was considered as one study in the overall utility because it allows NTP to evaluate how left truncation may operate (similar to Section 3) and any differences in risk based on age entering the cohort. A German-based occupational cohort study (Yong *et al.* 2014a) and an Australian case-control study (Walasa *et al.* 2018) both were considered to be of low study utility because they had poor classification of shift-work exposure, did not adequately account for smoking, and/or had poor sensitivity. A cohort of Danish nurses (Jørgensen *et al.* 2017) and a linkage study of the Swedish population (Schwartzbaum *et al.* 2007) were also determined to have inadequate utility based on critical concerns of exposure misclassification, and thus were not included in the hazard assessment.

4.2.3 Colorectal cancer hazard assessment

Findings for all the individual studies included in the analysis are available in Appendix E, Table E-2 and selected findings are graphed in the forest plots below.

As stated in Section 3.2.5, NTP did not consider the meta-analysis approach informative and thus did not include its own meta-analysis nor include the published meta-analyses in the cancer hazard assessment. One meta-analysis by Wang *et al.* (2015b) found significantly increased risk of colorectal cancer with ever exposure to night work, and a significant increase in risk for every 5 years duration of shift work. The utility of this analysis was limited by the inclusion of studies with insufficient or poorly characterized exposure to shift work or irrelevant outcomes of interest.

Consistency of the evidence across studies

Overall, the evidence for an association between rotating night shift work and colorectal cancer is unclear and is limited by a small number of informative studies (see Table 4-6). Two moderate-utility studies offer evidence (moderate to strong or some evidence) of an association based on significantly increased risks of colon, rectal, and colorectal cancers (Parent *et al.* 2012, Papantoniou *et al.* 2017). The Nurses' Health Study, which was considered to be a high-utility study, found evidence of an association with rectal but not colon or combined colorectal cancer in the older but not the younger NHS cohort (Papantoniou *et al.* 2018). Moreover, a positive exposure-response relationship by increasing duration of shift work was found for colorectal and for rectal cancers (Papantoniou *et al.* 2017, Papantoniou *et al.* 2018). A low-utility study by Yong *et al.* (2014a) found a non-significantly increased association of colorectal cancer with having ever worked rotating night shift work in both internal and external analyses, suggesting that there is some evidence of an association. In the supporting mortality study by Yong *et al.* (2014b), shift work was not associated with colorectal cancer mortality. Lastly, a low-utility case-control study (Walasa *et al.* 2018) reported inconclusive results, with a null association of colon and colorectal cancers, and a non-significantly increased association with rectal cancer.

Table 4-6. Evidence summary table for studies of shift work and colon and rectal cancers

			Key metric measured in study			
Reference	**Study utility**	**Study design**	**Ever worked**	**Years worked**	**Cancer type**	**Gender**
Strong evidence or some evidence of colorectal cancer risk						
Parent *et al.* 2012	+++/++	Case-control	***	**	C, R	M, F
Papantoniou *et al.* 2017	+++/++	Case-control	***	***	CRC	F
Papantoniou *et al.* 2018	+++/++	Cohort		**	C, R, CRC	M, F
Yong *et al.* 2014a	+	Cohort	*		CRC	M
Inconclusive evidence						
Walasa *et al.* 2018	+	Case-control	Null	*	C, R, CRC	F

+++/++ = informative (dark yellow); + = low utility (light yellow); strength of association increases with number of * and darker shade of blue for key metric measured in study; C = colon; CRC = colorectal cancer; F = female; M = male; R = rectum.

Issues relevant to the cancer hazard assessment include exposure metric, cancer sites (i.e., colon, rectum, or colon and rectum combined), and potential effect modifiers such as smoking status, body weight, and gender-specific differences.

Metrics of exposure

One study only examined ever exposure (Yong *et al.* 2014a), four studies reported on shift work duration (Parent *et al.* 2012, Papantoniou *et al.* 2017, Papantoniou *et al.* 2018, Walasa *et al.* 2018), and one study reported on type of shift (Papantoniou *et al.* 2017).

The main issues that may explain the observed heterogeneity across the studies include (a) the exposure metrics used and (b) the timing of night work.

Ever night work

Overall, the most informative studies suggest an increased risk of colorectal cancer associated with ever working night shifts (Figure 4-3). Papantoniou *et al.* (2017) reported statistically significant elevated risks for colorectal cancer among those working rotating shifts, but not fixed night shifts. Parent *et al.* (2012) saw a similar magnitude of risk of colon and rectal cancer in men who were ever employed in night work. Among the low-utility studies, internal analysis by Yong *et al.* (2014a) revealed an increased risk of incident colorectal cancer in rotating shift workers, although the association was not statistically significant. The study was limited by incomplete exposure history data. Walasa *et al.* (2018) reported null results in women for colorectal cancer and when stratifying by colon cancer, but did find a non-significantly increased risk of rectal cancer for ever having worked graveyard shifts (0.1+ months). The NHS/NHS2 study did not report on ever exposure.

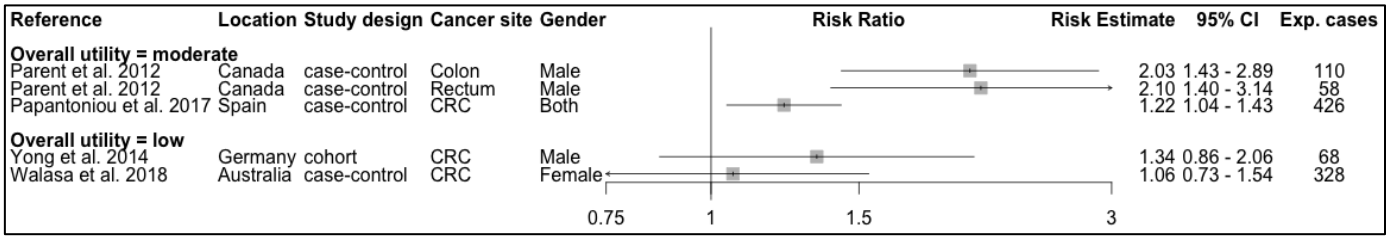

Figure 4-3. Forest plot of human studies on the risk of colon, rectal, and colorectal (CRC) cancers from ever exposure to night work; stratified by study utility

Note: Plotted confidence intervals (CI) are standardized and estimated based on software package, and therefore, may differ slightly from study confidence intervals. CRC = colorectal cancer.

Exposure duration

The three high- or moderate-utility studies also stratified by lifetime duration of night work exposure (Figure 4-4). In both the NHS and NHS2 cohorts, there were no significant exposure-response relationships with increasing exposure duration in women with colorectal or colon cancers. In the older NHS cohort, however, Papantoniou *et al.* (2018) found a significant positive trend with increasing duration in women with rectal cancer (P_{trend} = 0.02) and non-significant elevated risks for colorectal cancer for women working 20 to 29 years (RR = 1.26, 95% CI = 0.96 to 1.65) and 30+ years (RR = 1.17, 95% CI = 0.84 to 1.63). For the younger NHS2 cohort, only a moderate non-significant increase in colorectal cancer (CRC) risk was seen in nurses working 10 to 14 years (RR = 1.15, 95% CI = 0.73 to 1.81); however, this estimate was attenuated with the incorporation of an updated shift work history. In contrast, prior analysis of the same NHS cohort by Schernhammer *et al.* (2003) showed a significant positive trend of an elevated risk for colorectal cancer with increasing duration of rotating shift work; however, Schernhammer *et al.* (2003) analyzed the same cohort with 14 years less follow-up data. Considering the NHS cohort is an older population, the additional years of follow-up may have captured retirement years long after shift work was done, thereby diluting the effect with the added years of latency. The supporting NHS mortality study by Gu *et al.* (2015) found a borderline non-significant positive trend with increasing duration (P_{trend} = 0.07). For NHS2, only 15 CRC cases had 15+ years of shift-work history, and therefore, the study may have suffered from insufficient power.

Parent *et al.* (2012) did not report a positive exposure-response relationship; estimates exceeding 2.0 were reported for men working < 5 years for both colon and rectum cancer, as well as colon cancer among men working ≥ 10 years. Walasa *et al.* (2018) saw no increased risk of colorectal and colon cancers with increasing duration of graveyard shift or phase shift work; however, non-significantly elevated risk of rectal cancer was seen with both shorter (< 7.5 years) and longer durations (7.5+ years) of graveyard shifts. Similar results were seen with duration of phase shift exposure.

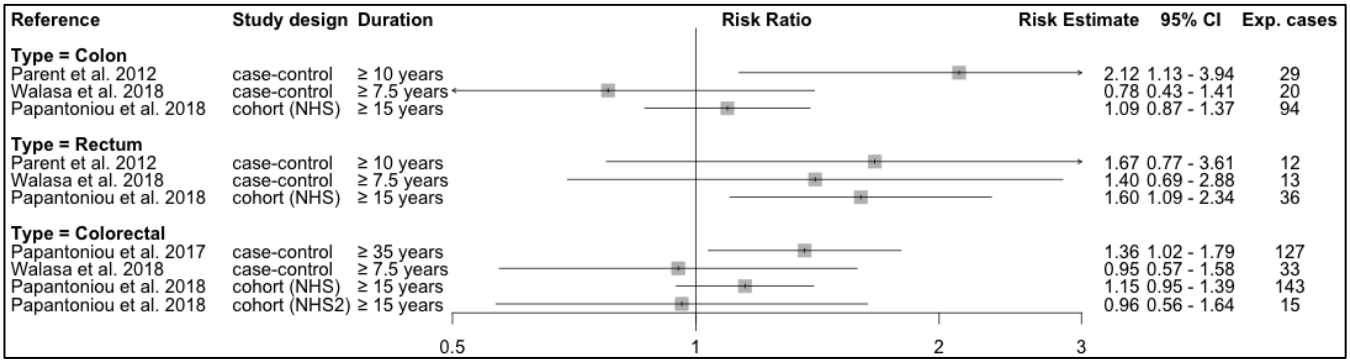

Figure 4-4. Forest plot of human studies on the risk of colon, rectal, and colorectal cancer and longest lifetime duration of shift work exposure; stratified by cancer type

Note: Plotted confidence intervals (CI) are standardized and estimated based on software package and, therefore, may differ slightly from study confidence intervals.

Type of cancer and effect modification

Differences in the magnitude of cancer risk were found after stratifying by cancer site (i.e., colon, rectum, colon and rectum), suggesting shift work may differentially impact rectal cancer. Walasa *et al.* (2018) did find elevated estimates for rectal but not colon cancer in women, but no estimates were significant. When stratifying by colon and rectal cancers, Papantoniou *et al.* (2018) found a significant risk and positive trend of rectal cancer in NHS cohort nurses working 15+ years of shift work (RR = 1.60, 95% CI = 1.09 to 2.34; P_{trend} = 0.02), but not in combined proximal and distal colon cancers. When examining colon cancer by tumor anatomical site, an increased non-significant risk of distal colon cancer, but not proximal colon cancer, was seen (RR = 1.27, 95% CI = 0.87 to 1.85).

Examining the association between shift work exposure and risk of colorectal cancer by gender (i.e., male, female, both) revealed conflicting results. The only study examining men and women (Papantoniou *et al.* 2017) showed significantly increased risk for colorectal cancer in men (OR = 1.32, 95% CI = 1.10 to 1.59), but not in women. Comparing studies of men and women, there were inconsistent results in the magnitude of effect, requiring a further evaluation into the potential for effect modification.

Walasa *et al.* (2018) did not find a significant increased risk of colorectal cancer with shift work involving phase shifts, LAN exposure, poor diet, insufficient vitamin D, sleep disturbance or physical inactivity. Those considered normal weight in the NHS mortality study (Gu *et al.* 2015) had a significant increasing trend in risk of colorectal cancer by years of shift work exposure (P_{trend} = 0.02); however, the trend did not remain in overweight and obese individuals. No

significant trend was seen by duration of exposure when stratifying risk of colorectal cancer by never, former, and current smoker.

Chance, bias, and confounding

Alternative explanations for the evidence in these studies cannot be completely ruled out. Two studies did not control for BMI, red meat consumption, physical activity, and/or alcohol consumption (Yong *et al.* 2014a, Walasa *et al.* 2018), suggesting that these studies may suffer from bias. However, Yong *et al.* (2014a) conducted an internal analysis restricted to production employees to achieve maximum comparability with respect to occupational risk profiles, socioeconomic status, age distribution, and employment duration, which may further control for unmeasured confounding. Additionally, the supporting NHS mortality study by Gu *et al.* (2015) did not find effect modification by smoking and overweight status. All other studies of colorectal cancer included relevant risk factors in multivariate models, but also included covariates that were either not necessarily related to colorectal cancer or were in the etiologic pathway, potentially over-controlling for confounders and introducing bias towards the null.

4.3 Hormonal cancers (ovarian and endometrial)

Female hormonal cancers include ovarian and endometrial cancers. Overall, based on SEER age-adjusted data from 2009 to 2013 (Howlader *et al.* 2017), the five-year survival rate for ovarian cancer is 46.5%, but two-thirds of cases are diagnosed at the distant stage or are not staged. The 5-year survival rate for these women is much lower (~25% to 29%); for localized ovarian cancer (14.8% of all cases), the 5-year survival rate is 92.5%. Thus, although mortality data may provide useful information, the reliance on mortality data is likely to miss about one-third of cases with longer survival and later death, likely resulting in non-differential misclassification and loss of power. On the other hand, endometrial cancer has a relatively high 5-year survival rate (81.3%, age-adjusted SEER data from 2007 to 2013), and only studies of incidence are relevant.

4.3.1 Overview of study methods and characteristics

Four cohort studies (Schwartzbaum *et al.* 2007, Poole *et al.* 2011, Carter *et al.* 2014, Jørgensen *et al.* 2017) and one population-based study (Bhatti *et al.* 2013a) of ovarian cancer, and one cohort study of incident endometrial cancer (Viswanathan *et al.* 2007) were eligible for review (Table 4-7). Study populations were from Sweden, Denmark, and the United States. Four studies were from nurses, with three studies being from the U.S. Nurses' Health Study. Mortality data from Gu *et al.* (2015) and incidence data from Poole *et al.* (2011) were taken from overlapping study populations. Jørgensen *et al.* (2017) also used ovarian cancer mortality data in Danish nurses. The remaining studies include a hospital-based case-control study, a prospective analysis using the American Cancer Prevention cohort, and a Swedish registry linkage study.

Table 4-7. Studies of hormonal cancer (ovarian cancer and endometrial cancer) and night work

Reference	Population	Outcome and source(s)	Exposure assessment and information
Ovarian cancer			
Schwartzbaum *et al.* 2007	**Swedish workers, registry-based cohort** See Table 4-1	Incident ovarian cancer and other cancer See Table 4-1	See Table 4-1
Poole *et al.* 2011 United States	**U.S. Nurses' Health Study cohorts (NHS/NHS2)** Follow-up NHS: 1988–2008 NHS2: 1989–2007 181,548 female nurses	Incident ovarian cancer Self-report, next of kin, postal service, death registry	Self-administered questionnaires *Night work*: undefined time for ≥ 3 rotating nights/mo *Metrics*: Ever worked rotating night shifts (≥ 1 yr), duration of rotating night work
Gu *et al.* 2015 (supporting study)	NHS (1988) Follow-up 1988–2010 74,862 female nurses	Fatal ovarian cancer, underlying causes Next of kin, postal authorities, death registry	
Carter *et al.* 2014	**American Cancer Prevention Study II (CPS) cohort** 1982 (enrollment) to 2010 (follow-up) 161,004 employed women (general population)	Fatal ovarian cancer Biennial death certificate and automatic linkages with NDI	Self-administered questionnaire *Night work:* 9:00 PM–midnight (fixed nights) *Metrics*: Current rotating shifts or fixed night shifts
Jørgensen *et al.* 2017	**Danish Nurses Organization study** See Table 4-4	Fatal ovarian cancer Underlying cause of death Danish Register of Causes of Death using underlying cause of death	See Table 4-4
Bhatti *et al.* 2013a	**Western Washington State population-based case-control study** 2002–2009 (enrolled) N = 1,101 invasive epithelial cases and 389 borderline epithelial tumors 1,832 randomly selected controls	Histologically confirmed epithelial ovarian cancer, including histological, morphological, and tumor stage Surveillance, Epidemiology, and End Results (SEER)	In-person interviews *Night work*: Worked from midnight–4:00 AM *Metrics*: Ever worked night shifts (≥ 4 continuous months), cumulative night shift work-years from age 25 to reference date; ever worked in a job with less than half of work days at night, age at diagnosis
Endometrial cancer			
Viswanathan *et al.* 2007	**U.S. Nurses' Health Study (NHS) cohort**	Incident endometrial cancer	Self-administered questionnaire

Reference	Population	Outcome and source(s)	Exposure assessment and information
	1976 (enrolled), 1988 (exposure collection), 1988–2010 (follow-up) 74,862 female nurses	Self-report, next of kin, postal service, death registry	*Night work*: undefined time for ≥ 3 rotating night shift/mo *Metrics*: Ever worked rotating night shifts (≥ 1 yr), duration of rotating night work

mo = month; NDI = National Death Index; yr = year.

4.3.2 Evaluation of study quality

A detailed evaluation of study quality for all potential biases is available in Appendix F, Table F-1 and an overview of the assessment is provided in Table 4-8. It should be noted that the breast cancer section (Section 3) evaluated Schwartzbaum *et al.* (2007), Jørgensen *et al.* (2017), and the study designs in the NHS studies (Viswanathan *et al.* 2007, Poole *et al.* 2011); therefore, detailed discussions have been excluded in this section except for overall study utility and study findings in Appendix F. Similar to the other cancer endpoints evaluated, Schwartzbaum *et al.* (2007) and Jørgensen *et al.* (2017) were ultimately excluded from the hazard evaluation due to poor exposure assessment.

Table 4-8. Summary of study quality: Shift work and hormonal cancers

Citation	Selection[a]	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility[b]
Cohort studies								
Schwartzbaum *et al.* 2007	++	0	+++	+	++	+++	+	0
Viswanathan *et al.* 2007	++	++	+++	+++	+++	+++	++	++
Poole *et al.* 2011	+++	++	+++	+++	+++	+++	++	+++
Carter *et al.* 2014	+++	0	++	+++	+++	+++	+	0
Jørgensen *et al.* 2017	+	0	++	+++	++	+++	+	0
Case-control study								
Bhatti *et al.* 2013a	+++	++	+++	+++	++	+++	++	++

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

Selection bias

Three analyses were conducted within the NHS cohort (Poole *et al.* 2011, Gu *et al.* 2015), with Viswanathan *et al.* (2007) and Gu *et al.* (2015) examining the original NHS cohort; Poole *et al.* (2011) included both the older and younger cohorts (NHS and NHS2, respectively). If ovarian and endometrial cancers are related to long-term exposures starting in early life, studies conducted in the older NHS cohort (Viswanathan *et al.* 2007, Gu *et al.* 2015) could be biased

towards the null as women with cancer from early exposure are not present in the cohort (i.e. healthy-worker survival bias), and the timing of exposure in early adult life is not known. Alternatively, the study by Poole *et al.* (2011) may not be as susceptible to this bias, as younger women from the NHS2 cohort were included in the study population. Concern was minimal in the other studies evaluated.

Exposure misclassification

Some degree of exposure misclassification is likely for all of the ovarian cancer cohort studies (see Section 4.2 for a more detailed discussion of Jørgensen *et al.* 2017), the NHS cohort study (Poole *et al.* 2011), and Schwartzbaum *et al.* 2007). Two of the studies limited exposure assessment only to the current or last job (Carter *et al.* 2014, Jørgensen *et al.* 2017), and thus had critical concern for misclassification.

Other issues that may increase the likelihood of exposure misclassification include undefined definitions of night work, and relying on broad questions to determine ever exposure to night work. Explicit timings of night work were defined for three cohorts (Schwartzbaum *et al.* 2007, Carter *et al.* 2014, Jørgensen *et al.* 2017) and one case-control study (Bhatti *et al.* 2013a). Bhatti *et al.* (2013a) calculated cumulative work-years by dividing the total number of hours engaged in night work for a particular job by the total number of hours worked in a 40-hour workweek over a year (i.e., 2,080 hours). This method did not allow for distinguishing duration and frequency separately. Considering elevated risks were seen in only some ovarian cancer subtypes but not others, this case-control study is likely to be less susceptible to recall bias.

Sensitivity

Due to the limited ability to differentiate levels of exposure, and a potentially less relevant window of exposure, most studies had low to moderate study sensitivity.

Overall study utility

For ovarian cancer, the most informative study was the NHS/NHS2 incidence study (Poole *et al.* 2011) because lifetime shift work history was examined, the study had a varying age range and a large number of exposed cases, and there was minimal concern of potential bias. The analysis of ovarian cancer mortality by Gu *et al.* (2015) was not considered to be as informative because mortality data is an imprecise proxy for incident ovarian cancer. The Washington State population-based case-control study (Bhatti *et al.* 2013a) had detailed information on ovarian cancer and subtypes, comprehensive data on night shift schedules, and high participation rates, but lacked detailed exposure information and was considered to have moderate utility for the evaluation. The studies by Schwartzbaum *et al.* (2007), Jørgensen *et al.* (2017), and Carter *et al.* (2014) were excluded from the hazard assessment due to their inadequate exposure assessment and/or sensitivity to detect a true effect.

The NHS study by Viswanathan *et al.* (2007) was considered to be somewhat informative (moderate utility) for evaluating endometrial cancer, but it was the only study reporting on this outcome.

4.3.3 Hormonal cancer hazard assessment

Findings for all the individual studies included in the analysis are available in Appendix F, Table F-2.

The database is inadequate to evaluate the level of evidence from studies of night work and risk of endometrial cancer, as only one study (Viswanathan *et al.* 2007) is available. This study found a significant association between 20+ years of rotating shift work and endometrial cancer, with a significant exposure-response relationship for duration of shift work. When stratified by BMI, the relationship and trend remained only in women considered obese.

The available data are also inadequate to evaluate the relationship between ovarian cancer and night work because of few informative (moderate- or high-utility) studies of independent populations. The case-control study of ovarian cancer (Bhatti *et al.* 2013a) provided the strongest evidence of a relationship because of consistent, significantly increased risk for both invasive (OR = 1.24, 95% CI = 1.04 to 1.49) and borderline (OR = 1.48, 95% CI = 1.15 to 1.90) ovarian tumors, three ovarian tumor subtypes (high grade serous, low grade and borderline serous, and invasive/borderline mucinous), and increasing risk in certain durations of night work. The combined NHS and NHS2 cohort study (Poole *et al.* 2011, based on 718 cases) reported a non-statistically significant elevated risk among women working rotating shifts for 10 to 14 years and 15 to 19 years. No excess risk was found for those working ≥ 20 years. When examining ovarian cancer mortality in the NHS cohort, Gu *et al.* (2015) found no excess risk of ovarian cancer mortality for women working rotating shifts for any number of years; however, the study population was older than the NHS2 and the analysis was restricted to fatal cases.

4.4 Lung cancer

Lung cancer is the leading cause of cancer-related mortality in the United States, with approximately 222,500 incident cases expected to have occurred in 2017 (Howlader *et al.* 2017). Furthermore, five-year survival rate for lung cancer is 18.1%. Thus, using mortality data to approximate incidence of lung cancer is less likely to result in reduced power or bias than for other cancers.

4.4.1 Overview of study methods and characteristics

Three cohort studies of incident lung cancer (Schwartzbaum *et al.* 2007, Schernhammer *et al.* 2013, [NHS], Yong *et al.* 2014a), one nested case-cohort study (Kwon *et al.* 2015), and one population-based case-control study (Parent *et al.* 2012) were identified; three cohort studies of fatal lung cancer were also identified (Taylor and Pocock 1972, Gu *et al.* 2015, Jørgensen *et al.* 2017) (Table 4-9). Gu *et al.* (2015) conducted a mortality analysis within the NHS which overlaps with Schernhammer *et al.* (2013), and therefore will be used in support of the incident lung cancer study. Yong *et al.* (2014b) conducted a mortality analysis in the same study population as Yong *et al.* (2014a), and therefore, will be used in support of the incident lung cancer study. Of the five cohort and nested case-cohort studies, two were composed of nurses (Schernhammer *et al.* 2013, Jørgensen *et al.* 2017), and three were occupational cohort studies in the textile (Kwon *et al.* 2015), chemical (Yong *et al.* 2014a), and manufacturing populations (Taylor and Pocock 1972). The remaining two studies were general population studies of workers (Schwartzbaum *et al.* 2007, Parent *et al.* 2012).

Table 4-9. Studies of lung cancer and night work

Reference	Population	Outcome and source(s)	Exposure assessment and information
Cohort studies			
Taylor and Pocock 1972	**United Kingdom retrospective cohort of manual workers** Enrolled 1956–1968 8,603 men (industry-based)	Fatal lung and bronchial cancers National Death Register (SMR study)	Company payroll records *Night work*: 80% worked 3 rotating shifts (rapid and weekly); 20% worked alternate day/night or other shift schedules *Metric*: Ever worked shift (≥ 10 years with ≤ 6 mo break)
Schwartzbaum *et al.* 2007	**Swedish workers, registry-based cohort** See Table 4-1	Incident lung and other cancers (see Table 4-1)	See Table 4-1
Schernhammer *et al.* 2013 Gu *et al.* 2015 (supporting study)	**US Nurses' Health Study (NHS)** 1976 (enrolled), 1988 (exposure collection) 1988–2008 (follow-up) N = 78,612 women NHS (1988) Follow-up 1988–2010 74,862 female nurses	Incident lung cancer, including histology subtypes Self-report, next of kin, postal service, death registry Fatal lung cancer, underlying causes Next of kin, postal authorities, death registry	Self-administered questionnaires *Night work*: undefined time for ≥ 3 nights/mo in addition to days/evenings in that month *Metrics*: Worked rotating night shifts (≥ 1 yr) by duration of rotating night work
Yong *et al.* 2014a (Yong *et al.* 2014b supporting study)	**German Rhineland-Palatinate chemical workers retrospective cohort** See Table 4-4	Incident, lung/bronchial and other cancers (see Table 4-4)	See Table 4-4
Jørgensen *et al.* 2017	**Danish Nurses Organization study** See Table 4-4	Fatal ovarian, lung, colorectal cancers Underlying cause of death Danish Register of Causes of Death using underlying cause of death	See Table 4-4
Case control and nested case-cohort studies			
Parent *et al.* 2012	**Montreal multisite case-control cancer study** See Table 4-1 761 male cases; 512 male population controls	Incident, histologically confirmed, lung and other cancers (see Table 4-1)	See Table 4-1

Reference	Population	Outcome and source(s)	Exposure assessment and information
Kwon *et al.* 2015	**Shanghai Textile Industry Bureau (STIB) nested case-cohort study** Enrolled 1989–1991 267,400 women textile workers 1,451 cases; 3,040 controls	Lung cancer incidence and mortality, ICD-9: 162 Shanghai Cancer Registry (SCR), the death registry of the Shanghai Textile Industry Bureau, medical records	JEM based on factory records *Night work*: any continuous hours between midnight & 6:00 AM as part of a rotating shift pattern *Metrics*: cumulative duration, cumulative frequency of night shifts

mo = month; SMR = standardized mortality ratio; yr = year.

4.4.2 Evaluation of study quality

A detailed evaluation of study quality for all potential bias is available in Appendix G, Table G-1 and an overview of the assessment is provided in Table 4-10.

It should be noted that the breast cancer section (Section 3) also evaluated Schwartzbaum *et al.* (2007), Jørgensen *et al.* (2017), Parent *et al.* (2012), and the older NHS cohort (Schernhammer *et al.* 2003, Gu *et al.* 2015); the prostate cancer section (Section 4.1) also evaluated the study population in Yong *et al.* (2014a). Therefore, detailed discussions have been excluded in this section except for overall study utility and study findings in Appendix G, Table G-2. Similar to the other cancer endpoints evaluated, Schwartzbaum *et al.* (2007) and Jørgensen *et al.* (2017) were ultimately excluded from the hazard evaluation due to poor exposure assessment.

Selection bias

None of the occupational cohort studies of prevalent surviving workers accounted for left truncation and the HWSE. Among these studies, HWSE was most clear in the Kwon *et al.* (2015) cohort study which reported that night work required a healthier physical profile for the completion of specific tasks, and the Taylor and Pocock (1972) study which only included men who had worked shifts at least ten years, likely selecting out those with shorter periods of work who may have left for illness related to lung cancer, or had low tolerance for night work.

Exposure misclassification

Critical concern for exposure misclassification in the Jørgensen *et al.* (2017) and Schwartzbaum *et al.* (2007) studies have been mentioned previously. There are major concerns (Yong *et al.* 2014a) and some concerns (Taylor and Pocock 1972, Parent *et al.* 2012, Schernhammer *et al.* 2013, Kwon *et al.* 2015) of exposure misclassification in lung cancer studies. This section will only review the studies unique to lung cancer (see Section 4.1 for Parent *et al.* 2012 and Schwartzbaum *et al.* 2007, and Section 4.2 for Jørgensen *et al.* 2017 and Yong *et al.* 2014a). Exposure assessments based on company records still raised concerns. Shift work exposure based on company records in Taylor and Pocock (1972) were adequately captured but insufficiently characterized. Exposure misclassification is also possible in a Chinese nested case-control study where shift work status was assessed at the factory level and not at the individual level (Kwon *et al.* 2015)

Definitions of night work varied among lung cancer studies. Among the lung-cancer-specific studies, only Kwon *et al.* (2015) specified night work as any hours completed between midnight and 6:00 AM. Taylor and Pocock (1972) categorized six rotating work schedules, including rotating and fixed night schedules, together to characterize shift work exposure.

Overall study utility

The most informative lung cancer studies were the NHS (Schernhammer *et al.* 2013, Gu *et al.* 2015), the Shanghai nested case-control study (Kwon *et al.* 2015), and the Canadian case-control study (Parent *et al.* 2012) (see Table 4-10). Two studies provided low study utility based on concerns for bias, primarily exposure misclassification and potential misclassification from smoking, a major risk factor for lung cancer which could be related to shift work status (Taylor and Pocock 1972, Yong *et al.* 2014a). Based on critical concerns for exposure misclassification, Jørgensen *et al.* (2017) and Schwartzbaum *et al.* (2007) were determined to have inadequate study utility and were not included in the hazard assessment.

Table 4-10. Summary of study quality: Shift work and lung cancer

Citation	Selection[a]	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility[b]
Cohort Studies								
Taylor and Pocock 1972	++	++	+++	+	+	+++	+	+
Schwartzbaum *et al.* 2007	++	0	+++	+	++	+++	+	0
Schernhammer *et al.* 2013	++	++	+++	+++	+++	+++	++	++
Yong *et al.* 2014a	++	+	++	++	+++	+++	+	+
Jørgensen *et al.* 2017	+	0	++	+++	++	+++	+	0
Case-control Studies								
Parent *et al.* 2012	+++	++	+++	+++	+++	+++	++	++
Kwon *et al.* 2015	++	++	++	+++	+++	+++	++	++

[a]Levels of concern for bias and for study sensitivity (columns for Selection through Sensitivity). Key: +++ = low/minimal concern or high quality; ++ = some concern or medium quality; + = major concern or low quality; 0 = critical concern.
[b]Utility of the study to inform the hazard evaluation. Key: +++ = high utility; ++ = moderate utility; + = low utility; 0 = inadequate utility.

4.4.3 Lung cancer hazard assessment

Findings for all the individual studies included in the analysis are available in Appendix G, Table G-1.

As stated in Section 3.2.5, NTP did not consider the meta-analyses approach informative and thus did not include its own meta-analyses.

Consistency of the evidence across studies

Of the literature reviewed, studies with high and moderate utility best informed the relationship between shift work exposure and risk of lung cancer (see Table 4-11). Of the three studies with high to moderate utility, a Canadian case-control study (Parent *et al.* 2012) and the NHS cohort (Schernhammer *et al.* 2013, Gu *et al.* 2015) provided evidence of an association between working night shifts and risk of lung cancer.

Table 4-11. Evidence summary table for studies of night work and lung cancer

Study utility or informativeness	Level of evidence	Cohort studies	Case-control, nested case-cohort studies
Moderate or high: 3 studies	Moderate to strong evidence: 2 studies	Schernhammer *et al.* 2003 (Gu *et al.* 2015)	Parent *et al.* 2012
	Null: 1 study	–	Kwon *et al.* 2015
Low: 2 studies	Null: 1 study	Yong *et al.* 2014a	–
	Inconclusive: 1 study	Taylor and Pocock 1972	–

Issues relevant to the cancer assessment include exposure metrics and potential effect modifiers, such as cancer sites and gender-specific differences.

Exposure metrics

Ever night work: Findings for ever exposure and the risk of lung cancer were inconsistent across the four studies reported on this metric. The moderate-utility Canadian case-control study (Parent *et al.* 2012) reported significantly elevated risks of lung cancer associated with having ever worked night shifts. Among the studies with low utility, one study reported a nonsignificantly elevated risk of lung cancer (Taylor and Pocock 1972, Schwartzbaum *et al.* 2007); however, the study did not control for smoking and thus the evidence was considered inconclusive. Yong *et al.* (2014a) did not find an elevated risk of lung cancer in shift workers. Similarly, after adjustment for cigarette smoking, the supporting mortality study by Yong *et al.* (2014b) did not find an elevated risk of lung cancer in shift workers.

Longest duration: Four analyses of three study populations reported on shift work duration and lung cancer risk. Among the most informative studies, an excess risk of lung cancer incidence and mortality was found in the NHS/NHS2 studies. Gu *et al.* (2015) reported those working ≥ 15 years had a significantly increased risk of lung cancer mortality (HR = 1.25, 95% CI = 1.05 to 1.51). Schernhammer *et al.* (2013) reported an overall 28% excess risk of incident lung cancer among women working rotating shifts for ≥ 15 years compared to women with no shift work history (HR = 1.28, 95% CI = 1.07 to 1.53). Both NHS studies (Schernhammer *et al.* 2013, Gu *et al.* 2015) reported significant trends in exposure-response estimates for the risk of lung cancer among women working rotating shifts. However, there did not appear to be a consistent dose-response relationship across studies (Figure 4-6). Kwon *et al.* (2015) and Parent *et al.* (2012) did

not find a significant trend with increasing duration of shift work, with Parent *et al.* (2012) finding the lowest shift work duration (6 months to < 5 years of shift work) had the highest risk of lung cancer incidence. Kwon *et al.* (2015) did not find an elevated risk of lung cancer when examining cumulative frequency of shift work (i.e., lifetime number of night shifts worked).

Effect modification and cancer subtype

Results from some of these studies suggest the risk of lung cancer due to shift work occurs primarily among smokers. In the NHS/NHS2 studies, shift workers who were smokers at the time of being interviewed had significantly elevated risks of lung cancer (Schernhammer *et al.* 2013, Gu *et al.* 2015). Furthermore, significant exposure-response trends were seen with increasing duration of shift-work years. Among never smokers, the risk was lower and did not reach statistical significance. There was no effect among former smokers. Based on NTP calculations of reported results by Kwon *et al.* (2015), there was a non-significant increased risk of lung cancer among ever smokers in the highest duration of night work (OR = 1.20, 95% CI = 0.60 to 2.39; 36 cases), whereas no association was found in the total population. There did not appear to be a consistent trend across duration of shift work by ever smokers.

Two studies examining subtypes of lung cancer suggest shift work increases one's risk of squamous-cell and small-cell carcinoma of the lung (Parent *et al.* 2012, Schernhammer *et al.* 2013).

Chance, bias, and confounding

Alternative explanations for the evidence in these studies cannot be completely ruled out. Given the risk of lung cancer in shift workers was occurring primarily among smokers, there is a potential for residual confounding from smoking. While most studies had low concern of potential confounding bias given they accounted for likely confounders, one study (Taylor and Pocock 1972) did not control for smoking or potential confounding from co-exposures in the occupational cohort. Considering Parent *et al.* (2012) found elevated risks of multiple cancer types, including lung cancer, among night workers compared to study controls, there is a possibility of selection bias. To determine the representativeness of the sample, the study population was compared to the overall Canadian population, and both its occupational distribution and proportion of shift workers were similar.

4.5 Other types of cancers and night shift work

In addition to the five cancers (Sections 3 & 4.1 to 4.4), studies have examined the relationship between night shift work and other cancers. Although the database was deemed inadequate for a full evaluation, this section will briefly summarize the results from studies on night work exposure and skin tumors, lymphohematopoietic cancers, stomach cancer, and pancreatic cancer.

4.5.1 Skin tumors

Four studies, including three cohorts (Schernhammer *et al.* 2011, Yong *et al.* 2014a, Heckman *et al.* 2017) and one case-control study (Parent *et al.* 2012) reported on incident cases of malignant melanoma with exposure to shift work. Two studies reported a significantly decreased risk of malignant melanoma among rotating workers (Schernhammer *et al.* 2011, Yong *et al.* 2014a), while the other two studies found null or non-significantly increased associations in overall

estimates (Parent *et al.* 2012, Heckman *et al.* 2017). Additionally, both NHS studies (Schernhammer *et al.* 2011, Heckman *et al.* 2017) also reported a significantly decreased risk of basal-cell carcinoma in relation to working shift rotations. Schernhammer *et al.* (2011) also found a significant downward trend of squamous-cell carcinoma among shift workers by increasing duration.

4.5.2 Lymphohematopoietic cancers

Three studies (two case-control and one cohort study) of incident leukemia in relation to shift work were available (Yong *et al.* 2014a, Costas *et al.* 2016, Talibov *et al.* 2018). Studies reported significantly increased risks of leukemia (Yong *et al.* 2014a) and chronic lymphocytic leukemia (Costas *et al.* 2016) among rotating shift workers. In addition, two studies of fatal leukemia in relation to shift work were examined (Taylor and Pocock 1972, Gu *et al.* 2015). In the population-based case-control study from Finland, Sweden, and Iceland (Talibov *et al.* 2018), a borderline non-significantly increased risk of leukemia (OR = 1.07, 95% CI = 0.99 to 1.16) and acute myeloid leukemia (OR = 1.15, 95% CI = 0.97 to 1.36) was seen in individuals with > 20 years of cumulative night work. Only the NHS mortality study (Taylor and Pocock 1972, Gu *et al.* 2015) found non-significantly increased risks of leukemia-related mortality among the longest rotating shift work durations.

The risk of non-Hodgkin lymphoma (NHL) in relation to shift work was reported in three cohort studies (Lahti *et al.* 2008, Carreón *et al.* 2014, Yong *et al.* 2014a) and two case-control studies (Parent *et al.* 2012, Talibov *et al.* 2018). Elevated risks of NHL were reported by Yong *et al.* (2014b) and Lahti *et al.* (2008). Lahti *et al.* (2008) found night-time work significantly increased the risk of NHL in men with the highest exposure (RR = 1.28, 95% CI = 1.03 to 1.59). In the chemical plant worker cohort study by Carreón *et al.* (2014), shift work did not increase risk of NHL mortality (standardized relative risk [SRR] = 0.69, 95% CI = 0.18 to 2.69). Talibov *et al.* (2018) did not see a significantly increased risk of other lymphohematopoietic cancers with night work.

4.5.3 Stomach and pancreatic cancer

Four studies of incident stomach cancer (two cohort and two case-control studies) were based on almost 600 exposed cases. In the two case-control studies (Parent *et al.* 2012, Gyarmati *et al.* 2016), risks for ever working nights were slightly elevated, but were not statistically significant (OR = 1.10, 95% CI = 0.80 to 1.40; OR = 1.34, 95% CI = 0.85 to 2.10, respectively). The two cohort studies reported a statistically significant elevated risk (Taylor and Pocock 1972) or non-statistically significant elevated risk for ever having worked night shifts (Yong *et al.* 2014a).

One study of incident pancreatic cancer reported on the risk of shift work among 221 exposed cases (Parent *et al.* 2012), and three mortality studies reported on the risk of shift work for 286 exposed deaths (Lin *et al.* 2013, Gu *et al.* 2015, Jørgensen *et al.* 2017). Only the case-control study of incident pancreatic cancer (Parent *et al.* 2012) reported a statistically significant elevated risk of ever working nights based on 70 exposed cases (OR = 2.27, 95% CI = 1.24 to 4.15); with those having worked nights within the past 20 years having a statistically elevated risk of cancer (OR = 3.81, 95% CI = 1.75 to 8.28). Risks did not increase with increasing duration, but were non-statistically significantly elevated in those working 5 to 10 and 10+ years. All other studies showed no elevation in risk of pancreatic cancer.

4.6 Other exposures and cancer

Two studies examined LAN exposure and risk of other cancers (Kloog *et al.* 2009, Garcia-Saenz *et al.* 2018). Kloog *et al.* (2009) found a positive correlation between incidence rates of prostate cancer, but not lung or colon cancers, with aggregate-level exposure to LAN. Garcia-Saenz *et al.* (2018) evaluated the risk of prostate cancer and exposure to both indoor and outdoor LAN in a Spanish case-control study. The study found an increased risk of prostate cancer with the highest exposure to both indoor LAN (OR = 2.79, 95% CI = 1.55 to 5.04) and outdoor blue LAN (OR = 2.05, 95% CI = 1.38 to 3.03). Although this was a well-conducted study (see evaluation in Section 3), it was the only study that met the inclusion criteria, as Kloog was an ecological study, and thus a formal cancer hazard evaluation was not conducted. Only one study was identified that evaluated transmeridian travel: a cancer registry study of Scandinavian flight attendants and cancer incidence (Pukkala *et al.* 2012). The study found increased incidence of multiple cancers in airline crew workers, compared to national estimates; however, no increased risk in any cancers was seen in the nested case-control sub-analysis.

Three studies were identified that evaluated position in a time zone and cancer risk. Circadian misalignment may be more severe in the western part of a time zone because people living in the western part of a time zone have greater light exposure later in the day compared to people living in the eastern part of a time zone. Gu *et al.* (2017) reported a positive association between moving from east to west in a time zone and county-level incidence rates for chronic lymphocytic leukemia in men and women; cancers of the stomach, liver, prostate, and non-Hodgkin lymphoma in men; and cancers of the esophagus, colorectum, lung, breast, and corpus uteri in women. A prospective analysis of over 56,000 liver cancer cases occurring in the United States between 2000 and 2014 also found that risk of liver cancer increased moving east to west after controlling, at a county level, for lifestyle factors, shift work, demographic, and environmental factors (VoPham *et al.* 2018). An early study conducted in 59 regions in Russia found that both latitude and position in a time zone were predictors of total cancer incidence and mortality; risk for most cancers increased with increasing latitude of residence and from the eastern to western border of the time zone. With respect to different cancer types, position in a time zone was the best predictor for breast and brain cancer incidence and mortality (Borisenkov 2011).

4.7 NTP level of evidence conclusion

There is limited evidence for prostate carcinogenicity of night shift work from human cancer epidemiology studies. Higher quality studies showed significant positive relationships, particularly with persistent night shift work, which includes increased risk of prostate cancer in those working nights for longer duration of exposure, a combination of duration, cumulative frequency, and length of the shift, or a significant positive trend of prostate cancer with night work duration. Despite the results, poor characterizations of night work exposure in many studies hindered the comparability across studies. Furthermore, only a few studies examined prostate cancer severity.

The available database was inadequate to evaluate the carcinogenicity of night shift work for other types of cancer (colorectal, female hormonal, and lung cancers) from human cancer epidemiology studies. The database was limited by the potential for exposure misclassification

and limited number of informative studies. The relevant data on night work and lung cancer suggests the potential for confounding bias due to smoking status may be impacting results.

5 Cancer Studies in Experimental Animals

This section reviews studies that examined the effects of (1) different light-dark cycles and daytime light exposure to blue light and (2) simulated shift work or jet lag on formation and growth of tumors in mice and rats. The effects of light exposure were studied in models of spontaneous tumor formation (i.e., occurring with no co-exposure), cancer xenografts and injection of cancer cells, and chemical initiation and promotion of cancer. Melatonin was the primary biomarker of circadian disruption evaluated, but some of these studies also measured markers of circadian disruption, such as activity, body temperature, estrus cycling, and clock gene expression. Indirect measurements of the urinary metabolite 6-sulfatoxymelatonin were also monitored, and some studies looked at the effects of melatonin supplementation (see Section 6). Most of these studies examined growth of tumors after chemical or genetic initiation or after injection of tumor cells or implantation of tissue; however, they were not designed to evaluate incidences of specific tumors as would be reported in chronic cancer studies. Therefore, while these studies provide information supportive of mechanistic findings, they are not informative for reaching a level of evidence conclusion for cancer in experimental animals.

Most mice and rats used in experimental studies are nocturnal animals and thus are most active during nighttime. It is during this period that some strains of rodents produce melatonin; however, most inbred strains of mice lack melatonin due to enzyme deficiencies in melatonin synthesis (Goto *et al.* 1989, Jilge and Kunz 2004, Steinlechner 2012, Peirson *et al.* 2018). The apparent lack of melatonin detection in some inbred mouse strains does not seem to make a difference in tumor growth in response to light intensity, as melatonin supplementation or increased darkness decreases tumor growth in the absence of detectable blood levels of melatonin (Schwimmer *et al.* 2014). Melatonin-deficient mice are nocturnal and have a circadian pattern similar to melatonin-proficient mice (Peirson *et al.* 2018), which could be explained by physiologic factors that can compensate for the lack of melatonin, or by a low, but sufficient, level of endogenous melatonin in these inbred strains, as melatonin-deficient mice have intact melatonin receptors (Stehle *et al.* 2002, 2003). A low, but significant, level of melatonin production was noted when melatonin-deficient C57BL/6 mice were exposed to long nights or norepinephrine stimulation, which lends credence to the latter hypothesis (Haim *et al.* 2010). In addition, in a study using pinealectomized mice, detectable blood levels of melatonin were measured (Travlos *et al.* 2001). If available, information on melatonin production by the experimental animal strain is noted after the strain of experimental mouse or rat in Tables 5-1 and 5-2.

5.1 Exposure models of LAN, and simulated shift work, and chronic jet lag

The animal studies of light are a surrogate for LAN human exposure studies. Aside from red light, rodents have more absolute and spectral sensitivity than humans to visible light, and may have vision into the ultraviolet light spectrum, and thus they may respond differently or more intensely to a light source or light protocol than humans (Peirson *et al.* 2018).

Several models with altered lighting schedules have been used in experimental animal studies (see Figure 5-1). A light:dark cycle of 12 hours light and 12 hours dark (12:12 L:D) is commonly used as the standard or control level. One variation is to keep the lights on continuously, i.e., 24 hours light (see the model in Figure 5-1A below). The period of darkness can be replaced with

dim light (usually about 0.2 lux) for 12 hours or a brief period with bright light (300 lux for 30 minutes) halfway through the dark period, or intermittent LAN (see the model in Figure 5-1B below) can be used. Another variation is to alter the length of both the light period and the dark period within a 24-hour period; this can be done by either lengthening the light period and shortening the dark period (e.g., 16:8 L:D) or shortening the period of light and increasing that of darkness (e.g., 8:16 LD) (see the model in Figure 5-1C below). Some studies have also evaluated exposure to blue light during the daytime.

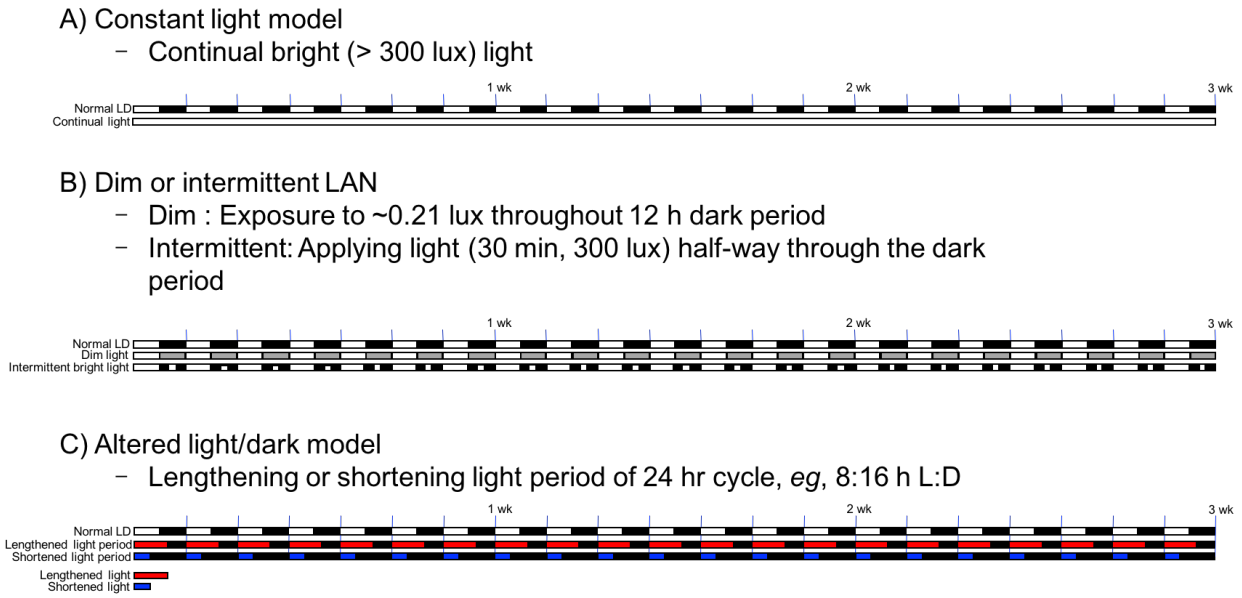

Figure 5-1. Light at night models. Control groups for all models are 12:12 hour L:D cycle.

The model commonly used to expose animals to the changes in light:dark patterns simulating those experienced by shift workers is to invert the light:dark cycle for a week so it is the opposite of the normal cycle and then invert it again to return to the normal cycle. This inversion can be repeated at weekly intervals for the course of an experiment (see Figure 5-2A below). The changes in the timing of light experienced by people who cross multiple time zones (transmeridian travel), which induces jet lag (see Figure 5-2B below), can be simulated by shifting the schedule forward by adding a longer light period every few days (simulating traveling across time zones from east to west) or shifting it backward by reducing the light period every few days (simulating traveling across time zones from west to east).

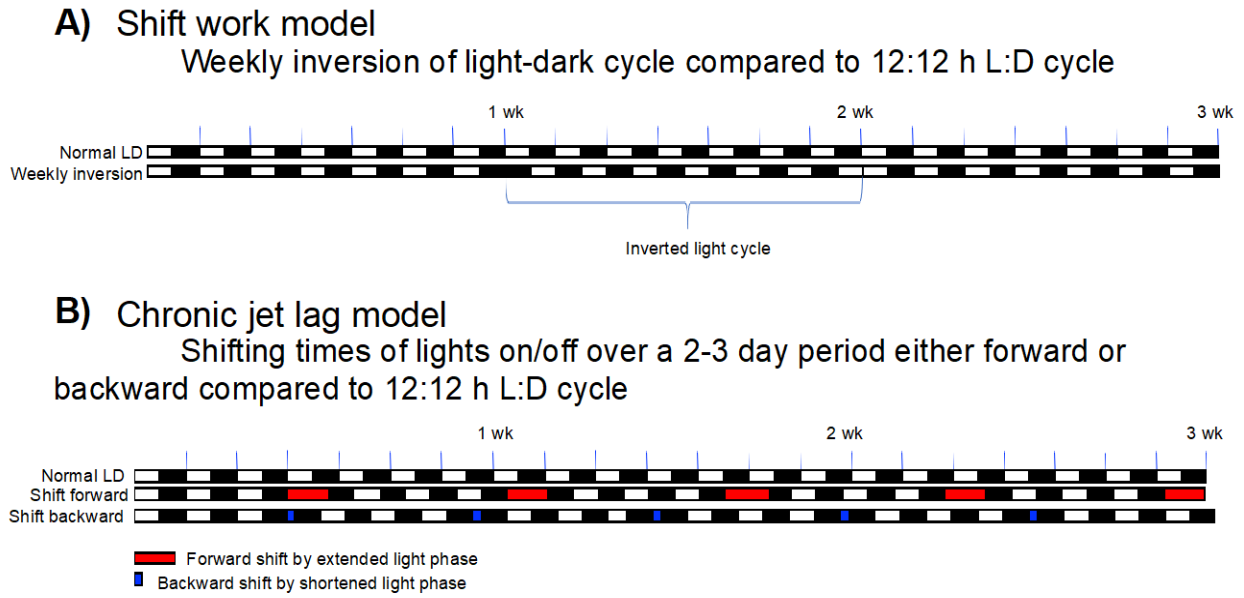

Figure 5-2. Simulated shift work and chronic jet lag models. Control groups for all models are 12:12 hour L:D cycle.

The human exposures most relevant are those involving dim or intermittent LAN. Although some might argue that the LAN protocols used in rodent studies do not strictly apply to humans, one could also counterargue that constant exposure to artificial LAN has become pervasive in modern society due to urban light pollution filtering into bedrooms, the glow at all hours from television, computer, and mobile device screens, and indoor lights that are kept on (Bedrosian and Nelson 2013). Exposure to constant light is even more pronounced for shift workers who are exposed to constant bright lights during night shifts and sleep during daylight hours (see Figure 5-2). Simulated shift work and chronic jet lag model lighting conditions only and do not take into account other changes and experiences, such as changes in dietary and sleep patterns, that humans may experience under these type of lighting conditions.

5.2 Findings from animal models of LAN or other relevant light exposures

This section reviews LAN animal models and are organized by animal model type (Sections 5.2.1 to 5.2.3) and summarized in Table 5-1. In addition, two studies evaluated exposure to daytime blue light and tumor growth (Section 5.2.4).

5.2.1 Initiation-promotion models

This section reviews chemical initiation of tumors in animal models and the effect of various light schedules on promotion of tumor growth. For this section, more details are given on study design as the exposure protocols varied and the initiation model varied. For rat models of mammary-gland tumors, both dimethylbenzanthracene (DMBA) which results in mutations in codon 61 of H-*Ras,* and *N*-nitroso-*N*-methylurea (NMU), which initiates with H-*Ras* mutations in codon 12 are used. Although mutations in *Ras* are uncommon in human breast cancer, rat mammary tumors initiated with NMU have been shown to have molecular gene expression profiles similar to those in human ductal carcinoma *in situ* (Chan *et al.* 2005). In some of the studies, the animals were acclimated to a standard LD cycle, exposure groups were randomized and chemical initiator or vehicle given, followed by exposure to the test light regimens (LD, LL,

or DD); in other studies, the chemical was more of a co-exposure, as it was administered after acclimatization to the test light schedules.

Mammary-gland tumors

Holtzman rats exposed from birth to LL or LD were injected with DMBA at approximately 55 days of age (Kothari *et al.* 1982). The incidence of DMBA-induced mammary gland tumors was significantly greater in animals maintained in continuous light as compared to control animals on a 10:14 LD schedule. In follow-up reports of additional exposure groups from the same study, co-exposure to melatonin in drinking water decreased tumor number or increased latency in the LL group (Mhatre *et al.* 1984, Shah *et al.* 1984, Kothari 1987). In another study, rats were exposed to LL or 12:12 LD from 43 days of age and DMBA was administered by gavage to female Sprague-Dawley rats at 50 days of age. Significantly more mammary fibroadenomas were identified in the LL group than in the LD control group; however, melatonin co-exposure by subcutaneous injection significantly increased mammary adenocarcinoma in the LD group with no significant effect on the LL group (Hamilton 1969). In another study (Anderson *et al.* 2000), Sprague-Dawley rats on a LL or 8:16 LD schedule starting at 26 days of age were injected with DMBA at 52 days of age. Significantly fewer mammary-gland tumors were observed in the LL group than in the 8:16 LD group 13 weeks after DMBA exposure; however, these rats were not exposed to experimental LAN conditions from birth. In another study, female Sprague-Dawley rats on a standard 12:12 LD schedule were exposed to DMBA at 55 days of age and palpated weekly for mammary-gland tumors (Cos *et al.* 2006). When mammary-gland tumors were about 1 cm in diameter, the rats were divided into one of four exposure groups for a 12-week period: (1) 12:12 LD, (2) LL (300 lux), (3) 12:12 LD with exposure to 300 lux for 30 minutes after 6 hours of dark, and (4) 12:12 LD with dim light (0.21 lux) throughout the dark phase. Rats exposed to LL, LD with intermittent light during the dark phase, and LD with dim light during the dark phase showed significantly higher rates of tumor growth than those under standard 12:12 LD conditions. The rats exposed to dim light throughout the dark period had the lowest survival of all groups and the highest rate of tumor growth.

Table 5-1. Summary of studies of LAN and cancer in experimental animals

Animal model: tumor type Rat or mouse strain; melatonin status is indicated by the footnote (Reference)	Constant light (LL) (bright LAN)	Dim or intermittent LAN	Change in daylight length or non-24 h LD cycles
Initiation-promotion			
DMBA: mammary-gland tumors Sprague-Dawley rats[a] (Hamilton 1969, Anderson *et al.* 2000, Cos *et al.* 2006) Holtzman rats[c] One study reported in several publications (Kothari *et al.* 1982, Mhatre *et al.* 1984, Shah *et al.* 1984, Kothari 1987)	*Tumors:* sign. growth with LL vs. LD, 3 of 4 studies in rats positive *Co-exposure*: melatonin decreased tumor number and increased latency in LL (one study reported in several reports by Mhatre *et al.* 1984, Shah *et al.* 1984, Kothari 1987)	*Tumors:* sign. growth with LD with intermittent light exposure or with dim light exposure throughout dark period (Cos *et al.* 2006) *Endogenous melatonin:* urinary melatonin metabolite decreased with light exposure (Cos *et al.* 2006)	
NMU: mammary-gland tumors F344/N rats[a] (Anisimov *et al.* 1994, Travlos *et al.* 2001)	*Tumors:* shorter latency and greater incidence in LL group (Anisimov *et al.* 1994)	*Tumors:* no difference in tumors between intermittent LAN and LD (Travlos *et al.* 2001) *Endogenous melatonin:* serum melatonin levels initially decreased with LAN, but at study end were 3-fold higher than LD levels (Travlos *et al.* 2001)	
DMH: aberrant colon crypt foci (ACF) Wistar rats[c] (Kannen *et al.* 2011)	*Precancers:* increased incidence in dysplastic and hyperplastic foci *Co-exposure*: melatonin decreased incidence of ACF; serum melatonin levels measured		
DEN: liver tumors Wistar rats[c] (van den Heiligenberg *et al.* 1999)	*Tumors:* foci and carcinoma greatest in LL group; 1 of 2 studies positive		

Animal model: tumor type Rat or mouse strain; melatonin status is indicated by the footnote (Reference)	Constant light (LL) (bright LAN)	Dim or intermittent LAN	Change in daylight length or non-24 h LD cycles
DEN: GST-P liver foci Wistar rats[c] (Isobe *et al.* 2008)	Preneoplastic GST-P liver foci greater in LD group than LL group		
NEU: peripheral nervous system and kidney Wistar rats[c] (Beniashvili *et al.* 2001)	*Tumors:* increased incidence, multiplicity, tumor types, shortened latency in LL vs. LD group		
DMBA: skin Deer mice[a] (Nelson and Blom 1994)			8:16 LD or 16:8 LD s.c. injection *Tumors*: squamous-cell carcinoma found with long day only
Urethane: lung tumors CD-1[c] and A/J mice[c] (Nakajima *et al.* 1994)			6:6 LD or 12:12 LD inhalation *Tumors*: Both mouse strains had sign. larger lung adenomas with short LD cycle
Xenografts/tumor growth			
MCF-7 breast cancer RNU rats[c] (Blask *et al.* 2003, Blask *et al.* 2005, Dauchy *et al.* 2011, Blask *et al.* 2014, Dauchy *et al.* 2014)	*Tumors*: growth increased under constant light (LL) condition, Blask et al. 2003; 2005. *Perfusion with human blood*: light intensity-dependent melatonin suppression with melatonin-deficient daytime- or LAN-collected blood; and light intensity-dependent decreased cell proliferation with melatonin-rich night-collected blood (Blask *et al.* 2005)	*Tumors*: growth dependent on LAN intensity; MCF-7 cells grew faster with dim LAN than with LD (5 out of 5 studies) *Perfusion with human blood*: light intensity-dependent melatonin suppression with melatonin-deficient daytime- or LAN-collected blood; and light intensity-dependent decreased cell proliferation with melatonin-rich night-collected blood (Blask *et al.* 2005)	

Animal model: tumor type Rat or mouse strain; melatonin status is indicated by the footnote (Reference)	Constant light (LL) (bright LAN)	Dim or intermittent LAN	Change in daylight length or non-24 h LD cycles
	Endogenous melatonin: Serum levels of melatonin measured; sign. decrease with LAN.	*Endogenous melatonin:* Serum levels of melatonin measured in all 5 studies; sign. decrease with LAN or dim LAN *Co-exposure*: exogenous melatonin decreased MCF-7 growth (Blask *et al.* 2014, Dauchy *et al.* 2014)	
Hepatoma Buffalo rats[a] (Dauchy *et al.* 1997, Dauchy *et al.* 1999, Blask *et al.* 2005, Dauchy *et al.* 2011)	*Tumors:* growth dependent on increasing LAN intensity (Dauchy *et al.* 2011 did not use LL): (4 out of 4 studies). *Perfusion with human blood:* Growth dependent on LAN intensity; high proliferation with melatonin-deficient daytime or LAN-exposed collected blood; decreased proliferation with melatonin-rich night-collected blood (Blask *et al.* 2005). *Endogenous melatonin:* Serum levels of melatonin measured in all 4 studies; sign. decrease with LL.	*Tumors:* growth dependent on increasing LAN intensity: (4 out of 4 studies.) *Perfusion with human blood:* Growth dependent on LAN intensity; high proliferation with melatonin-deficient daytime or LAN-exposed collected blood; decreased proliferation with melatonin-rich night-collected blood (Blask *et al.* 2005) *Endogenous melatonin:* Serum levels of melatonin measured in all 4 studies; sign. decrease with dim LAN	
Murine mammary-gland cancer cells Balb/c mice[b] (Schwimmer *et al.* 2014)		LAN 30 min exposure after 7 hr dark phase; group had sign. larger tumors than 8:16 LD group *Co-exposure*: melatonin exposure decreased tumor size compared to LAN 8:16 LD group	
HeLa human cervical cancer cells Balb/c nu/nu mice[b] (Yasuniwa *et al.* 2010)	*Tumors*: sign. increase in tumor volume		
Melanoma cells C57BL/6 mice[b]	*Tumors:* sign. increase in tumor weight		*Tumors*: sign. smaller tumor volume in the 6:18 LD group, intermediate in 12:12

Animal model: tumor type Rat or mouse strain; melatonin status is indicated by the footnote (Reference)	Constant light (LL) (bright LAN)	Dim or intermittent LAN	Change in daylight length or non-24 h LD cycles
(Lang *et al.* 2003, Otálora *et al.* 2008)	*Co-exposure*: continual melatonin exposure increased tumors in LL and decreased tumors in LD group (Otálora *et al.* 2008)		LD, and greatest in 18:6 LD group (Lang *et al.* 2003)
Murine colon cancer cells Balb/c mice[b] (Waldrop *et al.* 1989)			12:12 LD group had greatest tumor weight and area vs. 16:8 LD and 8:16 LD Tumor incidences were considered inconclusive due to variability across three experiments
Murine prostate cancer cells C57BL/6 mice[b] (Haim *et al.* 2010)		LAN 30 min after 7 hr dark phase sign. increased tumor size in the 8:16 LD group	Sign. larger tumors with 16:8 LD long day exposure vs. 8:16 LD short day *Co-exposure*: melatonin exposure sign. decreased tumor size in 16:8 LD group
Rat C6 glioma cells Wistar rats[c] (Guerrero-Vargas *et al.* 2017)	*Tumors:* sign. increase in tumor volume		
Spontaneous tumors			
Lung adenocarcinoma, leukemia/lymphoma CBA mice[a] (Anisimov *et al.* 2004)	Sign. increase in lung adenocarcinoma and leukemia/lymphoma with LL		
Mammary tumors (*Her2/neu*) FVB/N mice[c] (Baturin *et al.* 2001)	Increase in tumor multiplicity (but not incidence or tumor size) in Her-2/neu LL treated mice *Co-exposure* with melatonin reduced Her-2/neu mRNA expression by 2.5-		

Animal model: tumor type Rat or mouse strain; melatonin status is indicated by the footnote (Reference)	Constant light (LL) (bright LAN)	Dim or intermittent LAN	Change in daylight length or non-24 h LD cycles
	fold, decreased the size and incidence in LD group; no change in multiplicity between LL or LD groups		
ILO rats[c] (mammary-gland fibroadenoma) (Vinogradova *et al.* 2009, Vinogradova *et al.* 2010)	LL or natural light (NL) conditions decreased tumor latency; LL latency longer in 14 mo old vs. 25 d old rats (age at study start) (2 out of 2 studies)		
Leydig-cell tumors ILO rats[c] (Vinogradova *et al.* 2009, Vinogradova *et al.* 2010)	LL or NL conditions decreased tumor latency; LL latency longer in 14 mo old vs. 25 d old rats (age at study start) (2 out of 2 studies)		
Uterine hemangioma and sarcoma 129/Sv mice[b] (Popovich *et al.* 2013)	Decreased survival with LL, but no sign. differences between LL and LD in uterine or total tumors. Uterine tumors were the primary tumors identified in both exposure groups		

D = day; LD = light:dark; LL = 24-hour light; mo = month; NL = natural light (LL).
[a]Melatonin proficient.
[b]Melatonin deficient.
[c]Melatonin not determined.

In a 26-week experiment, *N*-nitroso-*N*-methylurea (NMU) was given at the start of the experiment (after animals acclimated for 2 weeks to 12:12 LD photoperiod) and was used to induce mammary-gland tumors in female F344/N rats. Animals were exposed intermittently to light during the dark phase of a 12:12 LD cycle (five 1-minute exposures to light every 2 hours after start of the dark phase) or to a standard 12:12 LD cycle after NMU injection (Travlos *et al.* 2001). At necropsy, no significant differences were observed in mammary-gland tumor incidence, multiplicity, or average tumor weight between vehicle and NMU 12:12 LD controls, NMU-initiated intact rats, or pinealectomized rats exposed to intermittent LAN. Serum melatonin was three-fold greater in animals exposed to intermittent LAN than to those on 12:12 LD cycle. Pinealectomized rats had detectable serum levels of melatonin, suggesting that melatonin was from a secondary source. Over 90% of tumors in all treatment groups were mammary-gland adenocarcinoma.

In another experiment, rats were exposed to experimental LAN conditions from 1 month of age and NMU was administered to female rats at 55 days of age. The incidence of mammary-gland adenocarcinoma was significantly higher and the latency of mammary-gland fibroadenoma and adenocarcinoma was significantly shorter in the LL group than in the 12:12 LD group (Anisimov *et al.* 1994).

Other tumors

Other initiation-promotion studies in mice and rats reported that increased light exposure or short, frequent light cycling (6:6 hours LD) resulted in reduced tumor latency and increased tumor incidence.

Female adult deer mice (*Peromyscus maniculatus bairdii*) were exposed to either short days (8:16 LD) or long days (16:8 LD) for 8 weeks before subcutaneous injection with DMBA or dimethylsulfoxide (DMSO), examined weekly, and necropsied 8 weeks after injection (Nelson and Blom 1994). Mice exposed to long days developed squamous-cell carcinoma (89% incidence), but those exposed to short days did not.

CD-l and A/J male mice were given urethane at 5 weeks of age after seven days on either a short-day or standard-day light cycle. Those exposed to a short LD cycle (6:6 LD) developed significantly larger lung tumors (papillary adenoma) than did those exposed to 12:12 LD (Nakajima *et al.* 1994).

Male Wistar rats were given diethylnitrosamine (DEN) for 6 weeks under a 12:12 LD light cycle and then randomized into three exposure groups: 12:12 LD, 12:12 LD + phenobarbital, and LL. On gross examination, the percentages of rats with macroscopic nodules on the liver surface were 72% in the 12:12 LD group, 89% in the 12:12 LD + phenobarbital group, and 95% in the LL group. All of the rats died with hepatocellular carcinoma; median survival was 5 months, similar in all three groups (van den Heiligenberg *et al.* 1999). Conflicting results were reported in another study (Isobe *et al.* 2008), in which male Wistar rats were given DEN or saline injections after acclimatization to either 12:12 LD, DD, or LL conditions. The levels of preneoplastic liver foci, as measured by immunostaining for glutathione S-transferase placental form (GST-P) at 8 weeks after DEN administration, were higher in the 12:12 LD group than in the DD and LL groups.

Tumor formation in pups following exposure of pregnant Wistar dams on gestational days 18 to 19 to *N*-nitroso-*N*-ethylurea was studied under conditions of exposure of the dams and pups to LL, DD, and 12:12 LD from mating (vaginal plug) to weaning (1 month after delivery), after which the pups were exposed to 12:12 LD throughout their lifetimes (Beniashvili *et al.* 2001). Full necropsies of the pups revealed that continuous light exposure significantly shortened tumor latency and increased the number and types of tumors, whereas continuous dark lengthened latency and decreased the number and types of tumors. Tumors were of the peripheral nervous system and kidney, but tumor incidences were not reported.

In a model of colon cancer initiation, dimethylhydrazine was administered to male Wistar rats and the rats were then exposed for 14 days to 12:12 LD or LL (300 lux). Exposure to LL significantly increased the incidence of aberrant crypt foci in colon tissue; the LL group had significantly more pre-cancerous lesions (hyperplastic and dysplastic foci) than did the 12:12 LD group. Co-exposure to melatonin in the LL group decreased the incidence of foci as compared to LL without melatonin (Kannen *et al.* 2011).

5.2.2 Animal models of xenografts or injected tumor cells

Studies in which rodents were injected with human or rodent cancer cells or implanted with xenografts found that tumor growth was increased with increasing duration of light exposure or exposure to light during the dark phase of a 12:12 LD cycle. Tumor models included implantation of human breast cancer tissue or cells and cervical cancer cells into nude rats or mice and injection of rodent mammary-gland, prostate-gland, glioma, colon, and skin cancer (melanoma) tumor cells or implantation of hepatocellular carcinoma tissue into syngeneic rats or mice.

The effect of light exposure at night as a potential risk factor for human breast cancer and for rat liver cancer was investigated in several studies by Blask *et al.* (2003, 2005, 2014) and Dauchy *et al.* (2014). MCF-7 (human breast cancer) cells in tissue xenografts were implanted into female Rowett nude rats (RNU). The rate of human breast tumor growth from implanted tumor tissue was greater with continuous light exposure as compared to 12:12 LD cycle (Blask *et al.* 2003). In another study, beginning two weeks before tumor implantation, animals on a 12:12 LD cycle were exposed to various light intensities during the 12-hour dark phase, from total darkness to constant light (345 $\mu W/cm^2$) (Blask *et al.* 2005). Tumor growth in response to light during the dark phase was found to depend on light intensity for estrogen- and progesterone-receptor-negative MCF-7 breast cancer tissue implants into female nude rats and also for hepatocellular carcinoma tissue implants into male Buffalo rats. In all of these studies, serum levels of melatonin were measured and showed a significant decrease with animal exposure to LAN or dim LAN. Both tissue implants exhibited decreased proliferation when perfused with venous blood from samples collected during the night from premenopausal human female volunteers; implants perfused with blood from samples collected during the daytime or following ocular exposure to LAN exhibited higher proliferation (Blask *et al.* 2005). Serum melatonin levels were measured in the female volunteers and were lowest in the daytime collection, intermediate following ocular exposure to LAN and highest in the night time collection (See Section 6.2.2 for further discussion).

In two additional studies, this same strain of female nude rats was exposed to a schedule of 12 hours of bright light (304 to 345 lux) and 12 hours of dim LAN (0.2 lux), compared with a 12:12

LD control group. Exposure began one week before injection of MCF-7 estrogen-receptor-positive breast tumor cells (Dauchy *et al.* 2014) or six weeks before implantation with estrogen- and progesterone-receptor-negative MCF-7 breast cancer tissue xenografts (Blask *et al.* 2014). In both cases, the dim LAN group had faster tumor growth, as measured by tumor weight, than did the 12:12 LD control group. Dim LAN was shown to suppress nocturnal melatonin but did not affect rat feeding activity (Blask *et al.* 2014, Dauchy *et al.* 2014). Dauchy *et al.* (2014) also demonstrated that MCF-7 tumor growth decreased with melatonin supplementation. The effect of light contaminating the dark phase was also investigated by Dauchy *et al.* (1997, 1999) using male Buffalo rats bearing rat hepatoma. Dim light (0.21 lux or 0.25 lux) during the dark phase increased tumor growth compared to the 12:12 LD group, with the tumor growth rate approaching that for continuous light exposure. The effect on tumor growth of dim-light contamination of animal rooms during the dark phase also was investigated in rat hepatoma and MCF-7 breast cancer tissue xenograft animal models (Dauchy *et al.* 2011). For both animal models, tumor latency decreased and tumor growth rates increased with increasing light contamination of the animal rooms.

HeLa (human cervical cancer) cells were injected into male nude mice exposed to continuous light or a 12:12 LD cycle (Yasuniwa *et al.* 2010). Tumor volume was significantly greater in the LL group than in the LD group, and tumor microvessels and stroma were more prevalent in the LL group. Subcutaneous injection of murine melanoma cells into C57BL/6 male mice under the same light exposure protocol resulted in lower survival, greater intraperitoneal dissemination, and greater tumor weight at death in the LL group than in the 12:12 LD group, and melatonin supplementation decreased tumor weight and intraperitoneal dissemination (Otálora *et al.* 2008).

Four studies in mice investigated the relationship between length of daily light exposure or LAN and tumor size following injection with mouse tumor cells. In one study (Waldrop *et al.* 1989), male mice exposed to long days (18:6 LD), short days (6:18 LD), or standard days (12:12 LD) were injected with mouse colon adenocarcinoma cells. At 22 days post-injection, tumor weight, tumor area, and mortality were significantly greater in the 12:12 LD group than in the long- or short-day groups, whereas findings for tumor incidences were inconsistent across three experiments, thus overall the results of this study are considered to be inconclusive. In another study, female mice exposed to the same light-dark cycles were injected with HFH18 melanoma cells. Although all animals developed exponentially growing tumors, the average tumor volume on day 31 post-injection was significantly smaller in the short-day group than in the long-day group, and tumor volume was intermediate in the 12:12 LD group (Lang *et al.* 2003). In male C57BL/6 mice injected with mouse prostate cancer cells (TRAMP-C2), tumors at 59 days post-injection were significantly larger in the long-day (18:6 LD) group than in the short-day (6:18 LD) group. Melatonin co-exposure significantly decreased tumor size in the 16:8 LD group, while the 6:18 LD group animals with 30 minutes LAN after 7 hours dark phase had significantly increased tumor size (Haim *et al.* 2010). In another study, mice injected with 4T1 mouse mammary-gland carcinoma cells were assigned to either a control group (8:16 LD) or to a group exposed to light for 30 minutes every night at seven hours after the start of the dark phase (Schwimmer *et al.* 2014). After three weeks, the light-at-night group had lower survival and significantly larger tumors than did the control group; melatonin co-exposure decreased tumor size compared to 8:16 LD group.

Growth of rat C6 glioma cells subcutaneously inoculated into male Wistar rats was increased in rats exposed to continuous light (Guerrero-Vargas *et al.* 2017). Tumors in LL animals were significantly larger after 13 days than tumors in rats maintained on a 12:12 LD cycle.

There is some evidence to suggest that exposure to bright light (blue light) during the daytime suppresses tumor growth, suggesting that insufficient daylight exposure (in addition to LAN) is important in carcinogenicity. Dauchy *et al.* (2015) reported that growth rates of human prostate cancer xenografts were delayed in nude mice exposed to blue light during the daytime (12-hour dark:12-hour light schedule using blue-tinted cages) compared to nude mice housed in clear cages (12 hour-light:12-hour dark cycle).

5.2.3 Spontaneous tumor formation

In general, four of the five studies reviewed in this section reported that exposure to LAN (continuous) light was related to carcinogenicity, e.g., increased incidence tumor incidence or multiplicity, decreased tumor latency and life span compared with exposure to a standard 12:12 LD cycle There was evidence that constant light exposure (such as irregular estrus cycling) caused circadian disruption in all these studies. However, because of poor reporting of necropsy and pathology methods, the findings for specific tumors are of limited utility. Because of these concerns, the most common tumor types as reported by the authors are noted, but the number or incidences of specific tumor types are not included.

Three studies in female mice examined the effect of continuous light exposure on the incidence and latency of spontaneous tumors and one of these studies used HER2/neu transgenic mice (which carry the *HER2/neu* breast-cancer oncogene). Exposures to continuous light or to 12:12 LD began at 8 weeks of age and continued until either natural death or moribund condition or, in the transgenic animals, the presence of palpable mammary-gland tumors. Popovich *et al.* (2013) observed mean lifespan significantly less in the LL group, but reported no significant difference in spontaneous uterine hemangioma and sarcoma or other tumor incidences between the LD and LL exposure groups. Anisimov *et al.* (2004) observed significant differences in spontaneous lung adenocarcinoma ($P < 0.05$) and lymphoma or leukemia ($P < 0.02$) and a non-significant increase in incidence of hepatocellular carcinoma between the LL and the LD exposure groups, with higher total and all malignant tumor incidences in the LL group. In the HER2/neu transgenic mice, the incidence and size of mammary-gland tumors did not differ between the LL and LD exposure groups; however, continuous light resulted in significantly increased mammary-gland tumor multiplicity and increased tumor latency (Baturin *et al.* 2001). This study also investigated the effect of melatonin supplementation on mammary-gland tumor formation. Melatonin supplementation had no effect on tumor incidence or size in the LL group, but significantly decreased tumor incidence and size in the LD group. In both groups, melatonin supplementation resulted in approximately a 60% reduction in HER2/neu mRNA expression.

In a study conducted in Russia, rats were exposed to continuous light, the natural light of northwest Russia (NL; in winter 4.5 hours maximum light, in summer 24 hours maximum light, additional information on light:dark period not reported), or 12:12 LD starting at 25 days of age (Vinogradova *et al.* 2009). LL or NL exposure resulted in an apparent shorter lifespan in both males and females and shorter total tumor latency in the LL and NL groups in males and in the LL group in females than in the 12:12 LD group (all values non-significant). Compared with 12:12 LD exposure, there was a significant increase in total spontaneous benign mammary-gland

tumors in females in the NL group (35% vs. 56.3%) but non-significant in the LL group (35% vs. 33%); however, total tumor incidences in both sexes were not significantly different compared with the LD group (Vinogradova *et al.* 2009). When this experiment was repeated with both sexes of rats exposed to LL or 12:12 LD beginning at either 25 days or 14 months of age (NL exposure was not tested), the older age of exposure to the different light schedules did not affect lifespan or specific or total tumor incidence as compared to the LD group (Vinogradova *et al.* 2010).

5.2.4 Effects of daytime blue light exposure on tumor growth

Two studies investigated the effects of blue-enriched lighting (465 to 485 nm) during daytime on tumor growth. In the first study, groups of male nude rats were exposed to overhead cool-white fluorescent lamps on a 12:12 LD schedule and placed in either blue-tinted cages (which increased transmittance of blue light) or clear cages (Dauchy *et al.* 2015). In the second study, both groups of male Buffalo rats were placed in clear cages and maintained on a 12:12 LD schedule but one group was exposed to blue-enriched LED lights during the day while the second group was exposed to cool white fluorescent lights (Dauchy *et al.* 2018). The nude rats were implanted with human prostate cancer PC3 xenografts and the male Buffalo rats were implanted with tissue-isolated 7288CTC-Morris rat hepatomas. Both studies reported that tumor latency (i.e., time from implantation to the first palpable mass) was increased by about 50% and tumor growth rates were reduced by 50% to 55% in rats exposed to blue-enriched light during the daytime (Dauchy *et al.* 2015, Dauchy *et al.* 2018). Blue light exposure during the day was associated with increased nocturnal plasma melatonin levels and reduced uptake and metabolism of linoleic acid, aerobic glycolysis, and growth signaling activities compared to the control rats (see Sections 2.2.2, 6.2.1, and 6.3.5).

5.3 Findings from animal models of simulated shift work and chronic jet lag

This section reviews studies with animal models simulating shift work or chronic jet lag (CJL), such as weekly inversion of the light-dark cycle or weekly light-phase shifts, either forward or backward, by 8 hours (see Figure 5-2). The studies are organized by animal model (Sections 5.3.1 to 5.3.3) and summarized in Table 5-2.

5.3.1 Initiation-promotion models

Fang *et al.* (2017) reported that simulated jet lag (8-hour advance or delay in light onset every 3 days for 3 to 4 months) enhanced the growth of NMU-induced mammary tumors in heterozygous female c3(1)/SV40 t-antigen [C3(1)/Tag] transgenic mice. The average tumor onset was 16 days earlier and the average tumor burden (a function of both tumor number and size) was greater in CJL mice compared to controls. In a study modeling CJL, DEN was administered over a period of 46 days to male B6D2F1 mice exposed to 12:12 LD (Filipski *et al.* 2009). The mice were then randomized to either remain on 12:12 LD or undergo 8-hour advances of the LD cycle every 2 days (from days 46 through 297). Up to four different histologic types of liver tumors per liver (hepatocellular or cholangiocarcinoma, sarcoma, or mixed tumors) were observed in CJL-exposed mice, compared with a single histologic tumor type per liver in the 12:12 LD group. Two or more liver tumors were found in 33% of LD vs. 77% CJL-exposed mice ($P = 0.026$). The mean diameter of the largest tumor per liver was approximately two-fold greater in CJL-exposed

mice ($P = 0.027$). Primary lung and kidney tumors also occurred, but their incidences were not reported.

Simulated jet lag increased lung tumor growth (as measured by area) initiated using a K-ras LSL-G12D/+; p53flox/flox mouse lung model (e.g., intratracheal administration of mice with CRE-recombinase viral vector activating K-rasG12D; $p53^{-/-}$ mutations). Mice that had been placed on a jet-lag schedule after tumor initiation had a significant increase in lung tumor area after 13 weeks as compared with those on 12:12 LD. In contrast, simulated jet lag did not promote lung tumor growth when given prior to tumor initiation (Papagiannakopoulos *et al.* 2016).

Simulated jet lag significantly increased lymphoma growth and decreased survival in animals initiated with gamma radiation; liver tumors, osteosarcoma, and ovarian tumors also occurred, but they were not significantly increased (Lee *et al.* 2010).

Table 5-2. Summary of cancer studies of simulated shiftwork/chronic jet lag in experimental animals

Animal model: tumor type Rat or mouse strain; melatonin status is indicated by the footnote (Reference)	Altered LD (light cycle inverted)	Chronic jet lag (advancing time on light cycle)
Initiation/promotion		
DEN: liver tumors B6D2F1 mice[c] (Filipski *et al.* 2009)		LD group had single tumor type; CJL group had 4 different histologic types of liver tumors. The percentage of mice with two or more liver tumors was higher in CJL- than LD-exposed mice with CJL-exposed mice having larger tumors. Lung and kidney tumors were reported, but not quantitated.
NMU: mammary tumors C3(1)/Tag transgenic mice[c] (Fang *et al.* 2017)		CJL exposure advanced mammary tumor onset, increased tumor multiplicity, and significantly increased tumor burden per animal compared to LD
K-rasG12D; p53-/- : lung tumors **K-ras LSL-** G12D/+; p53flox/flox transgenic mice[b] (Papagiannakopoulos *et al.* 2016)		CJL increased lung tumor burden (tumor area/lung area) compared to LD
Gamma radiation: lymphoma C57BL/6 mice[b] (Lee *et al.* 2010)		Irradiated/CJL group (vs. irradiated/LD) had decreased survival and a sign. increase in lymphomas ($P < 0.05$[d]). Liver tumors, osteosarcoma, and ovarian tumors were reported, but not significantly increased.
Xenografts/tumor growth		
Ehrlich carcinoma or sarcoma 180 Kunming strain mice[a] (Li and Xu 1997)	Light-inverted group had shorter survival and greater tumor growth and depressed immune response *Co-exposure:* Melatonin inhibited tumor growth and restored immune function	
Glasgow osteosarcoma B6D2F1 mice[c] (Filipski *et al.* 2004, Filipski *et al.* 2005, Filipski *et al.* 2006)		CJL exposure group tumors grew sign. faster than LD, but no effect with DD or LL exposure

Animal model: tumor type Rat or mouse strain; melatonin status is indicated by the footnote (Reference)	Altered LD (light cycle inverted)	Chronic jet lag (advancing time on light cycle)
Pancreatic adenocarcinoma B6D2F1 mice[b] (Filipski *et al.* 2006)		CJL exposure group tumors grew sign. faster than LD
Lewis lung carcinoma C57BL/6 mice[b] (Wu *et al.* 2012)		CJL exposure group tumors grew sign. faster with sign. increase in metastases to lung
Rat mammary gland adenocarcinoma Fischer 344 rats[a] (Logan *et al.* 2012)		CJL promoted mammary adenocarcinoma incidence and multiplicity in the lung with intravenous injection (Note: authors referred to the tumors as lung tumors)
Plasmacytoma LOU rats[c] (Wu *et al.* 1988)		Tumor latency, size and growth greater in CJL-exposed group vs. LD group
Spontaneous tumors		
Mammary gland *p53*$^{R270H^a/+}$ WAPCre FVB mice[b] (Van Dycke *et al.* 2015)	Light-inverted group had a 15% decrease in mammary-gland tumor latency, but no change in total number of tumors vs. LD group	
Hepatocellular carcinoma C57BL/6 mice[b] (Kettner *et al.* 2016)		CJL animals had significantly greater hepatocellular carcinoma incidence (8.8% vs. 0%) and shortened lifespan vs. LD group. Other tumors noted but tumor incidences not provided for pancreatic cancer, ovarian cancer, and lymphoma
Lymphoma *p53*$^{-/-}$ C57BL/6 mice[b] (Lee *et al.* 2010)		CJL animals had sign. decreased survival. Lymphoma was primary tumor type with 10% of tumors osteosarcoma; no further information on tumor incidences or statistical information was reported

[a]Melatonin proficient.
[b]Melatonin deficient or low levels.
[c]Not determined.
[d]Fisher pairwise test, NTP calculated.

5.3.2 Growth of injected tumor cells

All studies examining the effect of simulated CJL on growth and/or survival of tumor cells injected into rodents found that CJL exposure increased the growth rate of tumors or decreased survival.

B6D2F1 mice were exposed to 12:12 LD, LL, or DD versus 8-hour advances of a 12:12 LD cycle every two days (to mimic CJL) and were then injected with Glasgow osteosarcoma tissue (Filipski *et al.* 2004) or pancreatic adenocarcinoma cells (Filipski *et al.* 2006). Both types of tumor grew significantly faster in the CJL animals than in the 12:12 LD group, but osteosarcoma growth was not affected by exposure to continuous light or dark. In a separate study, osteosarcoma tumors grew faster in the CJL group than in the 12:12 LD synchronized animals, and the CJL effect on tumor growth was partially inhibited by feeding the mice only from the onset of activity to onset of rest (Filipski *et al.* 2005). In another study, C57BL/6 male mice were exposed for two weeks to 12:12 LD and then randomized into two groups: 12:12 LD and CJL (12:12 LD with light onset advanced 8 hours every 48 hours) (Wu *et al.* 2012). Lewis lung carcinoma cells were injected into both groups of mice on day 10 after the start of CJL exposure. Tumors grew significantly faster in the CJL mice than in the control group, and the CJL group had significantly more lung metastases.

Male Fischer rats were injected intravenously with mammary adenocarcinoma (MADB106) after being acclimatized to either a CJL protocol (6-hour LD phase advances repeated every 2 days for a total of 10 shifts followed by 5 to 7 days of continuous darkness) or a 12:12 LD control group. CJL exposure increased mammary tumor incidence and multiplicity in the lung compared to the 12:12 LD group (Logan *et al.* 2012). In another study, plasmacytoma cells were injected into Lou/c rats and lighting schedules were then advanced or delayed 6 hours every second day; tumor latency, size, and growth rate were greater in the CJL group than in the 12:12 LD control group (Wu *et al.* 1988). Mice with either Ehrlich carcinoma or sarcoma 180 tumor transplants that were shifted between 14:10 LD and 10:14 LD every three days had shorter survival and greater tumor growth than the 12:12 LD control group (Li and Xu 1997).

5.3.3 Spontaneous tumor formation

The effects of a shift-work paradigm of weekly inversion of the 12:12 LD cycle on development of mammary-gland tumors were assessed in female $p53^{R270H^{a}/+}$ WAPCre mice (which bear a mammary-gland-specific *p53* tumor-suppressor-gene mutation) (Van Dycke *et al.* 2015). Compared with the 12:12 LD control group, the weekly inversion group showed a 15% decrease [calculated by NTP; authors reported 17%] in mammary-gland tumor latency. Indicators of circadian disruption were body weight gain, longer period of inactivity, lower food consumption and dysregulation of core body temperature and corticosterone serum levels. The total number of tumors did not differ between the groups; mammary-gland carcinoma and fibrosarcoma or carcinosarcoma developed in both groups.

In both sexes of C57BL6/6J mice, a CJL model (weekly alternation between two rooms with light schedules offset by 8 hours, over an 86-week period) resulted in a shorter lifespan and a significantly greater incidence of hepatocellular carcinoma (8.8% vs. 0.0%) and non-alcoholic fatty liver disease than mice on an unchanging 12:12 LD cycle (Kettner *et al.* 2016). In addition to disruption of liver metabolism, irradiated and clock gene deficient mice (*Cry1*$^{-/-}$, *Cry2*$^{-/-}$,

Per1$^{-/-}$, *Per2*$^{-/-}$) had greater incidences of hepatocellular carcinoma with CJL than under 12:12 LD control lighting conditions. The incidence of hepatocellular carcinoma was higher in males than in females. Other tumors reported were pancreatic cancer, ovarian cancer, and lymphoma, but tumor incidences were not reported and the primary focus of the report was on the mechanism of fatty liver disease. In *p53*$^{-/-}$ C57BL6/6J mice, CJL-exposed animals had significantly decreased survival. Lymphoma was the primary tumor type and 10% of tumors were osteosarcoma (tumor details not reported) (Lee *et al.* 2010). Untreated mice with deficiencies in specific clock genes (*Bmal*1$^{+/-}$, *Cry1*$^{-/-}$ and *Cry2*$^{-/-}$, *Per1*$^{-/-}$ and *Per2*$^{m/m}$, *Per2*$^{-/-}$) had similar tumor profiles as with treatment with gamma radiation or radiation plus CJL.

5.4 Summary

Constant exposure to dim artificial LAN has become pervasive in modern society due to urban and indoor light pollution. Exposure to constant light is even more pronounced for shift workers that are exposed to constant dim light during daylight hours and bright lights during night shifts.

Most studies on the growth of injected tumor cells and some initiation-promotion studies showed that light exposure at night, including chronic exposure to dim light and intermittent exposure to dim light during the dark phase, and changes in daylight length promoted the rate of tumor growth, or tumor size, incidence, or multiplicity of several types of tumors including mammary gland, human breast, liver, lung, peripheral nervous system, kidney, human cervix, skin, prostate, or glioma (see Section 5.1 and Table 5-1). In addition, tumor growth in response to intermittent light exposure during the dark phase was found to be dependent on light intensity, and co-exposure with melatonin decreased liver and human breast tumor growth. Tumors derived from human breast cancer and grown in nude rats had a greater proliferation rate when perfused *in situ* with human blood collected during the daytime when blood melatonin levels were low and less proliferation with blood collected at nighttime when blood melatonin levels were high. From animal studies of spontaneous cancers, exposure to continuous light decreased the latency of spontaneous tumor formation and increased tumor multiplicity as compared to 12:12 LD exposure, but incidences of spontaneous tumor types between continuous light exposure and 12:12 LD were inconclusive and of limited utility. Most of these studies assessed total tumors and had limited pathological methods for assessing specific types of tumors. As discussed in Section 2, exposure to dim LAN (0.2 lux) can reduce melatonin secretion by 65%; none of the cancer animal studies using continual bright light measured melatonin levels.

Two studies evaluated the effects of exposure to blue-enriched light during the daytime on growth of tumor xenografts (human prostate cancer or rat hepatomas) in male rats maintained on a 12:12 LD cycle. Compared to rats exposed to 12 hours of polychromatic white fluorescent lighting, rats exposed to blue-enriched light for 12 hours during the daytime had decreased growth of prostate and liver xenografts.

Tumors initiated by chemical exposure, genetic manipulation, or gamma radiation from animals exposed to a simulated CJL model were larger and more numerous than in control animals, and the CJL-exposed group had shorter survival times. This was similar in rodents injected with tumor cells and exposed to conditions to simulate CJL; faster tumor growth and lower survival were reported, and one study reported an increase in tumors in the lung in CJL-exposed mice as compared to the 12:12 LD control group after intravenous injection of mammary gland adenocarcinoma cells (see Section 5.2 and Table 5-2). Types of tumors included Ehrlich

carcinoma, sarcoma 180, Glasgow osteosarcoma, pancreatic adenocarcinoma, lung carcinoma, and plasmacytoma. In initiation-promotion studies in mice, CJL increased multiplicity, tumor burden, or tumor size of liver tumors initiated with DEN or mammary-gland tumors initiated by NMU compared to 12:12 LD control mice. In a mouse model with increased susceptibility to mammary-gland cancer, exposure to light schedules simulating shift work decreased the latency of spontaneous mammary-gland tumor formation, but the final tumor incidences were similar to those of the 12:12 LD control group. In a mouse model with increased susceptibility to lung cancer, tumor initiation followed by a jet-lag exposure schedule increased tumor area. Mice exposed to CJL conditions had significantly greater spontaneous hepatocellular carcinoma incidence and shortened lifespan as compared to those on a 12:12 LD regimen and *p53*$^{-/-}$ mice exposed to CJL conditions had a shortened lifespan and increased incidence of lymphoma and osteosarcoma.

These studies provide strong evidence that LAN, CJL, or shift work can, through circadian disruption, promote tumor growth and decrease tumor latency. For most of these studies, evidence of circadian disruption was reported such as noting changes in food intake, body weight, activity, or hormone levels; however, the focus of these studies was on tumor growth and outcome, and these parameters, if noted, were not directly discussed. Therefore, although most studies reported some indication of circadian disruption, not all studies included this information and it was not possible to determine if negative tumor growth studies with light exposure were due to lack of circadian disruption. Exposure to blue light during the daytime has the opposite effect on tumor latency and growth, suggesting that total light exposure is important in circadian regulation and carcinogenicity. In the studies of light exposure (during the night or day), melatonin was shown to play a role in carcinogenicity (see Section 6.2.2). What is less certain is whether and how these factors affect spontaneous initiation of carcinogenesis. Studies of spontaneous tumor formation with LAN were of limited utility, and there were only two CJL and one shift-work study. All three of the latter studies provided data on circadian disruption affecting tumor growth. The CJL studies found significant increases in spontaneous liver tumor incidence and lymphoma, and the shift-work study found shortened tumor latency, but no change in tumor incidences. In all cases, circadian disruption outputs were measured that would affect the peripheral clock and potentially alter tumor development (see Section 6.2.3). Therefore, more carefully designed and detailed cancer studies to examine spontaneous tumor formation are needed to clearly answer whether LAN or CJL affects spontaneous cancer initiation events and which tissues may be most sensitive.

6 Mechanistic and Other Relevant Data

Epidemiological studies provide evidence that persistent night shift work increases the risk for breast cancer, and to a lesser degree, prostate cancer (see Sections 3 and 4, respectively). Some human studies have also reported an association between environmental exposure to light at night (LAN) (outdoor or indoor) and increased breast cancer risk; however, it is unclear whether these studies were measuring LAN that affects the circadian system or were using LAN as a proxy for other human activities associated with LAN. Studies in experimental animals demonstrate that exposure to light (including dim light) during the biological night or phase shifts in the light-dark cycle promote tumor growth and development (Section 5).

The proposed mechanism by which persistent night shift work and LAN cause cancer is by circadian disruption. As discussed in Section 2, studies in experimental animals and humans have shown that night shift work and LAN suppress nighttime melatonin secretion and cause circadian disruption. In addition to melatonin suppression, night shift work, transmeridian travel (i.e., jet lag), and LAN induce phase shifts to varying degrees in the central and peripheral clocks. Inherent differences in both the rate of phase shift and the rate of phase adjustment (i.e., re-entrainment) leads to internal desynchronization within and between various cells, tissues, and brain regions (Haus and Smolensky 2013).

This section reviews the mechanistic data associated with night shift work and LAN (or light during the biological night) and cancer including a discussion of mechanistic issues related to breast cancer (Section 6.1), proposed mechanisms of circadian disruption and cancer (Section 6.2), and a review of studies evaluating the relationship of LAN and shiftwork and key characteristics of carcinogens (Section 6.3) (Smith *et al.* 2016). As mentioned in Sections 1 and 2, shift work is a complex exposure scenario and includes other factors in addition to LAN (e.g., reduced exposure to sunlight and vitamin D deficiency, sleep deprivation, and altered meal timing). The potential link of these exposures to cancer are also reviewed (Section 6.4).

6.1 Overview of breast cancer development

Breast cancer is a heterogeneous and complex disease involving multiple risk factors, subtypes, and mechanisms of action that are not fully understood (Russo and Russo 2011, Institute of Medicine 2012, Anderson *et al.* 2014, Chollet-Hinton *et al.* 2017). It is clear that the mechanisms and etiologic factors involved in breast cancer development vary by age at exposure, intensity of exposure, genetic background, reproductive history, hormone receptor status, and stage of breast tissue development at the time of exposure (Institute of Medicine 2012).

There are two principal etiological subtypes (an earlier onset subtype with a peak frequency near age 50 and a later onset subtype with a peak frequency near age 70) that underlie the clinical spectrum of breast cancer (Anderson *et al.* 2014). In addition to differences in the age-specific incidence rate curves, these two clinical subtypes also have different risk factors, clinical courses, and molecular profiles. The earlier onset breast cancers are generally estrogen receptor (ER)-negative with an aggressive clinical course while the later onset breast cancers are ER-positive with a less aggressive clinical course. Molecular data show that these two breast cancer subtypes are fundamentally different diseases arising from two main cell types (luminal vs.

basal/myoepithelial) and are distinguished by differences in gene expression patterns (e.g., ER, progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]).

6.1.1 Breast development and susceptibility

Epidemiological data and rodent models of mammary carcinogenesis demonstrate that there are high risk tumor susceptibility windows that encompass different stages of development (i.e., prenatal life, infancy, puberty, early adulthood, and timing of first pregnancy) (Russo and Russo 2008, Russo and Russo 2011). Other than genetic susceptibility, some known risk factors for breast cancer are associated with reproductive events that influence lifelong estrogen exposure including age at menarche, age at menopause, absence of childbearing, age at first full-term pregnancy, and/or number of full-term pregnancies (Dall and Britt 2017). The protective effect of parity is restricted to hormone receptor-positive tumors (ER+, PR+) and diminishes with age such that women who give birth to their first child at age 35 or older have a greater risk of breast cancer than women who remain childless. The data further show that the timing of hormone exposure (i.e., early life) is more important to overall lifetime cancer risk than the number of years exposed or cumulative lifetime exposure (Rodgers *et al.* 2018).

Although the data clearly show that the young mammary gland represents a window of cancer susceptibility, the underlying mechanisms are less clear (Russo and Russo 2011, Dall and Britt 2017). Proposed mechanisms are related to the peripubertal stage when mammary growth is exponential, and highly proliferative terminal end buds are present throughout the gland (Fenton 2006). Increased sensitivity has been attributed to the high proliferative index of the mammary gland at puberty, thus increasing the probability of mutations and error-prone DNA repair (Dall and Britt 2017). Another possibility is that the increased number and density of terminal end buds is related to the presence of transformation-sensitive mammary stem cells; however, experimental support for mammary stem cells being housed and enriched in the terminal end buds is conflicting.

The mechanisms underlying the protective effect of parity against breast cancer are not completely understood; however, rodent models show that it is hormonally driven (Dall and Britt 2017). Pregnancy stimulates terminal differentiation in the mammary tissue through conversion of immature type 1 lobules to fully differentiated type 3 lobules. Mammary tissue in nulliparous women consists primarily of type 1 lobules. Type 3 lobules are more growth quiescent and are more resistant to oncogenic transformation than rapidly proliferating cells. However, the protective effect of parity may be eliminated if the mammary tissue is exposed to environmental carcinogens or endocrine disrupting chemicals prior to the pregnancy (Russo and Russo 2011).

6.1.2 Timing of shift work and LAN exposure and breast cancer development

The timing of exposure to LAN early in life affects breast cancer risk throughout life (Stevens 2012, Stevens *et al.* 2014). The risk of breast cancer among women beginning shift work at a younger age (i.e., before 30 or before their first full-term pregnancy) and continuing to work for 10 or more years was significantly elevated in several studies (see Section 3). Women shift workers also appear to have a greater risk for hormone receptor-positive breast cancers and have a shorter latency period than observed in day workers. Thus, the data suggest that timing of exposure to shift work or LAN during susceptible hormonal stages (e.g., working shifts at early ages and/or prior to the first full-term pregnancy) is more likely to increase breast cancer risk.

These data are consistent with the hypothesized hormonal pathway as a potential mechanism linking shift work and breast cancer. This pathway is related in part to melatonin suppression and is discussed in the following section.

Studies in experimental animals support the human findings. Rodent models show that the number and size of the terminal end buds are related to sensitivity to chemical carcinogens (Russo and Russo 1978, Dall and Britt 2017) and that the timing of light exposure affects tumor yield (Stevens *et al.* 2014). Constant light (150 lux), initiated *in utero* and continued immediately after birth, significantly increased mammary gland sensitivity to DMBA-induced carcinogenesis in rats when administered to female offspring at age 55 days (Mhatre *et al.* 1984, Shah *et al.* 1984). The increased sensitivity in the offspring was attributed to a clear positive correlation between circulating levels of prolactin and morphogenic and mitogenic effects on mammary epithelium as measured by development of terminal end buds and alveolar buds and DNA synthesis. In contrast, when female rats were exposed to constant light (~175 lux) at age 26 days and administered DMBA at age 52 days, tumor yield was significantly lower than in rats exposed to 8 hours light and 16 hours dark (Anderson *et al.* 2000). In this case, constant light exposure significantly accelerated mammary tissue development beyond the stage that is normally observed in virgin animals (i.e., to the lactation stage). Thus, the tissue had differentiated beyond the period of optimum sensitivity. The effects of LAN on sex hormones are further discussed in Section 6.3.6.

6.2 Circadian disruption and cancer: mechanistic links

Circadian disruption has been linked to cancer and thus is proposed to be the major mechanism by which night shift work and electric LAN cause cancer. Studies in humans and experimental animals provide evidence that these exposure scenarios disrupt melatonin homeostasis and deregulate clock genes in the central clock and peripheral tissues and that disruption of SCN clock-controlled neuroendocrine homeostasis drives symptoms associated with these exposures and promotes tumorigenesis. Sympathetic signaling has been hypothesized to regulate tumor suppression in a peripheral clock-dependent manner (Dibner *et al.* 2010, Greene 2012). Some of the major pathways linking circadian disruption and cancer include upregulation of oncogenes, downregulation of tumor suppressors, and altered fatty acid uptake and cell energy metabolism.

Other evidence that supports a link between circadian disruption and cancer comes from studies showing disruption of the clock regulatory loops, mutations, deregulated expression, and translocations of core clock genes in human breast, prostate, and other cancers. In addition, expression of some clock genes (Davis and Mirick 2006, Cadenas *et al.* 2014, Karantanos *et al.* 2014, Mazzoccoli *et al.* 2014, Altman 2016, Reszka and Przybek 2016) and other markers of circadian disruption (e.g., rest-activity rhythms and cortisol rhythms) have been identified as independent prognostic factors for overall survival in breast, colorectal, and other cancer patients (Mormont *et al.* 2000, Sephton *et al.* 2000, Lévi *et al.* 2014, Ballesta *et al.* 2017).This section describes the mechanistic data that link circadian disruption to cancer as measured by disruption of the sympathetic branch of the autonomic nervous system (SNS), melatonin suppression, and altered clock gene expression patterns.

6.2.1 Sympathetic nervous system

The SNS is a major neural output pathway of the SCN central clock as it innervates all peripheral organs except skeletal muscle (Buijs and Kalsbeek 2001, Furness 2006, McCorry 2007) and SNS dysfunction has been implicated as playing a role in various human cancers, including breast and prostate (reviewed in Lee *et al.* 2010). Although the link between SNS circadian dysfunction in human shift work and jet lag disorders is widely recognized (Adams *et al.* 1998, Carter *et al.* 2002, Ishii *et al.* 2004, Gangwisch *et al.* 2013, Reid and Abbott 2015), the role of SNS dysfunction in night shift work- or LAN-induced cancer has not been investigated in human epidemiological studies. However, a few studies in experimental animals show that chronic simulated jet lag desynchronizes the central clock-SNS-peripheral clock axis and that SNS circadian dysfunction can directly promote oncogenic activation. This section briefly describes studies of the links between SNS dysfunction and cancer, studies on shift work and SNS function, and possible mechanisms of circadian disruption-related cancer.

SNS and cancer

The relationship between the SNS and cancer is likely mediated by catecholamines (i.e., norepinephrine and epinephrine) via chronic stress-response pathways that can result in adverse biological effects, including cancer development and growth (reviewed by Greene 2012). Catecholamines or adrenergic receptors are involved in tumor cell proliferation, angiogenesis, metastasis, and expression of inflammatory and chemotactic cytokines. For example, epinephrine-mediated ß-adrenergic receptor activation reduced the sensitivity of prostate and breast cancer cells to apoptosis while breast cancer metastasis was strongly induced by chronic stress via ß-adrenergic receptors. Accumulated evidence has also shown that inhibition of ß-adrenergic receptor-mediated SNS dysfunction can reduce the risk of various cancers and also potentially improve anticancer therapeutic indices in humans (Sephton and Spiegel 2003, Cole *et al.* 2015, Simó *et al.* 2018). Since the SNS also controls melatonin secretion via ß1 adrenergic pathways (Nesbitt *et al.* 2014), it is likely that SNS circadian dysfunction is also a key pathophysiological mechanism that drives LAN-induced melatonin suppression.

Shift work and SNS

Two studies in mice show that chronic simulated jet lag desynchronizes the central clock-SNS-peripheral clock axis and that SNS circadian dysfunction can directly promote oncogenic activation (Lee *et al.* 2010, Kettner *et al.* 2016). These studies show that chronic jet lag-induced SNS dysfunction plays a key role in suppression of the ATM-p53 tumor suppressor pathway as well as promotion of multiple oncogenic pathways in peripheral tissues including those controlled by *Ap1*, *Creb*, *ß-Catenin*, and *c-Myc*. Ablation of genes encoding the three ß-adrenergic receptors in mice completely prevented chronic jet lag-induced *Ap1*, *Creb*, *ß-Catenin*, and *c-Myc* activation and spontaneous hepatocellular carcinoma (Kettner *et al.* 2016). Lee *et al.* (2010) demonstrated that chronic jet lag induced tumors in the same organ systems as observed in circadian gene-mutant mice. Fu *et al.* (2005) also demonstrated in a mutant mouse model that ß-adrenergic signaling simultaneously activated the peripheral clock via *Per* genes and the cell-cycle clock via the cAMP response element binding protein (CREB)-AP1-Myc signaling in osteoblasts. Activation of peripheral clocks by SNS signaling is required for preventing uncontrolled cell-cycle progression as clock-gene-deficient cells exhibit elevated CREB-AP1-

Myc signaling and accelerated cell proliferation in response to ß-adrenergic receptor activation (Fu *et al.* 2005, Lee *et al.* 2010).

6.2.2 Melatonin suppression

Melatonin has a prominent role in circadian biology and exerts its effects through both receptor-mediated and receptor-independent pathways. As such, it is often used as a biological marker of circadian regulation and disruption (IARC 2010). Although melatonin is produced in other tissues (e.g., skin and gastrointestinal tract), circulating levels of melatonin are primarily produced by the pineal gland (see Section 1.1.1). LAN exposure was first proposed as a possible risk factor for breast cancer in women in the late 1980s based on the observation that breast cancer risk increases dramatically as societies industrialize and that exposure to LAN suppresses melatonin production by the pineal gland and shifts its rhythm (Stevens 1987, Stevens *et al.* 1992, Papantoniou *et al.* 2014, Gómez-Acebo *et al.* 2015). These observations led to formulation of the *melatonin hypothesis* (Stevens 1987, Stevens and Davis 1996). The mechanism originally proposed for the melatonin hypothesis was as follows: (1) LAN and/or electric fields produced by electricity lowers melatonin production, (2) lower melatonin levels in the blood enhances estrogen production by the ovary and prolactin production by the pituitary gland, and (3) constant exposure to estrogen and prolactin increases the turnover rate of breast epithelial stem cells and increases the risk of breast cancer (Stevens 1987). Most of the information on the melatonin and prolactin relationship is from nocturnal rodents and shows that prolactin secretion is inhibited by melatonin via the MT1 receptor; however, this does not seem to be the case in humans where the prolactin and melatonin circadian rhythms are approximately in phase (Dubocovich *et al.* 2003, Dubocovich and Markowska 2005, Goel *et al.* 2009, Hardeland 2014).

Studies relevant to evaluating the relationship of melatonin suppression and cancer (primarily female breast cancer) are discussed below and include studies of melatonin levels and cancer in humans and experimental animals as well as mechanistic studies on the biological effects (primarily key characteristics of carcinogens) of melatonin.

Human studies of melatonin suppression and breast cancer and prostate cancer

Data for breast cancer and melatonin levels are available from six prospective studies in independent cohorts, including the Nurses' Health Study (NHS) (Schernhammer *et al.* 2009, Devore *et al.* 2017), Nurses' Health Study 2 (NHS2) (Schernhammer and Hankinson 2005, Brown *et al.* 2015), Women's Health Initiative (WHI) (Sturgeon *et al.* 2014), the Guernsey cohort (Wang *et al.* 2014), the Hormones and Diet in the Etiology of Breast Cancer Risk (ORDET) pre- and post-menopausal cohorts (Schernhammer *et al.* 2008, Schernhammer *et al.* 2010), and the Singapore Study (Wu *et al.* 2013). The findings suggest that melatonin levels are inversely associated with breast cancer risks among postmenopausal women; however, findings are conflicting in studies of pre-menopausal women (Figure 6-1).

The Singapore study (Wu *et al.* 2013) collected randomly timed spot urine specimens, which are not considered valid measures of the overnight peak and accumulation of melatonin, thus only five cohorts are included in the discussion or forest plot. Concern that preclinical breast cancer may influence melatonin levels led investigators in all cohorts, with the exception of Wang *et al.* (2014), to examine estimates by the number of years between the time the samples were collected and when breast cancer was first diagnosed. Two NHS2 studies reported no differences

in the association of melatonin levels (based on first morning spot urine samples) and breast cancer risk with or without shift workers (Schernhammer and Hankinson 2005, Brown *et al.* 2015); however, no information was provided on whether the populations included shift workers in the other studies (Schernhammer *et al.* 2008, Schernhammer *et al.* 2009, Schernhammer *et al.* 2010, Sturgeon *et al.* 2014, Wang *et al.* 2014, Devore *et al.* 2017).

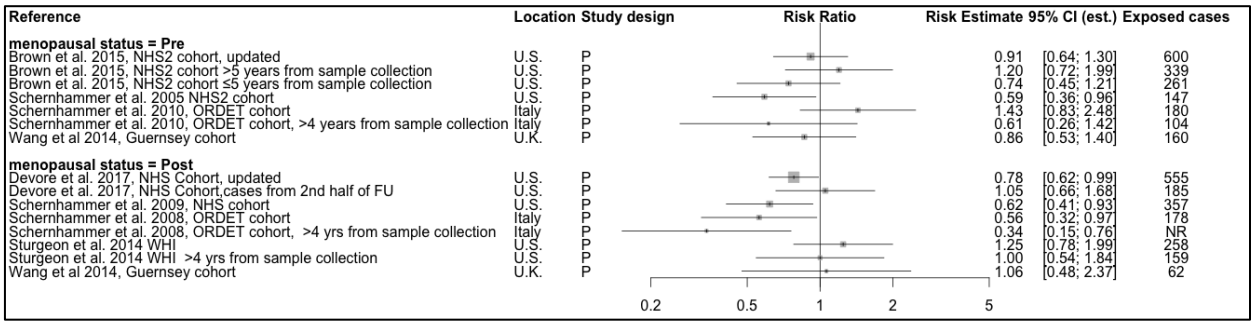

Figure 6-1. Relationship of urinary melatonin levels (top quartile vs. bottom quartile) and risk of breast cancer

Overall, results are mixed among premenopausal women. In the updated NHS2 study (Brown *et al.* 2015), the risk of breast cancer was significantly lower among women with melatonin levels in the lowest quartile who were diagnosed within 5 years of sample collection, but not among those diagnosed 5 or more years after collection; furthermore, this reduced risk was limited to cases accrued only during the early years of follow-up. Opposite results were found in the premenopausal ORDET cohort (Schernhammer *et al.* 2010), in which high melatonin levels were non-significantly associated with reduced risk of breast cancer among those diagnosed more than 4 years after sample collection. Among post-menopausal women, Devore *et al.* (2017) (NHS) and Schernhammer *et al.* (2008) (ORDET) reported overall statistically significant inverse relationships between melatonin levels and breast cancer risk. Similar to findings in the updated NHS2 premenopausal cohort (Brown *et al.* 2015), the updated NHS postmenopausal study (Devore *et al.* 2017) found no effect among cases recruited during the latter half of follow-up. In the ORDET post-menopausal cohort (Schernhammer *et al.* 2008), the inverse effect became stronger among women diagnosed four or more years after sample collection. Neither the WHI (Sturgeon *et al.* 2014) nor Guernsey cohorts (Wang *et al.* 2014) reported any effect.

Heterogeneity in the results could potentially arise from differences in urine sampling, with the ORDET cohorts using 12-hour overnight collections and the NHS/NHS2 cohorts primarily using first morning urines, with some small percentage using spot urines. In addition, an unreported number of urine samples collected in the WHI may not have been a first morning void (Sturgeon *et al.* 2014). Smoking prevalence, which varied widely across cohorts (e.g., 24.5% in the ORDET cohorts; 7% in the NHS2 cohort) may also influence the results, as smoking stimulates cytochrome P450 1A2 activity, which is the primary enzyme in melatonin metabolism.

While studies of hormone levels in recently diagnosed cases should be considered with some caution due to issues of temporality, two studies reported findings on melatonin levels in cancer cases and controls. A recent small cross-sectional clinical study in Brazil compared melatonin levels in women recently diagnosed with breast cancer, women under adjuvant chemotherapy, and nurses working night-shifts with melatonin levels in healthy, age-matched controls (de Castro *et al.* 2018). Breast cancer cases had lower levels of melatonin compared to healthy

controls, and levels were even lower in night-shift nurses and in patients under adjuvant chemotherapy. Tai *et al.* (2016) examined the relationship between two circadian-related hormones with oncostatic and immunosuppressive activity (melatonin and cortisol) and the presence of prostate cancer in a case-control study (120 prostate cancer patients and 240 age-matched controls). This study reported that patients with lower urinary melatonin sulfate levels or a lower urinary melatonin/cortisol ratio were more likely to have prostate cancer.

Human studies of melatonin suppression and cancer in blind populations

The melatonin hypothesis also predicted that studies of totally blind populations would show a decreased risk of LAN-induced cancers because melatonin levels would not be suppressed by LAN exposure (Feychting *et al.* 1998, Stevens 2009). Several studies support this prediction, reporting that breast cancer incidence in women is inversely associated with blindness as well as the degree of visual impairment (Hahn 1991, Feychting *et al.* 1998, Verkasalo *et al.* 1999, Kliukiene *et al.* 2001, Pukkala *et al.* 2006, Flynn-Evans *et al.* 2009). Severe visual impairment includes individuals with a complete lack of light perception (~15% of the legally blind population) as well as those with varying degrees of light perception (Lewy *et al.* 2004). Abnormally phased, or free running, circadian rhythms are common among individuals with no light perception; however, daily melatonin treatment usually helps them entrain. In a study of 49 registered blind individuals with different causes of visual loss, Lockley *et al.* (1997) reported that the majority of subjects (14 of 19) with some light perception had normally entrained melatonin rhythms while the majority of subjects with no light perception had abnormal melatonin rhythms (23 of 30) or free-running rhythms (17 of 30).

Two studies also suggest that prostate cancer risk may be lower in blind populations. Feychting *et al.* (1998) found a non-significantly decreased risk of prostate cancer in totally blind people with no light perception (SIR = 0.71, 95% CI = 0.43 to 1.09). Pukkula *et al.* (2006) reported a non-statistically significant decrease in the SIR of prostate cancer; however, this estimate was based on only one observed case (SIR = 0.28, 95% CI = 0.01 to 1.56) in 21 years of follow-up.

Overall, these data suggest that there may be a lower risk of hormone-dependent tumors in visually impaired individuals, and the protective effect may depend on the degree and type of visual impairment.

Animal studies of melatonin and cancer

There is compelling evidence that melatonin can reduce the incidence and growth of tumors, especially breast cancer, through mechanisms that affect tumor initiation, promotion, and progression (Blask *et al.* 2002a, Mediavilla *et al.* 2010, Blask *et al.* 2014, Hill *et al.* 2015). This section describes effects of melatonin on reducing development and growth of tumors promoted by LAN or independent from LAN (see Section 5 for more details of LAN effects on tumor growth).

LAN studies: LAN exposure, including dim LAN as low as 0.2 lux, suppresses nocturnal melatonin levels in a dose-dependent manner (as measured in serum or urinary metabolites) in rodents and stimulates tumor growth (Anisimov *et al.* 1994, Dauchy *et al.* 1997, Dauchy *et al.* 1999, Blask *et al.* 2002a, Blask *et al.* 2005, Cos *et al.* 2006, Blask *et al.* 2009, Blask *et al.* 2014, Dauchy *et al.* 2014, Schwimmer *et al.* 2014). Most of these studies used continuous bright or dim

LAN; however, two studies (Cos *et al.* 2006, Schwimmer *et al.* 2014) also used a 30-minute light pulse during the middle of the scotophase (i.e., period of darkness). Some of these studies also investigated the effects of exogenous melatonin (oral or injected), melatonin-enriched blood, and/or melatonin-depleted blood (collected from women exposed to LAN or collected during the daytime) on tumor growth and are described below.

Administration of exogenous melatonin inhibited the growth of LAN-induced spontaneous tumors and LAN promotion of chemically induced mammary and colon tumors (Tamarkin *et al.* 1981, Shah *et al.* 1984, Kothari 1987, Anisimov *et al.* 2012). In a similar fashion, LAN-promotion of MCF-7 xenografts (including steroid receptor-positive and -negative tumors) in nude rats or rat hepatomas implanted in Buffalo rats (see Section 5) was inhibited when tumors were perfused *in situ* with melatonin-enriched rat or human blood (i.e., rat blood enriched with synthetic melatonin or blood collected from human volunteers during the night) (Blask *et al.* 2005, Blask *et al.* 2009, Blask *et al.* 2014). In contrast, MCF-7 xenografts or rat hepatomas perfused with melatonin-depleted blood (i.e., blood collected from human volunteers either during the daytime or after exposure to LAN) exhibited high tumor-proliferative activity. Other studies showed that administration of exogenous melatonin in drinking water reversed LAN-promoted growth of MCF-7 xenografts in nude rats (Dauchy *et al.* 2014) and murine 4T1 mammary cancer cells in female BALB/c mice (Schwimmer *et al.* 2014). The tumor suppressive effects of exogenous melatonin in LAN-exposed animals were completely blocked when a nonselective melatonin receptor antagonist was added to the blood perfusate (Blask *et al.* 2005, Dauchy *et al.* 2014). However, one study reported that melatonin administered in drinking water had no effect on LAN promotion of murine B16 melanoma cells inoculated into male C57BL6 mice (Otálora *et al.* 2008).

Other studies investigated the effects of the daytime light exposure on melatonin and tumor growth (Dauchy *et al.* 2015, Dauchy *et al.* 2018). These studies reported that exposure to blue-enriched light during the daytime amplified the nocturnal melatonin signal and inhibited the growth of human PC3 prostate cancer xenografts in male nude rats and Morris 7288CTC rat hepatoma implants in male Buffalo rats. These studies provide further support that the total daily light exposure (light during the day and electric light at night) is important for circadian regulation.

Non-LAN studies: Several studies, including a few studies reviewed in the previous section, also investigated the effects of melatonin on tumor growth independent from LAN exposure. Melatonin administered in tap water inhibited growth of chemically induced mammary and colon tumors in rodents (Shah *et al.* 1984, Kothari 1987, Anisimov *et al.* 1997, Anisimov *et al.* 2000, Lenoir *et al.* 2005) and inhibited growth of human leiomyosarcoma xenografts in nude rats (Dauchy *et al.* 2009b), murine TRAMP-C2 prostate cancer cells implanted into male C57BL/6 mice (Haim *et al.* 2010), rat hepatoma implants in male Buffalo rats (Blask *et al.* 2004), and murine B16 melanoma cells in male mice (Otálora *et al.* 2008). Growth of hepatoma implants in male Buffalo rats was also inhibited by perfusion with melatonin-enriched rat blood (Blask *et al.* 1999). *In vitro* studies of several MCF-7 human breast cancer cell lines (ERα+, steroid receptor negative, Her2-positive SKBR-3, Her2.1, and caSrc) demonstrated that melatonin added to the culture medium at physiological concentrations significantly reduced the invasive/metastatic phenotype either by promoting mesenchymal-to-epithelial transition or inhibiting key metastatic

signaling pathways (Mao *et al.* 2012, Mao *et al.* 2016a). These studies also showed that exogenous melatonin suppressed metastasis of MCF-7 xenografts in nude mice and nude rats.

Studies using pinealectomized rodents also show enhanced growth of chemically induced or transplanted tumors that is the same as the response to LAN (Aubert *et al.* 1980, Tamarkin *et al.* 1981, Blask *et al.* 1999, Blask *et al.* 2004). In both cases, the effect has been attributed to suppressed melatonin production (Dauchy *et al.* 1999, Blask *et al.* 2005, IARC 2010) such that LAN exposure has been described as functional pinealectomy (Shah *et al.* 1984, Stevens *et al.* 2000, Anisimov *et al.* 2012). Mammary tumor incidence in pinealectomized rats administered exogenous melatonin during the tumor induction phase or after tumors were already present was decreased (Aubert *et al.* 1980, Tamarkin *et al.* 1981).

In addition, Hill *et al.* (2013) reported that the age-related decline in melatonin production in rats was directly related to the observed age-associated enhanced growth of NMU-induced mammary tumors and a reduced sensitivity to inhibition by exogenous melatonin. These data clearly show that melatonin has oncostatic activity and is discussed further in the following section.

Biological effects of melatonin related to cancer

Melatonin is known to exert multiple effects that are directly relevant to cancer development and progression. These effects include multiple tumor defense mechanisms that offer some protection against all the biological effects that are recognized as hallmarks of cancer (Erren 2005, Hill *et al.* 2015, Talib 2018). These oncostatic properties of melatonin have been demonstrated in numerous human cancers and cell lines including breast, prostate, sarcomas, colorectal, liver, skin, ovarian, cervical, neural, and larynx as well as in murine tumor models (Mediavilla *et al.* 2010).The anti-initiating and oncostatic effects of melatonin and supporting mechanistic data have been extensively reviewed (Blask *et al.* 2002a, Mirick and Davis 2008, Mediavilla *et al.* 2010, Srinivasan *et al.* 2011, Hardeland 2014, Gurer-Orhan and Suzen 2015, Haim and Zubidat 2015) and include anti-estrogenic properties, modulation of the cell cycle, anti-mitotic activity, differentiation and apoptosis, inhibition of telomerase activity, antioxidant effects, inhibition of angiogenesis, inhibition of metastasis, enhancing immune response, inhibiting fatty acid transport and metabolism, and modulating gene expression through interaction with clock genes and epigenetic events. In addition, several lines of evidence suggest that the oncostatic properties of melatonin involve epigenetic mechanisms relevant to cancer, and particularly breast cancer (Korkmaz *et al.* 2009, Hardeland 2014, Schwimmer *et al.* 2014). These epigenetic processes include the following: (1) influence on the transcriptional activity of nuclear receptors involved in the regulation of breast cancer cell growth (e.g., ERα, glucocorticoid receptor, retinoic acid receptor), (2) down-regulation of genes involved in the synthesis or activation of estrogens (e.g., aromatase), (3) inhibition of telomerase activity or expression induced by estrogens, (4) modulation of the cell cycle through inhibition of cyclin D1 expression, and (5) influence on circadian rhythm disturbances dependent on the light/dark cycle and deregulation of PER2 tumor suppressor gene activity (reviewed by Korkmaz *et al.* 2009). Studies of epigenetic effects in animal models of chronic jet lag or LAN and in shift workers are reviewed in Section 6.3.2.

Many of melatonin's oncostatic actions are mediated via the MT1 receptor and modulation of downstream cell proliferative and survival signaling pathways including aerobic glycolysis (Warburg effect), cAMP, linoleic acid uptake and metabolism to 13-hydroxyoctadecadienoic acid (13-HODE), tumor kinase signaling, and transcriptional activity of mitogenic nuclear

receptors (e.g., ERα, retinoic acid receptor-related orphan receptor alpha (RORα), and glucocorticoid receptors) (Blask *et al.* 2002b, Dauchy *et al.* 2003, Dauchy *et al.* 2007, Blask *et al.* 2011, Wu *et al.* 2011, Blask *et al.* 2014, Dauchy *et al.* 2014). Melatonin suppressed metastasis in human breast cancer cells by inhibiting epithelial to mesenchymal cell transition (Mao *et al.* 2012, Mao *et al.* 2016b). The molecular pathways involved included activating glycogen synthase kinase 3ß (GSK3ß) activity by inhibiting serine-threonine kinase Akt phosphorylation and inhibiting ribsomal S6 kinase 2 (RSK2) activity. GSK3ß and RSK2 are protein kinases that are key regulators in the signaling networks that modulate epithelial to mesenchymal cell transition and metastasis. Both human epithelial (MCF-7) and mesenchymal (leiomyosarcoma) cancer xenografts perfused *in situ* with human or rat blood with or without physiological nocturnal levels of melatonin exhibited dose-dependent suppression of tumor cAMP production, linoleic acid uptake, 13-HODE release, mitogen-activated protein kinase (MAPK) activation, and [^{3}H]-thymidine incorporation into DNA (Blask *et al.* 2005, Blask *et al.* 2009, Dauchy *et al.* 2009b, Mao *et al.* 2016a). The suppressive effects of melatonin were prevented by treatment with a melatonin receptor antagonist. These studies provide mechanistic evidence that melatonin, at nocturnal physiological concentrations, suppresses tumor growth via a melatonin-receptor mediated signal transduction pathway involving linoleic acid uptake and metabolism. *In vitro* studies with a variety of human and murine cancer cell lines (including breast and prostate) also show that physiological concentrations of melatonin generally inhibit cell proliferation and invasiveness while higher concentrations are cytostatic or cytotoxic (Cos *et al.* 1998, Blask *et al.* 2002b). However, the dose-response of tumor cells to melatonin varies from a bell-shaped to a linear pattern depending on the cell line and cell culture conditions (Blask *et al.* 2002b).

The oncostatic actions of melatonin are especially relevant for hormone-dependent neoplasms such as mammary and prostate cancer (Mediavilla *et al.* 2010). In particular, melatonin's anti-estrogenic properties are important for its oncostatic effects on hormone-dependent mammary tumors. Melatonin inhibits growth of MCF-7 breast cancer cells, in part, by modulating the estrogen response pathway (Hill *et al.* 1992, Kiefer *et al.* 2002). Melatonin treatment, via its MT1 G protein coupled receptor, significantly diminished 17ß-estradiol (E2)-induced ERα transactivation, altered ERα DNA binding activity, suppressed E2's induction of cAMP, and reduced E2-induced cell proliferation. Melatonin's anti-estrogenic effects are unique and involve a double mechanism of action: (1) interaction with enzymes involved in the formation and biotransformation of androgens and estrogens (i.e., Selective Estrogen Enzyme Modulator [SEEM], and (2) interaction with estrogenic receptors (i.e., Selective Estrogen Receptor Modulator [SERM]) (Mediavilla *et al.* 2010).

In addition, there is an increasing body of evidence that estrogens, estrogen receptors, and estrogen signaling mechanisms are required for prostate cancer initiation and progression (Yeh *et al.* 2014, Bonkhoff 2018). Sainz *et al.* (2005) reported that pharmacological concentrations of melatonin significantly reduced prostate cancer cell growth *in vitro* and stopped cell-cycle progression of human androgen-dependent (LNCaP) and -independent (PC3) cell lines. The various pathways and key events associated with melatonin's oncostatic effects are shown in Table 6-1.

Table 6-1. Oncostatic mechanisms of melatonin

Mechanism	Pathway	Key events: Cellular/molecular effects	Outcome
Selective Estrogen Receptor Modulator (SERM)	Estrogen signaling	↓ ERα expression ↓ ERα activation ↓ Transcription of ERα-dependent genes	↓ Estrogen response ↑ Oncostatic activity – estrogen-dependent tumors
Selective Estrogen Enzyme Modulator (SEEM)	Estrogen biosynthesis	↓ Aromatase ↓ 17ß-hydroxy steroid dehydrogenases ↓ Estrogen sulfatase ↑ Estrogen sulfotransferases	↑ Weak estrogens (i.e., estrone) ↓ Active estrogens (i.e., estradiol) ↑ Oncostatic activity – estrogen-dependent tumors
Cell proliferation, differentiation, apoptosis	Cell cycle, cell death	↑ GO-G1 phase, cell-cycle length ↑ p53, p21, Bax ↑ Caspases 3, 8, 9 ↑ Cytochrome c ↓ Cyclin D1	↓ Cell proliferation ↑ Cell differentiation ↑ Apoptosis (cancer cells) ↑ DNA damage repair ↑ Oncostatic activity – multiple tumor types
Inhibition of telomerase	Telomere maintenance	↓ Telomerase reverse transcriptase (hTERT) ↓ Estradiol-induced telomerase activity response	↓ Number of cell replication cycles ↑ Oncostatic activity – estrogen-dependent tumors
Antioxidant activity	Oxidative stress response	↓ Reactive oxygen species (ROS) ↓ Nitric oxide synthase (NOS) ↑ GSH, superoxide dismutase (SOD), catalase ↑ Cytokines	↓ DNA damage ↓ Side effects of chemo- and radiotherapy ↑ Oncostatic activity – multiple tumor types
Anti-angiogenesis	Neovascularization	↓ Vascular endothelial growth factor (VEGF) ↓ Hypoxia inducible factor-1α (HIF-1α) ↓ ROS	↓ Neovascularization ↑ Oncostatic activity – multiple tumor types
Inhibition of metastasis	Cell surface adhesion molecules and plaques	↑ E-cadherin ↑ $ß_1$-integrin ↑ MT1 receptor ↓ Stimulatory effects of 17ß-estradiol	↓ Cell invasiveness/metastasis ↑ Oncostatic activity – multiple tumor types
Immunomodulation	Cellular and humoral immunity	↑ Natural killer (NK) cells, monocytes, leukocytes ↑ Cytokines ↑ Interferon-γ ↑ TNF-α	↑ Immunosurveillance ↑ Oncostatic activity – multiple tumor types
Fatty acid transport and metabolism	Epidermal growth factor/mitogen activated protein kinase (EGFR/MAPK)	↓ Linoleic acid uptake ↓ 13-HODE	↓ Activation of EGFR/MAPK ↑ Oncostatic activity – multiple tumor types
Prevention of circadian disruption	Clock genes and epigenetic pathways	↓ Abnormal epigenetic modifications	↑ Internal clock synchronization

Mechanism	Pathway	Key events: Cellular/molecular effects	Outcome
		↓ Dysfunctional clock genes (SCN and peripheral)	↑ Oncostatic activity – multiple tumor types

Sources: Mediavilla *et al.* 2010, Srinivasan *et al.* 2011, Zubidat and Haim 2017.
↓ = decreases, ↑ = increases.

6.2.3 Other mechanisms of circadian disruption

Circadian disruption can affect cell-cycle homeostasis and alter the transcription level of clock and clock-controlled genes associated with cell-cycle progression, immune response, cell proliferation, chromatin remodeling, DNA damage repair, metabolism, and apoptosis, all of which could contribute to cancer development and progression (Fu and Kettner 2013, Ben-Shlomo 2014, Soták *et al.* 2014, Stevens and Zhu 2015). In addition to melatonin suppression, other mechanisms related to circadian disruption include altered clock gene function and expression and desynchronization of the master clock from the peripheral clocks. Filipski *et al.* (2002) provided the first experimental evidence that circadian disruption (i.e., SCN ablation by bilateral electrolytic lesions) was associated with accelerated growth of implanted Glasgow osteosarcoma or pancreatic adenocarcinoma in B6D2F1 mice that was independent of melatonin as these nocturnal mice have low levels of melatonin secretion and an atypical melatonin rhythm with production and secretion peaking during the day (Li *et al.* 2000, Filipski *et al.* 2004).

Overall, the evidence suggests that circadian disruption/desynchronization is an independent risk factor for cancer and that tumor suppression *in vivo* is, in part, a clock-controlled function (Lee *et al.* 2010, Kettner *et al.* 2014). This section reviews the evidence supporting this conclusion including genetic models of clock gene mutations in rodents, polymorphism studies in humans, and *in vivo* and *in vitro* gene expression studies.

Genetic models in experimental animals

Although circadian disruption in humans does not require mutations in clock genes, a number of clock gene mutant mouse models have been used to investigate the biological effects of circadian disruption and the specific role of the core clock genes. However, with the exception of *Bmal1*, other core clock genes have at least two functionally redundant isoforms such that clear phenotypic changes may be observed only in mouse models with multiple loss-of-function alleles (Schibler *et al.* 2015). In general, clock gene suppression (i.e., downregulation of specific genes) or knockouts and mutations in mice are associated with a cancer-prone phenotype and accelerated growth of tumors (Table 6-2) (Wood *et al.* 2008, Yang *et al.* 2009b, Lee *et al.* 2010, Zeng *et al.* 2010, Mteyrek *et al.* 2016, Papagiannakopoulos *et al.* 2016, Mteyrek *et al.* 2017). Some studies evaluated the effects of exposure to radiation or chemical carcinogens in clock gene mutant or deficient experimental animals.

Table 6-2. Cancer studies of genetic models of clock gene mutations or downregulation in mice

Reference	Animal model	Clock genes	Tumor site	Comments
Wood *et al.* 2008	Inactivation	*Per2*	Intestine Colon polyps	Downregulation enhanced proliferation of colon cells *in vitro*
Yang *et al.* 2009b	Downregulation	*Per2*	Breast	Accelerated tumor cell growth *in vivo* and *in vitro* and doubled the daily amplitude of the tumor growth rhythm
Lee *et al.* 2010	Mutant Spontaneous or radiation induced	*Bmal1,* *Per1* and/or *Per2* *Cry1* and/or *Cry2*	Lymphoma Liver Ovarian	Uncoupling of p53 and Myc signaling promotes tumor development
Zeng *et al.* 2010	Downregulation Inoculated with C26 mouse colon cancer cells	*Bmal1*	Colon	BALB/c mice inoculated with C26 mouse colon cancer cells; increased proliferation *in vitro*
Papagiannakopoulos *et al.* 2016	Germline mutations	*Per2,* *Bmal1*	Lung	Enhanced cell proliferation in lung tumors associated with increased c-Myc levels
Mteyrek *et al.* 2016, Mteyrek *et al.* 2017	Mutant	*Cry1, Cry2, and Per2*	Liver Bile duct	Co-exposure to DEN

Clock gene effects

The circadian timing system controls the expression of up to 40% to 50% of transcripts in mammalian genomes in a tissue- and time-specific manner, thus it is important in regulating many biological processes and has broad physiological and pharmacological implications (Huisman *et al.* 2016, Mure *et al.* 2018, Ruben *et al.* 2018). Many of these biological processes and pathways are associated with carcinogenesis (e.g., immune function, chronic inflammation, DNA repair, metabolic disorders and obesity, and premature aging (Fu *et al.* 2002, Fu *et al.* 2005, Antoch *et al.* 2008, Wood *et al.* 2008, Yang *et al.* 2009a, Lee *et al.* 2010, Geyfman *et al.* 2012, Kettner *et al.* 2014). Rodent studies have shown that the responses to both gamma and UV radiation damage follow a robust rhythm *in vivo* and that ablation of the core circadian genes *Per2* and *Bmal1* in mice was sufficient to abolish circadian rhythms of DNA damage response (Fu *et al.* 2002, Panda *et al.* 2002, Geyfman *et al.* 2012). Thus, one of the expected consequences of circadian disruption is altered DNA repair.

As discussed in Section 1.1, the central clock in the SCN regulates cell proliferation and apoptosis in peripheral tissues at the systemic level through the SNS and the neuroendocrine system (Fu and Lee 2003). Deregulated SNS signaling induces oncogenic activation and suppresses clock genes and ATM-p53 signaling, thus leading to uncontrolled cell proliferation and contributing to tumor initiation (Fu *et al.* 2005, Lee *et al.* 2010, Kettner *et al.* 2016). Estrogens and glucocorticoids also regulate cell proliferation and apoptosis in peripheral tissues (Fu and Lee 2003). Post-translational modifications of clock proteins are also important for

proper clock function and regulatory fine-tuning of the circadian molecular clockworks (Mehra *et al.* 2009, Hirano *et al.* 2016). Thus, circadian disruption can result in abnormal modifications and turnover of clock proteins. These data indicate that the circadian system plays an important role in suppressing the hallmarks of cancer (Greene 2012).

At the cellular and molecular level, the circadian clocks in peripheral tissues operate as interlocked feedback loops and are coupled to the cell cycle (Gérard and Goldbeter 2012, Fu and Kettner 2013, Ballesta *et al.* 2017). Therefore, disruption of either the positive or negative loop leads to loss of control in the circadian homeostasis of cell-cycle progression. Several molecular components of the cell cycle network exhibit circadian rhythms and, as such, can be entrained by the circadian clock (Gérard and Goldbeter 2012). Examples of genes involved in cell-cycle regulation, DNA damage checkpoints and apoptosis that are under circadian control include proto-oncogenes (e.g., *AP1*, *Creb*, *Ras*, *c-Myc*, *Mdm2, ß-catenin*), tumor suppressor genes (e.g., *Atm*, *p53*, *p21*, *Wee1*, *AMP-kinase*, *Gadd45α*), and genes that encode the caspases, cyclins, cyclin-dependent kinases (CDKs), transcription factors, and ubiquitin-associated factors (Fu and Lee 2003, Chen-Goodspeed and Lee 2007, Fu and Kettner 2013, Kelleher *et al.* 2014, Uth and Sleigh 2014, Altman 2016). The expression patterns of cell-cycle genes and p53 are synchronized with the expression patterns of the core circadian genes in human and rodent somatic tissues (Bjarnason *et al.* 1999, Bjarnason *et al.* 2001, Fu *et al.* 2002, Lee *et al.* 2010, Fu and Kettner 2013, Kettner *et al.* 2015). *Per2* binding modulates the stability of p53 by preventing ubiquitination in unstressed cells while increasing p53 transcriptional activity in response to genotoxic stress (Gotoh *et al.* 2016). Both these processes are related and are mediated by *Per2* regulation of p53 subcellular trafficking from the cytoplasm to the nucleus.

The CLOCK-BMAL1 heterodimer also directly regulates genes that play an essential role in cell-cycle control, including blocking *c-Myc* overexpression (Fu *et al.* 2002, Fu *et al.* 2005, Sahar and Sassone-Corsi 2007, Lee *et al.* 2010). CLOCK also possesses intrinsic histone acetyltransferase (HAT) activity that can affect cell proliferation and differentiation in multiple ways including chromatin remodeling and interaction with key cell-cycle proteins (e.g., p53 and c-MYC) and transcription factors (e.g., ERα, NF-κB, c-JUN) (Doi *et al.* 2006, Sahar and Sassone-Corsi 2007). PER1 and PER2 tumor-suppressor activity involves regulation of the ATM-Chk1/Chk2 DNA damage-response pathway (Gery *et al.* 2006, Chen-Goodspeed and Lee 2007, Takahashi *et al.* 2008, Lee *et al.* 2010). *PER1* also exerts tumor-suppressor activity by regulating the cyclin-CDK-cyclin-dependent kinase (cyclin-CDK-CK1) inhibitory regulatory network in human oral squamous cell-carcinoma cells (Fu *et al.* 2016). CRY2 interacts with ATR and CHK1 to regulate intra-S checkpoint function in UV-induced DNA damage response via Timeless (TIM), a natural partner of PER in *Drosophila* (Ünsal-Kaçmaz *et al.* 2005), while BMAL1 is involved in p53-dependent p21WAF1/CIP1 induction in human colorectal carcinoma cells (Mullenders *et al.* 2009). In addition, *Per2* expression was upregulated in murine NIH 3T3 fibroblasts and human hematopoietic leukemia cell lines by CCAAT/enhancer-binding proteins (C/EBPs) which include a family of transcription factors that regulate cell growth and differentiation (Gery *et al.* 2005). These data highlight the role of the circadian clock in regulating oncogenic mechanisms. A simplified model of circadian clock control of cell-growth regulation is shown in Figure 6-2.

Some studies have evaluated the role of clock genes specifically for breast cancer development (reviewed by Zubidat and Haim 2017). Studies that silenced *CLOCK* and *CRY2* genes in MCF-7

breast cancer cells and reported altered expression of a network of genes that are relevant for breast cancer including those involved in cellular growth and proliferation, cell signaling and interaction, tumor suppression, and DNA repair. In these same studies, *CLOCK* gene expression was lower in women without breast cancer while *CRY2* showed lower expression in breast cancer cells compared to normal cells. Another study also reported a link between *TIMELESS* overexpression and breast cancer risk. There was a significant positive association between breast cancer stage and *TIMELESS* promoter hypomethylation in peripheral blood lymphocytes taken from breast cancer patients compared to age-matched controls. In addition to breast cancer, *Per2*, *Cry1*, and *Cry2* were independently found as liver tumor suppressors (Lee *et al.* 2010, Kettner *et al.* 2016, Mteyrek *et al.* 2016, Mteyrek *et al.* 2017), and *Per2* and *Bmal1* had important roles as tumor suppressors in mouse models of lung adenocarcinoma (Papagiannakopoulos *et al.* 2016).

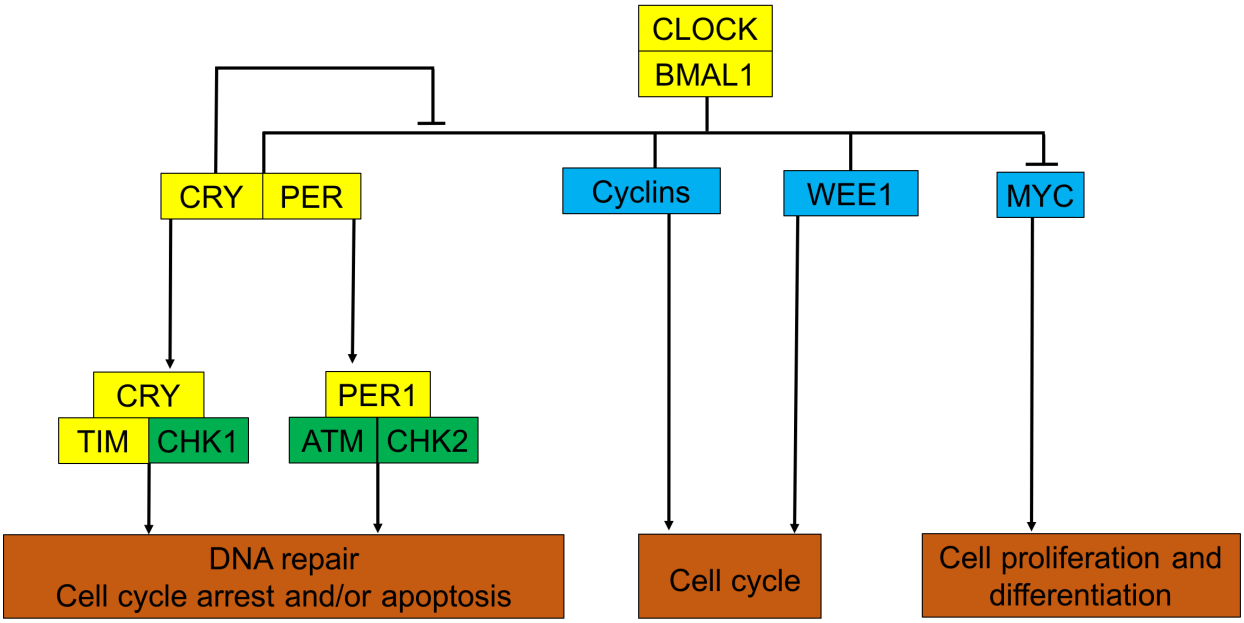

Figure 6-2. Circadian regulation of cell-cycle checkpoints and cell growth

Sources: Adapted from Takahashi *et al.* (2008) and Chen-Goodspeed and Lee (2007). The circadian clock controls cell growth by regulating expression of cell-cycle-related genes (e.g., *c-Myc, Wee1*, *Cyclin D1*) and interacting with cell-cycle checkpoint proteins (ATM, CHK1, CHK2). Transcription of these cell-cycle genes shows circadian rhythms, and they are direct targets of the CLOCK/BMAL1 complex. CLOCK/BMAl1 also initiates transcription of *Per* and *Cry* whose proteins combine to form a heterodimer that translocates to the nucleus and suppresses their own transcription by inhibiting CLOCK/BMAL1. In addition, the PER1 protein interacts with cell-cycle check-point proteins (ATM and CHK2) while CRY and TIMELESS (TIM) interact with CHK1 which can activate DNA damage-repair pathways and/or apoptosis and reset the phase of the circadian clock.

Cancer studies of simulated shift work, chronic jet lag, or LAN, and clock genes

Cancer studies of chronic jet lag in experimental animals have found similar effects of the role of clock genes in tumorigenesis as those observed in genetic models. A study in melatonin-deficient mice also demonstrated that simulation of chronic jet lag (8-hour advances in the light/dark cycle every 2 days) resulted in severe circadian disruption (i.e., ablated the rest-activity cycle, altered rhythms of body temperature, serum corticosterone, mPER1 protein expression in the SCN, suppressed *mPer2* and *mRev-erbα* mRNA in the liver and the tumor, and promoted growth of Glasgow osteosarcoma implants (Filipski *et al.* 2004). Filipski *et al.* (2005) reported that mice

subjected to a chronic jet lag protocol showed altered rhythms and reduced expression of clock genes in the liver of healthy mice and accelerated tumor growth in mice implanted with Glasgow osteosarcoma. The livers of otherwise healthy jet lagged mice showed increased *c-Myc* oncogene expression and amplified its rhythm while reducing expression of the tumor suppressor p53 by about 50%.

Polymorphisms in clock genes

Results from studies that investigated the association of clock gene single nucleotide polymorphisms (SNPs) in shift workers and breast cancer were mixed but reported some evidence that a few clock gene variants were associated with a greater risk of breast cancer (Monsees *et al.* 2012, Grundy *et al.* 2013b, Zienolddiny *et al.* 2013, Rabstein *et al.* 2014, Truong *et al.* 2014). A significant association with breast cancer risk was identified for 10 SNPs in five clock genes (*Clock*, *RorA*, *RorB*, *Per3*, and *Npas2*) in a recent comprehensive review that included 27 eligible studies, 38,231 cases, 96,756 subjects, and 687 SNPs in 14 clock genes (Benna *et al.* 2017). Reszka *et al.* (2017) reviewed results from 15 epidemiological studies (including 5 studies on shift work) that investigated the possible link between clock gene variants and breast cancer. These studies identified *BMAL1*, *BMAL2*, *CLOCK*, *NPAS2*, *CRY1*, *CRY2*, *PER1*, *PER3*, and *TIMELESS* as candidate breast cancer risk variants. SNPs in *CLOCK* and *NPAS2* were the most commonly reported variants modifying breast cancer risk.

Zhu *et al.* (2009) found that at least one SNP in nine core circadian genes was significantly associated with the risk of developing prostate cancer. Furthermore, risk estimates for four SNPs in three genes (*CLOCK*, *PER1*, and *PER3*) varied by disease aggressiveness. Markt *et al.* (2015) reported that a *CRY1* variant was nominally associated with fatal prostate cancer but did not find a strong and consistent association between clock gene variants and prostate cancer risk. Overall, the data suggest that polymorphisms in clock genes could affect susceptibility to shift work or LAN exposure.

6.3 Shift work and LAN studies: Key characteristics of carcinogens

This section presents evidence from human, animal, and/or relevant *in vitro* studies that shift work and LAN are associated with several biological effects that are commonly exhibited by established human carcinogens and/or other key events with a known connection to cancer. These effects have been shown to (1) alter DNA repair or cause genomic instability, (2) induce epigenetic alterations, (3) induce oxidative stress, (4), induce chronic inflammation and immunosuppression, (5) alter metabolism, and (6) alter hormone rhythms and signaling pathways, and are reviewed below.

6.3.1 DNA repair and genomic instability

There are limited data on the genotoxic effects of shift work or LAN in humans or experimental animals; however, the available data show that these exposures can contribute to DNA damage by altering DNA repair and promoting genomic instability. As discussed in Section 6.2, melatonin and the core clock genes have important roles in regulating cell-cycle control and DNA-damage repair.

Animal studies of simulated shift work/jet lag or LAN

Experimental animal studies support a link between exposure to simulated jet lag or LAN and inhibition of DNA repair, genomic instability, and mammary, liver, and colon cancer development. Rats exposed to shifting light schedules showed differential expression of 51 genes with a known link to breast cancer (Kochan *et al.* 2016) and downregulation of genes associated with DNA repair and p53 pathways that promote genomic instability in mammary tissues. Another study reported that simulated jet lag disrupted circadian expression of DNA damage response and repair genes in rats and accelerated mammary tumorigenesis (Fang *et al.* 2017). Chronic jet lag induced spontaneous hepatocellular carcinoma in wild type C57BL/6J mice by inducing persistent and genome-wide gene deregulation in the liver including genes involved in DNA repair, oxidative stress response, innate and adaptive inflammatory responses, and liver metabolism (see Sections 6.3.3, 6.3.4, and 6.3.5) (Kettner *et al.* 2016). The finding that p53-null mice developed tumors (e.g., lymphoma, osteosarcoma, liver, ovarian, kidney, and intestinal) under simulated chronic jet lag conditions provided genetic evidence, which supports a role for the p53 pathway in suppressing chronic circadian disruption-induced genomic instability caused by LAN (Lee *et al.* 2010).

In an initiation-promotion study, rats exposed to 1,2-dimethylhydrazine and held in constant light also had higher rates of DNA damage in colonic epithelial and enteric glial cells and increased development of colon preneoplasia compared to animals exposed to 1,2-dimethylhydrazine and maintained on a standard 12-hour light/dark cycle (Frajacomo *et al.* 2015).

Studies in shift workers

Two studies in humans provide evidence that night shift work is associated with decreased DNA repair and one study suggested that the effects may be related to melatonin. A study of 223 night shift workers and 217 day shift workers found that urinary clearance of 8-OH-dG was significantly lower among night shift workers during their day sleep periods compared to their night sleep periods on their first day off from work and were non-significantly lower than dayworkers suggesting that night work was associated with a reduced capacity to repair oxidative DNA damage. Among night shift workers, urinary levels of 6-sulfatoxymelatonin were positively correlated with clearance of 8-OH-dG (i.e., higher 6-sulfatoxymelatonin levels were associated with higher urinary 8-OH-dG levels) (Bhatti *et al.* 2016, 2017) An analysis of 50 night shift workers with the highest melatonin suppression (e.g., difference in melatonin level between night work and night sleep) had very reduced levels (20%) of urinary 8-OH-dG after night work compared to night sleep. Decreased sleep quality may also have contributed (see Section 6.4.2). Manzella *et al.* (2015) reported a 3-fold decrease in 8-oxoguanine DNA glycosylase (*OGG1*) gene expression in 60 rotating shift workers (with deregulation of clock genes) compared to 54 day shift workers in samples taken in the morning after a day off. *OGG1* is the primary gene in the DNA base excision repair pathway responsible for removal of oxidative damage. These authors also conducted *in vitro* studies with human dermal fibroblasts and reported that *OGG1* expression modulation depended on a correctly functioning molecular circadian clock that could be disrupted in shift workers.

Three studies reported some association between shift work and telomere length (Liang *et al.* 2011, Parks *et al.* 2011, Samulin Erdem *et al.* 2017a). A nested case-control study (699 cases, 895 controls) from the Norwegian Nurses cohort reported that persistent night work schedules

(e.g., working 4, 5, or 6 consecutive nights for > 5 years) was associated with decreased telomere length independent of case-control status and among breast cancer cases. Combined analysis of night shift work and telomere length found a decreased risk of breast cancer per one unit increase in telomere length among persistent night workers (high frequency and > 5 year duration) compared to dayworkers whereas no significant association was found with telomere length independent of shift work status (Samulin Erdem *et al.* 2017a). Liang *et al.* (2011) reported that among > 4,000 participants in the NHS, women with a longer history of rotating night shift work tended to have shorter telomeres; however, the trend between telomere length and duration of rotating shift work was not statistically significant although it appeared to be more pronounced for women younger than 50 years. Sleep duration was positively associated with telomere length among women younger than 50 years (see Section 6.4.2). Parks *et al.* (2011) reported that long-term work in multiple jobs, shift work, or work at night was associated with shorter relative telomere length in postmenopausal women; however, the effect was attenuated by covariate adjustment. Telomere shortening is generally associated with genomic instability and increased cancer risk.

Regulation of long interspersed element-1 (LINE1) activity is a potential mechanism for genomic instability associated with LAN or shift-work induced melatonin suppression (deHaro *et al.* 2014, Belancio 2015). LINE1 is an endogenous agent that can induce genomic instability via insertional mutagenesis and DNA double-strand breaks and is upregulated in many human tumors. Mobilization of LINE1 in cultured HeLa cells was inhibited by overexpression of the MT1 receptor (deHaro *et al.* 2014). This effect was abolished by addition of a melatonin receptor antagonist. This study also reported that *in situ* perfusion of PC3 human prostate cancer xenografts in nude rats with melatonin-rich human blood (but not melatonin-poor blood) also suppressed endogenous LINE1 mRNA. A receptor-mediated action of melatonin on LINE1 expression was further demonstrated when PC3 xenografts were perfused with human blood supplemented with exogenous melatonin or melatonin antagonist.

6.3.2 Epigenetic effects and gene expression

Almost all human cancers are characterized by vast genomic reprogramming and aberrant epigenetic modifications including DNA methylation and histone modifications that affect gene expression, and disrupted regulation of these epigenetic modifications actively contribute to cancer initiation and progression (Korkmaz and Reiter 2008, Korkmaz *et al.* 2009, Chi *et al.* 2010, Hardeland 2014, Masri *et al.* 2015, Salavaty 2015). The circadian clock is regulated at the epigenetic level and aberrant DNA methylation patterns have been detected in all core clock genes in many types of cancer (Joska *et al.* 2014, Masri *et al.* 2015). In addition to DNA methylation, chromatin remodeling has an important role in circadian regulation of gene expression (Doi *et al.* 2006, Masri *et al.* 2015). Chromatin remodeling involves a number of histone modifying enzymes (e.g., HATs, histone deacetylases, methyltransferases, demethylases and others) and occurs through post-translational modifications of the core histone proteins (Nakahata *et al.* 2008). The finding that CLOCK has intrinsic HAT activity confirms that chromatin remodeling is linked to circadian physiology (Doi *et al.* 2006, Masri *et al.* 2015). The activity of NAD^{+}-dependent deacetylases, sirtuin 1 (SIRT1) and sirtuin 6 (SIRT6), is regulated in a circadian manner and SIRT1 activity correlates with the rhythmic CLOCK-induced acetylation of BMAL1 (Nakahata *et al.* 2008, Masri *et al.* 2015). The data indicate that CLOCK and SIRT1 are associated during all times of the circadian cycle and contribute to histone acetylation

rhythms, regulate acetylation patterns as the promoters of clock-controlled genes, and regulate the deacetylation and degradation of *PER2*, a clock gene with tumor-suppressor activity (Asher *et al.* 2008, Nakahata *et al.* 2008, Zubidat and Haim 2017). SIRT1 appears to act as a tumor suppressor or a tumor promoter, depending on the biological system studied, while SIRT6 acts as a tumor suppressor and is an important regulator of aerobic glycolysis in cancer cells (Masri *et al.* 2015). These data suggest that chromatin remodeling is crucial for maintaining the core clock transcription/translation machinery and that the carcinogenic effects of circadian disruption may have an epigenetic basis (Doi *et al.* 2006, Salavaty 2015).

Rodent studies show that circadian transcription is coupled with rhythmic chromatin modifications including histone and non-histone protein acetylation, SIRT1 and SIRT6 deacetylation, and histone methylation (Masri *et al.* 2015). Mice entrained to a 12-hour light/dark cycle and sacrificed at various times show that transcriptional regulation of the core clock mechanism in mouse liver or vasculature is accompanied by rhythms in histone H3 acetylation and that the rhythmic conversion of transcriptionally permissive chromatin to facultative heterochromatin is dependent on the presence of functional BMAL1-CLOCK binding sites (Etchegaray *et al.* 2003, Curtis *et al.* 2004, Ripperger and Schibler 2006).

Animal studies of simulated jet lag or LAN

Rodents exposed to jet lag or LAN also showed evidence of epigenetic changes that are associated with cancer growth and development. Female rats exposed to simulated jet lag showed differential expression of 19 miRNAs in mammary tissue (Kochan *et al.* 2015). All but one of the 19 differentially expressed miRNAs play a role in breast cancer development and most had predicted circadian-relevant targets linked to breast cancer development. Another study reported that mice injected (subcutaneous in the left flank) with murine breast cancer cells and exposed to LAN (450 lux) for 30 minutes each night showed global DNA hypomethylation in tumors, reduced melatonin levels, and increased tumor growth compared to controls (Schwimmer *et al.* 2014). Treatment with exogenous melatonin reduced hypomethylation and tumor growth.

Studies in shift workers

There is some evidence that shift work is associated with epigenetic changes, with most studies reporting significant epigenetic effects. Importantly, the effects of methylation were observed in genes involved in inflammation and carcinogenicity, suggesting that epigenetic mechanisms are a potential link between shift work, circadian disruption, and cancer. However, the database is limited because only a few studies were conducted in independent populations or evaluated the same endpoints. Details of the scope of the database and study findings are reported below and in Table 6-3.

Ten studies conducted in six different study populations examined various epigenetic mechanisms in night shift and day workers. One study was a breast cancer case-control study and the remaining studies were cross-sectional analyses. Study populations were from Denmark (a general population cohort: Zhu *et al.* 2011, Jacobs *et al.* 2013, Shi *et al.* 2013, Liu *et al.* 2015), Norway (nurses: Samulin Erdem *et al.* 2017b), Italy (male chemical workers: Bollati *et al.* 2010), Poland (nurses and midwives: Peplonska *et al.* 2017, Reszka *et al.* 2018), and (presumably) from two different populations of health care providers in Seattle, Washington U.S.A. (Bhatti *et al.*

2015, Adams *et al.* 2017). The studies also varied in the molecular methods; some studies looked at genome-wide methylation patterns, while others looked at methylation in miRNA, or specific circadian, immune, or other genes.

Four studies, all conducted within the Danish Diet, Cancer and Health prospective cohort, investigated different aspects of epigenetic modifications in the same small subset of long-term shift workers. Long-term shift work was found to be associated (1) with altered epigenetic methylation patterns for *CLOCK* (decreased) and *CRY2* (increased) that were consistent with epigenetic changes in breast cancer patients as well as changes in global methylation (Zhu *et al.* 2011) and (2) with altered methylation patterns of imprinted genes which may increase cancer risk by inducing expression of normally silent alleles or repressing normally expressed alleles (Jacobs *et al.* 2013). Shi *et al.* (2013) and Liu *et al.* (2015) found that the promoter regions of several miRNAs were differentially methylated in shift workers including hypermethylation of miR-219 and miR-34b. The effect of miR-219 is to dampen cancer cell sensitivity to apoptosis; it affects many of the same immunological pathways as miR-34b. Inhibition of miR-34b reduces downstream p53 signaling and immunomediated tumor suppression, thus increasing cancer risk.

Two other studies specifically evaluated clock genes. Reszka *et al.* (2018) reported that PER1, PER2, and BMAL1 showed decreased methylation attributable to rotating-shift work among nurses and midwives but no effects were observed for other clock genes. Samulin Erdem *et al.* (2017b) found that among breast cancer cases, shift work was associated with changes in 5mC methylation levels at various CpG sites of the promoter region in *BMAL1* (increased), *PER1* (decreased), and *CRY1* (increased) but no effects were observed for other clock genes. In analyses of cases matched to controls with similar night shift work exposure, increases in the methylation index were observed for all three of these genes in cases compared to controls suggesting that epigenetic regulation of core clock genes may contribute to breast cancer in shift workers. However, it is unclear whether the patterns are due to night shift work, cancer progression, or a combination of these factors.

Additional findings regarding the effect of shift work on genes involved in immune function were reported by Bhatti *et al.* (2015). This study of Seattle health care workers looked at genome methylation and found that shift work was related to DNA methylation changes in a wide variety of genes, noting the largest changes were for clock genes and genes involved in immune function. In a presumably different population of health care workers in Seattle, Adams *et al*. (2017), using different molecular genome methylation techniques and types of analyses, reported non-statistically significant associations in BACH2 (immunosuppression in tumors), JRK (overexpressed in breast, colorectal, and ovarian cancers), and RPS6KA2 (downstream signaler of MAPK and putative tumor suppressor for ovarian cancer), but no association with other genes.

Bollati *et al.* (2010) found long-term shift work (but not ever-worked shift work) was inversely related to Alu, TNF-α, and IFN-γ methylation (hypomethylation). They also reported significant differences in TNF-α methylation between morning and evening type persons with morningness related to hypomethylation. Finally, Peplonska *et al.* (2017) limited their analysis to BRCA1 and BRCA2, and found no association between rotating night shift work and promoter methylation.

In summary, three of the four studies that evaluated genome-wide methylation found that methylation patterns significantly differ between night and day shift workers; the one study that did not report a significant association found non-statistically significant associations for two

genes involved in carcinogenicity. All three studies that evaluated promoter methylation in specific circadian clock genes reported that methylation patterns differed by shift work status. A study evaluating genome methylation also found evidence of an association between shift work and hypomethylation of genes involved in immune function. However, the type of methylation and the specific genes involved were not consistent across studies. Importantly, one of the studies evaluated clock gene expression in breast cancer cases, whereas the other two studies analyzed cancer-free subjects. Three studies provide evidence that night shift work is related to methylation in immune function-related genes. In general, methylation of other specific genes was only reported in a single study for each gene.

An experimental study reported that four days of simulated night shift work in healthy volunteers resulted in circadian disruption characterized by reduced amplitudes and overall misalignment of rhythmic transcripts with the shifted sleep/wake cycle (Kervezee *et al.* 2018). Approximately 3% of the transcriptome was either up-regulated or down-regulated in peripheral blood mononuclear cells. Functional analysis revealed that the key biological processes affected included suppression of natural killer (NK) cell-mediated immune response, down-regulation of JUN/AP1 pathway (an important regulator of cell proliferation, differentiation, and apoptosis), and up-regulation of several members of the signal transducer and activator of transcription (STAT) family (STAT1, STAT2, and STAT5A) that is involved in regulating defense mechanisms against viruses and tumors.

Table 6-3. Epigenetic effects of circadian disruption in shift workers

Reference Location	Population/exposure	DNA methylation	Results	Comments and gene effects
Bollati *et al.* 2010 Northern Italy	Chemical workers 100 backward rotating shift workers; 50 dayworkers Shift work duration (assessed by job seniority) **Shift work subpopulations** Chronotype: 35 morning; 25 evening Tolerance to shift work: 40 good; 35 poor	Global methylation: Alu and LINE-1 elements (repetitive elements) Specific genes: promoter of GCR, TNF-α, and IFN-γ	**Night shift work vs. day shift work** Ever shift work: no effect for global or specific genes Increasing shift work duration (trend): ↓ methylation (hypomethylation) of Alu and IFN-γ- and ↑ of GCR **Chronotype (evening and morning)** Significant differences in TNF-α methylation **Good vs. poor tolerance shift work** No differences	Selection of population restricted day and night workers to same production departments with same exposure to chemicals. Only one blood sample per subject instead of 24-hr pattern which might better assess if methylation changes are due to phase shifts vs. total increase or decrease. Genes: inflammatory and cancer-relevant pathways
Zhu *et al.* 2011 Denmark	Diet, Cancer and Health Cohort Long term shift workers ages 50–64 yr **Analyses** Specific genes: 19 shift workers; 98 day workers Genome-wide association study (GWAS): 10 age- and folate-intake matched night and day workers	Specific genes *CLOCK* promoter hypomethylation *CRY2* promoter hypermethylation Genome wide methylation changes Pathway analysis of genes with altered methylation patterns	**Night shift work vs. dayworkers** *Specific genes* ↓ *CLOCK* methylation ↑ CRY2 methylation *GWAS* Significant changes across 4,752 genes 66.4% hypermethylated 33.6% hypomethylated	*CLOCK* and *CRY2* patterns are consistent with epigenetic changes in breast cancer patients. **Pathway analysis** Prominent role for DNA replication, recombination, repair, gene expression, behavior with ESR1

Reference Location	Population/exposure	DNA methylation	Results	Comments and gene effects
Jacobs *et al.* 2013 Denmark	Same 10 night and day shift worker pair from Diet, Cancer and Health Cohort	397 CpG sites in promoter regions of 56 imprinted genes	**Night shift work vs. dayworkers** *Significant changes in 26 imprinted genes* ↑ methylation: 5.04% CpG sites ↓ methylation: 7.56% CpG sites Hypermethylation: DLX5 and IGF2AS Hypomethylation of TP73	
Shi *et al.* 2013 Denmark	Same 10 pairs of subjects as the subset from Zhu *et al.* 2011, Diet, Cancer and Health Cohort	Promoter regions of specific miRNA precursors, including circadian-relevant miR-219 promoter	**Night vs. day workers** *miRNA methylation* 50 CpG loci of 31 miRNAs, including miR-219. Hypermethylated: 48 CpG loci of 29 miRNAs Hypomethylated: 2 loci of 2 miRNAs **miR-219 over-expressed MCF-7 breast adenocarcinoma cell model** 319 mRNAs differentially expressed transcripts	Hypermethylation of miR-219 may dampen cancer cell proliferation and sensitivity to apoptosis miR-219 affects many of the same immunological pathways as miR-34b **Pathway analysis** Immunomediated antitumor activity (antimicrobial response, inflammatory response, infectious disease, cell growth, and apoptosis)
Liu *et al.* 2015 Denmark	Same 10 pairs of subjects as the subset from Zhu *et al.* 2011, Diet, Cancer and Health Cohort	miR-34b promoter hypermethylation	**Night shift work vs. dayworkers** ↑ miR-34b promoter methylation at a CpG site **Transfection of the miR-34b mimic in an MCF-7 breast cancer cell line** Differential expression of 230 mRNA transcripts	**Pathway analysis** Interferon-mediated antiviral response and apoptotic and antiproliferative gene networks including inflammatory response, immunological disease, gene expression, cell signaling and cellular development, cell cycle, cell death, and cancer

Reference Location	Population/exposure	DNA methylation	Results	Comments and gene effects
Bhatti *et al.* 2015 Seattle, USA	Seattle metro healthcare workers Cross sectional study Men and women aged 20–40 yr 65 day workers and 59 night shift workers	Genome wide methylation patterns	**Night shift work vs. dayworkers** ↓ average methylation in each significant locus, gene, CpG island, or gene region Statistically significant differences at 16,135 loci, 3,769 genes, 7,173 CpG islands, and 5,508 gene regions Hypomethylated patterns: 21 loci in the core circadian genes; largest differences in *PER3* and *CSNK1ε*	Genes include clock genes and genes involved in immune function and host defense Limited cumulative years of night shift work and type of rotations
Adams *et al.* 2017 Seattle, USA	Seattle metro healthcare workers Cross-sectional study **Types of shift** 86 day workers and 111 night shift workers, premenopausal women 20–49 yr of age **Chronotype** 110 female night shift workers and 131 male night workers	Genome-wide DNA methylation	**Night shift work vs. dayworkers** No statistically significant associations Suggestive associations in some genes with links to cancer: *BACH2, JRK* **Chronotype among night shift workers** No statistically significant associations Suggestive associations in some genes with links to cancer: *RPS6KA2*	Genes: *BACH2* (immunosuppression in tumors) *JRK* (overexpressed in breast, colorectal, and ovarian cancers) *RPS6KA2* (downstream signaler of MAPK pathway and putative tumor suppressor for ovarian cancer) Underpowered to detect low to moderate effects This study used different molecular methods and statistical analyses than Bhatti *et al.* 2015 study

Reference Location	Population/exposure	DNA methylation	Results	Comments and gene effects
Samulin Erdem *et al.* 2017b Norway	Norwegian Nurses Nested case-control study 278 breast cancer cases; 280 matched controls matched on type of night shift work exposure Night shift work categories: none, low, medium, high	5mC methylation levels at CpG sites of the promoter region in five circadian genes *CLOCK*, *BMAL1*, *CRY1, PER1* and *PER2*	**Breast cancer cases vs. controls matched for shift category** ↑ methylation index in *CLOCK, BMAL1*, *CRY1,* and *PER1* for medium exposure to shift work No significant effects for other night work exposure categories **Case-case analysis: Referent day workers** ↓ *CRY1*: ever, low, and high exposure ↑ *BMAL1* and *PER1:* medium exposure **Control analyses** No differences	Study limitations include sample collection time, and DNA source (saliva vs. blood) 0/19 polymorphisms in the 5 circadian genes had an effect on the methylation levels of the respective genes No association between methylation levels of 5 core circadian genes and estrogen and progesterone receptors status of the tumor in cases
Peplonska *et al.* 2017 Lodz, Poland,	Nurses and midwives Cross-section study Fast forward rotating shift workers ages 40–60 yr 347 night shift workers; 363 day workers	BRCA1 and BRCA2 promoter methylation-methylated vs. unmethylated	**OR (95% CI) for methylation status** > 20 yr night work *BRCA1*: 1.04 (0.66–1.64) *BRCA2:* 1.02 (0.64–1.64)	Limited to analysis of two genes Used only one blood sample Positive association found between methylation status of BRCA1 and current smoking, which is inconsistent with two other similar studies
Reszka *et al.* 2018 Poland.	Nurses and midwives working 347 rotating night shift workers and 363 day workers Current and lifetime rotating shift work Same population as Peplonska *et al.* 2017	CpG promoter methylation in circadian genes *PER1, PER2, PER3, CRY1, CRY2, BMAL1, CLOCK, NPAS2*	**Night shift work vs. day shift work** ↓ *PER2* Current night shift work More frequent vs. less frequent Longer vs. shorter lifetime duration (non-significant) ↓ *PER1* Longer vs. shorter lifetime duration ↓ *BMAL1* hypomethylation > 10 years shift work	Isolation of genomic DNA from whole blood with various proportions of leukocytes could have an impact on DNA-based epigenetic status, as authors did not analyze the mix of leukocytes, nor control for it

6.3.3 Oxidative stress

Levels of pro- and antioxidant markers show circadian rhythms in humans and experimental animals, thus disruption of these daily rhythms could affect sensitivity to oxidative stress and increase oxidative damage (Faraut *et al.* 2013). Simulated jet lag and LAN exposure studies in mice, as well as studies of shift workers, report evidence of a direct association of diminished melatonin and oxidative stress.

Animal studies of simulated jet lag or LAN

Two simulated jet lag studies and three LAN exposure studies reported evidence of oxidative stress in rodents. Kishi and Sunagawa (2011) reported that experimental jet lag in wild type and hypertensive rats increased blood pressure and SNS activity via oxidative stress. Kettner *et al.* (2016) reported that simulated chronic jet lag induced SNS dysfunction and global gene deregulation in livers of C57BL6J mice including global overexpression of prooxidant stress genes and suppression of antioxidant genes. 8-OH-dG levels were significantly higher in lung tissues but not the liver of nude mice injected with HeLa or PC3 cells and exposed to constant light compared to mice held in a normal 12-hour light/dark cycle (Yasuniwa *et al.* 2010). Oxidative stress was associated with enhanced expression of WNT10A signaling, hypervascularization in tumors, and increased tumor growth. In the other two studies, LAN exposure induced a clear increase in pulmonary superoxide dismutase (SOD) expression and significantly reduced serum total antioxidant status in rats (Benot *et al.* 1998, Temneanu *et al.* 2012). Serum total antioxidant status paralleled the 24-hour melatonin cycle and administration of exogenous melatonin increased the total antioxidant status (Benot *et al.* 1998).

Studies in shift workers

Over 9 studies provide moderate evidence of oxidative stress in shift workers. These include studies that measured 8-OH-dG levels in urine samples (Ishihara *et al.* 2008, Bhatti *et al.* 2016, 2017); oxidative stress indices in blood (ratio of total oxidant status to total anti-oxidant status) (Buyukhatipoglu *et al.* 2010, Ulas *et al.* 2012), malondialdehyde and SOD levels in red blood cells (Casado *et al.* 2008, Casado *et al.* 2011), malondialdehyde and/or glutathione reductase activity in blood serum (Kulikov *et al.* 2007, Muhammad and Qadir 2017), 8-isoprostane in urine (Nagata *et al.* 2017); and total plasma antioxidant capacity (Sharifian *et al.* 2005). Melatonin suppression, as measured by urinary excretion of 6-sulfatoxymelatonin, was directly associated with increased markers of oxidative damage in shift workers (Bhatti *et al.* 2016, 2017). Melatonin is a known antioxidant (see Section 6.2) that acts as a potent free radical scavenger, antioxidant enzyme promotor (e.g., SOD, glutathione peroxidase, glutathione reductase), and prooxidant enzyme inhibitor (e.g., lipoxygenases and nitric oxide synthase) (Reiter 2001, Reiter *et al.* 2001, Colín-González *et al.* 2015). Gromadzinska *et al.* (2013) reported clear evidence of oxidative stress in premenopausal nurses working night shifts but not for postmenopausal night shift nurses based on red blood cell glutathione peroxidase (GSH-Px) activity compared to day shift nurses. Significantly lower levels of vitamins A and E were found in premenopausal women working night shifts but, overall, no associations were reported between shift work and SOD, thiobarbituric acid reactive substances (TBARs), or plasma selenium levels.

6.3.4 Chronic inflammation and immunosuppression

The immune system and the circadian system are interconnected at multiple levels (i.e., neural, humoral, and systemic) (Habbal and Al-Jabri 2009, Cermakian *et al.* 2014). Many immune cell types (e.g., T and B lymphocytes, monocytes, macrophages, natural killer (NK) cells, neutrophils, eosinophils), cytokines, and other immune and inflammatory biomarkers show circadian rhythms in cell number or expression level (Haus and Smolensky 1999, Faraut *et al.* 2013, Scheiermann *et al.* 2013, Cermakian *et al.* 2014, Geiger *et al.* 2015). Thus, it is not surprising that studies of experimental animals exposed to simulated jet lag or LAN and studies of shift workers have reported evidence of altered immune and inflammatory responses. These studies are reviewed below. Other factors that may affect immune and inflammatory responses include sunlight exposure and vitamin D, sleep deprivation, and meal timing and are discussed in Section 6.4.

Animal studies of simulated jet lag or LAN

Rodents subjected to various chronic jet lag protocols showed evidence of circadian disruption and altered immune and inflammatory responses in 5 studies (Castanon-Cervantes *et al.* 2010, Wu *et al.* 2010, Logan *et al.* 2012, Guerrero-Vargas *et al.* 2015, Kettner *et al.* 2016). Logan *et al.* (2012) reported that suppressed circadian expression of NK cell cytolytic activity was associated with increased growth of tumors following i.v. injection of MADB106 mammary adenocarcinoma cells in phase-shifted rats. Two studies reported an increased release of pro-inflammatory cytokines following lipopolysaccharide (LPS) challenge (Castanon-Cervantes *et al.* 2010, Guerrero-Vargas *et al.* 2015). Furthermore, the altered innate immune response was not due to sleep loss or stress in phase-shifted mice; however, the effects of simulated shift work on the inflammatory response was prevented when food was not available during the working schedule suggesting that mistimed food consumption contributes to the inflammatory response (Guerrero-Vargas *et al.* 2015). Kettner *et al.* (2016) reported that chronic jet lag induced deregulation of both innate and adaptive inflammatory responses in C57BL6J mice and dramatically accelerated pathophysiological progression in the liver. Another study found that simulated jet lag changed the rhythmic profiles of peripheral lymphocytes and T helper cells in the spleen and increased plasma IL-6 levels in mice (Wu *et al.* 2010).

Three studies in Siberian hamsters reported that continuous dim LAN (5 lux) or a light pulse at night impaired cell-mediated immunity, as evidenced by suppressed delayed type hypersensitivity following dermal application of 2,4-dinitro-1-fluorobenzene (Bedrosian *et al.* 2011, Prendergast *et al.* 2013, Aubrecht *et al.* 2014). Bedrosian *et al.* (2011) also reported a reduced bactericidal activity in blood after LPS treatment and Prendergast *et al.* (2013) reported that a functional central clock was required to generate circadian rhythms in leukocyte trafficking and for driving peripheral clocks in secondary lymphoid organs. Although pinealectomy did not affect circadian rhythms in leukocyte trafficking, melatonin was necessary to convey circadian time information to the spleen clock genes. These studies demonstrate that a functional circadian system is critical for maintaining optimal immunosurveillance and T-cell-dependent immune responses.

Studies in shift workers

Human studies are generally consistent with the studies in rodents, which also show evidence that circadian disruption can affect the immune system and inflammatory response. Six studies reported that night shift, or rotating shift work, is associated with altered cytokine (e.g., Il-2, IL-6, TNF-α, IFN-γ) rhythms or levels and inflammatory responses in the blood compared to day shift workers (Zheng *et al.* 2006, Burgueño *et al.* 2010, Khosro *et al.* 2011, Puttonen *et al.* 2011, Cuesta *et al.* 2016, Muhammad and Qadir 2017). In contrast, three studies did not report evidence of altered cytokine levels in shift workers (Copertaro *et al.* 2010, van Mark *et al.* 2010, Copertaro *et al.* 2011). Four studies also reported evidence that shift work increased C-reactive protein levels (a marker of inflammation that is associated with increased risk of cancer, cardiovascular disease, and other inflammation-related disorders) (Zheng *et al.* 2006, Khosro *et al.* 2011, Puttonen *et al.* 2011, Kim *et al.* 2016).

Two studies reported evidence of lower NK cell activity in nurses or emergency room physicians performing shift work (Okamoto *et al.* 2008, Nagai *et al.* 2011). The effects on NK cell activity in both these studies were related to the degree of fatigue. NK cells are part of the innate immune system and low NK activity has been associated with increased tumor growth in humans and laboratory animals (Logan *et al.* 2012). However, two studies of nurses did not report evidence of suppressed NK cell function in shift workers compared to day workers at baseline or after one year of follow-up (Copertaro *et al.* 2010, Copertaro *et al.* 2011). Some epigenetic studies reported an association between night shift work and altered methylation of genes involved in immune function (see Section 6.3.2)

Nine studies reported that shift workers had elevated counts of various immune cells (e.g., white blood cells, lymphocytes, leukocytes, neutrophils, monocytes) (Nakano *et al.* 1982, Nishitani and Sakakibara 2007, Sookoian *et al.* 2007, Khosro *et al.* 2011, Nagai *et al.* 2011, Puttonen *et al.* 2011, Kim *et al.* 2016, Lu *et al.* 2016, Wirth *et al.* 2017). In contrast, a recent study that included almost 8,500 participants, including 1,779 shift workers, in the National Health and Nutrition Examination Survey (2005 to 2010) found no association between self-reported current shift work and leukocyte counts (Buss *et al.* 2018).

Overall, the data show that shift work may contribute to inflammation and an altered immune response; however, as evidenced by some negative studies, these exposures may not always trigger an immune or inflammatory response. The circadian phase alterations in immune cell and cytokine levels are potential confounding factors in most of these studies because the day workers and shift workers often have different circadian patterns when measured at the same time point and must be interpreted with caution (Faraut *et al.* 2013).

6.3.5 Metabolic alterations

Experimental animal studies provide evidence that LAN induces metabolic disturbances via circadian disruption and promotes the formation and growth of spontaneous tumors, xenografts, or chemically induced tumors (Blask *et al.* 2005, Vinogradova *et al.* 2009, Blask *et al.* 2014, Dauchy *et al.* 2014, Guerrero-Vargas *et al.* 2017). The underlying mechanisms associated with enhanced tumor growth in experimental studies include LAN-induced melatonin suppression and circadian disruption leading to hyperglycemia, hyperinsulinemia, runaway aerobic glycolysis (Warburg effect), altered lipid signaling, and increased proliferative activity (Blask *et al.* 2005,

Dauchy *et al.* 2009a, Blask *et al.* 2014, Dauchy *et al.* 2014, Mao *et al.* 2016a, Guerrero-Vargas *et al.* 2017). Impaired glucose and lipid metabolism, metabolic syndrome, weight gain, altered food intake and activity rhythms, disrupted liver transcriptome rhythms, and altered rhythms of metabolically active hormones have been reported in rodents exposed to continuous light, non-24-hour light schedules, dim LAN, and simulated shift work or jet lag (Vinogradova *et al.* 2009, Arble *et al.* 2010, Fonken *et al.* 2013a, Fonken *et al.* 2013b, Fonken and Nelson 2014). In addition, studies of rats exposed to blue-enriched light during the daytime reported that tumor cAMP levels, linoleic acid uptake and metabolism, growth signaling pathways, and aerobic glycolysis (Warburg effect) were markedly downregulated compared to rats exposed to broad-spectrum cool white fluorescent lighting during the day, thus suggesting that exposure to daytime blue light also affects tumor metabolic signaling and proliferative activities (Dauchy *et al.* 2015, Dauchy *et al.* 2018). Kettner *et al.* (2016) also reported that chronic jet lag is an independent risk factor for spontaneous hepatocellular carcinoma in wild-type C57BL6J mice. The reported mechanism involved jet lag-induced global dysregulation of liver metabolic function leading to non-alcoholic fatty liver disease and promotion of the Warburg effect. Together with chronic jet lag-induced oncogenic activation, immune suppression, and loss of control in DNA surveillance and cell proliferation, the persistent liver metabolic circadian dysfunction provides one of the key pathophysiological mechanisms that drives progression from non-alcoholic fatty liver disease to steatohepatitis, fibrosis, and eventually hepatocellular carcinoma. The importance of the circadian system in maintaining metabolic homeostasis is further supported by clock gene mutant mouse models (Rudic *et al.* 2004, Turek *et al.* 2005, Fonken and Nelson 2014, Kettner *et al.* 2015, Kettner *et al.* 2016). These studies show that clock gene mutants are susceptible to obesity, metabolic syndrome, impaired glucose tolerance and regulation, diabetic-like phenotype, defective insulin production, altered endocrine signaling, and an altered feeding rhythm (Fonken and Nelson 2014).

Obesity, metabolic syndrome, and other metabolic disorders such as type 2 diabetes are recognized risk factors for some cancers and are often associated with long-term shift work and circadian disruption in humans (De Bacquer *et al.* 2009, Pan *et al.* 2011, Wang *et al.* 2011, Guo *et al.* 2013, Ika *et al.* 2013, Renehan *et al.* 2015, Arnold *et al.* 2016, Zubidat and Haim 2017). Guo *et al.* (2013) reported evidence that shift work was an independent risk factor for diabetes and that the risk significantly increased with a duration of shift work of at least 10 years. Thus, the evidence suggests that circadian disruption in humans may contribute to cancer by altering metabolism and increasing risk of metabolic disease and obesity.

6.3.6 Sex hormone rhythms and signaling pathways

LAN-induced melatonin suppression and circadian disruption also affects sex hormone rhythms by influencing the hypothalamic-pituitary-gonadal axis (Mirick and Davis 2008). Evidence from animal and clinical studies show that melatonin inhibits the release of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), testosterone, and estrogen. Studies in nocturnal rodents or rodent cells also show that melatonin inhibits prolactin secretion (Dubocovich *et al.* 2003, Dubocovich and Markowska 2005, Ogura-Ochi *et al.* 2017); however, in humans the melatonin and prolactin rhythms are in phase (Goel *et al.* 2009). A study using cultured primary pituitary cells from female baboons reported that melatonin increased prolactin release in a dose- and time-dependent fashion (Ibáñez-Costa *et al.* 2015).

Animal studies of exposure to LAN

Various LAN protocols induced or promoted tumor growth in rodents (see Section 5). Several of these studies reported that constant dim light or LAN also affects hormone levels and rhythms. Rats exposed to constant dim light or LAN had lower nocturnal excretion of 6-sulfatoxymelatonin and higher levels of serum estradiol compared to animals maintained on a 12:12 light-dark cycle (Cos *et al.* 2006). As mentioned in Section 6.1.2, the increased sensitivity to DMBA-induced mammary tumors in female mice exposed to LAN from birth was attributed in part to increased circulating levels of prolactin (Mhatre *et al.* 1984, Shah *et al.* 1984). Other studies show that rodents exposed to LAN had significantly accelerated age-related disturbances in estrous function and rhythm (Anisimov *et al.* 2004, Prata Lima *et al.* 2004, Vinogradova and Chernova 2006, Popovich *et al.* 2013). These disturbances in estrous function were followed by hyperplastic processes in the mammary gland, ovaries, and uterus and support the hypothesis that circadian and endocrine disruption induced by LAN is involved in development and growth of hormone-responsive tumors.

Studies in shift workers

Epidemiological studies of LAN and shift work (Section 3) indicate the strongest statistically significant associations of night work with hormone receptor-positive (ER+, PR+, and/or HER+) breast cancer (Grundy *et al.* 2013b, Lie *et al.* 2013, Papantoniou *et al.* 2015a, Wang *et al.* 2015a, Cordina-Duverger *et al.* 2016, Vistisen *et al.* 2017, Wegrzyn *et al.* 2017). LAN and/or shift work exposure studies in humans and experimental animals (discussed below) also show effects on sex hormones (i.e., estrogens, progesterone, prolactin, testosterone), some of which are known risk factors for breast and prostate cancer and are summarized in Table 6-4a,b,c,d. Some of these effects could be mediated by melatonin-induced changes in hormone levels (see Section 6.2).

Overall, the available studies provide consistent evidence that night shift work is associated with elevated estrogen levels. Six published studies of independent populations reported higher levels of various estrogen metabolites in night shift workers compared to day workers (Schernhammer *et al.* 2004, for postmenopausal women in NHS, Nagata *et al.* 2008, Bracci *et al.* 2013, Bracci *et al.* 2014, Gómez-Acebo *et al.* 2015, Papantoniou *et al.* 2015c, Peplonska *et al.* 2016) although findings were not statistically significant in the Spanish study of permanent workers (Papantoniou *et al.* 2015a). Positive findings were found in both reports of the study of workers from Northern Italy (Bracci *et al.* 2013, Bracci *et al.* 2014; however, it is not clear if these populations overlap.) Although a study of Seattle health care workers found similar estrone conjugates in night shift workers as in day workers, in an analysis within night shift workers, estrone conjugates were higher after night work or day time sleep compared to night sleep on a day off (Davis *et al.* 2012) (see Table 6-4a). No clear patterns were observed between estrogens and the number of night shifts worked in the two weeks before sample collection among premenopausal women in the NH2 study; however, only 14 women worked greater than 1 night (Schernhammer *et al.* 2004). Three studies suggested a relationship between estradiol levels and persistent night shift work. The highest estradiol levels were reported among women working night shifts for the longest number of years (Schernhammer *et al.* 2004 [estradiol in all fractions in postmenopausal women], Langley *et al.* 2012 and Peplonska *et al.* 2012) although findings were no longer significant in the study by Langley *et al.* (2012) in the adjusted analysis (P = 0.11). Comparability of these studies, however, is limited by differences across studies in shift

schedules, control of confounders, sample size, specific estrogen metabolite measured, and sampling protocols, including timing of sampling after shifts and during the menstrual cycle.

There is little evidence that estrogens levels are related to urinary melatonin levels. The NHS II study found a significant inverse association of urinary melatonin levels with estradiol among a sample of 80 premenopausal women using the average of 3 urinary measurements (Schernhammer *et al.* 2004); however, the evidence was weaker in a later study of a larger sample of premenopausal women (including the 80 from the 2004 study) based on 1 urinary measurement performed on the follicular phase sample ($P = 0.07$) (Schernhammer *et al.* 2006a). No association was found between melatonin levels in studies from Italy, Spain, Canada, and Japan (See Table 6-4a).

Table 6-4a. Studies of estrogens in night shift workers

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Bracci *et al.* 2013 Northern Italy	National Health Service: nurses with ≥ 2 yr shift work Premenopausal women 31 rotating NSW; 31 DSW	Serum 17β-estradiol from fasting blood End of night or beginning of morning shift	⬆17β-estradiol levels NSW vs. DSW (ns) NSW without nap vs. NSW with nap NSW without nap vs. DSW Similar 17β-estradiol levels NSW with nap vs. DSW No significant association of 17β-estradiol levels with clock gene expression or aMT6s
Bracci *et al.* 2014 Northern Italy	National Health Service; nurses with ≥ 2 yr of shift work 60 rotating NSW; 56 DSW	Serum 17β-estradiol from fasting blood Start of morning shift after a regular night's sleep on a day off	⬆17β-estradiol levels NSW vs. DSW Morning chronotype Correlations Chronotype score: positive ($P = 0.011$) Clock gene expression: negative Urinary aMT6s: null
Davis *et al.* 2012 Seattle, WA	Seattle female health care workers, ages 20–49; ≥ 20 hr/week at night or days 172 NSW; 151 DSW	Urinary estrone conjugates (E1C) NSW: Nighttime sleep on day off, daytime sleep after 1 shift, and night work after ≥ 2 consecutive night shifts, DSW: Night time sleep after ≥ 1-day shift	⬆ E1C within NSW Night work vs. night sleep Day sleep vs. night sleep Similar level: NSW vs. DSW Night sleep, night work, or day sleep (NSW)
Gómez-Acebo *et al.* 2015 Spain	Female health care workers or teachers ages 20–65 yr 63 rotating NSW; 73 DSW	Serum estradiol Start of morning day shift or end of night shift Urinary aMT6s over 24 hours	⬆ Estradiol levels NSW vs. DSW, both pre- and post-menopausal combined; pre-menopausal in adjusted analyses for menstrual cycle phase, and for women in follicular phase No association of plasma sex hormones with urinary aMT6s (data not shown)

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Langley *et al.* 2012 Canada	82 premenopausal nurses; rotating NSW (DD, NN, 5 days off)	Serum estradiol and estrone, and urinary aMT6s Start of a day shift in summer and in winter	⬆ Estrone levels Greater than 20 years NSW: but non-significant after adjustment (*P = 0.11*) Estradiol levels No significant association with NSW in adjusted analysis Significant association between urinary aMT6s and estradiol in the winter but no longer significant in adjusted analysis
Nagata *et al.* 2008 Japan	206 postmenopausal women in general breast cancer screening population Ever or never worked grave yard shift assessed by questionnaire 3 years 7 NSW; 170 DSW	Serum estradiol and estrone Urinary aMT6s Blood sampled at 2:00 PM on day of interview; first-void urine collected next day	⬆ Estrone Ever NSW vs. DSW ($P = 0.006$) Years working NSW ($P = 0.03$) Worked NSW within past 3 years ⬆ Estradiol Ever NW vs. DSW ($P = 0.11$) Worked NSW within past 3 years No correlation of estrogen levels with urinary aMT6s levels (only 7 NSW)
Papantoniou *et al.* 2015c Spain	Male and female workers from hospitals (56, mainly women), car and train companies (61, mainly men), ages 22–64 yr 75 permanent NSW; 42 DSW	Urinary estradiol, estrone, and estriol Sampled from all voids in 24-hr working day or night Cosinor analysis used to evaluate hormone rhythms	NSW vs. DSW (ns) ⬆ Total estrogens: premenopausal ⬆ Estrone: full population ⬆ Estradiol: full population No correlation of estrogen with urinary aMT6s levels
Peplonska *et al.* 2016 Poland	Polish nurses and midwives, 40–60 years of age Pre- and post-menopausal 263 fast rotating NSW; 269 DSW	Plasma estradiol (E2) Start of morning shift or at end of night shift	⬆ Estradiol (E2) postmenopausal women NSW duration: 15–25 yr or > 25 yr vs. ≤ 5 NSW ⬆ with increasing years of night work in postmenopausal women ($P_{trend} = 0.051$) ⬆ Estradiol in morning chronotype: NSW vs. DSW Ever NSW ($P < 0.05$) Higher frequency NSW ($P_{trend} = 0.082$) Longer duration NSW ($P_{trend} < 0.001$)

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Schernhammer *et al.* 2004, Schernhammer *et al.* 2006a U.S.A.	Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) 2004: 663 postmenopausal nurses from NHS and 80 NHS II primarily pre-menopausal nurses (ages from NHS II; 18% reported night work in the two weeks prior to urine collection 2006: 459 rotating NSW from NHS II, primarily pre-menopausal nurses (ages 33 –50), includes 80 nurses from 2004 study	Estrogens 2004: Plasma estradiol as three fractions (total, free, bioavailable) and estrone, and estrone sulfate 2006: Plasma estradiol, estrone sulfate, and estrone collected in follicular and luteal phase Urinary aMT6s (premenopausal women) 2004: Luteal phase first spot morning urine; 3 samples) 2006: Luteal or follicular phase; 1 sample	663 postmenopausal women (2004) ⬆ Estradiol (total, free, and bioavailable) Longer NW durations (≥ 15 yr) vs. never night work Significant trend with increasing duration all 3 estradiol fractions No association with estrone or estrone sulfate 80 premenopausal women (2004) and number of nights worked in last 2 weeks No clear or significant trends with estradiol, estrone, or estrone sulfate levels; analyses limited by small numbers of nurses who worked > 1 night. Significant inverse association of urinary melatonin levels with bioavailable estradiol but not other fractions, estrone, or estrone sulfate; attenuated with adjustment for age and BMI 459 premenopausal women (2006) Estradiol inversely related to urinary aMT6s for follicular phase *(P* = 0.07) No clear association of urinary aMT6s with estrone or estrone sulfate

aMT6s = 6-sulfatoxymelatonin; D = day; DSW = day worker; E1C = estrone conjugate; N = night; ns = not significant; NSW = night worker.

There is some evidence that progestogens are associated with night shift work. Two studies reported higher progesterone levels or total progestogens in night in shift workers compared to day workers (Gómez-Acebo *et al.* 2015, Papantoniou *et al.* 2015c). However, no clear association was found between night shift work and progestogen levels for pre-menopausal or post-menopausal women in the Nurse Health Studies (Schernhammer *et al.* 2004) (see Table 6-4b). In an analysis restricted to rotating night shift workers, Langley *et al.* (2012) found higher progesterone levels among women with long-term night shift work; however, the findings were no longer significant in adjusted analysis.

The NHS II study found a significant positive association of urinary melatonin levels with progesterone among premenopausal women in the 2004 publication (Schernhammer *et al)* but not in the 2006 publication. None of the three remaining studies found a correlation with urinary melatonin levels.

Table 6-4b. Studies of progestogens in night shift workers

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Gómez-Acebo *et al.* 2015 Spain	Female health care workers or teachers ages 20–65 yr 63 rotating NSW; 73 DSW	Serum progesterone Start of a day shift in summer and in winter Urinary aMT6s over 24 hours	↑ Progesterone NSW vs. DSW in adjusted analysis; estimate attenuated somewhat ($P = 0.059$) when other hormones were added to the model. No association of plasma sex hormones with 24-hr urinary aMT6s (data not shown)
Langley *et al.* 2012 Canada	82 premenopausal nurses; rotating NSW (DD, NN, 5 days off)	Serum progesterone Start of a day shift in summer and in winter	↑ progesterone ≥ 20 yr NSW in unadjusted analysis but no association as observed in adjusted analysis ($P = 0.79$) No correlation with urinary aMT6s levels
Papantoniou *et al.* 2015c Spain	Male and female workers from hospitals (56, mainly women), car and train companies (61, mainly men), ages 22–64 yr 75 permanent NSW; 42 DSW	Urinary progestogens (pregnanediol, pregnanetriol, and 16-androstenol) Sampled from all voids in 24-hr working day or night Cosinor analysis used to evaluate hormone rhythms	NSW vs. DSW (significant findings in adjusted analysis) ↑ Total progestogens: Overall and pre-menopausal ↑ Pregnanediol: Overall and pre-menopausal ↑ 16-androstenol: Pre-menopausal ↑ Pregnanetriol: Overall No correlation of progestogens with urinary aMT6s levels
Schernhammer *et al.* 2004, Schernhammer *et al.* 2006a U.S.A.	Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) 2004: 663 postmenopausal nurses from NHS and 80 NHS II primarily pre-menopausal nurses (ages from NHS II; 18% reported night work in the two weeks prior to urine collection 2006: 459 rotating NSW from NHS II, primarily pre-menopausal nurses (ages 33–50), includes 80 nurses from 2004 study	Plasma progesterone; follicular and luteal phase (2006) Urinary aMT6s (premenopausal women) 2004: Luteal phase first spot morning urine; 3 samples) 2006: Luteal or follicular phase; 1 sample	663 postmenopausal women (2004) No association with NSW duration 80 premenopausal women (2004) ↑ progesterone level in NSW > 1 night in the last 2 weeks higher than those working 0 nights but no clear trend with # of nights worked ($P = 0.14$) Significant positive correlation between urinary aMT6s and progesterone, attenuated with adjustment for age and current BMI 459 premenopausal women (2006) No clear correlation between progesterone measured in the luteal samples

aMT6s = 6-sulfatoxymelatonin; DSW = day shift worker; ns = not significant; NSW = night shift worker.

Overall, there is no evidence of an association with prolactin levels and night shift work. Three studies comparing prolactin levels in night shift workers and day workers reported no relationship between night work and prolactin levels (Schernhammer *et al.* 2004, Korompeli *et al.* 2009, Bukowska *et al.* 2015). Two studies of only night shift workers reported either no difference in prolactin levels after a normal night sleep compared to levels taken after sleep preceded by a night shift (Aktan *et al.* 1997), nor differences by duration of night work (Langley *et al.* 2012) (see Table 6-4c). In addition, a few small field or experimental studies measuring prolactin levels in night shift workers only, or in night and day shift workers at multiple time points found (1) decreased prolactin levels during or after night work compared to levels measured during day shifts in the same workers (Aulitzky *et al.* 1984, Touitou *et al.* 1990, Costa *et al.* 1997), or (2) increased (Weibel and Brandenberger 1998) or decreased (Touitou *et al.* 1990) prolactin levels in night shift workers compared to controls or day shift workers. One study found that prolactin patterns were similar in day sleep after night work as day workers subjected to an abrupt sleep delay (Spiegel *et al.* 1996).

Table 6-4c. Studies of prolactin in night shift workers

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Aktan *et al.* 1997 Turkey	20 pre-menopausal NSW nurses	Serum prolactin in follicular phase Two samples: morning after a typical night's sleep and after a typical night shift	Night sleep vs. night work No difference in prolactin levels
Bukowska *et al.* 2015 Poland	Polish nurses and midwives, 40–60 years of age Pre- and post-menopausal 327 NSW; 330 DSW	Serum prolactin Morning: start of morning shift or at end of night shift	NSW vs. DSW ⬆ Prolactin (crude) in both pre- (P = 0.001) and post-menopausal (P = 0.02); attenuated in adjusted analysis and not significant No association between prolactin and NSW duration, frequency, total number of nights worked or current night work status
Korompeli *et al.* 2009 Greece	32 intensive care nurses 25 NSW; 7 DSW	Plasma prolactin Sampled at start and end of each type of shift (morning, evening, and night shifts for NSW and morning shift for DSW)	NSW vs. DSW No significant difference in samples from morning shift; analysis for night shift of NSW vs. DSW not reported
Langley *et al.* 2012 Canada	82 premenopausal nurses; rotating NSW (DD, NN, 5 days off)	Serum prolactin Start of a day shift in summer and in winter	No association of prolactin with NSW duration (continuous or working long durations) No relationship of prolactin with urinary aMT6s levels

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Schernhammer *et al.* 2004 U.S.A.	Nurses' Health Study (NHS) and 663 postmenopausal nurses from NHS (Prolactin only measured in NHS postmenopausal women)	Serum prolactin	NSW vs. DSW No association of prolactin by # years worked

aMT6s = 6-sulfatoxymelatonin; DD = 2 day shifts; DSW = day shift worker; D = day shift; NN = 2 night shifts; ns = not significant; NSW = night shift worker; N = night shift.

Findings for studies of androgens and night shift work are unclear. Five independent studies compared levels of androgens in shift workers and day workers, with study populations varying by gender, occupational status, androgen metabolites, and biological tissue (Schernhammer *et al.* 2004, Nagata *et al.* 2008, Gómez-Acebo *et al.* 2015, Papantoniou *et al.* 2015c, Peplonska *et al.* 2016); only one of the studies included men (Papantoniou *et al.* 2015c) (see Table 6-4d). The Spanish study (Papantoniou *et al.* 2015c) found evidence of an association of shift work and an increase in several androgens in men (although not statistically significant), pre-menopausal women, and the total population. However, Gómez-Acebo *et al.* (2015) found lower serum levels of testosterone in pre-menopausal women whose samples were drawn during their luteal phase. In general, no association or only non-significant associations were found in the other 3 studies.

No association was found between urinary melatonin levels and androgens in most studies reporting this association (Schernhammer *et al.* 2004, Gómez-Acebo *et al.* 2015, Papantoniou *et al.* 2015c). Schernhammer *et al.* (2006a) reported modest positive correlations of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) with urinary melatonin levels among pre-menopausal women in unadjusted, but not adjusted analyses.

Table 6-4d. Studies of androgens in night shift workers

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Gómez-Acebo *et al.* 2015 Spain	Female health care workers or teachers ages 20–65 yr 63 rotating NSW; 73 DSW	Serum testosterone, DHEA, DHEAS Start of a day shift in summer and in winter Urinary aMT6s over 24 hr	NSW vs. DSW ⬇ Testosterone: Pre- and post-menopausal women, and pre-menopausal women adjusted for menstrual cycle phase in all models; pre-menopausal women in the luteal phase when hormones were not added to the model ⬆ DHEA: pre-menopausal women in the follicular phase, no longer significant in models including other hormones; post-menopausal women in models including other hormones (ns, P =0.067) No association of plasma sex hormones with 24-hr urinary aMT6s (data not shown)
Nagata *et al.* 2008 Japan	206 postmenopausal women in general breast cancer screening population Ever or never worked grave yard shift assessed by questionnaire 3 yr 7 NSW; 170 DSW	Serum testosterone, DHEA Blood sampled at 2:00 PM on day of interview Urinary aMT6s First-void urine collected next day after interview	NSW vs. DSW No association: Testosterone and DHEA: Testosterone and DHEAS levels not significantly correlated with urinary aMT6s Not informative study due to small numbers of NSW
Papantoniou *et al.* 2015c Spain	Male and female workers from hospitals (56, mainly women), car and train companies (61, mainly men), ages 22–64 yr 75 permanent NSW; 42 DSW	Urinary androgens: testosterone, epitestosterone, DHEA, androsterone, etiocholanolone, 11β-OH-androsterone, androstenedione, 6α-OH-androstenedione, 3α,5α-androstanediol, and 3α,5β-androstanediol 24-hr urine sample Cosinor analysis used to evaluate rhythm of aMT6s and androgens	NSW vs. DSW ⬆ Total population (significant or borderline significant): Total androgens, all androgens and their metabolites except epitestosterone, etiocholanolone, and 3α,5β-androstanediol ⬆ Males (ns): Most androgens and metabolites ⬆ Premenopausal women (significant): Testosterone and 3α,5α-androstanediol Later peak time of all androgen metabolites No correlation between androgens and urinary aMT6s

Reference Location	Population/exposure	Hormone, methods, and timing	Results
Peplonska *et al.* 2016 Poland	Polish nurses and midwives, 40–60 yr of age Pre- and post-menopausal 263 fast rotating NSW; 269 DSW	Plasma testosterone, DHEAS Start of morning shift or at end of night shift	NSW vs. DSW Testosterone: no association with ever, frequency or duration of NSW in pre- or postmenopausal women DHEAS: ↑ (borderline) levels in postmenopausal women with longer duration of night work, (P = 0.082). No heterogeneity of effect by chronotype.
Schernhammer *et al.* 2004, Schernhammer *et al.* 2006a U.S.A.	Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) 2004: 663 postmenopausal nurses from NHS and 80 NHS II primarily pre-menopausal nurses (ages from NHS II; 18% reported night work in the two weeks prior to urine collection 2006: 459 rotating NSW from NHS II, primarily pre-menopausal nurses (ages 33–50), includes 80 nurses from 2004 study	Plasma testosterone and androstenedione, DHEA Urinary aMT6s (premenopausal women) 2004: Luteal phase first spot morning urine; 3 samples) 2006: Luteal or follicular phase; 1 sample	663 postmenopausal women (2004) No clear patterns with NSW history 80 premenopausal women (2004) ↑ DHEA (P = 0.09) with ↑ nights worked in 2 wk prior to sampled collection 2004 & 2006: No correlation with urinary aMT6s except for DHEA and DHEAS unadjusted analysis, but not in multivariate analysis (2006).

aMT6s = 6-sulfatoxymelatonin; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; DSW = day shift worker; ns = not significant; NSW = night shift worker.

6.4 Other exposures associated with shift work or LAN

Circadian disruption is a complex process involving interactions of multiple factors. In addition to LAN-induced melatonin suppression and desynchronization of central and peripheral clock and clock-controlled gene expression, other exposures commonly associated with shift work may contribute to circadian disruption including: vitamin D deficiency related to reduced sunlight, sleep deprivation, and meal timing (Costa *et al.* 2010, Asher and Sassone-Corsi 2015, Smolensky *et al.* 2015, Figueiro 2017, Zubidat and Haim 2017). Interactions with various lifestyle factors (e.g., physical activity, alcohol, drugs, chronic disease, exposure to environmental chemicals and pollutants, etc.) may also be important. However, current data cannot disentangle the relative roles of LAN, melatonin suppression, clock gene disruption, sleep disruption, and other factors in shift-work carcinogenicity (Stevens *et al.* 2014).

6.4.1 Sunlight and vitamin D

Modern electric lighting practices not only increase exposure to LAN but also possibly contribute to decreased exposure to sunlight, resulting in weaker circadian entrainment and vitamin D deficiency (Smolensky *et al.* 2015). Vitamin D includes a group of fat-soluble compounds that are produced in two forms (D_2 and D_3). Vitamin D_2 comes from plant sources; however, up to 90% of vitamin D comes from endogenous production of D_3 from skin exposure to UV-B radiation in sunlight (Atoum and Alzoughool 2017). Vitamin D and melatonin are intimately linked to the circadian system and regulate, in a complimentary fashion, many of the same biological processes in cells, tissues, and organ systems. Although there is no evidence to date that suggests that vitamin D affects core clock gene expression, vitamin D directly or indirectly regulates more than 2,000 genes in many pathways that are associated with malignancy including metabolism, DNA repair, antioxidant activity, anti-inflammatory activity, angiogenesis, immune function, cell proliferation, cell differentiation, and apoptosis (Holick 2016).

Overall, the available evidence that vitamin D deficiency plays a role in shift work carcinogenicity is inconclusive. Two studies did not find that night shift work was associated with a decreased level of sunlight exposures (Hansen and Lassen 2012, Gómez-Acebo *et al.* 2015), which would argue against the vitamin D hypothesis. Studies that have examined the effects of shift work on vitamin D status have reported mixed results (Maeda *et al.* 2007, Itoh *et al.* 2011, Alefishat and Abu Farha 2016). A recent systematic review of vitamin D and various occupations (Sowah *et al.* 2017) found that shift workers (may include evening and night shift workers together) had the lowest average levels of serum 25-hydroxyvitamin D (33.8 ± 10.1 nmol/L) among all occupations, with ~80% having serum vitamin D levels ≤ 50 nmol/L, indicating vitamin D deficiency.

Although vitamin D deficiency has been associated with increased risk of various cancers, including breast cancer in some studies (Chen *et al.* 2010, Gandini *et al.* 2011, Touvier *et al.* 2011, Holick 2016, Reichrath *et al.* 2016, Atoum and Alzoughool 2017, O'Brien *et al.* 2017), a recent report by the World Cancer Research Fund (WCRF 2018) concluded that the evidence linking vitamin D and breast cancer risk was limited and that a firm conclusion could not be made. Vitamin D exerts its effects via the vitamin D receptor (VDR). Some VDR polymorphisms in humans have been associated with increased breast cancer risk while VDR knockout mice have higher rates of preneoplastic mammary lesions (reviewed by Atoum and Alzoughool 2017). However, in addition to vitamin D deficiency, poor sunlight exposure could contribute to other pathways (i.e., insulin resistance, estrogen deficiency, thyroxin deficiency, immune system modulation, degradation of folic acid, and circadian disruption) that increase cancer risk (Suba 2012).

6.4.2 Sleep

Night shift work misaligns the sleep/wake cycle with the daily and seasonal light-dark cycle. A common consequence of this misalignment is sleep deprivation derived from both sleep loss and poor sleep quality (Ackermann *et al.* 2013, Korsiak *et al.* 2017). The sleep-wake cycle is strongly and bidirectionally associated with the circadian system such that changes in one affects the other. Moreover, sleep is critical for maintaining optimal immune, cellular, metabolic, and endocrine functioning. Dysfunction in each of these physiological systems has been linked to

carcinogenesis (Samuelsson *et al.* 2018). Overall, the database is inadequate to evaluate the contribution of sleep disturbances in shift work-mediated carcinogenicity as few studies have evaluated the interaction between shift work and sleep and cancer risk.

Studies that have examined the effects of shift work on sleep have reported that shift workers more frequently experience disturbed sleep, poor sleep quality, excessive sleepiness, and a significantly higher prevalence of short sleep duration (< 7 hours per day) compared with day workers (Drake *et al.* 2004, Luckhaupt and Sestito 2013). Yong *et al.* (2017), using NHANES data, reported that several sleep problems were significantly higher among night shift workers than a representative sample of U.S. workers. Self-reported short sleep duration (61.8%), poor sleep quality (30.7%), sleep-related activities of daily living (ADL) (36%), and insomnia (18.5%) were all highest for night shift workers in the United States, with night shift workers having the highest likelihood of these sleep problems in a multivariate analysis. Even in retirement, persons who worked shifts during their pre-retirement years had significantly worse scores on the Pittsburgh Sleep Quality Index by 0.96 units (1 to 15 years) and 0.61 units (> 15 years) relative to retired day workers independent of gender, former occupation, morningness, or current health (Monk *et al.* 2013). Guo *et al.* (2013) also investigated the effects of shift work on sleep quality in a cohort of retired workers (> 26,000 workers including > 9,000 shift workers) from a motor corporation in China. This study reported poorer sleep quality in retired shift workers that gradually improved to baseline quality levels after 20 years. Rahman *et al.* (2013) reported that both daytime and nighttime sleep are adversely affected in rotating-shift workers and suggested that filtering short wavelengths may reduce sleep disruption.

Overall, the epidemiological evidence that sleep duration is related to breast cancer risk is unclear (reviewed by Samuelsson *et al.* 2018), with some studies finding no association and others finding an increased risk with long sleep durations, short durations, or both short and long sleep durations. A recent meta-analysis (Lu *et al.* 2017) modeled the estimates from 10 studies of breast cancer and sleep duration and reported a significant excess risk of breast cancer among women sleeping for longer durations, especially of ER+ breast cancer. Other studies found that short sleep duration (≤ 6 hours) was associated with ER− and PR− breast cancer in all women (Xiao *et al.* 2016), black women (Xiao *et al.* 2016), or never shift workers (Wang *et al.* 2015a). An earlier meta-analysis (Yang *et al.* 2014) reported no relationship between sleep duration and breast cancer risk. The small excess risks associated with long sleep duration reported in each study may be an "epiphenomenon" of comorbidity as suggested by Stranges *et al.* (2008) who found that several sociodemographic, lifestyle, and comorbidity factors could confound or mediate U-shaped associations between sleep duration and health (e.g., longer and shorter sleep durations related to breast cancer risk).

Four studies, including the Million Women Study (Travis *et al.* 2016) contributed information about sleep duration among night shift workers. McElroy *et al.* (2006) and Pinheiro *et al.* (2006) investigated the impact of night work history on the relationship between sleep duration and breast cancer risk and found no differences. Wang *et al.* (2015a) reported a statistically significant 83% increased risk among women who had ever worked nights and reported sleep durations of ≤ 6 hours. In the Million Women Study, consideration of sleep duration made no difference in the relationship between shift work and breast cancer risk.

Fritschi *et al.* (2013) reported on a composite variable of self-reported "sleep disturbances" including short (< 6 hours) or long (≥ 9 hours) sleep duration, poor sleep quality, and frequent difficulty falling or staying asleep. A non-significantly elevated risk of breast cancer was found among those reporting ever having any sleep disturbance (OR = 1.21, 95% CI = 0.95 to 1.55). Girschik *et al.* (2013) reported on sleep duration in this same case-control population and found no relationship between short or long sleep duration and breast cancer.

Possible mechanisms and other factors contributing to adverse effects of sleep deprivation include interactions with melatonin, oxidative stress, immune suppression, DNA damage repair, timing and quality of food intake, alcohol intake, tobacco use, and physical inactivity (Anjum *et al.* 2012, Bhatti *et al.* 2016, Nagata *et al.* 2017). Acute sleep deprivation affects the melatonin rhythm and core clock gene expression in peripheral tissues (Ackermann *et al.* 2013, Archer and Oster 2015). Independent of melatonin suppression, sleep deprivation is associated with many of the chronic diseases (e.g., obesity, type II diabetes, hypertension, and cancer) that are associated with circadian disruption, and can lead to immune suppression and a shift to a cancer-stimulatory cytokine secretion pattern (Balachandran 2011, Nagai *et al.* 2011, Faraut *et al.* 2012, Gamaldo *et al.* 2012). Mistimed sleep significantly reduced the number of rhythmic transcripts in the human blood transcriptome and altered the expression of key regulators of gene expression (including methylases and acetylases involved in chromatin modifications, RNA polymerase, ribosomal proteins involved in translation, and some core clock genes) (Archer *et al.* 2014). In addition, sleep deprivation affects the appetite hormones leptin and ghrelin, resulting in increased hunger and possibly contributing to increased prevalence of obesity among shift workers (Taheri *et al.* 2004, Figueiro *et al.* 2012, Zubidat and Haim 2017). Figueiro *et al.* (2017) also showed that exposure to high levels of circadian-effective light during the morning or during the entire day was associated with higher sleep quality, reduced depression, and improved circadian entrainment. Taking a short nap during nighttime shift work may also have some benefits. Female nurses who took a short nap during night shift work had significantly lower 17ß-estradiol levels compared to night-shift nurses who did not take a nap (Bracci *et al.* 2013).

6.4.3 Meal timing

The feeding-fasting cycle is recognized as an important nonphotic zeitgeber for peripheral clocks, and meal timing is particularly important for glucose homeostasis (Asher and Sassone-Corsi 2015, Wehrens *et al.* 2017). Fonken *et al.* (2010) reported that mice exposed to constant bright light or dim LAN had significantly increased body mass and reduced glucose tolerance compared to mice exposed to a standard LD cycle, even though the total caloric intake and daily activity were similar among the groups. The primary difference was that exposure to LAN shifted the time of food intake and disrupted metabolic signals. The effects of simulated shift work on the pro-inflammatory response to a LPS challenge in rats was eliminated by food restriction during their forced activity schedule and indicates that mistimed food consumption was a major factor contributing to the inflammatory response (Guerrero-Vargas *et al.* 2015). Time-restricted feeding studies in rodents show that meal timing can reset circadian clocks in peripheral tissues (Wu *et al.* 2004, Filipski and Levi 2009). Filipski and Levi (2009) reported that meal timing (12 hours on and 12 hours off) counterbalanced circadian disruption produced by simulated chronic jet lag in mice by restoring near-normal circadian patterns in the liver and slowed tumor growth. Wu *et al.* (2004) examined the effects of meal timing on growth of transplanted Glasgow osteosarcoma in male mice. Tumors grew more slowly in mice on a

restricted feeding schedule (i.e., restricted to 4 or 6 hours during the light or dark phase) compared to mice given food *ad libitum*. Overall survival was longer and tumor growth was slower in mice fed during the light phase, suggesting that meal timing during the light phase reduced tumor growth by modifying circadian clock function or signaling pathways within peripheral tissues and tumor cells.

The effects of time-restricted feeding have not been thoroughly investigated in humans (Asher and Sassone-Corsi 2015). One study reported that eating after 10:00 PM was significantly associated with breast cancer (OR = 1.5, 95% CI = 1.06 to 2.12; $P = 0.02$). Those with ≥ 20 years duration of eating after 10:00 PM had an OR of 2.28 (95% CI = 1.13 to 4.61); those who ate between midnight and 2:00 AM had an OR of 2.73 (1.01 to 6.99) (Li *et al.* 2017). The effect was strongest among women who ate staple foods such as noodles (OR = 2.79, 95% CI = 1.58 to 4.94; $P < 0.001$) or rice (OR = 2.58, 95% CI = 1.42 to 4.69; $P = 0.002$); however, there was no evidence of a relationship between breast cancer risk among women eating fruits and vegetables at these times. Simulated shift work in healthy volunteers (i.e., mistimed food intake and sleep) altered the circadian patterns of 127 plasma proteins (including 30 proteins showing strong circadian regulation) compared to volunteers with sleep and food intake patterns in phase with the endogenous circadian clock (Depner *et al.* 2018). The biological pathways associated with the altered proteins included immune function, glucose homeostasis and/or energy metabolism, and cancer (e.g., tyrosine kinase signaling, receptor tyrosine-protein kinase erbB-2, DNA damage checkpoints). There is some evidence that meal timing and eating frequency are associated with metabolic and inflammatory biomarkers that are putatively associated with breast cancer risk (Marinac *et al.* 2015a, Marinac *et al.* 2015b, Marinac *et al.* 2016). C-reactive protein concentrations increased 3% for every 10% increase in the proportion of calories consumed in the evening. There was also a significant association between calories consumed during the evening and fasting duration with C-reactive protein levels and glucose metabolism. A nightly fasting duration of < 13 hours was associated with an increased risk of breast cancer recurrence but not with a higher risk of breast cancer mortality compared with fasting ≥ 13 hours per night (Marinac *et al.* 2016). Shift workers, and especially rotating shift workers, had significantly higher dietary inflammatory index scores compared to day workers (Wirth *et al.* 2014a, Wirth *et al.* 2014b). Some of the most likely factors contributing to poorer dietary habits among shift workers include nighttime consumption of food, increased snacking compared to day workers, stress, fatigue, and sleep loss. Although it is uncertain whether or not the differences in inflammatory potential are biologically significant, it is known that chronic inflammation is a risk factor for several chronic diseases including cancer. Nagata *et al.* (2017) reported that women shift workers who ate nighttime snacks at irregular hours had higher levels of oxidative stress compared to those who did not eat snacks or who ate snacks on a regular schedule.

6.4.4 Co-exposure to carcinogens or toxicants

Night shift workers can also be exposed to other carcinogens in the work place. Studies have shown that absorption, distribution, metabolism, and excretion of xenobiotic agents can vary by circadian stage of exposure raising the possibility that risk from co-exposure to other carcinogens may differ depending on the time of exposure in the 24-hour day. A review by Smolensky *et al.* (2017) found evidence suggesting that circadian timing of exposure to xenobiotics affects tolerance and adverse outcomes (although cancer was not reviewed specifically). Clinical studies have demonstrated that timing of medication administration also affects efficacy of treatment.

Some initiation-promotion studies found that time of day of carcinogen application affected tumor burden (Clausen *et al.* 1984, Iversen and Iversen 1995, Wille 2003, Gaddameedhi *et al.* 2011) with one study finding that tumor multiplicity was correlated with timing of peak activity of a DNA repair protein (Gaddameedhi *et al.* 2011). Finally, the initiation-promotion studies of simulated shift work or LAN in animals also support a potential interaction between circadian disruption (induced by shift work or LAN) and cancer growth (see Section 5).

6.5 Synthesis

Human and animal studies show that exposure to shift work, jet lag, and/or LAN can induce circadian disruption as evidenced by desynchronization of the central clock-SNS-peripheral clock axis, melatonin suppression, alterations of physiological or hormonal circadian biomarkers, and/or altered clock gene expression. Shift work is the best studied LAN-associated exposure in humans and represents extensive LAN exposure conditions. Epidemiological studies of night shift workers suggest an increased risk of breast cancer in women, and to a lesser degree, an increased risk of prostate cancer in men (see Sections 3 and 4). LAN, shift work, and jet lag studies in humans and experimental animals also show direct evidence of several biological effects with a known connection to cancer (i.e., hallmarks of cancer and/or characteristics of carcinogens). These include reduced DNA repair and genomic instability, epigenetic modifications and altered gene expression, oxidative stress, chronic inflammation and immunosuppression, metabolic disturbances, and altered hormone rhythms. Several of these studies also reported a connection of these effects with accelerated tumor growth.

The proposed mechanisms linking shift work and LAN, circadian disruption, and cancer focus on the biological properties of melatonin and the broader role of the circadian system, autonomic and neuroendocrine signaling, and clock genes (circadian disruption theory) in tumor suppression and maintaining cellular and tissue homeostasis. There is substantial experimental evidence that both melatonin and the circadian timing system can protect against tumor development and progression and affect mechanisms and pathways that are relevant to all the hallmarks of cancer. Although interconnected, both factors can also protect against tumor development independently. Studies in experimental animals demonstrate that LAN-induced melatonin suppression accelerates tumor growth while melatonin treatment inhibits tumor growth via several oncostatic pathways. Experimental studies also strongly support the role of clock genes in maintaining cell and tissue homeostasis and in tumor suppression. Genetic models in rodents show that knockouts or mutations in the core clock genes are associated with circadian disruption and a cancer-prone phenotype. Disrupted clock gene expression is characteristic of many human cancers. Consequently, melatonin suppression and other types of circadian disruption may promote neoplastic transformation via multiple pathways involving disrupted circadian homeostatic controls that affect energy balance, DNA repair, immune function, hormone levels and signaling pathways, angiogenesis, cell cycle, and apoptosis.

Although the detailed mechanisms are not fully understood, it is clear that shift work and LAN represent complex exposure scenarios that contribute to circadian disruption and other biological effects that are directly relevant to cancer initiation, promotion, and progression. In addition to the complex interactions among melatonin, other hormones, the central clock, peripheral clocks, and clock-controlled genes, interactions also occur with other factors that are associated with shift work and LAN that may mitigate or exacerbate circadian disruption. These include sleep

and sleep deprivation, vitamin D, meal timing, chronic disease, and various lifestyle factors (e.g., smoking, drinking, drugs, exposure to environmental chemicals and pollutants, social factors, and physical activity). Because of the complex interactions and overlapping effects of LAN-induced melatonin suppression, circadian disruption, sleep deprivation, and other factors, it is currently impossible to separate their relative individual contributions to cancer development and progression. All of the proposed mechanisms or modes of action have experimental support from studies in humans, human cell lines, and experimental animals and are relevant to humans.

7 Evidence Integration and Overall Cancer Hazard Assessment

Modern electric lighting practices have helped to transform our society into one in which people work, sleep, and receive goods and services at any time of the day or night. These practices have resulted in, among others, exposure to LAN and night shift work.

- Night shift work is defined as typically working at least 3 hours between midnight and 5:00 AM and includes exposure to electric LAN, sleep disturbances, or changes in meal timing, as well as other potential factotrs (e.g., decreased exposure to sunlight, and lower vitamin D levels).
- LAN refers to excessive exposure to electric light during the biological night which is the time when the circadian clock promotes sleep.

Because light is the critical regulator of circadian rhythms, exposure to LAN can cause circadian disruption, which can be linked to potential adverse health effects, such as cancer. Other characteristics of night shift work such as meal time changes are also related to circadian regulation.

The objective of this cancer hazard assessment is to define exposure to (1) LAN and (2) night shift work in ways that are supported by the scientific evidence and to reach an overall cancer hazard assessment for these two exposure scenarios. Although the evidence is evaluated separately for LAN and night shift work, these exposures overlap; studies specific to LAN may be relevant to night shift work and vice versa.

This section describes the methods for evidence integration (Section 7.1), summarizes the cancer evaluations for night shift work (Section 7.2) and LAN (Section 7.3), and presents the cancer hazard assessment conclusions (Section 7.4). Because the data on transmeridian travel were inadequate for evaluation, no overall preliminary recommendation was made for this exposure scenario. Section 7.5 provides a brief summary of resources and recommendations for limiting night shift work practices or lighting conditions that would cause circadian disruption.

7.1 Methods for evidence integration

The cancer hazard assessment integrates relevant evidence across many studies using a triangulation approach that investigated the pathway from exposure (LAN and night shift work) to circadian disruption to cancer, including the following relationships:

- LAN and night shift work and cancer in humans (Sections 3 and 4) and experimental animals (Section 5)
- LAN and night shift work and biomarkers of circadian disruption (Section 2)
- Circadian disruption and cancer, including biological effects associated with cancer (Section 6)
- LAN and night shift work and biological effects associated with cancer (Section 6)

This section presents a series of evidence-based figures and tables that summarize the assessments from those sections, to provide transparency of the decision-making process for

reaching a cancer hazard assessment conclusion for LAN and night shift work. In general, for each relationship, the tables provide information regarding the approaches used to evaluate the relationship, strengths and limitations of the studies, an assessment of confidence in the evidence, and integration of the evidence. The process starts with assessment of the evidence for each relationship (such as between exposure and breast cancer) for a specific evidence stream (such as human epidemiology studies) (see Table 7-2). The assessments of the various types of evidence are brought forward to the overall evaluation to reach cancer hazard assessment conclusion (see Table 7-1). The level-of-evidence conclusions from studies in humans and the overall cancer hazard assessment were reached by applying the RoC listing criteria to these assessments. Because of the complexity of the carcinogenicity pathway, the confidence in the mechanistic data requires integrating many types of data before these data are integrated with the toxicology and epidemiology data (Table 7-3). The tables are focused on breast cancer; evidence from humans for cancer at other tissue sites is also summarized.

7.2 Night shift work

Epidemiology studies provide evidence that persistent night shift work (permanent or rotating) increases breast cancer risk. Biomonitoring, toxicology, and mechanistic studies provide evidence that night-shift-induced circadian disruption is associated with several key events that are relevant to carcinogenicity pathways and also provide support for the patterns of risks observed in the epidemiology studies. An overview of the key evidence is discussed below and summarized in greater detail in Tables 7-1 through 7-3. Figure 7-1 is a schematic diagram of the evidence for the links from night shift work exposure to circadian disruption to biological effects to breast cancer.

Few night shift workers are able to adapt their circadian rhythms to their altered sleep-work cycle (Jensen *et al.* 2016), and women with more persistent shift work may have health problems. The epidemiology data are inadequate to determine the specific roles of LAN, altered sleep patterns, or other factors in development of breast cancer. However, lifestyle behaviors (such as smoking or alcohol consumption) not related to circadian disruption were controlled for in the epidemiology studies and cannot explain the excess risk. Therefore, the exposure scenario that best fits the available epidemiological evidence is “persistent night shift work,” which includes exposure to LAN, sleep disruptions, changes in meal timing, and other characteristics of night shift work. Persistent shift work may be a surrogate for conditions that are associated with chronic circadian disruption.

Numerous epidemiology studies provide strong evidence that “persistent night shift work” — defined as frequent, long-term, or working a large number of night shifts over a lifetime, especially beginning in early adulthood (see Section 3 and Table 7-1) — increases the risk of developing breast cancer. Night shift work was associated with an increased risk of breast cancer in 11 of the 13 most informative studies and in 6 of 8 studies that were considered less informative because of study limitations. Moreover, the excess risk was observed in studies of different occupations and in different geographic locations, which helps to minimize concerns that chance or bias may explain the positive findings.

The most convincing evidence for a positive association between night shift work and breast cancer was from studies of women who started working nights at an early age and worked nights frequently or for many years. A pooled analysis of 5 case-control studies conducted in Australia,

Canada, and Europe, all using the same definition of night shift work (Cordina-Duverger *et al.* 2018), found the highest risk of breast cancer among pre-menopausal women who worked at least 3 nights per week for 10 years, 10-hour shifts, and within the last 2 years. No excess risk was found in post-menopausal women. These findings are supported by the Nurses' Health Studies (Wegrzyn *et al.* 2017), which applied similar methods to younger and older cohorts and found an excess risk for long duration of rotating night shift work among the women in the younger cohort but not in the older cohort, and in both cohorts among women followed for at least 10 years — that is, starting at younger ages. Excess risk of breast cancer was also found in some cohorts of older women with long duration of working night shifts; however, in most cases, the age when they started working nights was not known.

The finding of an association with more recent exposure may suggest that night shift work is acting as a promoter, which is supported by cancer studies finding that (1) simulated shift work decreased the latency of mammary gland tumors in a cancer-prone mouse model (Van Dycke *et al.* 2015), chronic jet lag promoted mammary tumors initiated by *N*-nitroso-*N*-methylurea (Fang *et al.* 2017), and (2) numerous studies in experimental animals showing that LAN (defined as exposure to continuous light, dim light, interrupted light during sleeping, or changes in the duration of LAN) promoted proliferation of mammary-gland tumors or growth of human breast-tumor xenografts (see Section 5 and Table 7-2). Finally, the evidence from human cancer studies is stronger for hormone-receptor-positive subtypes of breast cancer (e.g., ER+, PR+, and HER2+), which is consistent with the mechanistic data (see Sections 3 and 6 and Table 7-1).

The available mechanistic and other relevant data primarily provide (1) evidence that simulated shift work or chronic jet lag promotes the growth of mammary-gland and other types of tumors in experimental animals (see Section 5 and Table 7-2), (2) evidence that circadian disruption, including effects mediated by the sympathetic nervous system, melatonin suppression and clock-gene desynchrony, plays a role in shift-work-mediated carcinogenicity, and (3) evidence (from studies in humans and experimental animal models) that night shift work is associated with biological effects that are recognized as key characteristics of carcinogens (see Sections 2 and 6 and Table 7-2). In general, although it is likely that other exposures associated with shift work (e.g., sleep deprivation, altered meal timing, or vitamin D deficiency), some of which also contribute to circadian disruption, also plays a role in the carcinogenicity associated with shift work; the cancer databases are generally less well developed than the data from studies of LAN and circadian disruption.

The key evidence supporting a role for circadian disruption mechanisms in carcinogenicity includes (1) field studies showing that night shift work is associated with melatonin suppression and circadian disruption (see Section 2), (2) cancer studies in animals and humans showing a link between low melatonin levels and breast cancer risk or mammary-gland tumor growth, and (3) mechanistic studies showing that both clock-gene regulation and melatonin are important in suppressing cancer development (see Tables 7-2 and 7-3). There is also evidence that night shift work causes several other biological effects that are known to be key characteristics of carcinogens or are associated with carcinogenicity (e.g., decreased DNA repair, increased oxidative stress, increased inflammation, altered circulating levels of estrogen, and epigenetic changes that modify the expression of core clock genes or clock-controlled genes), including some that are consistent with development of hormone-receptor-related breast cancer (e.g., altered estrogen levels or function). A strength of the database is that several of the animal

cancer studies (involving exposure to LAN or simulated shift work/chronic jet lag) also measured some effects associated with cancer (e.g., DNA damage repair), thus providing links between exposure, intermediate biological effects, and cancer. Moreover, several biological effects observed in night shift workers (including some of the key characteristics of carcinogens) were the same as some of those mediated by low melatonin levels or deregulation of core clock genes. Overall, these data provide strong, although indirect, support for the role of circadian disruption in breast cancer carcinogenicity among night shift workers. A key early event may be the epigenetic changes reported in some studies of night shift workers, which are considered to be paramount for both the clock-gene-deregulation and melatonin-suppression modes of action. Epidemiology studies also provide some evidence that working night shifts is related to an increased risk of prostate cancer; this database is not as robust as that for breast cancer, and the evidence is not as strong. The database was inadequate to evaluate the relationship of night shift work with colorectal cancer, lung cancer, or other hormonal cancers in women.

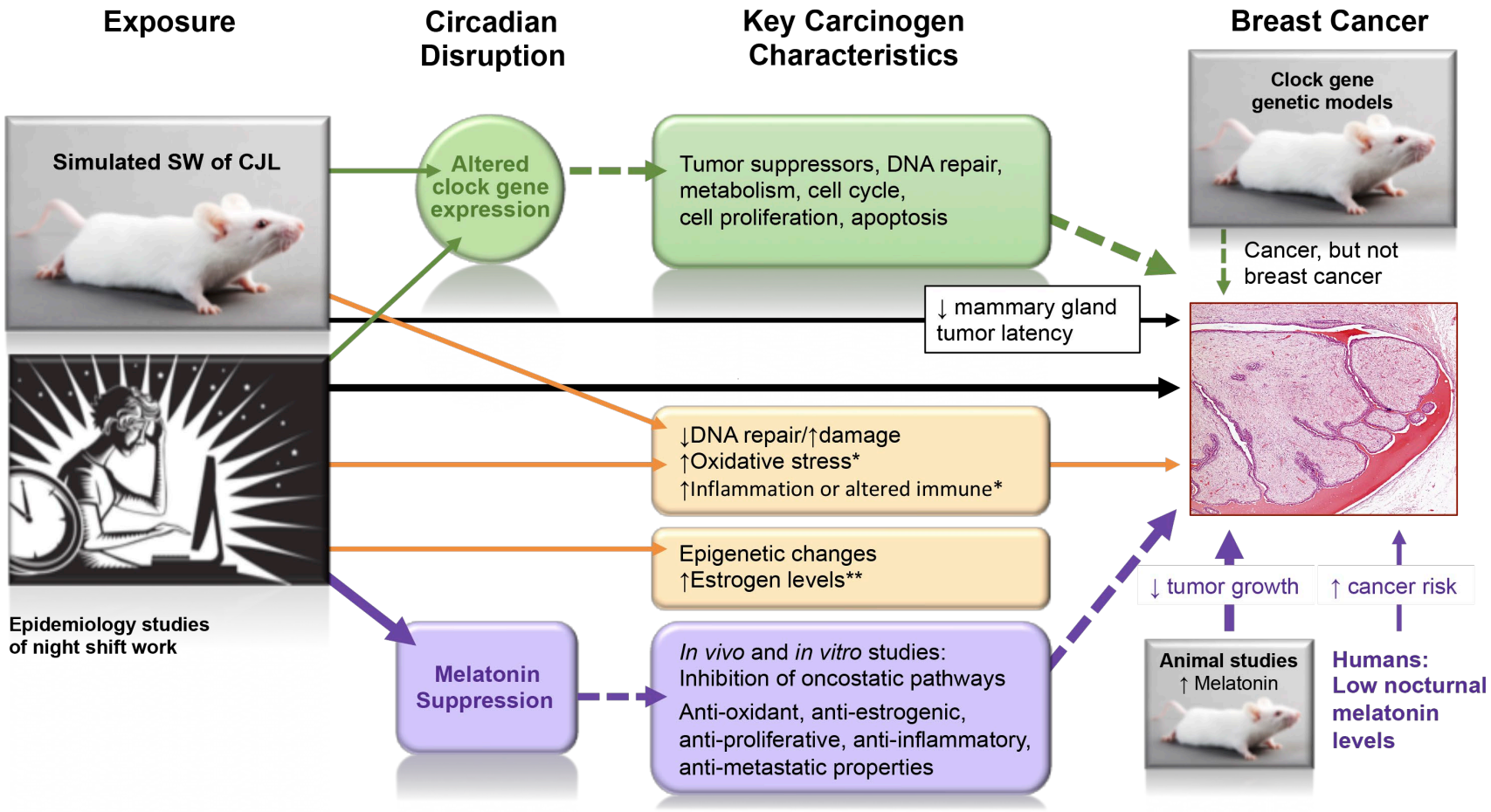

Figure 7-1. Integration of evidence from studies relevant to night shift work and breast cancer

Evidence from studies in humans and experimental animals for the relationship between night shift work and biomarkers of circadian disruption, biological effects (e.g., mainly key characteristics of carcinogens), and cancer. The evidence supporting this figure is outlined in Tables 7-1 to 7-3. The strength and directness of the evidence are indicated by the weight (thin, medium, or thick) and pattern (solid = direct, dashed = indirect) of the arrows. Proposed mechanism: purple = melatonin; green = circadian clock gene desynchrony; and peach = direct biological effects of night shift work. * = Biological effect was measured in animal cancer study. ** = Biological effects were measured in animal cancer study of LAN.

7.3 LAN

Toxicological and mechanistic studies in animals provide strong evidence that LAN promotes breast cancer proliferation and growth (see Section 5 and Table 7-2), causes biological effects that are identified as key characteristics of carcinogens or associated with carcinogenicity (see Section 6 and Table 7-2), and that the effects are mediated in part by circadian disruption (see Sections 2 and 6, and Tables 7-2 and 7-3). Figure 7-2 is a schematic diagram of the evidence for the links between excessive exposure to LAN, circadian disruption, intermediate biological effects, and breast cancer. Other studies suggest that total light, including the type of light received during the day, is important in circadian regulation, night time melatonin secretion, and carcinogenicity.

The database of animal studies on mammary-gland tumors is much larger for LAN exposure than for simulated shift work. These studies clearly demonstrate that melatonin suppression plays a direct role in LAN-associated carcinogenicity. A limitation of the experimental animal studies is that rodents are more sensitive to light-induced melatonin suppression than are humans. However, human breast tumors grew rapidly in nude rats perfused (*in situ*) with melatonin-depleted blood collected from pre-menopausal women exposed to bright LAN or during the daytime, whereas perfusion with melatonin-rich blood collected from women during the nighttime without exposure to LAN suppressed tumor growth (Blask *et al.* 2005, Blask *et al.* 2009). These data support the relevance of the LAN animal models to humans. In almost all studies, LAN also promoted the growth of other types of cancer — of the brain (glioma), cervix (human cells), liver, lung, kidney, peripheral nervous system, prostate, and skin — in studies that either co-exposed the animals to chemical carcinogens or transplanted human or animal cancer cells into LAN-exposed animals (see Section 5). Exposure of rats to continuous LAN increased the incidences of leukemia and lung tumors and the total incidence of tumors (Anisimov *et al.* 2004).

As in the shift-work studies, there is evidence for an indirect role of altered clock-gene expression in LAN-induced carcinogenicity, which is induced by altering neural and endocrine signaling pathways of the circadian timing system to peripheral tissues. Some studies found that experimental animals exposed to LAN showed biological effects (e.g., oxidative stress or altered DNA damage repair, increased inflammation or immune effects, metabolic effects) that are key characteristics of carcinogens or associated with carcinogenicity. Although the database is limited by the number of studies that evaluated each specific effect, the collective evidence from studies of both LAN and night shift work (which includes exposure to LAN) supports the conclusion that LAN causes similar biological effects in humans and animals that are consistent with the proposed carcinogenicity mechanisms associated with circadian disruption (see Section 6 and Tables 7-1 and 7-2).

Other evidence indicates that total light exposure, not limited to LAN, is important in regulating circadian disruption. Some experimental studies suggest that blue light exposure during the daytime or morning can help reduce LAN-induced melatonin suppression (Kozaki *et al.* 2015, 2016, Nagashima *et al.* 2018) and improve measures of sleep quality and mood (Viola *et al.* 2008). In addition, night-time sensitivity to light-induced circadian disruption (usually measured by melatonin suppression) is influenced by light exposure during the day (reviewed by Figueiro 2017).

Two cohort studies in the United States (Hurley *et al.* 2014, James *et al.* 2017), a case-referent study (using lung cancer cases as the comparison group) (Bauer *et al.* 2013), and a population-based case-control study in Spain (Garcia-Saenz *et al.* 2018) found an increased risk of breast cancer among women in the highest category of LAN exposure or blue-light LAN exposure (Garcia-Saenz *et al.* 2018). These findings are supported by a case-control study which found that Israeli women living near strong artificial LAN sources had a 50% increased risk of breast cancer; however, no information was provided on the sources or proximity of the LAN (Keshet-Sitton *et al.* 2016). However, it is not clear whether exposure to outdoor LAN, as measured by satellite data, is a relevant direct measure of light or is rather a surrogate for other activities enabled by light. The Spanish case-control study (Garcia-Saenz *et al.* 2018) found an increased risk of breast cancer among long-term residents of areas with the highest levels of exposure to outdoor light in the blue spectrum but not outdoor light in the overall visible spectrum, suggesting a possible link to LAN exposure. Findings from studies of light exposure in the bedroom or sleep areas were inconsistent. Overall, the database for exposure to LAN (indoor or outdoor) was considered inadequate to evaluate the risk of breast cancer.

Finally, whether light causes circadian disruption depends on many characteristics, including level or intensity, duration of exposure, wavelength(s), timing of exposure, and photic history (e.g., the amount of daytime light). Studies in experimental animals found that compared to exposure to white light during the day, enriched blue light exposure during the day had a positive effect on circadian regulation and decreased the growth of implanted prostate and liver tumors. The term “LAN” does not fully capture these characteristics; therefore, the recommended cancer hazard assessment conclusion is for “certain lighting practices that cause circadian disruption.”

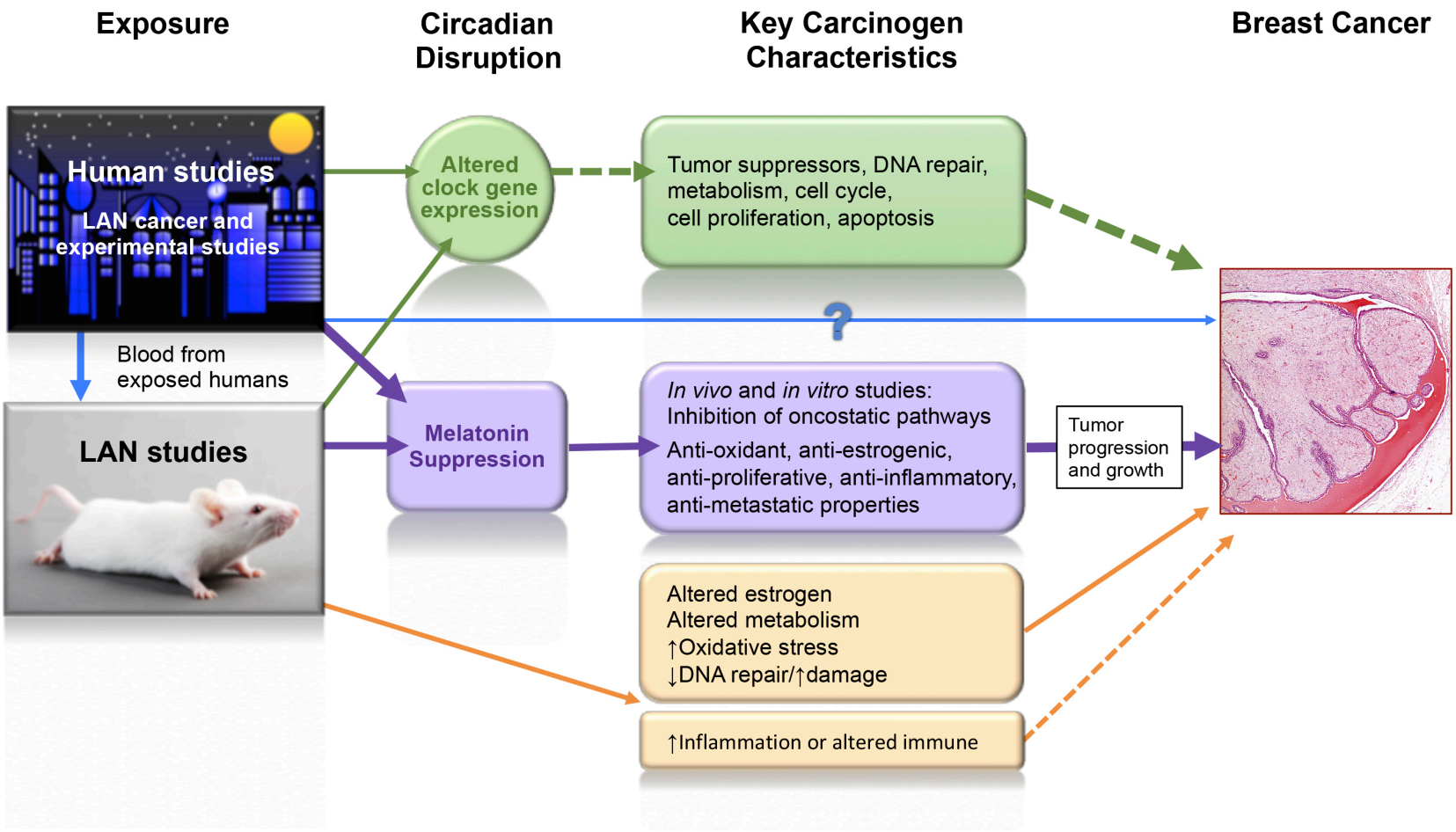

Figure 7-2. Integration of evidence from studies relevant to LAN and breast cancer

Evidence from studies in humans and experimental animals for the relationship between LAN and biomarkers of circadian disruption, biological effects (e.g., mainly key characteristics of carcinogens), and cancer. The evidence supporting this figure is outlined in Tables 7-1 to 7-3. The strength and directness of the evidence are indicated by the weight (thin, medium, or thick) and pattern (solid = direct, dashed = indirect) of the arrows. Proposed mechanism: purple = melatonin; green = circadian clock gene desynchrony; and peach = direct biological effects of night shift work.

7.4 NTP cancer hazard assessment conclusions

Table 7-1 summarizes the evidence supporting the cancer hazard assessment conclusions. Tables 7-2 and 7-3 summarize in more detail the key evidence from human and animal cancer studies

There is high confidence for a causal relationship between human cancer and persistent night shift work — i.e., frequent and long-term night shift work, especially beginning in early adulthood—that causes circadian disruption.

- This conclusion is based on sufficient evidence of carcinogenicity from the collective body of cancer epidemiological studies and mechanistic studies in humans and in experimental animals. Human epidemiological studies provide strong evidence that persistent night shift work is associated with an increased risk of breast cancer and mechanistic and other related studies provide evidence that circadian disruption plays a major role in the cancer pathway in humans.
- In a pooled analysis of 5 case-control studies, female night shift workers found to be at elevated risk for breast cancer in epidemiology studies are those who started working before age 30 and worked at least 3 times/week and for 10 or more years; however, the exact conditions (e.g., number of years worked) that put an individual at increased risk may depend on the specific combination of these metrics (e.g., duration may be longer if frequency is less) or other factors.

There is moderate confidence for a causal relationship between human cancer and certain lighting conditions — i.e., excessive LAN exposure combined with insufficient daylight exposure — that cause circadian disruption. This conclusion is based on strong evidence that LAN acts through mechanisms that are likely to cause cancer in humans.

- Toxicological and mechanistic data indicate that exposure to LAN causes melatonin suppression and other types of circadian disruption, which lead to the proliferation and growth of breast or mammary-gland cancer in experimental animals.
- LAN causes biological effects that are characteristics of recognized carcinogens.
- Studies in humans show that LAN causes melatonin suppression.
- The characteristics of electric light that are most likely to cause circadian disruption include a combination of short wavelengths (e.g., blue light), longer duration, exposure to electric light during the biological night, and higher light intensity or levels. The exact conditions (e.g., duration) depends on the combination of these metrics. In addition to exposure to electric LAN, total light exposure (e.g., insufficient exposure to daylight) is also important in circadian regulation and thus is part of certain lighting conditions.

Table 7-1. Overall evaluation: Evidence integration

Exposure or MOA	End point or outcome	Evidence stream or approach	Confidence in the evidence	Overall evaluation
Night shift work	Breast cancer	**Human epidemiology studies** 21 studies of independent populations Pooled analysis of 5 case-control studies **Experimental animal study** Simulated shift work and jet lag in susceptible transgenic mice **Mechanistic and biomonitoring data** Melatonin suppression hypothesis Circadian disruption hypothesis Biological effects associated with cancer Other effects: sleep deprivation and vitamin D deficiency	Strong evidence that persistent night shift work (frequent and long-term night shift work, especially among women who began night shift work at a younger age) is associated with an increased risk of breast cancer Some evidence that simulated shift work or chronic jet lag decreased latency to mammary-gland tumor development or increased mammary-gland multiplicity Indirect evidence that melatonin suppression contributes to breast cancer development in night shift workers Strong but indirect evidence that circadian disruption contributes to breast cancer development Night shift work is associated with effects that are consistent with several of the key characteristics of carcinogens and also consistent with effects mediated by melatonin and altered clock-gene expression. Epigenetic effects may be a key early step responsible for altered gene expression Role of vitamin D and sleep in night shift work is unclear	**High confidence to establish a causal relationship with human cancer** *Persistent night shift work that causes circadian disruption* Sufficient evidence of carcinogenicity of persistent night shift work from studies in humans, including cancer epidemiology studies and human mechanistic studies Limited but strong evidence of carcinogenicity of persistent night shift work from human epidemiology studies Strong toxicological and mechanistic data providing evidence that circadian disruption plays a role in the cancer pathway in humans Risk patterns in human cancer studies — younger age, hormone-receptor positive — supported by mechanistic data and biology of breast cancer development Exposure to LAN may contribute to cancer risk, but data are inadequate to evaluate a direct association
Night shift work	Prostate cancer	**Human epidemiology studies** 10 studies of independent populations	Limited evidence that night shift work causes prostate cancer in humans Some evidence that exposure to LAN promotes prostate cancer growth in experimental animals	**Limited** evidence of carcinogenicity of night shift work from studies in humans

Exposure or MOA	End point or outcome	Evidence stream or approach	Confidence in the evidence	Overall evaluation
		Experimental animal studies LAN (long vs. short day and mouse prostate xenograft study) LAN and other cancers: numerous initiation-promotion and xenograft studies Simulated shift work or chronic jet lag (other cancer) **Mechanistic and biomonitoring data** See breast cancer	Strong evidence that simulated shift work promotes tumor proliferation and growth in experimental animals Although prostate cancer has not been evaluated to the same extent as breast cancer, many of the conclusions from the mechanistic data are applicable to prostate cancer, which is also a hormone-related cancer	
LAN	Breast cancer	**Human epidemiology studies** 5 studies of outdoor light 10 studies of light in the sleeping area (2 studies also reported on outdoor light) **Experimental animal studies** Primarily initiation-promotion studies of continuous, dim, or interrupted light or bright blue-enriched light during the day **Mechanistic and biomonitoring data** Melatonin suppression hypothesis Circadian disruption theory Biological effects associated with cancer	Inadequate evidence that LAN (indoor or outdoor) causes breast cancer risk Strong evidence from studies in experimental animals that exposure to LAN promotes human breast cancer proliferation or growth and mouse mammary-gland tumor growth Bright blue-enriched light during the day increased the level of nighttime melatonin levels and decreased tumor growth in experimental animals Strong evidence that melatonin suppression plays a role in LAN-induced breast carcinogenicity in experimental animals	***Moderate confidence to establish a causal relationship with human cancer*** *Certain lighting conditions —i.e., excessive LAN exposure combined with insufficient exposure to daylight — that cause circadian disruption* Strong toxicological and mechanistic data that exposure to LAN causes melatonin suppression and other types of circadian disruption, which leads to breast or mammary-gland cancer proliferation and growth in experimental animals LAN induces biological effects in experimental animals associated with (1) carcinogenicity and (2) melatonin suppression and circadian clock gene deregulation Some of these biological effects are observed among night shift workers Exposure to excessive LAN can cause circadian disruption in humans

Table 7-2. Detailed analysis of key evidence

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
Studies of night shift work (or simulated shift work) and cancer				
Night shift work	Breast cancer	**Human cancer epidemiology studies** 21 independent populations 12 case-control studies 1 pooled analysis of 5 case-control studies 9 cohort studies	**Case-control studies** *Strengths* Detailed exposure assessment *Limitations* Retrospective exposure assessment **Cohort studies** *Strengths* No differential recall bias or issues with confounding NHS/NHS2 was able to evaluate timing of exposure, as similar methods were used for both young and old cohorts *Limitations* Biases towards the null: left truncation, non-differential exposure misclassification, low sensitivity	**Collective evidence (21 studies)** *Strengths* Adequacy of database: 13 informative (high or moderate quality) studies 9 case-control and 4 cohort studies Consistency across studies, geographic locations, and occupations; evidence of an association in 11 of 13 informative studies and 6 of 8 lower-utility studies Consistent patterns of risk for work at younger ages at high duration or frequency seen in pooled analysis and a high-quality cohort study Unlikely to be explained by lifestyles confounders Patterns of exposure: highest risk found for persistent night shift work (duration, timing, frequency); exposure response found for duration and frequency in several studies High-quality pooled case-control analysis provides strong evidence of an association of night work with increased breast cancer risk *Limitations* Evidence primarily from case-control studies and 2 cohort studies; somewhat inconsistent evidence in cohort studies Unable to evaluate circadian disruption *per se*, or other components of night shift work.
Night shift work	Prostate cancer	10 studies of independent populations 5 cohort studies	**Strength** Controlled for known risk factors for prostate cancer **Limitations**	Adequacy of the database: 5 informative studies; potential biases in low-quality studies are most likely towards the null

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
		5 case-control studies	Non-differential exposure misclassification Low sensitivity	Consistent findings of an association among the most informative studies, with some support from lower-quality studies Some evidence for an exposure-duration response in 2 studies; risks found for long duration of working nights Few informative studies, and limited metrics evaluated
Night shift work	Colorectal cancer	5 studies of 6 independent populations	**Limitations** Potential for unmeasured confounding Non-differential exposure misclassification Low sensitivity	Adequacy of the database: only 3 informative studies Limited metrics evaluated Increased risk with ever exposure or long duration of exposure found in the informative studies, and some evidence of an exposure-duration response Potential differential risk between colon and rectal cancers Possibility of unmeasured confounding
	Lung cancer	5 studies of independent populations	**Strengths** Controlled for known risk factors **Limitations** Non-differential exposure misclassification Low sensitivity	Adequacy of the database: only 3 informative studies Four studies showed inconsistent findings with ever exposure to night shift work One study population (NHS/NHS2 cohort) saw an exposure-duration response Some evidence of increased risk among smokers, likely confounding the relationship
	Female hormonal cancers	3 studies of independent populations 2 ovarian 1 endometrial	**Strengths** Controlled for known risk factors **Limitations** Non-differential exposure misclassification Low sensitivity	Database was inadequate, given limited number of studies
Simulated shift work or jet lag	Mammary-gland tumors	**Experimental animals (mice)** 2 studies	**Strengths**	Simulated shift work or jet lag decreased latency to mammary-gland tumor development or increased multiplicity

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
		Shift work Transgenic mouse (*p53* conditional mutant); melatonin deficient Inverted LD cycle **Jet-lagged model** Female C3(1)/Tag transgenic mice Advance light onset by 12 hr, followed by a 12-hr LD cycle for seven days.	Both studies measured markers of circadian disruption (e.g., clock genes) **Limitations** Limited reporting on number of tumors for each exposure group Cancer-susceptible model or initiation/promotion design limited the ability to look at tumor incidence or spontaneous tumors Melatonin-deficient mice	Only 2 studies of mammary-gland tumors available Simulated shift work or jet lag promoted progression or growth of other types of tumors
Simulated shift work or jet lag	Other tumors	**Experimental animals (rats and mice)** *Animal models* Spontaneous tumors Initiation/promotion Xenografts	**Strengths** Multiple studies that included melatonin-proficient animals **Limitations** Some studies of spontaneous tumors were of limited utility because of poor reporting; pathology and necropsy methods were unclear, especially for looking at number or incidences of specific tumor types Other studies looked only at tumor growth, latency or animal survival	Consistent evidence of tumor promotion and growth Tumors: liver, lymphoma, Ehrlich carcinoma, sarcoma 180, Glasgow osteosarcoma, pancreatic adenocarcinoma, lung carcinoma, plasmacytoma Some evidence that chronic jet lag increased spontaneous liver tumors
LAN and transmeridian travel cancer studies				
LAN	Breast cancer	**Humans (epidemiology)** 2 cohort studies, 1 case referent study, and 1 case-control study of outdoor light	**Strengths** One study evaluated exposure to blue light **Limitations** Non-differential misclassification in exposure assessment	A few studies found an association with outdoor light or living near a strong LAN source; however, it is not clear whether LAN was a proxy for other activities Inconsistent across studies of indoor light; somewhat more consistent for measures of presumed higher exposure

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
		using satellite data and addresses 1 case-control study of living near strong LAN source, 10 studies (2 cohort and 8 case-control studies) on light in the sleep area, based on self-report	Potential confounding from lifestyle factors	Difficult to compare findings across studies, as exposure metrics varied
LAN (proxy)	Mammary-gland tumors or human breast tumors	**Experimental animals** **(rats and mice)** *Light exposures* Continuous light Dim or interrupted light Blood from humans exposed to LAN *Animal models* Spontaneous tumors Initiation/promotion Xenografts	**Strengths** Some studies used human breast tissue or cells and measured tumor growth **Limitations** Studies of spontaneous tumors were of limited utility because of poor reporting; pathology and necropsy methods were unclear, especially for looking at number or incidences of specific tumor types Other studies looked only at tumor growth, latency, or animal survival	Consistent evidence of tumor promotion from studies of continuous light or dim LAN Consistent evidence that dim LAN promotes human breast cancer growth and mouse mammary-gland tumor growth Melatonin-depleted blood from humans exposed to LAN promoted breast cancer growth Decreased latency of all tumors in rats exposed at early but not late age; non-significant increase in incidence of mammary-gland tumors Animals more sensitive to LAN than humans Dim LAN or light during the night may be more relevant to human exposure than continuous light
LAN (proxy)	Other tumors	Same as above	**Strengths** Some studies used human tumors or cells (cervical) and measured tumor growth **Limitations** same as above	Consistent evidence of tumor promotion and growth from studies of continuous light, intermittent light, or dim LAN Tumor types: brain (glioma), mammary gland, human breast, human cervix, liver, lung, skin, kidney, peripheral nervous system, and prostate. Some evidence that continuous light or long light days (natural lighting conditions of NW Russia) increased spontaneous tumors or decreased latency of several types

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
				of spontaneous tumors including mammary gland, lung, leukemia/lymphoma, and Leydig-cell tumors.
Transmeridian travel	Breast cancer	**Humans (epidemiology)** 1 prospective cohort, 2 retrospective cohorts, and 1 nested case-control study of female flight attendants	**Strengths** Large cohorts of flight attendants; linkage with population-based cancer registries. **Limitations** Potential selection of oldest survivors; inadequate information on number of time zones crossed; exposure metrics highly correlated; potentially uncontrolled confounding; limited ability to differentiate most highly exposed individuals	Inadequate evidence to assess carcinogenicity of transmeridian travel from studies in humans Strongest evidence is for a small subset of high-parity women from a nested case-control study with high-quality exposure assessment; some evidence from 2 low-utility studies based on poor exposure assessment that failed to adequately capture number of time zones crossed
Melatonin studies				
LAN exposure among night shift workers	Melatonin suppression or breast cancer	Melatonin: Field studies Breast cancer: 1 case-control study	**Strengths** Measured light exposure **Limitations** Few subjects in each study Some studies done on shift workers (compared day vs. night shift workers) Some studies measured day and night at same calendar but not chronological time (e.g., related to sleep)	Unclear because of limited studies Some studies found an inverse relationship between light levels and melatonin levels Some studies found evidence of melatonin suppression for night shift vs. day shift in rotating-shift workers Case-control study found a modest association with high level of exposure to LAN during night work (OR = 1.25, 95% CR = 0.98–1.59)
LAN	Melatonin suppression and human breast cancer or mammary-	Studies in experimental animals Light initiation-promotion studies ± melatonin	**Strengths** Evaluated role of melatonin in LAN-induced tumors Human relevance **Limitations**	Co-exposure to melatonin restored mammary-gland tumor inhibitory activity in initiation-promotion studies of continuous light Co-exposure to melatonin restored human breast cancer inhibitory activity in xenograft studies of dim light or blood from women exposed to LAN

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
	gland tumors	Dim light human cancer xenograft or implant studies ± melatonin Human blood from women exposed to LAN	Measured only tumor progression and growth	
Melatonin levels	Breast cancer	5 informative cohort studies measuring urinary melatonin levels and follow-up for breast cancer	**Strength** Well-designed large cohorts **Limitations** Inconsistencies across studies in urine sampling	Some evidence of inverse relationship with urinary melatonin level, especially among post-menopausal women; inconsistent findings, especially with time period of follow-up, in pre-menopausal women
Abnormal melatonin rhythms (proxy)	Breast cancer Prostate cancer	**Breast cancer** 2 cohort studies (3 publications) and 1 cross-sectional survey of visually impaired people **Prostate cancer** 2 cohort studies	**Strengths** Information on different types of visual impairment **Limitations** No control for other potential confounders; however, confounding would likely overestimate the risk Small number of cases Cross-sectional study	Decreased breast cancer incidence in blind people; cancer risk decreased with increasing amount of vision loss Some evidence of decreased prostate cancer among blind people The degree of melatonin suppression varied with the causes of vision loss Most blind people have abnormal circadian rhythms; some may have normal rhythms

Table 7-3. Evidence-based mechanistic data

Exposure or MOA	End point or outcome	Evidence stream or approach	Confidence in the evidence	Overall evaluation
Circadian disruption: Melatonin suppression	Breast cancer	Molecular epidemiology studies measuring nocturnal urinary melatonin levels (or cosinor analysis) in night-shift workers Some studies measured LAN and melatonin level among shift workers Experimental studies of LAN and melatonin suppression in humans Experimental studies of LAN, melatonin suppression, and tumor promotion in animals Melatonin studies and cancer in humans (levels or using blind people as a surrogate) and animals Experimental studies: *in vivo* or *in vitro* mechanistic studies	Strong evidence for melatonin suppression in night-shift workers Database for melatonin suppression in shift-work animal models is inadequate Strong evidence that electrical LAN exposure in people's everyday lives (depending on the wavelength, level, duration, and photic history) can cause melatonin suppression Some evidence that higher melatonin levels are related to decreased cancer incidence Strong evidence that melatonin can reduce tumor growth and for its oncostatic properties, which may offer protection from all biological effects considered to be hallmarks of cancer Oncostatic properties involve epigenetic mechanisms relevant to cancer, particularly breast cancer	Indirect evidence that melatonin suppression contributes to breast cancer development in night-shift workers Strong evidence that melatonin suppression plays a role in LAN-induced breast carcinogenicity in experimental animals Data inadequate to evaluate whether LAN during night work contributes to cancer risk
Circadian disruption: Altered clock-gene expression SNS dysfunction	Cancer	Molecular epidemiology studies of clock gene expression in night shift workers Experimental animal studies of simulated shift work or jet lag and SNS dysfunction and/or clock-gene expression; three were carcinogenicity studies Experimental studies of light and clock-gene expression in humans and animals Experimental animal studies: clock-gene genetic models	Some evidence that shift work and LAN alter clock-gene expression in humans and experimental animals Limited number of studies with varied protocols Most studied Period genes Moderate evidence that altered clock-gene expression and SNS dysfunction are related to tumor growth Strong evidence that the circadian system plays an important role in suppressing the hallmarks of cancer Tumor suppressor, role in DNA repair, metabolism, cell cycle, cell proliferation, and apoptosis Circadian clock is regulated at the epigenetic level	Strong (although indirect) evidence that disrupted circadian homeostasis (i.e., altered clock-gene expression and SNS signaling) play a role in LAN and shift-work-associated cancers

Exposure or MOA	End point or outcome	Evidence stream or approach	Confidence in the evidence	Overall evaluation
		(knockout or mutation) and cancer Experimental studies: *in vivo* or *in vitro* mechanistic studies	Studies in mice show some evidence that chronic CJL-induced SNS dysfunction has a key role in inhibiting the ATM-p53 tumor suppressor pathway while promoting oncogenic pathways in the liver and other tissues Some studies in shift workers have found effect modification of clock-gene polymorphisms for both breast and prostate cancer	
Night-shift work	Key characteristics of carcinogens	Molecular epidemiology studies among shift workers Experimental animal studies: simulated shift work or jet-lag models	Moderate evidence for epigenetic changes (clock genes or cancer pathways) in humans Moderate evidence for changes in estrogen levels in humans Some evidence to moderate evidence for ↓ DNA repair, ↑ oxidative DNA damage, and ↑ inflammation in night shift workers or animal studies DNA repair and inflammation linked to breast tumors in experimental animals Oxidative DNA damage correlated with low melatonin levels in shift workers	Shift-work-induced biological effects are related to those controlled by clock genes and/or melatonin Epigenetic effects are consistent with modes of action involving melatonin circadian clock-gene deregulation; these may be early events Studies in experimental animals provide a link between biological effects and tumor progression or growth
LAN	Key characteristics of carcinogens	Experimental animal studies	Strong evidence for metabolic changes that promote tumor growth Linked to LAN-promoted growth and progression of breast and other tumors in animals Some evidence for ↑ oxidative stress, ↑ DNA damage, ↑ inflammation, and changes in estrogen levels or function DNA damage, oxidative stress, and estrogen effects linked to mammary-gland or other tumor growth in experimental animals	LAN-induced biological effects are related to those controlled by clock genes and/or melatonin Studies in experimental animals provide a link between biological effects and tumor progression or growth

7.5 Resources and Recommendations for Limiting Exposure

The cancer hazard conclusion for night shift work is for specific working conditions, i.e., persistent night shift work that causes circadian disruption. Several agencies and health organizations — e.g., National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA) and the Canadian Centre for Occupational Health and Safety (CCOHS) — have provided recommendations for limiting the types of working conditions that may be associated with cancer. They include: (1) guidelines for employers regarding scheduling worker shifts such as the type, number of shifts and recovery, and rest periods and (2) recommendations, training, and factual information for employees working night shifts. Links to these resources are listed below.

- NIOSH: https://www.cdc.gov/niosh/topics/workschedules/
- OSHA: https://www.osha.gov/SLTC/workerfatigue/additionalinformation.html
- CCOHS: https://www.ccohs.ca/oshanswers/ergonomics/shiftwrk.html

Several federal agencies have issued regulations regarding night shift schedules (such as limiting the frequency and length of night shifts and requiring recovery or rest periods) or provide guidance to reduce working conditions that could lead to circadian disruption; these are listed below. Other federal regulatory agencies (e.g., the Federal Motor Carrier Safety Administration and the Department of Veterans Affairs) have promulgated regulations associated with duty time. Those regulations limit the number of hours worked in general (e.g., limitations on driving time), without specifically addressing work performed within the time period (midnight to 5:00 AM) defined as night work in this profile, and therefore are not included here. Currently, no specific OSHA standard exists for extended or unusual work shifts; however, OSHA does provide recommendations for shift workers and employees as mentioned above.

Table 7-4. Federal regulations to limit exposure to night shift work resulting in circadian disruption

Agency	Limits hours worked during night	Limits frequency consecutive night shifts	Provides for recovery or rest periods
Federal Aviation Administration (FAA)	X	X	X
Federal Railroad Administration (FRA)		X	X
Nuclear Regulatory Commission (NRC)			X

American Conference of Governmental Industrial Hygienists (ACGIH) has provided guidance for optimizing lighting conditions (e.g. balance of using blue wavelength-depleted light and blue-wavelength-enriched light that is appropriate for the task) in occupational settings to minimize circadian disruption.

Abbreviations

ACF	aberrant colon crypt foci
ACS	American Cancer Prevention Study II
Akt	protein kinase B
ALAN	artificial light at night
AMOLED	active-matrix organic LEDs
aMT6s	6-sulfatoxymelatonin
BCEES	Breast Cancer Employment and Environment Study
BLS	Bureau of Labor Statistics
BMAL1	brain and muscle aryl hydrocarbon receptor nuclear translocator [ARNT]-like
BMI	body mass index
CBCS	Canadian Breast Cancer Study
CDC	Centers for Disease Control and Prevention
CECILE	Cote d'Or and Ille-et-Vilaine, France
CFL	compact fluorescent light
CI	confidence intervals
CJL	chronic jet lag
CLA	circadian light
CLOCK	circadian locomotor output cycles kaput
CRC	colorectal cancer
CS	circadian stimulus
D	day
DD	continuous dark; 24-hour dark
DEN	diethylnitrosamine
DLMO	dim light melatonin onset
DMBA	dimethylbenzanthracene
DMH	1,2 dimethylhydrazine
DMSO	dimethylsulfoxide
DMSP	U.S. Defense Meteorological Satellite Program
DMSP-OLS	Defense Meteorological Satellite Program-Operational Linescan System
DNA	deoxyribonucleic acid
DOE	U.S. Department of Energy

DSLR	digital single-lens reflex
DSW	day shift workers
EBCLIS	Electromagnetic Fields and Breast Cancer on Long Island Study
EPICAP	Epidemiology of Prostate Cancer (study)
ER	estrogen receptor
ERK 1/2	extracellular signal-regulated kinase
F	female
FSH	follicle-stimulating hormone
GENICA	Gene Environment Interaction and Breast Cancer (study)
GSH-Px	glutathione peroxidase
HAL	halogen
HAT	histone acetyltransferase
HeLa	Henrietta Lacks cell line (namesake)
HER2	human epidermal growth factor receptor-2
HHS	Department of Health and Human Services
HPA	hypothalamic-pituitary-adrenal axis
HPG	hypothalamic-pituitary-gonadal axis
hr	hour
HR	hazard ratio
hTERT	telomerase reverse transcriptase
HWSE	healthy-worker survivor effect
I	inconclusive conclusions
IARC	International Agency for Research on Cancer
INC	incandescent
ISS	International Space Station
JEM	job exposure matrix
JRK	Jerky protein homolog
LAN	light at night
LCDs	liquid crystal displays
LD cycles	light:dark
LED	light emitting diode
LH	luteinizing hormone

LINE 1	long interspersed element-1
LL	24-hour light; constand light; continuous light
LPS	lipopolysaccharide
M	male
MAPK	mitogen-activated protein kinase
MCC-Spain	Multi Case-Control-Spain (study)
miRNAs	micro ribonucleic acid
mo	month
mRNA	messenger ribonucleic acid
MSI	melatonin suppression index
N	night; number of particpants; study population
NASA	National Aeronautics and Space Administration
NCTR/FDA	National Center for Toxicological Research of the Food and Drug Administration
NDI	National Death Index
NEU	*N*-nitrosoethylurea
NHANES	National Health and Nutritional Examination Survey
NHIS–OHS	National Health Interview Survey and Occupational Health Supplement
NHL	non-Hodgkin lymphoma
NHS	Nurses Health Study
NHS2	Nurses' Health Study 2
NIEHS/NIH	National Institutes of Health
NIOSH/CDC	National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention
NK	natural killer (cell)
NMU	*N*-nitroso-*N*-methylurea
NOS	nitric oxide synthase
NR	not reported
ns	not statistically significant
NSW	night shift workers
NTP	National Toxicology Program
OLED	organic LED(s)
OR	odds ratio
ORDET	Hormones and Diet in the Etiology of Breast Cancer Risk

P	probability value
PHS	Public Health Service
PR	progesterone receptor
Pre	premenopausal women
PSA	prostate-specific antigen
Ptrend	probability value-test for trend
REM	rapid eye movement
RGB	red [R], green [G], blue [B]
RNA	ribonucleic acid
RNU	Rowett nude rats
RoC	Report on Carcinogens
ROS	reactive oxygen species
RR	relative risk ratio
SAS	Swedish Scandinavian Airline System
SCN	suprachiasmatic nucleus
SD	standard deviation
SEEM	Selective Estrogen Enzyme Modulator
SEER	Surveillance, Epidemiology, and End Results
SERM	selective estrogen receptor modulator
SHR	spontaneously hypertensive rat
sign.	statistically significant
SIR	standardized incidence rate
SIR study	Swedish Cancer Registry or Cause of Death Register
SIRT1	sirtuin 1
SIRT6	sirtuin 6
SNPs	single nucleotide polymorphisms
SNS	sympathetic nervous system
SOD	superoxide dismutase
SPDs	spectral power distributions
SRR	standardized relative risk
STAT	signal transducer and activator of transcription
TBARs	thiobarbituric acid reactive substances

UaMT6s	urinary 6-sulphatoxymelatonin
UV-B	ultraviolet B radiation
VDR	vitamin D receptor
VEGF	vascular endothelial growth factor
WHI	Women's Health Initiative
WOLF	Work, Lipids, and Fibrinogen
YA	younger age
yr	year

Units of Measurement

Area

cm^2	square centimeter
m^2	square meter

Concentration

kg/m^2	kilogram per square meter

Light

cd	candela; the approximate luminous intensity of a standard candle
fc	foot-candle; the intensity of light cast on a surface by a 1-cd source 1 ft away
lumen	the SI unit of luminous flux, equal to the amount of light emitted per second in a unit solid angle of one steradian from a uniform source of one candela
lux	the SI unit of illuminance, equal to one lumen per square meter
$nW \cdot sr^{-1}/cm^2$	unit of radiance; nanowatt(s) per steradian per square centimeter (also, $nW/cm^2/sr$)
$\mu W/cm^2$	unit of irradiance; microwatt(s) per centimeter squared

Solid angles

sr	steradian; the SI unit of solid angle, i.e., of a cone within a sphere

Time

d	day(s)
hr	hour(s)
hr/night	hours(s) per night
hr/week	hour(s) per week
hour/week	hour(s) per week
min	minute(s)
mo	month(s)
yr	year(s)

Wavelength

nm	nanometer(s)

Glossary

Acrophase – The time of the highest or peak melatonin levels based on the parameters of a cosine function fitted to the raw data.

Amplitude – The difference between the lowest and highest level of melatonin based on the parameters of a cosine function fitted to the raw data.

Block hours – A term used in the airline industry to measure the time an aircraft is in use (or the period of work for the air crew), beginning with the time the aircraft pushes back from the departure gate and ending when it reaches the arrival gate following landing.

Chronotype – A measure of preference for activity earlier or later in the day.

Circadian disruption – Internally or externally induced, acute or chronic temporal disorganization including but not limited to misalignment of the time structure in living systems potentially leading to adverse health outcomes.

Circadian light – Light that impacts the circadian system, which is measured by the light that causes suppression of melatonin synthesis

Cosinor modeling – A procedure for the analysis of biological rhythms based on the fitting of a cosine wave to the raw data.

D'Amico classification – A system designed to evaluate the risk of recurrence of prostate cancer as low, intermediate, or high based on a combination of measures such as blood PSA levels, Gleason scores, and tumor stages.

Dim light melatonin onset – The onset of melatonin secretion (prior to bedtime) under dim light conditions. Dim light melatonin onset is the most sensitive and direct index for identifying an individual's biorhythm.

Diurnal – Occurring or active during the daytime.

Entrainment – The synchronization of a self-sustaining oscillation (such as a circadian rhythm) by a forcing oscillation (the zeitgeber). Under conditions of steady entrainment, the period of the self-sustaining oscillation conforms to that of the zeitgeber, and there is a stable phase relationship between the two of them.

Evening types – Evening-types (E-types) find difficult to get up in the morning and require more time to reach their optimal status.

Gleason score – A grading system used to determine the aggressiveness of prostate cancer on a scale up to 10 based on evaluation of tissue from a biopsy.

Jet lag – A malaise associated with the disruption of bodily rhythms caused by high speed air travel across time zones.

Job exposure matrix – A cross classification between a list of job titles and occupational exposures which may be chemicals, physical or biological agents, or psychosocial or ergonomic factors.

Light exposure/activity monitor – A device to approximate eye-level exposure to light, which also records the physical activity of the subject wearing the device.

Light intensity data loggers – A device to approximate eye-level exposure to light.

Light trespass – Light being cast where it is not wanted or needed.

Likert scale – A rating system used in questionnaires that offers a range or resonses to a specific question or statement that may range from very positive (e.g., "strongly agree") to very negative (e.g., "strongly disagree"); the categories are often coded numerically.

Lux – A photometric unit that takes into account the sensitivity of the human visual system to different wavelengths.

Mesor –A circadian rhythm-adjusted mean based on the parameters of a cosine function fitted to the raw data, or the average level of melatonin.

Morning types – Morning-types (M-types), are active early in the morning and soon reach their peak in mental and physical performance but tire early in the evening.

Nocturnal – Occurring or active during the nighttime.

Phase shift – A discrete displacement of an oscillation along the time axis. Phase shifts may be either advances (i.e., the phase reference point occurs earlier than normal) or delays (i.e., the phase reference point occurs later than normal).

Retinohypothalamic tract – the monosynaptic pathway that connects the retina (in the eye) to the hypothalamus (in the diencephalon).

Self-luminous display – An electronic device (e.g., cell phones, computer screens, e-readers, or tablets) display having in itself the property of emitting light, thereby requiring no backlight.

Shift work – Any arrangement of daily working hours other than standard daylight hours (7:00 AM or 8:00 AM to 5:00 PM or 6:00 PM). Night work is typically defined as working time that extends into the night (e.g., at least 3 hours worked between midnight and 5:00 AM).

Sky glow at night – The brightening of the sky caused by outdoor lighting and natural atmospheric and celestial factors.

Social jet lag – Misalignment between one's circadian and social clocks, e.g. waking to an alarm clock on weekdays for work or school and then sleeping and waking without an alarm on the weekend (i.e., "sleeping in").

Spectral power distribution – A pictorial representation of the radiant power emitted by a light source at each wavelength or band of wavelengths in the visible region of the electromagnetic spectrum.

Suprachiasmatic nucleus (SCN) – a small group of nerve cells lying in the ventral hypothalamus and possessing the properties of a circadian pacemaker.

Transmeridian travel – East-to-west or west-to-east travel.

Visible light – Light that reaches the eye, which can be either monochromatic (light of a single wavelength or limited range of wavelengths interpreted by the human eye as a single color, such as violet, blue, green, yellow, orange, or red) or polychromatic (light composed of more than one wavelength, including white light, which includes all wavelengths of visible light from 380 to about 780 nm).

Xenograft – A surgical graft of tissue from one species to an unlike species.

Zeitgeber – German word for *time giver*; is used in circadian biology to describe any daily environmental cue that synchronizes or entrains the circadian system

References

1. Ackermann K, Plomp R, Lao O, Middleton B, Revell VL, Skene DJ, Kayser M. 2013. Effect of sleep deprivation on rhythms of clock gene expression and melatonin in humans. *Chronobiol Int* 30(7): 901-909. (Supported by Philips Lighting, the Netherlands Forensic Institute , the Netherlands Genomics Initiative [NGI]/Netherlands Organization for Scientific Research [NOW] within the framework of the Forensic Genomics Consortium Netherlands [FGCN], by the 6th Framework project EUCLOCK, and by the UK Biotechnology and Biological Sciences Research Council [BBSRC]. Authors affiliated with Erasmus MC University Medical Center Rotterdam, Netherlands; University of Surrey, UK.)

2. Adams CD, Jordahl KM, Copeland W, Mirick DK, Song X, Sather CL, Kelsey K, Houseman A, Davis S, Randolph T, Bhatti P. 2017. Nightshift work, chronotype, and genome-wide DNA methylation in blood. *Epigenetics* 12(10): 833-840. (Supported by NIEHS, NCI, the Safeway Foundation, Cancer Research UK and the Medical Research Council. Authors affiliated with University of Bristol, UK; Fred Hutchinson Cancer Research Center, WA; Brown University, RI; Oregon State University, OR.)

3. Adams SL, Roxe DM, Weiss J, Zhang F, Rosenthal JE. 1998. Ambulatory blood pressure and Holter monitoring of emergency physicians before, during, and after a night shift. *Acad Emerg Med* 5(9): 871-877. (Supported by Mr. and Mrs. Everett P. Weaver. Authors affiliated with Northwestern University Medical School, IL.)

4. Åkerstedt T, Knutsson A, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. 2015. Night work and breast cancer in women: a Swedish cohort study. *BMJ Open* 5(4): e008127. (Supported by the AFA Insurance Company. Authors affiliated with Karolinska Institutet, Sweden; Stockholm University, Sweden; Mid Sweden University, Sweden; Radboud University, Netherlands.)

5. Åkerstedt T, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. 2017. Night work and prostate cancer in men: a Swedish prospective cohort study. *BMJ Open* 7(6): e015751. (Supported by the AFA Insurance Company. Authors affiliated with Karolinska Institutet, Sweden; Stockholm University, Sweden; Radboud University, Netherlands.)

6. Aktan E, Kaleli B, Alatas E. 1997. Is there any change in the prolactin levels of nurses in the morning after night shift? *Aust N Z J Obstet Gynaecol* 37(4): 429-430. (Support not reported. Authors affiliated with Pamukkale University Medical Faculty, Turkey.)

7. Alefishat E, Abu Farha R. 2016. Determinants of vitamin D status among Jordanian employees: Focus on the night shift effect. *Int J Occup Med Environ Health* 29(5): 859-870. (Supported by the University of Jordan. Authors affiliated with University of Jordan, Jordan; Applied Science Private University, Jordan.)

8. Allott EH, Masko EM, Freedland SJ. 2013. Obesity and prostate cancer: weighing the evidence. *Eur Urol* 63(5): 800-809. (Supported by NCI, the Department of Defense Prostate Cancer Research Program, and NIH. Authors affiliated with Duke University Medical Center, NC.)

9. Alterman T, Luckhaupt SE, Dahlhamer JM, Ward BW, Calvert GM. 2013. Prevalence rates of work organization characteristics among workers in the U.S.: data from the 2010 National Health Interview Survey. *Am J Ind Med* 56(6): 647-659. (Support not reported. Authors affiliated with CDC, OH and MD.)

10. Altman BJ. 2016. Cancer clocks out for lunch: Disruption of circadian rhythm and metabolic oscillation in cancer. *Front Cell Dev Biol* 4: 62. (Supported by NCI and NIH. Authors affiliated with Abramson Family Cancer Research Institute, PA; Abramson Cancer Center, PA; University of Pennsylvania Perelman School of Medicine, PA.)

11. AMA. 2016. *AMA Adopts Guidance to Reduce Harm from High Intensity Street Lights*. American Medical Association. Updated on 6/14/16. https://www.ama-assn.org/ama-adopts-guidance-reduce-harm-high-intensity-street-lights

12. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. 2009. Breast cancer before age 40 years. *Semin Oncol* 36(3): 237-249. (Support not reported. Authors affiliated with University of North Carolina at Chapel Hill, NC; Seattle Children's Hospital, WA; University of Texas M.D. Anderson Cancer Center, TX; Princess Margaret Hospital for Children, Australia; St. Charles Medical Center, OR.)

13. Andersen M, Mardaljevic J, Lockley SW. 2012. A framework for predicting the non-visual effects of daylight - part I: Photobiology-based model. *Light Res Technol* 44(1): 37-53. (Supported by the Velux Corporation, the Ecole Polytechnique Fédérale de Lausanne and John Mardaljevic by De Montfort University. Authors affiliated with Ecole Polytechnique Fédérale de Lausanne, Switzerland; De Montfort University, UK.)

14. Anderson LE, Morris JE, Sasser LB, Stevens RG. 2000. Effect of constant light on DMBA mammary tumorigenesis in rats. *Cancer Lett* 148(2): 121-126. (Support not reported. Authors affiliated with Pacific Northwest National Laboratory, WA.)

15. Anderson WF, Rosenberg PS, Prat A, Perou CM, Sherman ME. 2014. How many etiological subtypes of breast cancer: two, three, four, or more? *J Natl Cancer Inst* 106(8). (Supported by NIH and NCI. Authors affiliated with National Cancer Institute, MD; Vall d´Hebron Institute of Oncology, Spain; University of North Carolina at Chapel Hill, NC.)

16. Anisimov VN, Baturin DA, Popovich IG, Zabezhinski MA, Manton KG, Semenchenko AV, Yashin AI. 2004. Effect of exposure to light-at-night on life span and spontaneous carcinogenesis in female CBA mice. *Int J Cancer* 111(4): 475-479. (Supported by the Russian Foundation for Basic Research and Duke University. Authors affiliated with N.N. Petrov Research Institute of Oncology, Russia; Duke University, NC; Max-Planck Institute for Demographic Research, Germany.)

17. Anisimov VN, Popovich IG, Shtylik AV, Zabezhinski MA, Ben-Huh H, Gurevich P, Berman V, Tendler Y, Zusman I. 2000. Melatonin and colon carcinogenesis. III. Effect of melatonin on proliferative activity and apoptosis in colon mucosa and colon tumors induced by 1,2-dimethylhydrazine in rats. *Exp Toxicol Pathol* 52(1): 71-76. (Supported by the Russian Ministry of Science State Program "National Priorities in Medicine and Health." Authors affiliated with N.N. Petrov Research Institute of Oncology, Russia;

Kaplan Hospital, Israel; Hebrew University of Jerusalem, Israel; Rambam Medical Center, Israel.)

18. Anisimov VN, Popovich IG, Zabezhinski MA. 1997. Melatonin and colon carcinogenesis: I. Inhibitory effect of melatonin on development of intestinal tumors induced by 1,2-dimethylhydrazine in rats. *Carcinogenesis* 18(8): 1549-1553. (Supported by the The Russian Ministry of Science State Program 'National Priorities in Medicine and Health.' Authors affiliated with N.N. Petrov Research Institute of Oncology, Russia.)

19. Anisimov VN, Vinogradova IA, Panchenko AV, Popovich IG, Zabezhinski MA. 2012. Light-at-night-induced circadian disruption, cancer and aging. *Curr Aging Sci* 5(3): 170-177. (Supported by the Russian Federation and The Program of the Strategic Development 2012-2016 "Petrozavodsk State University Complex in Scientific-Education Space of European North"; from the Russian Foundation for Humantarian Research. Authors affiliated with N.N. Petrov Research Institute of Oncology, Russia; Petrozavodsk State University, Russia.)

20. Anisimov VN, Zhukova OV, Beniashvili DS, Bilanishvili VG, Menabde MZ. 1994. Light deprivation, electromagnetic fields and mammary carcinogenesis. *Adv Pineal Res* 7: 229-234. (Support not reported. Authors affiliated with N.N. Petrov Research Institute of Oncology, Russia; Oncology Research Center, Republic of Georgia.)

21. Anjum B, Singh RB, Verma N, Singh R, Mahdi AA, Singh RK, de Meester F, Wilczynska A, Takahashi T, Dharwadkar S, Wilson DW. 2012. Associations of circadian disruption of sleep and nutritional factors with risk of cancer. *Open Nutraceuticals J* 5(Suppl.1): 124-135. (Support not reported. Authors affiliated with C S M Medical University, India; Halberg Hospital and Research Institute, India; SGRRIM & HS, India; Tsim Tsoum Institute, Poland; Fukuoka Women's University, Japan; SB College of Science, India; School of Medicine and Health, UK.)

22. Anjum B, Verma NS, Tiwari S, Singh R, Fatima G, Singh P, Mishra S, Mahdi AA. 2013. Light exposure at night and rotating night shift associated with circadian disruption of 6-sulfatoxy melatonin. *Int J Med Res Health Sci* 2(4): 809-815. (Supported by the Council of Science & Technology, UP. Authors affiliated with King George's Medical University, India.)

23. Antoch MP, Gorbacheva VY, Vykhovanets O, Toshkov IA, Kondratov RV, Kondratova AA, Lee C, Nikitin AY. 2008. Disruption of the circadian clock due to the Clock mutation has discrete effects on aging and carcinogenesis. *Cell Cycle* 7(9): 1197-1204. (Supported by NCI and a NCRR/NIH Midcareer Award in Mouse Pathobiology. Authors affiliated with Roswell Park Cancer Institute, NY; Cleveland Clinic Foundation, OH; Cornell University, NY; Cleveland State University, OH; Florida State University, FL.)

24. Arble DM, Ramsey KM, Bass J, Turek FW. 2010. Circadian disruption and metabolic disease: findings from animal models. *Best Pract Res Clin Endocrinol Metab* 24(5): 785-800. (Supported by NIH/NIA and NIH/NHLBI. Authors affiliated with Northwestern University, IL.)

25. Archer SN, Laing EE, Moller-Levet CS, van der Veen DR, Bucca G, Lazar AS, Santhi N, Slak A, Kabiljo R, von Schantz M, Smith CP, Dijk DJ. 2014. Mistimed sleep disrupts circadian regulation of the human transcriptome. *Proc Natl Acad Sci U S A* 111(6): E682-691. (Supported by the Biotechnology and Biological Sciences Research Council, the Air Force Office of Scientific Research, and the Royal Society. Authors affiliated with University of Surrey, UK.)

26. Archer SN, Oster H. 2015. How sleep and wakefulness influence circadian rhythmicity: effects of insufficient and mistimed sleep on the animal and human transcriptome. *J Sleep Res* 24(5): 476-493. (Supported by the UK Biotechnology and Biological Sciences Research Council, the Air Force Office of Scientific Research, the German Research Foundation, and the Volkswagen Foundation. Authors affiliated with University of Surrey, UK; University of Lübeck, Germany.)

27. Arellanes-Licea E, Caldelas I, De Ita-Pérez D, Díaz-Muñoz M. 2014. The circadian timing system: A recent addition in the physiological mechanisms underlying pathological and aging processes. *Aging Dis* 5(6): 406-418. (Supported by CONACYT and DGAPA-PAPIIT. Authors affiliated with UNAM, Mexico.)

28. Arendt J. 2010. Shift work: coping with the biological clock. *Occup Med (Lond)* 60(1): 10-20. (Support not reported. Authors affiliated with University of Surrey, UK.)

29. Arnold M, Leitzmann M, Freisling H, Bray F, Romieu I, Renehan A, Soerjomataram I. 2016. Obesity and cancer: An update of the global impact. *Cancer Epidemiol* 41: 8-15. (Supported by the World Cancer Research Fund International. Authors affiliated with IARC, France; University of Regensburg, Germany; University of Manchester, UK.)

30. Asher G, Gatfield D, Stratmann M, Reinke H, Dibner C, Kreppel F, Mostoslavsky R, Alt FW, Schibler U. 2008. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell* 134(2): 317-328. (Supported by the Swiss National Foundation, the State of Geneva, the Louis Jeantet Foundation of Medicine, the Bonizzi-Theler Stiftuung, the 6th European Framework Project EUCLOCK, EMBO, the Human Frontier Science Program, and FEBS. Authors affiliated with University of Geneva, Switzerland; University of Ulm, Germany; Harvard Medical School, MA.)

31. Asher G, Sassone-Corsi P. 2015. Time for food: the intimate interplay between nutrition, metabolism, and the circadian clock. *Cell* 161(1): 84-92. (Supported by the Israel Science Foundation, the Abish-Frenkel Foundation, the HFSP Career Development Award, the European Research Council, NIH, ABOCA SpA [Italy], Institut National de la Sante et Recherche Medicale [INSERM, France], and a Novo Nordisk Foundation Challenge Grant. Authors affiliated with Weizmann Institute of Science, Israel; University of California, CA.)

32. Atoum M, Alzoughool F. 2017. Vitamin D and breast cancer: Latest evidence and future steps. *Breast Cancer (Auckl)* 11: 1178223417749816. (Supported by the Hashemite University. Authors affiliated with Hashemite University, Jordan.)

33. Aubert C, Janiaud P, Lecalvez J. 1980. Effect of pinealectomy and melatonin on mammary tumor growth in Sprague-Dawley rats under different conditions of lighting. *J Neural*

Transm 47(2): 121-130. (Supported by the Institut National de la Santé et de la Recherche Médicale. Authors affiliated with Institut Gustave-Roussy, France.)

34. Aubrecht TG, Weil ZM, Nelson RJ. 2014. Dim light at night interferes with the development of the short-day phenotype and impairs cell-mediated immunity in Siberian hamsters (*Phodopus sungorus*). *J Exp Zool A Ecol Genet Physiol* 321(8): 450-456. (Supported by NSF and NIDCR. Authors affiliated with Ohio State University Wexner Medical Center, OH.)

35. Aulitzky W, Keen F, Daxenbichler G. 1984. The circadian rhythms of serum prolactin in nurses working on a night shift. *Arch Gynecol* 236(2): 73-75. (Support not reported. Authors affiliated with Universitätsklinik für Frauenheilkunde, Austria.)

36. Balachandran D. 2011. Sleep and the immune system: Implications for health and mortality. In *Sleep & Safety* S Surani, S Subramanian, eds. Bentham Science Publishers Ltd. p. 52-59. (Support not reported. Author affiliated with University of Texas MD Anderson Cancer Center, TX.)

37. Ballesta A, Innominato PF, Dallmann R, Rand DA, Lévi FA. 2017. Systems chronotherapeutics. *Pharmacol Rev* 69(2): 161-199. (Supported by the 7th Framework Programme of the European Union through the Coordinating Action on Systems Medicine and by Cancer Research UK. Authors affiliated with University of Warwick, UK; Senate House, UK; INSERM, France; University Hospitals Birmingham National Health Service Foundation Trust, UK.)

38. Balsalobre A, Brown SA, Marcacci L, Tronche F, Kellendonk C, Reichardt HM, Schütz G, Schibler U. 2000. Resetting of circadian time in peripheral tissues by glucocorticoid signaling. *Science* 289(5488): 2344-2347. (Supported by the Swiss National Science Foundation, the Louis-Jeantet Foundation for Medicine, and the State of Geneva [U.S.] and by the Deutsche Forschungsgemeinschaft and the European Union. Authors affiliated with Université de Genève, Switzerland; Deutsches Krebsforschungzentrum, Germany.)

39. Baturin DA, Alimova IN, Anisimov VN, Popovich IG, Zabezhinski MA, Provinciali M, Mancini R, Franceschi C. 2001. The effect of light regimen and melatonin on the development of spontaneous mammary tumors in HER-2/neu transgenic mice is related to a downregulation of HER-2/neu gene expression. *Neuro Endocrinol Lett* 22(6): 441-447. (Supported by the Russian Foundation for Basic Research and Duke University. Authors affiliated with N.N. Petrov Research Institute of Oncology, Russia; INRCA, Italy; University of Bologna, Italy.)

40. Bauer SE, Wagner SE, Burch J, Bayakly R, Vena JE. 2013. A case-referent study: light at night and breast cancer risk in Georgia. *Int J Health Geogr* 12: 23. (Supported by the Georgia Cancer Coalition. Authors affiliated with University of Georgia, GA; University of South Carolina, SC; Georgia Comprehensive Cancer Registry, GA.)

41. Bedrosian TA, Fonken LK, Walton JC, Nelson RJ. 2011. Chronic exposure to dim light at night suppresses immune responses in Siberian hamsters. *Biol Lett* 7(3): 468-471. (Supported by the U.S. National Science Foundation and the U. S. Department of Defense

through the National Defense Science and Engineering Graduate Fellowship [NDSEG] program. Authors affiliated with Ohio State University Medical Center, OH.)

42. Bedrosian TA, Galan A, Vaughn CA, Weil ZM, Nelson RJ. 2013. Light at night alters daily patterns of cortisol and clock proteins in female Siberian hamsters. *J Neuroendocrinol* 25(6): 590-596. (Supported by a National Defense Science and Engineering Graduate [NDSEG] fellowship and NSF. Authors affiliated with Ohio State University Wexner Medical Center, OH.)

43. Bedrosian TA, Nelson RJ. 2013. Influence of the modern light environment on mood. *Mol Psychiatry* 18(7): 751-757. (Support not reported. Authors affiliated with Ohio State University Wexner Medical Center, OH.)

44. Behrens T, Rabstein S, Wichert K, Erbel R, Eisele L, Arendt M, Dragano N, Brüning T, Jöckel KH. 2017. Shift work and the incidence of prostate cancer: a 10-year follow-up of a German population-based cohort study. *Scand J Work Environ Health* 43(6): 560-568. (Supported by the German Social Accident Insurance, the Heinz Nixdorf Foundation, the German Ministry of Education and Science, the Kulturstiftung Essen, and the German Research Foundation. Authors affiliated with Institute of the Ruhr-Universität Bochum, Germany; University Hospital of Essen, Germany; Heinrich Heine University, Germany.)

45. Belancio VP. 2015. LINE-1 activity as molecular basis for genomic instability associated with light exposure at night. *Mob Genet Elements* 5(3): 1-5. (Support not reported. Authors affiliated with Tulane University, LA.)

46. Ben-Shlomo R. 2014. Chronodisruption, cell cycle checkpoints and DNA repair. *Indian J Exp Biol* 52(5): 399-403. (Support not reported. Author affiliated with University of Haifa, Israel.)

47. Beniashvili DS, Benjamin S, Baturin DA, Anisimov VN. 2001. Effect of light/dark regimen on *N*-nitrosoethylurea-induced transplacental carcinogenesis in rats. *Cancer Lett* 163(1): 51-57. (Support not reported. Authors affiliated with G. Wolfson Medical Center, Israel; N.N. Petrov Research Institute of Oncology, Russia.)

48. Benna C, Helfrich-Förster C, Rajendran S, Monticelli H, Pilati P, Nitti D, Mocellin S. 2017. Genetic variation of clock genes and cancer risk: a field synopsis and meta-analysis. *Oncotarget* 8(14): 23978-23995. (Supported by the University of Padova. Authors affiliated with University of Padova, Italy; University of Würzburg, Germany; Azienda Ospedaliera Padova, Italy; Sant'Antonio Hospital, Italy; IOV-IRCSS, Italy.)

49. Benot S, Molinero P, Soutto M, Goberna R, Guerrero JM. 1998. Circadian variations in the rat serum total antioxidant status: correlation with melatonin levels. *J Pineal Res* 25(1): 1-4. (Supported by the Dirección General de Investigación Científica y Técnica. Authors affiliated with University of Seville School of Medicine, Spain; Virgen Macarena Hospital, Spain.)

50. Berson DM, Dunn FA, Takao M. 2002. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295(5557): 1070-1073. (Supported by NIH. Authors affiliated with Brown University, RI.)

51. Bhatti P, Cushing-Haugen KL, Wicklund KG, Doherty JA, Rossing MA. 2013a. Nightshift work and risk of ovarian cancer. *Occup Environ Med* 70(4): 231-237. (Supported by the US National Cancer Institute. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; Geisel School of Medicine at Dartmouth, NH.)

52. Bhatti P, Mirick DK, Davis S. 2013b. Racial differences in the association between night shift work and melatonin levels among women. *Am J Epidemiol* 177(5): 388-393. (Supported by NIH. Authors affiliated with Fred Hutchinson Cancer Research Center, WA.)

53. Bhatti P, Mirick DK, Davis S. 2014. The impact of chronotype on melatonin levels among shift workers. *Occup Environ Med* 71(3): 195-200. (Supported by the US National Cancer Institute. Authors affiliated with Fred Hutchinson Cancer Research Center, WA.)

54. Bhatti P, Mirick DK, Randolph TW, Gong J, Buchanan DT, Zhang JJ, Davis S. 2016. Oxidative DNA damage during sleep periods among nightshift workers. *Occup Environ Med* 73(8): 537-544. (Supported by the V Foundation for Cancer Research and the US National Cancer Institute. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; Duke University, NC; University of Washington, WA.)

55. Bhatti P, Mirick DK, Randolph TW, Gong J, Buchanan DT, Zhang JJ, Davis S. 2017. Oxidative DNA damage during night shift work. *Occup Environ Med* 74: 680-683. (Supported by the Fred Hutchinson Cancer Research Center, V Foundation for Cancer Research and the US National Cancer Institute. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; Duke University, NC; Peking University, China; University of Washington, WA.)

56. Bhatti P, Zhang Y, Song X, Makar KW, Sather CL, Kelsey KT, Houseman EA, Wang P. 2015. Nightshift work and genome-wide DNA methylation. *Chronobiol Int* 32(1): 103-112. (Supported by the Fred Hutchinson Cancer Research Center and the Safeway Foundation. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; Brown University, RI; Oregon State University, OR; Mount Sinai Hospital, NY.)

57. Bierman A, Klein TR, Rea MS. 2005. The daysimeter: A device for measuring optical radiation as a stimulus for the human circadian system. *Measure Sci Technol* 16: 2292-2299. (Supported by the California Energy Commission, Connecticut Light and Power, Iowa Energy Center, New York State Energy Research and Development Authority, North Carolina Daylighting Consortium, Northwest Energy Efficiency Alliance, and the United States Department of Energy. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

58. Bjarnason GA, Jordan RC, Sothern RB. 1999. Circadian variation in the expression of cell-cycle proteins in human oral epithelium. *Am J Pathol* 154(2): 613-622. (Supported by the PMAC Health Research Foundation/Medical Research Council of Canada, The Sunnybrook Research Foundation, and a donation from Kathy and Paul Potvin. Authors affiliated with University of Toronto, Canada; Sunnybrook Health Science Centre, Canada; University of Minnesota, MN.)

59. Bjarnason GA, Jordan RC, Wood PA, Li Q, Lincoln DW, Sothern RB, Hrushesky WJ, Ben-David Y. 2001. Circadian expression of clock genes in human oral mucosa and skin: association with specific cell-cycle phases. *Am J Pathol* 158(5): 1793-1801. (Supported by the Pharmaceutical Manufacturers Association of Canada Health Research Foundation/Medical Research Council of Canada, The Medical Research Council of Canada, the National Cancer Institute of Canada, the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, the Robison Family Foundation, and the National Institutes of Health. Authors affiliated with Toronto-Sunnybrook Regional Cancer Centre, Canada; University of Toronto, Canada; Sunnybrook and Women's College Health Sciences Centre, Canada; WJB Dorn VA Medical Center, SC; Stratton Veterans Affairs Medical Center, NY; University of Minnesota, MN.)

60. Blask DE, Brainard GC, Dauchy RT, Hanifin JP, Davidson LK, Krause JA, Sauer LA, Rivera-Bermudez MA, Dubocovich ML, Jasser SA, Lynch DT, Rollag MD, Zalatan F. 2005. Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res* 65(23): 11174-11184. (Supported by NIH, the Laura Evans Memorial Breast Cancer Research Award of the Edwin W. Pauley Foundation, the Louis Busch Hager Cancer Center and the Stephen C. Clark Foundation. Authors affiliated with Bassett Research Institute, NY; Thomas Jefferson University, PA; Northwestern University Feinberg School of Medicine, IL; Uniformed Services University of the Health Sciences, MD.)

61. Blask DE, Dauchy RT, Brainard GC, Hanifin JP. 2009. Circadian stage-dependent inhibition of human breast cancer metabolism and growth by the nocturnal melatonin signal: consequences of its disruption by light at night in rats and women. *Integr Cancer Ther* 8(4): 347-353. (Supported by NIH and the Laura Evans Memorial Breast Cancer Research Award of the Edwin W. Pauley Foundation. Authors affiliated with Tulane University School of Medicine, LA; Jefferson Medical College, PA.)

62. Blask DE, Dauchy RT, Dauchy EM, Mao L, Hill SM, Greene MW, Belancio VP, Sauer LA, Davidson L. 2014. Light exposure at night disrupts host/cancer circadian regulatory dynamics: impact on the Warburg effect, lipid signaling and tumor growth prevention. *PLoS One* 9(8): e102776. (Supported by the American Association for Laboratory Animal Science, the National Institutes of Health, Tulane University School of Medicine and Louisiana Cancer Research Consortium. Authors affiliated with Tulane University School of Medicine, LA; Tulane Cancer Center and Louisiana Cancer Research Consortium, LA; Bassett Research Institute, NY.)

63. Blask DE, Dauchy RT, Sauer LA, Krause JA. 2004. Melatonin uptake and growth prevention in rat hepatoma 7288CTC in response to dietary melatonin: melatonin receptor-mediated inhibition of tumor linoleic acid metabolism to the growth signaling molecule 13-hydroxyoctadecadienoic acid and the potential role of phytomelatonin. *Carcinogenesis* 25(6): 951-960. (Supported by NCI. Authors affiliated with Bassett Research Institute, NY.)

64. Blask DE, Dauchy RT, Sauer LA, Krause JA, Brainard GC. 2002a. Light during darkness, melatonin suppression and cancer progression. *Neuro Endocrinol Lett* 23 Suppl 2: 52-56. (Supported by NCI, the Laura Evans Memorial Breast Cancer Research Fund of the E.W

Pauley Foundation and the Louis Busch-Hager Cancer Center Research Fund. Authors affiliated with Bassett Research Institute, NY; Thomas Jefferson Medical College, PA.)

65. Blask DE, Dauchy RT, Sauer LA, Krause JA, Brainard GC. 2003. Growth and fatty acid metabolism of human breast cancer (MCF-7) xenografts in nude rats: impact of constant light-induced nocturnal melatonin suppression. *Breast Cancer Res Treat* 79(3): 313-320. (Supported by NCI, the Laura Evans Memorial Breast Cancer Award of the Edwin W. Pauley Foundation and the Stephen C. Clark Research Fund. Authors affiliated with Bassett Research Institute, NY; Thomas Jefferson University, PA.)

66. Blask DE, Hill SM, Dauchy RT, Xiang S, Yuan L, Duplessis T, Mao L, Dauchy E, Sauer LA. 2011. Circadian regulation of metabolic signaling mechanisms of human breast cancer growth by the nocturnal melatonin signal and the consequences of its disruption by light at night. *J Pineal Res* 51(3): 259-269. (Supported by NIH, the Army Department Of Defense, NIEHS, the Edwin W. Pauley Foundation, and Grants for Laboratory Animal Science. Authors affiliated with Laboratory of Chrono-Neuroendocrine Oncology, LA; Tulane University School of Medicine, LA; Tulane Cancer Center, LA; Louisiana Cancer Research Consortium, LA.)

67. Blask DE, Sauer LA, Dauchy R, Holowachuk EW, Ruhoff MS. 1999. New actions of melatonin on tumor metabolism and growth. *Biol Signals Recept* 8(1-2): 49-55. (Support not reported. Authors affiliated with Bassett Research Institute, NY.)

68. Blask DE, Sauer LA, Dauchy RT. 2002b. Melatonin as a chronobiotic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based cancer therapy. *Curr Top Med Chem* 2(2): 113-132. (Supported by NCI and the Stephen C. Clark Research Fund. Authors affiliated with Bassett Research Institute, NY.)

69. BLS. 2004. *Current Population Survey, May 2004: Work Schedules and Work at Home Supplement File.* Technical Documentation CPS—04. Washington, D.C.: Bureau of Labor Statistics, US Department of Labor. 221 pp.

70. BLS. 2005. *Workers on Flexible and Shift Schedules in May 2004.* USDL 05-1198. U.S. Department of Labor, Bureau of Labor Statistics. 14 pp. https://www.bls.gov/news.release/flex.nr0.htm.

71. BLS. 2017a. *Occupational Outlook Handbook: Airline and Commercial Pilots*. Bureau of Labor Statistics. Accessed on 11/7/17. https://www.bls.gov/ooh/transportation-and-material-moving/airline-and-commercial-pilots.htm

72. BLS. 2017b. *Occupational Outlook Handbook: Flight Attendants*. Bureau of Labor Statistics. Accessed on 11/7/17. https://www.bls.gov/ooh/transportation-and-material-moving/flight-attendants.htm

73. Boivin DB, Boudreau P. 2014. Impacts of shift work on sleep and circadian rhythms. *Pathol Biol (Paris)* 62(5): 292-301. (Support not reported. Authors affiliated with McGill University, Canada.)

74. Bollati V, Baccarelli A, Sartori S, Tarantini L, Motta V, Rota F, Costa G. 2010. Epigenetic effects of shiftwork on blood DNA methylation. *Chronobiol Int* 27(5): 1093-1104. (Support not reported. Authors affiliated with Università degli Studi di Milano, Italy; Foundation IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Italy.)

75. Bonde JP, Hansen J, Kolstad HA, Mikkelsen S, Olsen JH, Blask DE, Harma M, Kjuus H, de Koning HJ, Olsen J, Moller M, Schernhammer ES, Stevens RG, Akerstedt T. 2012. Work at night and breast cancer--report on evidence-based options for preventive actions. *Scand J Work Environ Health* 38(4): 380-390. (Supported by the Danish Society of Cancer, Danish regions, and the Danish Nurses' Organization. Authors affiliated with University of Copenhagen, Denmark; Danish Cancer Society, Denmark; Aarhus University Hospital, Denmark; Tulane University, LA; Finnish Institute of Occupational Health, Finland; National Institute of Occupational Health, Norway; University Medical Center Rotterdam, Netherlands; University of California, CA; University of Aarhus, Denmark; Brigham and Women's Hospital and Harvard Medical School, MA; Harvard School of Public Health, MA: University of Connecticut Health Center, CT; Stockholm University, Sweden; Karolinska Institutet, Sweden.)

76. Bonkhoff H. 2018. Estrogen receptor signaling in prostate cancer: Implications for carcinogenesis and tumor progression. *Prostate* 78(1): 2-10. (Support not reported. Authors affiliated with Pathology Laboratory, Germany.)

77. Boquet A, Cruz C, Nesthus T, Detwiler C, Knecht W, Holcomb K. 2004. Clockwise and counterclockwise rotating shifts: effects on temperature and neuroendocrine measures. *Aviat Space Environ Med* 75(10): 898-904. (Support not reported. Authors affiliated with Federal Aviation Administration Civil Aerospace Medical Institute, OK.)

78. Borisenkov MF. 2011. Latitude of residence and position in time zone are predictors of cancer incidence, cancer mortality, and life expectancy at birth. *Chronobiol Int* 28(2): 155-162. (Support not reported. Authors affiliated with Russian Academy of Science, Russia.)

79. Borugian MJ, Gallagher RP, Friesen MC, Switzer TF, Aronson KJ. 2005. Twenty-four-hour light exposure and melatonin levels among shift workers. *J Occup Environ Med* 47(12): 1268-1275. (Supported by the Workers' Compensation Board of British Columbia and the National Cancer Institute of Canada. Authors affiliated with British Columbia Cancer Research Centre, Canada; Queen's University, Canada.)

80. Bracci M, Ciarapica V, Copertaro A, Barbaresi M, Manzella N, Tomasetti M, Gaetani S, Monaco F, Amati M, Valentino M, Rapisarda V, Santarelli L. 2016. Peripheral skin temperature and circadian biological clock in shift nurses after a day off. *Int J Mol Sci* 17(5). (Support not reported. Authors affiliated with Polytechnic University of Marche, Italy; Loreto Hospital, Italy; University of Catania, Italy.)

81. Bracci M, Copertaro A, Manzella N, Staffolani S, Strafella E, Nocchi L, Barbaresi M, Copertaro B, Rapisarda V, Valentino M, Santarelli L. 2013. Influence of night-shift and napping at work on urinary melatonin, 17-beta-estradiol and clock gene expression in pre-menopausal nurses. *J Biol Regul Homeost Agents* 27(1): 267-274. (Supported by the Italian Institute of Insurance against Professional Illness and Injuries [INAIL]. Authors affiliated

with Polytechnic University of Marche, Italy; Loreto Hospital, Italy; University of Catania, Italy.)

82. Bracci M, Manzella N, Copertaro A, Staffolani S, Strafella E, Barbaresi M, Copertaro B, Rapisarda V, Valentino M, Santarelli L. 2014. Rotating-shift nurses after a day off: peripheral clock gene expression, urinary melatonin, and serum 17-beta-estradiol levels. *Scand J Work Environ Health* 40(3): 295-304. (Supported by the Italian Institute of Insurance against Professional Illness and Injuries [INAIL]. Authors affiliated with Polytechnic University of Marche, Italy; Loreto Hospital, Italy; University of Catania, Italy.)

83. Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, Rollag MD. 2001. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* 21(16): 6405-6412. (Supported by the National Institutes of Health, the NASA Cooperative Agreement with the National Space Biomedical Research Institute, a National Science Foundation Grant and a Department of Defense Grant. Authors affiliated with Thomas Jefferson University, PA; Uniformed Services University of Health Sciences, MD.)

84. Brown GM. 1994. Light, melatonin and the sleep-wake cycle. *J Psychiatry Neurosci* 19(5): 345-353. (Support not reported. Authors affiliated with Clarke Institute of Psychiatry, Canada.)

85. Brown SA, Azzi A. 2013. Peripheral circadian oscillators in mammals. In *Circadian Clocks* 2013/04/23. A Kramer, M Merrow, eds. Berlin: Springer. pp. 45-66. (Supported by the Swiss National Science Foundation, the Swiss Cancer League, the Velux Foundation, the Zurich Neurozentrum [ZNZ] and Molecular Life Sciences Program. Authors affiliated with Institute of Pharmacology and Toxicology, Switzerland.)

86. Brown SB, Hankinson SE, Eliassen AH, Reeves KW, Qian J, Arcaro KF, Wegrzyn LR, Willett WC, Schernhammer ES. 2015. Urinary melatonin concentration and the risk of breast cancer in Nurses' Health Study II. *Am J Epidemiol* 181(3): 155-162. (Supported by NIH. Authors affiliated with University of Massachusetts, MA; Harvard School of Public Health, MA; Brigham and Women's Hospital, MA; Harvard Medical School, MA.)

87. Buhr ED, Takahashi JS. 2013. Molecular components of the mammalian circadian clock. *Handb Exp Pharmacol*(217): 3-27. (Support not reported. Authors affiliated with University of Texas Southwestern Medical Center, TX.)

88. Buhr ED, Yoo SH, Takahashi JS. 2010. Temperature as a universal resetting cue for mammalian circadian oscillators. *Science* 330(6002): 379-385. (Supported by NIH and the Howard Hughes Medical Institute. Authors affiliated with Northwestern University, IL; University of Texas Southwestern Medical Center, TX.)

89. Buijs RM, Kalsbeek A. 2001. Hypothalamic integration of central and peripheral clocks. *Nat Rev Neurosci* 2(7): 521-526. (Support not reported. Authors affiliated with Netherlands Institute for Brain Research, Netherlands.)

90. Bukowska A, Sobala W, Peplonska B. 2015. Rotating night shift work, sleep quality, selected lifestyle factors and prolactin concentration in nurses and midwives. *Chronobiol Int* 32(3): 318-326. (Supported by the Polish-Norwegian Research Programme and the Nofer Institute of Occupational Medicine. Authors affiliated with Nofer Institute of Occupational Medicine, Poland.)

91. Bullough JD, Rea MS, Figueiro MG. 2006. Of mice and women: light as a circadian stimulus in breast cancer research. *Cancer Causes Control* 17(4): 375-383. (Supported by the Lighting Research Center and by the National Institute of Environmental Health Sciences. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

92. Burch JB, Yost MG, Johnson W, Allen E. 2005. Melatonin, sleep, and shift work adaptation. *J Occup Environ Med* 47(9): 893-901. (Supported by the National Institute for Occupational Safety and Health, National Institutes of Health. Authors affiliated with Colorado State University, CO; University of Washington, WA.)

93. Burgueño A, Gemma C, Gianotti TF, Sookoian S, Pirola CJ. 2010. Increased levels of resistin in rotating shift workers: a potential mediator of cardiovascular risk associated with circadian misalignment. *Atherosclerosis* 210(2): 625-629. (Supported by the Universidad de Buenos Aires, the Agencia Nacional de Promoción Científica y Tecnológica and the Consejo Nacional de Investigaciones Científicas. Authors affiliated with University of Buenos Aires-National Council of Scientific and Technological Research [CONICET], Argentina.)

94. Business Management Systems. 2017. *Metropolitan Rotating Shift Schedule: 24/7 Shift Coverage*. Business Management Systems. Accessed on 2/6/18. http://www.bmscentral.com/learn-employee-scheduling/metropolitan-shift-schedule/

95. Buss MR, Wirth MD, Burch JB. 2018. Association of shiftwork and leukocytes among national health and nutrition examination survey respondents. *Chronobiol Int* 35(3): 435-439. (Support not reported. Authors affiliated with University of South Carolina, SC; Connecting Healthy Innovations, SC; WJB Dorn VA Medical Center, SC.)

96. Buyukhatipoglu H, Kirhan I, Vural M, Taskin A, Sezen Y, Dag OF, Turan MN, Aksoy N. 2010. Oxidative stress increased in healthcare workers working 24-hour on-call shifts. *Am J Med Sci* 340(6): 462-467. (Support not reported. Authors affiliated with Harran University School of Medicine, Turkey.)

97. Cadenas C, van de Sandt L, Edlund K, Lohr M, Hellwig B, Marchan R, Schmidt M, Rahnenführer J, Oster H, Hengstler JG. 2014. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. *Cell Cycle* 13(20): 3282-3291. (Supported by BMBF. Authors affiliated with TU Dortmund University, Germany; Johannes Gutenberg University, Germany; University of Lübeck, Germany.)

98. Cajochen C, Frey S, Anders D, Späti J, Bues M, Pross A, Mager R, Wirz-Justice A, Stefani O. 2011. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. *J Appl Physiol* 110(5): 1432-1438. (Supported by the Daimler-Benz-Foundation and by the EU 6th Framework Project

EUCLOCK. Authors affiliated with University of Basel, Switzerland; Fraunhofer IAO/University Stuttgart IAT, Germany.)

99. Cajochen C, Jud C, Münch M, Kobialka S, Wirz-Justice A, Albrecht U. 2006. Evening exposure to blue light stimulates the expression of the clock gene *PER2* in humans. *Eur J Neurosci* 23(4): 1082-1086. (Supported by the Velux Foundation, Switzerland, and in part by the Swiss National Foundation Grants START, the State of Fribourg, the EC grant 'Braintime,' the Federal Office for Science and Education, and by the EU 6th Framework Project EUCLOCK. Authors affiliated with University of Basel, Switzerland; University of Fribourg, Switzerland.)

100. Carreón T, Hein MJ, Hanley KW, Viet SM, Ruder AM. 2014. Coronary artery disease and cancer mortality in a cohort of workers exposed to vinyl chloride, carbon disulfide, rotating shift work, and o-toluidine at a chemical manufacturing plant. *Am J Ind Med* 57(4): 398-411. (Supported by NIOSH. Authors affiliated with National Institute for Occupational Safety and Health, OH; Westat, MD.)

101. Carter BD, Diver WR, Hildebrand JS, Patel AV, Gapstur SM. 2014. Circadian disruption and fatal ovarian cancer. *Am J Prev Med* 46(3 Suppl 1): S34-41. (Supported by the American Cancer Society. Authors affiliated with American Cancer Society, GA.)

102. Carter N, Henderson R, Lal S, Hart M, Booth S, Hunyor S. 2002. Cardiovascular and autonomic response to environmental noise during sleep in night shift workers. *Sleep* 25(4): 457-464. (Supported by ARRB Transport Research Ltd., Vermont South, Victoria, Australia, and the Roads and Traffic Authority of New South Wales, Sydney, Australia. Authors affiliated with University of Sydney, Australia; University of Technology, Australia; Royal Prince Alfred Hospital, Australia; Royal North Shore Hospital. Australia.)

103. Casado A, Castellanos A, López-Fernández ME, Ruíz R, Aroca CG, Noriega F. 2008. Relationship between oxidative and occupational stress and aging in nurses of an intensive care unit. *Age (Dordr)* 30(4): 229-236. (Supported by the Foundation Yebenes Velo. Authors affiliated with CSIC, Spain; Hospital General Universitario Gregorio Marañón, Spain.)

104. Casado A, Castellanos A, López-Fernández ME, Ruiz R, López Imedio E, Castillo C, Fernández-Nieto AM. 2011. Determination of oxidative and occupational stress in palliative care workers. *Clin Chem Lab Med* 49(3): 471-477. (Supported by the Yebenes Velo Foundation. Authors affiliated with CSIC, Spain; Hospital General Universitario Gregorio Marañón, Spain.)

105. Castanon-Cervantes O, Wu MW, Ehlen JC, Paul K, Gamble KL, Johnson RL, Besing RC, Menaker M, Gewirtz AT, Davidson AJ. 2010. Dysregulation of inflammatory responses by chronic circadian disruption. *J Immunol* 185(10): 5796-5805. (Supported by NIH, NCRR, RCMI, NCMHHD, the Georgia Research Alliance, and the NSF Center for Behavioral Neuroscience. Authors affiliated with Morehouse School of Medicine, GA; University of Alabama at Birmingham, AL; University of Virginia, VA; Emory University, GA.)

106. CDC. 2015. *CDC-NIOSH Worker Health Charts. Work Organization*. Centers for Disease Control and Prevention. Accessed on 3/21/18. https://wwwn.cdc.gov/Niosh-whc/chart/ohs-

workorg/work and select “All Work Organization” from drop-down menu for work organization and “adjusted prevalence” from drop-down menu for value to chart to find adjusted prevalence of frequent night work and shift work (with estimates of numbers of workers exposed). See PDF cover page for other query instructions

107. Cermakian N, Westfall S, Kiessling S. 2014. Circadian clocks and inflammation: reciprocal regulation and shared mediators. *Arch Immunol Ther Exp (Warsz)* 62(4): 303-318. (Supported by the Canadian Institutes for Health Research, and FRQS. Authors affiliated with McGill University, Canada.)

108. Chan MM, Lu X, Merchant FM, Iglehart JD, Miron PL. 2005. Gene expression profiling of NMU-induced rat mammary tumors: cross species comparison with human breast cancer. *Carcinogenesis* 26(8): 1343-1353. (Supported by the Womens’ Cancers Program, Dana Farber Cancer Institute, the Breast Cancer Research Foundation, the Dana Farber/Harvard SPORE in Breast Cancer from the NCI, and the Ruth L. Kirschstein National Research Service Award. Authors affiliated with Beth Israel Deaconess Medical Center, MA; Harvard School of Public Health, MA; Massachusetts General Hospital, MA; Brigham and Women’s Hospital, MA; Dana-Farber Cancer Institute, MA.)

109. Chang AM, Aeschbach D, Duffy JF, Czeisler CA. 2015. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proc Natl Acad Sci U S A* 112(4): 1232-1237. (Supported by the Harvard Catalyst CTSC, National Center for Research Resources [NCRR], the National Center for Advancing Translational Sciences, National Institutes of Health, the Brigham and Women’s Hospital [BWH], Harvard University, the German Aerospace Center, NASA, and the National Space Biomedical Research Institute. Authors affiliated with Brigham and Women’s Hospital, MA; Harvard Medical School, MA; German Aerospace Center, Germany; Pennsylvania State University, PA.)

110. Chen-Goodspeed M, Lee CC. 2007. Tumor suppression and circadian function. *J Biol Rhythms* 22(4): 291-298. (Support not reported. Authors affiliated with University of Texas Health Science Center, TX.)

111. Chen A, Du L, Xu Y, Chen L, Wu Y. 2005. The effect of blue light exposure on the expression of circadian genes: bmal1 and cryptochrome 1 in peripheral blood mononuclear cells of jaundiced neonates. *Pediatr Res* 58(6): 1180-1184. (Support not reported. Authors affiliated with Children’s Hospital of Zhejiang University School of Medicine, China.)

112. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. 2010. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. *Breast Cancer Res Treat* 121(2): 469-477. (Supported by the One Hundred Talents Program of the Chinese Academy of Sciences, the National Nature Science Foundation, the Ministry of Science and Technology of China, the Science and Technology Commission of Shanghai Municipality, the Food Safety Research Center and Key Laboratory of Nutrition and Metabolism. Authors affiliated with Chinese Academy of Sciences, China.)

113. Chi P, Allis CD, Wang GG. 2010. Covalent histone modifications--miswritten, misinterpreted and mis-erased in human cancers. *Nat Rev Cancer* 10(7): 457-469.

(Supported by NIH and the Starr Cancer Consortium. Authors affiliated with Rockefeller University, NY; Memorial Sloan-Kettering Cancer Center, NY.)

114. Chinoy ED, Duffy JF, Czeisler CA. 2018. Unrestricted evening use of light-emitting tablet computers delays self-selected bedtime and disrupts circadian timing and alertness. *Physiol Rep* 6(10): e13692. (Supported by NIH, Brigham and Women's Hospital, and Harvard University and its affiliated academic health care centers. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA.)

115. Chollet-Hinton L, Olshan AF, Nichols HB, Anders CK, Lund JL, Allott EH, Bethea TN, Hong CC, Cohen SM, Khoury T, Zirpoli GR, Borges VF, Rosenberg LA, Bandera EV, Ambrosone CB, Palmer JR, Troester MA. 2017. Biology and etiology of young-onset breast cancers among premenopausal African American women: Results from the AMBER Consortium. *Cancer Epidemiol Biomarkers Prev* 26(12): 1722-1729. (Supported by NCI, NIH, the University of North Carolina LCCC Cancer Control and Education Program, the Department of Defense Breast Cancer Research Program, the University Cancer Research Fund of North Carolina, the Susan G. Komen for the Cure Foundation, and the Breast Cancer Research Foundation. Authors affiliated with University of North Carolina at Chapel Hill, NC; Boston University, MA; Roswell Park Cancer Institute, NY; University of Colorado School of Medicine, CO; Rutgers Cancer Institute of New Jersey, NJ.)

116. Chowdhury I, Sengupta A, Maitra SK. 2008. Melatonin: Fifty years of scientific journey from the discovery in bovine pineal gland to delineation of functions in human. *Indian J Biochem Biophys* 45(5): 289-304. (Supported by DAAD, DBT, DST, and CSIR. Authors affiliated with Morehouse School of Medicine, GA; Visva-Bharati University, India.)

117. Clausen OP, Iversen OH, Thorud E. 1984. Circadian variation in the susceptibility of mouse epidermis to tumour induction by methylnitrosourea. *Virchows Arch B Cell Pathol Incl Mol Pathol* 45(3): 325-329. (Support not reported. Authors affiliated with University of Oslo, Norway.)

118. Cole RJ, Kripke DF, Wisbey J, Mason WJ, Gruen W, Hauri PJ, Juarez S. 1995. Seasonal variation in human illumination exposure at two different latitudes. *J Biol Rhythms* 10(4): 324-334. (Supported by NIMH and the Department of Veteran's Affairs. Authors affiliated with University of California - San Diego, CA; Synchrony Applied Health Sciences, CA; Mayo Clinic Sleep Disorders Center, MN; Ambulatory Monitoring, Inc., NY.)

119. Cole SW, Nagaraja AS, Lutgendorf SK, Green PA, Sood AK. 2015. Sympathetic nervous system regulation of the tumour microenvironment. *Nat Rev Cancer* 15(9): 563-572. (Supported by the United States National Institutes of Health, the Department of Defense, the Betty Ann Asche Murray Distinguished Professorship, the Cancer Prevention and Research Institute of Texas, and the Breast Cancer Research Foundation. Authors affiliated with University of California - Los Angeles, CA; University of Texas M. D. Anderson Comprehensive Cancer Center, TX; University of Iowa, IA; United States National Cancer Institute, MD.)

120. Colín-González AL, Aguilera G, Serratos IN, Escribano BM, Santamaría A, Túnez I. 2015. On the relationship between the light/dark cycle, melatonin and oxidative stress. *Curr*

Pharm Des 21(24): 3477-3488. (Support not reported Authors affiliated with Instituto Nacional de Neurologia y Neurocirugia, Mexico; Universidad Autonoma Metropolitana-Iztapalapa, Mexico; Universidad de Cordoba, Spain; IMIBIC, Spain; RETICEF.)

121. Conlon M, Lightfoot N, Kreiger N. 2007. Rotating shift work and risk of prostate cancer. *Epidemiology* 18(1): 182-183. (Support not reported. Authors affiliated with Sudbury Regional Hospital, Canada; Ontario School of Medicine, Canada; University of Toronto, Canada.)

122. Copertaro A, Bracci M, Gesuita R, Carle F, Amati M, Baldassari M, Mocchegiani E, Santarelli L. 2011. Influence of shift-work on selected immune variables in nurses. *Ind Health* 49(5): 597-604. (Support not reported. Authors affiliated with Loreto Hospital, Italy; Polytechnic University of Marche, Italy; Biostatistics and Medical Information Technology, Italy; United Hospitals of Ancona, Italy; Istituto Nazionale Riposo e Cura Anziani (INRCA), Italy.)

123. Copertaro A, Bracci M, Monica A, Mocchegiani E, Barbaresi M, Copertaro B, Santarelli L. 2010. [Biological risk and health care workers: Analysis of the effects of work chronobiology on the immune system]. *Med Lav* 101(6): 427-436. (Support unknown due to foreign language. Authors affiliated with Medicina Del Lavoro-Servizio Del Medico Competente, Italy; Università Politecnica Delle Marche, Italy; INCRA, Italy.)

124. Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, Guénel P. 2016. Night work and breast cancer risk defined by human epidermal growth factor receptor-2 (HER2) and hormone receptor status: A population-based case-control study in France. *Chronobiol Int* 33(6): 783-787. (Supported by the Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [ANSES], the Agence Nationale de la Recherche [ANR]; Fondation de France, the Institut National du Cancer [INCA], and the Ligue contre le Cancer. Authors affiliated with INSERM, France; Centre Georges-François Leclerc, France; Centre Eugène Marquis, France.)

125. Cordina-Duverger E, Menegaux F, Popa A, Rabstein S, Harth V, Pesch B, Brüning T, Fritschi L, Glass DC, Heyworth JS, Erren TC, Castaño-Vinyals G, Papantoniou K, Espinosa A, Kogevinas M, Grundy A, Spinelli JJ, Aronson KJ, Guénel P. 2018. Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol*. (Support not reported. Authors affiliated with INSERM, France; Institute of the Ruhr-Universität Bochum, Germany; University Medical Center Hamburg-Eppendorf, Germany; Curtin University, Australia; Monash University, Australia; University of Western Australia, Australia; University of Cologne, Germany; CREAL, Spain; IMIM, Spain; Universitat Pompeu Fabra, Spain; CIBERESP, Spain; Medical University of Vienna, Austria; CRCHUM, Canada; Universite´ de Montréal, Canada; BC Cancer, Canada; University of British Columbia, Canada; Queen's University, Canada.)

126. Cos S, Fernández R, Güézmes A, Sánchez-Barceló EJ. 1998. Influence of melatonin on invasive and metastatic properties of MCF-7 human breast cancer cells. *Cancer Res* 58(19): 4383-4390. (Supported by the Spanish General Direction of Scientific and Technological

Investigation [DGICYT] and the Marqués de Valdecilla Foundation. Authors affiliated with University of Cantabria, Spain; "Sierrallana " Hospital, Spain.)

127. Cos S, Mediavilla D, Martínez-Campa C, González A, Alonso-González C, Sanchez-Barceló EJ. 2006. Exposure to light-at-night increases the growth of DMBA-induced mammary adenocarcinomas in rats. *Cancer Lett* 235(2): 266-271. (Supported by the Spanish MCYT and Institute of Health 'Carlos III.' Authors affiliated with University of Cantabria, Spain.)

128. Costa G, Bertoldi A, Kovacic M, Ghirlanda G, Minors DS, Waterhouse JM. 1997. Hormonal secretion of nurses engaged in fast-rotating shift systems. *Int J Occup Environ Health* 3(Suppl 2): S35-S39. (Support not reported. Authors affiliated with University of Verona, Italy; Policlinic Hospital, Italy; Universiiy of Manchester, UK; John Moores University of Liverpool, UK.)

129. Costa G, Ghirlanda G, Tarondi G, Minors D, Waterhouse J. 1994. Evaluation of a rapidly rotating shift system for tolerance of nurses to nightwork. *Int Arch Occup Environ Health* 65(5): 305-311. (Support not reported. Authors affiliated with University of Verona, Italy; Policlinic and General Hospital Staff Management, Italy; University of Manchester, UK.)

130. Costa G, Haus E, Stevens R. 2010. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. *Scand J Work Environ Health* 36(2): 163-179. (Support not reported. Authors affiliated with University of Milano/Fondazione IRCCS "Cà Granda – Ospedale Maggiore Policlinico," Italy; University of Minnesota/HealthPartners Medical Group/Regions Hospital, MO; University of Connecticut Health Center, CT.)

131. Costas L, Benavente Y, Olmedo-Requena R, Casabonne D, Robles C, Gonzalez-Barca EM, de la Banda E, Alonso E, Aymerich M, Tardón A, Marcos-Gragera R, Gimeno-Vázquez E, Gómez-Acebo I, Papantoniou K, Castaño-Vinyals G, Aragonés N, Pollán M, Kogevinas M, de Sanjosé S. 2016. Night shift work and chronic lymphocytic leukemia in the MCC-Spain case-control study. *Int J Cancer*. (Supported by the Spanish Ministry of Economy and Competitiveness, Carlos III Institute of Health, and the Catalan Government. Authors affiliated with Catalan Institute of Oncology, Spain; University of Barcelona, Spain; Consortium for Biomedical Research in Epidemiology and Public Health, Spain; University of Granada, Spain; IARC, France; Hospital Universitari de Bellvitge, Spain; University of Oviedo, Spain; Universitat de Girona, Spain; Hospital del Mar, Spain; Grup de Recerca Aplicada en Neoplasies Hematològiques-PSMAR, Spain; Universidad de Cantabria, Spain; Centre for Research in Environmental Epidemiology, Spain; Medical University of Vienna, Austria; Hospital del Mar Medical Research Institute, Spain; Universitat Pompeu Fabra, Spain; Carlos III Institute of Health, Spain; IIS Puerta de Hierro, Spain; National School of Public Health, Greece.)

132. Crowley SJ, Cain SW, Burns AC, Acebo C, Carskadon MA. 2015. Increased sensitivity of the circadian system to light in early/mid-puberty. *J Clin Endocrinol Metab* 100(11): 4067-4073. (Supported by the National Institute of Mental Health and the National Heart Lung and Blood Institute. Authors affiliated with Rush University Medical Center, IL; Monash University, Australia; Bradley Hospital Sleep and Chronobiology Research Laboratory, RI; Brown University, RI; University of S Australia, Australia.)

133. Cuesta M, Boudreau P, Dubeau-Laramée G, Cermakian N, Boivin DB. 2016. Simulated night shift disrupts circadian rhythms of immune functions in humans. *J. Immunol.* 196(6): 2466-2475. (Supported by the Canadian Institutes of Health Research, the McGill–Neuroscience Center Zurich partnership in Neurosciences, the Institut de recherche Robert-Sauvé en santé et en sécurité du travail du Québec, and the Fonds de Recherche du Québec–Sante. Authors affiliated with McGill University, Canada.)

134. Curtis AM, Seo SB, Westgate EJ, Rudic RD, Smyth EM, Chakravarti D, FitzGerald GA, McNamara P. 2004. Histone acetyltransferase-dependent chromatin remodeling and the vascular clock. *J Biol Chem* 279(8): 7091-7097. (Supported by NIH. Authors affiliated with University of Pennsylvania, PA; Seoul National University, Korea; Phenomix Corporation, CA.)

135. Dall GV, Britt KL. 2017. Estrogen effects on the mammary gland in early and late life and breast cancer risk. *Front Oncol* 7: 110. (Supported by the National Breast Cancer Research Foundation of Australia, The National Health and Medical Research Council of Australia, and the Peter MacCallum Cancer Centre. Authors affiliated with Peter MacCallum Cancer Centre, Australia; University of Melbourne, Australia.)

136. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U. 2000. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev* 14(23): 2950-2961. (Supported by the Swiss National Science Foundation, the State of Geneva, the Bonizzi-Theler Stiftung, and the Louis-Jeantet Foundation for Medicine. Authors affiliated with Université de Genève, Switzerland.)

137. Datta K, Roy A, Nanda D, Das I, Guha S, Ghosh D, Sikdar S, Biswas J. 2014. Association of breast cancer with sleep pattern--a pilot case control study in a regional cancer centre in South Asia. *Asian Pac J Cancer Prev* 15(20): 8641-8645. (Support not reported. Authors affiliated with Chittaranjan National Cancer Institute, India.)

138. Dauchy R, Blask D, Dauchy E, Hill C, Davidson L, Tirrell P, Greene M, Wu JH, Tirrell R, Lynch D, Sauer L. 2009a. Expression and light at night induced disruption of circadian dynamics in fatty acid and glucose metabolism, signal transduction, proliferative activity and clock gene expression in tissue-isolated human breast cancer xenografts in nude rats. *Cancer Res* 69: 1. (Support not reported. Authors affiliated with Tulane University School of Medicine, LA; The Mary Imogene Bassett Hospital, NY.)

139. Dauchy RT, Blask DE, Dauchy EM, Davidson LK, Tirrell PC, Greene MW, Tirrell RP, Hill CR, Sauer LA. 2009b. Antineoplastic effects of melatonin on a rare malignancy of mesenchymal origin: melatonin receptor-mediated inhibition of signal transduction, linoleic acid metabolism and growth in tissue-isolated human leiomyosarcoma xenografts. *J Pineal Res* 47(1): 32-42. (Supported by the National Leiomyosarcoma Foundation. Authors affiliated with Tulane University School of Medicine, LA; Bassett Research Institute, NY.)

140. Dauchy RT, Blask DE, Sauer LA, Brainard GC, Krause JA. 1999. Dim light during darkness stimulates tumor progression by enhancing tumor fatty acid uptake and metabolism. *Cancer Lett* 144(2): 131-136. (Supported by the Stephen C. Clark Research

Fund and NIH. Authors affiliated with Bassett Research Institute, NY; Thomas Jefferson University, PA.)

141. Dauchy RT, Blask DE, Sauer LA, Davidson LK, Krause JA, Smith LC, Dauchy EM. 2003. Physiologic melatonin concentration, omega-3 fatty acids, and conjugated linoleic acid inhibit fatty acid transport in rodent hind limb skeletal muscle *in vivo*. *Comp Med* 53(2): 186-190. (Supported by NCI and the Stephen C. Clark Research Fund. Authors affiliated with Bassett Research Institute, NY.)

142. Dauchy RT, Dauchy EM, Davidson LK, Krause JA, Lynch DT, Tirrell PC, Tirrell RP, Sauer LA, Van der Riet P, Blask DE. 2007. Inhibition of fatty acid transport and proliferative activity in tissue-isolated human squamous cell cancer xenografts perfused in situ with melatonin or eicosapentaenoic or conjugated linoleic acids. *Comp Med* 57(4): 377-382. (Supported by the National Cancer Institute and by the Stephen E Clark Research Fund. Authors affiliated with Bassett Research Institute, NY.)

143. Dauchy RT, Dauchy EM, Hanifin JP, Gauthreaux SL, Mao L, Belancio VP, Ooms TG, Dupepe LM, Jablonski MR, Warfield B, Wren MA, Brainard GC, Hill SM, Blask DE. 2013. Effects of spectral transmittance through standard laboratory cages on circadian metabolism and physiology in nude rats. *J Am Assoc Lab Anim Sci* 52(2): 146-156. (Supported by the Tulane University School of Medicine, the Louisiana Cancer Research Consortium, NIH, AALAS, the Ellison Medical Foundation, and the Institute of Integrative Health. Authors affiliated with Tulane University School of Medicine, LA; Thomas Jefferson University, PA.)

144. Dauchy RT, Dupepe LM, Ooms TG, Dauchy EM, Hill CR, Mao L, Belancio VP, Slakey LM, Hill SM, Blask DE. 2011. Eliminating animal facility light-at-night contamination and its effect on circadian regulation of rodent physiology, tumor growth, and metabolism: a challenge in the relocation of a cancer research laboratory. *J Am Assoc Lab Anim Sci* 50(3): 326-336. (Supported by the Tulane University School of Medicine, the Louisiana Cancer Research Consortium, NIH, the National Institute on Aging, the the Ellison Medical Foundation New Scholar in Aging Award, and the American Association for Laboratory Animal Science Grants for Laboratory Animal Science [GLAS] Award. Authors affiliated with Tulane University School of Medicine, LA.)

145. Dauchy RT, Hoffman AE, Wren-Dail MA, Hanifin JP, Warfield B, Brainard GC, Xiang S, Yuan L, Hill SM, Belancio VP, Dauchy EM, Smith K, Blask DE. 2015. Daytime blue light enhances the nighttime circadian melatonin inhibition of human prostate cancer growth. *Comp Med* 65(6): 473-485. (Supported by the Tulane University School of Medicine, the Louisiana Cancer Research Consortium, the American Association for Laboratory Animal Science, the Institute for Integrative Health, and the National Science Foundation. Authors affiliated with Tulane University School of Medicine, LA; Thomas Jefferson University, PA.)

146. Dauchy RT, Sauer LA, Blask DE, Vaughan GM. 1997. Light contamination during the dark phase in "photoperiodically controlled" animal rooms: effect on tumor growth and metabolism in rats. *Lab Anim Sci* 47(5): 511-518. (Supported by the Stephen C. Clark

Research Fund. Authors affiliated with Bassett Healthcare, NY; U.S. Army Institute of Surgical Research, TX.)

147. Dauchy RT, Wren-Dail MA, Dupepe LM, Hill SM, Xiang S, Anbalagan M, Belancio VP, Dauchy EM, Blask DE. 2018. Effect of daytime blue-enriched LED light on the nighttime circadian melatonin inhibition of hepatoma 7288CTC Warburg effect and progression. *Comp Med* 68(4): 1-11. (Supported by the Tulane University School of Medicine, the Louisiana Cancer Research Consortium, NIH, and the American Association for Laboratory Animal Science. Authors affiliated with Tulane University School of Medicine, LA.)

148. Dauchy RT, Wren-Dail MA, Hoffman AE, Hanifin JP, Warfield B, Brainard GC, Hill SM, Belancio VP, Dauchy EM, Blask DE. 2016. Effects of daytime exposure to light from blue-enriched light-emitting diodes on the nighttime melatonin amplitude and circadian regulation of rodent metabolism and physiology. *Comp Med* 66(5): 373-383. (Supported by the Tulane University School of Medicine and Louisiana Cancer Research Consortium Startup, NIH, the American Association for Laboratory Animal Science Grants for Laboratory Animal Science, The Institute for Integrative Health, and the National Science Foundation. Authors affiliated with Tulane University School of Medicine, LA; Thomas Jefferson University, PA.)

149. Dauchy RT, Xiang S, Mao L, Brimer S, Wren MA, Yuan L, Anbalagan M, Hauch A, Frasch T, Rowan BG, Blask DE, Hill SM. 2014. Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer. *Cancer Res* 74(15): 4099-4110. (Supported by NIH, the American Association for Laboratory Animal Science, and the the Edmond and Lily Safra Endowed Chair for Breast Cancer Research. Authors affiliated with Tulane University School of Medicine, LA; Tulane Cancer Center and Louisiana Cancer Research Consortium, LA; Tulane Circadian Cancer Biology Group, LA.)

150. Daugaard S, Garde AH, Bonde JPE, Christoffersen J, Hansen AM, Markvart J, Schlünssen V, Skene DJ, Vistisen HT, Kolstad HA. 2017. Night work, light exposure and melatonin on work days and days off. *Chronobiol Int*: 1-14. (Supported by the Danish Working Environment Research Fund. Authors affiliated with Aarhus University Hospital, Denmark; National Research Centre for the Working Environment, Denmark; Bispebjerg Hospital, Denmark; University of Copenhagen, Denmark; Velux Danmark A/S, Denmark; Aalborg Universitet, Denmark; University of Surrey, UK.)

151. Davidson AJ, Castanon-Cervantes O, Leise TL, Molyneux PC, Harrington ME. 2009. Visualizing jet lag in the mouse suprachiasmatic nucleus and peripheral circadian timing system. *Eur J Neurosci* 29(1): 171-180. (Supported by the Keck Genomics Center at the Morehouse School of Medicine Neuroscience Institute, NIH, and NSF. Authors affiliated with Morehouse School of Medicine, GA; Amherst College, MA; Smith College, MA.)

152. Davis S, Kaune WT, Mirick DK, Chen C, Stevens RG. 2001a. Residential magnetic fields, light-at-night, and nocturnal urinary 6-sulfatoxymelatonin concentration in women. *Am J Epidemiol* 154(7): 591-600. (Supported by the Electric Power Research Institute. Authors

affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; EM Factors, WA; University of Connecticut Health Center, CT.)

153. Davis S, Mirick DK. 2006. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. *Cancer Causes Control* 17(4): 539-545. (Support not reported. Authors affiliated with Fred Hutchinson Cancer Research Center, WA.)

154. Davis S, Mirick DK, Chen C, Stanczyk FZ. 2012. Night shift work and hormone levels in women. *Cancer Epidemiol Biomarkers Prev* 21(4): 609-618. (Support not reported. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; University of Southern California, CA.)

155. Davis S, Mirick DK, Stevens RG. 2001b. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 93(20): 1557-1562. (Supported by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Connecticut Health Center, CT.)

156. De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L. 2009. Rotating shift work and the metabolic syndrome: a prospective study. *Int J Epidemiol* 38(3): 848-854. (Supported by the Belgian Federal Public Service Employment, Labor and Social Dialogue and by the European Social Fund. Authors affiliated with Ghent University, Belgium; Université Libre de Bruxelles, Belgium.)

157. de Castro TB, Bordin-Junior NA, de Almeida EA, de Campos Zuccari DAP. 2018. Evaluation of melatonin and AFMK levels in women with breast cancer. *Endocrine*(Epub ahead of print). (Supported by FAPESP and FAPERP. Authors affiliated with São Paulo State University, Brazil; São José do Rio Preto Medical School, Brazil; Regional University of Blumenau Foundation, Brazil.)

158. deHaro D, Kines KJ, Sokolowski M, Dauchy RT, Streva VA, Hill SM, Hanifin JP, Brainard GC, Blask DE, Belancio VP. 2014. Regulation of L1 expression and retrotransposition by melatonin and its receptor: implications for cancer risk associated with light exposure at night. *Nucleic Acids Res* 42(12): 7694-7707. (Supported by the Ellison Medical Foundation New Scholar in Aging Research, the Life Extension Foundation, the National Institutes of Health, the American Association for Laboratory Animal Science Grants for Laboratory Animal Science, and The Institute for Integrative Health. Authors affiliated with Tulane School of Medicine, LA; Tulane Center for Aging, LA; Thomas Jefferson University, PA.)

159. Depner CM, Melanson EL, McHill AW, Wright KP, Jr. 2018. Mistimed food intake and sleep alters 24-hour time-of-day patterns of the human plasma proteome. *Proc Natl Acad Sci U S A*. (Supported by NIH, the Sleep Research Society Foundation, and SomaLogic, Inc. Authors affiliated with University of Colorado Boulder, CO; University of Colorado Anschutz Medical Campus, CO; VA Eastern Colorado Health Care System, CO; Oregon Health and Science University, OR; Brigham and Women's Hospital, MA; Harvard Medical School, MA.)

160. Devore EE, Warner ET, Eliassen AH, Brown SB, Beck AH, Hankinson SE, Schernhammer ES. 2017. Urinary melatonin in relation to postmenopausal breast cancer risk according to melatonin 1 receptor status. *Cancer Epidemiol Biomarkers Prev* 26(3): 413-419. (Supported by NCI, CDC, and NIOSH. Authors affiliated with Brigham and Women's Hospital and Harvard Medical School, MA; Massachusetts General Hospital, MA; Harvard T.H. Chan School of Public Health, MA; University of Massachusetts Amherst, MA; Beth Israel Deaconess Medical Center and Harvard Medical School, MA; Medical University of Vienna, Austria.)

161. Dibner C, Schibler U, Albrecht U. 2010. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol* 72: 517-549. (Support not reported. Authors affiliated with Geneva University Hospital, Switzerland; University of Geneva, Switzerland; University of Fribourg, Switzerland.)

162. Dickerman BA, Markt SC, Koskenvuo M, Hublin C, Pukkala E, Mucci LA, Kaprio J. 2016. Sleep disruption, chronotype, shift work, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. *Cancer Causes Control* 27(11): 1361-1370. (Suppored by NCI, NIH, and the Academy of Finland. Authors affiliated with Harvard T.H. Chan School of Public Health, MA; University of Helsinki, Finland; Finnish Institute of Occupational Health, Finland; Finnish Cancer Registry, Finland; University of Tampere, Finland; National Institute for Health and Welfare, Finland.)

163. Dijk DJ, Duffy JF, Silva EJ, Shanahan TL, Boivin DB, Czeisler CA. 2012. Amplitude reduction and phase shifts of melatonin, cortisol and other circadian rhythms after a gradual advance of sleep and light exposure in humans. *PLoS One* 7(2): e30037. (Supported by the National Aeronautics and Space Administration, the National Space Biomedical Research Institute, the National Institute of Mental Health, the National Institutes of Health and by the Brigham and Women's Hospital. Authors affiliated with Harvard Medical School, MA: Brigham and Women's Hospital, MA.)

164. DOE. 2017. *Street Lighting and Blue Light: Frequently Asked Questions.* U.S. Department of Energy. 21 pp. https://www.energy.gov/eere/ssl/downloads/street-lighting-and-blue-light-faqs.

165. DOE. 2018. *Fluorescent Lighting and LED Lighting*. U.S. Department of Energy. Accessed on 5/31/18. https://www.energy.gov/energysaver/save-electricity-and-fuel/lighting-choices-save-you-money/fluorescent-lighting and https://www.energy.gov/energysaver/save-electricity-and-fuel/lighting-choices-save-you-money/led-lighting

166. Doi M, Hirayama J, Sassone-Corsi P. 2006. Circadian regulator CLOCK is a histone acetyltransferase. *Cell* 125(3): 497-508. (Supported by the Centre National de la Recherche Scientifique, Institut National de la Santé et de la Recherche Médicale, Université Louis Pasteur, Fondation de la Recherche Médicale, and Association pour la Recherche sur le Cancer. Authors affiliated with Institut de Génétique et de Biologie Moléculaire et Cellulaire, France; University of California, CA; Kobe University Graduate School of Medicine, Japan.)

167. DOT. 2018. *International Aviation Development Series: U.S. International Air Passenger and Freight Statistics: September 2017.* U.S. Department of Transportation. 37 pp. https://www.transportation.gov/sites/dot.gov/files/docs/mission/office-policy/aviation-policy/306551/us-international-air-passenger-and-freight-statistics-september-2017.pdf.

168. Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. 2004. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. *Sleep* 27(8): 1453-1462. (Supported by NIMH. Authors affiliated with Henry Ford Hospital Sleep Disorders and Research Center. MI; Wayne State College of Medicine, MI; St. Louis University, MO.)

169. Dubocovich ML, Markowska M. 2005. Functional MT_1 and MT_2 melatonin receptors in mammals. *Endocrine* 27(2): 101-110. (Supported by the Foundation for Polish Science and the USPHS. Authors affiliated with Northwestern University, IL; Warsaw University, Poland.)

170. Dubocovich ML, Rivera-Bermudez MA, Gerdin MJ, Masana MI. 2003. Molecular pharmacology, regulation and function of mammalian melatonin receptors. *Front Biosci* 8: d1093-1108. (Supported by the USPHS, and the American Heart Association. Authors affiliated with Northwestern University Feinberg School of Medicine, IL; Northwestern University Institute for Neuroscience, IL; Northwestern University, IL.)

171. Dumont M, Lanctot V, Cadieux-Viau R, Paquet J. 2012. Melatonin production and light exposure of rotating night workers. *Chronobiol Int* 29(2): 203-210. (Supported by NSERC. Authors affiliated with Sacre-Coeur Hospital of Montreal, Canada; University of Montreal, Canada.)

172. Dumont M, Paquet J. 2014. Progressive decrease of melatonin production over consecutive days of simulated night work. *Chronobiol Int* 31(10): 1231-1238. (Supported by the Natural Science and Engineering Research Canada. Authors affiliated with Sacre-Coeur Hospital of Montreal, Canada; University of Montreal, Canada.)

173. Eastman CI, Tomaka VA, Crowley SJ. 2016. Circadian rhythms of European and African-Americans after a large delay of sleep as in jet lag and night work. *Sci Rep* 6: 36716. (Supported by NIH and NINR. Authors affiliated with Rush University Medical Center, IL.)

174. EIA. 2017. *Commercial Buildings Energy Consumption Survey (CBECS) Trends in Lighting in Commercial Buildings*. U.S. Energy Information Administration. Updated on 5/17/17. Accessed on 5/31/18. https://www.eia.gov/consumption/commercial/reports/2012/lighting/

175. EIA. 2018. *Commercial Buildings Energy Consumption Survey (CBECS) Building Type Definitions*. U.S. Energy Information Administration. Accessed on 5/31/18. https://www.eia.gov/consumption/commercial/building-type-definitions.php

176. Elert G. 2018. *Nature of Light*. The Physic Hypertextbook. Accessed on 5/25/18. https://physics.info/light/

177. Erren TC. 2005. Could visible light contribute to the development of leukaemia and other cancers in children? *Med Hypotheses* 64(4): 864-871. (Supported by the Children with Leukaemia Charity. Authors affiliated with University of Cologne, Germany.)

178. Escobar C, Martínez-Merlos MT, Angeles-Castellanos M, del Carmen Miñana M, Buijs RM. 2007. Unpredictable feeding schedules unmask a system for daily resetting of behavioural and metabolic food entrainment. *Eur J Neurosci* 26(10): 2804-2814. (Supported by CONACyT, DGAPA PAPIIT, and UNAM. Authors affiliated with Universidad Nacional Autónoma de México, Mexico; Moore House Medical School, GA; Netherlands Institute for Neuroscience, Netherlands.)

179. Espiritu RC, Kripke DF, Ancoli-Israel S, Mowen MA, Mason WJ, Fell RL, Klauber MR, Kaplan OJ. 1994. Low illumination experienced by San Diego adults: association with atypical depressive symptoms. *Biol Psychiatry* 35(6): 403-407. (Supported by the Department of Veterans Affairs. Authors affiliated with Sam and Rose Stein Institute For Research on Aging, CA; UCSD, CA; San Diego Veterans Affairs Medical Center, CA; San Diego Stale University, CA.)

180. Esquirol Y, Bongard V, Mabile L, Jonnier B, Soulat JM, Perret B. 2009. Shift work and metabolic syndrome: respective impacts of job strain, physical activity, and dietary rhythms. *Chronobiol Int* 26(3): 544-559. (Support not reported. Authors affiliated with INSERM, France; Service de Santé au Travail de Lacq, France.)

181. Etchegaray JP, Lee C, Wade PA, Reppert SM. 2003. Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. *Nature* 421(6919): 177-182. (Supported by the NIH and the Defense Advanced Research Projects Agency. Authors affiliated with University of Massachusetts Medical School, MA; Emory University, GA.)

182. Evans JA, Davidson AJ. 2013. Health consequences of circadian disruption in humans and animal models. *Prog Mol Biol Transl Sci* 119: 283-323. (Support not reported. Authors affiliated with Morehouse School of Medicine, GA.)

183. EWG. 2007. *Chemical Exposures on the Job May Be Linked to Diseases in Nurses*. Environmental Working Group. Updated on 12/11/07. Accessed on 1/5/18. https://www.ewg.org/news/news-releases/2007/12/11/chemical-exposures-job-may-be-linked-diseases-nurses#.WiBxsrQ-dqw

184. Falchi F, Cinzano P, Duriscoe D, Kyba CC, Elvidge CD, Baugh K, Portnov BA, Rybnikova NA, Furgoni R. 2016. The new world atlas of artificial night sky brightness. *Sci Adv* 2(6): e1600377. (Supported by the Italian Space Agency. Authors affiliated with Istituto di Scienza e Tecnologia dell'Inquinamento Luminoso, Italy; U.S. Department of Interior, CO; Deutsches GeoForschungsZentrum GFZ, Germany; Leibniz–Institute of Freshwater Ecology and Inland Fisheries, Germany; National Oceanic and Atmospheric Administration's National Centers for Environmental Information, CO; University of Colorado, CO; University of Haifa, Israel; Association of Variable Star Observers, MA.)

185. Fang L, Yang Z, Zhou J, Tung JY, Hsiao CD, Wang L, Deng Y, Wang P, Wang J, Lee MH. 2015a. Circadian clock gene CRY2 degradation is involved in chemoresistance of colorectal cancer. *Mol Cancer Ther* 14(6): 1476-1487. (Supported by NIH, the Fidelity

Foundation, the Susan G. Komen Breast Cancer Foundation, the Program of Introducing Talents of Discipline to Universities, and the International S&T Cooperation Program of China. Authors affiliated with The Sixth Affiliated Hospital of Sun Yat-Sen University, China; University of Texas MD Anderson Cancer Center, TX; Academia Sinica, Taiwan.)

186. Fang M, Ohman Strickland PA, Kang HG, Zarbl H. 2017. Uncoupling genotoxic stress responses from circadian control increases susceptibility to mammary carcinogenesis. *Oncotarget* 8(20): 32752-32768. (Supported by NIH, a V Foundation Grant for Cancer Research, and an International Collaboration Fund from the Animal and Plant Quarantine Agency, South Korea. Authors affiliated with State University of New Jersey, NJ; Veterinary Drugs & Biologics Division, Animal and Plant Quarantine Agency, Korea.)

187. Fang MZ, Ohman-Strickland P, Kelly-McNeil K, Kipen H, Crabtree BF, Lew JP, Zarbl H. 2015b. Sleep interruption associated with house staff work schedules alters circadian gene expression. *Sleep Med* 16(11): 1388-1394. (Supported by the V Foundation for Cancer Research, the National Institute of Environmental Health Sciences and the State University of New Jersey. Authors affiliated with Robert Wood Johnson Medical School, NJ; NIEHS, NJ; State University of New Jersey, NJ; School of Public Health, NJ; Children's National Medical Center, Washington, DC.)

188. Faraut B, Bayon V, Léger D. 2013. Neuroendocrine, immune and oxidative stress in shift workers. *Sleep Med Rev* 17(6): 433-444. (Supported by the Direction Générale du Travail, Ministère du Travail, de l'Emploi et de la Santé auprès de la Société Française de Médecine du Travail. Authors affiliated with Université Paris Descartes, France; Consensus Group on Shift Work, France.)

189. Faraut B, Boudjeltia KZ, Vanhamme L, Kerkhofs M. 2012. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Med Rev* 16(2): 137-149. (Supported by the European Union, and the Scientific Research Fund of the ISPPC-CHU de Charleroi. Authors affiliated with Université Libre de Bruxelles, Belgium; Université Paris Descartes, France.)

190. Fekedulegn D, Burchfiel CM, Violanti JM, Hartley TA, Charles LE, Andrew ME, Miller DB. 2012. Associations of long-term shift work with waking salivary cortisol concentration and patterns among police officers. *Ind Health* 50(6): 476-486. (Support not reported. Authors affiliated with National Institute for Occupational Safety and Health, GA; State University of New York, NY.)

191. Fenton SE. 2006. Endocrine-disrupting compounds and mammary gland development: early exposure and later life consequences. *Endocrinology* 147(6 Suppl): S18-24. (Supported by the US EPA. Author affiliated with U.S. EPA, NC.)

192. Feychting M, Österlund B, Ahlbom A. 1998. Reduced cancer incidence among the blind. *Epidemiology* 9(5): 490-494. (Supported by Martin Rind's Foundation. Authors affiliated with Karolinska Institutet, Sweden.)

193. Figueiro M. 2018. Personal communication from Dr. Mariana Figueiro of Renssalaer Polytechnic Institute, Troy, NY, on 1/4/2018.

194. Figueiro M, Overington D. 2016. Self-luminous devices and melatonin suppression in adolescents. *Light Res Technol* 48(8): 966-975. (Supported by the Lighting Research Center at Rensselaer Polytechnic Institute. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

195. Figueiro M, Wood B, Plitnick B, Rea M. 2011. The impact of light from computer monitors on melatonin levels in college students. *Biogenic Amines* 25(2): 106-116. (Supported by the Office of Naval Research. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

196. Figueiro MG. 2017. Disruption of circadian rhythms by light during day and night. *Curr Sleep Med Rep* 3(2): 76-84. (Supported by NIOSH. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

197. Figueiro MG, Plitnick B, Rea MS. 2012. Light modulates leptin and ghrelin in sleep-restricted adults. *Int J Endocrinol* 2012: 530726. (Supported by Seoul Semiconductors. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

198. Figueiro MG, Rea MS, Bullough JD. 2006. Does architectural lighting contribute to breast cancer? *J Carcinog* 5: 20. (Supported by the Lighting Research Center and NIEHS. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

199. Figueiro MG, Steverson B, Heerwagen J, Kampschroer K, Hunter CM, Gonzales K, Plitnick B, Rea MS. 2017. The impact of daytime light exposures on sleep and mood in office workers. *Sleep Health* 3(3): 204-215. (Supported by the US General Services Administration. Authors affiliated with Rensselaer Polytechnic Institute, NY; US General Services Administration.)

200. Filipski E, Delaunay F, King VM, Wu MW, Claustrat B, Gréchez-Cassiau A, Guettier C, Hastings MH, Francis L. 2004. Effects of chronic jet lag on tumor progression in mice. *Cancer Res* 64(21): 7879-7885. (Supported by the Association pour la Recherche sur le Temps Biologique et la Chronothérapeutique [hôpital Paul Brousse], Action Thématique Concertée Nutrition from the Institut National de la Santé et de la Recherche Médicale (France), the Association pour la Recherche sur le Cancer, the Fondation pour la Recherche Médicale, Université de Nice-Sophia Antipolis, and a Research Training Fellowship from the Medical Research Council. Authors affiliated with INSERM, France; Université de Nice-Sophia Antipolis, France; University of Cambridge, UK; Hôpital Neurocardiologique, France; Hôpital Paul Brousse, France; MRC, UK.)

201. Filipski E, Innominato PF, Wu M, Li XM, Iacobelli S, Xian LJ, Lévi F. 2005. Effects of light and food schedules on liver and tumor molecular clocks in mice. *J Natl Cancer Inst* 97(7): 507-517. (Supported by INSERM Action Thématique Concertée Nutrition, the Programme de Recherches Avancées de Coopération Franco-Chinoises, the Association pour la Recherche sur le Temps Biologique et la Chronothérapie and Association pour la Recherche sur le Cancer, Paul Brousse Hospital, France, and Clinical Important Program of Ministry of Public Health of P.R. China. Authors affiliated with INSERM, France; Università “G. D’Annunzio," Italy; Sun Yat-sen University, China.)

202. Filipski E, King VM, Li X, Granda TG, Mormont MC, Liu X, Claustrat B, Hastings MH, Lévi F. 2002. Host circadian clock as a control point in tumor progression. *J Natl Cancer Inst* 94(9): 690-697. (Supported by the Association pour la Recherche sur le Cancer, the Association pour la Recherche sur le Temps Biologique et la Chronothérapeutique, Institut de Cancer et d'Immunogénétique and by a Research Training Fellowship from Medical Research Council. Authors affiliated with INSERM, France; University of Cambridge, UK; Hôpital Neurocardiologique, France; Medical Research Council, UK.)

203. Filipski E, Levi F. 2009. Circadian disruption in experimental cancer processes. *Integr Cancer Ther* 8(4): 298-302. (Supported by the European Union through the Network of Excellence BioSim, STREP TEMPO, and Association Internationale pour la Recherche sur le Temps Biologique et la Chronothérapie (ARTBC International), Paul Brousse Hospital, France. Authors affiliated with Hôpital Paul Brousse, France; Université Paris-Sud, France.)

204. Filipski E, Li XM, Levi F. 2006. Disruption of circadian coordination and malignant growth. *Cancer Causes Control* 17(4): 509-514. (Support not reported. Authors affiliated with INSERM, France.)

205. Filipski E, Subramanian P, Carriere J, Guettier C, Barbason H, Lévi F. 2009. Circadian disruption accelerates liver carcinogenesis in mice. *Mutat Res* 680(1-2): 95-105. (Supported by the European Union trough the Network of Excellence BioSim, STREP TEMPO, the Association Internationale pour la Recherche sur le Temps Biologique et la Chronothérapie (ARTBC International), Paul Brousse Hospital, France and the University Paris Sud XI. Authors affiliated with INSERM, France; Université Paris-Sud, France; Hôpital Paul Brousse, France.)

206. Flynn-Evans EE, Mucci L, Stevens RG, Lockley SW. 2013. Shiftwork and prostate-specific antigen in the National Health and Nutrition Examination Survey. *J Natl Cancer Inst* 105(17): 1292-1297. (Supported by the Harvard Medical School Division of Sleep Medicine Training Program in Sleep, Circadian and Respiratory Neurobiology. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; University of Connecticut Health Center, CT.)

207. Flynn-Evans EE, Stevens RG, Tabandeh H, Schernhammer ES, Lockley SW. 2009. Total visual blindness is protective against breast cancer. *Cancer Causes Control* 20(9): 1753-1756. (Supported by a Department of Defense Breast Cancer Research Program Idea Award and the Harvard Medical School Division of Sleep Medicine Training Program in Sleep, Circadian, and Respiratory Neurobiology. Authors affiliated with Brigham and Women's Hospital, MA; University of Surrey, UK; University of Connecticut, CT; Retina-Vitreous Associates, CA; Harvard Medical School, MA.)

208. Folkard S. 2008. Do permanent night workers show circadian adjustment? A review based on the endogenous melatonin rhythm. *Chronobiol Int* 25(2): 215-224. (Supported by the UK's Health and Safety Executive. Author affiliated with Université Paris Descartes, France; Swansea University, UK.)

209. Fonken LK, Aubrecht TG, Meléndez-Fernández OH, Weil ZM, Nelson RJ. 2013a. Dim light at night disrupts molecular circadian rhythms and increases body weight. *J Biol Rhythms* 28(4): 262-271. (Supported by NSF and the American Heart Association. Authors affiliated with Ohio State University, OH.)

210. Fonken LK, Lieberman RA, Weil ZM, Nelson RJ. 2013b. Dim light at night exaggerates weight gain and inflammation associated with a high-fat diet in male mice. *Endocrinology* 154(10): 3817-3825. (Supported by the National Science Foundation and the American Heart Association. Authors affiliated with Ohio State University, OH.)

211. Fonken LK, Nelson RJ. 2014. The effects of light at night on circadian clocks and metabolism. *Endocr Rev* 35(4): 648-670. (Supported by the American Heart Association and the National Science Foundation. Authors affiliated with Ohio State University, OH.)

212. Fonken LK, Workman JL, Walton JC, Weil ZM, Morris JS, Haim A, Nelson RJ. 2010. Light at night increases body mass by shifting the time of food intake. *Proc Natl Acad Sci U S A* 107(43): 18664-18669. (Supported by the National Science Foundation and by the United States–Israel Binational Science Foundation. Authors affiliated with Ohio State University, OH; University of Haifa, Israel.)

213. Frajacomo FT, de Paula Garcia W, Fernandes CR, Garcia SB, Kannen V. 2015. Pineal gland function is required for colon antipreneoplastic effects of physical exercise in rats. *Scand J Med Sci Sports* 25(5): e451-458. (Supported by the National Council for Scientific and Technological Development [CNPq–Brazil] and University of São Paulo [Brazil]. Authors affiliated with University of São Paulo, Brazil.)

214. Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, Boyle T, El-Zaemey S, Rogers P, Peters S, Slevin T, D'Orsogna A, de Vocht F, Vermeulen R, Heyworth JS. 2013. The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer* 109(9): 2472-2480. (Supported by the National Health and Medical Research Council Australia, the Cancer Council Western Australia, the University of Western Australia, and the Lions Cancer Institute. Authors affiliated with University of Western Australia, Australia; University of Cologne, Germany; Monash University, Australia; Cancer Council Western Australia, Australia; Health Consumer Representative, Australia; University of Manchester, UK; Utrecht University, Netherlands.)

215. Fritschi L, Valérie Groß J, Wild U, Heyworth JS, Glass DC, Erren TC. 2018. Shift work that involves circadian disruption and breast cancer: a first application of chronobiological theory and the consequent challenges. *Occup Environ Med* 75(3): 231-234. (Supported by the National Health and Medical Research Council Australia, and the Cancer Council Western Australia. Authors affiliated with Curtin University, Australia; University of Cologne, Germany; University of Western Australia, Australia; Monash University, Australia.)

216. Fu L, Kettner NM. 2013. The circadian clock in cancer development and therapy. *Prog Mol Biol Transl Sci* 119: 221-282. (Supported by USDA/ARS, NIH/NCI and NIH/NIDDK. Authors affiliated with Baylor College of Medicine, TX.)

217. Fu L, Lee CC. 2003. The circadian clock: pacemaker and tumour suppressor. *Nat Rev Cancer* 3(5): 350-361. (Support not reported. Authors affiliated with Baylor College of Medicine, TX.)

218. Fu L, Patel MS, Bradley A, Wagner EF, Karsenty G. 2005. The molecular clock mediates leptin-regulated bone formation. *Cell* 122(5): 803-815. (Supported by NIH and the Canadian Institutes for Health Research. Authors affiliated with Baylor College of Medicine, TX; Wellcome Trust Sanger Institute, UK; Research Institute of Molecular Pathology, Austria)

219. Fu L, Pelicano H, Liu J, Huang P, Lee C. 2002. The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response in vivo. *Cell* 111(1): 41-50. (Supported by the National Institute of Health and Clayton Foundation for Research. Authors affiliated with Baylor College of Medicine, TX; University of Texas, TX.)

220. Fu XJ, Li HX, Yang K, Chen D, Tang H. 2016. The important tumor suppressor role of PER1 in regulating the cyclin-CDK-CKI network in SCC15 human oral squamous cell carcinoma cells. *Onco Targets Ther* 9: 2237-2245. (Support not reported. Authors affiliated with First Affiliated Hospital of Chongqing Medical University, China.)

221. Fujino Y, Japan Collaborative Cohort Study for Evaluation of C. 2007. Occupational factors and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev* 8 Suppl: 97-104. (Support not reported. Author affiliated with University of Occupational and Environmental Health, Japan.)

222. Furness JB. 2006. The organisation of the autonomic nervous system: peripheral connections. *Auton Neurosci* 130(1-2): 1-5. (Supported by the Australian Research Council and the National Health and Medical Research Council of Australia. Author affiliated with University of Melbourne, Australia.)

223. Gaddameedhi S, Selby CP, Kaufmann WK, Smart RC, Sancar A. 2011. Control of skin cancer by the circadian rhythm. *Proc Natl Acad Sci U S A* 108(46): 18790-18795. (Supported by NIH and NIEHS. Authors affiliated with University of North Carolina School of Medicine, NC; North Carolina State University, NC.)

224. Gall D, Bieske K. 2004. Definition and measurement of circadian radiometric quantities. In *Light and Health - Non-Visual Effects: Proceedings of the CIE Symposium '04 : 30 September - 2 October 2004* Vienna, Austria: Commission Internationale de L'éclairage. p. 129-132. (Supported by OSRAM GmbH. Authors affiliated with Technische Universität Ilmenau, Germany.)

225. Gamaldo CE, Shaikh AK, McArthur JC. 2012. The sleep-immunity relationship. *Neurol Clin* 30(4): 1313-1343. (Support not reported. Authors affiliated with Johns Hopkins Sleep Disorders Center, MD; Emory University Rollins School of Public Health, GA; Johns Hopkins University School of Medicine, MD.)

226. Gamble KL, Motsinger-Reif AA, Hida A, Borsetti HM, Servick SV, Ciarleglio CM, Robbins S, Hicks J, Carver K, Hamilton N, Wells N, Summar ML, McMahon DG, Johnson CH. 2011. Shift work in nurses: contribution of phenotypes and genotypes to adaptation.

PLoS One 6(4): e18395. (Supported by Vanderbilt University, the National Center for Research Resources of the National Institutes of Health, the Vanderbilt Joint Center for Nursing Research, and the National Institute of Mental Health. Authors affiliated with Vanderbilt University, TN; North Carolina State University, NC; Children's National Medical Center, Washington, D.C.)

227. Gan Y, Li L, Zhang L, Yan S, Gao C, Hu S, Qiao Y, Tang S, Wang C, Lu Z. 2018. Association between shift work and risk of prostate cancer: a systematic review and meta-analysis of observational studies. *Carcinogenesis* 39(2): 87-97. (No funding received. Authors affiliated with Huazhong University of Science and Technology, China; Jiangxi Science and Technology Normal University, China; Xiamen University, China; Chinese Center for Disease Control and Prevention, China; Changsha Medical University, China.)

228. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, Mullie P, Autier P. 2011. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. *Int J Cancer* 128(6): 1414-1424. (Supported by the Director's Cancer Research Trust, University of Otago, New Zealand. Authors affiliated with European Institute of Oncology, Italy; International Prevention Research Institute, France; University of Helsinki, Finland; IARC, France; University of Otago, New Zealand; Catholic University Leuven, Belgium.)

229. Gangwisch JE, Feskanich D, Malaspina D, Shen S, Forman JP. 2013. Sleep duration and risk for hypertension in women: results from the nurses' health study. *Am J Hypertens* 26(7): 903-911. (Supported by the National Institutes of Health, the National Heart, Lung, and Blood Institute, and the American Heart Association. Authors affiliated with Columbia University, NY; Brigham and Woman's Hospital and Harvard Medical School, MA; New York University, NY.)

230. Gapstur SM, Diver WR, Stevens VL, Carter BD, Teras LR, Jacobs EJ. 2014. Work schedule, sleep duration, insomnia, and risk of fatal prostate cancer. *Am J Prev Med* 46(3 Suppl 1): S26-33. (Supported by the American Cancer Society. Authors affiliated with American Cancer Society, GA.)

231. Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, Amiano P, Martín Sánchez V, Guevara M, Capelo R, Tardón A, Peiró-Perez R, Jiménez-Moleón JJ, Roca-Barceló A, Pérez-Gómez B, Dierssen-Sotos T, Fernández-Villa T, Moreno-Iribas C, Moreno V, García-Pérez J, Castaño-Vinyals G, Pollán M, Aubé M, Kogevinas M. 2018. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain Study). *Environ Health Perspect* 126(4): 047011. (Supported by the Accion Transversal del Cancer, Instituto de Salud Carlos III-FEDER, the Fundación Marqués de Valdecilla, the ICGC International Cancer Genome Consortium CLL, MINECO, RTICC, the Junta de Castillay León, Consejería de Salud of the Junta de Andalucía, the Conselleria de Sanitat of the Generalitat Valenciana, the Regional Government of the Basque Country, the Consejería de Sanidad de la Región de Murcia, the European Commission, AECC, the Catalan Government– Agency for Management of University and Research, the Fundación Caja de Ahorros de Asturias, the University of Oviedo, CERCA, the STARS4ALL project, the European Union, and the Cities at Night project. Authors affiliated with Barcelona Institute for Global Health, Spain;

CIBER, Spain, CIBERESP, Spain; IAA, Spain; CSIC, Spain; Universidad Complutense de Madrid, Spain; Cégep de Sherbrooke, Canada; University Exeter, UK; IMIM, Spain; National Centre for Epidemiology, Spain; IDIVAL, Spain; Health Department of Basque Region, Spain; University of León, Spain; IdiSNA, Spain; CYSMA, Spain; IUOPA, Spain; FISABIO, Spain; University of Granada, Spain; ibs.GRANADA, Spain; Autonomous Government of Catalonia, Spain; REDISSEC, Spain; IDIBELL, Spain; University of Barcelona, Spain.)

232. Garde AH, Hansen J, Kolstad HA, Larsen AD, Hansen AM. 2016. How do different definitions of night shift affect the exposure assessment of night work? *Chronobiol Int* 33(6): 595-598. (Support not reported. Authors affiliated with National Research Centre for the Working Environment, Denmark; University of Copenhagen, Denmark; Danish Cancer Society, Denmark; Aarhus University Hospital, Denmark.)

233. Geiger SS, Fagundes CT, Siegel RM. 2015. Chrono-immunology: progress and challenges in understanding links between the circadian and immune systems. *Immunology* 146(3): 349-358. (Supported by the Wellcome Trust and the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the U.S. National Institutes of Health. Authors affiliated with NIH, MD; Universidade Federal de Minas Gerais, Brazil.)

234. Gérard C, Goldbeter A. 2012. Entrainment of the mammalian cell cycle by the circadian clock: modeling two coupled cellular rhythms. *PLoS Comput Biol* 8(5): e1002516. (Supported by the Fonds de la Recherche Scientifique Médicale, the Belgian Federal Science Policy Office, and the F.R.S.-FNRS in conjunction with the ErasysBio+ project C5Sys, ‘‘Circadian and Cell Cycle Clock Systems in Cancer.’’ Authors affiliated with Université Libre de Bruxelles, Belgium.)

235. Gery S, Gombart AF, Yi WS, Koeffler C, Hofmann WK, Koeffler HP. 2005. Transcription profiling of C/EBP targets identifies *Per2* as a gene implicated in myeloid leukemia. *Blood* 106(8): 2827-2836. (Supported by NIH, and the Ronald Havner, Parker Hughes, and the Cindy, Alan Horn, and Inger funds. Authors affiliated with UCLA, CA; University Hospital “Benjamin Franklin,” Germany.)

236. Gery S, Komatsu N, Baldjyan L, Yu A, Koo D, Koeffler HP. 2006. The circadian gene per1 plays an important role in cell growth and DNA damage control in human cancer cells. *Mol Cell* 22(3): 375-382. (Supported by NIH, the Parker Hughes Trust, and the Inger Foundation. Authors affiliated with UCLA School of Medicine, CA.)

237. Geyfman M, Kumar V, Liu Q, Ruiz R, Gordon W, Espitia F, Cam E, Millar SE, Smyth P, Ihler A, Takahashi JS, Andersen B. 2012. Brain and muscle Arnt-like protein-1 (BMAL1) controls circadian cell proliferation and susceptibility to UVB-induced DNA damage in the epidermis. *Proc Natl Acad Sci U S A* 109(29): 11758-11763. (Supported by the Irving Weinstein Foundation, the National Institutes of Health, and the National Institute on Drug Abuse. Authors affiliated with University of California - Irvine, CA; University of Texas Southwestern Medical Center, TX; University of Pennsylvania School of Medicine, PA.)

238. Giannoulia-Karantana A, Vlachou A, Polychronopoulou S, Papassotiriou I, Chrousos GP. 2006. Melatonin and immunomodulation: connections and potential clinical applications.

Neuroimmunomodulation 13(3): 133-144. (Support not reported. Authors affiliated with Athens University Medical School, Greece; 'Aghia Sophia' Children's Hospital, Greece.)

239. Girschik J, Heyworth J, Fritschi L. 2013. Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. *Am J Epidemiol* 177(4): 316-327. (Supported by the Australian National Health and Medical Research Council, the University of Western Australia, and the Cancer Council Western Australia. Authors affiliated with University of Western Australia, Australia.)

240. Glickman G, Levin R, Brainard GC. 2002. Ocular input for human melatonin regulation: relevance to breast cancer. *Neuro Endocrinol Lett* 23 Suppl 2: 17-22. (Supported by NCI, NIH, and National Space Biomedical Research Institute under a NASA Cooperative Agreement. Authors affiliated with Jefferson Medical College, PA; Rensselaer Polytechnic Institute, NY.)

241. Goel N, Stunkard AJ, Rogers NL, Van Dongen HP, Allison KC, O'Reardon JP, Ahima RS, Cummings DE, Heo M, Dinges DF. 2009. Circadian rhythm profiles in women with night eating syndrome. *J Biol Rhythms* 24(1): 85-94. (Supported by NIH, the Institute for Experimental Psychiatry Research Foundation, the NHMRC Howard Florey Centenary Research Fellowship and a NSW BioFirst award. Authors affiliated with University of Pennsylvania School of Medicine, PA; University of Washington, WA; Albert Einstein College of Medicine, NY.)

242. Gómez-Acebo I, Dierssen-Sotos T, Papantoniou K, García-Unzueta MT, Santos-Benito MF, Llorca J. 2015. Association between exposure to rotating night shift versus day shift using levels of 6-sulfatoxymelatonin and cortisol and other sex hormones in women. *Chronobiol Int* 32(1): 128-135. (Supported by the Instituto de Formación e Investigación Marqués de Valdecilla [IFIMAV]. Authors affiliated with University of Cantabria, Spain; IDIVAL, Spain; CIBER Epidemiología y Salud Pública [CIBERESP], Spain; Centre for Research in Environmental Epidemiology [CREAL], Spain; Hospital del Mar Medical Research Institute, Spain; Universitat Pompeu Fabra, Spain; Marques de Valdecilla University Hospital, Spain.)

243. Gooley JJ, Chamberlain K, Smith KA, Khalsa SB, Rajaratnam SM, Van Reen E, Zeitzer JM, Czeisler CA, Lockley SW. 2011. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *J Clin Endocrinol Metab* 96(3): E463-472. (Supported by Brigham and Women's Hospital General Clinical Research Center, Harvard Clinical and Translational Science Center, the National Center for Research Resources, NIH, NIMH, NCCAM, NINDS, and the National Space Biomedical Research Institute through NASA. Authors affiliated with Brigham and Women's Hospital and Harvard Medical School, MA; University of Surrey, UK.)

244. Goto M, Oshima I, Tomita T, Ebihara S. 1989. Melatonin content of the pineal gland in different mouse strains. *J Pineal Res* 7(2): 195-204. (Supported by the Ministry of Education, Science and Culture of Japan. Authors affiliated with Nagoya University, Japan.)

245. Gotoh T, Kim JK, Liu J, Vila-Caballer M, Stauffer PE, Tyson JJ, Finkielstein CV. 2016. Model-driven experimental approach reveals the complex regulatory distribution of p53 by the circadian factor Period 2. *Proc Natl Acad Sci U S A* 113(47): 13516-13521. (Supported by the National Science Foundation Molecular and Cellular Biosciences Division, the Fralin Life Science Institute, the Korea Advanced Institute of Science and Technology Research, the National Research Foundation of Korea, and a T. J. Park Science Fellowship of POSCO. Authors affiliated with Virginia Polytechnic Institute and State University, VA; Korea Advanced Institute of Science and Technology, Korea.)

246. Goulet G, Mongrain V, Desrosiers C, Paquet J, Dumont M. 2007. Daily light exposure in morning-type and evening-type individuals. *J Biol Rhythms* 22(2): 151-158. (Supported by the Canadian Institute of Health Research, Fonds de la Recherche en Santé du Québec and the Natural Sciences and Engineering Research Council. Authors affiliated with Sacré-Coeur Hospital of Montréal, Canada; Université de Montréal, Canada.)

247. Gradisar M, Wolfson AR, Harvey AG, Hale L, Rosenberg R, Czeisler CA. 2013. The sleep and technology use of Americans: findings from the National Sleep Foundation's 2011 Sleep in America poll. *J Clin Sleep Med* 9(12): 1291-1299. (Supported by Merck, Pfizer, Astra Zeneca, Philips/Respironics, Vanda Pharmaceuticals, Cephalon, Inc., Koninklijke Philips Electronics, N.V., ResMed, the Brigham and Women's Hospital. Authors affiliated with Flinders University, Australia; College of the Holy Cross, MA; University of California - Berkeley, CA; Stony Brook University, NY; Atlanta School of Sleep and Medicine Technology, GA; National Sleep Foundation, Washington, DC; Brigham and Women's Hospital, MA; Harvard Medicine School, MA.)

248. Grajewski B, Nguyen MM, Whelan EA, Cole RJ, Hein MJ. 2003. Measuring and identifying large-study metrics for circadian rhythm disruption in female flight attendants. *Scand J Work Environ Health* 29(5): 337-346. (Supported by the Federal Aviation Administration. Authors affiliated with NIOSH, OH; Synchrony Applied Health Sciences, CA.)

249. Green A, Cohen-Zion M, Haim A, Dagan Y. 2017. Evening light exposure to computer screens disrupts human sleep, biological rhythms, and attention abilities. *Chronobiol Int* 34: 855-865. (Support not reported. Authors affiliated with University of Haifa, Israel; Assuta Medical Center, Israel; Academic College of Tel Aviv, Israel; Academic College of Tel-Hai, Israel.)

250. Greene MW. 2012. Circadian rhythms and tumor growth. *Cancer Lett* 318(2): 115-123. (Supported by the Stephan C. Clark Foundation. Author affiliated with Bassett Research Institute, NY.)

251. Griefahn B, Kuenemund C, Robens S. 2006. Shifts of the hormonal rhythms of melatonin and cortisol after a 4 h bright-light pulse in different diurnal types. *Chronobiol Int* 23(3): 659-673. (Supported by the Deutsche Forschungsgemeinschaft. Authors affiliated with Dortmund University, Germany.)

252. Gritton HJ, Sutton BC, Martinez V, Sarter M, Lee TM. 2009. Interactions between cognition and circadian rhythms: attentional demands modify circadian entrainment. *Behav*

Neurosci 123(5): 937-948. (Supported by PHS. Authors affiliated with University of Michigan, MI.)

253. Gromadzinska J, Peplonska B, Sobala W, Reszka E, Wasowicz W, Bukowska A, Lie JA. 2013. Relationship between intensity of night shift work and antioxidant status in blood of nurses. *Int Arch Occup Environ Health* 86(8): 923-930. (Supported by the Polish-Norwegian Research Fund. Authors affiliated with Nofer Institute of Occupational Medicine, Poland; Institute of Occupational Health, Norway.)

254. Grundy A, Richardson H, Burstyn I, Lohrisch C, SenGupta SK, Lai AS, Lee D, Spinelli JJ, Aronson KJ. 2013a. Increased risk of breast cancer associated with long-term shift work in Canada. *Occup Environ Med* 70(12): 831-838. (Supported by the Canadian Institutes of Health Research. Authors affiliated with Queen's University, Canada; Drexel University, PA; British Columbia Cancer Agency, Canada; University of British Columbia, Canada.)

255. Grundy A, Sanchez M, Richardson H, Tranmer J, Borugian M, Graham CH, Aronson KJ. 2009. Light intensity exposure, sleep duration, physical activity, and biomarkers of melatonin among rotating shift nurses. *Chronobiol Int* 26(7): 1443-1461. (Supported by Breast Cancer Action Kingston. Authors affiliated with Queen's University, Canada; British Columbia Cancer Agency, Canada.)

256. Grundy A, Schuetz JM, Lai AS, Janoo-Gilani R, Leach S, Burstyn I, Richardson H, Brooks-Wilson A, Spinelli JJ, Aronson KJ. 2013b. Shift work, circadian gene variants and risk of breast cancer. *Cancer Epidemiol* 37(5): 606-612. (Supported by the Canadian Institutes of Health Research. Authors affiliated with Queen's University, Canada; British Columbia Cancer Agency, Canada; Drexel University, PA; Simon Fraser University, Canada; University of British Columbia, Canada.)

257. Grundy A, Tranmer J, Richardson H, Graham CH, Aronson KJ. 2011. The influence of light at night exposure on melatonin levels among Canadian rotating shift nurses. *Cancer Epidemiol Biomarkers Prev* 20(11): 2404-2412. (Supported by the Workplace Safety and Insurance Board of Ontario and the Canadian Institutes of Health Research. Authors affiliated with Queen's University, Canada; Queen's Cancer Research Institute, Canada.)

258. Gu F, Han J, Laden F, Pan A, Caporaso NE, Stampfer MJ, Kawachi I, Rexrode KM, Willett WC, Hankinson SE, Speizer FE, Schernhammer ES. 2015. Total and cause-specific mortality of U.S. nurses working rotating night shifts. *Am J Prev Med* 48(3): 241-252. (Supported by NCI, NIH Heart, Lung and Blood Institute, and the CDC/The National Institute for Occupational Safety and Health. Authors affiliated with NCI, MD; Brigham and Women's Hospital, MA; Harvard Medical School, MA; University of Massachusetts, MA; Indiana University, IN; National University of Singapore, Singapore; National University Health System, Singapore; Applied Cancer Research– Institution for Translational Research Vienna, Austria.)

259. Gu F, Xu S, Devesa SS, Zhang F, Klerman EB, Graubard BI, Caporaso NE. 2017. Longitude position in a time zone and cancer risk in the United States. *Cancer Epidemiol Biomarkers Prev* 26(8): 1306-1311. (Supported by NCI. Authors affiliated with National

Cancer Institute, MD; Roswell Park Cancer Institute, NY; Harvard University, MA: Information Management Services, Inc., MD; Brigham and Women's Hospital, MA.)

260. Gubareva E, Maidin MA, Tyndyk ML, Vinogradova IA, Panchenko AV. 2016. [Role of clock proteins in skin carcinogenesis in 14-month-old SHR mice maintained under disrupted light regimen]. *Vopr Oncol* 62(5): 666-670. (Support unknown due to foreign language. Authors affiliated with N. N. Petrov Research Institute of Oncology, Russia; Petrozavodsk State University, Russia.)

261. Guerrero-Vargas NN, Guzmán-Ruiz M, Fuentes R, García J, Salgado-Delgado R, Basualdo Mdel C, Escobar C, Markus RP, Buijs RM. 2015. Shift work in rats results in increased inflammatory response after lipopolysaccharide administration: A role for food consumption. *J Biol Rhythms* 30(4): 318-330. (Supported by DGAPA, CONACYT, and PROLAB IBRO LARC. Authors affiliated with Universidad Nacional Autónoma de México, Mexico; Universidad Autónoma de San Luis Potosí, Mexico; University of São Paulo, Brazil.)

262. Guerrero-Vargas NN, Navarro-Espíndola R, Guzmán-Ruíz MA, Basualdo MDC, Espitia-Bautista E, López-Bago A, Lascurain R, Córdoba-Manilla C, Buijs RM, Escobar C. 2017. Circadian disruption promotes tumor growth by anabolic host metabolism; experimental evidence in a rat model. *BMC Cancer* 17(1): 625. (Supported by DGAPA-UNAM, PAPIIT-UNAM, and CONACyT. Authors affiliated with Universidad Nacional Autónoma de México, Mexico.)

263. Guo Y, Liu Y, Huang X, Rong Y, He M, Wang Y, Yuan J, Wu T, Chen W. 2013. The effects of shift work on sleeping quality, hypertension and diabetes in retired workers. *PLoS One* 8(8): e71107. (Supported by the National Basic Research Program. Authors affiliated with Huazhong University of Science and Technology, China.)

264. Gurer-Orhan H, Suzen S. 2015. Melatonin, its metabolites and its synthetic analogs as multi-faceted compounds: antioxidant, prooxidant and inhibitor of bioactivation reactions. *Curr Med Chem* 22(4): 490-499. (Supported by The Scientific and Technological Research Council of Turkey. Authors affiliated with Ege University, Turkey; Ankara University, Turkey.)

265. Gyarmati G, Turner MC, Castano-Vinyals G, Espinosa A, Papantoniou K, Alguacil J, Costas L, Perez-Gomez B, Martin Sanchez V, Ardanaz E, Moreno V, Gomez-Acebo I, Fernandez-Tardon G, Villanueva Ballester V, Capelo R, Chirlaque MD, Santibanez M, Pollan M, Aragones N, Kogevinas M. 2016. Night shift work and stomach cancer risk in the MCC-Spain study. *Occup Environ Med* 73(8): 520-527. (Supported by the 'Accion Transversal del Cancer,' approved by the Spanish Ministry Council on 11 October 2007, the Instituto de Salud Carlos III-FEDER, the Fundación Marqués de Valdecilla, the Junta de Castilla y León, the Consejería de Salud of the Junta de Andalucía, the Conselleria de Sanitat of the Generalitat Valenciana, the Recercaixa, the Regional Government of the Basque Country, the Consejería de Sanidad de la Región de Murcia, the European Commission, the Spanish Association Against Cancer [AECC] Scientific Foundation, the Catalan Government, the Fundación Caja de Ahorros de Asturias, the University of Oviedo, and the Canadian Institutes of Health. Authors affiliated with ISGlobal, Spain;

Universitat Pompeu Fabra, Spain; CIBERESP, Spain; University of Ottawa, Canada; IMIM, Spain; Medical University of Vienna, Austria; Universidad de Huelva, Spain; Catalan Institute of Oncology, Spain; University of Barcelona, Spain; Carlos III Health Institute, Spain; Cancer Epidemiology Research Group, Spain; Universidad de León, Spain; Navarra Public Health Institute, Spain; Navarra Institute for Health Research, Spain; University of Cantabria, Spain; Universidad de Oviedo, Spain; FISABIO, Spain; Murcia Health Council, Spain.)

266. Habbal OA, Al-Jabri AA. 2009. Circadian rhythm and the immune response: a review. *Int Rev Immunol* 28(1): 93-108. (Support not reported. Authors affiliated with Sultan Qaboos University, Oman.)

267. Hadden H, Soldin SJ, Massaro D. 2012. Circadian disruption alters mouse lung clock gene expression and lung mechanics. *J Appl Physiol* 113(3): 385-392. (Supported by the National Heart, Lung, and Blood Institute. Authors affiliated with Georgetown University School of Medicine, Washington, D.C.; NIH, MD.)

268. Hahn RA. 1991. Profound bilateral blindness and the incidence of breast cancer. *Epidemiology* 2(3): 208-210. (Support not reported. Author affiliated with Centers for Disease Control, GA.)

269. Haim A, Yukler A, Harel O, Schwimmer H, Fares F. 2010. Effects of chronobiology on prostate cancer cells growth in vivo. *Sleep Sci.* 3(1): 32-35. (Supported by the Research authority of the University of Haifa. Authors affiliated with University of Haifa, Israel.)

270. Haim A, Zubidat AE. 2015. Artificial light at night: melatonin as a mediator between the environment and epigenome. *Philos Trans R Soc Lond B Biol Sci* 370(1667). (Support not reported. Authors affiliated with University of Haifa, Israel.)

271. Hamilton T. 1969. Influence of environmental light and melatonin upon mammary tumour induction. *Br J Surg* 56(10): 764-766. (Support not reported. Author affiliated with University of Edinburgh, UK.)

272. Hammer GP, Emrich K, Nasterlack M, Blettner M, Yong M. 2015. Shift work and prostate cancer incidence in industrial workers: A historical cohort study in a German chemical company. *Dtsch Arztebl Int* 112(27-28): 463-470. (Supported by the German Social Accident Insurance. Authors affiliated with Johannes Gutenberg University, Germany; Laboratoire National de Santé, Luxembourg; Occupational Medicine and Health Protection, BASF SE, Germany.)

273. Hansen AM, Helene Garde A, Hansen J. 2006. Diurnal urinary 6-sulfatoxymelatonin levels among healthy Danish nurses during work and leisure time. *Chronobiol Int* 23(6): 1203-1215. (Supported by the Danish Cancer Society and the National Institute of Occupational Health. Authors affiliated with National Institute of Occupational Health, Denmark; Danish Cancer Society, Denmark.)

274. Hansen J. 2001. Increased breast cancer risk among women who work predominantly at night. *Epidemiology* 12(1): 74-77. (Support not reported. Author affiliated with Danish Cancer Society, Denmark.)

275. Hansen J. 2006. Risk of breast cancer after night- and shift work: current evidence and ongoing studies in Denmark. *Cancer Causes Control* 17(4): 531-537. (Support not reported. Author affiliated with Danish Cancer Society, Denmark.)

276. Hansen J, Lassen CF. 2012. Nested case-control study of night shift work and breast cancer risk among women in the Danish military. *Occup Environ Med* 69(8): 551-556. (Supported by the Danish Ministry of Defence. Authors affiliated with Danish Cancer Society, Denmark.)

277. Hansen J, Stevens RG. 2012. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. *Eur J Cancer* 48(11): 1722-1729. (Supported by the Danish Cancer Society and from the National Programme of Environmental Health Research. Authors affiliated with Danish Cancer Society, Denmark; University of Connecticut Health Center, CT.)

278. Hardeland R. 2013. Chronobiology of melatonin beyond the feedback to the suprachiasmatic nucleus-consequences to melatonin dysfunction. *Int J Mol Sci* 14(3): 5817-5841. (Support not reported. Author affiliated with University of Göttingen, Germany.)

279. Hardeland R. 2014. Melatonin, noncoding RNAs, messenger RNA stability and epigenetics--evidence, hints, gaps and perspectives. *Int J Mol Sci* 15(10): 18221-18252. (Support not reported. Author affiliated with University of Göttingen, Germany.)

280. Härmä M, Koskinen A, Ropponen A, Puttonen S, Karhula K, Vahtera J, Kivimäki M. 2017. Validity of self-reported exposure to shift work. *Occup Environ Med* 74(3): 228-230. (Supported by the Finnish Work Environment Fund and NordForsk. Authors affiliated with Finnish Institute of Occupational Health, Finland; University of Turku, Finland; Turku University Hospital, Finland; University of Helsinki, Finland; University College London Medical School, UK.)

281. Hattar S, Liao HW, Takao M, Berson DM, Yau KW. 2002. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 295(5557): 1065-1070. (Supported by the U.S. National Eye Institute. Authors affiliated with Johns Hopkins University School of Medicine, MD; Brown University, RI.)

282. Haus E, Smolensky MH. 1999. Biologic rhythms in the immune system. *Chronobiol Int* 16(5): 581-622. (Support not reported. Authors affiliated with Healthpartners Research Foundation, MN; University of Minnesota, MN; University of Texas, TX; Health Science Center, TX.)

283. Haus EL, Smolensky MH. 2013. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. *Sleep Med Rev* 17(4): 273-284. (Supported by the HealthPartners Research Foundation and the and Department of Pathology, Regions Hospital, Departmental Funds. Authors affiliated with University of Minnesota and HealthPartners Medical Group, MN; University of Texas, TX.)

284. He C, Anand ST, Ebell MH, Vena JE, Robb SW. 2015. Circadian disrupting exposures and breast cancer risk: a meta-analysis. *Int Arch Occup Environ Health* 88(5): 533-547.

(Supported by the Georgia Cancer Coalition. Authors affiliated with University of Georgia, GA; Medical University of South Carolina, SC.)

285. Heckman CJ, Kloss JD, Feskanich D, Culnan E, Schernhammer ES. 2017. Associations among rotating night shift work, sleep and skin cancer in Nurses' Health Study II participants. *Occup Environ Med* 74(3): 169-175. (Supported by NCI, NIH, CDC. NIOSH, and Drexel University. Authors affiliated with Fox Chase Cancer Center, PA; Drexel University, PA; Brigham and Women's Hospital, MA; Harvard Medical School, MA; Medical University of Vienna, Austria.)

286. Hemiö K, Puttonen S, Viitasalo K, Härmä M, Peltonen M, Lindström J. 2015. Food and nutrient intake among workers with different shift systems. *Occup Environ Med* 72(7): 513-520. (Supported by the Finnish Funding Agency for Technology and Innovation, the Yrjö Jahnsson Foundation, the Academy of Finland, the Juho Vainio Foundation, and the Finnish Work Environment Fund. Authors affiliated with National Institute for Health and Welfare, Finland; Finnish Institute of Occupational Health, Finland; University of Helsinki, Finland; Finnair Health Services, Finland.)

287. Heo JY, Kim K, Fava M, Mischoulon D, Papakostas GI, Kim MJ, Kim DJ, Chang KJ, Oh Y, Yu BH, Jeon HJ. 2017. Effects of smartphone use with and without blue light at night in healthy adults: A randomized, double-blind, cross-over, placebo-controlled comparison. *J Psychiatr Res* 87: 61-70. (Supported by Samsung Display, Original Technology Research Program for Brain Science through the National Research Foundation of Korea [NRF] funded by the Ministry of Education, Science and Technology, and the Korean Mental Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea. Authors affiliated with Sungkyunkwan University School of Medicine, South Korea; Harvard Medical School, MA: Samsung Medical Center, South Korea.)

288. Hersh C, Sisti J, Richiutti V, Schernhammer E. 2015. The effects of sleep and light at night on melatonin in adolescents. *Hormones (Athens)* 14(3): 399-409. (Supported by NIH and NCI. Authors affiliated with Brown University, RI; Harvard T.H. Chan School of Public Health, MA; University of Cincinnati College of Medicine, OH; Brigham and Women’s Hospital, MA; Harvard Medical School, MA; ACR-ITR VIEnna, Austria.)

289. Higuchi S, Motohashi Y, Ishibashi K, Maeda T. 2007. Influence of eye colors of Caucasians and Asians on suppression of melatonin secretion by light. *Am J Physiol Regul Integr Comp Physiol* 292(6): R2352-2356. (Supported by the Japanese Ministry of Education, Culture, Sports, Science, and Technology. Authors affiliated with Akita University School of Medicine, Japan; Kyushu University, Japan; National Institute of Occupational Safety and Health, Japan; Hokkaido University, Japan.)

290. Higuchi S, Nagafuchi Y, Lee SI, Harada T. 2014. Influence of light at night on melatonin suppression in children. *J Clin Endocrinol Metab* 99(9): 3298-3303. (Supported by the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology of Japan. Authors affiliated with Kyushu University, Japan; Kochi University, Japan.)

291. Hill SM, Belancio VP, Dauchy RT, Xiang S, Brimer S, Mao L, Hauch A, Lundberg PW, Summers W, Yuan L, Frasch T, Blask DE. 2015. Melatonin: an inhibitor of breast cancer. *Endocr Relat Cancer* 22(3): R183-204. (Supported by NIH, the American Association for Laboratory Animal Science, the Life Extension Foundation, and the Edmond and Lily Safra Endowed Chair for Breast Cancer Research at Tulane Cancer Center. Authors affiliated with Tulane University School of Medicine, LA.)

292. Hill SM, Cheng C, Yuan L, Mao L, Jockers R, Dauchy B, Blask DE. 2013. Age-related decline in melatonin and Its MT1 receptor are associated with decreased sensitivity to melatonin and enhanced mammary tumor growth. *Curr. Aging Sci.* 6(1): 125-133. (Supported by NIH and the Army DOD. Authors affiliated with Tulane University School of Medicine, LA; Institute Cochin, France.)

293. Hill SM, Spriggs LL, Simon MA, Muraoka H, Blask DE. 1992. The growth inhibitory action of melatonin on human breast cancer cells is linked to the estrogen response system. *Cancer Lett* 64(3): 249-256. (Supported by NCI and the American Cancer Society. Authors affiliated with Tulane University, LA; Abilene Christian University, TX; Mary Imogene Bassett Hospital, NY.)

294. Hirano A, Fu YH, Ptáček LJ. 2016. The intricate dance of post-translational modifications in the rhythm of life. *Nat Struct Mol Biol* 23(12): 1053-1060. (Supported by NIH, the the William Bowes Neurogenetics Fund, the Howard Hughes Medical Institute, and the Uehara memorial foundation. Authors affiliated with University of California - San Francisco, CA; Kavli Institute for Fundamental Neuroscience, CA; Weill Institute of Neurosciences, CA; Howard Hughes Medical Institute, CA.)

295. Holick MF. 2016. Biological effects of sunlight, ultraviolet radiation, visible light, infrared radiation and vitamin D for health. *Anticancer Res* 36(3): 1345-1356. (Support not reported. Authors affiliated with Boston University Medical Center, MA.)

296. Honda K, Kondo M, Hiramoto D, Saneyasu T, Kamisoyama H. 2017. Effects of continuous white light and 12h white-12h blue light-cycles on the expression of clock genes in diencephalon, liver, and skeletal muscle in chicks. *Comp Biochem Physiol A Mol Integr Physiol* 207: 73-78. (Supported by the Project of the NARO Bio-oriented Technology Research Advancement Institution [The Special Scheme to Create Dynamism in Agriculture, Forestry and Fisheries through Deploying Highly Advanced Technology]. Authors affiliated with Kobe University, Japan.)

297. Honma S. 2018. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. *J Physiol Sci* 68(3): 207-219. (Support not reported. Authors affiliated with Hokkaido University, Japan.)

298. Hoogerwerf WA, Hellmich HL, Cornelissen G, Halberg F, Shahinian VB, Bostwick J, Savidge TC, Cassone VM. 2007. Clock gene expression in the murine gastrointestinal tract: Endogenous rhythmicity and effects of a feeding regimen. *Gastroenterology* 133(4): 1250-1260. (Supported by R21 DK074477-01A1. Authors affiliated with University of Michigan, MI; University of Texas Medical Branch, TX; University of Minnesota, MN; Texas A&M University, TX.)

299. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. 2017. *SEER Cancer Statistics Review, 1975-2014*. National Cancer Institute. https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017

300. Huisman SA, Ahmadi AR, IJzermans JNM, Verhoef C, van der Horst GTJ, de Bruin RWF. 2016. Disruption of clock gene expression in human colorectal liver metastases. *Tumour Biol* 37(10): 13973-13981. (Supported by the Dutch Cancer Society. Authors affiliated with Erasmus University Medical Center, Netherlands.)

301. Hung EW, Aronson KJ, Leung M, Day A, Tranmer J. 2016. Shift work parameters and disruption of diurnal cortisol production in female hospital employees. *Chronobiol Int* 33(8): 1045-1055. (Support not reported. Authors affiliated with Queen's University, Canada; Hospital for Sick Children, Canada; Kingston General Hospital, Canada.)

302. Hurley S, Goldberg D, Nelson D, Hertz A, Horn-Ross PL, Bernstein L, Reynolds P. 2014. Light at night and breast cancer risk among California teachers. *Epidemiology* 25(5): 697-706. (Supported by the Regents of the University of California, California Breast Cancer Research Program and the National Cancer Institute. Authors affiliated with Cancer Prevention Institute of California, CA; Beckman Research Institute, CA; Stanford University School of Medicine, CA.)

303. Hurley S, Nelson DO, Garcia E, Gunier R, Hertz A, Reynolds P. 2013. A cross-sectional analysis of light at night, neighborhood sociodemographics and urinary 6-sulfatoxymelatonin concentrations: implications for the conduct of health studies. *Int J Health Geogr* 12: 39. (Supported by the California Breast Cancer Research Program and National Cancer Institute. Authors affiliated with Cancer Prevention Institute of California, CA; Stanford University School of Medicine, CA.)

304. Husse J, Eichele G, Oster H. 2015. Synchronization of the mammalian circadian timing system: Light can control peripheral clocks independently of the SCN clock: alternate routes of entrainment optimize the alignment of the body's circadian clock network with external time. *Bioessays* 37(10): 1119-1128. (Supported by the Max Planck Society and the Volkswagen Foundation. Authors affiliated with Max Planck Institute for Biophysical Chemistry, Germany; University of Lübeck, Germany.)

305. IARC. 2010. Shift work. In *Painting, Firefighting, and Shiftwork*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. vol. 98. Lyon, France: International Agency for Research on Cancer. p. 563-764.

306. IARC. 2012. *EUCAN: Breast Cancer*. International Agency for Research on Cancer. Last accessed: 1/8/18. http://eco.iarc.fr/EUCAN/CancerOne.aspx?Cancer=46&Gender=2

307. Ibáñez-Costa A, Córdoba-Chacón J, Gahete MD, Kineman RD, Castaño JP, Luque RM. 2015. Melatonin regulates somatotrope and lactotrope function through common and distinct signaling pathways in cultured primary pituitary cells from female primates. *Endocrinology* 156(3): 1100-1110. (Supported by Junta de Andalucía, the Ministerio de Economía y Competitividad, Gobierno de España, the Instituto de Salud Carlos III, the

Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición, Ayuda Merck Serono 2013, the Department of Veterans Affairs, and NIH. Authors affiliated with University of Cordoba, Spain; University of Illinois at Chicago, IL.)

308. Ijaz S, Verbeek J, Seidler A, Lindbohm ML, Ojajärvi A, Orsini N, Costa G, Neuvonen K. 2013. Night-shift work and breast cancer – a systematic review and meta-analysis. *Scand J Work Environ Health* 39(5): 431-447. (Supported by the Danish Work and Environment Fund. Authors affiliated with Finnish Institute of Occupational Health, Finland; Technical University of Dresden, Germany; Karolinska Institute, Sweden; University of Milan, Italy; IRCCS Ca' Granda Foundation, Italy.)

309. Ika K, Suzuki E, Mitsuhashi T, Takao S, Doi H. 2013. Shift work and diabetes mellitus among male workers in Japan: does the intensity of shift work matter? *Acta Med Okayama* 67(1): 25-33. (Support not reported. Authors affiliated with Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan.)

310. Illnerová H, Vanecek J, Hoffmann K. 1989. Different mechanisms of phase delays and phase advances of the circadian rhythm in rat pineal *N*-acetyltransferase activity. *J Biol Rhythms* 4(2): 187-200. (Support not reported. Authors affiliated with Czechoslovak Academy of Sciences, Czechoslovakia; Max-Planck-Gesellschaft Clinical Research Unit for Reproductive Medicine, Germany.)

311. ILO. 2004. *Shift Work.* Information Sheet No. WT-8. Geneva, Switzerland: International Labour Office. 4 pp.

312. Institute of Medicine. 2012. Examining mechanisms of breast cancer over the lifecourse: Implications for risk. In *Breast Cancer and the Environment: A Life Course Approach* Washington, DC: The National Academies Press. p. 239-281. https://www.nap.edu/read/13263/chapter/7.

313. Ishihara I, Nakano M, Ikushima M, Hara Y, Yoshimine T, Haraga M, Nakatani J, Kawamoto R, Kasai H. 2008. Effect of work conditions and work environments on the formation of 8-OH-dG in nurses and non-nurse female workers. *J UOEH* 30(3): 293-308. (Supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan. Authors affiliated with University of Occupational and Environmental Health, Japan; Kyushu University, Japan.)

314. Ishii N, Iwata T, Dakeishi M, Murata K. 2004. Effects of shift work on autonomic and neuromotor functions in female nurses. *J Occup Health* 46(5): 352-358. (Supported by the Ministry of Education, Culture, Science and Technology, Japan. Authors affiliated with Akita University School of Medicine, Japan.)

315. Isobe Y, Fukamachi K, Hida H, Tsuda H, Nishino H. 2008. Diethylnitrosamine-induced hepatic lesions are greater in rats maintained under a light-dark cycle than under constant light, related to the locomotor activity rhythm. *Asian Pac J Cancer Prev* 9(4): 619-624. (Supported by the Ministry of Education, Sports, Science and Culture of Japan and the Ministry of Health, Labor and Welfare, Japan.)

316. Itoh H, Weng Z, Saito H, Ogawa Y, Nakayama K, Hasegawa-Ohira M, Morimoto K, Maki S, Takahashi M. 2011. Association between night-shift work and serum 25-hydroxyvitamin D levels in Japanese male indoor workers: a cross-sectional study. *Ind Health* 49(5): 658-662. (Supported by the National Institute of Occupational Safety and Health, Japan. Authors affiliated with National Institute of Occupational Safety and Health, Japan; Osaka University Graduate School of Medicine, Japan; Osaka University of Health and Sport Sciences, Japan.)

317. Iversen OH, Iversen UM. 1995. A diurnal variation in the tumorigenic response of mouse epidermis to a single application of the strong short-acting chemical carcinogen methylnitrosourea. A dose-response study of 1, 2 and 10 mg. *In Vivo* 9(2): 117-132. (Supported by the Norwegian Cancer Society and the University of Oslo. Authors affiliated with University of Oslo, Norway; Rikshospitalet, Norway.)

318. Iwamoto A, Kawai M, Furuse M, Yasuo S. 2014. Effects of chronic jet lag on the central and peripheral circadian clocks in CBA/N mice. *Chronobiol. Int.* 31(2): 189-198. (Supported by the Japanese Society for the Promotion of Science, the Uehara Memorial Foundation, the Nisshin Seifun Foundation, and the Research Grant for Young Investigators of Faculty of Agriculture, Kyushu University. Authors affiliated with Kyushu University, Japan.)

319. Jacobs DI, Hansen J, Fu A, Stevens RG, Tjonneland A, Vogel UB, Zheng T, Zhu Y. 2013. Methylation alterations at imprinted genes detected among long-term shiftworkers. *Environ Mol Mutagen* 54(2): 141-146. (Supported by NIEHS, Yale University, and the Danish Cancer Society. Authors affiliated with Yale School of Public Health, CT; Danish Cancer Society, Denmark; University of Connecticut Health Center, CT; National Research Centre for the Working Environment, Denmark.)

320. James FO, Cermakian N, Boivin DB. 2007. Circadian rhythms of melatonin, cortisol, and clock gene expression during simulated night shift work. *Sleep* 30(11): 1427-1436. (Supported by the Fonds de Recherche en Santé du Québec and the Canadian Institutes of Health Research. Authors affiliated with Douglas Mental Health University Institute, Canada; McGill University, Canada.)

321. James P, Bertrand KA, Hart JE, Schernhammer ES, Tamimi RM, Laden F. 2017. Outdoor light at night and breast cancer incidence in the Nurses' Health Study II. *Environ Health Perspect* 125(8): 087010. (Supported by the Harvard National Heart, Lung, and Blood Institute, NIH, NCI, and the Susan G. Komen for the Cure® organization. Authors affiliated with Harvard T. H. Chan School of Public Health, MA; Brigham and Women's Hospital and Harvard Medical School, MA; Boston University, MA; Medical University of Vienna, Austria; University of California Los Angeles, CA.)

322. Jensen MA, Garde AH, Kristiansen J, Nabe-Nielsen K, Hansen AM. 2016. The effect of the number of consecutive night shifts on diurnal rhythms in cortisol, melatonin and heart rate variability (HRV): a systematic review of field studies. *Int Arch Occup Environ Health* 89(4): 531-545. (Supported by the Danish Working Environment Research Fund and the University of Copenhagen. Authors affiliated with University of Copenhagen, Denmark; National Research Centre for the Working Environment, Denmark.)

323. Ji BT, Gao YT, Shu XO, Yang G, Yu K, Xue SZ, Li HL, Liao LM, Blair A, Rothman N, Zheng W, Chow WH. 2012. Nightshift work job exposure matrices and urinary 6-sulfatoxymelatonin levels among healthy Chinese women. *Scand J Work Environ Health* 38(6): 553-559. (Supported by NIH and the National Center for Research Resources. Authors affiliated with National Cancer Institute, MD; Vanderbilt University School of Medicine, TN; Shanghai Cancer Institute, China.)

324. Jia Y, Lu Y, Wu K, Lin Q, Shen W, Zhu M, Huang S, Chen J. 2013. Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol* 37(3): 197-206. (Support not reported. Authors affiliated with Shanghai Jiaotong University School of Medicine, China.)

325. Jilge B, Kunz E. 2004. Chapter 20: Circadian rhythms of the mouse. In *The Laboratory Mouse* H Hedrich, G Bullock, eds. San Diego, CA: Elsevier. p. 311-325. (Support not reported. Authors affiliated with University of Ulm, Germany.)

326. Johns LE, Jones ME, Schoemaker MJ, McFadden E, Ashworth A, Swerdlow AJ. 2018. Domestic light at night and breast cancer risk: a prospective analysis of 105 000 UK women in the Generations Study. *Br J Cancer* 118(4): 600-606. (Supported by Breast Cancer Now, The Institute of Cancer Research, and NHS. Authors affiliated with Institute of Cancer Research, UK; Breast Cancer Now Research Centre, UK.)

327. Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ. 2017. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 43(2): 117-126. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Illinois at Chicago School of Public Health, IL; Danish Cancer Society, Denmark.)

328. Joska TM, Zaman R, Belden WJ. 2014. Regulated DNA methylation and the circadian clock: implications in cancer. *Biology (Basel)* 3(3): 560-577. (Supported by the Nation Institute of General Medical Sciences and the New Jersey Agriculture Experiment Station. Authors affiliated with State University of New Jersey, NJ.)

329. Kamdar BB, Tergas AI, Mateen FJ, Bhayani NH, Oh J. 2013. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 138(1): 291-301. (Support not reported. Authors affiliated with Johns Hopkins University, MD; Johns Hopkins Bloomberg School of Public Health, MD; Howard University Hospital, Washington, D.C.)

330. Kane S. 2016. *These incredible maps show the most lightpolluted places in the world*. Business Insider. Updated on: 6/14/16. http://www.businessinsider.com/worst-light-pollution-skyglow-map-2016-6

331. Kannen V, Marini T, Zanette DL, Frajacomo FT, Silva GE, Silva WA, Jr., Garcia SB. 2011. The melatonin action on stromal stem cells within pericryptal area in colon cancer model under constant light. *Biochem Biophys Res Commun* 405(4): 593-598. (Supported by CAPES, CNPq and FAPESP. Authors affiliated with University of São Paulo, Brazil; Center for Cell Therapy and Regional Blood Center, Brazil.)

332. Kantermann T, Duboutay F, Haubruge D, Hampton S, Darling AL, Berry JL, Kerkhofs M, Boudjeltia KZ, Skene DJ. 2014. The direction of shift-work rotation impacts metabolic risk independent of chronotype and social jetlag – an exploratory pilot study. *Chronobiol Int* 31(10): 1139-1145. (Supported by the German Research Foundation, the Technology foundation STW, the 6th Framework Project EUCLOCK, a Royal Society Wolfson Research Merit Award, and the ISPPC Research Fund. Authors affiliated with University of Groningen, Netherlands; Clinical Centre Ludwig-Maximilians University, Germany; CMBT, Belgium; ArcelorMittal Industeel Belgium, Belgium; University of Surrey, UK; Manchester Royal Infirmary, UK; Université Libre de Bruxelles, Belgium.)

333. Karantanos T, Theodoropoulos G, Pektasides D, Gazouli M. 2014. Clock genes: their role in colorectal cancer. *World J Gastroenterol* 20(8): 1986-1992. (Support not reported. Authors affiliated with University of Athens, Greece.)

334. Kelleher FC, Rao A, Maguire A. 2014. Circadian molecular clocks and cancer. *Cancer Lett* 342(1): 9-18. (Support not reported. Authors affiliated with Peter MacCallum Cancer Centre, Australia; St. Vincent's University Hospital, Ireland.)

335. Kervezee L, Cuesta M, Cermakian N, Boivin DB. 2018. Simulated night shift work induces circadian misalignment of the human peripheral blood mononuclear cell transcriptome. *Proc Natl Acad Sci U S A* 115(21): 5540-5545. (Supported by the Canadian Institutes of Health Research, and the Fonds de Recherche du Québec–Santé. Authors affiliated with McGill University, Canada.)

336. Keshet-Sitton A, Or-Chen K, Huber E, Haim A. 2017. Illuminating a risk for breast cancer: A preliminary ecological study on the association between streetlight and breast cancer. *Integr Cancer Ther* 16(4): 451-463. (No financial support recieved. Authors affiliated with University of Haifa, Israel.)

337. Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A. 2016. Can avoiding light at night reduce the risk of breast cancer? *Integr Cancer Ther* 15(2): 145-152. (No financial support received. Authors affiliated with University of Haifa, Israel; Poria Medical Center, Israel; Soroka University Medical Center, Israel.)

338. Kettner NM, Katchy CA, Fu L. 2014. Circadian gene variants in cancer. *Ann Med* 46(4): 208-220. (Supported by the USDA/ARS and the NIH/NCI. Authors affiliated with Baylor College of Medicine, TX.)

339. Kettner NM, Mayo SA, Hua J, Lee C, Moore DD, Fu L. 2015. Circadian dysfunction induces leptin resistance in mice. *Cell Metab* 22(3): 448-459. (Supported by USDA/ARS, NIH/NCI, NIH/NIDDK, and NIH/NICHD. Authors affiliated with Baylor College of Medicine, TX; Florida State University, FL.)

340. Kettner NM, Voicu H, Finegold MJ, Coarfa C, Sreekumar A, Putluri N, Katchy CA, Lee C, Moore DD, Fu L. 2016. Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. *Cancer Cell* 30(6): 909-924. (Supported by NIH, NCI, USDA, CRPIT, NIDDK, the BCM Dan L. Duncan Cancer Center, the Alkek Center for Molecular Discovery, and the BCM Agilent Technologies Center of Excellence. Authors affiliated with Baylor College of Medicine, TX; Florida State University, FL.)

341. Khosro S, Alireza S, Omid A, Forough S. 2011. Night work and inflammatory markers. *Indian J Occup Environ Med* 15(1): 38-41. (Supported by the Tehran University of Medical Sciences. Authors affiliated with Tehran University of Medical Sciences, Iran; Dr. Sharifi Medical Lab, Iran.)

342. Kiefer T, Ram PT, Yuan L, Hill SM. 2002. Melatonin inhibits estrogen receptor transactivation and cAMP levels in breast cancer cells. *Breast Cancer Res Treat* 71(1): 37-45. (Supported by NIH. Authors affiliated with Tulane University School of Medicine, LA.)

343. Kim SW, Jang EC, Kwon SC, Han W, Kang MS, Nam YH, Lee YJ. 2016. Night shift work and inflammatory markers in male workers aged 20-39 in a display manufacturing company. *Ann Occup Environ Med* 28: 48. (Support not reported. Authors affiliated with Soonchunhyang University Cheonan Hospital, Korea.)

344. Kim YJ, Lee E, Lee HS, Kim M, Park MS. 2015. High prevalence of breast cancer in light polluted areas in urban and rural regions of South Korea: An ecologic study on the treatment prevalence of female cancers based on National Health Insurance data. *Chronobiol Int* 32(5): 657-667. (Supported by the Korean Environmental Industry and Technology Institute. Authors affiliated with Korea University, South Korea; Sungshin Women's University College of Natural Sciences, South Korea.)

345. Kishi T, Sunagawa K. 2011. Experimental 'jet lag' causes sympathoexcitation via oxidative stress through AT1 receptor in the brainstem. *Conf Proc IEEE Eng Med Biol Soc* 2011: 1969-1972. (Supported by the Japan Society for the Promotion of Science. Authors affiliated with Kyushu University Graduate School of Medical Sciences, Japan.)

346. Kiss Z, Ghosh PM. 2016. Circadian rhythmicity and the influence of 'clock' genes on prostate cancer. *Endocr Relat Cancer* 23(11): T123-T134. (Supported by the Department of Veterans Affairs and NIH. Authors affiliated with VA Northern California Health Care System, CA; University of California at Davis, CA.)

347. Kliukiene J, Tynes T, Andersen A. 2001. Risk of breast cancer among Norwegian women with visual impairment. *Br J Cancer* 84(3): 397-399. (Supported by Telenor AS. Authors affiliated with Cancer Registry of Norway, Norway; Norwegian Radiation Protection Authority, Norway.)

348. Kloog I, Haim A, Stevens RG, Barchana M, Portnov BA. 2008. Light at night co-distributes with incident breast but not lung cancer in the female population of Israel. *Chronobiol Int* 25(1): 65-81. (Supported by NIH. Authors affiliated with University of Haifa, Israel; University of Connecticut Health Center, CT; Ministry of Health, Israel.)

349. Kloog I, Haim A, Stevens RG, Portnov BA. 2009. Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men. *Chronobiol Int* 26(1): 108-125. (Support not reported. Authors affiliated with University of Haifa, Israel; University of Connecticut Health Center, CT.)

350. Kloog I, Portnov BA, Rennert HS, Haim A. 2011. Does the modern urbanized sleeping habitat pose a breast cancer risk? *Chronobiol Int* 28(1): 76-80. (Support not reported.

Authors affiliated with University of Haifa, Israel; Technion–Israel Institute of Technology and Clalit Health Services National Cancer Control Center, Israel; Harvard School of Public Health, MA.)

351. Kloog I, Stevens RG, Haim A, Portnov BA. 2010. Nighttime light level co-distributes with breast cancer incidence worldwide. *Cancer Causes Control* 21(12): 2059-2068. (Support not reported. Authors affiliated with University of Haifa, Israel; University of Connecticut Health Center, CT.)

352. Knutsson A, Alfredsson L, Karlsson B, Åkerstedt T, Fransson EI, Westerholm P, Westerlund H. 2013. Breast cancer among shift workers: results of the WOLF longitudinal cohort study. *Scand J Work Environ Health* 39(2): 170-177. (Support not reported. Authors affiliated with Mid Sweden University, Sweden; Karolinska Institutet, Sweden; Norrlands University Hospital, Sweden; Stockholm University, Sweden; Jönköping University, Sweden; Uppsala University, Sweden.)

353. Ko CH, Takahashi JS. 2006. Molecular components of the mammalian circadian clock. *Hum Mol Genet* 15(Spec No 2): R271-277. (Supported by NIH. Authors affiliated with Northwestern University, IL; University of Toronto, Canada.)

354. Kochan DZ, Ilnytskyy Y, Golubov A, Deibel SH, McDonald RJ, Kovalchuk O. 2015. Circadian disruption-induced microRNAome deregulation in rat mammary gland tissues. *Oncoscience* 2(4): 428-442. (Supported by the Canadian Breast Cancer Foundation. Authors affiliated with University of Lethbridge, Canada.)

355. Kochan DZ, Ilnytskyy Y, Golubov A, Deibel SH, McDonald RJ, Kovalchuk O. 2016. Circadian-disruption-induced gene expression changes in rodent mammary tissues. *Oncoscience* 3(2): 58-70. (Supported by the Canadian Breast Cancer Foundation. Authors affiliated with University of Lethbridge, Canada.)

356. Kolstad HA, Garde AH, Hansen AM, Frydenberg M, Christiansen P, Vistisen HT, Bonde JP. 2017. Response to Dr Stevens' letter ref. Visitisen *et al*: "Short-term effects of night shift work on breast cancer risk: a cohort study of payroll data". *Scand J Work Environ Health* 43(1): 95. (Support not reported. Authors affiliated with Aarhus University Hospital, Denmark; National Research Centre for the Working Environment, Denmark; University of Copenhagen, Denmark; Danish Breast Cancer Corporative Group, Denmark; Bispebjerg University Hospital, Denmark.)

357. Koopman A, Rauh S, van't Riet E, Groeneveld L, van der Heijden A, Elders PJ, Dekker JM, Nijpels G, Beulens J, Rutters F. 2017. The association between social jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population. *J Biol Rhythms* 32(4): 359-368. (Support not reported. Authors affiliated with VU Medical Centre, Netherlands; University Medical Centre Utrecht, Netherlands.)

358. Koppes LL, Geuskens GA, Pronk A, Vermeulen RC, de Vroome EM. 2014. Night work and breast cancer risk in a general population prospective cohort study in The Netherlands. *Eur J Epidemiol* 29(8): 577-584. (Supported by the Dutch Ministry of Social Affairs and Employment. Authors affiliated with Netherlands Organization for Applied Scientific Research, Netherlands; Utrecht University, Netherlands.)

359. Korkmaz A, Reiter RJ. 2008. Epigenetic regulation: a new research area for melatonin? *J Pineal Res* 44(1): 41-44. (Support not reported. Authors affiliated with Gulhane Military Medical Academy, Turkey; University of Texas Health Science Center at San Antonio, TX.)

360. Korkmaz A, Sanchez-Barcelo EJ, Tan DX, Reiter RJ. 2009. Role of melatonin in the epigenetic regulation of breast cancer. *Breast Cancer Res Treat* 115(1): 13-27. (Supported by the Spanish Ministry of Education and Science. Authors affiliated with Gulhane Military Medical Academy, Turkey; University of Texas Health Science Center at San Antonio, TX; University of Cantabria, Spain.)

361. Korompeli A, Sourtzi P, Tzavara C, Velonakis E. 2009. Rotating shift-related changes in hormone levels in intensive care unit nurses. *J Adv Nurs* 65(6): 1274-1282. (No funding received. Authors affiliated with University of Athens, Greece.)

362. Korsiak J, Tranmer J, Leung M, Borghese MM, Aronson KJ. 2017. Actigraph measures of sleep among female hospital employees working day or alternating day and night shifts. *J Sleep Res*. (Supported by the Canadian Institutes for Health Research and the Workplace Safety and Insurance Board. Authors affiliated with Queen's University, Canada.)

363. Kothari LS. 1987. Influence of chronic melatonin on 9,10-dimethyl-1,2-benzanthracene-induced mammary tumors in female Holtzman rats exposed to continuous light. *Oncology* 44(1): 64-66. (Support not reported. Authors affiliated with Tata Memorial Center, India.)

364. Kothari LS, Shah PN, Mhatre MC. 1982. Effect of continuous light on the incidence of 9,10-dimethyl-1,2-benzanthracene induced mammary tumors in female Holtzman rats. *Cancer Lett* 16(3): 313-317. (Support not reported. Authors affiliated with Cancer Research Institute, India.)

365. Kozaki T, Kubokawa A, Taketomi R, Hatae K. 2015. Effects of day-time exposure to different light intensities on light-induced melatonin suppression at night. *J Physiol Anthropol* 34: 27. (Support not reported. Authors affiliated with Kyushu University, Japan.)

366. Kozaki T, Kubokawa A, Taketomi R, Hatae K. 2016. Light-induced melatonin suppression at night after exposure to different wavelength composition of morning light. *Neurosci Lett* 616: 1-4. (Supported by the Department of Design, Kyushu University. Authors affiliated with Kyushu University, Japan.)

367. Kräuchi K, Cajochen C, Pache M, Flammer J, Wirz-Justice A. 2006. Thermoregulatory effects of melatonin in relation to sleepiness. *Chronobiol Int* 23(1-2): 475-484. (Support not reported. Authors affiliated with University Psychiatric Clinics, Switzerland; University Eye Clinic, Switzerland.)

368. Kubo T, Oyama I, Nakamura T, Kunimoto M, Kadowaki K, Otomo H, Fujino Y, Fujimoto N, Matsumoto T, Matsuda S. 2011. Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. *Int J Urol* 18(3): 206-211. (Supported by KAKENHI from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Occupational Health Promotion Foundation, Japan. Authors affiliated with University of Occupational and Environmental Health, Japan; Asahi Kasei Nobeoka Office

Health Care Center, Japan; Asahi Kasei Chemicals Mizushima Works Health Care Center, Japan.)

369. Kubo T, Ozasa K, Mikami K, Wakai K, Fujino Y, Watanabe Y, Miki T, Nakao M, Hayashi K, Suzuki K, Mori M, Washio M, Sakauchi F, Ito Y, Yoshimura T, Tamakoshi A. 2006. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. *Am J Epidemiol* 164(6): 549-555. (Supported by the Ministry of Education, Science, Sports and Culture of Japan. Authors affiliated with University of Occupational and Environmental Health, Japan; Kyoto Prefectural University of Medicine, Japan; Aichi Cancer Center Research Institute, Japan; Fukuoka Institute of Occupational Health, Japan; Meiji University of Oriental Medicine, Japan; Fujita Health University School of Health Sciences, Japan; Sapporo Medical University School of Medicine, Japan; Nagoya University Graduate School of Medicine, Japan; Fukuoka Institute of Health and Environmental Sciences, Japan.)

370. Kulikov VY, Fridman YM, Fomin AN. 2007. Role of oxidative stress in mechanisms of premature aging in shift labor workers. *Alaska Med* 49(2 Suppl): 81-84. (Support not reported. Authors affiliated with Scientific Center of Clinical and Experimental Medicine SB RAMS, Russia.)

371. Kwon P, Lundin J, Li W, Ray R, Littell C, Gao D, Thomas DB, Checkoway H. 2015. Night shift work and lung cancer risk among female textile workers in Shanghai, China. *J Occup Environ Hyg* 12(5): 334-341. (Supported by NIH. Authors affiliated with Bassett Army Community Hospital, Alaska; University of Washington, WA; Fred Hutchinson Cancer Research Center, WA; Walter Reed Army Institute of Research, MD; Fudan University, China; University of California San Diego, CA.)

372. Lahti TA, Partonen T, Kyyrönen P, Kauppinen T, Pukkala E. 2008. Night-time work predisposes to non-Hodgkin lymphoma. *Int J Cancer* 123(9): 2148-2151. (Supported by the Academy of Finland. Authors affiliated with National Public Health Institute, Finland; Finnish Institute of Occupational Health, Finland; Institute of Statistical and Epidemiological Cancer Research, Finland.)

373. Lang R, Hintner H, Hermann A, Brandstaetter R. 2003. Photoperiod modulates melanoma growth in C57BL/6 mice. *Exp Dermatol* 12(4): 510-513. (Supported by the Medical Research Centre of the University of Salzburg, the Austrian Academy of Sciences, and the Austrian National Bank. Authors affiliated with University of Salzburg, Austria; General Hospital Salzburg, Austria; Max-Planck Research Centre for Ornithology, Germany.)

374. Langley AR, Graham CH, Grundy AL, Tranmer JE, Richardson H, Aronson KJ. 2012. A cross-sectional study of breast cancer biomarkers among shift working nurses. *BMJ Open* 2(1): e000532. (Supported by the Workplace Safety and Insurance Board of Ontario and Breast Cancer Action Kingston. Authors affiliated with Queen's University, Canada.)

375. Lee S, Donehower LA, Herron AJ, Moore DD, Fu L. 2010. Disrupting circadian homeostasis of sympathetic signaling promotes tumor development in mice. *PLoS ONE* 5(6). (Supported by NIH and the USDA. Authors affiliated with Baylor College of Medicine, TX.)

376. LeGates TA, Fernandez DC, Hattar S. 2014. Light as a central modulator of circadian rhythms, sleep and affect. *Nat Rev Neurosci* 15(7): 443-454. (Support not reported. Authors affiliated with Johns Hopkins University, MD.)

377. Lenoir V, de Jonage-Canonico MB, Perrin MH, Martin A, Scholler R, Kerdelhué B. 2005. Preventive and curative effect of melatonin on mammary carcinogenesis induced by dimethylbenz[a]anthracene in the female Sprague-Dawley rat. *Breast Cancer Res* 7(4): R470-476. (Support not reported. Authors affiliated with Université René Descartes, France; Hôpital Avicenne, France.)

378. Leung M, Tranmer J, Hung E, Korsiak J, Day AG, Aronson KJ. 2016. Shift work, chronotype, and melatonin patterns among female hospital employees on day and night shifts. *Cancer Epidemiol Biomarkers Prev* 25(5): 830-838. (Supported by the Workplace Safety and Insurance Board of Ontario and the Canadian Institutes of Health Research Canada. Authors affiliated with Queen's University, Canada; Kingston General Hospital, Canada.)

379. Levallois P, Dumont M, Touitou Y, Gingras S, Mâsse B, Gauvin D, Kröger E, Bourdages M, Douville P. 2001. Effects of electric and magnetic fields from high-power lines on female urinary excretion of 6-sulfatoxymelatonin. *Am J Epidemiol* 154(7): 601-609. (Supported by Hydro-Québec and Électricité de France. Authors affiliated with Centre hospitalier universitaire de Québec, Canada; Institut national de santé publique du Québec and Université Laval, Canada; Hôpital du Sacré-Coeur and Université de Montréal, Canada; Faculté de médecine Pitié-Salpétrière, France; Institut de recherche d'Hydro-Québec, Varennes, Canada; Hôpital de l'Hôtel-Dieu de Québec, Canada.)

380. Lévi F, Dugué P-A, Innominato P, Karaboué A, Dispersyn G, Parganiha A, Giacchetti S, Moreau T, Focan C, Waterhouse J, Spiegel D. 2014. Wrist actimetry circadian rhythm as a robust predictor of colorectal cancer patients survival. *Chronobiol Int* 31(8): 891-900. (Supported by the Association Internationale pour la Recherche sur le Temps Biologique et la Chronothérapie [ARTBC International], Paul Brousse Hospital, France, the European Union through the 7th Framework Programme project In-CASA, and Paris Sud University. Authors affiliated with INSERM, France; Université Paris Sud, France; Paul Brousse Hospital, France; Pt. Ravishankar Shukla University, India; Hospitalier Chrétien, Belgium; John Moores University, UK; Stanford University School of Medicine, CA.)

381. Lewy AJ. 1999. The dim light melatonin onset, melatonin assays and biological rhythm research in humans. *Biol Signals Recept* 8(1-2): 79-83. (Supported by the Public Health Service. Authors affiliated with Oregon Health Sciences University, OR.)

382. Lewy AJ, Emens JS, Bernert RA, Lefler BJ. 2004. Eventual entrainment of the human circadian pacemaker by melatonin is independent of the circadian phase of treatment initiation: clinical implications. *J Biol Rhythms* 19(1): 68-75. (Supported by the Public Health Service, and the National Alliance for Research on Schizophrenia and Depression. Authors affiliated with Oregon Health & Science University, OR.)

383. Li JC, Xu F. 1997. Influences of light-dark shifting on the immune system, tumor growth and life span of rats, mice and fruit flies as well as on the counteraction of melatonin. *Biol*

Signals 6(2): 77-89. (Support not reported. Authors affiliated with Shenyang Pharmaceutical University, China.)

384. Li M, Tse LA, Chan WC, Kwok CH, Leung SL, Wu C, Yu WC, Lee PM, Tsang KH, Law SH, Vermeulen R, Gu F, Caporaso NE, Yu IT, Wang F, Yang XR. 2017. Nighttime eating and breast cancer among Chinese women in Hong Kong. *Breast Cancer Res* 19(1): 31. (Supported by the Research Grants Council of Hong Kong. Authors affiliated with Chinese University of Hong Kong, China; North District Hospital, China; Princess Margaret Hospital, China; Pamela Youde Nethersole Eastern Hospital, China; Yan Chai Hospital, China; Utrecht University, Netherlands; NIH, MD.)

385. Li Q, Zheng T, Holford TR, Boyle P, Zhang Y, Dai M. 2010. Light at night and breast cancer risk: results from a population-based case-control study in Connecticut, USA. *Cancer Causes Control* 21(12): 2281-2285. (Supported by the National Cancer Institute/National Institute of Environmental Health Science. Authors affiliated with Huazhong University of Science and Technology, China; Yale School of Public Health, CT; International Prevention Research Institute, France; Chinese Academy of Medical Sciences, China.)

386. Li W, Ray RM, Thomas DB, Davis S, Yost M, Breslow N, Gao DL, Fitzgibbons ED, Camp JE, Wong E, Wernli KJ, Checkoway H. 2015. Shift work and breast cancer among women textile workers in Shanghai, China. *Cancer Causes Control* 26(1): 143-150. (Supported by NIOSH, NCI, and NIH. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; Zhong Shan Hospital Branch, China; Group Health Research Institute, WA; University of California - San Diego, CA.)

387. Li X-M, Liu X-H, Filipski E, Metzger G, Delagrange P, Jeanniot JP, Lévi F. 2000. Relationship of atypical melatonin rhythm with two circadian clock outputs in B6D2F$_1$ mice. *Am J Physiol Reg Integr Comp Physiol* 278: R924-R930. (Supported by the ‘‘Association pour la Recherche sur le Temps Biologique et la Chronothérapeutique,’’ Hôpital Paul Brousse, Villejuif, and the Institut de Recherches Internationales Servier, Courbevoie, France. Authors affiliated with Hôpital Paul Brousse, France; Institut de Recherches Internationales Servier, France; Technologie Servier, France.)

388. Liang G, Schernhammer E, Qi L, Gao X, De Vivo I, Han J. 2011. Associations between rotating night shifts, sleep duration, and telomere length in women. *PLoS One* 6(8): e23462. (Supported by NIH. Authors affiliated with Harvard Medical School, MA; Southeast University, China; Brigham and Women’s Hospital, MA; Harvard School of Public Health, MA; LBI-ACR, ACR-ITR, VIEnna/CEADDP, Austria.)

389. Lie JA, Kjuus H, Zienolddiny S, Haugen A, Kjærheim K. 2013. Breast cancer among nurses: is the intensity of night work related to hormone receptor status? *Am J Epidemiol* 178(1): 110-117. (Supported by the Research Council of Norway, the South-Eastern Norway Regional Health Authority, the Norwegian Cancer Society, and the “Raagholtstiftelsen” foundation. Authors affiliated with National Institute of Occupational Health, Norway; Cancer Registry of Norway, Norway.)

390. Lie JA, Kjuus H, Zienolddiny S, Haugen A, Stevens RG, Kjærheim K. 2011. Night work and breast cancer risk among Norwegian nurses: assessment by different exposure metrics. *Am J Epidemiol* 173(11): 1272-1279. (Supported by the Research Council of Norway, the South-Eastern Norway Regional Health Authority, and the Norwegian Cancer Society. Authors affiliated with National Institute of Occupational Health, Norway; University of Connecticut Health Center, CT; Cancer Registry of Norway, Norway.)

391. Lighting Research Center (2018). Estimated corneal illuminance data provided by the Lighting Research Center, Rensselaer Polytechnic Institute (Troy, NY) (personal correspondence, 1/4/18, Mariana Figuiero).

392. Lin X, Chen W, Wei F, Ying M, Wei W, Xie X. 2015. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. *Sleep Med* 16(11): 1381-1387. (Support not reported. Authors affiliated with Sun Yat-sen University, China; Teaching Hospital of Fujian Medical University, China; Fujian University of Traditional Chinese Medicine, China.)

393. Lin Y, Ueda J, Yagyu K, Kurosawa M, Tamakoshi A, Kikuchi S. 2013. A prospective cohort study of shift work and the risk of death from pancreatic cancer in Japanese men. *Cancer Causes Control* 24(7): 1357-1361. (Supported by the Ministry of Education, Science, Sports and Culture of Japan, and the Japanese Ministry of Education, Culture, Sports, Science and Technology of Japan. Authors affiliated with Aichi Medical University School of Medicine, Japan; Juntendo University School of Medicine, Japan; Hokkaido University Graduate School of Medicine, Japan.)

394. Linnersjö A, Hammar N, Dammström BG, Johansson M, Eliasch H. 2003. Cancer incidence in airline cabin crew: experience from Sweden. *Occup Environ Med* 60(11): 810-814. (Supported by the Swedish Council for Work Life Research. Authors affiliated with Stockholm Center of Public Health, Sweden; Swedish SAS, Sweden; Swedish Air Force, Sweden.)

395. Liu R, Jacobs DI, Hansen J, Fu A, Stevens RG, Zhu Y. 2015. Aberrant methylation of miR-34b is associated with long-term shiftwork: a potential mechanism for increased breast cancer susceptibility. *Cancer Causes Control* 26(2): 171-178. (Supported by NIH, the China Scholarship Council and the Danish Cancer Society. Authors affiliated with Yale School of Public Health, CT; Southeast University, China; Danish Cancer Society, Denmark.)

396. Lizama N, Heyworth J, Thomson A, Slevin T, Fritschi L. 2017. Self-reported shift work, recall bias, and belief about disease causation in a case-control study of breast cancer. *Cancer Epidemiol* 50(Pt A): 9-15. (Supported by the National Health and Medical Research Council Australia and the Cancer Council Western Australia. Authors affiliated with University of Western Australia, Australia; Curtin University, Australia; Cancer Council Western Australia, Australia.)

397. Lockley SW, Brainard GC, Czeisler CA. 2003. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. *J Clin Endocrinol Metab* 88(9): 4502-4505. (Supported by NINDS, NIMH, NCRR, and the Wellcome Trust, UK. Authors

affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Thomas Jefferson University, PA.)

398. Lockley SW, Skene DJ, Arendt J, Tabandeh H, Bird AC, Defrance R. 1997. Relationship between melatonin rhythms and visual loss in the blind. *J Clin Endocrinol Metab* 82(11): 3763-3770. (Supported by the South Thames Regional Health Authority, United Kingdom, Stockgrand Ltd., University of Surrey, United Kingdom, and Servier Research and Development, France. Authors affiliated with University of Surrey, UK; Moorfields Eye Hospital, UK; Institut de Recherches Internationales Servier, France.)

399. Logan RW, Zhang C, Murugan S, O'Connell S, Levitt D, Rosenwasser AM, Sarkar DK. 2012. Chronic shift-lag alters the circadian clock of NK cells and promotes lung cancer growth in rats. *J Immunol* 188(6): 2583-2591. (Supported by NIH. Authors affiliated with State University of New Jersey, NJ; University of Maine, ME.)

400. Lowrey PL, Takahashi JS. 2004. Mammalian circadian biology: elucidating genome-wide levels of temporal organization. *Annu Rev Genomics Hum Genet* 5: 407-441. (Support not reported. Authors affiliated with Northwestern University, IL.)

401. Lowrey PL, Takahashi JS. 2011. Genetics of circadian rhythms in mammalian model organisms. *Adv Genet* 74: 175-230. (Supported by NIH. Authors affiliated with Rider University, NJ; University of Texas Southwestern Medical Center, TX.)

402. Lu C, Sun H, Huang J, Yin S, Hou W, Zhang J, Wang Y, Xu Y, Xu H. 2017. Long-term sleep duration as a risk factor for breast cancer: Evidence from a systematic review and dose-response meta-analysis. *Biomed Res Int* 2017: 4845059. (Supported by the National Natural Science Foundation of China and Key Laboratory Programme of Education Department of Liaoning Province. Authors affiliated with First Hospital of China Medical University, China.)

403. Lu LF, Wang CP, Tsai IT, Hung WC, Yu TH, Wu CC, Hsu CC, Lu YC, Chung FM, Jean MC. 2016. Relationship between shift work and peripheral total and differential leukocyte counts in Chinese steel workers. *J Occup Health* 58(1): 81-88. (Supported by the E-Da Hospital, Kaohsiung City, Taiwan. Authors affiliated with I-Shou University, Taiwan.)

404. Lucas RJ, Peirson SN, Berson DM, Brown TM, Cooper HM, Czeisler CA, Figueiro MG, Gamlin PD, Lockley SW, O'Hagan JB, Price LL, Provencio I, Skene DJ, Brainard GC. 2014. Measuring and using light in the melanopsin age. *Trends Neurosci* 37(1): 1-9. (Supported by ZVEI [German Electrical and Electronic Manufacturer's Association]. Authors affiliated with University of Manchester, UK; University of Oxford, UK; Brown University, RI; INSERM, France; Harvard Medical School, MA; Rensselaer Polytechnic Institute, NY; University of Alabama at Birmingham, AL; Public Health England, UK; University of Virginia, VA; University of Surrey, UK; Thomas Jefferson University, PA.)

405. Luckhaupt SE, Sestito JP. 2013. Examining national trends in worker health with the National Health Interview Survey. *J Occup Environ Med* 55(12 Suppl): S58-62. (Supported by the US government. Authors affiliated with NIOSH, OH.)

406. Lunn RM, Blask DE, Coogan AN, Figueiro MG, Gorman MR, Hall JE, Hansen J, Nelson RJ, Panda S, Smolensky MH, Stevens RG, Turek FW, Vermeulen R, Carreón T, Caruso CC, Lawson CC, Thayer KA, Twery MJ, Ewens AD, Garner SC, Schwingl PJ, Boyd WA. 2017. Health consequences of electric lighting practices in the modern world: A report on the National Toxicology Program's workshop on shift work at night, artificial light at night, and circadian disruption. *Sci Total Environ* 607-608: 1073-1084. (No financial support recieved. Authors affiliated with NIEHS, NC; Tulane University School of Medicine, LA; National University of Ireland, Ireland; Rensselaer Polytechnic Institute, NY; University of California San Diego, CA; Danish Cancer Society, Denmark; Ohio State University Wexner Medical Center, OH; Salk Institute for Biological Studies, CA; University of Texas at Austin, TX; University of Texas-Houston McGovern School of Medicine, TX; University of Connecticut, CT; Northwestern University, IL; Utrecht University, Netherlands; NIOSH, OH; NHLBI, MD; Integrated Laboratory Systems, NC.)

407. Maeda SS, Kunii IS, Hayashi L, Lazaretti-Castro M. 2007. The effect of sun exposure on 25-hydroxyvitamin D concentrations in young healthy subjects living in the city of São Paulo, Brazil. *Braz J Med Biol Res* 40(12): 1653-1659. (Supported by FAPESP. Authors affiliated with Universidade Federal de São Paulo, Brazil.)

408. Malone SK, Zemel B, Compher C, Souders M, Chittams J, Thompson AL, Lipman TH. 2016. Characteristics associated with sleep duration, chronotype, and social jet lag in adolescents. *J Sch Nurs* 32(2): 120-131. (Supported by the National Association of School Nurses, National Institute of Nursing Research Ruth L. Kirschstein National Research Service Award, The Rockefeller University Heilbrunn Nurse Scholar Award, University of Pennsylvania School of Nursing Biobehavioral Research Center, and University of Pennsylvania Office of Nursing Research. Authors affiliated with University of Pennsylvania School of Nursing, PA: University of Pennsylvania, PA; Children's Hospital of Philadelphia, PA.)

409. Mancio J, Leal C, Ferreira M, Norton P, Lunet N. 2018. Does the association of prostate cancer with night-shift work differ according to rotating vs. fixed schedule? A systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*(21): 337-344. (Supported by the Fundação Portuguesa para a Ciência e Tecnologia and by the Sociedade Portuguesa de Cardiologia ["Bolsa de investigação João Porto"]. Authors affiliated with University of Porto, Portugal; Centro Hospitalar de Vila Nova de Gaia, Portugal.)

410. Manenschijn L, van Kruysbergen RG, de Jong FH, Koper JW, van Rossum EF. 2011. Shift work at young age is associated with elevated long-term cortisol levels and body mass index. *J Clin Endocrinol Metab* 96(11): E1862-1865. (Supported by the Netherlands Organization for Scientific Research. Authors affiliated with Erasmus Medical Center, Netherlands; Arbo Unie Nijverdal, Netherlands.)

411. Manzella N, Bracci M, Strafella E, Staffolani S, Ciarapica V, Copertaro A, Rapisarda V, Ledda C, Amati M, Valentino M, Tomasetti M, Stevens RG, Santarelli L. 2015. Circadian modulation of 8-oxoguanine DNA damage repair. *Scientific Rep* 5: 12. (Supported by the Italian Institute of Insurance against Professional Illness and Injuries. Authors affiliated with Polytechnic University of Marche, Italy; Loreto Hospital, Italy; University of Catania, Italy; University of Connecticut Health Center, CT.)

412. Mao L, Dauchy RT, Blask DE, Dauchy EM, Slakey LM, Brimer S, Yuan L, Xiang S, Hauch A, Smith K, Frasch T, Belancio VP, Wren MA, Hill SM. 2016a. Melatonin suppression of aerobic glycolysis (Warburg effect), survival signalling and metastasis in human leiomyosarcoma. *J Pineal Res* 60(2): 167-177. (Support not reported. Authors affiliated with Tulane University School of Medicine, LA; Tulane Cancer Center, LA; Louisiana Cancer Research Consortium, LA.)

413. Mao L, Dauchy RT, Blask DE, Slakey LM, Xiang S, Yuan L, Dauchy EM, Shan B, Brainard GC, Hanifin JP, Frasch T, Duplessis TT, Hill SM. 2012. Circadian gating of epithelial-to-mesenchymal transition in breast cancer cells via melatonin-regulation of GSK3beta. *Mol Endocrinol* 26(11): 1808-1820. (Supported by NIH, the Army Department of Defense, the American Association for Laboratory Animal Science, and the Institute for Integrative Health. Authors affiliated with Tulane University School of Medicine, LA; Thomas Jefferson University, PA.)

414. Mao L, Summers W, Xiang S, Yuan L, Dauchy RT, Reynolds A, Wren-Dail MA, Pointer D, Frasch T, Blask DE, Hill SM. 2016b. Melatonin represses metastasis in her2-postive human breast cancer cells by suppressing RSK2 expression. *Mol Cancer Res* 14(11): 1159-1169. (Supported by NIH, NCI, the Edmond and Lily Safra Chair for Breast Cancer Research, and the Tulane Center for Circadian Biology. Authors affiliated with Tulane University School of Medicine, LA: Tulane Cancer Center and Louisiana Cancer Research Consortium, LA.)

415. Marinac CR, Natarajan L, Sears DD, Gallo LC, Hartman SJ, Arredondo E, Patterson RE. 2015a. Prolonged nightly fasting and breast cancer risk: Findings from NHANES (2009-2010). *Cancer Epidemiol Biomarkers Prev* 24(5): 783-789. (Supported by NCI and Ms. Carol Vassiliadis and her family. Authors affiliated with University of California - San Diego, CA; San Diego State University, CA.)

416. Marinac CR, Nelson SH, Breen CI, Hartman SJ, Natarajan L, Pierce JP, Flatt SW, Sears DD, Patterson RE. 2016. Prolonged nightly fasting and breast cancer prognosis. *JAMA Oncol* 2(8): 1049-1055. (Supported by NCI and NIH. Authors affiliated with University of California - San Diego, CA; San Diego State University, CA.)

417. Marinac CR, Sears DD, Natarajan L, Gallo LC, Breen CI, Patterson RE. 2015b. Frequency and circadian timing of eating may influence biomarkers of inflammation and insulin resistance associated with breast cancer risk. *PLoS One* 10(8): e0136240. (Supported by NCI. Authors affiliated with University of California San Diego, CA; San Diego State University, CA.)

418. Markt SC, Valdimarsdottir UA, Shui IM, Sigurdardottir LG, Rider JR, Tamimi RM, Batista JL, Haneuse S, Flynn-Evans E, Lockley SW, Czeisler CA, Stampfer MJ, Launer L, Harris T, Smith AV, Gudnason V, Lindstrom S, Kraft P, Mucci LA. 2015. Circadian clock genes and risk of fatal prostate cancer. *Cancer Causes Control* 26(1): 25-33. (Supported by the National Institutes on Aging Intramural Research Program, the Hjartavernd [the Icelandic Heart Association], the Althingi [the Icelandic Parliament], the Harvard Catalyst Award, the Icelandic Cancer Society, the National Cancer Institute at the National Institutes of Health, the National Heart, Lung, and Blood Institute at the National Institutes of Health,

the Prostate Cancer Foundation, and the US Army Department of Defense Prostate Cancer Research Program Fellowship. Authors affiliated with Harvard School of Public Health, MA: University of Iceland, Iceland; Icelandic Cancer Society, Iceland; Brigham and Women's Hospital, MA; Harvard Medical School, MA; Icelandic Heart Association, Iceland; National Institute on Aging, MD.)

419. Masri S, Kinouchi K, Sassone-Corsi P. 2015. Circadian clocks, epigenetics, and cancer. *Curr Opin Oncol* 27(1): 50-56. (Supported by NIH, INSERM, KAUST, Merieux Pharmaceuticals, the UC Irvine Chao Family Cancer Center, and JSPS. Authors affiliated with University of California - Irvine, CA.)

420. Matulka R, Wood D. 2013. *The History of the Light Bulb*. Energy.gov. Updated on: 11/22/13. https://energy.gov/articles/history-light-bulb

421. Mavroudis PD, Scheff JD, Calvano SE, Lowry SF, Androulakis IP. 2012. Entrainment of peripheral clock genes by cortisol. *Physiol Genomics* 44(11): 607-621. (Supported by the NIGMS. Authors affiliated with Rutgers University, NJ; UMDNJ-Robert Wood Johnson Medical School, NJ.)

422. Mazzoccoli G, Vinciguerra M, Papa G, Piepoli A. 2014. Circadian clock circuitry in colorectal cancer. *World J Gastroenterol* 20(15): 4197-4207. (Supported by the "5x1000" voluntary contribution, the Italian Ministry of Health through Department of Medical Sciences, Division of Internal Medicine and Chronobiology Unit, IRCCS Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", Opera di Padre Pio da Pietrelcina, San Giovanni Rotondo [FG], Italy, and AIRC. Authors affiliated with IRCCS Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", Italy; IEMEST, Italy; University of Chieti, Italy.)

423. McBean AL, Montgomery-Downs HE. 2015. What are postpartum women doing while the rest of the world is asleep? *J Sleep Res* 24(3): 270-278. (Support not reported. Authors affiliated with West Virginia University, WV.)

424. McCorry LK. 2007. Physiology of the autonomic nervous system. *Am J Pharm Educ* 71(4): 78. (Support not reported. Authors affiliated with Bay State College, MA.)

425. McElroy JA, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, Hampton JM, Egan KM. 2006. Duration of sleep and breast cancer risk in a large population-based case-control study. *J Sleep Res* 15(3): 241-249. (Supported by NIH. Authors affiliated with University of Wisconsin, WI; Fred Hutchinson Cancer Research Center, WA; Dartmouth Medical School, NH; Vanderbilt University, TN; Vanderbilt-Ingram Cancer Center, TN.)

426. McMahon DM, Burch JB, Wirth MD, Youngstedt SD, Hardin JW, Hurley TG, Blair SN, Hand GA, Shook RP, Drenowatz C, Burgess S, Hebert JR. 2018. Persistence of social jetlag and sleep disruption in healthy young adults. *Chronobiol Int* 35(3): 312-328. (Supported by the Dept. of Veterans Affairs Office of Research and Development, NCI, the National Institute of Diabetes and Digestive and Kidney Diseases, BodyMedia, Technogym, the U.S. Department of Defense, and the Coca-Cola Company. Authors affiliated with University of South Carolina, SC; WJB Dorn Department of Veterans Affairs Medical Center, SC; Arizona State University, AZ; Phoenix VA Health Care

System, AZ; West Virginia University, WV; Children's Mercy Hospital, MO; University of Education Upper Austria, Austria.)

427. McMenamin T. 2007. A time to work: recent trends in shift work and flexible schedules. *Mon Labor Rev* December: 3-15. (Support not reported. Author affiliated with Bureau of Labor Statistics.)

428. Mediavilla MD, Sanchez-Barcelo EJ, Tan DX, Manchester L, Reiter RJ. 2010. Basic mechanisms involved in the anti-cancer effects of melatonin. *Curr Med Chem* 17(36): 4462-4481. (Supported by the Spanish Ministry of Science and Education. Authors affiliated with University of Cantabria, Spain; University of Texas Health Science Centre, TX.)

429. Mehra A, Baker CL, Loros JJ, Dunlap JC. 2009. Post-translational modifications in circadian rhythms. *Trends Biochem Sci* 34(10): 483-490. (Supported by NIH and a CIHR Postdoc Fellowship. Authors affiliated with Dartmouth Medical School, NH.)

430. Mendoza J, Pévet P, Challet E. 2008. High-fat feeding alters the clock synchronization to light. *J Physiol* 586(24): 5901-5910. (Supported by CNRS, University Louis Pasteur, Fondation pour la Recherche Médicale, and the Institut Servier. Authors affiliated with Université Louis Pasteur, France.)

431. Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, Kerbrat P, Févotte J, Guénel P. 2013. Night work and breast cancer: a population-based case-control study in France (the CECILE study). *Int J Cancer* 132(4): 924-931. (Supported by the Agence Nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [ANSES], the Agence Nationale de la Recherche [ANR], the Fondation de France, the Institut National du Cancer [INCA]; Ligue contre le Cancer Grand Ouest, and the Association pour le recherche contre le cancer [ARC]. Authors affiliated with INSERM, France; Univ Paris-Sud, France; Center Georges-François Leclerc, France; Center Eugène Marquis, France; Institut de Veille Sanitaire [InVS], France.)

432. Mhatre MC, Shah PN, Juneja HS. 1984. Effect of varying photoperiods on mammary morphology, DNA synthesis, and hormone profile in female rats. *J Natl Cancer Inst* 72(6): 1411-1416. (Support not reported. Authors affiliated with Cancer Research Institute, India; Institute for Research in Reproduction, India.)

433. Miller D, Bierman A, Figueiro M, Schernhammer E, Rea M. 2010. Ecological measurements of light exposure, activity, and circadian disruption. *Light Res Technol* 42(3): 271-284. (Supported by the CDC and the Trans-NIH Genes, Environment and Health Initiative. Authors affiliated with Rensselaer Polytechnic Institute, NY; Brigham and Women's Hospital, MA; Harvard Medical School, MA.)

434. Miller NJ, Kinzey BR. 2018. *Home Nighttime Light Exposures: How Much Are We Really Getting?* International Association of Lighting Designers. Last accessed: 6/11/18. https://www.iald.org/News/In-the-News/Home-Nighttime-Light-Exposures-How-Much-Are-We-Re

435. Mirick DK, Bhatti P, Chen C, Nordt F, Stanczyk FZ, Davis S. 2013. Night shift work and levels of 6-sulfatoxymelatonin and cortisol in men. *Cancer Epidemiol Biomarkers Prev* 22(6): 1079-1087. (Support not reported. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; Rhein Consulting Laboratories, OR; University of Southern California, CA.)

436. Mirick DK, Davis S. 2008. Melatonin as a biomarker of circadian dysregulation. *Cancer Epidemiol Biomarkers Prev* 17(12): 3306-3313. (Support not reported. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA.)

437. Mohawk JA, Green CB, Takahashi JS. 2012. Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci* 35: 445-462. (Support not reported. Authors affiliated with University of Texas Southwestern Medical Center, TX.)

438. Monk TH, Buysse DJ, Billy BD, Fletcher ME, Kennedy KS, Begley AE, Schlarb JE, Beach SR. 2013. Shiftworkers report worse sleep than day workers, even in retirement. *J Sleep Res* 22(2): 201-208. (Supported by the National Institute on Aging. Authors affiliated with University of Pittsburgh Medical Center, PA; University of Pittsburgh, PA.)

439. Monsees GM, Kraft P, Hankinson SE, Hunter DJ, Schernhammer ES. 2012. Circadian genes and breast cancer susceptibility in rotating shift workers. *Int J Cancer* 131(11): 2547-2552. (Supported by NIH, the Broad Institute Center for Genotyping and Analysis, the National Center for Research Resources, the Public Health Service, and NCI. Authors affiliated with Harvard School of Public Health, MA; Brigham and Women's Hospital, MA; Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; LBI-ACR and ACR-ITR VIEnna/CEADDP, Austria.)

440. Mormont MC, Waterhouse J, Bleuzen P, Giacchetti S, Jami A, Bogdan A, Lellouch J, Misset JL, Touitou Y, Lévi F. 2000. Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. *Clin Cancer Res* 6(8): 3038-3045. (Supported by CNAMTS INSERM, ARTBC Internationale, Compagnie de Développement Aguettant, and Université Paris XI-Debiopharm. Authors affiliated with Université Paris XI and I.C.I.G., France; Hopital Paul Brousse, France; Liverpool John Moores University, UK; Hopital de la Pitié-Salpêtrière, France.)

441. Mteyrek A, Filipski E, Guettier C, Oklejewicz M, van der Horst GT, Okyar A, Lévi F. 2017. Critical cholangiocarcinogenesis control by cryptochrome clock genes. *Int J Cancer* 140(11): 2473-2483. (Supported by ERASySBio+ and FP7, and the Association pour la Recherche sur le Temps Biologique et la Chronotherapie [ARTBC International, Hospital Paul Brousse, Villejuif, France]. Authors affiliated with INSERM, France; Paris Sud University, France; Hôpital Paul Brousse, France; Erasmus University Medical Center, Netherlands; Istanbul University Faculty of Pharmacy, Turkey; Warwick Medical School, UK.)

442. Mteyrek A, Filipski E, Guettier C, Okyar A, Lévi F. 2016. Clock gene *Per2* as a controller of liver carcinogenesis. *Oncotarget* 7(52): 85832-85847. (Supported by ERASySBio+ and FP7 to the C5Sys project, the Association pour la Recherche sur le Temps Biologique et la

Chronothérapie [ARTBC International, Paul Brousse hospital, Villejuif, France] and Cancer Research UK. Authors affiliated with INSERM, France; Paris Sud University, France; Hôpital Paul Brousse, France; Istanbul University Faculty of Pharmacy, Turkey; Warwick Medical School, UK.)

443. Muhammad DH, Qadir FA. 2017. Effects of night shift working on some immunological, prostate specific antigen, cortisol level and malondialdehyde in male nurses at Hawler City. *AIP Conf Proc* 1888(020035). (Support not reported. Authors affiliated with Ministry of Education, Iraq; Salahaddin University-Erbil, Iraq.)

444. Mullenders J, Fabius AW, Madiredjo M, Bernards R, Beijersbergen RL. 2009. A large scale shRNA barcode screen identifies the circadian clock component ARNTL as putative regulator of the p53 tumor suppressor pathway. *PLoS One* 4(3): e4798. (Supported by the Dutch Cancer Society and the EU 6th framework program TRANSFOG. Authors affiliated with Netherlands Cancer Institute, Netherlands.)

445. Mure LS, Le HD, Benegiamo G, Chang MW, Rios L, Jillani N, Ngotho M, Kariuki T, Dkhissi-Benyahya O, Cooper HM, Panda S. 2018. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. *Science* 359(6381). (Supported by the Salk Institute Innovation, U.S. Department of Defense, NIH, NCI, the Chapman Foundation, the Helmsley Charitable Trust, the Glenn Center for Aging Research, and the Fyssen and Catharina Foundations. Authors affiliated with Salk Institute for Biological Studies, CA; University of California - San Diego, CA; National Museums of Kenya, Kenya; Université Lyon, France.)

446. Nagai M, Morikawa Y, Kitaoka K, Nakamura K, Sakurai M, Nishijo M, Hamazaki Y, Maruzeni S, Nakagawa H. 2011. Effects of fatigue on immune function in nurses performing shift work. *J Occup Health* 53(5): 312-319. (Supported by the Ministry of Education, Culture, Sports, Science, and Technology of Japan. Authors affiliated with Kanazawa Medical University, Japan.)

447. Nagare R, Plitnick B, Figueiro M. 2018. Effect of exposure duration and light spectra on nighttime melatonin suppression in adolescents and adults. *Lighting Res Technol*. (Supported by the Lighting Research Center's Light and Health Alliance [Acuity Brands, CREE, Current by GE, Ketra, OSRAM, Philips and USAI Lighting]. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

448. Nagashima S, Osawa M, Matsuyama H, Ohoka W, Ahn A, Wakamura T. 2018. Bright-light exposure during daytime sleeping affects nocturnal melatonin secretion after simulated night work. *Chronobiol Int* 35(2): 229-239. (Supported by JSPS KAKENHI. Authors affiliated with Kyoto University, Japan; Japan Society for the Promotion of Science, Japan.)

449. Nagata C, Nagao Y, Yamamoto S, Shibuya C, Kashiki Y, Shimizu H. 2008. Light exposure at night, urinary 6-sulfatoxymelatonin, and serum estrogens and androgens in postmenopausal Japanese women. *Cancer Epidemiol Biomarkers Prev* 17(6): 1418-1423. (Supported by the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Authors affiliated with Gifu University Graduate School of Medicine, Japan; Gihoku General Hospital, Japan.)

450. Nagata C, Tamura T, Wada K, Konishi K, Goto Y, Nagao Y, Ishihara K, Yamamoto S. 2017. Sleep duration, nightshift work, and the timing of meals and urinary levels of 8-isoprostane and 6-sulfatoxymelatonin in Japanese women. *Chronobiol Int* 34(9): 1187-1196. (Supported by the Ministry of Education, Science, Sports, Culture and Technology of Japan. Authors affiliated with Gifu University Graduate School of Medicine, Japan; Gihoku Kousei Hospital, Japan.)

451. Nakahata Y, Kaluzova M, Grimaldi B, Sahar S, Hirayama J, Chen D, Guarente LP, Sassone-Corsi P. 2008. The NAD^+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. *Cell* 134(2): 329-340. (Supported by the Cancer Research Coordinating Committee of the University of California and NIH. Authors affiliated with University of California - Irvine, CA; Massachusetts Institute of Technology, MA.)

452. Nakajima H, Narama I, Matsuura T, Nomura T. 1994. Enhancement of tumor growth under short light/dark cycle in mouse lung. *Cancer Lett* 78(1-3): 127-131. (Supported by the Osaka Cancer Research Fund. Authors affiliated with Osaka University, Japan; Setsunan University, Japan.)

453. Nakano Y, Miura T, Hara I, Aono H, Miyano N, Miyajima K, Tabuchi T, Kosaka H. 1982. The effect of shift work on cellular immune function. *J Hum Ergol (Tokyo)* 11 Suppl: 131-137. (Support not reported. Authors affiliated with Osaka Prefectural Institute of Public Health, Japan.)

454. NASA. 2018. *Gateway to Astronaut Photography of Earth*. National Aeronautics and Space Administration. Last accessed: 8/14/18. https://eol.jsc.nasa.gov/

455. Navara KJ, Nelson RJ. 2007. The dark side of light at night: physiological, epidemiological, and ecological consequences. *J Pineal Res* 43(3): 215-224. (Supported by NIH, NSF, and NRSA. Authors affiliated with Ohio State University, OH.)

456. Neil-Sztramko SE, Gotay CC, Demers PA, Campbell KL. 2016. Physical activity, physical fitness, and body composition of Canadian shift workers: Data from the Canadian Health Measures Survey cycles 1 and 2. *J Occup Environ Med* 58(1): 94-100. (Supported by the Canadian Institutes of Health Research and the Canadian Cancer Research Institute. Authors affiliated with University of British Columbia, Canada; British Columbia Cancer Research Centre, Canada; Cancer Care Ontario, Canada; University of Toronto, Canada.)

457. Neil-Sztramko SE, Pahwa M, Demers PA, Gotay CC. 2014. Health-related interventions among night shift workers: a critical review of the literature. *Scand J Work Environ Health* 40(6): 543-556. (Supported by the Canadian Cancer Society Research Institute, the Canadian Institute for Health Research, the Canadian Cancer Society British Columbia-Yukon, and the Workplace Safety and Insurance Board of Ontario. Authors affiliated with University of British Columbia, Canada; Cancer Care Ontario, Canada; University of Toronto, Canada; BC Cancer Research Centre, Canada.)

458. Nelson RJ, Blom JM. 1994. Photoperiodic effects on tumor development and immune function. *J Biol Rhythms* 9(3-4): 233-249. (Supported by the National Institute of Child and Human Development, NCI, and Mr. Ted C. Hanf. Authors affiliated with Johns Hopkins University, MD.)

459. Nesbitt AD, Leschziner GD, Peatfield RC. 2014. Headache, drugs and sleep. *Cephalalgia* 34(10): 756-766. (Supported by the Patrick Berthoud Charitable Trust. Authors affiliated with King's College London, UK; University of Surrey, UK; Guy's and St Thomas' NHS Foundation Trust, UK; Imperial College Healthcare NHS Foundation Trust, UK.)

460. Nesthus T, Cruz C, Boquet A, Detwiler C, Holcomb K, Della Rocco P. 2001. Circadian temperature rhythms in clockwise and counter-clockwise rapidly rotating shift schedules. *J Hum Ergol (Tokyo)* 30(1-2): 245-249. (Support not reported. Authors affiliated with Federal Aviation Administration Civil Aerospace Medical Institute, OK.)

461. Nishitani N, Sakakibara H. 2007. Subjective poor sleep and white blood cell count in male Japanese workers. *Ind Health* 45(2): 296-300. (Support not reported. Authors affiliated with Nagoya University Graduate School of Medicine, Japan.)

462. Niu SF, Chung MH, Chu H, Tsai JC, Lin CC, Liao YM, Ou KL, O'Brien AP, Chou KR. 2015. Differences in cortisol profiles and circadian adjustment time between nurses working night shifts and regular day shifts: A prospective longitudinal study. *Int J Nurs Stud* 52(7): 1193-1201. (No funding received. Authors affiliated with Shin Kong Wu Ho-Su Memorial Hospital, Taiwan; Taipei Medical University, Taiwan; Taipei Medical University-Shuang Ho Hospital, Taiwan; Tri-Service General Hospital, Taiwan; National Defense Medical Center, Taiwan; Centre for Practice Opportunity and Development, Australia; Fu Jen Catholic University, Taiwan; University of Newcastle, Australia.)

463. NOAA. 2015. *Defense Meteorological Satellite Program (DMSP)*. NOAA, National Centers for Environmental Information. Last accessed: 1/8/18. https://ngdc.noaa.gov/eog/dmsp.html

464. NOAO. 2015. *Recommended Light Levels (Illuminance) for Outdoor and Indoor Venues*. National Optical Astronomy Observatory. Last accessed: 5/31/18. https://www.noao.edu/education/QLTkit/ACTIVITY_Documents/Safety/LightLevels_outdoor+indoor.pdf

465. NOAO. 2018. *Types of Light.* National Optical Astronomy Observatory. 6 pp. https://www.noao.edu/education/QLTkit/ACTIVITY_Documents/Energy/Types_of_Lights.pdf.

466. Nobel Prize. 2017. *Press Release on The Nobel Prize in Physiology or Medicine 2017*. Last updated: 10/2/17. https://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/press.html

467. Nogueira LM, Sampson JN, Chu LW, Yu K, Andriole G, Church T, Stanczyk FZ, Koshiol J, Hsing AW. 2013. Individual variations in serum melatonin levels through time: Implications for epidemiologic studies. *Plos One* 8(12): e83208. (Supported by NCI, NIH. Authors affiliated with NCI, MD; Cancer Prevention Institute of California, CA;

Washington University School of Medicine, MO; University of Minnesota School of Public Health, MN; University of Southern California Los Angeles, CA.)

468. NTP. 2015. *Handbook for Preparing Report on Carcinogens Monographs.* Research Triangle Park, NC: National Toxicology Program. 89 pp. https://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf.

469. NTP. 2016. *Workshop: Shift Work at Night, Artificial Light at Night, and Circadian Disruption*. National Toxicology Program. Updated on 7/27/16. http://ntp.niehs.nih.gov/pubhealth/roc/candidates/meetings/workshop_alan.html

470. NTP. 2018. *Night Shift Work and Light at Night (LAN): Human cancer studies* Research Triangle Park, NC: National Toxicology Program. 46 pp. https://ntp.niehs.nih.gov/ntp/roc/protocols/electric-light_508.pdf.

471. NTP. 2019a. *All Past Events: Peer Review of the Draft Report on Carcinogens Monograph on Night Shift Work and Light at Night, October 5, 2018*. National Toxicology Program. Last updated: 4/30/19. https://ntp.niehs.nih.gov/go/meeting

472. NTP. 2019b. *Report on Carcinogens Process & Listing Criteria*. National Toxicology Program. Last updated: 8/16/19. https://ntp.niehs.nih.gov/go/rocprocess

473. O'Brien KM, Sandler DP, Taylor JA, Weinberg CR. 2017. Serum vitamin D and risk of breast cancer within five years. *Environ Health Perspect* 125(7): 077004. (Supported by the Office of Dietary Supplement Research Scholars Program, NIH, and NIEHS. Authors affiliated with NIH, NC.)

474. O'Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, Gammon MD, Leske MC, for the Electromagnetic Fields Breast Cancer on Long Island Study Group. 2006. Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol* 164(4): 358-366. (Supported by NCI and NIEHS. Authors affiliated with Stony Brook University, NY; University of Connecticut Health Center, CT; University of North Carolina at Chapel Hill, NC.)

475. Ogura-Ochi K, Fujisawa S, Iwata N, Komatsubara M, Nishiyama Y, Tsukamoto-Yamauchi N, Inagaki K, Wada J, Otsuka F. 2017. Regulatory role of melatonin and BMP-4 in prolactin production by rat pituitary lactotrope GH3 cells. *Peptides* 94: 19-24. (Supported by the Grants-in-Aid for Scientific Research, Foundation for Growth Science and Astellas Foundation for Research on Metabolic Disorders, Japan Foundation for Applied Enzymology [Japan], and The Uehara Memorial Foundation. Authors affiliated with Department of Medicine and Clinical Science, Japan; Okayama University Graduate School of Medicine, Japan.)

476. Oh JH, Yoo H, Park HK, Do YR. 2015. Analysis of circadian properties and healthy levels of blue light from smartphones at night. *Sci Rep* 5: 11325. (Supported by the National Research Foundation [NRF] of Korea and the Korean government. Authors affiliated with Kookmin University, Korea.)

477. Okamoto H, Tsunoda T, Teruya K, Takeda N, Uemura T, Matsui T, Fukazawa S, Ichikawa K, Takemae R, Tsuchida K, Takashima Y. 2008. An occupational health study of emergency physicians in Japan: health assessment by immune variables (CD4, CD8, CD56, and NK cell activity) at the beginning of work. *J Occup Health* 50(2): 136-146. (Supported by the Pfizer Health Research Foundation. Authors affiliated with Kyorin University, Japan.)

478. Otálora BB, Madrid JA, Alvarez N, Vicente V, Rol MA. 2008. Effects of exogenous melatonin and circadian synchronization on tumor progression in melanoma-bearing C57BL6 mice. *J Pineal Res* 44(3): 307-315. (Supported by the Ministry of Science and Technology, and the Instituto de Salud Carlos III. Authors affiliated with University of Murcia, Spain.)

479. Pahwa M, Labrèche F, Demers PA. 2018. Night shift work and breast cancer risk: what do the meta-analyses tell us? *Scand J Work Environ Health* 44(4): 432-435. (Supported by the Canadian Cancer Society, Ontario Ministry of Labor, and Cancer Care Ontario. Authors affiliated with Cancer Care Ontario, Canada; Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Canada; Université de Montréal, Canada; University of Toronto, Canada; Simon Fraser University, Canada.)

480. Pan A, Schernhammer ES, Sun Q, Hu FB. 2011. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med* 8(12): e1001141. (Supported by NIH, and the National Heart, Lung, and Blood Institute. Authors affiliated with Harvard School of Public Health, MA; Brigham and Women's Hospital, MA; Harvard Medical School, MA.)

481. Panda S. 2016. Circadian physiology of metabolism. *Science* 354(6315): 1008-1015. (Supported by NIH, the American Federation of Aging, the Harry B. Helmsley Charitable Trust, and the Glenn Center for Aging Research. Author affiliated with Salk Institute of Biological Studies, CA.)

482. Panda S, Antoch MP, Miller BH, Su AI, Schook AB, Straume M, Schultz PG, Kay SA, Takahashi JS, Hogenesch JB. 2002. Coordinated transcription of key pathways in the mouse by the circadian clock. *Cell* 109(3): 307-320. (Supported by the Novartis Research Foundation, the National Science Foundation [NSF] Center for Biological Timing, and the National Institute of Mental Health. Authors affiliated with Genomics Institute of the Novartis Research Foundation. CA; Northwestern University, IL; Scripps Research Institute, CA; University of Virginia, VA.)

483. Papagiannakopoulos T, Bauer MR, Davidson SM, Heimann M, Subbaraj L, Bhutkar A, Bartlebaugh J, Vander Heiden MG, Jacks T. 2016. Circadian rhythm disruption promotes lung tumorigenesis. *Cell Metab* 24(2): 324-331. (Supported by a NCI Cancer Center Support Core Grant, the Lung Cancer Research Foundation, the Koch Institute Frontier Fund, the American Cancer Society, and Hope Funds for Cancer Research. Authors affiliated with Massachusetts Institute of Technology, MA; New York University School of Medicine, NY.)

484. Papantoniou K, Castaño-Vinyals G, Espinosa A, Aragonés N, Pérez-Gómez B, Ardanaz E, Altzibar JM, Sanchez VM, Gómez-Acebo I, Llorca J, Muñoz D, Tardón A, Peiró R, Marcos-Gragera R, Pollan M, Kogevinas M. 2015a. Breast cancer risk and night shift work in a case-control study in a Spanish population. *Eur J Epidemiol* 31(9): 867-878. (Supported by the ''Accion Transversal del Cancer,'' approved on the Spanish Ministry Council on the 11th October 2007, by the Instituto de Salud Carlos III-FEDER, the Fundación Marqués de Valdecilla, the ICGC International Cancer Genome Consortium CLL, the Spanish Ministerio de Economía y Competitividad, the Red Temática de Investigación del Cáncer, the Junta de Castilla y León, the the Consejería de Salud of the Junta de Andalucía, the Conselleria de Sanitat of the Generalitat Valenciana, the Recercaixa, the European Commission, the Spanish Association Against Cancer, the Scientific Foundation, the Catalan Government DURSI Grant and a predoctoral Grant PFIS. Authors affiliated with Centre for Research in Environmental Epidemiology, Spain; IMIM [Hospital del Mar Medical Research Institute], Spain; Universitat Pompeu Fabra, Spain; Carlos III Health Institute, Spain; Cancer Epidemiology Research Group, Spain; Instituto de Salud Publica de Navarra, Spain; Basque Regional Health Department, Spain; Universidad de León, Spain; University of Cantabria, Spain; IDIVAL, Spain; Universidad de Huelva, Spain; Universidad de Oviedo, Spain; Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana, Spain; Girona Biomedical Research Institute, Spain; CIBER Epidemiologıía y Salud Pública, Spain; National School of Public Health, Greece.)

485. Papantoniou K, Castaño-Vinyals G, Espinosa A, Aragonés N, Pérez-Gómez B, Burgos J, Gómez-Acebo I, Llorca J, Peiró R, Jimenez-Moleón JJ, Arredondo F, Tardón A, Pollan M, Kogevinas M. 2015b. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. *Int J Cancer* 137(5): 1147-1157. (Supported by the "Accion Transversal del Cancer," Spanish Ministry Council, the Instituto de Salud Carlos III-FEDER, and a predoctoral grant PFIS. Authors affiliated with Centre for Research in Environmental Epidemiology [CREAL], Spain; IMIM (Hospital Del Mar Medical Research Institute), Spain; Universitat Pompeu Fabra [UPF], Spain; CIBER Epidemiologıa Y Salud Publica, Spain; Carlos III Health Institute, Spain; Cancer Epidemiology Research Group, Spain; Hospital Ramon Y Cajal, Spain; Instituto Ramon Y Cajal De Investigacion Sanitaria, Spain; Universidad De Alcala De Henares, Spain; University of Cantabria, Spain; IDIVAL, Spain; Fundacion Para El Fomento De La Investigacion Sanitaria Y Biomedica De La Comunidad Valenciana, Spain; Hospitales Universitarios De Granada/Universidad De Granada, Spain; Hospital Infanta Elena, Spain; Universidad De Huelva, Spain; Universidad De Oviedo, Spain; National School of Public Health, Greece.)

486. Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Alonso-Aguado MH, Martin V, Aragonés N, Pérez-Gómez B, Pozo BM, Gómez-Acebo I, Ardanaz E, Altzibar JM, Peiro R, Tardon A, Lorca JA, Chirlaque MD, García-Palomo A, Jimenez-Moleon JJ, Ierssen T, Ederra M, Amiano P, Pollan M, Moreno V, Kogevinas M. 2017. Shift work and colorectal cancer risk in the MCC-Spain case-control study. *Scand J Work Environ Health* 43(3): 250-259. (Supported by the "Accion Transversal del Cancer", approved on the Spanish Ministry Council on 11 October 2007, by the Instituto de Salud Carlos III-FEDER, by the Fundación Marqués de Valdecilla, by the ICGC International Cancer Genome Consortium CLL [The ICGC CLL-Genome Project is funded by Spanish Ministerio de

Economía y Competitividad [MINECO] through the Instituto de Salud Carlos III [ISCIII] and Red Temática de Investigación del Cáncer [RTICC] del ISCIII], by the Junta de Castilla y León, by the Consejería de Salud of the Junta de Andalucía, by the Conselleria de Sanitat of the Generalitat Valenciana, by the Recercaixa, by the European Commission grants, by the Spanish Association Against Cancer [AECC] Scientific Foundation, by the Catalan Government DURSI grant, by a predoctoral grant PFIS, by FEDER, by the European Commission, by the the Catalan Government DURSI, and by the Canadian Institutes of Health Research. Authors affiliated with CREAL, Spain; Medical University of Vienna, Austria; IMIM, Spain; Universitat Pompeu Fabra, Spain; University of Ottawa, Canada; IDIBELL, Spain; Hospitalet de Llobregat, Spain; Universidad de León, Spain; Carlos III Health Institute, Spain; IIS Puerta de Hierro, Spain; Complejo Hospitales Universitarios de Granada, Spain; University of Cantabria, Spain; Instituto de Salud Publica de Navarra, Spain; Navarra Institute for Health Research, Spain; Public Health Division of Gipuzkoa, Spain; Biodonostia Research Institute, Spain; FISABIO, Spain; Universidad de Oviedo, Spain; CYSMA, Spain; Universidad de Huelva, Spain; IMIB-Arrixaca, Spain; Universidad Murcia, Spain; Universidad de Granada, Spain; University of Barcelona, Spain; CIBERESP, Spain.)

487. Papantoniou K, Devore EE, Massa J, Strohmaier S, Vetter C, Yang L, Shi Y, Giovannucci E, Speizer F, Schernhammer ES. 2018. Rotating night shift work and colorectal cancer risk in the Nurses' Health Studies. *Int J Cancer* 143(11): 2709-2717. (Supported by CDC/NIOSH and NIH. Authors affiliated with Medical University of Vienna, Austria; Brigham and Women’s Hospital, MA: Harvard Medical School, MA; Harvard T. H. Chan School of Public Health, MA; University of Colorado, CO; Chinese PLA General Hospital, China.)

488. Papantoniou K, Pozo OJ, Espinosa A, Marcos J, Castaño-Vinyals G, Basagaña X, Juanola Pagès E, Mirabent J, Martin J, Such Faro P, Gascó Aparici A, Middleton B, Skene DJ, Kogevinas M. 2015c. Increased and mistimed sex hormone production in night shift workers. *Cancer Epidemiol Biomarkers Prev* 24(5): 854-863. (Supported by the Instituto de Salud Carlos III, the Centre for Research in Environmental Epidemiology, and the Royal Society Wolfson. Authors affiliated with CREAL, Spain; IMIM, Spain; UPF, Spain; CIBERESP, Spain; Deparatment d'Empresa i Ocupacio de la Generalitat de Catalunya, Spain; Parc de Salut Mar, Spain; Ferrocarrils de la Generalitat de Catalunya, Spain; SEAT, Spain; Hospital de Viladecans, Spain; University of Surrey, UK; National School of Public Health, Greece.)

489. Papantoniou K, Pozo OJ, Espinosa A, Marcos J, Castaño-Vinyals G, Basagaña X, Ribas FC, Mirabent J, Martín J, Carenys G, Martín CR, Middleton B, Skene DJ, Kogevinas M. 2014. Circadian variation of melatonin, light exposure, and diurnal preference in day and night shift workers of both sexes. *Cancer Epidemiol Biomarkers Prev* 23(7): 1176-1186. (Supported by the Instituto de Salud Carlos III and the Centre for Research in Environmental Epidemiology. Authors affiliated with Centre for Research in Environmental Epidemiology [CREAL], Spain; IMIM [Hospital del Mar Medical Research Institute], Spain; Universitat Pompeu Fabra, Barcelona [UPF], Spain; Departament d´Empresa i Ocupacio, Spain; Parc de Salut Mar, Spain; Ferrocarrils de la Generalitat de Catalunya, Spain; SEAT, S.A., Spain; Hospital de Viladecans, Spain; CIBER

Epidemiología y Salud Publica [CIBERESP], Spain; University of Surrey, UK; National School of Public Health, Greece.)

490. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. 2012. Night work and the risk of cancer among men. *Am J Epidemiol* 176(9): 751-759. (Supported by the Health Canada, the National Cancer Institute of Canada, the Institut de recherche en santé et sécurité au travail du Québec, the Fonds de la recherche en santé du Québec, and the Canadian Institutes of Health Research. Authors affiliated with INRS, Canada; University of Quebec, Canada; CRCHUM, Canada; University of Montreal, Canada.)

491. Parks CG, DeRoo LA, Miller DB, McCanlies EC, Cawthon RM, Sandler DP. 2011. Employment and work schedule are related to telomere length in women. *Occup Environ Med* 68(8): 582-589. (Supported by NIH, NIEHS, and a Department of Defense Breast Cancer Research Concept Award. Authors affiliated with NIEHS, NC; NIOSH, WV; University of Utah, UT.)

492. Pauley SM. 2004. Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. *Med Hypotheses* 63(4): 588-596. (Support and author affiliations not reported.)

493. Peirson SN, Brown LA, Pothecary CA, Benson LA, Fisk AS. 2018. Light and the laboratory mouse. *J Neurosci Methods* 300: 26-36. (Supported by the BBSRC and the Wellcome Trust. Authors affiliated with University of Oxford, UK.)

494. Penney KL, Stampfer MJ, Jahn JL, Sinnott JA, Flavin R, Rider JR, Finn S, Giovannucci E, Sesso HD, Loda M, Mucci LA, Fiorentino M. 2013. Gleason grade progression is uncommon. *Cancer Res* 73(16): 5163-5168. (Supported by the Dana-Farber/Harvard Cancer Center Prostate SPORE, the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Research Service Award, and the Prostate Cancer Foundation. Authors affiliated with Harvard School of Public Health, MA; Brigham and Women's Hospital, MA; Harvard Medical School, MA; Dana-Farber Cancer Institute, MA; Trinity College, Ireland; Broad Institute, MA; University of Bologna, Italy.)

495. Peplonska B, Bukowska A, Gromadzinska J, Sobala W, Reszka E, Lie JA, Kjuus H, Wasowicz W. 2012. Night shift work characteristics and 6-sulfatoxymelatonin (MT6s) in rotating night shift nurses and midwives. *Occup Environ Med* 69(5): 339-346. (Supported by the Polish-Norwegian Research Fund. Authors affiliated with Nofer Institute of Occupational Medicine, Poland; National Institute of Occupational Health, Norway.)

496. Peplonska B, Bukowska A, Lie JA, Gromadzinska J, Zienolddiny S. 2016. Night shift work and other determinants of estradiol, testosterone, and dehydroepiandrosterone sulfate among middle-aged nurses and midwives. *Scand J Work Environ Health* 42(5): 435-446. (Supported by the Polish-Norwegian Research Programme. Authors affiliated with Nofer Institute of Occupational Medicine, Poland; National Institute of Occupational Health, Norway.)

497. Peplonska B, Bukowska A, Wieczorek E, Przybek M, Zienolddiny S, Reszka E. 2017. Rotating night work, lifestyle factors, obesity and promoter methylation in *BRCA1* and *BRCA2* genes among nurses and midwives. *PLoS One* 12(6): e0178792. (Supported by the

Polish-Norwegian Research Programme. Authors affiliated with Nofer Institute of Occupational Medicine, Poland; National Institute of Occupational Health, Norway.)

498. Pesch B, Harth V, Rabstein S, Baisch C, Schiffermann M, Pallapies D, Bonberg N, Heinze E, Spickenheuer A, Justenhoven C, Brauch H, Hamann U, Ko Y, Straif K, Brüning T. 2010. Night work and breast cancer – results from the German GENICA study. *Scand J Work Environ Health* 36(2): 134-141. (Supported by the German Federal Ministry of Education and Research, the Research Institute of Occupational Medicine of the German Social Accident Insurance, the Robert Bosch Foundation of Medical Research, the Evangelische Kliniken Bonn GmbH, and the Deutsches Krebsforschungszentrum. Authors affiliated with Ruhr University Bochum, Germany; Evangelische Kliniken Bonn gGmbH, Germany; University Tübingen, Germany; Deutsches Krebsforschungszentrum, Germany; IARC, France; Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Germany.)

499. Pfeffer M, Korf HW, Wicht H. 2018. Synchronizing effects of melatonin on diurnal and circadian rhythms. *Gen Comp Endocrinol* 258: 215-221. (Supported by the Dr. Senckenbergische Stiftung. Authors affiliated with Goethe-Universität Frankfurt, Germany.)

500. Pinheiro SP, Schernhammer ES, Tworoger SS, Michels KB. 2006. A prospective study on habitual duration of sleep and incidence of breast cancer in a large cohort of women. *Cancer Res* 66(10): 5521-5525. (Supported by NIH. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; LBI-ACR VIEnna and ACR-IRT VIEnna, Austria; Harvard School of Public Health, MA.)

501. Pinkerton LE, Hein MJ, Anderson JL, Little MP, Sigurdson AJ, Schubauer-Berigan MK. 2016. Breast cancer incidence among female flight attendants: exposure-response analyses. *Scand J Work Environ Health* 42(6): 538-546. (Supported by NCI, USDHHS, and NIOSH. Authors affiliated with NIOSH, OH; CACI, Inc., OH; NCI, MD.)

502. Pinkerton LE, Waters MA, Hein MJ, Zivkovich Z, Schubauer-Berigan MK, Grajewski B. 2012. Cause-specific mortality among a cohort of U.S. flight attendants. *Am J Ind Med* 55(1): 25-36. (Supported by the Office of Women's Health of the U.S. Department of Health and Human Services. Authors affiliated with NIOSH, OH.)

503. Poole EM, Schernhammer ES, Tworoger SS. 2011. Rotating night shift work and risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 20(5): 934-938. (Supported by NCI. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA: Harvard School of Public Health, MA; LBI-ACR & ACR-ITR VIEnna/CEADDP, Austria.)

504. Popovich IG, Zabezhinski MA, Panchenko AV, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Anisimov VN. 2013. Exposure to light at night accelerates aging and spontaneous uterine carcinogenesis in female 129/Sv mice. *Cell Cycle* 12(11): 1785-1790. (Supported by the President of the Russian Federation. Authors affiliated with N.N. Petrov Research Institute of Oncology, Russia.)

505. Portnov BA, Stevens RG, Samociuk H, Wakefield D, Gregorio DI. 2016. Light at night and breast cancer incidence in Connecticut: An ecological study of age group effects. *Sci Total*

Environ 572: 1020-1024. (Support not reported. Authors affiliated with University of Connecticut, CT; University of Haifa, Israel; Connecticut Children's Medical Center, CT.)

506. Prata Lima MF, Baracat EC, Simões MJ. 2004. Effects of melatonin on the ovarian response to pinealectomy or continuous light in female rats: similarity with polycystic ovary syndrome. *Braz J Med Biol Res* 2004(37): 987-995. (Support not reported. Authors affiliated with Faculdade de Medicina do Triângulo Mineiro, Brazil; Universidade Federal de São Paulo, Brazil.)

507. Prendergast BJ, Cable EJ, Patel PN, Pyter LM, Onishi KG, Stevenson TJ, Ruby NF, Bradley SP. 2013. Impaired leukocyte trafficking and skin inflammatory responses in hamsters lacking a functional circadian system. *Brain Behav Immun* 32: 94-104. (Supported by the National Institute of Allergy and Infectious Diseases. Authors affiliated with University of Chicago, IL; Stanford University, CA.)

508. Presser HB, Ward BW. 2011. Nonstandard work schedules over the life course: a first look. *Mon Labor Rev* July: 3-16. (Supported by the Alfred P. Sloan Foundation. Authors affiliated with University of Maryland, MD.)

509. Pronk A, Ji BT, Shu XO, Xue S, Yang G, Li HL, Rothman N, Gao YT, Zheng W, Chow WH. 2010. Night-shift work and breast cancer risk in a cohort of Chinese women. *Am J Epidemiol* 171(9): 953-959. (Supoprted by NIH. Authors affiliated with NCI, MD; Vanderbilt University School of Medicine, TN; Shanghai Cancer Institute, China.)

510. Pukkala E, Helminen M, Haldorsen T, Hammar N, Kojo K, Linnersjö A, Rafnsson V, Tulinius H, Tveten U, Auvinen A. 2012. Cancer incidence among Nordic airline cabin crew. *Int J Cancer* 131(12): 2886-2897. (Supported by the Nordic Cancer Union. Authors affiliated with Finnish Cancer Registry, Finland; University of Tampere, Finland; Cancer Registry of Norway, Norway; Karolinska Institutet, Sweden; STUK-Radiation and Nuclear Safety Authority, Finland; University of Iceland, Iceland; Icelandic Cancer Registry, Iceland; Institute for Energy Technology, Norway.)

511. Pukkala E, Ojamo M, Rudanko SL, Stevens RG, Verkasalo PK. 2006. Does incidence of breast cancer and prostate cancer decrease with increasing degree of visual impairment. *Cancer Causes Control* 17(4): 573-576. (Support not reported. Authors affiliated with Finnish Cancer Registry, Finland; Finnish Register of Visual Impairment, Finland; University of Connecticut Health Center, CT; National Public Health Institute, Finland.)

512. Puttonen S, Viitasalo K, Härmä M. 2011. Effect of shiftwork on systemic markers of inflammation. *Chronobiol Int* 28(6): 528-535. (Supported by the Academy of Finland and the Finnish Work Environment Fund. Authors affiliated with Finnish Institute of Occupational Health, Finland; Finnair Health Services, Finland; University of Helsinki, Finland.)

513. Rabstein S, Harth V, Justenhoven C, Pesch B, Plöttner S, Heinze E, Lotz A, Baisch C, Schiffermann M, Brauch H, Hamann U, Ko Y, Brüning T, GENICA Consortium. 2014. Polymorphisms in circadian genes, night work and breast cancer: results from the GENICA study. *Chronobiol Int* 31(10): 1115-1122. (Supported by the German Federal Ministry of Education and Research, the Institute for Prevention and Occupational Medicine of the

German Social Accident Insurance, Ruhr-University Bochum [IPA], the Robert Bosch Foundation, Stuttgart, Evangelische Kliniken Bonn GmbH, and Deutsches Krebsforschungszentrum, Heidelberg. Authors affiliated with Institute of the Ruhr-Universität Bochum [IPA], Germany; University Medical Centre Hamburg-Eppendorf, Germany; Bioscientia Center for Human Genetics, Germany; Evangelische Kliniken Bonn gGmbH, Germany; Dr. Margarete Fischer-Bosch – Institute of Clinical Pharmacology, Germany; University of Tübingen, Germany; German Cancer Research Center, Germany.)

514. Rabstein S, Harth V, Pesch B, Pallapies D, Lotz A, Justenhoven C, Baisch C, Schiffermann M, Haas S, Fischer HP, Heinze E, Pierl C, Brauch H, Hamann U, Ko Y, Brüning T, GENICA Consortium. 2013. Night work and breast cancer estrogen receptor status – results from the German GENICA study. *Scand J Work Environ Health* 39(5): 448-455. (Supported by the German Federal Ministry of Education and Research, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Ruhr-University Bochum, the Robert Bosch Foundation, Stuttgart, Evangelische Kliniken Bonn GmbH, and the Deutsches Krebsforschungszentrum. Authors affiliated with Institute of the Ruhr-Universität Bochum, Germany; University Medical Centre Hamburg-Eppendorf, Germany; Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Germany; University of Tübingen, Germany; Medical Faculty of the University of Bonn, Germany; Deutsches Krebsforschungszentrum, Germany; Evangelische Kliniken Bonn gGmbH, Germany.)

515. Radetsky LC, Rea MS, Bierman A, Figueiro MG. 2013. Circadian disruption: comparing humans with mice. *Chronobiology Int* 30(8): 1066-1071. (Supported by the Office of Naval Research and NCI. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

516. Rahman SA, Shapiro CM, Wang F, Ainlay H, Kazmi S, Brown TJ, Casper RF. 2013. Effects of filtering visual short wavelengths during nocturnal shiftwork on sleep and performance. *Chronobiol Int* 30(8): 951-962. (Supported by the Canadian Institutes of Health Research, the Government of Ontario/Pharmacia Canada Inc./Genesis Research Foundation/OBGYN Graduate Scholarship in Science and Technology at the University of Toronto, Faculty of Medicine, and the Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Award from the Canadian Institutes of Health Research. Authors affiliated with Mount Sinai Hospital, Canada; University of Toronto, Canada; The Youthdale Child and Adolescent Sleep Centre, Canada.)

517. Rahman SA, St Hilaire MA, Lockley SW. 2017. The effects of spectral tuning of evening ambient light on melatonin suppression, alertness and sleep. *Physiol Behav* 177: 221-229. (Supported by the Biological Illuminations LLC, a subsidiary of Lighting Science Group Corporation [LSGC], the National Center for Advancing Translational Sciences, and NIH/NHLBI. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA.)

518. Rångtell FH, Ekstrand E, Rapp L, Lagermalm A, Liethof L, Búcaro MO, Lingfors D, Broman JE, Schiöth HB, Benedict C. 2016. Two hours of evening reading on a self-luminous tablet vs. reading a physical book does not alter sleep after daytime bright light exposure. *Sleep Med* 23: 111-118. (Supported by AFA Insurance, the Novo Nordisk

Foundation, the Swedish Brain Foundation, and the Swedish Research Council. Authors affiliated with Uppsala University, Sweden.)

519. Rao D, Yu H, Bai Y, Zheng X, Xie L. 2015. Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. *Onco Targets Ther* 8: 2817-2826. (Supported by the National Key Clinical Specialty Construction Project of China, Key Medical Disciplines of Zhejiang Province, Health Sector Scientific Research Special Project, Combination of Traditional Chinese and Western Medicine Key Disciplines of Zhejiang Province, Zhejiang Province Key Project of Science and Technology, National Natural Science Foundation of China, and Scientific Research Foundation of the Ministry of Public Health of China. Authors affiliated with Zhejiang University, China; Second Affiliated Hospital of Wenzhou Medical University, China; Yunnan Tumor Hospital and Third Affiliated Hospital of Kunming Medical University, China.)

520. Rea MS, Bierman A, Figueiro MG, Bullough JD. 2008. A new approach to understanding the impact of circadian disruption on human health. *J Circadian Rhythms* 6: 7. (Supported by the CDC and the Trans-NIH Genes, Environment and Health Initiative Grant. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

521. Rea MS, Figueiro MG. 2014. Quantifying light-dependent circadian disruption in humans and animal models. *Chronobiol Int* 31(10): 1239-1246. (Supported by the Office of Naval Research, the National Cancer Institute, and the National Institute on Drug Abuse. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

522. Rea MS, Figueiro MG, Bullough JD, Bierman A. 2005. A model of phototransduction by the human circadian system. *Brain Res Brain Res Rev* 50(2): 213-228. (Support not reported. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

523. Reddy AB, Field MD, Maywood ES, Hastings MH. 2002. Differential resynchronisation of circadian clock gene expression within the suprachiasmatic nuclei of mice subjected to experimental jet lag. *J Neurosci* 22(17): 7326-7330. (Support not reported. Authors affiliated with University of Cambridge, UK.)

524. Reichrath J, Berg K, Emmert S, Lademann J, Seckmeyer G, Zastrow L, Vogt T, Holick MF. 2016. Biologic effects of light: An enlighting prospective. *Anticancer Res* 36(3): 1339-1343. (Support not reported. Authors affiliated with Saarland University Hospital, Germany; Oslo University Hospital – Radium Hospital Montebello, Norway; University Medical Center Rostock, Germany; Universitätsmedizin Berlin, Germany; University of Hannover, Germany; Boston University Medical Center, MA.)

525. Reid KJ, Abbott SM. 2015. Jet lag and shift work disorder. *Sleep Med Clin* 10(4): 523-535. (Support not reported. Authors affiliated with Northwestern University, IL.)

526. Reinberg A, Ashkenazi I. 2008. Internal desynchronization of circadian rhythms and tolerance to shift work. *Chronobiol Int* 25(4): 625-643. (Supported by the Therese Tremel-Pontremoli donation for chronobiologic research at the Fondation Adolphe de Rothschild, Paris. Authors affiliated with Fondation A. de Rothschild, France; Tel Aviv University, Israel.)

527. Reiter R. 2001. Reactive oxygen species, DNA damage and carcinogenesis: Intervention with melatonin. In *Pineal Gland and Cancer. Neuroimmunoendocrine Mechanisms in Malignancy* C Bartsch, H Bartsch, D Blask, eds. Heidelberg: Springer. p. 442-455. (Support and author affiliations not reported.)

528. Reiter RJ, Acuña-Castroviejo D, Tan DX, Burkhardt S. 2001. Free radical-mediated molecular damage. Mechanisms for the protective actions of melatonin in the central nervous system. *Ann N Y Acad Sci* 939: 200-215. (Support not reported. Authors affiliated with University of Texas Health Science Center at San Antonio, TX.)

529. Reiter RJ, Tan DX, Galano A. 2014. Melatonin: exceeding expectations. *Physiology (Bethesda)* 29(5): 325-333. (Support not reported. Authors affiliated with UT Health Science Center, TX; Universidad Autonoma Metropolitana-Iztapalapa, Mexico.)

530. Renehan AG, Zwahlen M, Egger M. 2015. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer* 15(8): 484-498. (Support not reported. Authors affiliated with University of Manchester, UK; University of Bern, Switzerland.)

531. Rensselaer Polytechnic Institute. 2018. *Lighting Answers: What is Light Pollution?* Rensselaer Polytechnic Institute. Last accessed: 6/14/18. http://www.lrc.rpi.edu/programs/nlpip/lightinganswers/lightpollution/lightPollution.asp# Glossary can be found at http://www.lrc.rpi.edu/programs/nlpip/lightinganswers/lightpollution/glossary.asp

532. Reszka E, Peplonska B, Wieczorek E, Sobala W, Bukowska A, Gromadzinska J, Lie JA, Kjuus H, Wasowicz W. 2013. Circadian gene expression in peripheral blood leukocytes of rotating night shift nurses. *Scand J Work Environ Health* 39(2): 187-194. (Supported by the Polish-Norwegian Research Fund and ECNIS2. Authors affiliated with Nofer Institute of Occupational Medicine, Poland; National Institute of Occupational Health, Norway.)

533. Reszka E, Przybek M. 2016. Circadian genes in breast cancer. *Adv Clin Chem* 75: 53-70. (Supported by the Polish-Norwegian Research Program, the National Centre for Research and Development, and the National Science Center, Poland. Authors affiliated with Nofer Institute of Occupational Medicine, Poland.)

534. Reszka E, Przybek M, Muurlink O, Peplonska B. 2017. Circadian gene variants and breast cancer. *Cancer Lett* 390: 137-145. (Supported by the Polish-Norwegian Research Program, the National Centre for Research and Development, and the National Science Center, Poland. Authors affiliated with Nofer Institute of Occupational Medicine, Poland; Central Queensland University, Australia; Griffith Institute of Educational Research, Australia.)

535. Reszka E, Wieczorek E, Przybek M, Jablońska E, Kalużny P, Bukowska-Damska A, Zienolddiny S, Peplońska B. 2018. Circadian gene methylation in rotating-shift nurses: a cross-sectional study. *Chronobiol Int* 35(1): 111-121. (Supported by the Nofer Institute of Occupational Medicine and the Polish-Norwegian Research Program carried out by the National Centre for Research and Development. Authors affiliated with Nofer Institute of Occupational Medicine, Poland; National Institute of Occupational Health, Norway.)

536. Reynolds P, Cone J, Layefsky M, Goldberg DE, Hurley S. 2002. Cancer incidence in California flight attendants (United States). *Cancer Causes Control* 13(4): 317-324. (Supported by the California Breast Cancer Research Program. Authors affiliated with California Department of Health Services, CA; Public Health Institute, CA.)

537. Ripperger JA, Schibler U. 2006. Rhythmic CLOCK-BMAL1 binding to multiple E-box motifs drives circadian *Dbp* transcription and chromatin transitions. *Nat Genet* 38(3): 369-374. (Supported by the Canton of Geneva, the Swiss National Science Foundation [through an individual grant to U.S. and the Swiss National Center for Competence in Research program grant 'Frontiers in Genetics'], the Louis Jeantet Foundation of Medicine and the Bonizzi-Theler Stiftung. Authors affiliated with University of Geneva, Switzerland; University of Fribourg, Switzerland.)

538. Rodgers KM, Udesky JO, Rudel RA, Brody JG. 2018. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. *Environ Res* 160: 152-182. (Supported by charitable gifts to Silent Spring Institute and grants from Avon Foundation for Women. Authors affiliated with Silent Spring Institute, MA.)

539. Roenneberg T. 2012. What is chronotype? *Sleep Biol Rhythms* 10: 75-76. (Support not reported. Author affiliated with Ludwig-Maximilians-University, Germany.)

540. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. 2012. Social jetlag and obesity. *Curr Biol* 22(10): 939-943. (Supported by the European Commission, the Netherlands Organization for Scientific Research, the University of Groningen Rosalind Franklin Program, and the Hersenstichting Nederland. Authors affiliated with University of Munich, Germany; University of Groningen, Netherlands.)

541. Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, Merrow M. 2007. Epidemiology of the human circadian clock. *Sleep Med Rev* 11(6): 429-438. (Supported by the 6th European Framework Programme EUCLOCK and the Daimler-Benz-Stiftung project CLOCKWORK. Authors affiliated with University of Munich, Germany; University of Groningen, Netherlands.)

542. Roenneberg T, Merrow M. 2007. Entrainment of the human circadian clock. *Cold Spring Harb Symp Quant Biol* 72: 293-299. (Supported by the supported by the 6th European Framework Programme EUCLOCK and the Daimler-Benz-Stiftung project CLOCKWORK. Authors affiliated with University of Munich, Germany; University of Groningen, Netherlands.)

543. Rose DM, Jung D, Parera D, Konietzko J. 1999. [Time zone shifts and jet lag after long-distance flights]. *Z Arztl Fortbild Qualitatssich* 93(7): 485-490. (Support unknown due to foreign language. Authors affiliated with Johannes Gutenberg-Universität Mainz, Germany.)

544. Ruben MD, Wu G, Smith DF, Schmidt RE, Francey LJ, Lee YY, Anafi RC, Hogenesch JB. 2018. A database of tissue-specific rhythmically expressed human genes has potential applications in circadian medicine. *Sci Transl Med* 10(eaat8806): 1-7. (Supported by the Cincinnati Children's Hospital Medical Center, the National Institute of Neurological

Disorders and Stroke, and the National Human Genome Research Institute, NIH, NCI, NHGRI, the National Heart, Lung, and Blood Institute, the National Institute on Drug Abuse, the National Institute of Mental Health, and NINDS. Authors affiliated with Cincinnati Children's Hospital Medical Center, OH; University of Cincinnati School of Medicine, OH; University of Pennsylvania Perelman School of Medicine, PA.)

545. Ruby NF, Joshi N, Heller HC. 1998. Phase shift magnitude and direction determine whether Siberian hamsters reentrain to the photocycle. *J Biol Rhythms* 13(6): 506-517. (Supported by the National Institute of Child Health and Human Development and the National Institute of Aging. Authors affiliated with Stanford University, CA.)

546. Rudic RD, McNamara P, Curtis AM, Boston RC, Panda S, Hogenesch JB, FitzGerald GA. 2004. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. *PLoS Biol* 2(11): e377. (Supported by the Penn Diabetes Center/Mouse Phenotyping, Physiology, and Metabolism Core, NIH, and the American Heart Association. Authors affiliated with University of Pennsylvania, PA; Phenomix Corporation, CA; Genomics Institute of the Novartis Research Foundation, CA.)

547. Russo IH, Russo J. 1978. Developmental stage of the rat mammary gland as determinant of its susceptibility to 7,12-dimethylbenz[*a*]anthracene. *J Natl Cancer Inst* 61(6): 1439-1449. (Supported by the United Foundation of Greater Detroit and NCI. Authors affiliated with Michigan Cancer Foundation, MI.)

548. Russo IH, Russo J. 2011. Pregnancy-induced changes in breast cancer risk. *J Mammary Gland Biol Neoplasia* 16(3): 221-233. (Support not reported. Authors affiliated with Fox Chase Cancer Center, PA.)

549. Russo J, Russo IH. 2008. Breast development, hormones, and cancer. In *Innovative Endocrinology of Cancer* LM Berstein, RJ Santen, eds. Landes Bioscience and Springer Science+Business Media. p. 52-56. (Support not reported. Authors affiliated with Fox Chase Cancer Center, PA.)

550. Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, Dekker JM. 2014. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? *J Biol Rhythms* 29(5): 377-383. (Support not reported. Authors affiliated with VU University Medical Centre, Netherlands; Maastricht University, Netherlands.)

551. Rybnikova N, Haim A, Portnov BA. 2015. Artificial Light at Night (ALAN) and breast cancer incidence worldwide: A revisit of earlier findings with analysis of current trends. *Chronobiol Int* 32(6): 757-773. (Support not reported. Authors affiliated with University of Haifa, Israel.)

552. Rybnikova N, Portnov BA. 2018. Population-level study links short-wavelength nighttime illumination with breast cancer incidence in a major metropolitan area. *Chronobiol Int*: 1-11. (Supported by the Israel Ministry of Science, Technology and Space. Authors affiliated with University of Haifa, Israel.)

553. Sahar S, Sassone-Corsi P. 2007. Circadian clock and breast cancer: a molecular link. *Cell Cycle* 6(11): 1329-1331. (Support not reported. Authors affiliated with University of California at Irvine, CA.)

554. Sainz RM, Mayo JC, Tan DX, León J, Manchester L, Reiter RJ. 2005. Melatonin reduces prostate cancer cell growth leading to neuroendocrine differentiation via a receptor and PKA independent mechanism. *Prostate* 63(1): 29-43. (Supported by Fulbright, the Spanish Ministry of Education, Culture & Sports, and FICYT. Authors affiliated with University of Texas Health Science Center, TX.)

555. Saksvik IB, Bjorvatn B, Hetland H, Sandal GM, Pallesen S. 2011. Individual differences in tolerance to shift work – a systematic review. *Sleep Med Rev* 15(4): 221-235. (Support not reported. Authors affiliated with University of Bergen, Norway.)

556. Salavaty A. 2015. Carcinogenic effects of circadian disruption: an epigenetic viewpoint. *Chin J Cancer* 34(9): 375-383. (No support received. Author affiliated with Shahid Chamran University of Ahvaz, Iran.)

557. Salgado-Delgado R, Ángeles-Castellanos M, Buijs MR, Escobar C. 2008. Internal desynchronization in a model of night-work by forced activity in rats. *Neuroscience* 154(3): 922-931. (Supported by Servier Monde, DGAPA-PAPIIT-UNAM, and CONACyT. Authors affiliated with Universidad Nacional Autónoma de México, Mexico.)

558. Salgado-Delgado R, Nadia S, Angeles-Castellanos M, Buijs RM, Escobar C. 2010. In a rat model of night work, activity during the normal resting phase produces desynchrony in the hypothalamus. *J Biol Rhythms* 25(6): 421-431. (Supported by CONACyT, DGAPA-PAPIIT-UNAM and the Programa de Becas posdoctorales de la UNAM. Authors affiliated with Universidad Nacional Autónoma de México, Mexico.)

559. Salgado-Delgado RC, Saderi N, Basualdo Mdel C, Guerrero-Vargas NN, Escobar C, Buijs RM. 2013. Shift work or food intake during the rest phase promotes metabolic disruption and desynchrony of liver genes in male rats. *PLoS One* 8(4): e60052. (Supported by CONACyT, DGAPA-PAPIIT- UNAM, and PROMEP. Authors affiliated with Universidad Nacional Autónoma de México, Mexico; Universidad Autónoma de San Luis Potosí, Mexico.)

560. Samuelsson LB, Bovbjerg DH, Roecklein KA, Hall MH. 2018. Sleep and circadian disruption and incident breast cancer risk: An evidence-based and theoretical review. *Neurosci Biobehav Rev* 84: 35-48. (Supported by the National Institute of General Medical Sciences and NCI. Authors affiliated with University of Pittsburgh, PA.)

561. Samulin Erdem J, Notø HØ, Skare Ø, Lie J-AS, Petersen-Øverleir M, Reszka E, Peplońska B, Zienolddiny S. 2017a. Mechanisms of breast cancer risk in shift workers: association of telomere shortening with the duration and intensity of night work. *Cancer Med* 6(8): 1988-1997. (Supported by the Norway Grants, under the Polish-Norwegian Research Program and NIOH. Authors affiliated with National Institute of Occupational Health, Norway; Nofer Institute of Occupational Medicine, Poland.)

562. Samulin Erdem J, Skare Ø, Petersen-Øverleir M, Notø HØ, Lie JS, Reszka E, Peplońska B, Zienolddiny S. 2017b. Mechanisms of breast cancer in shift workers: DNA methylation in five core circadian genes in nurses working night shifts. *J Cancer* 8(15): 2876-2884. (Supported by the Norway Grants, under the Polish-Norwegian Research Program and NIOH. Authors affiliated with National Institute of Occupational Health, Norway; Nofer Institute of Occupational Medicine, Poland.)

563. Scheiermann C, Kunisaki Y, Frenette PS. 2013. Circadian control of the immune system. *Nat Rev Immunol* 13(3): 190-198. (Supported by NIH, the German Academic Exchange Service, and the Japan Society for the Promotion of Science. Authors affiliated with Albert Einstein College of Medicine, NY.)

564. Schernhammer ES, Berrino F, Krogh V, Secreto G, Micheli A, Venturelli E, Grioni S, Sempos CT, Cavalleri A, Schünemann HJ, Strano S, Muti P. 2010. Urinary 6-sulphatoxymelatonin levels and risk of breast cancer in premenopausal women: the ORDET cohort. *Cancer Epidemiol Biomarkers Prev* 19(3): 729-737. (Supported by a Department of Defense Grant and NCI. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; LBI-ACR-CTO & ACR-ITR VIEnna/CEADDP, Austria; Fondazione IRCCS Istituto Nazionale Tumori, Italy; University of Buffalo, NY; McMaster University, Canada; Istituto Nazionale Tumori Regina Elena IRCCS, Italy.)

565. Schernhammer ES, Berrino F, Krogh V, Secreto G, Micheli A, Venturelli E, Sieri S, Sempos CT, Cavalleri A, Schünemann HJ, Strano S, Muti P. 2008. Urinary 6-sulfatoxymelatonin levels and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 100(12): 898-905. (Supported by the Department of Defense. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; LBI-ACR and ACR-ITR VIEnna/CEADDP, Austria; Fondazione Istituto di Ricovero e Cura a Carattere Scientifico [IRCCS] Istituto Nazionale Tumori, Italy; University at Buffalo, NY; Istituto Nazionale Tumori Regina Elena IRCCS, Italy; McMaster University, Canada.)

566. Schernhammer ES, Feskanich D, Liang G, Han J. 2013. Rotating night-shift work and lung cancer risk among female nurses in the United States. *Am J Epidemiol* 178(9): 1434-1441. (Supported by NIH. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; ACR-ITR, Austria; LBI-ACR, Austria; Southeast University, China; Tianjin Medical University Cancer Institute and Hospital, China.)

567. Schernhammer ES, Feskanich D, Niu C, Dopfel R, Holmes MD, Hankinson SE. 2009. Dietary correlates of urinary 6-sulfatoxymelatonin concentrations in the Nurses' Health Study cohorts. *Am J Clin Nutr* 90(4): 975-985. (Supported by NCI. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; LBI-ACR VIEnna & ACR-ITR VIEnna, Austria; Harvard University, MA.)

568. Schernhammer ES, Hankinson SE. 2005. Urinary melatonin levels and breast cancer risk. *J Natl Cancer Inst* 97(14): 1084-1087. (Supported by NCI. Authors affiliated with Brigham

and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; LBI-ACR VIEnna and ACR-ITR VIEnna, Austria.)

569. Schernhammer ES, Kroenke CH, Dowsett M, Folkerd E, Hankinson SE. 2006a. Urinary 6-sulfatoxymelatonin levels and their correlations with lifestyle factors and steroid hormone levels. *J Pineal Res* 40(2): 116-124. (Supported by NCI. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; LBI-ACR Vienna & ACR-ITR, Austria; Royal Marsden Hospital, UK.)

570. Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. 2006b. Night work and risk of breast cancer. *Epidemiology* 17(1): 108-111. (Support not reported. Authors affiliated with Harvard Medical School, MA; LBI-ACR VIEnna & ACR-ITR VIEnna, Austria; Brigham and Women's Hospital, MA; Harvard School of Public Health, MA.)

571. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Colditz GA. 2001. Rotating night shifts and risk of breast cancer in women participating in the Nurses' Health Study. *J Natl Cancer Inst* 93(20): 1563-1568. (Supported by NCI, NIEHS, and the Austrian Federal Ministry of Education, Science and Culture. Authors affiliated with Harvard Medical School, MA; Brigham and Women's Hospital, MA; Harvard Center for Cancer Prevention, MA; Dana-Faber/Harvard Cancer Center, MA; Harvard School of Public Health, MA.)

572. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Fuchs CS, Colditz GA. 2003. Night-shift work and risk of colorectal cancer in the Nurses' Health Study. *J Natl Cancer Inst* 95(11): 825-828. (Supported by NCI, NIH, and the Austrian Research Centers [ARC] Seibersdorf Research, Health Physics Division. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Kaiser Franz-Josef-Spital, Austria; Harvard School of Public Health, MA; Dana-Farber Cancer Institute/Harvard Cancer Center, MA; Harvard Center for Cancer Prevention, MA.)

573. Schernhammer ES, Razavi P, Li TY, Qureshi AA, Han J. 2011. Rotating night shifts and risk of skin cancer in the Nurses' Health Study. *J Natl Cancer Inst* 103(7): 602-606. (Supported by NIH and the Department of Dermatology, Brigham and Women's Hospital. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; LBI-ACR & ACR-ITR VIEnna/CEADDP, Austria; University of Southern California Los Angeles, LA.)

574. Schernhammer ES, Rosner B, Willett WC, Laden F, Colditz GA, Hankinson SE. 2004. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. *Cancer Epidemiol Biomarkers Prev* 13(6): 936-943. (Supported by NCI. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard School of Public Health, MA; KFJ-Spital, Austria; Dana Farber/Harvard Cancer Center, MA; Harvard Center for Cancer Prevention, MA.)

575. Schibler U, Gotic I, Saini C, Gos P, Curie T, Emmenegger Y, Sinturel F, Gosselin P, Gerber A, Fleury-Olela F, Rando G, Demarque M, Franken P. 2015. Clock-talk: Interactions between central and peripheral circadian oscillators in mammals. *Cold Spring Harb Symp Quant Biol* 80: 223-232. (Supported by the University of Geneva, the State of

Geneva, the European Research Council [ERCAdG TimeSignal], the Swiss National Science Foundation, the Louis Jeantet Foundation of Medicine, a Federation of European Biochemical Societies [FEBS] long-term postdoctoral fellowship, a European Molecular Biology Organization [EMBO] long-term fellowship, the University of Lausanne, the State of Vaud, the Swiss National Science Foundation, the European Mouse Disease Clinic [EUMODIC], a fellowship of the Marie Curie Intra-European program, and the Novartis Foundation. Authors affiliated with University of Geneva, Switzerland; Geneva University Hospitals, Switzerland; University of Lausanne, Switzerland; Rockefeller University, NY.)

576. Schmidt TM, Chen SK, Hattar S. 2011. Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. *Trends Neurosci* 34(11): 572-580. (Supported by the National Institute of General Medical Sciences, National Eye Institute and the David and Lucile Packard Foundation. Authors affiliated with Johns Hopkins University, MD.)

577. Schubauer-Berigan MK, Anderson JL, Hein MJ, Little MP, Sigurdson AJ, Pinkerton LE. 2015. Breast cancer incidence in a cohort of U.S. flight attendants. *Am J Ind Med* 58(3): 252-266. (Supported by the National Cancer Institute and the Office of Women's Health of the U.S. Department of Health and Human Services. Authors affiliated with NIOSH, OH; NCI, MD.)

578. Schwartzbaum J, Ahlbom A, Feychting M. 2007. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 33(5): 336-343. (Supported by the Swedish Council for Working Life. Authors affiliated with Ohio State University, OH; Karolinska Institutet, Sweden.)

579. Schwimmer H, Metzer A, Pilosof Y, Szyf M, Machnes ZM, Fares F, Harel O, Haim A. 2014. Light at night and melatonin have opposite effects on breast cancer tumors in mice assessed by growth rates and global DNA methylation. *Chronobiol Int* 31(1): 144-150. (Supported by the University of Haifa. Authors affiliated with University of Haifa, Israel; McGill University, Canada.)

580. SEER. 2018. *Surveillance, Epidemiology, and End Results Program*. National Cancer Institute. http://seer.cancer.gov/statfacts/html/breast.html

581. Sephton S, Spiegel D. 2003. Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease? *Brain Behav Immun* 17(5): 321-328. (Support not reported. Authors affiliated with University of Louisville School of Medicine, KY; Stanford University School of Medicine, CA.)

582. Sephton SE, Sapolsky RM, Kraemer HC, Spiegel D. 2000. Diurnal cortisol rhythm as a predictor of breast cancer survival. *J Natl Cancer Inst* 92(12): 994-1000. (Supported by the National Institute of Mental Health and the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, the John D. and Catherine T. MacArthur Foundation and by the Fetzer Institute. Authors affiliated with University of Louisville School of Medicine, KY; Stanford University, CA.)

583. Shah PN, Mhatre MC, Kothari LS. 1984. Effect of melatonin on mammary carcinogenesis in intact and pinealectomized rats in varying photoperiods. *Cancer Res* 44(8): 3403-3407. (Support not reported. Authors affiliated with Cancer Research Institute, India.)

584. Sharifian A, Farahani S, Pasalar P, Gharavi M, Aminian O. 2005. Shift work as an oxidative stressor. *J Circadian Rhythms* 3: 15. (Support not reported. Authors affiliated with Tehran University of Medical Sciences, Iran.)

585. Sharma A, Shrivastava J. 2004. Jet lag and cabin crew: Questionnaire survey. *Ind J Aerospace Med* 48(1): 10-14. (Support not reported. Authors affiliated with Air India, India.)

586. Shavers VL, Harlan LC, Stevens JL. 2003. Racial/ethnic variation in clinical presentation, treatment, and survival among breast cancer patients under age 35. *Cancer* 97(1): 134-147. (Support not reported. Authors affiliated with NCI, MD; Information Management Systems, MD.)

587. Shi F, Chen X, Fu A, Hansen J, Stevens R, Tjonneland A, Vogel UB, Zheng T, Zhu Y. 2013. Aberrant DNA methylation of miR-219 promoter in long-term night shiftworkers. *Environ Mol Mutagen* 54(6): 406-413. (Supported by NIEHS, Yale University, Danish Cancer Society, and the National Science Foundation of China. Authors affiliated with Yale School of Public Health, CT; Beijing University of Chinese Medicine, China; Danish Cancer Society, Denmark; University of Connecticut Health Center, CT; National Research Centre for the Working Environment, Denmark.)

588. Shuboni D, Yan L. 2010. Nighttime dim light exposure alters the responses of the circadian system. *Neuroscience* 170(4): 1172-1178. (Supported by the Psychology Department Start-up fund, MSU IRGP award and PURI award from College of Social Science of MSU. Authors affiliated with Michigan State University, MI.)

589. Simó M, Navarro X, Yuste VJ, Bruna J. 2018. Autonomic nervous system and cancer. *Clin Auton Res* 28(3): 301-314. (Supported by the Instituto de Salud Carlos III and Fondo Europeo de Desarrollo Regional. Authors affiliated with IDIBELL, Spain; Universitat Autòmoma de Barcelona, Spain; CIBERNED, Spain.)

590. Slawik H, Stoffel M, Riedl L, Veselý Z, Behr M, Lehmberg J, Pohl C, Meyer B, Wiegand M, Krieg SM. 2016. Prospective study on salivary evening melatonin and sleep before and after pinealectomy in humans. *J Biol Rhythms* 31(1): 82-93. (Support not reported. Authors affiliated with Klinikum rechts der Isar, Germany; Helios Klinikum, Germany; Universitäre Psychiatrische Kliniken, Switzerland.)

591. Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Paus R. 2008. Melatonin in the skin: synthesis, metabolism and functions. *Trends Endocrinol Metab* 19(1): 17-24. (Support not reported. Authors affiliated with University of Tennessee HSC, TN; University of Bradford, UK; Southern Illinois University, IL; University of Luebeck, Germany.)

592. Slominski AT, Zmijewski MA, Jetten AM. 2016. RORα is not a receptor for melatonin. *Bioessays* 38(12): 1193-1194. (Supported by NIH and the Polish Ministry of Science and Higher Education. Authors affiliated with University of Alabama at Birmingham, AL; VA Medical Center, AL; Medical University of Gdańsk, Poland; NIEHS, NC.)

593. Slominski RM, Reiter RJ, Schlabritz-Loutsevitch N, Ostrom RS, Slominski AT. 2012. Melatonin membrane receptors in peripheral tissues: distribution and functions. *Mol Cell*

Endocrinol 351(2): 152-166. (Supported by NIH/NIAMS and NIH/NHLBI. Authors affiliated with University of Tennessee Health Science Center, TN; UT Health Science Center, TX.)

594. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 124(6): 713-721. (Supported by NIH and NIEHS. Authors affiliated with University of California - Berkeley, CA; IARC, France; US EPA, Washington, DC and NC; Environmental Defense Fund, Washington, DC; Texas A&M University, TX; University of Wisconsin School of Medicine and Public Health, WI; University of Minnesota, MN; NIEHS, NC; University of New South Wales, Australia.)

595. Smolensky MH, Reinberg AE, Sackett-Lundeen L. 2017. Perspectives on the relevance of the circadian time structure to workplace threshold limit values and employee biological monitoring. *Chronobiol Int* 34(10): 1439-1464. (Support not reported. Authors affiliated with University of Texas at Austin, TX; Fondation A. de Rothschild, France; American Association for Medical Chronobiology and Chronotherapeutics, MN.)

596. Smolensky MH, Sackett-Lundeen LL, Portaluppi F. 2015. Nocturnal light pollution and underexposure to daytime sunlight: Complementary mechanisms of circadian disruption and related diseases. *Chronobiol Int* 32(8): 1029-1048. (Support not reported. Authors affiliated with University of Texas at Austin, TX; American Association for Clinical Chronobiology and Chronotherapeutics, MN; University of Ferrara, Italy.)

597. Sollars PJ, Pickard GE. 2015. The neurobiology of circadian rhythms. *Psychiatr Clin North Am* 38(4): 645-665. (Supported by NIH. Authors affiliated with University of Nebraska, NE.)

598. Song G, Yoon KA, Chi H, Roh J, Kim JH. 2016. Decreased concentration of serum melatonin in nighttime compared with daytime female medical technologists in South Korea. *Chronobiol Int* 33(9): 1305-1310. (Support not reported. Authors affiliated with Seegene Medical Foundation, Korea; Konkuk University, Korea; Samkwang Medical Laboratories, Korea; Institute for Occupational Health, Korea; Yonsei University College of Medicine, Korea; Cheongju University, Korea.)

599. Sookoian S, Gemma C, Fernández Gianotti T, Burgueño A, Alvarez A, González CD, Pirola CJ. 2007. Effects of rotating shift work on biomarkers of metabolic syndrome and inflammation. *J Intern Med* 261(3): 285-292. (Supported by the Universidad de Buenos Aires, the Agencia Nacional de Promoción Científica y Tecnológica, the Consejo Nacional de Investigaciones Científicas y Técnicas, and the Beca Ramón Carrillo-Arturo Oñativia Ministerio de Salud y Ambiente de la Nación. Authors affiliated with Universidad de Buenos Aires, Argentina.)

600. Soták M, Sumová A, Pácha J. 2014. Cross-talk between the circadian clock and the cell cycle in cancer. *Ann Med* 46(4): 221-232. (Supported by the Czech Science Foundation. Authors affiliated with Academy of Sciences of the Czech Republic, Czech Republic.)

601. Sowah D, Fan X, Dennett L, Hagtvedt R, Straube S. 2017. Vitamin D levels and deficiency with different occupations: a systematic review. *BMC Public Health* 17(1): 519. (Supported by the Department of Medicine, University of Alberta. Authors affiliated with University of Alberta, Canada.)

602. Spiegel K, Weibel L, Gronfier C, Brandenberger G, Follenius M. 1996. Twenty-four-hour prolactin profiles in night workers. *Chronobiol Int* 13(4): 283-293. (Supported by the Institut de Recherches Internationales Servier, France. Authors affiliated with Laboratoire de Physiologie et de Psychologie Environnementales, France.)

603. Srinivasan V, Pandi-Perumal SR, Brzezinski A, Bhatnagar KP, Cardinali DP. 2011. Melatonin, immune function and cancer. *Recent Pat Endocr Metab Immune Drug Discov* 5(2): 109-123. (Supported by the Argentine National Research Council. Authors affiliated with Sri Sathya Sai Medical Educational and Research Foundation, India; Karpagam University, India; Somnogen Inc., NY; The Hebrew University-Hadassah Medical School, Israel; University of Louisville, KY; Pontificia Universidad Católica Argentina, Argentina; University of Buenos Aires, Argentina.)

604. Srinivasan V, Spence DW, Pandi-Perumal SR, Trakht I, Cardinali DP. 2008. Therapeutic actions of melatonin in cancer: possible mechanisms. *Integr Cancer Ther* 7(3): 189-203. (Support not reported. Authors affiliated with University Sains Malaysia, Malaysia; University Health Network, Canada; Somnogen Inc., NY; Columbia University, NY; University of Buenos Aires, Argentina.)

605. Stehle JH, von Gall C, Korf HW. 2002. Organisation of the circadian system in melatonin-proficient C3H and melatonin-deficient C57BL mice: a comparative investigation. *Cell Tissue Res* 309(1): 173-182. (Supported by the Deutsche Forschungsgemeinschaft and the Heinrich und Fritz Riese-Stiftung. Authors affiliated with Johann Wolfgang Goethe University Frankfurt, Germany; University of Massachusetts Medical School, MA.)

606. Stehle JH, von Gall C, Korf HW. 2003. Melatonin: a clock-output, a clock-input. *J Neuroendocrinol* 15(4): 383-389. (Supported by the Deutsche Forschungsgemeinschaft and the Heinrich und Fritz Riese-Stiftung. Authors affiliated with Johann Wolfgang Goethe-University Frankfurt, Germany; University of Massachusetts Medical School, MA.)

607. Steinlechner S. 2012. Chapter 2.12: Biological rhythms of the mouse. In *The Laboratory Mouse* H Hedrich, ed. San Diego, CA: Elsevier. p. 383-407. (Support not reported. Author affiliated with University of Veterinary Medicine, Germany.)

608. Stevens RG. 1987. Electric power use and breast cancer: a hypothesis. *Am J Epidemiol* 125(4): 556-561. (Supported by the US Department of Energy. Author affiliated with Pacific Northwest Laboratory, WA.)

609. Stevens RG. 2009. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol* 38(4): 963-970. (Supported by NIEHS. Author affiliated with University of Connecticut Health Center, CT.)

610. Stevens RG. 2012. Does electric light stimulate cancer development in children? *Cancer Epidemiol Biomarkers Prev* 21(5): 701-704. (Supported by Children with Cancer UK. Author affiliated with University of Connecticut Health Center, CT.)

611. Stevens RG. 2017. Letter in reference to Vistisen *et al*: "Short-term effects of night shift work on breast cancer risk: a cohort study of payroll data". *Scand J Work Environ Health* 43(1): 95. (Support not reported. Author affiliated with University of Connecticut, CT.)

612. Stevens RG, Brainard GC, Blask DE, Lockley SW, Motta ME. 2014. Breast cancer and circadian disruption from electric lighting in the modern world. *CA Cancer J Clin* 64(3): 207-218. (Supported by the Institute for Integrative Health, NCI, and the National Space Biomedical Research Institute. Authors affiliated with Thomas Jefferson Medical College, PA; Tulane University School of Medicine, LA; Harvard Medical School, MA; Tufts Medical School, MA.)

613. Stevens RG, Davis S. 1996. The melatonin hypothesis: electric power and breast cancer. *Environ Health Perspect* 104(Suppl 1): 135-140. (Supported by NCI and the US Department of Energy. Authors affiliated with Pacific Northwest Laboratory, WA; University of Washington, WA.)

614. Stevens RG, Davis S, Mirick DK, Kheifets L, Kaune W. 2000. Alcohol consumption and urinary concentration of 6-sulfatoxymelatonin in healthy women. *Epidemiology* 11(6): 660-665. (Supported by the Electric Power Research Institute, NCI, and NIH. Authors affiliated with University of Connecticut Health Center, CT; Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; Electric Power Research Institute, CA; EM Factors, WA.)

615. Stevens RG, Davis S, Thomas DB, Anderson LE, Wilson BW. 1992. Electric power, pineal function, and the risk of breast cancer. *FASEB J* 6(3): 853-860. (Supported by the US Department of Energy. Authors affiliated with Pacific Northwest Laboratory, WA; Fred Hutchinson Cancer Research Center, WA.)

616. Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, Castaño-Vinyals G, Davis S, Frings-Dresen MH, Fritschi L, Kogevinas M, Kogi K, Lie JA, Lowden A, Peplonska B, Pesch B, Pukkala E, Schernhammer E, Travis RC, Vermeulen R, Zheng T, Cogliano V, Straif K. 2011. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 68(2): 154-162. (Supported by the Health and Safety Executive and the German Social Accident Insurance. Authors affiliated with University of Connecticut Health Center, CT; Danish Cancer Society, Denmark; University of Milan, Italy; University of Minnesota, MN; Finnish Institute of Occupational Health, Finland; Queen's University, Canada; CREAL, Spain; IMIM-Hospital del Mar, Spain; Fred Hutchinson Cancer Research Center, WA; Academic Medical Center, Netherlands; University of Western Australia, Australia; Municipal Institute of Medical Research, Spain; Institute for Science of Labour, Japan; National Institute of Occupational Health, Norway; Stockholm University, Sweden; Nofer Institute of Occupational Medicine, Poland; Ruhr-University Bochum, Germany; Finnish Cancer Registry, Finland; Brigham and Women's Hospital and Harvard Medical School, MA;

University of Oxford, UK; University of Utrecht, Netherlands; Yale University School of Medicine, CT; IARC, France.)

617. Stevens RG, Rea MS. 2001. Light in the built environment: potential role of circadian disruption in endocrine disruption and breast cancer. *Cancer Causes Control* 12(3): 279-287. (Supported by the US Department of Energy. Authors affiliated with University of Connecticut Health Center, CT; Rensselaer Polytechnic Institute, NY.)

618. Stevens RG, Zhu Y. 2015. Electric light, particularly at night, disrupts human circadian rhythmicity: is that a problem? *Philos Trans R Soc Lond B Biol Sci* 370(1667). (Supported by the University of Connecticut and Yale University. Authors affiliated with University of Connecticut Health Center, CT; Yale University, CT.)

619. Storch KF, Lipan O, Leykin I, Viswanathan N, Davis FC, Wong WH, Weitz CJ. 2002. Extensive and divergent circadian gene expression in liver and heart. *Nature* 417(6884): 78-83. (Supported by the Edward R. and Anne G. Lefler Center, Harvard Medical School and the National Eye Institute, a Deutsche Forschungsgemeinschaft Postdoctoral Fellowship, the National Institute of Child Health and Human Development, and the National Human Genome Research Institute. Authors affiliated with Harvard Medical School, MA; Harvard School of Public Health, MA; Northeastern University, MA; Harvard University, MA.)

620. Stranges S, Dorn JM, Shipley MJ, Kandala NB, Trevisan M, Miller MA, Donahue RP, Hovey KM, Ferrie JE, Marmot MG, Cappuccio FP. 2008. Correlates of short and long sleep duration: a cross-cultural comparison between the United Kingdom and the United States: the Whitehall II Study and the Western New York Health Study. *Am J Epidemiol* 168(12): 1353-1364. (Supported by the Medical Research Council, the British Heart Foundation, the United Kingdom Health and Safety Executive, the United Kingdom Department of Health, the US National Heart, Lung, and Blood Institute, the US National Institute on Aging, the Agency for Health Care Policy and Research, US Department of Health and Human Services, the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health, the US National Institute on Alcohol Abuse and Alcoholism, and the US National Institutes of Health. Authors affiliated with University of Warwick Medical School, UK; State University of New York at Buffalo, NY; University College London Medical School, UK.)

621. Sturgeon SR, Doherty A, Reeves KW, Bigelow C, Stanczyk FZ, Ockene JK, Liu S, Manson JE, Neuhouser ML. 2014. Urinary levels of melatonin and risk of postmenopausal breast cancer: Women's health initiative observational cohort. *Cancer Epidemiol Biomarkers Prev* 23(4): 629-637. (Supported by NCI, the National Heart, Lung, and Blood Institute, NIH, and the U.S. Department of Health and Human Services. Authors affiliated with University of Massachusetts Amherst, MA; University of Massachusetts Medical School, MA; Harvard Medical School, MA; University of Southern California Keck School of Medicine, CA; Brown University, RI; Rhode Island Hospital, RI; Fred Hutchinson Cancer Research Center, WA.)

622. Suba Z. 2012. Light deficiency confers breast cancer risk by endocrine disorders. *Recent Pat Anticancer Drug Discov* 7(3): 337-344. (Support not reported. Author affiliated with Surgical and Molecular Tumor Pathology Centre, Hungary.)

623. Taheri S, Lin L, Austin D, Young T, Mignot E. 2004. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 1(3): e62. (Supported by NIH and the Howard Hughes Medical Institute. Authors affiliated with Stanford University, CA; University of Wisconsin, WI.)

624. Tai SY, Huang SP, Bao BY, Wu MT. 2016. Urinary melatonin-sulfate/cortisol ratio and the presence of prostate cancer: A case-control study. *Sci Rep* 6: 29606. (Supported by the Kaohsiung Medical University Hospital, the Institute of Labor, Occupational Safety and Health, Ministry of Labor, the Ministry of Science and Technology, Taiwan's National Health Research Institutes, and the Research Center for Environmental Medicine, Kaohsiung Medical University. Authors affiliated with Kaohsiung Medical University, Taiwan; Kaohsiung Municipal Ta-Tung Hospital, Taiwan; National Sun Yat-Sen University, Taiwan; China Medical University, Taiwan; China Medical University Hospital, Taiwan; Asia University, Taiwan; Kaohsiung Municipal Hsiao-Kang Hospital, Taiwan; Kaohsiung Medical University Hospital, Taiwan.)

625. Takahashi JS, Hong HK, Ko CH, McDearmon EL. 2008. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet* 9(10): 764-775. (Support not reported. Authors affiliated with Northwestern University, IL)

626. Talib WH. 2018. Melatonin and cancer hallmarks. *Molecules* 23(3): 518. (Supported by the Applied Science Private University, Amman, Jordan. Author affiliated with Applied Science Private University, Jordan.)

627. Talibov M, Pukkala E, Martinsen JI, Tryggvadottir L, Weiderpass E, Hansen J. 2018. Night-shift work and hematological cancers: a population based case-control study in three Nordic countries. *Scand J Work Environ Health* 44(3): 258-264. (No financial support recieved. Authors affiliated with University of Tampere, Finland; Finnish Cancer Registry, Finland; Cancer Registry of Norway, Norway; Icelandic Cancer Registry, Iceland; University of Iceland, Iceland; Karolinska Institutet, Sweden; University of Tromsø, Norway; Folkhälsan Research Center, Finland; Danish Cancer Society Research Center, Denmark.)

628. Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B. 1981. Melatonin inhibition and pinealectomy enhancement of 7,12-dimethylbenz(*a*)anthracene-induced mammary tumors in the rat. *Cancer Res* 41(11 Pt 1): 4432-4436. (Support not reported. Authors affiliated with NIH, MD.)

629. Taylor PJ, Pocock SJ. 1972. Mortality of shift and day workers 1956-68. *Br J Ind Med* 29(2): 201-207. (Support not reported. Authors affiliated with London School of Hygiene and Tropical Medicine, UK.)

630. Teboul M, Barrat-Petit MA, Li XM, Claustrat B, Formento JL, Delaunay F, Lévi F, Milano G. 2005. Atypical patterns of circadian clock gene expression in human peripheral blood mononuclear cells. *J Mol Med (Berl)* 83(9): 693-699. (Supported by the Ministère de la

Recherche, Association pour la Recherche sur le Cancer, and Fondation pour la Recherche Médicale. Authors affiliated with Université de Nice-Sophia Antipolis, France; Pôle universitaire St Jean D'Angely, France; Université Paris XI, France; Hôpital Neurocardiologique, France; Centre Antoine-Lacassagne, France.)

631. Temneanu RO, Motoc A, Zugun FE, Folescu R, Lupuşoru CE, Zamfir CL. 2012. The relevance of circadian rhythms disruption on pulmonary SOD expression in rat. *Rom J Morph Embryol* 53(3): 789-793. (Support not reported. Authors affiliated with "Grigore T. Popa" University of Medicine and Pharmacy, Romania; "Victor Babeş" University of Medicine and Pharmacy, Romania.)

632. Thapan K, Arendt J, Skene DJ. 2001. An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *J Physiol* 535(Pt 1): 261-267. (Supported by EUBIOMED2. Authors affiliated with University of Surrey, UK.)

633. Torpey E. 2015. *Careers for Night Owls and Early Birds*. U.S. Bureau of Labor Statistics. Published on 10/15. https://www.bls.gov/careeroutlook/2015/article/night-owls-and-early-birds.htm

634. Touitou Y, Motohashi Y, Reinberg A, Touitou C, Bourdeleau P, Bogdan A, Auzéby A. 1990. Effect of shift work on the night-time secretory patterns of melatonin, prolactin, cortisol and testosterone. *Eur J Appl Physiol Occup Physiol* 60(4): 288-292. (Supported by le Conseil Scientifique de l'Université P. et M. Curie [Formation recommandée par la Direction de la Recherche] and Caisse Nationale d'Assurance Maladie des Travailleurs Salariés. Authors affiliated with Faculté de Médecine Pitié-Salpêtrière, France; CNRS, France; Service Médical Shell Française, France.)

635. Touitou Y, Reinberg A, Touitou D. 2017. Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption. *Life Sci* 173: 94-106. (Support not reported. Authors affiliated with Fondation Ophtalmologique A. de Rothschild, France; UHSA - Groupe Hospitalier Paul Guiraud, France.)

636. Touvier M, Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, Riboli E, Hercberg S, Norat T. 2011. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 20(5): 1003-1016. (Supported by the World Cancer Research Fund. Authors affiliated with Imperial College London, UK; INSERM/INRA/CNAM/Paris13 University, France; University of Leeds, UK; Wageningen University and Research Centre, Netherlands.)

637. Travis RC, Balkwill A, Fensom GK, Appleby PN, Reeves GK, Wang XS, Roddam AW, Gathani T, Peto R, Green J, Key TJ, Beral V. 2016. Night shift work and breast cancer incidence: Three prospective studies and meta-analysis of published studies. *J Natl Cancer Inst* 108(12): djw169. (Supported by the UK Health and Safety Executive, Cancer Research UK, and the Medical Research Council. Authors affiliated with University of Oxford, UK; GlaxoSmithKline R&D, UK; Oxford University Hospitals NHS Trust, UK.)

638. Travis RC, Reeves GK, Peto R, Key TJ, Beral V. 2017. Response. *J Natl Cancer Inst* 109(4): djx008. (Support not reported. Authors affiliated with University of Oxford, UK.)

639. Travlos GS, Wilson RE, Murrell JA, Chignell CF, Boorman GA. 2001. The effect of short intermittent light exposures on the melatonin circadian rhythm and NMU-induced breast cancer in female F344/N rats. *Toxicol Pathol* 29(1): 126-136. (Support not reported. Authors affiliated with NIEHS, NC; Analytical Sciences, Inc., NC.)

640. Trivedi AK, Kumar V. 2014. Melatonin: an internal signal for daily and seasonal timing. *Indian J Exp Biol* 52(5): 425-437. (Support not reported. Authors affiliated with University of Delhi, India.)

641. Truong T, Liquet B, Menegaux F, Plancoulaine S, Laurent-Puig P, Mulot C, Cordina-Duverger E, Sanchez M, Arveux P, Kerbrat P, Richardson S, Guénel P. 2014. Breast cancer risk, nightwork, and circadian clock gene polymorphisms. *Endocr Relat Cancer* 21(4): 629-638. (Supported by the French National Institute of Cancer, the Fondation de France, the French Agency for Environmental and Occupational Health Safety [ANSES – ex-AFSSET], the French National Research Agency [ANR], and the League against Cancer. Authors affiliated with INSERM, France; Université Paris-Sud, France; MRC, UK; University of Queensland, Australia; Université Paris Descartes, France; Center Georges-François Leclerc, France; Center Eugène Marquis, France.)

642. Tsai RJ, Luckhaupt SE, Sweeney MH, Calvert GM. 2014. Shift work and cancer screening: do females who work alternative shifts undergo recommended cancer screening? *Am J Ind Med* 57(3): 265-275. (Supported by the U.S. government. Authors affiliated with NIOSH, OH.)

643. Tse LA, Lee PMY, Ho WM, Lam AT, Lee MK, Ng SSM, He Y, Leung KS, Hartle JC, Hu H, Kan H, Wang F, Ng CF. 2017. Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. *Environ Int* 107: 1-7. (Supported by the Health and Medical Research Fund, Hong Kong Special Administrative Region, China. Authors affiliated with Chinese University of Hong Kong, China; Prince of Wales Hospital, China; Guilin Medical College, China; Hong Kong Polytechnic University, China; San Jose State University, CA; University of Toronto, Canada; Fudan University, China.)

644. Tucker P, Folkard S. 2012. *Working Time, Health and Safety: A Research Synthesis Paper.* Conditions of Work and Employment Series No. 31. Geneva: International Labour Office. 67 pp. https://ideas.repec.org/p/ilo/ilowps/994704513402676.html.

645. Turek FW. 2016. Circadian clocks: Not your grandfather's clock. *Science* 354(6315): 992-993. (Support not reported. Author affiliated with Northwestern University, IL.)

646. Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J. 2005. Obesity and metabolic syndrome in circadian *Clock* mutant mice. *Science* 308(5724): 1043-1045. (Supported by NIH. Authors affiliated with Northwestern University and the Feinberg School of Medicine, IL; ENH Research Institute, IL; Howard Hughes Medical Institute, MD; University of Colorado Medical School, CO.)

647. Turner PL, Mainster MA. 2008. Circadian photoreception: ageing and the eye's important role in systemic health. *Br J Ophthalmol* 92(11): 1439-1444. (Supported by Advanced Medical Optics, Incorporated. Authors affiliated with University of Kansas School of Medicine, KS.)

648. Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. 1996. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control* 7(2): 197-204. (Support not reported. Authors affiliated with Cancer Registry of Norway, Norway; Radiation Protection Authority, Norway; University of Oslo, Norway.)

649. Ulas T, Buyukhatipoglu H, Kirhan I, Dal MS, Eren MA, Hazar A, Demir ME, Aydogan T, Karababa F, Uyanikoglu A, Kurkcuoglu IC. 2012. The effect of day and night shifts on oxidative stress and anxiety symptoms of the nurses. *Eur Rev Med Pharmacol Sci* 16(5): 594-599. (Support not reported. Authors affiliated with Harran University, Turkey; Dicle University, Turkey.)

650. Ulhôa MA, Marqueze EC, Burgos LG, Moreno CR. 2015. Shift work and endocrine disorders. *Int J Endocrinol* 2015: 826249. (Supported by FAPESP. Authors affiliated with UNEC, Brazil; IMES, Brazil; Catholic University of Santos, Brazil; University of São Paulo, Brazil; Stockholm University, Sweden.)

651. UNESCO. 2015. *About the Year of Light*. United Nations Educational, Scientific, and Cultural Organization. Last accessed: 3/21/18. http://www.light2015.org/Home/About.html

652. Ünsal-Kaçmaz K, Mullen TE, Kaufmann WK, Sancar A. 2005. Coupling of human circadian and cell cycles by the timeless protein. *Mol Cell Biol* 25(8): 3109-3116. (Supported by NIH, NCI, and NIEHS. Authors affiliated with University of North Carolina, NC.)

653. Uth K, Sleigh R. 2014. Deregulation of the circadian clock constitutes a significant factor in tumorigenesis: a clockwork cancer. Part I: clocks and clocking machinery. *Biotechnol Biotechnol Equip* 28(2): 176-183. (Support not reported. Authors affiliated with CMCBR, UK.)

654. Uzoigwe CE, Sanchez Franco LC. 2018. Night shifts: chronotype and social jetlag. *BMJ* 361: k1666. (Support not reported. Authors affiliated with Harcourt House, UK; Stepping Hill Hospital, UK.)

655. van den Heiligenberg S, Deprés-Brummer P, Barbason H, Claustrat B, Reynes M, Lévi F. 1999. The tumor promoting effect of constant light exposure on diethylnitrosamine-induced hepatocarcinogenesis in rats. *Life Sci* 64(26): 2523-2534. (Supported by INSERM, ARTBC, Hôpital Paul Brousse, and the "Dr. Saal van Zwanenbergstichting." Authors affiliated with Université Paris XI, France; Hôpital Paul Brousse, France; Hôpital Neurocardiologique, France; Service de Cancérologie Expérimentale, Belgium.)

656. van der Lely S, Frey S, Garbazza C, Wirz-Justice A, Jenni OG, Steiner R, Wolf S, Cajochen C, Bromundt V, Schmidt C. 2015. Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. *J Adolesc Health* 56(1): 113-119. (Supported by Jacobs Foundation, Zurich, Switzerland.

Authors affiliated with Psychiatric Hospital of the University of Basel, Switzerland; University Children's Hospital Zürich, Switzerland; University of Basel, Switzerland; Ilmenau University of Technology, Germany.)

657. Van der Maren S, Moderie C, Duclos C, Paquet J, Daneault V, Dumont M. 2018. Daily profiles of light exposure and evening use of light-emitting devices in young adults complaining of a delayed sleep schedule. *J Biol Rhythms* 33(2): 192-202. (Supported by the Natural Sciences and Engineering Research Council of Canada, the Université de Montréal, Fonds de la Recherche du Québec-Santé [FRQS], and NSERC. Authors affiliated with Sacre-Coeur Hospital of Montreal, Canada; University of Montreal, Canada.)

658. Van Dycke KC, Rodenburg W, van Oostrom CT, van Kerkhof LW, Pennings JL, Roenneberg T, van Steeg H, van der Horst GT. 2015. Chronically alternating light cycles increase breast cancer risk in mice. *Curr Biol* 25(14): 1932-1937. (Supported by the RIVM Strategic Programme and the Dutch Ministry of Social Affairs and Employment. Authors affiliated with National Institute for Public Health and the Environment, Netherlands; Erasmus University Medical Center, Netherlands; Ludwig-Maximilian University, Germany; Leiden University Medical Center, Netherlands.)

659. van Mark A, Weiler SW, Schröder M, Otto A, Jauch-Chara K, Groneberg DA, Spallek M, Kessel R, Kalsdorf B. 2010. The impact of shift work induced chronic circadian disruption on IL-6 and TNF-α immune responses. *J Occup Med Toxicol* 5: 18. (Support not reported. Authors affiliated with University of Lübeck, Germany; AUDI AG Ingolstadt, Germany; Free University and Humboldt-University, Germany; EUGT, Germany; Research Center Borstel, Germany.)

660. VanderWeele DJ, Brown CD, Taxy JB, Gillard M, Hatcher DM, Tom WR, Stadler WM, White KP. 2014. Low-grade prostate cancer diverges early from high grade and metastatic disease. *Cancer Sci* 105(8): 1079-1085. (Supported by the AACI Fellowship for Translational Cancer Research and DOD Prostate Cancer Research Program PRTA and the Chicago Cancer Genomes Project. Authors affiliated with University of Chicago, IL; University of Pennsylvania, PA; NorthShore University Health System, IL.)

661. Vangelova KK. 2008. Variations of cortisol, fatigue and sleep disturbances in sound engineers: effect of job task and fast backward-rotating shifts. *Rev Environ Health* 23(1): 83-89. (Support not reported. Authors affiliated with National Center of Public Health Protection, Bulgaria.)

662. Verkasalo PK, Pukkala E, Stevens RG, Ojamo M, Rudanko SL. 1999. Inverse association between breast cancer incidence and degree of visual impairment in Finland. *Br J Cancer* 80(9): 1459-1460. (Supported by the Academy of Finland, the Finnish Cancer Foundation, and the US Department of Energy. Authors affiliated with University of Helsinki, Finland; National Public Health Institute, Finland; Finnish Cancer Registry, Finland; Pacific Northwest National Laboratory, WA; Finnish Register of Visual Impairment, Finland.)

663. Vermeulen R. 2016. *Types and Characteristics of Shift Work and the Concept of Shift Work as a Complex Exposure Scenario.* Universitat Utrecht, Institute for Risk Assessment Science. 26 pp.

664. Vinogradova IA, Anisimov VN, Bukalev AV, Ilyukha VA, Khizhkin EA, Lotosh TA, Semenchenko AV, Zabezhinski MA. 2010. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in young but not in old rats. *Aging (Albany NY)* 2(2): 82-92. (Supported by the President of the Russian Federation and the Russian Foundation for Basic Research. Authors affiliated with Petrozavodsk State University, Russia; N.N. Petrov Research Institute of Oncology, Russia; Russian Academy of Sciences, Russia.)

665. Vinogradova IA, Anisimov VN, Bukalev AV, Semenchenko AV, Zabezhinski MA. 2009. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats. *Aging (Albany NY)* 1(10): 855-865. (Supported by the President of the Russian Federation, the Russian Foundation for Basic Research, and the Russian Foundation for Humanistic Research. Authors affiliated with Petrozavodsk State University, Russia; N.N. Petrov Research Institute of Oncology, Russia.)

666. Vinogradova IA, Chernova IV. 2006. [Effect of light regimens on the age dynamics of estrous function and serum prolactin level in rats]. *Adv Gerontol* 19: 60-65. (Support unknown due to foreign language. Authors affiliated with Petrozavodsk State University, Russia.)

667. Viola AU, James LM, Schlangen LJ, Dijk DJ. 2008. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand J Work Environ Health* 34(4): 297-306. (Supported by Philips Lighting. Authors affiliated with University of Surrey, UK; Philips Lighting, Netherlands.)

668. Vistisen HT, Garde AH, Frydenberg M, Christiansen P, Hansen AM, Andersen J, Bonde JP, Kolstad HA. 2017. Short-term effects of night shift work on breast cancer risk: a cohort study of payroll data. *Scand J Work Environ Health* 43(1): 59-67. (Supported by the Danish Work Environment Research Fund and NordForsk, Nordic Program on Health and Welfare. Authors affiliated with Aarhus University Hospital, Denmark; National Research Centre for the Working Environment, Denmark; Aarhus University, Denmark; Danish Breast Cancer Corporative Group, Denmark; University of Copenhagen, Denmark; Danish Cancer Society Research Center, Denmark; Bispebjerg University Hospital, Denmark.)

669. Viswanathan AN, Hankinson SE, Schernhammer ES. 2007. Night shift work and the risk of endometrial cancer. *Cancer Res* 67(21): 10618-10622. (Supported by NIH. Authors affiliated with Dana-Farber Cancer Institute, MA; Harvard Medical School, MA; Brigham and Women's Hospital, MA; Applied Cancer Research-Institute for Translational Research Vienna, Austria; Harvard School of Public Health, MA.)

670. VoPham T, Weaver MD, Vetter C, Hart JE, Tamimi RM, Laden F, Bertrand KA. 2018. Circadian misalignment and hepatocellular carcinoma incidence in the United States. *Cancer Epidemiol Biomarkers Prev* 27(7): 719-727. (Supported by NIH and NHLBI. Authors affiliated with Harvard T.H. Chan School of Public Health, MA; Brigham and Women's Hospital, MA; Harvard Medical School, MA; University of Colorado, CO; Broad Institute of Harvard and MIT, MA; Slone Epidemiology Center at Boston University, MA.)

671. Wada K, Nakamura K, Tamai Y, Tsuji M, Masue T, Watanabe K, Ando K, Nagata C. 2013. Associations of urinary 6-sulfatoxymelatonin with demographics, body mass, sex steroids, and lifestyle factors in preschool Japanese children. *Ann Epidemiol* 23(2): 60-65. (Supported by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labor, and Welfare of Japan. Authors affiliated with Gifu University Graduate School of Medicine, Japan; Aichi Bunkyo Women's College, Japan.)

672. Wahnschaffe A, Haedel S, Rodenbeck A, Stoll C, Rudolph H, Kozakov R, Schoepp H, Kunz D. 2013. Out of the lab and into the bathroom: evening short-term exposure to conventional light suppresses melatonin and increases alertness perception. *Int J Mol Sci* 14(2): 2573-2589. (Supported by BMBF. Authors affiliated with Charité–Universitätsmedizin Berlin, Germany; Trilux GmbH & Co.KG, Germany; Leibniz Institute for Plasma Science and Technology, Germany; German Heart Institute, Germany.)

673. Walasa WM, Carey RN, Si S, Fritschi L, Heyworth JS, Fernandez RC, Boyle T. 2018. Association between shiftwork and the risk of colorectal cancer in females: a population-based case-control study. *Occup Environ Med* 75: 344-350. (Supported by the Australian National Health and Medical Research Council, the University of Adelaide, NHMRC, Canadian Institutes of Health Research, and the Cancer Council Western Australia. Authors affiliated with Curtin University, Australia; University of Western Australia, Australia; University of Adelaide, Australia; University of South Australia, Australia.)

674. Waldrop RD, Saydjari R, Rubin NH, Rayford PL, Townsend CM, Jr., Thompson JC. 1989. Photoperiod influences the growth of colon cancer in mice. *Life Sci* 45(8): 737-744. (Support not reported. Authors affiliated with University of Texas Medical Branch, TX; University of Arkansas for Medical Sciences Little Rock, AR.)

675. Wang F, Yeung KL, Chan WC, Kwok CC, Leung SL, Wu C, Chan EY, Yu IT, Yang XR, Tse LA. 2013. A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. *Ann Oncol* 24(11): 2724-2732. (Supported by the Research Grants Council of Hong Kong. Authors affiliated with Chinese University of Hong Kong, China; North District Hospital, China; Princess Margaret Hospital, China; Yan Chai Hospital, China; NCI, MD.)

676. Wang P, Ren FM, Lin Y, Su FX, Jia WH, Su XF, Tang LY, Ren ZF. 2015a. Night-shift work, sleep duration, daytime napping, and breast cancer risk. *Sleep Med* 16(4): 462-468. (Supported by the National Natural Science Foundation of China and the Guangdong Provincial Natural Science Foundation. Authors affiliated with Sun Yat-sen University, China; Chinese University of Hong Kong, China; CUHK Shenzhen Research Institute, China.)

677. Wang X, Ji A, Zhu Y, Liang Z, Wu J, Li S, Meng S, Zheng X, Xie L. 2015b. A meta-analysis including dose-response relationship between night shift work and the risk of colorectal cancer. *Oncotarget* 6(28): 25046-25060. (Supported by the National Natural Science Foundation of China, the Scientific research foundation of the ministry of public health, and the Zhejiang province key project of science and technology. Authors affiliated with Zhejiang University, China.)

678. Wang XS, Armstrong ME, Cairns BJ, Key TJ, Travis RC. 2011. Shift work and chronic disease: the epidemiological evidence. *Occup Med (Lond)* 61(2): 78-89. (Supported by the Health and Safety Executive, UK, Cancer Research UK, and the Medical Research Council, UK. Authors affiliated with University of Oxford, UK.)

679. Wang XS, Tipper S, Appleby PN, Allen NE, Key TJ, Travis RC. 2014. First-morning urinary melatonin and breast cancer risk in the guernsey study. *Am J Epidemiol* 179(5): 584-593. (Supported by Cancer Research UK and the Lloyds TSB Charitable Foundation for the Channel Islands. Authors affiliated with University of Oxford, UK.)

680. Waters MA, Grajewski B, Pinkerton LE, Hein MJ, Zivkovich Z. 2009. Development of historical exposure estimates of cosmic radiation and circadian rhythm disruption for cohort studies of Pan Am flight attendants. *Am J Ind Med* 52(10): 751-761. (Support not reported. Authors affiliated with NIOSH, OH.)

681. WCRF. 2018. *Continuous Update Project: Diet, Nutrition, Physical Activity and Breast Cancer*. World Cancer Research Fund/American Institute for Cancer Research. Last accessed: 5/4/18. http://dietandcancerreport.org

682. WebFinance. 2018. *Compressed Workweek*. WebFinance, Inc. Last accessed: 6/14/18. http://www.businessdictionary.com/definition/compressed-workweek.html

683. Wegrzyn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, Laden F, Willett WC, Hankinson SE, Schernhammer ES. 2017. Rotating night shift work and risk of breast cancer in the nurses' health studies. *Am J Epidemiol* 186(5): 532-540. (Supported by the CDC, NIOSH, and NIH. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard T.H. Chan School of Public Health, MA; University of Massachusetts, MA; University of Connecticut Health Center, CT; Medical University of Vienna, Austria; Applied Cancer Research-Institution for Translational Research Vienna, Austria.)

684. Wehrens SMT, Christou S, Isherwood C, Middleton B, Gibbs MA, Archer SN, Skene DJ, Johnston JD. 2017. Meal timing regulates the human circadian system. *Curr Biol* 27(12): 1768-1775. (Supported by the UK Biotechnology and Biological Sciences Research Council. Authors affiliated with University of Surrey, UK.)

685. Weibel L, Brandenberger G. 1998. Disturbances in hormonal profiles of night workers during their usual sleep and work times. *J Biol Rhythms* 13(3): 202-208. (Support not reported. Authors affiliated with Institut de Physiologie-Faculté de Médecine, France)

686. Wendeu-Foyet MG, Bayon V, Cénée S, Trétarre B, Rébillard X, Cancel-Tassin G, Cussenot O, Lamy PJ, Faraut B, Kheder SB, Léger D, Menegaux F. 2018. Night work and prostate cancer risk: Results from the EPICAP study. *OEM* 75(8): 573-581. (Supported by the Institut National du Cancer, Fondation ARC, the Ligue nationale contre le cancer, the Ligue contre le cancer du Val-de-Marne, Fondation de France, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [ANSES], and Paris-Sud University. Authors affiliated with INSERM, France; Hôtel Dieu, France; VIFASOM, France; Hérault Cancer Registry, France; Clinique Beau Soleil, France; Hopital Tenon, France; Sorbonne Université, France; Imagenome, France.)

687. White AJ, Weinberg CR, Park YM, D'Aloisio AA, Vogtmann E, Nichols HB, Sandler DP. 2017. Sleep characteristics, light at night and breast cancer risk in a prospective cohort. *Int J Cancer* 141(11): 2204-2214. (Supported by NIH. Authors affiliated with NIEHS, NC; NIH, NC; Social & Scientific Systems, Inc., NC; University of North Carolina, NC.)

688. Wille JJ, Jr. 2003. Circadian rhythm of tumor promotion in the two-stage model of mouse tumorigenesis. *Cancer Lett* 190(2): 143-149. (Supported by NIDDK. Author affiliated with Southern Research Institute, AL.)

689. Winter M, Blettner M, Zeeb H. 2014. Prevalence of risk factors for breast cancer in German airline cabin crew: a cross-sectional study. *J Occup Med Toxicol* 9: 27. (Support not reported. Authors affiliated with Johannes Gutenberg University Mainz, Germany; Leibniz Institute for Prevention Research and Epidemiology-BIPS, Germany; University of Bremen, Germany.)

690. Wirth MD, Andrew ME, Burchfiel CM, Burch JB, Fekedulegn D, Hartley TA, Charles LE, Violanti JM. 2017. Association of shiftwork and immune cells among police officers from the Buffalo Cardio-Metabolic Occupational Police Stress study. *Chronobiol Int*: 1-11. (Supported by NIOSH. Authors affiliated with University of South Carolina, SC; Connecting Health Innovations, SC; NIOSH, WV; WJB Dorn VA Medical Center, SC; State University of New York, NY.)

691. Wirth MD, Burch J, Shivappa N, Steck SE, Hurley TG, Vena JE, Hébert JR. 2014a. Dietary inflammatory index scores differ by shift work status: NHANES 2005 to 2010. *J Occup Environ Med* 56(2): 145-148. (Supported by the South Carolina Statewide Cancer Prevention and Control Program, NCI, and the University of South Carolina Office of Research and by the South Carolina Cancer. Authors affiliated with University of South Carolina, SC; WJB Dorn VA Medical Center, SC; University of Georgia, GA.)

692. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, Andrew ME, Hartley TA, Miller DB, Mnatsakanova A, Charles LE, Steck SE, Hurley TG, Vena JE, Hébert JR. 2014b. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. *J Occup Environ Med* 56(9): 986-989. (Supported by NIOSH, the University of South Carolina Office of Research and by the South Carolina Cancer Prevention and Control Research Network funded under a Cooperative Agreement from the Centers for Disease Control and Prevention and the National Cancer Institute. Authors affiliated with University of South Carolina, SC; WJB Dorn VA Medical Center, SC; State University of New York, NY; CDC, WV; University of Georgia, GA.)

693. Wittenbrink N, Ananthasubramaniam B, Münch M, Koller B, Maier B, Weschke C, Bes F, de Zeeuw J, Nowozin C, Wahnschaffe A, Wisniewski S, Zaleska M, Bartok O, Ashwal-Fluss R, Lammert H, Herzel H, Hummel M, Kadener S, Kunz D, Kramer A. 2018. High-accuracy determination of internal circadian time from a single blood sample. *J Clin Invest* 128(9): 3826-3839. (Supported by the Bundesministerium für Bildung und Forschung, Germany, and Intellux Berlin GmbH, Germany. Authors affiliated with Charité Universitätsmedizin Berlin, Germany; Humboldt-Universität zu Berlin, Germany; St-

Hedwig-Krankenhaus, Germany; Intellux Berlin GmbH, Germany; Hebrew University, Israel; Brandeis University, MA;)

694. Wood B, Rea MS, Plitnick B, Figueiro MG. 2013. Light level and duration of exposure determine the impact of self-luminous tablets on melatonin suppression. *Appl Ergon* 44(2): 237-240. (Supported by Sharp Laboratories of America. Authors affiliated with Rensselaer Polytechnic Institute, NY.)

695. Wood PA, Yang X, Taber A, Oh EY, Ansell C, Ayers SE, Al-Assaad Z, Carnevale K, Berger FG, Peña MM, Hrushesky WJ. 2008. *Period 2* mutation accelerates *Apc*$^{Min/+}$ tumorigenesis. *Mol Cancer Res* 6(11): 1786-1793. (Supported by the NIH Centers of Biomedical Research Excellence [COBRE] and COBRE Pathology and Animal Core. Authors affiliated with University of South Carolina, SC.)

696. Wu AH, Stanczyk FZ, Wang R, Koh WP, Yuan JM, Yu MC. 2013. Sleep duration, spot urinary 6-sulfatoxymelatonin levels and risk of breast cancer among Chinese women in Singapore. *Int J Cancer* 132(4): 891-896. (Supported by NCI. Authors affiliated with University of Southern California Keck School of Medicine, CA; University of Pittsburgh Cancer Institute, PA; National University of Singapore, Singapore.)

697. Wu G, Ruben MD, Schmidt RE, Francey LJ, Smith DF, Anafi RC, Hughey JJ, Tasseff R, Sherrill JD, Oblong JE, Mills KJ, Hogenesch JB. 2018. Population-level rhythms in human skin with implications for circadian medicine. *Proc Natl Acad Sci U S A*. (Supported by Proctor and Gamble, the National Institute of Neurological Disorders and Stroke, the National Human Genome Research Institute, the Defense Advanced Research Projects Agency, and the National Institute of General Medical Sciences. Authors affiliated with Cincinnati Children's Hospital Medical Center, OH; University of Cincinnati School of Medicine, OH; Perelman School of Medicine at the University of Pennsylvania, PA; Vanderbilt University School of Medicine, TN; Procter & Gamble Company, OH.)

698. Wu J, Dauchy RT, Tirrell PC, Wu SS, Lynch DT, Jitawatanarat P, Burrington CM, Dauchy EM, Blask DE, Greene MW. 2011. Light at night activates IGF-1R/PDK1 signaling and accelerates tumor growth in human breast cancer xenografts. *Cancer Res* 71(7): 2622-2631. (Supported by the Stephen C. Clark Fund, E. Donnall Thomas Resident Research Fund, the American Association for Laboratory Animal Science Grants for Laboratory Animal Science [GLAS] Award, and a Tulane University School of Medicine and Louisiana Cancer Research Consortium Startup Grant. Authors affiliated with Bassett Healthcare Network, NY; Tulane University School of Medicine and Tulane Cancer Center, LA.)

699. Wu J, Sánchez de la Peña S, Halberg F, Cornélissen G, Wetterberg L, Halberg E, Lakatua D, Bingham C, Harvey J, Bazin H, Zheng T, Leung B, Tran B. 1988. Chronosynergistic effects of lighting schedule-shift and cefodizime on plasmacytoma growth and host survival time. *Chronobiologia* 15(1-2): 105-128. (Supported by the U.S. Public Health Service, Colin Medical Instruments, Komaki, Japan, Hoechst Foundation, Milan, Italy, Medtronic Inc., Minneapolis, MN, USA, Minnesota Medical Foundation, Earl Bakken and Dr. Betty Sullivan Funds. Authors affiliated with Chengdu College of Traditional Chinese Medicine, China; University of Minnesota, MN; St. Göran's Hospital and Karolinska

Institute, Sweden; St. Paul-Ramsey Medical Center, MN; Université Catholique de Louvain, Belgium; Beijing University of Medical Sciences, China.)

700. Wu M, Zeng J, Chen Y, Zeng Z, Zhang J, Cai Y, Ye Y, Fu L, Xian L, Chen Z. 2012. Experimental chronic jet lag promotes growth and lung metastasis of Lewis lung carcinoma in C57BL/6 mice. *Oncol Rep* 27(5): 1417-1428. (Supported by the National Natural Science Foundation of China and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry of China. Authors affiliated with Sun Yat-Sen University, China.)

701. Wu MW, Cai YC, Sun JA, Yang H, Li JL, Wang L, Zhang JX, Zhu L, Xian LJ. 2010. Effects of experimental chronic jet lag on hematological and immune parameters in mice. *Biol Rhythm Res* 41(5): 363-378. (Supported by the National Natural Science Foundation of China, and by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry, PR China. Authors affiliated with Sun Yat-sen University, China; Guangxi Medical University, China.)

702. Wu MW, Li XM, Xian LJ, Lévi F. 2004. Effects of meal timing on tumor progression in mice. *Life Sci* 75(10): 1181-1193. (Supported by the Programme de Recherches Avancées de Coopération Franco-Chinoises, INSERM ARTBC, Hôpital Paul Brousse, and the Villejuif [France] Clinical Key Program of the Ministry of Public Health of P.R. China. Authors affiliated with ISERM, France; Sun Yat-sen University, China.)

703. Xiao Q, Signorello LB, Brinton LA, Cohen SS, Blot WJ, Matthews CE. 2016. Sleep duration and breast cancer risk among black and white women. *Sleep Med* 20: 25-29. (Supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Authors affiliated with NIH, MD; International Epidemiology Institute, MD; Vanderbilt University Medical Center, TN.)

704. Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, Ueda M, Block GD, Sakaki Y, Menaker M, Tei H. 2000. Resetting central and peripheral circadian oscillators in transgenic rats. *Science* 288(5466): 682-685. (Supported by NIH, the Japanese Ministry of Education, Science, Sports, and Culture, and the Japanese Ministry of Health and Welfare. Authors affiliated with University of Virginia, VA; University of Tokyo, Japan; Y.S. New Technology Institute Inc., Japan.)

705. Yang WS, Deng Q, Fan WY, Wang WY, Wang X. 2014. Light exposure at night, sleep duration, melatonin, and breast cancer: a dose-response analysis of observational studies. *Eur J Cancer Prev* 23(4): 269-276. (Supported by Health Science and Technology Project from Jiangxi Provincial Health Department of China. Authors affiliated with Jiujiang University, China.)

706. Yang X, Wood PA, Ansell CM, Quiton DF, Oh EY, Du-Quiton J, Hrushesky WJ. 2009a. The circadian clock gene Per1 suppresses cancer cell proliferation and tumor growth at specific times of day. *Chronobiol Int* 26(7): 1323-1339. (Support not reported. Authors affiliated with WJB Dorn Veterans Affairs Medical Center, SC; University of South Carolina, SC.)

707. Yang X, Wood PA, Oh EY, Du-Quiton J, Ansell CM, Hrushesky WJ. 2009b. Down regulation of circadian clock gene Period 2 accelerates breast cancer growth by altering its daily growth rhythm. *Breast Cancer Res Treat* 117(2): 423-431. (Support not reported. Authors affiliated with WJB Dorn VA Medical Center, SC; University of South Carolina, SC.)

708. Yasuniwa Y, Izumi H, Wang K-Y, Shimajiri S, Sasaguri Y, Kawai K, Kasai H, Shimada T, Miyake K, Kashiwagi E, Hirano G, Kidani A, Akiyama M, Han B, Wu Y, Ieiri I, Higuchi S, Kohno K. 2010. Circadian disruption accelerates tumor growth and angio/stromagenesis through a wnt signaling pathway. *PLoS One* 5(12): e15330. (Supported by KAKENHI and the UOEH Grants for Advanced Research and the Vehicle Racing Commemorative Foundation. Authors affiliated with University of Occupational and Environmental, Japan; Kyushu University, Japan; Nihon Medical School, Japan; China Medical University, China.)

709. Yeh CR, Da J, Song W, Fazili A, Yeh S. 2014. Estrogen receptors in prostate development and cancer. *Am J Clin Exp Urol* 2(2): 161-168. (Support not reported. Authors affiliated with University of Rochester Medical Center, NY.)

710. Yong LC, Li J, Calvert GM. 2017. Sleep-related problems in the US working population: prevalence and association with shiftwork status. *Occup Environ Med* 74(2): 93-104. (Support not reported. Authors affiliated with NIOSH, OH.)

711. Yong M, Blettner M, Emrich K, Nasterlack M, Oberlinner C, Hammer GP. 2014a. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. *Scand J Work Environ Health* 40(5): 502-510. (Supported by the Deutsche Gesetzliche Unfallversicherung. Authors affiliated with BASF SE, Germany; Johannes Gutenberg University Mainz, Germany; Laboratoire National de Santé, Luxembourg.)

712. Yong M, Fischer D, Germann C, Lang S, Vetter C, Oberlinner C. 2016. Are chronotype, social jetlag and sleep duration associated with health measured by Work Ability Index? *Chronobiol Int* 33(6): 721-729. (Support not reported. Authors affiliated with BASF Societas Europaea, Germany; Ludwig-Maximilians-University, Germany; Brigham and Women's Hospital and Harvard Medical School, MA.)

713. Yong M, Nasterlack M, Messerer P, Oberlinner C, Lang S. 2014b. A retrospective cohort study of shift work and risk of cancer-specific mortality in German male chemical workers. *Int Arch Occup Environ Health* 87(2): 175-183. (Support not reported. Authors affiliated with BASF Societas Europaea, Germany.)

714. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. 2000. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol* 526 Pt 3: 695-702. (Supported by the National Aeronautics and Space Administration, the National Institute of Mental Health, National Heart, Lung, and Blood Institute, the National Institute on Aging, National Space Biomedical Research Institute, the National Institute of General Medical Sciences, the General Clinical Research Center Program of the National Center for Research Resources, and a Phillips fellowship. Authors

affiliated with Harvard Medical School, MA; Brigham and Women's Hospital, MA; Harvard University, MA; Massachusetts General Hospital, MA; MIT Division of Health Sciences and Technology, MA.)

715. Zeng ZL, Wu MW, Sun J, Sun YL, Cai YC, Huang YJ, Xian LJ. 2010. Effects of the biological clock gene *Bmal1* on tumour growth and anti-cancer drug activity. *J Biochem* 148(3): 319-326. (Supported by the Clinical Key Program of Public Health Ministry, P. R. China and the National Natural Science Fund, P. R. China. Authors affiliated with Sun Yat-sen University, China.)

716. Zheng H, Patel M, Hryniewicz K, Katz SD. 2006. Association of extended work shifts, vascular function, and inflammatory markers in internal medicine residents: a randomized crossover trial. *JAMA* 296(9): 1049-1050. (Supported by NIH and the National Heart, Lung, and Blood Institute. Authors affiliated with Yale University School of Medicine, CT.)

717. Zhu Y, Stevens RG, Hoffman AE, FitzGerald LM, Kwon EM, Ostrander EA, Davis S, Zheng TZ, Stanford JL. 2009. Testing the circadian gene hypothesis in prostate cancer: A population-based case-control study. *Cancer Res* 69(24): 9315-9322. (Supported by NIH, the Fred Hutchinson Cancer Research Center, Yale University and the National Human Genome Research Institute. Authors affiliated with Yale University School of Medicine, CT; University of Connecticut Health Center, CT; Fred Hutchinson Cancer Research Center, WA; NIH, MD.)

718. Zhu Y, Stevens RG, Hoffman AE, Tjonneland A, Vogel UB, Zheng T, Hansen J. 2011. Epigenetic impact of long-term shiftwork: pilot evidence from circadian genes and whole-genome methylation analysis. *Chronobiol Int* 28(10): 852-861. (Supported by NIEHS, Yale University, and the Danish Cancer Society. Authors affiliated with Yale University School of Medicine, CT; University of Connecticut Health Center, CT; Danish Cancer Society, Denmark; National Research Centre for the Working Environment, Denmark.)

719. Zielinska-Dabkowska KM. 2018. Make lighting healthier. *Nature* 553(7688): 274-276. (Support not reported. Author affiliated with Gdansk University of Technology, Poland.)

720. Zienolddiny S, Haugen A, Lie JA, Kjuus H, Anmarkrud KH, Kjærheim K. 2013. Analysis of polymorphisms in the circadian-related genes and breast cancer risk in Norwegian nurses working night shifts. *Breast Cancer Res* 15(4): R53. (Supported by the Research Council of Norway and the Norwegian Cancer Society. Authors affiliated with National Institute of Occupational Health, Norway; Institute of Population-based Cancer Research, Norway.)

721. Zubidat AE, Haim A. 2017. Artificial light-at-night – a novel lifestyle risk factor for metabolic disorder and cancer morbidity. *J Basic Clin Physiol Pharmacol* 28(4): 295-313. (No support received. Authors affiliated with University of Haifa, Israel.)

National Toxicology Program
U.S. Department of Health and Human Services

NTP Cancer Hazard Assessment on Night Shift Work and Light at Night

Appendices

November 2020

National Toxicology Program
U.S. Department of Health and Human Services

NTP Cancer Hazard Assessment on Shift Work and Light at Night

Appendix A: Literature Search Strategy

November 2020

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

Appendix A: Literature Search Strategy

Introduction

The objective of the literature search is to identify published literature that is relevant for evaluating the potential carcinogenicity of circadian disruption and/or light at night. As discussed in the Concept Document for shift work, light at night, and circadian disruption (NTP 2014), the goal of the literature search strategy is to identify information on environmental exposures associated with circadian disruption and/or light at night for the broad range of subjects covered by a NTP report, as listed below:

- Properties and Human Exposure (focusing on the U.S. population)
- Human Cancer Studies
- Studies of Cancer in Experimental Animals
- Mechanisms and Other Relevant Effects

A.1 General approach

Database searching encompasses selecting databases and search terms and conducting the searches. Searches of several citation databases are generally conducted using search terms for the individual environmental exposures, combined with search terms for cancer and/or specific topics, including epidemiological and mechanistic studies. A critical step in the process involves consultation with an information specialist to develop relevant search terms. These terms are used to search bibliographic databases.

Citation databases, including PubMed, Scopus, and Web of Science, were searched up until December 2017 for epidemiological studies evaluating cancer and shift work, light at night, or transmeridian travel using the strategy outlined in the table below. In addition, searches were conducted to identify other types of unnatural light exposures (such as the use of consumer electronics or exposure scenarios associated with social jet lag). Because this exposure scenario is less defined than the other exposure scenarios, these search terms were limited (e.g., combined using the word “and”) by terms focused for circadian disruption before being combined with epidemiological and cancer search strings. Cancer studies measuring biomarker-related circadian disruption or among shift workers or people exposed to LAN were retrieved by these searches. Approximately 6,500 citations were identified from these searches and uploaded to web-based systematic review software for separate evaluation by two reviewers applying the inclusion/exclusion criteria. Based on these criteria, 722 references were selected for final inclusion in the cancer hazard assessment. Literature searches were updated on a monthly basis prior to posting the peer-review draft on August 24, 2018. References recommended by the peer reviewers were also considered for the final version. NTP has continued to monitor the literature through August 2019 but has not identified any studies would affect the overall cancer hazard conclusions. No studies from the updated monitoring have been included in this final assessment because these studies would not have been peer reviewed.

The results for the Human Cancer, Animal Cancer, Specific Biomarkers, and Mechanisms searches were then processed in EndNote to remove duplicates before being transferred to Health Assessment Workplace Collaborative (HAWC) for screening. Review at Level 1 identifies

studies that should be included in the next level of review for (1) Exposure, (2) Human Cancer/Biomarkers, (3) and (4) Mechanisms (including animal cancer studies). Review at Level 2 includes more detailed tagging for specific topics covered by a particular section of the report The HAWC assessments for Human/Biomarkers (HAWC 2018a) and Mechanisms (HAWC 2018b) are publiclly available.

Figure A-1 illustrates the overall approach to the searches and screening and the numbers of citations identified. Table A-1 highlights the general concepts searched and databases consulted. To review all the terms used, please refer to the full search strings below.

Figure A-1. Literature search strategy and review

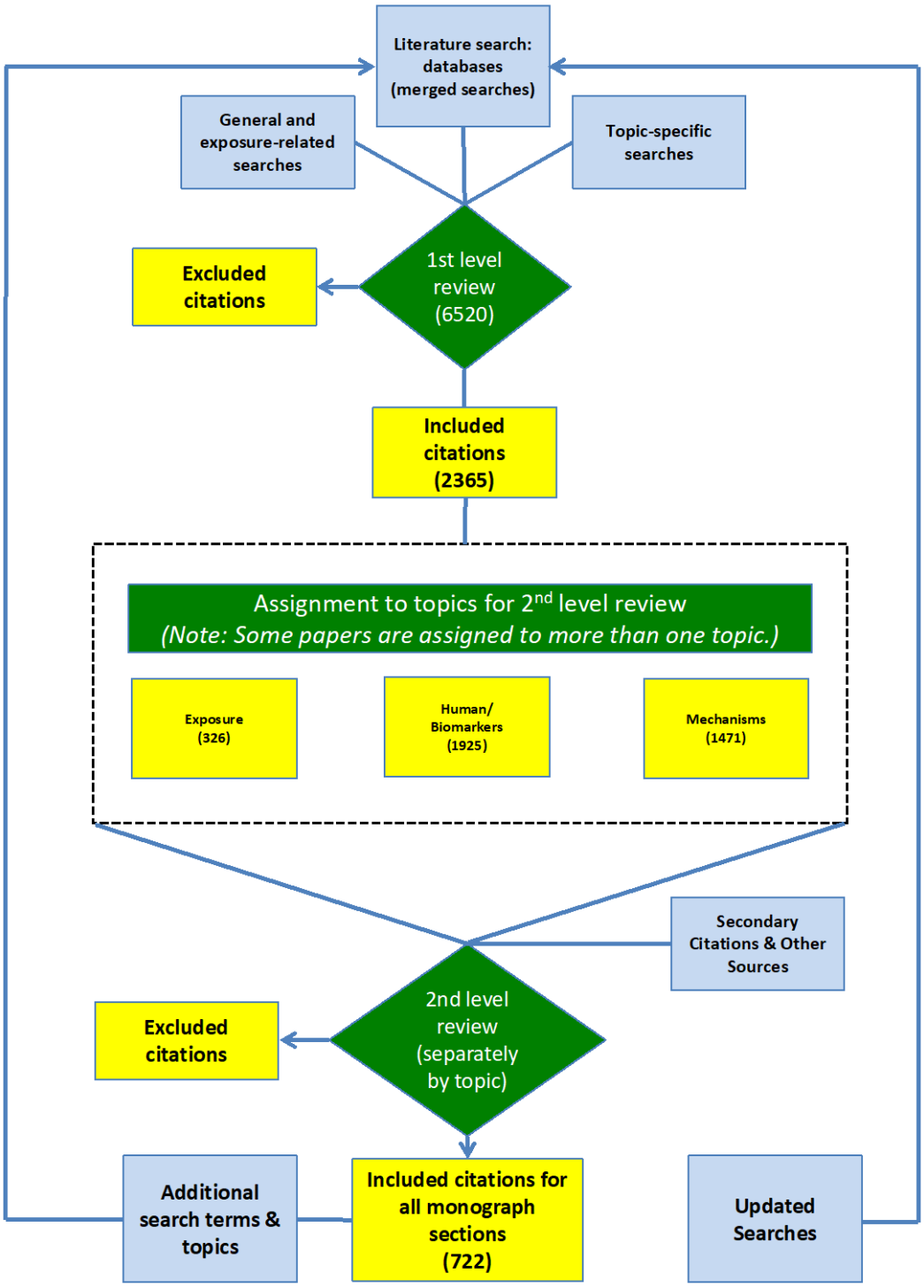

Table A-1. Major topics searched

Topic	Search Method	Databases searched
Human Cancer Studies	(shift work **OR** shiftwork **OR** night work **OR** "light at night" **OR** jet lag) **AND** (cancer **OR** tumor)	PubMed
Experimental Animal Studies	(Shift Work String **OR** Light String) **AND** Experimental Animals Studies Search **AND** ORoC Cancer Search	PubMed, Scopus, Web of Science
Biomarkers Studies	ORoC Cancer Search **AND** (Shift Work String **OR** Light String) **AND** Specific Biomarkers String **AND** (Humans & Epidemiology Combined String **OR** Experimental Animals Studies Search)	PubMed
Mechanism	(Shift Work String **OR** Light String) **AND** ORoC Characteristics of Carcinogens Search **AND** ORoC Cancer Search	PubMed, Scopus, Web of Science

A.2 Standard Searches

A.2.1 Shift Work

PubMed:

(work-schedule*[tiab] OR Alternative-shift*[tiab] OR duty-shift*[tiab] OR Midnight-shift*[tiab] OR night-call[tiab] OR night-shift*[tiab] OR nightshift*[tiab] OR night-work*[tiab] OR nightwork*[tiab] OR rotating-schedule*[tiab] OR rotating-shift*[tiab] OR shift-work*[tiab] OR shiftwork*[tiab] OR split-shift*[tiab] OR swing-shift*[tiab] OR third-shift*[tiab]) OR ((“personnel staffing and scheduling”[mh] OR “work schedule tolerance”[mh]) AND (shift* OR schedul*[tiab] OR hours[tiab] OR night[tiab] OR evening[tiab] OR duty-hour*[tiab] OR duty-period*[tiab] OR night-float*[tiab] OR overtime[tiab] OR on-call[tiab] OR 12-hour[tiab] OR twelve-hour[tiab] OR "long working hours"[tiab] OR "working long hours"[tiab] OR sleep[tiab] OR fatigue[tiab]))

Web of Science:

(TS=("work schedule*" OR "Alternative shift*" OR "duty shift*" OR "Midnight shift*" OR "night call" OR "night shift*" OR "nightshift*" OR "night work*" OR "nightwork*" OR "rotating schedule*" OR "rotating shift*" OR "shift work*" OR "shiftwork*" OR "split shift*" OR "swing shift*" OR "third shift*")) OR ((TS=("personnel OR "staffing" OR "work schedule tolerance")) AND (TS=("shift*" OR "schedul*" OR "hours" OR "night" OR "evening" OR "duty hour*" OR "duty period*" OR "night float*" OR "overtime" OR "on-call" OR "12-hour" OR "twelve-hour" OR "long working hours" OR "working long hours" OR "sleep" OR "fatigue")))

Scopus:

(TITLE-ABS-KEY ("work schedule*" OR "Alternative shift*" OR "duty shift*" OR "Midnight shift*" OR "night call" OR "night shift*" OR "nightshift*" OR "night work*" OR "nightwork*" OR "rotating schedule*" OR "rotating shift*" OR "shift work*" OR "shiftwork*" OR "split shift*" OR "swing shift*" OR "third shift*")) OR ((KEY ("personnel staffing and scheduling" OR "work schedule tolerance")) AND (TITLE-ABS-KEY ("shift*" OR "schedul*" OR "hours" OR "night" OR "evening" OR "duty hour*"

OR "duty period*" OR "night float*" OR "overtime" OR "on-call" OR "12-hour" OR "twelve-hour" OR "long working hours" OR "working long hours" OR "sleep" OR "fatigue")))

A.2.2 Light at Night

PubMed:

(light-dark-cycle*[tiab] OR light-cycle[tiab] OR light-cycles[tiab] OR dark-light-cycle*[tiab] OR Evening-light* OR Light-at-night OR Light-pollut* OR Night-light* OR Night-time-ligt* OR Nocturnal-light* OR bedroom-light* OR Sleeping-habitat*)

Web of Science:

TS=("light-dark cycle*" OR "light cycle" OR "light cycles" OR "dark-light cycle*" OR "Evening light*" OR "Light at night" OR "Light pollut*" OR "Night light*" OR "Night time light*" OR "Nocturnal light*" OR (bedroom NEAR/3 light*) OR “Sleeping habitat*”)

Scopus:

(TITLE-ABS-KEY(“light-dark cycle*" OR "light cycle" OR "light cycles" OR "dark-light cycle*" OR "Evening light*" OR "Light at night" OR "Light pollut*" OR "Night light*" OR "Night time light*" OR "Nocturnal light*” OR (bedroom w/3 light*) OR “Sleeping habitat*”))

A.2.3 Animal Studies

The PubMed, Web of Science, and Scopus Strings are the same as described in the Handbook Appendix (NTP 2016).

A.2.4 Humans & Epidemiology Combined

PubMed:

((humans[mh] OR human development[mh] OR household*[tiab] OR public[tiab] OR neighborhood*[tiab] OR human*[tiab] OR person*[tiab] OR people[tiab] OR age groups[mh] OR pediatric*[tiab] OR paediatric*[tiab] OR baby[tiab] OR babies[tiab] OR newborn*[tiab] OR infant*[tiab] OR toddler*[tiab] OR child*[tiab] OR youth*[tiab] OR youngster*[tiab] OR tween*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab]) OR (("in utero"[tiab] OR prenat*[tiab] OR perinat*[tiab] OR neonat*[tiab] OR postnat*[tiab] OR adult*[tiab] OR juvenile*[tiab]) NOT (mice[tiab] OR mouse[tiab] OR rat[tiab] OR rats[tiab])) OR preschool*[tiab] OR pre-school*[tiab] OR kindergarten*[tiab] OR schoolchild*[tiab] OR student*[tiab] OR middle-age*[tiab] OR aged[tiab] OR elder*[tiab] OR senior-citizen*[tiab] OR seniors[tiab] OR retiree*[tiab] OR septuagenarian*[tiab] OR octagenarian*[tiab] OR sexagenarian*[tiab] OR nonagenarian*[tiab] OR centenarian*[tiab] OR nuclear family[mh] OR parent[tiab] OR parents[tiab] OR father*[tiab] OR mother*[tiab] OR sibling*[tiab] OR brother*[tiab] OR sister*[tiab] OR twin[tiab] OR twins[tiab] OR step-father*[tiab] OR step-mother*[tiab] OR step-daughter*[tiab] OR step-son*[tiab] OR aunt*[tiab] OR uncle*[tiab] OR niece*[tiab] OR nephew*[tiab] OR grandparent*[tiab] OR grandfather*[tiab] OR grand-father*[tiab] OR grandmother*[tiab] OR grand-mother*[tiab] OR grandchild*[tiab] OR granddaughter*[tiab] OR grandson*[tiab] OR spouse*[tiab] OR partner*[tiab] OR

husband*[tiab] OR wife[tiab] OR wives[tiab] OR guardian*[tiab] OR caregiver*[tiab] OR care-giver*[tiab] OR men[mh] OR women[mh] OR men[tiab] OR man[tiab] OR boy[tiab] OR boys[tiab] OR boyhood[tiab] OR women[tiab] OR woman[tiab] OR girl[tiab] OR girls[tiab] OR girlhood[tiab] OR population groups[mh] OR vulnerable populations[mh] OR African-American*[tiab] OR Asian-American*[tiab] OR hispanic*[tiab] OR latina*[tiab] OR latino*[tiab] OR Mexican-American*[tiab] OR underserved[tiab] OR disadvantaged[tiab] OR underprivileged[tiab]) OR (epidemiolog*[tiab] OR epidemiology[sh] OR "epidemiologic studies"[mh] OR "double-blind method"[mh] OR "single-blind method"[mh] OR epidemiology[sh] OR case-control*[tiab] OR cohort[tiab] OR "cross sectional"[tiab] OR "follow-up study"[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR case-reports[pt] OR "clinical trial"[pt] OR "observational study"[pt] OR "randomized controlled trial"[pt] OR "twin study"[pt] OR case-report*[tiab] OR clinical-trial*[tiab] OR observational[tiab] OR randomized-control-trial*[tiab]) OR ("research subjects"[mh] OR "human experimentation"[mh] OR patients[mh] OR "patient participation"[mh] OR human-subject*[tiab] OR research-subject*[tiab] OR client*[tiab] OR patient*[tiab] OR inpatient*[tiab] OR outpatient*[tiab] OR participant*[tiab] OR volunteer*[tiab] OR "occupational groups"[mh] OR "occupational exposure"[mh] OR occupation*[tiab] OR workplace[tiab] OR "work place"[tiab] OR work-related[tiab] OR administrator*[tiab] OR aides[tiab] OR assistant*[tiab] OR crew[tiab] OR crews[tiab] OR employee*[tiab] OR personnel[tiab] OR professional*[tiab] OR staff[tiab] OR technician*[tiab] OR worker*[tiab] OR educator*[tiab] OR instructor*[tiab] OR teacher*[tiab] OR clinician*[tiab] OR doctor*[tiab] OR physician*[tiab] OR pharmacist*[tiab] OR nurse*[tiab] OR residents[tiab] OR veterinarian*[tiab] OR adolescent[tiab]) OR "meta-analysis"[pt] OR workmen*[tiab] OR seroepidemiologic-stud*[tiab] OR ecological-study[tiab] OR ecological-studies[tiab] OR correlation-stud*[tiab] OR case-series[tiab] OR case-referent[tiab] OR record-link*[tiab])

A.2.5 Specific Biomarkers

PubMed:

(corticosterone[tiab] OR cortisol[mh] OR cortisol[tiab] OR melatonin[mh] OR melatonin[tiab] OR "body temperature"[mh] OR body-temperature*[tiab])

A.2.6 Characteristics of Carcinogens

The PubMed, Web of Science, and Scopus Strings are the same as described in the Appendix to the RoC Handbook (NTP 2016).

A.2.7 RoC Cancer String:

The PubMed, Web of Science, and Scopus Strings are the same as described in the Appendix to the RoC Handbook (NTP 2016).

References

1. HAWC. 2018a. *HAWC: Health Assessment Workspace Collaborative. Public Assessment of LAN Level 2 Human/Biomarkers*. https://hawcproject.org/assessment/390/.

2. HAWC. 2018b. *HAWC: Health Assessment Workspace Collaborative. Public Assessment of LAN Level 2 Mechanistic*. https://hawcproject.org/assessment/393/.

3. NTP. 2014. *Report on Carcinogens (RoC) Concept: Shiftwork at Night, Light at Night, and Circadian Disruption*. National Toxicology Program. 12 pp. https://ntp.niehs.nih.gov/ntp/roc/concept_docs/2014/shiftworkconcept_508.pdf.

4. NTP. 2016. *Standard Search Strings for Literature Database Searches: Appendix to the Draft Handbook for Preparing Report on Carcinogens Monographs*. National Toxicology Program. 32 pp. https://ntp.niehs.nih.gov/ntp/roc/handbook/rochandbookappendix_508.pdf.

National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night

Appendix B: Night Shift Work and Breast Cancer

November 2020

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

List of Tables

Appendix B. Shiftwork and Breast Cancer Studies – Quality rankings and results.

This appendix includes the rationales for quality rankings of studies of breast cancer and shift work reported in Section 3.2 by type of quality criteria (e.g., (a) selection bias, (b) exposure assessment, (c) outcome assessment, (d) sensitivity, (e) potential confounding, (f) analysis rating).

Quality rankings are reported in Section 3.2 in Tables 3-2 and 3-3; their rationales are shown in Appendix B: Table B-1a-f for cohort studies of breast cancer and shift work; and in Appendix B: Table B-2a-f for case-control studies of breast cancer and shift work.

Results for the cohort studies of breast cancer and shift work are found in Appendix B, Table B-3; results for case-control studies of breast cancer and shift work are found in Appendix B: Table B-4.

Table B-1a: Breast cancer and shiftwork COHORT studies: Selection bias rationale

Reference	Selection bias rating
Åkerstedt *et al.* 2015	++ ⬇ The cohort is clearly defined. 74% of cohort responded to interview but no information was provided as to how this differed by exposure. This is an older survivor cohort recruited at ages 41–60 years, thus young cases who worked long durations of night work may be missing.
Jørgensen *et al.* 2017	+ ⬇ The cohort was clearly defined by exposed/non-exposed for a specific time period and location. Follow-up did not differ by exposure status. Left truncation is an issue in this older survivor cohort. Authors indicated most nurses have to participate in rotating shift work early in their careers, and this is a > 44 year old cohort, so selection of exposure status may not be appropriate. Mortality analysis is likely to miss cases having longer survival. If fatal cases are more or less likely to be exposed to shift work, selection bias can result.
Knutsson *et al.* 2013	+ ↔ The cohort is not clearly defined (in that it does not clear elucidate the relevant exposed, non-exposed, or referent group for a specific time period/location); no information is provided to assess whether follow-up differed between exposed and non-exposed subjects. No evidence presented to assess presence of healthy worker survival effect. Overall cohort participation rate for those with information on shift work was 53% from 1992 to 2009. Individuals were added at various points during the study.
Koppes *et al.* 2014	+++ ↔ Cohort was randomly selected from national survey respondents and linked to national hospital admission data.
Li *et al.* 2015	++ ⬇ The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location), with no evidence presented to assess if follow-up differed between exposed and non-exposed subjects. This is not necessarily an older cohort (average age is 54.3 at baseline), but the high percentage of ever night workers with half working at least 20 years suggests that it is a survivor cohort.

Reference	Selection bias rating
Pronk *et al.* 2010	++ ⬇ The cohort is clearly defined (e.g., includes the relevant exposed and nonexposed for a specific time period/location), with no evidence offered that follow-up differed between exposed and non-exposed subjects. No evaluation of healthy worker survival effect was conducted in this employed older cohort of women. Initial response rate was 92% from women invited to participate. This was an older group of surviving women (~26% premenopausal at baseline, with questions first asked 6 years later), and if early exposures were related to breast cancer risk, this group may be biased based on left truncation or healthy worker survivor effect.
Schwartzbaum *et al.* 2007	++ ↔ The cohort is clearly defined, with no evidence that follow-up differed between exposed and non-exposed subjects; no evidence of healthy worker effect, as the overall SIR for cancer was 1.02 (95% CI = 1.0–1.05). No discussion of healthy worker survival effect. For the youngest women right truncation may be operating, with insufficient accumulation of night work to assess effect.
Travis *et al.* 2016	++ ⬇ **UK Oxford EPIC**. The cohort of general population and vegetarians is somewhat clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location). This is a survivor cohort population aged ~37–90, with a mean of 58 years at the time of data collection and is likely to be unable to detect early breast cancers arising from long-term early exposure.
Travis *et al.* 2016	+ ⬇ **Million Women Study**. The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location), with no evidence that follow-up differed between exposed and non-exposed subjects. In this general population cohort, no analysis of healthy worker survival effect. This is an older cohort of survivors (mean age 68 at time when questions on night work were asked). If women with night work died, or left night work due to inability to adapt to night work, they wouldn't be present in this cohort to query about night work, and therefore a survivor bias could exist.
Travis *et al.* 2016	+ ⬇ **UK Biobank cohort.** The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location); No difference in follow-up time between exposed and non-exposed subjects. In this general population cohort, no analysis of healthy worker survival effect. This cohort is on average 56 years of age, and while not the oldest of the cohorts, may still suffer from left truncation due to elimination of early cancers after shift work early in one's career.
Tynes *et al.* 1996	+++ ↔ The cohort is clearly defined and includes the relevant exposed and non-exposed for a specific time period/location. Cases and controls in the nested study were selected from the same population by similar methods and criteria. No evidence that selection was related to both exposure and disease.

Reference	Selection bias rating
Vistisen *et al.* 2017	+ ⬇ The cohort is clearly defined with no evidence that follow-up differed for exposed and non-exposed. Data before January 1, 2007 was unavailable so two analytic cohorts were examined - the total population with records from Jan 1, 2007 and an "inception cohort" including women a) first ever employed Jan 1 2008 or later or no recorded employment in 2007. Both cohorts suffered from left-truncation, and lack of exposure information prior to either 2007 or 2008. Women were 35.5/39.4 years of age in the inception cohort and total population, respectively; the two populations differed in the joint distribution of shift work and education and shiftwork and parity, suggesting unknown selection factors that were operating in this subpopulation beyond simply left-truncation.
Wegrzyn *et al.* 2017	+++ ↔ The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location), with no evidence that follow-up differed between exposed and non-exposed subjects. Together, the two cohorts cover broad windows of exposure for women of different ages. The authors explored associations separately for the first 10 years of follow-up and the remaining 14 years of follow-up, to understand the long-term findings in the context of the Nurses Health Study their previously published shorter-term associations. In both cohorts, and for both measures of shift work in NHS2, breast cancer risk associated with night shift work was higher in the earlier versus later portion of follow-up. The estimates were higher in NHS2, where the shift work performance was likely closer in proximity to breast cancer risk than in NHS. The inverse finding (< 1.0) in the latter part of follow-up for NHS potentially reflected a healthy worker effect, but the authors did not see any evidence of differential dropping out of the analysis by shift work category, and therefore believe it to be due to chance.

Table B-1b: Breast cancer and shiftwork COHORT studies: Exposure assessment rationale

Reference	Exposure assessment rating
Åkerstedt *et al.* 2015	+ ⬇ The exposure assessment methods have poor sensitivity and specificity, leading to unreliable classification (or discrimination) with respect to ever-exposure as "night work" was not defined. Thus it was unclear if individuals working late afternoons or early mornings considered themselves "night workers," which would attenuate results. No information on frequency/intensity, timing, or recency. Exposure was assessed prior to diagnosis.
Jørgensen *et al.* 2017	0 ⬇ Current information on work status at baseline only. No information on past employment status casting doubt on those classified as unexposed. No data on duration of shift schedule and shift work intensity lead to a less sensitive exposure categorization. Furthermore, authors mention the high likelihood of exposure misclassification for nurses whose training involves shift work early in their career.
Knutsson *et al.* 2013	++ ⬇ The exposure assessment methods have adequate sensitivity and specificity to distinguish ever/never shift work. Most detailed questions concern the current job only and answers to the question on lifetime history of night work is available on only 53% of subjects, and in 36% only baseline information on shift work was available due to the design of their data collection on shift work. However, the comparison group, i.e., day workers, reported working only during the day on current job in 3 follow-ups; while night workers reported in at least one of the follow-ups that they worked some nights. No information on duration or intensity provided. Of those reporting no experince of shiftwork at final follow-up 22% reported shiftwork at baseline; but this figure was only 2% when NIGHT work was considered indicating night work was remembered better.
Koppes *et al.* 2014	0 ⬇ The study has poor sensitivity and specificity, resulting in poor discrimination between exposed and non-exposed and among exposure categories. Information asked only about current night work and number of hours per week of night work. A poor proxy of lifetime nightwork was estimated based on length of duration in current job. Authors mention that the Dutch have a high proportion of part time workers; also a co-author mentioned that shift workers have a 59% attrition rate over 5 year periods, indicating assumptions in this study are not supported.
Li *et al.* 2015	++ ⬇ Industry level information on exposure setting (shift work policies) allows for individual level discrimination between exposed and non-exposed to rotating shift work as shift work was mandated by factory. Lifetime # of night shifts measured intensity of night work; 33% day workers. Use of company records avoids recall bias, but no information existed on lifetime exposure to night work.
Pronk *et al.* 2010	++ ⬇ The exposure assessment methods have moderate to good sensitivity and specificity, leading to reliable classification (or discrimination) with respect to ever-exposure. Duration, intensity, and cumulative # nights were assessed; no assessment of consecutive nights worked or rotations. The job exposure matrix was likely to have over-estimated night work as compared to self-report: 44% worked nights by job exposure matrix; 26% worked nights by self-report.

Reference	Exposure assessment rating
Schwartzbaum *et al.* 2007	0 ⬇ Exposure assignment is based on aggregate categories, as exposure was defined according to % of those in each job category reporting shift work in an external large national survey. True night workers working in industries with fewer night workers are likely to be missed (sensitivity analyses in men indicated that resulting bias from this misclassification would be small); but women who are less likely to work nights in occupations with significant night work could be misclassifed as exposed. No data on intensity or timing.
Travis *et al.* 2016	++ ⬇ **UK Oxford EPIC.** The exposure assessment methods have moderate sensitivity and specificity, leading to reliable classification (or discrimination) with respect to ever-exposure and duration of exposure. However, the definition of night work as 1+ shift/month for jobs held at least 1 year likely mixed highly exposed and individuals with minimal exposure.
Travis *et al.* 2016	++ ⬇ **Million Women Study.** The exposure assessment methods have good sensitivity and specificity leading to reliable classification (or discrimination) with respect to overall ever-exposure and duration of exposure, although the question was asked as a summary question and not as a job-by-job history. Also, no information is presented on level of intensity, timing in relation to first full-term pregnancy, consecutive nights, or rotations. No information on exposure setting across many different types of occupations, none of which were specified, was reported.
Travis *et al.* 2016	0 ⬇ **UK Biobank Cohort.** The exposure assessment methods have inadequate sensitivity and specificity and are not able to differentiate ever/never exposure, as only current job was assessed. In this population of older survivors, likely that current job with short follow-up would not include the appropriate exposure window.
Tynes *et al.* 1996	+ ⬇ Exposure assessment methods have low sensitivity and specificity with respect to ever/never exposure and duration as they were based on employment records; intensity was implied but not sufficiently explained; shift work was not defined clearly. Information on rotations, or timing was absent.
Vistisen *et al.* 2017	+ ⬇ Administrative records avoid recall bias. However, left-truncation of the cohorts may misclassify exposed and unexposed as data from Time 0 is missing. (1) Women classified as "unexposed" may include exposed women working at earlier times in their careers dropping out for various reasons and diluting estimates of effect. (2) Workers on evening shifts could be misclassified as day workers. While sensitivity analyses revealed that bias from such misclassification may be minimal, assumptions about the proportion of women who were previously working may be in error.

Reference	Exposure assessment rating
Wegrzyn *et al*. 2017	+++ ↔ The exposure assessment methods have moderate to good sensitivity and specificity. The assessment was an improvement over the 2001 and 2006 report as (1) authors specified that women contributed person-time only as long as exposure status was captured; (2) NHS2 included a cumulative SW measure which incorporated follow-up updated information; (3) a secondary assessment was included to conduct analyses by follow-up time period to separate early vs. late associations of rotating night shift work on breast cancer risk; (4) in NHS2, a recency analysis was conducted using time since stopping shift work; and (5) stratified analysis was done by menopausal status, receptor status, shift work before and after first pregnancy, and shift work before and after menopause. A correlation of r = 0.53 was reported between answers to shift work questions about the 1995–1997 period asked in the 2001 follow-up questions and answers provided in 1995–1991. As in previous reports, no information on frequency or intensity was provided.

Table B-1c: Breast cancer and shiftwork COHORT Studies: Outcome assessment rationale

Reference	Outcome Assessment rating
Åkerstedt *et al.* 2015	+++ ↔ Outcome methods distinguish between diseased and non-diseased subjects, no ICD code indicated, nor detail on validation of case status. Follow-up and diagnoses were conducted independent of exposure status.
Jørgensen *et al.* 2017	++ ⬇ Breast cancer has a very high survival rate, so mortality will miss cases that do not result in death.
Knutsson *et al.* 2013	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.
Koppes *et al.* 2014	+ ↔ Outcome methods do not clearly distinguish between diseased and non-diseased subjects. Using hospital admission data to estimate incidence may lead to bias if differential access to medical treatment exists. Prevalent cases may have been included in the population which may mean there is a different distribution of aggressive and slow growing cancers compared to incident studies.
Li *et al.* 2015	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects and cases were verified by pathology/histology. Follow-up and diagnoses were conducted independent of exposure status. No cancer subtypes were examined.
Pronk *et al.* 2010	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. No sub-types were examined.
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. 97% of cases were morphologically verified.
Travis *et al.* 2016	+++ ↔ **UK Oxford EPIC**. Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. No subtypes were ascertained.
Travis *et al.* 2016	+++ ↔ **Million Women Study**. Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. No subtypes were ascertained
Travis *et al.* 2016	+++ ↔ **UK Biobank Cohort.** Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.
Tynes *et al.* 1996	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects and follow-up and diagnoses were conducted independent of exposure status.
Vistisen *et al.* 2017	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnosis conducted independent of exposure. Subtypes analyzed.

Reference	Outcome Assessment rating
Wegrzyn *et al*. 2017	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. Only confirmed cases were included; estrogen and progesterone receptor status determined but the number of lobular cases was too small to evaluate the risk of breast cancer by histologic type.

Table B-1d: Breast cancer and shiftwork COHORT Studies: Sensitivity rationale

Reference	Sensitivity rating
Åkerstedt *et al.* 2015	+ ⬇ The study has a moderate number of ever exposed subjects, but a small number of subjects with substantial exposure duration; information about level of intensity or timing unavailable. Follow-up time is only 8.7 years; if cases occur early after night work, this older aged cohort may have missed these cases.
Jørgensen *et al.* 2017	+ ⬇ Small number of night and rotating breast cancer cases, likely underpowered. Poor sensitivity of exposure status due to lack of level, duration, or range of exposure. Adequate follow-up duration.
Knutsson *et al.* 2013	++ ↔ The study has an inadequate number of case subjects exposed to night work (N = 14) or shift work without nights (N = 20), without information on level, duration, or range; there is adequate duration of follow-up for latency (average follow-up time is 12.4 years from baseline to censorship).
Koppes *et al.* 2014	0 ⬇ The study has an adequate number of exposed subjects, but a narrow range of exposure based on the few numbers working full time; and missing information on past or lifetime exposure to night work. Short follow-up time.
Li *et al.* 2015	+ ⬇ The study has an adequate number of exposed subjects with substantial duration of exposure; however, there was little exposure variation and this is likely a survivor cohort which could miss early cases.
Pronk *et al.* 2010	+ ⬇ The study has a small number of exposed subjects, with substantial exposure (# nights and duration). However, follow-up for cases once shift work history was known from self-report was only 4.4 years. In this older survivor population, effects would not be seen if any do exist.
Schwartzbaum *et al.* 2007	0 ⬇ The proportion of ever exposed is 0.06%, much lower than the expected 15%–20% of female nightworkers in the Swedish workforce. Study has small number of exposed cases, without sufficient information about how to characterize the level, duration, or range of exposure. For the youngest women included, duration of work through 1970 may not be sufficient to assess effect. Right truncation may be operating to reduce sensitivity.
Travis *et al.* 2016	+ ↔ **UK Oxford EPIC Study**. The study has an inadequate number of exposed subjects with substantial exposure duration, and no analyses on direction of shift or intensity. Very short follow-up unlikely to capture effect if there is one. This somewhat older survivor cohort may not be able to capture a relationship with long duration of early night work and breast cancer if one exists. Definition of night work as 1+ shift/month for jobs held at least 1 year mixed likely mixed highly exposed and those with minimal exposure.
Travis *et al.* 2016	+ ⬇ **Million Women Study**. The study has an adequate number of exposed subjects with substantial exposure duration, but no information on direction of shift, intensity, or contiguous days working. Mean follow-up time is very short (2.6 years); this older survivor cohort may not have captured cases occurring after shift work at an early age

Reference	Sensitivity rating
Travis *et al.* 2016	0 ↔ **UK Biobank Cohort.** The study did not assess lifetime exposure to nightwork, and the unexposed are likely to have been a mix of previously exposed and currently unexposed. Very short follow-up.
Tynes *et al.* 1996	+ ⬇ The study has a small number of exposed cases with ill-defined moderate duration of exposure.
Vistisen *et al.* 2017	+ ⬇ The study has an adequate number of ever-exposed subjects but follow-up is very short (up to 5 years); intensity (# shifts per period) is included to denote a range of exposure, and duration up to 5 years is incorporated into the analysis.
Wegrzyn *et al.* 2017	++ ↔ The study has an adequate number of exposed subjects, but small numbers with 20+ years of exposure (N = 13, or 35); the two cohorts together cover broad windows of exposure in relation to the occurrence of breast cancer which increases the sensitivity over the previous two reports

Table B-1e: Breast cancer and shiftwork COHORT studies: Confounding rationale

Reference	Confounding rating
Åkerstedt *et al.* 2015	Breast: ++ ↔ The study measured all relevant potential confounders and addressed alcohol in a separate model which included only cases with these data.
Jørgensen *et al.* 2017	Breast: +++ ↔ None.
Knutsson *et al.* 2013	Breast: +++ ↔ The study measured many relevant potential confounders and used appropriate analyses to address them; no co-exposures were included.
Koppes *et al.* 2014	Breast: + ↔ The study did not measure alcohol, measured occupation as a proxy for SES/education, and used number of children in household as an imperfect proxy for parity.
Li *et al.* 2015	Breast: +++ ↔ The study measured relevant potential confounders. Joint effects of magnetic field exposure and shift work were evaluated by stratifying subjects into 4 groups with 2 levels of exposure for each.
Pronk *et al.* 2010	Breast: +++ ↔ The study measured all relevant potential confounders and addressed alcohol in a separate model which included only cases with these data.
Schwartzbaum *et al.* 2007	Breast: + ↔ The study did not measure all relevant potential confounders as data were not available (e.g., parity, age at first full-term pregnancy, alcohol use)
Travis *et al.* 2016	Breast: ++ ↓ **UK Oxford EPIC**. The study measured and controlled for important potential confounders; however, BMI and age at menarche are in the pathway, and inclusion of these and other variables that are not necessarily confounders may have reduced risk estimate
Travis *et al.* 2016	Breast: ++ ↓ **Million Women Study**. The study measured and controlled for important potential confounders; however, BMI and age at menarche, which are both in the pathway, and inclusion of other variables that are not necessarily related to both exposure and risk may have lowered the estimate of the risk.
Travis *et al.* 2016	Breast: ++ ↓ **UK Biobank Cohort**. The study measured and controlled for important potential confounders; however, BMI and age at menarche, which are both in the pathway, and inclusion of other variables that are not necessarily related to both exposure and risk may have lowered the estimate of the risk.
Tynes *et al.* 1996	Breast: + ↑ The study did not measure all relevant potential confounders. Data on parity, age at first birth were available for a subset of women, but main analyses did not control for these, as these data were only available for the "fertility cohort" within the total cohort. For these women, no control was made for coexposures or alcohol; socioeconomic status was considered to be somewhat homogenous although no data were reported to support this.

Reference	Confounding rating
Vistisen *et al.* 2017	Breast: ++ ⬇ All relevant potential confounders were considered. Given similarity between these for night and day workers, adding them to the models may have reduced estimates. Adjusted and crude estimates were reported, and adjusting tended to move negative values towards 1.0.
Wegrzyn *et al.* 2017	Breast: ++ ⬇ The study measured all relevant potential confounders and used appropriate analyses to address them, but included variables in the pathway (age at menarche, menopause, BMI) in the model, as well as others (benign breast disease, family history of breast cancer, physical activity) which may have resulted in reducing the estimate.

Table B-1f: Breast cancer and shiftwork COHORT studies: Analysis and selective reporting rationales

Reference	Analysis rating	Selective reporting rating
Åkerstedt *et al.* 2015	+++ ↔ Study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. Timing of nightwork unknown.
Jørgensen *et al.* 2017	++ ↔ Inclusion of multiple covariates not related to the exposure and outcome of interest may have attenuated results and widened confidence intervals.	+++ ↔ There is no evidence that data or analysis were limited to a subset of data.
Knutsson *et al.* 2013	++ ↔ The study used appropriate assumptions and methods of analysis but did not use all the information they collected in the analysis.	++ ↔ Data on various aspects of night work were collected, but only information about ever night work was reported. Only 53% of subjects had information about lifetime exposure to shift work; among these only 36% had baseline information.
Koppes *et al.* 2014	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis. Women with missing data on at least one of the potential confounders were excluded from analyses.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Li *et al.* 2015	+++ ↔ The study used relevant data and analyses; Lagged analyses were included.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Pronk *et al.* 2010	++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them. Did not describe stratification analyses sufficiently in detail.	++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. Did not show results of stratified analyses
Schwartzbaum *et al.* 2007	++ ↔ Study used relevant data and appropriate assumptions and methods of analysis. The authors incorporated several sensitivity analyses to test various hypotheses. Sub-analyses used to investigate duration included women who reported working in high shift work occupations in both 1960 and 1970.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.

Reference	Analysis rating	Selective reporting rating
Travis *et al.* 2016	++ ↔ **UK Oxford EPIC**. The study used appropriate data and analyses or designs to address them.	+ ↔ The authors collected data on many metrics of shift work such as type (permanent), frequency, age at first shift work and provided frequency by duration of night shift work (for total population) but did not calculate or report risk estimates for these metrics. While numbers were small, they may have done some stratification.
Travis *et al.* 2016	++ ↔ **Million Women Study**. The study measured most relevant potential confounders, and used appropriate analyses or designs to address them. Collected data on chronotype but did not present analysis by chronotype.	++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. However, very little infomation from analyses were shown.
Travis *et al.* 2016	++ ↔ **UK Biobank Cohort.** The study measured most relevant potential confounders and used appropriate analyses or designs to address them. However, information on analysis was insufficient.	+ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. Very little information shown.
Tynes *et al.* 1996	++ ↔ Analysis methods were satisfactory with given data.	++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. However, reporting on several key issues was limited which hampered interpretation of study
Vistisen *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis. Given that the time periods under analysis are short, the Poisson model can be used in lieu of Cox proportional hazards models.	++ ↔ No evidence that reporting of the data or analyses were limited to a subset of the data collected. However, more information about the characteristics of the inception cohort (first time workers and those not working in 2007) would have been helpful.
Wegrzyn *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.

Table B-2a: Breast cancer and shiftwork CASE-CONTROL studies: Selection bias rationale

Reference	Selection bias rating
Cordina-Duverger *et al.* 2016	+++ ↔ Selection bias was unlikely as all incident cases in both study areas were recruited; cases were frequency-matched to controls by 10-year age strata and by socioeconomic status (SES) calculated from census data in each study area to obtain an SES distribution similar for cases and controls. SES of cases and controls was compared after the selection process and no significant difference was found. Data were collected in detail and factors that differed between cases and controls were included in models. The proportion of night workers among controls was similar to that in the French population and employed in industries where night work is common. However, only 79% of the cases were tested for human epidermal growth factor receptor 2 (HER2), but no information was provided on whether there were any differences in women tested or not tested for HER2.
Davis *et al.* 2001	+++ ↔ Cases and controls were selected from the same population by similar methods and criteria. No evidence that selection of the subjects was related to both exposure and disease.
Fritschi *et al.* 2013	++ ↔ Cases and controls were selected from same population with similar criteria; there was no evidence that selection was related to both exposure and disease. Some attrition bias suspected given the relatively low response fractions; however, the authors used sensitivity analysis to examine what level of selection bias would hide a real effect of 1.5 for ever working the graveyard shift, and found that substantial differences in responses would have to be present to create a bias. However, it may be that they could have missed an elevated risk of 1.2.
Grundy *et al.* 2013	+++ ↔ Cases and controls were not strictly selected from the same population by similar methods and criteria. However, there is no evidence that selection of the subjects was related to both exposure and disease as sensitivity analysis taking selection factors into account produced similar results. Methods differed in the two study areas, but study area was included in all models. Response bias due to differences in response rates of cases and controls is ruled out since participation would have had to be related to night shift work and breast cancer, which is unlikely based on the manner shift work was assessed (e.g., job history).
Hansen 2001	+++ ↔ Countrywide study, thus cases and controls were selected from the same Danish population. There is no evidence that selection of the subjects was related to both exposure and disease.
Hansen and Lassen 2012	++ ↓ Cohort is clearly defined, with cases and controls selected from same population by similar criteria; no evidence that selection of subjects was related to both exposure and disease. Modest participation rates could bias results if night shift workers were more willing to participate than day workers and if this differed by cases and controls. Sensitivity analyses suggested that shift working controls would have to be twice as likely to refuse as shift working cases to negate the observed effect (indicate selection bias). Only 40% of original cohort cases participated, potentially introducing selection bias if cases were more exposed to night shift work than controls. In this older population, such loss is a concern if breast cancer occurs after shift work in early life.

Reference	Selection bias rating
Hansen and Stevens 2012	++ ⬇ The prevalence cohort (only living members) from across Denmark is clearly defined (e.g., includes the relevant exposed, non-exposed, or referent group for a specific time period); response rates are similarly high for cases and controls in the nested study. The older survivor population suggests that there may be some selection bias, in that cases occurring at earlier ages after night work early in careers would not be present in the cohort.
Lie *et al.* 2011	++ ⬇ Prevalent case inclusion could create a bias as 39% of deceased cases were lost thru death or non-participation in this older cohort leaving long-term survivors; sensitivity analyses using cases from 2004–2007 concluded that this bias is likely to be negligible, although the value of this test late in follow-up is questionable.
Menegaux *et al.* 2013	+++ ↔ Selection bias was unlikely as all incident cases in both study areas were recruited; cases were frequency-matched to controls by 10-year age strata and by SES calculated from census data in each study area to obtain an SES distribution similar for cases and controls. SES of cases and controls was compared after the selection process and no significant difference was found. Data were collected in detail and factors that differed between cases and controls were included in models. The proportion of night workers among controls was similar to that in the French population and employed in industries where night work is common.
O'Leary *et al.* 2006	++ ↔ Highly selected population based on long-term residence. This analytic subset also differed from the full set of cases and controls - they were older, postmenopausal, white, parous, heavier, ever users of alcohol and HRT, and less likely to have more than high school degree or to have breastfed. Likely some selection bias was operating.
Papantoniou *et al.* 2015	++ ↔ Cases and controls were selected from the same underlying population to ensure that they were comparable. There is no evidence that selection of the subjects was related to both exposure and disease; however, attrition bias is a potential as recruitment differed between cases and controls with only 52% of the controls responding. Calls were made repeatedly at different times during the day to avoid missing night shift workers.
Pesch *et al.* 2010	+++ ↔ Cases and controls were selected from the same population by similar methods and criteria. Selection of the subjects was made independent of exposure or disease ascertainment. Bootstrapping analyses was conducted to account for the fact that the 90% of participants taking part in the second round of interviews were more educated than those in the first round; however these analyses indicated no evidence of selection bias. Those reporting shift work were recalled, with another loss of subjects. Data on how these groups compared were not adequately reported.
Wang *et al.* 2015	++ ↔ Whether cases and controls came from the same population is somewhat of a question in any hospital-based case-control study. However, cases and controls were recruited from the same hospital during the same study period, and all subjects must have resided in the Guangzhou area for at least five years. There is no indication if the 3 hospitals are tertiary care hospitals; while controls with chronic disease were not included, if trauma events were over represented among controls, it could be that controls were from a more "local" area than cases and therefore potentially different. In fact, controls were more educated than cases.

Table B-2b: Breast cancer and shiftwork CASE-CONTROL studies: Exposure assessment rationale

Reference	Exposure assessment rating
Cordina-Duverger *et al.* 2016	++ ↔ Type of night work (late evening, early morning, overnight), duration in years, average frequency of nights/week, and duration/frequency combinations were assessed; however, due to large differences between night shift systems across occupations, shift rotation, direction and rate of rotation, and number of consecutive nights on various rotations, could not be assessed.
Davis *et al.* 2001	++ ⬇ Exposure assessment methods reliably discriminate ever and never exposure; shift work ascertained only for the 10 years prior to diagnosis/reference date. Intensity and duration were evaluated separately. The unexposed in the reported analysis may have worked early in their careers, thus they may not be completely unexposed. Recall bias is unlikely as lifetime occupational history is queried.
Fritschi *et al.* 2013	+++ ⬇ Exposure assessment methods have very good sensitivity and specificity leading to reliable classification with respect to ever/never exposure, intensity, duration, type of rotation, and window of exposure. While exposure assessment was based on expert review, and the study asked about every job, recall bias in this case-control study cannot be completely excluded, particularly as a special interview was conducted for women indicating shiftwork on their questionnaire and data were collected after the 2007 IARC report.
Grundy *et al.* 2013	++ ⬇ The exposure assessment methods have only moderate sensitivity as exposure to night work was defined as working either evening or night shifts; permanent and rotating shifts were also not considered separately. Duration was provided for categories of intensity/frequency of evening/night shifts (from 20% to 100%). Duration of lifetime cumulative exposure of night work defined as starting or ending work between 11:00 PM and 7:00 AM. Collection of lifetime job histories reduced likelihood of recall bias.
Hansen 2001	+ ⬇ The exposure assessment methods have minimal sensitivity and specificity, with only moderate discrimination with respect to ever-exposure; details of exposure level, timing, or other relevant metrics not available. No individual level information of exposure; to minimize misclassification women working in trades with 40%–59% night work are excluded leaving only those in occupations with little or much shift work.
Hansen and Lassen 2012	+++ ↔ Exposure assessment methods have good sensitivity and specificity for reliably classifying ever/never exposure, intensity/frequency, and duration from lifelong job histories; rotations and permanent shifts could not be differentiated. Recall bias was ruled out after a question on (1) electromagnetic fields or radar exposure (known to be unrelated to breast cancer) was found also to be unrelated to breast cancer in this set of cases and controls, (2) focus of 28-page questionnaire was military exposure, and (3) data were mostly collected before publication of IARC findings.
Hansen and Stevens 2012	+++ ↔ Exposure assessment methods have good sensitivity/specificity leading to reliable discrimination between ever and never exposure, duration and intensity. Various shift systems were ascertained; Recall bias only slightly likely as nurses were told this was an environmental study; data collection took place pre-IARC report; a question about electromagnetic fields (no association with breast cancer) was inserted to assess potential recall.

Reference	Exposure assessment rating
Lie *et al.* 2011	++ ↔ Multiple exposure assessment metrics provided sensitivity and specificity with respect to exposure; however, as all nurses had some exposure to night work (3 years during nursing school), there is no unexposed group. Methods of assessing exposure level included consecutive nights worked, duration, intensity, type of pattern (rotation/permanent). Recall bias is a concern, however, as the study was designed to investigate a broad array of work-related factors; no difference was found between cases and controls on duration in jobs reported to include night work; and the structure of questions on lifetime occupational history and schedules is likely to minimize this bias. However, authors note that shift work and cancer was widely discussed in Denmark during this time.
Menegaux *et al.* 2013	++ ⬇ Type of night work (late evening, early morning, overnight), duration in years, average frequency of nights/week, and duration/frequency combinations were assessed; due to large differences between night shift systems across occupations, shift rotation, direction and rate of rotation, number of consecutive nights on various rotations was not assessed
O'Leary *et al.* 2006	+ ↔ No lifetime exposure assessment, but only jobs in the last 15 years in this older population of women were queried; frequency and duration were included. Only nights or only evening categories provided information on permanent nights, with the other categories a mix of rotating schedules. Recall bias may be possible given this subset of subjects was selected for a second interview for electromagnetic measurements and light at night which took place on average 200 days later. Categories reported made it difficult to differentiate evening workers who worked through 2:00 AM or earlier, potentially diluting exposure categories which included evening workers (e.g., all but never or permanent night workers)
Papantoniou *et al.* 2015	+++ ⬇ The methods were sufficient to differentiate exposed and unexposed with respect to ever-exposure, frequency, and duration. Recall bias is unlikely as the issue of shift work and cancer was not widely discussed in Spain during the study period, and querying lifetime job histories limits opportunity for recall bias.
Pesch *et al.* 2010	++ ⬇ Exact methods by which shift information was collected is unclear. Ever shift work, ever night shift work, duration, and frequency were collected, and while the methods were not very detailed, they appeared to allow discrimination between exposed and non-exposed, and those with long/short duration, and timing of work relative to first pregnancy and time since last night shift. No information on rotation vs. permanent shifts, or direction of rotation. The three rounds of interviewing to get to the shift work questions raises the potential for recall bias.
Rabstein *et al.* 2013	++ ⬇ The exposure assessment methods rely on self-report, and exact methods by which shift information was collected is unclear based on the two papers (Pesch *et al.* 2010). Ever shift work, ever night shift work, duration, and frequency were collected, and while not very detailed, appeared to allow discrimination between exposed and non-exposed. No information on rotation vs. permanent shifts, or direction of rotations is provided. The three rounds of interviewing to get to the shift work questions raises the potential for recall bias.

Reference	Exposure assessment rating
Wang *et al.* 2015	+ ↔ Exposure assessment methods have limited sensitivity/specificity and classify with respect only to ever/never lifetime employment at night. No metrics of level, duration, or intensity were collected. Exposure settings vary across the population and are not further described. Interviews in hospitals may introduce observer bias.

Table B-2c: Breast cancer and shiftwork CASE-CONTROL studies: Outcome assessment rationale

Reference	Outcome assessment rating
Cordina-Duverger *et al.* 2016	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. Appropriate methods used regarding the determination of receptor status.
Davis *et al.* 2001	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnoses were conducted independent of exposure status. No cancer subtypes analyzed.
Fritschi *et al.* 2013	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnoses were conducted independent of exposure status.
Grundy *et al.* 2013	++ ↓ Outcome methods clearly distinguish between cases and non-cases, however, Invasive and in situ cases were combined in analyses, except for estrogen receptor/progesterone receptor (ER/PR) analyses. Authors indicated that there were no differences in results when In situ cases removed. No mention of histologic confirmation.
Hansen 2001	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Hansen and Lassen 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects; disease follow-up using linkage with the Danish Cancer registry were conducted independent of exposure ascertainment
Hansen and Stevens 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects (histologically confirmed primary breast cancers). Follow-up and diagnoses were conducted independent of exposure status. Internal comparisons among nurses eliminate concern about lead-time bias that can arise due to nurses' enhanced knowledge of the medical system when compared with general population. No information on subtypes.
Lie *et al.* 2011	+++ ↔ Outcome methods clearly distinguish between cases and controls. Follow-up and diagnoses are conducted independent of exposure status.
Menegaux *et al.* 2013	+++ ↔ Histologic confirmation of cancers is appropriate; companion publication on this cohort provides detail on estrogen, progesterone, and HER2 receptor status (Cordina-Duverger 2013).
O'Leary *et al.* 2006	+++ ↔ Subtypes were evaluated (ER status). Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis was conducted independent of exposure assessment.
Papantoniou *et al.* 2015	+++ ↔ Diagnoses appear to have been conducted independent of exposure assessment; cases were histologically verified.
Pesch *et al.* 2010	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnoses were conducted independent of exposure status.

Reference	Outcome assessment rating
Wang *et al.* 2015	++ ↔ Outcome methods distinguish between diseased and non-diseased subjects; follow-up and diagnosis were conducted independent of exposure status. However, variations in coding across hospitals may have introduced error in the diagnosis of breast cancer.

Table B-2d: Breast cancer and shiftwork CASE-CONTROL studies: Sensitivity rationale

Reference	Sensitivity rating
Cordina-Duverger *et al.* 2016	++ ↔ Adequate number of exposed cases, particularly in ER, PR, and HER2 subgroups. Category of "any night work" may not be a sensitive metric but authors state similar findings were found for other definitions of night shift work.
Davis *et al.* 2001	+ ⬇ The study has a low number of exposed subjects with what can be determined at most to be moderate exposure levels; limiting duration to 10 years before diagnosis/reference date in an older population of women is likely to miss any cases due to early exposure in the career.
Fritschi *et al.* 2013	++ ↔ The study has a moderately adequate number of exposed subjects with substantial exposure (medium/high level and high duration) (N = 24 cases). To investigate latency assumptions, authors repeated the analysis indicating whether exposure occurred in the windows of time > 30 years, > 20 and < 30 years, > 10 and < 20 years, and < 10 years before enrollment compared with those who were unexposed during that window of time.
Grundy *et al.* 2013	++ ⬇ Combined evening and night work as well as combined permanent and rotating shifts minimized the ability to look at those most highly exposed to night work. The proportion of participants exposed to "night shift work" (combined definition) was relatively high (33%), but only a small percentage worked nights exclusively for 30+ years (N = 16), and no additional information on intensity of night work was available (without including evening work).
Hansen 2001	+ ⬇ Large number of exposed cases, and cases classified as having 6+ years in jobs with 60%+ night work. However, as the exposure assessment derives from aggregated data, and not individual level data, uncertainty about actual level of exposure for any specific individual exists.
Hansen and Lassen 2012	+++ ↔ Adequate number of cases with range of exposures and adequate duration of follow-up in the cohort.
Hansen and Stevens 2012	++ ↔ Very small reference group of permanent day workers. There are an adequate number of exposed subjects with substantial duration, or duration that may be meaningful for this exposure. There are also a substantial number of subjects with day-evening-night shifts.
Lie *et al.* 2011	+++ ↔ The study had adequate number of exposed subjects at a substantial exposure level and duration (N = 64 cases with 5+ years working 6+ consecutive nights), and adequate follow-up.
Menegaux *et al.* 2013	++ ⬇ Adequate numbers of cases ever working nights; however, less than adequate number of exposed subjects with substantial exposure (duration or intensity).
O'Leary *et al.* 2006	+ ⬇ The study has a very small number of exposed subjects with substantial exposure. The exposure window of 15 years is limited, particularly in this older subset of residentially stable subjects and may or may not be etiologically relevant (60% of overnight shift workers were post-menopausal), which is borderline for being an "older cohort".

Reference	Sensitivity rating
Papantoniou *et al.* 2015	++ ⬇ For main analyses, the study has an adequate number of exposed subjects, with substantial exposure (level, duration, or range); there was low power to assess possible effect modification by key variables due to small numbers in some subgroups.
Pesch *et al.* 2010	+ ⬇ The study had a moderately small number of exposed subjects particularly in the highest exposure category; measures of intensity and duration were included, again with small numbers, and highest exposed intensity not very intense (3+ night shifts per month).
Wang *et al.* 2015	+ ↔ The study has an adequate number of exposed subjects, but no indication of their level, duration, or range of exposure.

Table B-2e: Breast cancer and shiftwork CASE-CONTROL studies: Confounding rationale

Reference	Confounding rating
Cordina-Duverger *et al.* 2016	Breast: +++ ↔ The study measured relevant potential confounders and used appropriate analyses to address them. However, models included additional variables such as BMI and age at menarche (in pathway); both parity and age at first full-term pregnancy were included; and family history of breast cancer was included, as well as tobacco smoking.
Davis *et al.* 2001	Breast: +++ ↔ Study measured all relevant potential confounders with the exception of socioeconomic status/education which was addressed in selection of cases and controls, and did not include variables that had a small effect when added to the models (alcohol, etc.).
Fritschi *et al.* 2013	Breast: +++ ↔ The study measured all relevant confounders and used appropriate methods of analysis to control them.
Grundy *et al.* 2013	Breast: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them, without overloading the model with risk factors that did not change the odds ratio (OR).
Hansen 2001	Breast: ++ ↑ The study did not directly measure SES but used job title; little information on co-exposure, indirect information on alcohol consumption (trade not individual).
Hansen and Lassen 2012	Breast: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them.
Hansen and Stevens 2012	Breast: +++ ↔ The study measured all relevant potential confounders.
Lie *et al.* 2011	Breast: ++ ↑ The study measured all relevant potential confounders with the exception of socioeconomic status, and used appropriate analyses to address them.
Menegaux *et al.* 2013	Breast: +++ ↔ The study measured relevant potential confounders and used appropriate analyses to address them. However, models included additional variables including BMI and age at menarche (in pathway); both parity and age at first full-term pregnancy were included; and family history of breast cancer was included, as well as tobacco smoking.
O'Leary *et al.* 2006	Breast: +++ ↔ All relevant potential confounders measured and appropriate analyses were used to address them.
Papantoniou *et al.* 2015	Breast: +++ The study measured all relevant potential confounders and used appropriate analyses to address them. Included a direct acyclic graph (DAG) in supplemental materials.
Pesch *et al.* 2010	Breast: ++ ↔ The study measured relevant potential confounders with the exception of alcohol use.
Wang *et al.* 2015	Breast: ++ ↔ Given that some variables in the pathway were added to the model even when they were similar between cases and controls likely reduced the estimate towards the null.

Table B-2f: Breast cancer and shiftwork CASE-CONTROL studies: Analysis and selective reporting rationale

Reference	Analysis rating	Selective reporting rating
Cordina-Duverger *et al.* 2016	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting was limited to a subset of the data. Rather, clear statements provided regarding analyses which were run but not included and why.
Davis *et al.* 2001	++ ↔ Study used relevant data and appropriate assumptions and methods of analysis. Given the wide age span in the population (20–74) and the availability of lifetime data on jobs, an age-stratified analysis could have been useful to explore the impact of recent night work among younger and older women in the 10 years preceding diagnosis.	++ ↔ Data on timing of exposure was available given collection of lifetime data, but not reported.
Fritschi *et al.* 2013	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis. Amount of light was controlled for.	+++ ↔ No evidence that selective reporting of data or analyses compromised the interpretation of the study.
Grundy *et al.* 2013	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Hansen 2001	+++ ↔ The study appeared to use relevant data and appropriate assumptions and methods of analysis, but provided little detail. However, lagging analyses was important in this population.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Hansen and Lassen 2012	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis and conducted sensitivity analyses which suggested that shift working controls would have to be twice as likely to refuse as shift working cases to negate the observed effect.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the collected data.
Hansen and Stevens 2012	+++ ↔ Study used relevant data and appropriate assumptions and methods of analysis. Much detail about calculation of various shift types, intensity, and duration.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Lie *et al.* 2011	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.

Reference	Analysis rating	Selective reporting rating
Menegaux *et al.* 2013	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that results were selectively reported.
O'Leary *et al.* 2006	++ ⬇ Duration comparisons were made to women with lower frequency of shift work rather than non-workers which may introduce some downward bias.	++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected. However, information on none of the stratified analyses was shown.
Papantoniou *et al.* 2015	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis including a DAG.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Pesch *et al.* 2010	+++ ↔ Study used relevant data and appropriate assumptions and methods of analysis.	++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected. Inadequate reporting of loss of shift workers and non-shift workers.
Wang *et al.* 2015	++ ↔ Study used relevant data and appropriate assumptions and methods of analysis. Somewhat thin on detail.	+++ ↔ No indication that reporting of data or analyses were limited to a subset of the data.

Table B-3: Breast cancer and shiftwork COHORT study results

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Åkerstedt *et al.* 2015 Cohort Sweden **Enrollment or follow-up:** 1998–2003; follow-up 12 yrs	**Population:** Swedish Twin Registry cohort **Exposure assessment method:** questionnaire	**HR Duration (yrs) of night work: Followed to age 60**		Age, education, smoking status, BMI, parity, coffee consumption, previous cancer, hormone and oral contraceptives	**Exposure information:** Number of years with work hours that meant working nights at least "now and then" **Strengths:** Nationwide prospective cohort in unique twin registry population. **Limitations:** Night work poorly defined so that it is not clear if exposed and unexposed were correctly classified. Length of follow-up may not be long enough to detect cases. The study is limited by including only an older age range (41–60) of survivors, such that if starting nightwork early in life is a factor in development of breast cancer some cases may have been missed. **Additional results:** - **Confidence in evidence:** Some evidence
		No night work	1; 354		
		1–45 yr	0.96 (0.74–1.24); 109		
		1–5 yr	0.93 (0.66–1.31); 57		
		6–10 yr	0.79 (0.45–1.38); 16		
		11–20 yr	0.8 (0.45–1.42); 18		
		21–45 yr	1.77 (1.03–3.04); 18		
Gu *et al.* 2015 Cohort 11 U.S. states **Enrollment or follow-up:**	**Population:** Nurses Health Study (NHS) 74,862 **Exposure assessment method:** questionnaire	**HR**		Age, alcohol, physical exercise, multivitamin use, menopausal status, HRT use, physical exam in past	**Exposure information:** Rotating shift work: ≥ 3 shifts/month **Strengths:** Large prospective study of nurses with well documented follow-up procedures and outcome
		Never	1; 269		
		1–5 yr rotating work	1.07 (0.9–1.26); 293		
		6–14 yr rotating work	0.99 (0.76–1.27); 79		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Enrolled 1976; follow-up 1988–2008		≥ 15 yr rotating work	0.99 (0.74–1.33); 55	2 years, healthy eating score, smoking status, pack years, BMI, husband's education	definitions and adequate control for potential confounders. **Limitations:** Mortality study likely to miss cases given the high survival rate for breast cancer leading to potential for selection bias if fatal cases are more or less likely to be exposed to shift work. Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed. No analyses on healthy worker survival in this occupational cohort. **Additional results:** - **Confidence in evidence:** Supporting evidence.
Jørgensen *et al.* 2017 Cohort	**Population:** Theh Danish Nurses Cohort (DNC)	**Mortality: HR Type of shift:**		Age, smoking status, pack years, physical activity, BMI, alcohol	**Exposure information:** Current work in evening (3:00 PM to midnight), night (11:00 PM to 7:00 AM) or rotating shifts
		Day shifts	1; 119		
		Night shifts	1.2 (0.7–2.08); 16		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Denmark **Enrollment or follow-up:** 1993–2013	18,015 **Exposure assessment method:** questionnaire	Rotating shifts	0.96 (0.66–1.37); 38	consumption, diet (veggies, fruit, meat), pre-existing disease (hypertension, diabetes, MI), self-reported health, stressful work enviornment, marital status, parity, use of HRT, OC use	(day/evening or day/evening/night). **Strengths:** Nationwide prospective cohort of female nurses with detailed information on current work schedules only at baseline, and potential confounders. **Limitations:** Small numbers of breast cancer deaths, no information on duration or intensity, type of rotation schedule, nor past information on shift work. No cancer validation. Due to high breast cancer survival, mortality analyses may select for fatal cases that may or may not be related to shift work. **Additional results:** - **Confidence in evidence:** No confidence, not included in the assessment
Knutsson *et al.* 2013 Cohort Sweden **Enrollment or follow-up:** 1992–95 (Stockholm) and 1996–97 (Norrland); and 2000–2003 (Norrland)	**Population:** Work, Lipids, and Fibrinogen (WOLF) occupational cohort 4,036 **Exposure assessment method:** questionnaire	**HR All ages**		Parity (4 levels), Alcohol consumption (high/low)	**Exposure information:** 3 rounds of questionnaires used to create exposure variable to classify women as day workers, and shift workers with and without night shifts. **Strengths:** Prospectively collected data; unique person ID enabling linkage of data to cancer registry; information on several potential confounders. Relatively young cohort. **Limitations:** Low response rate and high attrition from baseline to follow-up; small numbers of exposed cases; limited information on exposure –only ever/never night work, no information on
		Only day shifts	1; NR		
		Shifts without nights	1.23 (0.7–2.17); 20		
		Shifts with nights	2.02 (1.03–3.95); 14		
		HR Age < 60		Parity (4 levels), Alcohol consumption (high/low)	
		Only day shifts	1; NR		
		Shifts without nights	1.18 (0.67–2.07); 17		
		Shifts with nights	2.15 (1.1–4.21); 12		
		Mean Time in years (cumulative incidence): schedule type			
		Only day shifts	2.4; 60		
		Shifts without nights	2; 20		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Shifts with nights	2.6; 14		intensity, duration or timing. **Additional results:** Shift worker cases had shorter time to diagnosis than day worker cases. incidence info is included in additional results box in the first result for this study. **Confidence in evidence:** Some evidence.
		Trend-test *p*-value: 0.01			
Koppes *et al.* 2014 Cohort Netherlands **Enrollment or follow-up:** 1996–2009; follow-up 1996–2009	**Population:** Netherlands general population prospective cohort 285,723 women **Exposure assessment method:** interview	**HR (RR) Current shift work**		Age, origin, children in the household, education, occupational group, contractual working hours, job tenure	**Exposure information:** Current night work, sometimes or regularly, midnight to 6:00 AM. **Strengths:** Large, general population, prospective study linked with national hospital admission registration. **Limitations:** Only current shift work captured with no data on past exposure. Assumes duration of work at current job is an adequate proxy for lifetime exposure to night work; relevant confounders not adjusted for in analysis; short latency. Admission data as a proxy for incidence data may introduce bias if access to hospital is differential for shift workers and non-shift workers. **Additional results:** - **Confidence in evidence:** No confidence; not included in assessment.
		No current night work	1; 2312		
		Occasional	1.04 (0.85–1.27); 102		
		Regular	0.87 (0.72–1.05); 117		
		HR (RR) Occasional night work in current job: Job tenure (yrs)		Age, origin, children in the household, education, contractual working hours, occupational group	
		No current night work	1; 2312		
		> 0–3 yr	1.05 (0.7–1.57); 25		
		4–9 yr	1.05 (0.71–1.55); 25		
		10–19 yr	1.21 (0.85–1.73); 26		
		≥ 20 yr	0.78 (0.48–1.28); 17		
		Trend-test *p*-value: 0.66			
		HR (RR) Duration (yrs) of regular night work in current job		Same as above	
		No current night work	1; 2312		
		0–3 yr	0.7 (0.47–1.04); 46		
		4-9 yr	0.94 (0.66–1.34); 46		
		10-19 yr	0.91 (0.65–1.28); 47		
		> 20 yr	0.95 (0.62–1.45); 30		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *p*-value: 0.26			
		HR (RR) Nurses; Night work in current job		Age, origin, children in the household, education, job tenure, contractual working hours	
		No current night work	1; NR		
		Occasional	1.42 (0.92–2.19); NR		
		Regular	0.93 (0.66–1.31); NR		
Li *et al.* 2015 Nested Case-Control Shanghai, China **Enrollment or follow-up:** 1989–1991: follow-up 2002	**Population:** Female textile workers in Shanghai textile industry Cases: 1,709; Controls: 4,780 **Exposure assessment method:** company records	**HR (RR) Duration (yrs) of rotating night work: All women**		Age	**Exposure information:** Number of years worked on ratiating night shift (continuous work hours between midnight and 5:00 AM); all rotating shift workers with set forwarding schedule; usually 7.5 nights/month. **Strengths:** Well-defined occupational cohort, with sufficient number of cases; work histories complete for all women; detailed shift work information for each job including several metrics. **Limitations:** Older cohort with a high percentage of long-term shift workers may represent a survivor cohort. No information on lifetime exposure history. **Additional results:** For these >50 year-old women, there was a 22%–23% increased nonsignificant risk in both the unlagged (reported here) and 10-year lagged analysis, but not in the 20-year lagged analysis. **Confidence in evidence:** No evidence.
		None	1; 557		
		> 0–12.8 yr	0.99 (0.83–1.17); 286		
		> 12.8–19.92 yr	0.97 (0.82–1.15); 290		
		> 19.92–27.67 yr	0.9 (0.76–1.06); 289		
		> 27.67 yr	0.88 (0.74–1.05); 287		
		Trend-test *p*-value: .095			
		HR (RR) Duration (yrs) worked rotating night shift: < 50 yrs old		Age	
		None	1; 273		
		> 0 –11 yr	0.87 (0.67–1.12); 114		
		> 11–6.8 yr	0.94 (0.73–1.22); 118		
		> 16.8–21.54 yr	1.06 (0.81–1.37); 112		
		> 21.54 yr	0.94 (0.72–1.22); 115		
		Trend-test *p*-value: .453			
		HR (RR) Duration (yrs) worked rotating night shift: ≥ 50 yrs old		Age	
		None	1; 284		
		> 0–14.5 yr	1.23 (0.97–1.56); 173		
		> 14.5 –24.2 yr	0.86 (0.68–1.09); 173		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		> 24.2 –31.17 yr	0.85 (0.67–1.07); 174		
		> 31.17 yr	0.96 (0.76–1.23); 173		
		Trend-test *p*-value: .430			
		HR (RR) All women: # rotating night shifts		Age	
		None	1; 557		
		> 0–1,316.79	0.96 (0.81–1.14); 288		
		> 1,316.79–2,018.71	1 (0.84–1.19); 287		
		> 2,018.71–2,880	0.88 (0.74–1.04); 288		
		> 2,880	0.89 (0.75–1.07); 289		
		Trend-test *p*-value: .155			
		HR (RR) # of rotating night shifts: < 50 yrs		Age	
		None	1; 273		
		> 0–1,114.29	0.83 (0.64–1.07); 115		
		> 1,114.29-–1,603.39	0.95 (0.73–1.23); 113		
		> 1,603.39 -– 2,116.61	1.08 (0.83–1.4); 117		
		> 2,116.61	0.96 (0.74–1.26); 114		
		Trend-test *p*-value: .200			
		HR (RR) # of rotating night shifts: ≥ 50 yrs old		Age	
		None	1; 284		
		> 0–1,627.5	1.09 (0.88–1.36); 173		
		> 1,627.5–2,588.21	0.84 (0.68–1.04); 172		
		> 2,588.21 – 3,453.78	0.91 (0.74–1.13); 174		
		> 3,453.78	0.93 (0.74–1.16); 174		
		Trend-test *p*-value: .140			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Pronk *et al.* 2010 Cohort Shanghai **Enrollment or follow-up:** 1996–2000; follow-up 2000–2007	**Population:** Shanghai Women's Health Study 73,049 **Exposure assessment method:** interview	**HR (RR) Duration (years) of night work: jobs with JEM scores > 0**		Age, education, Fam hx BRCA, # pregnancies, age at first birth, occupational physical activity	**Exposure information:** Job exposure matrix (JEM) for night shift work 0=no, 1=incidental, 2= likely, 3=probably; self report night shift work: start 10:00 PM ≥ 3 /mo for ≥1yr. **Strengths:** Large, prospective cohort with exposure data collected prior to breast cancer diagnosis; appropriate analysis and control for confounding. Supplementary individual level data collected to verify night shifts assessed by JEM based on job title alone. **Limitations:** This older (ages 40–70) surviving cohort of women may have been subject to the healthy worker survivor effect (HWSE); if breast cancer is likely to occur early on in a person's career, this would not be captured in this survivor cohort; also, very short follow-up time. **Additional results:** A JEM analysis was also performed, but it showed different exposure assessment results from the self-reported data, though the findings were approximately the same. **Confidence in evidence:** No evidence
		Never worked at night	1; 423		
		Ever worked at night	1 (0.9–1.2); 294		
		> 0 and ≤ 14 yr	1.1 (0.9–1.3); 108		
		> 14 and ≤ 25 yr	0.9 (0.7–1.1); 89		
		> 25 yr	1 (0.8–1.3); 97		
		Trend-test *p*-value: 0.72			
		HR (RR) Average shift work JEM score		Same as above	
		0	1; 423		
		> 0 and ≤ 1.29	1 (0.8–1.2); 102		
		> 1.29 and ≤ 2.38	1.1 (0.9–1.3); 109		
		> 2.38	0.9 (0.7–1.2); 83		
		Trend-test *p*-value: 0.73			
		HR (RR) Lifetime cumulative night shift JEM Score		Same as above	
		0	1; 423		
		> 0–< 34	1 (0.8–1.3); 102		
		> 34–< 66	1 (0.8–1.2); 103		
		> 66	1 (0.8–1.2); 89		
		Trend-test *p*-value: 0.84			
		HR (RR) Age started working first job with JEM score > 0		Same as above	
		No shift work	1; 423		
		> 26	1 (0.8–1.2); 87		
		> 20–≤ 26	1 (0.8–1.3); 98		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		> 0–≤ 20	1 (0.8–1.2); 109		
		HR (RR) Frequency (night shifts/mo): Self reported		Same as above	
		Never	1; 276		
		Ever	0.9 (0.7–1.1); 73		
		> 0–<8 shfits	0.6 (0.3–1.2); 8		
		8 shifts	0.9 (0.7–1.3); 45		
		> 8 shifts	0.9 (0.5–1.3); 20		
		Trend-test *p*-value: 0.29			
		HR (RR) Duration (years) night shift work: Self-reported		Same as above	
		Never	1; 276		
		> 0–≤ 5 yr	0.9 (0.6–1.3); 25		
		> 5–≤ 17 yr	0.9 (0.6–1.4); 29		
		> 17 yr	0.8 (0.5–1.2); 19		
		Trend-test *p*-value: 0.26			
		HR (RR) Age (years) starting night shift work: self-reported		Same as above	
		Never worked at night	1; 276		
		> 30	0.7 (0.5–1.2); 18		
		> 21–≤ 30 yrs	0.9 (0.6–1.3); 25		
		> 0–≤ 21 years	0.9 (0.6–1.4); 30		
		Trend-test *p*-value: 0.26			
		HR (RR) Ever worked night shift: Both JEM and self report		Same as above	
		Never	1; NR		
		Ever	0.9 (0.7–1.3); NR		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *p*-value: 0.26			
Schernhammer *et al.* 2001 Cohort 11 U.S. states **Enrollment or follow-up:** Enrolled 1976; followed June 1988–May 1998	**Population:** Nurses Health Study (NHS) 78,562 **Exposure assessment method:** questionnaire	**RR Duration (years) of rotating night shift work: All**		Age, age at menarche, age 1st ft preg, parity, weight change between 18 yrs and menopause, BMI at age 18 years, Fam hx BRCA, benign breast disease, OC use, current alcohol consumption, age at menopause, use of post menopausal hormones, menopausal status, height, time period of follow-up	**Exposure information:** Rotating night shift work ≥ 3/month **Strengths:** Large prospective study of nurses with well-documented follow-up procedures and outcome definitions, with adequate data on potential confounders. **Limitations:** Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed. No information on intensity. Analysis included many variables unrelated to both exposure and outcome, potentially biasing results towards the null. Shiftwork exposures were assessed once as lifetime exposures near the end of the surviving breast cancer-free nurses' working careers with a follow-up period well into post-retirement years. **Additional results:** - **Confidence in evidence:** Supporting evidence.
		Never worked	1; 925		
		1-14 yr	1.08 (0.99–1.18); 1324		
		15-29 yr	1.08 (0.9–1.3); 134		
		≥ 30 yr	1.36 (1.04–1.78); 58		
		Trend-test *p*-value: .02			
		RR Duration of work (years): Post menopausal		Same as above	
		Never worked	1; 801		
		1–14 yr	1.06 (0.97–1.16); 1146		
		15–29 yr	1.05 (0.87–1.27); 120		
		≥ 30 yr	1.36 (1.04–1.78); 58		
		Trend-test *p*-value: .05			
		RR Duration (years) of work: Pre-menopausal		Same as above	
		Never worked	1; 121		
		1-14 yrs	1.23 (0.97–1.55); 174		
		≥ 15 yrs	1.34 (0.77–2.33); 14		
		Trend-test *p*-value: .1			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Schernhammer *et al.* 2006 Cohort 14 U.S. states **Enrollment or follow-up:** Enrolled 1989; followed 1989–June 1, 2001	**Population:** Nurses Health Study (NHS2) 115,022 women **Exposure assessment method:** questionnaire	**RR Duration (years) of working shift work: primarily premenopausal**		Age, age at menarche, age 1st ft preg, parity, Fam hx BRCA, benign breast disease, OC use, age at menopause, use of post menopausal hormones, menopausal status, height, BMI, Smoking status, alcohol consumption, physical activity	**Exposure information:** Rotating shift defined as working nights ≥ 3/month **Strengths:** Large cohort of nurses with well-documented follow-up procedures and case definitions. **Limitations:** Small number of women exposed for 20+years; and no information on intensity or timing of exposure. **Additional results:** - **Confidence in evidence:** Supporting evidence.
		Never worked	1; 441		
		1-9 years	0.98 (0.87–1.1); 816		
		10-19 years	0.91 (0.72–1.16); 80		
		≥ 20 years	1.79 (1.06–3.01); 15		
		Trend-test *p*-value: 0.65			
Schwartzbaum *et al.* 2007 Cohort Sweden **Enrollment or follow-up:** 1960 and 1970; follow-up: 1971–1989	**Population:** Swedish working women registered in 1960 and 1970 census data 1,148,661 female workers **Exposure assessment method:** JEM	**SIR Among women working in jobs defined as mostly shift work in the 1969 and 1970 census**		Age, socioeconomic status, occupational position, county of residence	**Exposure information:** Workplace had rotating schedule or work between 1 and 4 AM **Strengths:** Nationwide cohort of working age women in diverse industries followed for 19 years. **Limitations:** Exposure underestimated; small number of exposed cases, aggregate exposure data, lack of data on relevant potential confounders or co-exposures. Misclassification of exposure likely. **Additional results:** - **Confidence in evidence:** No confidence; not included in assessment.
		Shiftwork in 1970	0.94 (0.74–1.18); 70		
		Shiftwork in 1960 and 1970	0.97 (0.67–1.4); 28		
Travis *et al.* 2016 Oxford, U.K. Cohort **Enrollment or**	**Population:** U.K. EPIC Oxford Study 22,274 women **Exposure assessment method:**	**RR (Hazard Ratio) Duration (years) of night work**		Age, SES, parity, age at first birth, BMI, alcohol consumption, physical activity,	**Exposure information:** Night shift work: Midnight to 6:00 AM for at least 3 nights/month **Strengths:**
		Never	1; 153		
		Ever worked	1.07 (0.71–1.62); 28		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
follow-up: 2010 (4th Survey); follow-up 2012	questionnaire	< 10 yr	1.18 (0.69–2.01); 15	Strenuous, age at menarche, OC use, smoking, living with a partner, HRT use, method of recruitment, region of residence	Prospective design and data collection on night work prior to diagnosis; individual level data on potential confounders. Data collected on duration of exposure **Limitations:** Small numbers of exposed, and only 1 exposed case with 20+ years of night work; information on multiple exposure metrics not reported. Follow-up less than 4 years; half of the population over the age of 58, meaning that this may also be somewhat of a survivor cohort with little information about long-term night work at early ages. **Additional results:** An analysis of nurses alone was done to compare these results with the NHS study. No elevated risk, nonsignificant or statistically significant, was found. NTP combined 10–19 and 20+ years into a category of 10+ years estimating it with a fixed effects model. **Confidence in evidence:** Some evidence.
		10–19 yr	1.92 (1.03–3.57); 11		
		≥ 20 yr	0.22 (0.03–1.61); 1		
		≥ 10 yr	[1.58 (0.88–2.85); 12]		
		Trend-test *p*-value: 0.75			
Travis *et al.* 2016 Cohort England and Scotland **Enrollment or follow-up:** 2009–2012 (4th survey); follow-up 2013	**Population:** U.K. Million Women Cohort **Exposure assessment method:** questionnaire	**RR (Hazard Ratio) Duration (years) of night work: women who last worked night shifts in the past 10 years**		Study area, age, SES, parity, age at first birth, BMI, alcohol consumption, physical activity, Strenuous, age at menarche, OC use, smoking, living with a partner, HRT use, family history of breast cancer	**Exposure information:** Night work: Midnight to 6:00 AM, for at least 3 nights/month. **Strengths:** Prospective design with night shift work data collected prior to diagnosis; large numbers of exposed; individual level data on potential confounders and control for potential confounders. Analysis by time since last worked night shifts. **Limitations:**
		Never worked	1; 4136		
		Ever worked	1.1 (0.94–1.3); 156		
		< 10 yr	0.97 (0.74–1.26); 55		
		10–19 yr	1.41 (1.07–1.86); 52		
		≥ 20 yr	0.98 (0.72–1.33); 42		
		Trend-test *p*-value: 0.42			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		RR (Hazard Ratio) Duration (yrs) of night work: All women		Same as above	Lack of exposure assessment regarding intensity, direction of rotation, contiguous shifts. Older cohort of survivors (post menopausal women) may not capture cases occurring after shift work at an early age. **Additional results:** For women last working night shifts more than 10 years in the past, all estimates by duration were similar to 1.0. **Confidence in evidence:** Some evidence.
		Never	1; 4136		
		Ever	1 (0.92–1.08); 673		
		<10 yr	0.93 (0.83–1.03); 400		
		10–19 yr	1.14 (0.96–1.35); 140		
		≥ 20 yr	1 (0.81–1.23); 89		
		Trend-test *p*-value: 0.68			
Travis *et al.* 2016 Cohort England, Scotland, and Wales **Enrollment or follow-up:** 2006–2010; Follow-up Dec 2012	**Population:** U.K.Biobank Cohort 251,045 **Exposure assessment method:** questionnaire	**RR (Hazard Ratio) Current (main job)**		Study area, age, SES, parity, age at first birth, BMI, alcohol consumption, physical activity, Strenuous, age at menarche, OC use, smoking, living with a partner, HRT use, family history of breast cancer	**Exposure information:** Worked between midnight to 5:00 AM. Low prevalence of exposure (3%) **Strengths:** Prospective design measuring exposure prior to diagnosis; individual level data on potential confounders and control for potential confounders. **Limitations:** Lack of exposure assessment regarding ever/never lifelong exposure to nightwork, Unexposed participants were a mix of previously exposed and currently unexposed. Very short follow-up; cohort of surviving women 40–69 yrs of age. Women working shifts early in their careers and developing cancer may have been excluded from the cohort. **Additional results:** - **Confidence in evidence:** No confidence; no included in assessment.
		Not current night shift work	1; 2653		
		Current night shift work	0.78 (0.61–1); 67		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Tynes *et al.* 1996 Nested Case-Control Norway **Enrollment or follow-up:** 1920–1980; follow-up 1961-1991	**Population:** Norwegian radio and telegraph operators study Cases: 50; Controls: 259 **Exposure assessment method:** company records	**OR < 50 years of age: Cumulative shift work exposure (category x years)**		Duration of employment	**Exposure information:** Shift work defined as frequent presence in radio room both at night and day **Strengths:** Prospective occupational cohort with complete data from occupational and cancer registries. **Limitations:** Exposure assessment was limited; no individual level data for electromagnetic fields and radiofrequency fields, potential co-exposures. Incomplete control for potential confounding by breast cancer risk factors. **Additional results:** - **Confidence in evidence:** Some evidence.
		No shift work	1; 12		
		Low (> 0–3.1 yr)	0.3 (0.1–1.2); 5		
		High (> 3.1– 0.7 yr)	0.9 (0.3–2.9); 12		
		Trend-test *p*-value: 0.97			
		OR < 50 years of age: Cumulative shift work (category x years) before the age of 30.		Duration of employment	
		No shift work	1; 7		
		Low (> 0–2.7 yr)	0.9 (0.2–3); 12		
		High (> 2.7–17.1 yr)	1.9 (0.5–7); 10		
		Trend-test *p*-value: 0.31			
		OR ≥ 50 years of age: Cumulative shift work exposure (category x years)		Duration of employment	
		No shift work	1; 3		
		Low (> 0–3.1 yr)	3.2 (0.6–17.3); 6		
		High (> 3.1– 20.7 yr)	4.3 (0.7–26); 12		
		Trend-test *p*-value: 0.13			
		OR ≥ 50 yrs of age: Cumulative shift work (category x years) before age 30		Duration of employment	
		No shift work	1; 7		
		Low (> 0–2.7 yr)	3.1 (0.7–14.2); 6		
		High (> 2.7–17.1 yr)	4.6 (0.1–7.5); 8		
		Trend-test *p*-value: 0.06			
Vistisen *et al.* 2017 Cohort	**Population:** Danish payroll data cohort. 156,927 (full population);	**RR Ever night (short-term exposure); shiftwork by breast cancer subtype**		Calendar year, age, age at birth of first child, number of	**Exposure information:** Nightwork defined as ≥ 3 hours between midnight and 5:00 AM
		Only day workers	1; 751		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Denmark **Enrollment or follow-up:** 2007–2012	55,381 (inception population) **Exposure assessment method:** company records	Ever: All breast cancers	0.9 (0.8–1.01); 425	births, OC use, HRT use, other sex hormone use, medication related to alcoholism, number of mammograms, family education level, family history of breast cancer, family history of ovarian cancer	**Strengths:** Large population with detailed individual level day-to-day information on working hours from a complete countrywide payroll register with linkages to cancer registry, the civil registration system, and family income register. **Limitations:** Left truncation of the dataset with no supplementary information on lifetime history of shiftwork; and there is no information on duration of shiftwork beyond 5 years. The subpopulation of women with a washout period differ from the total population in ways that could bias the results. **Additional results:** - **Confidence in evidence:** No evidence.
		Ever: ER-/HER2-	0.85 (0.59–1.23); 49		
		Ever: ER+/HER2-	0.8 (0.68–0.95); 250		
		Ever: ER-/HER2+	1.49 (0.93–2.39); 37		
		Ever: ER+/HER2+	1.26 (0.84–1.89); 48		
		RR Inception subpopulation: Shift work since entry and during the past 1 to 1–4 years time windows		Same as above	
		Since entry	0.88 (0.66–1.17); 69		
		Past 1–2 yr	0.82 (0.56–1.18); 37		
		Past 1–3 yr	1.14 (0.76–1.71); 36		
		Past 1–4 yr	1.33 (0.82–2.17); 29		
		Past 1–5 yr	1.01 (0.44–2.32); 10		
Wegrzyn *et al.* 2017 Cohort U.S.A. **Enrollment or follow-up:** NHS 1988–2012;	**Population:** Nurses Health Study (NHS and NHS2) NHS 78,516; NHS2 114,559 **Exposure assessment method:** questionnaire	**RR NHS2: Duration (years) of rotating night shift work: exposure at baseline**		Age, age at menarche, Fam hx BRCA, benign breast disease, OC use, age at menopause, use of post menopausal hormones,	**Exposure information:** Working rotating shifts at least 3/month. **Strengths:** The two NHS cohorts together reveal important information about timing of night work in relation to breast cancer. 24 years of follow-up data and large number of breast cancer cases; complete
		Never worked	1; 1318		
		1–9 yr	1.05 (0.98–1.13); 2071		
		10–19 yr	1 (0.85–1.17); 168		
		≥ 20 yr	2.15 (1.23–3.73); 13		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
NHS2 1989–2013		Trend-test *p*-value: 0.23		menopausal status, height, BMI, alcohol consumption, physical activity, BMI at age 18 years, adolescent body size at age 10 and age 20, ag at first birth and parity combined, breastfeeding duration, duration of estrogen alone HRT, current mammography use	information on potential confounders; ability to analyze by subtype; ability to compare two similar, but age differentiated cohorts. **Limitations:** Potential misclassification of unexposed including permanent night workers and non-shiftworkers as most nurses are exposed to some shift work. Small number of NHS2 women exposed for 20+years; no information on intensity or pattern of nightshift work most disruptive to circadian rhythms. **Additional results:** - **Confidence in evidence:** Moderate to strong evidence.
		RR NHS2: Duration (years) of rotating night shift work in 24 years of follow-up: updated exposure		Same as above	
		Never worked	1; 950		
		1–9 yr	1.04 (0.96–1.12); 2002		
		10–19 yr	0.94 (0.81–1.1); 201		
		≥ 20 yr	1.4 (1–1.97); 35		
		Trend-test *p*-value: 0.74			
		HR NHS2: Women with ≥ 20 years rotating shiftwork by follow-up interval (<10 or ≥ 10 years)		Same as above	
		≥ 20 yr: < 10 yr follow-up, baseline exposure	2.35 (1.04–5.31); 6		
		≥ 20 yr: ≥ 10 yr follow-up, baseline exposure	1.95 (0.92–4.15); 7		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		≥ 20 yr: < 10 yr, updated exposure	2.13 (1.19–3.81); 12		
		≥ 20 yr: ≥ 10 yr, updated exposure	1.19 (0.78–1.81); 23		
		HR NHS2: Women with ≥ 20 years rotating shiftwork and ER+PR+ status; baseline or updated exposure information.		Same as above	
		Baseline exposure	1.58 (0.65–3.83); 5		
		Updated exposure	1.62 (1.07–2.45); 24		
		RR NHS: Duration (years) rotating shiftwork in 24 years of follow-up		Age, age at menarche, benign breast disease, OC use, age at menopause, use of post menopausal hormones, menopausal status, height, BMI, alcohol consumption, physical activity, BMI at age 18 years, adolescent body size at age 10 and age 20, ag at first birth and parity combined, breastfeeding duration, duration of estrogen alone HRT, current mammography use, family history of breast cancer	
		Never worked	1; 2382		
		1–14 yr	1.01 (0.96–1.07); 3162		
		15–29 yr	1.06 (0.94–1.19); 331		
		≥ 30 yr	0.95 (0.77–1.17); 96		
		Trend-test *p*-value: 0.63			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		RR NHS: Women with ≥30 years rotating shiftwork by follow-up interval		Same as above	
		<10 yr	1.26 (0.97–1.64); 60		
		≥10 yr	0.68 (0.49–0.95); 36		
		RR NHS: ≥30 yrs rotating shiftwork (yrs) in 24 years of follow-up		Same as above	
		ER+/PR+ receptor status	0.96 (0.73–1.27); 54		
		Mortality: RR NHS: Mortality. Rotating shiftwork duration (years) (Gu *et al.* 2015)		Age, menopausal status, BMI, alcohol consumption, physical activity, multivitamin use, HRT use, physical exam in past 2 years, healthy eating score, smoking status, pack years, Husband's education	
		Never worked	1; 269		
		1–5 yr	1.01 (0.9–1.26); 293		
		6–14 yr	0.99 (0.76–1.27); 79		
		≥ 15 yr	0.99 (0.74–1.33); 55		

Table B-4: Breast cancer and shiftwork CASE-CONTROL study results

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Cordina-Duverger *et al.* 2018 Case-control Pooled analysis of 5 case-control studies	**Population:** Population-based studies from Australia, Canada, France, Germany, Spain **Exposure assessment method:** Questionnaire	**OR Ever/never worked at night - pooled, All women**		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, oral contraceptive (OC) use, body mass index (BMI), alcohol, tobacco, hormone replacement therapy (HRT), menopausal status	**Exposure information:** Jobs that included at least 3 hours of work between midnight and 5:00 AM **Strengths:** Pooled data from 5 studies to create a single definition of nightwork**;** multiple metrics of exposure; large population **Limitations:** Self-reported data, some collected after 2007, the date of the IARC report on shiftwork. **Additional results:** - **Confidence in evidence:** Moderate to strong evidence
		Never worked at night	1; 5,322		
		Ever worked at night	1.12 (1–1.25); 771		
		OR Ever/never worked at night - pooled, Premenopausal women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, Family history of breast cancer, OC use, BMI, alcohol, tobacco	
		Never worked at night	1; 1,669		
		Ever worked at night	1.26 (1.06–1.51); 324		
		OR Ever/never worked at night - pooled, Postmenopausal women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, Family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT	
		Never worked at night	1; 3,652		
		Ever worked at night	1.04 (0.9–1.19); 447		
		OR Duration (years) of night work - pooled, All women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, Family	
		Never worked at night	1; 5,322		
		< 10 yr	1.18 (1.03–1.36); 461		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		10–19 yr	0.98 (0.78–1.22); 154	history of breast cancer, OC use, BMI, alcohol, tobacco, HRT, menopausal status	
		≥ 20 yr	1.1 (0.87–1.39); 151		
		OR Duration of night work - pooled, Premenopausal women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco	
		Never worked at night	1; 1,669		
		< 10 yr	1.33 (1.07–1.65); 210		
		10–19 yr	1.05 (0.74–1.47); 69		
		≥ 20 yr	1.34 (0.85–2.13); 42		
		OR Duration of night work - pooled, Postmenopausal women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco	
		Never worked at night	1; 3,652		
		< 10 yr	1.09 (0.91–1.31); 251		
		10–19 yr	0.92 (0.68–1.23); 85		
		≥ 20 yr	1.04 (0.8–1.36); 109		
		OR Length of nightshifts - pooled, All women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT, menopausal status	
		Never worked at night	1; 5,322		
		< 8 hr	1.06 (0.78–1.43); 84		
		8–9 hr	1.15 (0.98–1.34); 324		
		≥ 10 hr	1.12 (0.96–1.31); 344		
		OR Length of night shifts - pooled, Premenopausal women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast	
		Never worked at night	1; 1,669		
		< 8 hr	1.03 (0.65–1.64); 37		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		8–9 hr	1.2 (0.91–1.6); 111	cancer, OC use, BMI, alcohol, tobacco	
		≥ 10 hr	1.36 (1.07–1.74); 167		
		OR Length of night shifts - pooled, Postmenopausal women		Age, age at menarche, parity, age at first full-term pregnancy, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT	
		Never worked at night	1; 3,652		
		< 8 hr	1.09 (0.73–1.65); 47		
		8–9 hr	1.12 (0.92–1.36); 213		
		≥ 10 hr	0.96 (0.78–1.19); 177		
Cordina-Duverger *et al.* 2016 Case-control France, Cote d'Or and Ille-et-Vilaine departments **Enrollment or follow-up:** 2005-2007	**Population:** CECILE Study Cases: 975; Controls: 1,317 **Exposure assessment method:** questionnaire	**OR Any night shift: post menopausal women**		Age, study area, age at menarche, parity, age at first full-term pregnancy, breastfeeding duration, OC use, menopausal hormone therapy, alcohol consumption, tobacco consumption, BMI, Fam hx BRCA	**Exposure information:** Night work is defined as working the entire time period between 11:00 PM and 5:00 AM. **Strengths:** Large, well-designed general population based case-control study with detailed, quality data on HER2, and ER and PR status. **Limitations:** Some subtypes with small numbers (e.g., ER-, PR-, and combinations of various subtypes) **Additional results:** - **Confidence in evidence:** Moderate to strong evidence
		Never worked at night	1; 540		
		Ever worked at night	0.97 (0.61–1.54); 39		
		ER+	0.96 (0.59–1.58); 33		
		ER-	1.08 (0.43–2.72); 6		
		PR+	0.92 (0.54–1.57); 25		
		PR-	1.06 (0.54–2.07); 14		
		ER+/PR+	0.91 (0.53–1.56); 24		
		ER+/PR-	1.2 (0.52–2.75); 9		
		HER2+	1.03 (0.38–2.81); 5		
		HER2-	0.96 (0.59–1.57); 34		
		HER2+ and (ER+ or PR+)	1.59 (0.55–4.59); 5		
		HER2+ and (ER- and PR-)	-		
		OR Any night shift: all women		Age, study area, age at menarche, parity, age at first full-term	
		Never worked at night	1; 876		
		Ever worked at night	1.38 (1.01–1.88); 99		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		ER +	1.49 (1.08–2.05); 87	pregnancy, breastfeeding duration, OC use, family history of breast cancer, menopausal hormone therapy, alcohol consumption, tobacco consumption, menopausal status, BMI	
		ER-	0.86 (0.44–1.7); 12		
		PR+	1.48 (1.06–2.06); 74		
		PR-	1.12 (0.68–1.84); 25		
		ER+/PR+	1.48 (1.06–2.07); 73		
		ER+/PR-	1.56 (0.82–2.98); 14		
		ER-/PR-	0.83 (0.41–1.67); 11		
		HER2+	1.91 (1.09–3.33); 20		
		HER2-	1.29 (0.93–1.78); 79		
		HER2+ and (ER+ or PR+)	2.52 (1.36–4.68); 17		
		HER2+ and (ER- and PR-)	0.75 (0.16–3.38); 3		
		OR Any night shift: pre-menopausal women		Age, age at menarche, study area, parity, age at first full-term pregnancy, breastfeeding duration, OC use, family history of breast cancer, alcohol consumption, tobacco consumption, BMI	
		Never worked at night	1; 336		
		Ever worked at night	1.77 (1.14–2.73); 60		
		ER +	2.04 (1.3–3.19); 54		
		ER -	0.7 (0.25–1.9); 6		
		PR +	1.98 (1.25–3.12); 49		
		PR -	1.12 (0.52–2.43); 11		
		ER+ PR+	2.02 (1.28–3.19); 49		
		ER+ PR-	2.24 (0.73–6.84); 5		
		HER2+	2.8 (1.36–5.76); 15		
		HER2-	1.58 (1–2.52); 45		
		HER2+ and (ER+ or PR+)	3.3 (1.42–7.67); 12		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		HER2+ and (ER- and PR-)	2.3 (0.36–14.7); 3		
Davis *et al.* 2001 Case-control Seattle, WA **Enrollment or follow-up:** 1992–1995	**Population:** Population-based study Cases: 813; Controls: 793 **Exposure assessment method:** questionnaire	**OR Duration of work (years) graveyard shift (≥ 1/week) within the past 10 years before diagnosis**		Parity, family history of breast cancer, OC use, use of HRT discontinued <5 years, age	**Exposure information:** At least 1 graveyard shift (7:00 PM–9:00 AM) per week within the 10 years before diagnosis **Strengths:** Detail on graveyard shifts; strong population based methods; limited potential for recall bias. **Limitations:** Small numbers of exposed; exposure window limited and excludes early exposures among the older women. **Additional results:** - **Confidence in evidence:** Moderate to strong evidence
		Never graveyard shift	1; 713		
		Ever graveyard shift	1.6 (1–2.5); 54		
		< 3 yr	1.4 (0.6–3.2); 15		
		≥ 3 yr	1.6 (0.8–3.2); 19		
		Continuous (per yr)	1.13 (1.02–1.27); 767		
		Trend-test *P*-value = 0.04			
		OR Hours of graveyard shift per week		Parity, Fam hx BRCA, OC use, use of HRT discontinued < 5 years, age	
		Never graveyard shift	1; 713		
		< 1.2 hr/wk	1.3 (0.5–3.1); 11		
		1.2–2.7 hr/wk	1.4 (0.6–3.2); 13		
		2.7–5.7 hr/wk	1.5 (0.6–3.6); 13		
		≥ 5.7 hr/wk	2.3 (1–5.3); 17		
		Continuous (per hr/wk)	1.06 (1.01–1.13); 767		
		Trend-test *P*-value = 0.04			
Fritschi *et al.* 2013, 2018 Case-control Western Australia **Enrollment or follow-up:**	**Population:** Population-based study Cases: 1,202; Controls: 1,785 **Exposure assessment method:** expert assessment	**OR Graveyard shift: Ever/Never, 2013 and 2018 reclassified exposure, All women**		For 2017 analysis, only age. For 2018 analysis, age, age at menarche, age at first full-term pregnancy, parity, breastfeeding,	**Exposure information:** **2013 Report:** Night shift: midnight to 5:00 AM. Phase shift: High exposure (> 4 nights forward or > 6 nights backward rotation); medium (3–4 forward, or 4–6 backward rotation); low (3 nights
		Never, 2013	1; 914		
		Ever, 2013	1.16 (0.97–1.38); 288		
		Never, 2018	1; 949		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
May 2009 - January 2011		Ever, 2018	1.27 (1.05–1.54); 250	family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT, menopausal status.	backward rotation). **2018 Report:** Reclassified exposure data by incorporating concepts of chronotype and circadian disruption into the definition of exposure. Circadian disruption (CD) was defined as occurring if working ≥ 1 hour during preferred hours of sleep ("biological night"). Late CD occurred if ≥ 1 hour of evening work day was after the start of the biological night; early CD occurred if start of the morning work day was before the end of biological night. **Strengths:** Large population-based study with exposure assessment closely linked to biological mechanisms; good examination of and control for potential confounders occurring at relevant time periods. Strong analytic methods. Adequate number (N = 24) of exposed cases at medium/high levels of exposure for long duration. **Limitations:** Low response rate, particularly among controls. **Additional results:** - **Confidence in evidence:** Some evidence
		OR Graveyard shift: Ever/Never, 2018 reclassified, premenopausal women		Age, age at menarche, age at first full-term pregnancy, parity, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco	
		Never, 2018 reclassified	1; 276		
		Ever, 2018 reclassified	1.48 (1.02–2.15); 79		
		OR Graveyard shift: Ever/Never, 2018 reclassified, postmenopausal women		Age, age at menarche, age at first full -erm pregnancy, parity, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT	
		Never, 2018 reclassified	1; 673		
		Ever, 2018 reclassified	1.24 (0.99–1.55); 171		
		OR Graveyard shift: Duration (years)		Age	
		Never	1; 914		
		< 10 yr	1.25 (1–1.56); 164		
		10–19 yr	1.09 (0.79–1.5); 71		
		≥ 20 yr	1.02 (0.71–1.45); 53		
		OR Phase shift: Intensity and duration (years)		Age	
		Never phase shift	1; 959		
		Ever phase shift	1.22 (1.01–1.47); 242		
		Low phase shift	1.09 (0.7–1.68); 36		
		Medium phase shift	1.24 (0.97–1.57); 140		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		High phase shift	1.25 (0.9–1.75); 66		
		< 10 yr medium/high phase shift	1.35 (1.06–1.72); 140		
		10–19 yr medium/high phase shift	1.12 (0.74–1.68); 42		
		≥ 20 yr medium/high phase shift	0.96 (0.58–1.61); 24		
		OR Circadian preference: Morning type		Age	
		Graveyard shift	1.12 (0.81–1.55); 344		
		Phase shift	1.23 (0.87–1.72); 77		
		OR Circadian preference: Neutral type		Age	
		Graveyard shift	1.34 (1.04–1.73); 594		
		Phase shfit	1.34 (1.02–1.77); 119		
		OR Circadian preference: Evening type		Age	
		Graveyard shift	0.95 (0.66–1.38); 248		
		Phase shift	1.02 (0.68–1.52); 57		
		OR Menopausal status: premenopausal and postmenopausal		Age	
		Premenopausal: Graveyard shift	1.13 (0.81–1.57); 92		
		Postmenopausal: Graveyard shift	1.18 (0.96–1.45); 196		
		Premenopausal: Phase shift	1.22 (0.85–1.74); 74		
		Postmenopausal: Phase shift	1.21 (0.97–1.51); 168		
		OR Early and Late CD, 2018		Age, age at menarche,	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Early CD: ever	1 (0.82–1.21); 204	age at first full -erm pregnancy, parity, breastfeeding, family history of breast cancer, OC use, BMI, alcohol, tobacco, HRT	
		Early CD: > 11.5 yr	0.94 (0.65–1.35); 48		
		Late CD: ever	1.17 (0.97–1.41); 254		
		Late CD: > 11.5 yr	0.88 (0.65–1.19); 74		
Grundy *et al.* 2013 Case-control Vancouver, BC and Kingston, ON **Enrollment or follow-up:** 2005–2010	**Population:** Population-based study Cases: 1,134; Controls: 1,179 **Exposure assessment method:** questionnaire	**OR Duration (years) of night work starting or ending 11:00 PM-7:00 AM**		Age, study center, household income, education, age at first mammogram	**Exposure information:** Night work: jobs starting or ending between 11:00 PM and 7:00 AM. **Strengths:** Use of lifetime occupatonal history; start and end times collected, categories created for intensity/frequency of night or evening shifts worked for each job. Compared risk in health workers and non-health workers. **Limitations:** Analyses combined evening and night workers and those working permanent and rotational shifts. *In situ* and invasive cancers combined. **Additional results:** The interaction with yrs of 50% eve/nights and menopausal status was p=0.01 (>0-14 yrs); p=0.7 (15-29 yrs); and p=0.2 (≥30 yrs). **Confidence in evidence:** Moderate to strong evidence
		None	1; 826		
		> 0–14 yr	1.29 (1.01–1.65); 172		
		15–29 yr	1.27 (0.83–1.95); 49		
		≥ 30 yr	1.68 (0.74–3.79); 16		
		OR 50% evenings and/or nights: Duration (years of work)		Age, study center	
		None	1; 751		
		> 0–14 yr	0.95 (0.79–1.16); 283		
		15–29 yr	0.93 (0.67–1.3); 72		
		≥ 30 yr	2.21 (1.14–4.31); 28		
		Trend-test *P*-value = 0.5			
		OR 80% evenings and/or nights: Duration (years) of work		Same as above	
		None	1; 941		
		> 0–14 yr	0.95 (0.75–1.2); 162		
		15–29 yr	0.98 (0.53–1.82); 20		
		≥ 30 yr	3.73 (1.04–13.42); 11		
		Trend-test *P*-value = 0.5			
		OR 100% evenings and/or nights: Duration (years) of shift work		Same as above	
		None	1; 976		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		> 0–14 yr	1.05 (0.82–1.35); 136		
		15–29 yr	1.93 (0.86–4.36); 17		
		≥ 30 yr	2.63 (0.51–13.64); 5		
		Trend-test *P*-value = 0.5			
		OR Type of occupation: ≥ 30 years working shifts (50% evening and/or nights)		Same as above	
		Health occupations	3.11 (1.1–8.77); 12		
		Non-health occupations	2.25 (0.92–5.52); 16		
		OR Premenopausal: Duration (years) of working shifts (50% evenings and/or nights)		Age, study center, BMI	
		None	1; 220		
		> 0–14 yr	1.32 (0.97–1.8); 126		
		15–29 yr	0.99 (0.57–1.7); 27		
		≥ 30 yr	1.3 (0.66–2.58); 18		
		Trend-test *P*-value = 0.3			
		OR Postmenopausal: Duration (years) of working shifts (50% evenings and/or nights)		Age, study center, BMI	
		None	1; 531		
		> 0–14 yr	0.75 (0.58–0.97); 142		
		15–29 yr	0.97 (0.63–1.49); 48		
		≥ 30 yr	1.63 (0.8–3.35); 22		
		Trend-test *p*-value: 0.8			
		OR Hormone receptor status: ≥ 30 yrs working 50% night and/or eventings		Age, study center	
		ER+/PR+	2.37 (1.18–4.76); 22		
		ER-/PR-	1.06 (0.24–4.75); 2		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Hansen 2001 Case-control Denmark **Enrollment or follow-up:** NR	**Population:** Danish female breast cancer cases and matched controls from the central population registry 30-54 years of age linked to national pension fund data on employment. Cases: 7,035; Controls: 7,035 **Exposure assessment method:** job title	**OR Work trades with ≥ 60% night time jobs, 5 year lag**		Age, age at first birth, age at last birth, social status	**Exposure information:** Ever working in trades with ≥60% night work **Strengths:** Nationwide study of breast cancer. Employment histories assessed independently of cancer diagnoses. **Limitations:** The exposure assessment methods have only weak sensitivity and specificity; confounders were not all measured on an individual level. Aggregated data from a separate survey were used to estimate exposure to night work. **Additional results:** The upper confidence interval (CI) for the estimate on all night trades for duration of > 6 years is incorrect in the publication. **Confidence in evidence:** Some evidence
		Ever work in trades with < 40% night time work	1; 5,847		
		Ever work in trades with ≥ 60% night time work	1.5 (1.3–1.7); 434		
		Work in trades with ≥60% night time work for > 6 years	1.7 (1.3–1.7); 117		
Hansen and Lassen 2012 Nested case-control Denmark **Enrollment or follow-up:** 2005–2006	**Population:** Danish female military workers Cases: 141; Controls: 551 **Exposure assessment method:** questionnaire	**OR Duration (years) of night work**		Age, HRT use, age at menarche, education, parity/nulliparity, smoking status	**Exposure information:** Night shift work beginning by 5:00 PM and ending before 9:00 AM for 1 year (includes both rotating and permanent) **Strengths:** Well-defined cohort based on complete routinely collected employment data and identification of all breast cancer cases from the national registry. Exposure assessment methods have good sensitivity and specificity for reliably classifying ever/never exposure, intensity/frequency, and duration from lifelong job histories; low chance of recall bias. **Limitations:** Potential exposure misclassification due to broad exposure definition.
		Never	1; 89		
		Ever	1.4 (0.9–2.1); 43		
		1–5.9 yr	0.9 (0.4–1.7); 13		
		6–14.9 yr	1.7 (0.9–3.2); 18		
		≥ 15 yr	2.1 (1–4.5); 12		
		Trend-test *P*-value: 0.03			
		OR Cumulative # of night shifts		Same as above	
		Never	1; 82		
		< 416	0.8 (0.4–1.9); 9		
		416–1,560	1.4 (0.7–2.9); 14		
		≥ 1,560	2.3 (1.2–4.6); 17		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *P*-value = 0.02			**Additional results:** - **Confidence in evidence:** Moderate to strong evidence
		OR Duration (years) and frequency (shifts/wk)		Same as above	
		Never	1; 82		
		1–2 night shifts/wk, all durations	1 (0.5–1.9); 15		
		1–5.9 yr, ≥ 3/wk	1.1 (0.5–2.3); 9		
		6–14.9 yr, ≥ 3/wk	2.1 (1–4.8); 11		
		≥ 15yr, ≥ 3/wk	2.5 (1–6.6); 9		
		Trend-test *P*-value = 0.02			
		OR > 844 total night shifts and chronotype		Same as above	
		Morning	3.9 (1.6–9.5); 12		
		Evening	2 (0.7–5.8); 10		
		Neither	0.7 (0.1–3); 3		
Hansen and Stevens 2012 Nested case-control Denmark **Enrollment or follow-up:** 2002–2005	**Population:** Danish Female Nurse Cohort Cases: 267; Controls: 1,035 **Exposure assessment method:** questionnaire	**OR Shift work schedule type**		Age, weight regularity, HRT use, family history of breast cancer, age at menarche, menstrual regularity, menopausal status, age at first birth, parity, breastfeeding duration	**Exposure information:** Night shift 11:00 PM to 9:00 AM; permanent and type of rotating: day-evening, day-night, day-evening-night **Strengths:** Large nationwide cohort of female nurses in Denmark with similar shift systems; detailed exposure assessment of various shift systems with opportunity to look at duration and intensity; sufficient numbers of exposed subjects; control of potential confounders **Limitations:** Limited number of referents; overlapping shift system categories. **Additional results:**
		Permanent day shifts	1; 28		
		Ever evening, never night	0.9 (0.4–1.9); 9		
		Ever night,rotating (no permanent nights)	1.8 (1.2–2.8); 212		
		Ever permanent + rotating nights	2.9 (1.1–8); 18		
		OR Duration (yrs) working night			
		Day/evening workers	1; 37		
		1–5 yr	1.5 (0.99–2.5); 55		
		5–10 yr	2.3 (1.4–3.5); 70		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		10–20 yr	1.9 (1.1–2.8); 66		- **Confidence in evidence:** Moderate to strong evidence
		≥ 20 yr	2.1 (1.3–3.2); 39		
		Continuous (per year)	1.018 (1.01–1.027); 267		
		OR Cumulative number of night shfts		Same as above	
		Day/evening workers	1; 37		
		< 468	1.6 (1–2.6); 63		
		468–1,095	2 (1.3–3); 80		
		≥ 1,095	2.2 (1.5–3.2); 87		
		OR # Rotating day-night shifts		Same as above	
		Permanent day	1; 28		
		< 732	1.5 (0.9–2.4); 30		
		≥ 733	2.6 (1.8–3.8); 11		
		Other non-day shifts	2 (1.3–3.1); 198		
		OR # Rotating day/evening/night shifts		Same as above	
		Permanent day	1; 28		
		< 732	1.8 (1.2–3.1); 127		
		≥ 733	1.9 (1.1–3.3); 86		
		Other non-day shifts	1.2 (0.7–2.3); 26		
Lie *et al.* 2013 Nested case-control Norway **Enrollment or follow-up:** Jan 1996–Dec 2007, restricted	**Population:** Norwegian nurses cohort. Cases: 513; Controls: 757 **Exposure assessment method:** questionnaire	**OR ER positive; duration of work with ≥ 6 consecutive nights**		Period of diagnosis, parity, history of breast cancer in mother and/or sister, alcohol consumption at time of diagnosis, age at diagnosis, hormonal treatment	**Exposure information:** Working for ≥ 5 yr working for on average ≥ 6 consecutive nights, midnight to 6:00 AM **Strengths:** Large cohort of nurses with large number of breast cancer cases; complete cancer registration for the study period. Exposure metrics based on prior detailed analysis in same cohort.
		Never worked nights	1; 63		
		Never worked ≥ 6 consecutive nights	1.2 (0.9–1.8); 274		
		< 5 yr	1.3 (0.8–2); 73		
		≥ 5 yr	1.8 (1–3.1); 36		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *P*-value = 0.06		within 2 years of diagnosis	**Limitations:** Small numbers of ER/PR subgroups; limited sensitivity in some subgroups. **Additional results:** - **Confidence in evidence:** Moderate to strong evidence
		OR ER negative; duration of work (years) with ≥ 6 consecutive nights		Same as above	
		Never worked nights	1; 6		
		Never worked ≥ 6 consecutive nights	2 (0.8–4.8); 45		
		< 5 yr	1.7 (0.6–4.8); 10		
		≥ 5 yr	2.8 (0.8–9.2); 6		
		Trend-test *P*-value = 0.19			
		OR PR positive; Duration of work (years) with ≥ 6 consecutive nights		Same as above	
		Never worked nights	1; 45		
		Never worked ≥ 6 consecutive nights	1.3 (0.9–2); 203		
		< 5 yr	1.4 (0.9–2.4); 57		
		≥ 5 yr	2.4 (1.3–4.3); 33		
		Trend-test *P*-value = 0.01			
		OR PR negative; Duration of work (years) with ≥ 6 consecutive nights		Same as above	
		Never worked nights	1; 22		
		Never worked 6+ consecutive nights	1.4 (0.8–2.4); 114		
		< 5 yrs	1.2 (0.7–2.3); 26		
		≥ 5 yrs	1.2 (0.5–2.8); 9		
		Trend-test *p*-value: 0.76			
		OR ER+/PR+: Duration of work (years) with ≥ 6 consecutive night shifts		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Never worked nights	1; 45		
		Never worked ≥ 6 consecutive nights	1.3 (0.9–1.9); 197		
		< 5 yr	1.4 (0.9–2.3); 56		
		≥ 5 yr	2.2 (1.2–4.1); 31		
		Trend-test *P*-value = 0.01			
		OR ER+/PR-: Duration of work (years) with ≥ 6 consecutive night shifts		Same as above	
		Never worked nights	1; 16		
		Never worked ≥ 6 consecutive nights	1.3 (0.7–2.3); 75		
		< 5 yr	1.1 (0.5–2.4); 17		
		≥ 5 yr	0.9 (0.3–2.6); 5		
		Trend-test *p*-value: 0.89			
		OR ER-/PR-: Duration of work (years) with ≥ 6 consecutive night shifts		Same as above	
		Never worked nights	1; 6		
		Never worked ≥ 6 consecutive nights	1.7 (0.7–4.2); 39		
		< 5 yr	1.5 (0.5–4.4); 9		
		≥ 5 yr	1.9 (0.5–7); 4		
		Trend-test *P*-value = 0.45			
Lie *et al.* 2011 Nested case-control Norway **Enrollment or**	**Population:** Norwegian nurses cohort Cases: 699; Controls: 895 **Exposure assessment method:** Questionnaire	**OR Duration of work (years) with ≥ 3 consecutive night shift**		Period of diagnosis, parity, history of breast cancer in mother and/or sister, alcohol consumption	**Exposure information:** Night shiftw were those shifts lasting at least from midnight to 6:00 AM. **Strengths:** Large cohort of nurses with large number of
		Never worked nights	1; 102		
		Never worked 3 consecutive nights	1.4 (1–2.1); 125		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
follow-up: Jan 1990–Dec 2007, update		< 5 yr	1.1 (0.8–1.6); 194	at time of diagnosis, age at diagnosis	breast cancer cases; complete cancer registration for the study period; thorough analysis of multiple exposure metrics. **Limitations:** Potential recall bias; loss of cases in this prevalent cohort may have introduced a selection bias towards the null. **Additional results:** - **Confidence in evidence:** Moderate to strong evidence
		≥ 5 yr	1.1 (0.8–1.5); 278		
		Trend-test *p*-value: 0.92			
		OR Duration of work (years) with ≥ 4 consecutive nights		Same as above	
		Never worked 4 consecutive nights	1.1 (0.8–1.5); 306		
		< 5 yr	1.2 (0.8–1.6); 160		
		≥ 5 yr	1.4 (0.9–1.9); 131		
		Trend-test *p*-value: 0.10			
		OR Duration of work (years) with ≥ 5 consecutive nights		Same as above	
		Never worked 5 consecutive nights	1.1 (0.8–1.5); 386		
		< 5 yr	1.2 (0.8–1.7); 137		
		≥ 5 yr	1.6 (1–2.4); 74		
		Trend-test *P*-value = 0.05			
		OR Duration of work (years) with ≥ 6 consecutive nights		Same as above	
		Never worked 6 consecutive nights	1.1 (0.8–1.5); 414		
		< 5 yr	1.2 (0.8–1.7); 119		
		≥ 5 yr	1.8 (1.1–2.8); 64		
		Trend-test *P*-value = 0.02			
		OR Duration of work (years) with ≥ 7 consecutive nights		Same as above	
		Never worked 7 consecutive nights	1.1 (0.9–1.5); 430		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		< 5 yr	1.1 (0.8–1.6); 109		
		≥ 5 yr	1.7 (1.1–2.8); 58		
		Trend-test *P*-value = 0.05			
Menegaux *et al.* 2013 Case-control France, Cote d'Or and Ille-et-Vilaine departments **Enrollment or follow-up:** 2005–2007	**Population:** CECILE Study Women 25–75 years of age living in two administrative departments. Cases: 1,232; Controls: 1,317 **Exposure assessment method:** questionnaire	**OR Type of shift**		Age, study area, age at menarche, parity, age at first full-term pregnancy, alcohol consumption, tobacco consumption, BMI, Current menopausal hormone therapy, family history of breast cancer	**Exposure information:** Working ≥ 6 months for at least 6 hours between 11:00 PM and 5:00 AM was defined as overnight work. Any night work could also include late evening (work shift ending between 11:00 PM and 3:00 AM) or early morning (work shift starting between 3:00 AM and 5:00 AM. **Strengths:** Large, well-designed general population-based case-control study able to categorize type of night work, and intensity and duration and timing of night work relative to first full-term pregnancy. **Limitations:** Rotating types of night work, direction and rate of rotation, and number of consecutive nights at work were not quantified due to large number of work systems represented in the population. **Additional results:** - **Confidence in evidence:** Moderate to strong evidence
		Never worked at night	1; 1,068		
		Ever worked overnight)	1.35 (1.01–1.8); 120		
		OR Duration of work (years)		Age, study area, age at menarche, parity, age at first full-term pregnancy, family history of breast cancer, alcohol consumption, tobacco consumption, BMI, current menopausal hormone therapy	
		< 4.5 yr overnight	1.27 (0.83–1.94); 51		
		≥ 4.5 yr overnight	1.4 (0.96–2.04); 69		
		OR Frequency(shift/wk)		Age, study area, age at menarche, parity,	
		< 3 overnight	1.61 (1.07–2.42); 64		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		≥ 3 overnight	1.13 (0.76–1.68); 56	age at first full-term pregnancy, alcohol consumption, tobacco consumption, BMI, Current menopausal hormone therapy, family history of breast cancer	
		OR Any night shift: Pre-menopausal status		Age, study area, age at menarche, parity, age at first full-term pregnancy, family history of breast cancer, alcohol consumption, tobacco consumption, BMI, Current menopausal hormone therapy	
		Never worked	1; 492		
		Ever worked	1.36 (0.98–1.87); 110		
		Ever worked overnight	1.48 (1.03–2.13); 85		
		< 4.5 yr	1.4 (0.89–2.21); 49		
		≥ 4.5 yr	1.32 (0.87–2); 61		
		< 3 any night shift/wk	1.32 (0.87–2.01); 61		
		≥ 3 any night shift/wk	1.4 (0.89–2.21); 49		
		1st worked before first full-term pregnancy	1.59 (1.05–2.4); 55		
		OR Any night shift: post menopausal		Age, study area, age at menarche, parity, age 1st ft preg, family history of breast cancer, alcohol consumption, tobacco consumption, BMI, Current menopausal hormone therapy	
		Never	1; 576		
		Ever	1.08 (0.72–1.63); 54		
		Ever overnight	1.03 (0.62–1.71); 35		
		< 4.5 yr any night shift	0.63 (0.33–1.2); 17		
		≥ 4.5 yr any night shift	1.54 (0.91–2.61); 37		
		< 3 shifts/wk	1.82 (0.92–3.61); 23		
		≥ 3 shifts/wk	0.82 (0.5–1.36); 31		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		First worked before first full-term pregnancy	1.13 (0.62–2.06); 21		
		OR All women, duration (years) and frequency (overnight shift/wk)		Age, study area, age at menarche, parity, age at first full-term pregnancy, family history of breast cancer, alcohol consumption, tobacco consumption, BMI, Current menopausal hormone therapy	
		≥ 4.5 yr and < 3 nights/wk	1.83 (1.15–2.93); 54		
		≥ 4.5 yr and ≥ 3 nights/wk	1.1 (0.71–1.69); 44		
		≥ 4.5 yr and < 3 nights/wk	2.09 (1.26–3.45); 49		
		≥ 4.5 yr and ≥ 3 nights/wk	0.91 (0.55–1.5); 31		
		OR Parous women: 1st worked before first full-term pregnancy (FFTP) and type of night shift		Age, study area, age at menarche, parity, age at first full-term pregnancy, family history of breast cancer, alcohol consumption, tobacco consumption, BMI, Current menopausal hormone therapy	
		Never night work	1; 954		
		1st work after first full-term pregnancy	1.09 (0.77–1.55); 66		
		1st work before first full-term pregnancy	1.47 (1.02–2.12); 76		
		Late evening work before first full-term pregnancy	1.89 (0.87–4.08); 18		
		Early morning work before first full-term pregnancy	1.09 (0.38–3.12); 6		
		Overnight work before first full-term pregnancy	1.49 (0.96–2.32); 52		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		OR Parous women: Duration (years) of any night work before the first full-term pregnancy		Age, study area, age at menarche, parity, age at first full-term pregnancy, family history of breast cancer, alcohol consumption, tobacco consumption, BMI, Current menopausal hormone therapy	
		≤ 4 yr	1.15 (0.7–1.89); 33		
		> 4 yr	1.95 (1.13–3.35); 43		
		< 3 shifts	2.24 (1.35–3.71); 47		
		≥ 3 shifts	0.96 (0.56–1.62); 29		
		> 4 yr and < 3 shifts	3.03 (1.41–6.5); 26		
		> 4 yr and ≥ 3 shifts	1.3 (0.61–2.77); 17		
O'Leary *et al.* 2006 Case-control Long Island, NY **Enrollment or follow-up:** August 1996–June 1997	**Population:** Electromagnetic fields and breast cancer on Long Island Cases: 487; Controls: 509 **Exposure assessment method:** questionnaire	**OR Type of shift work**		Age, parity, family history of breast cancer, education, benign breast disease	**Exposure information:** Any shift work in the past 15 years including evenings (afternoon to 2:00 AM) and overnight (7:00 PM to morning) shifts **Strengths:** Population-based study nested in well-conducted larger study; analytic control for potential confounders. **Limitations:** Highly selected population based on long term residence; exposure assessment was limited to the past 15 years in this somewhat older subset of participants. Small number of women with overnight exposure history. **Additional results:** - **Confidence in evidence:** No evidence
		No evening or overnight	1; 313		
		Any overnight	0.55 (0.32–0.94); 26		
		Only overnight	0.64 (0.28–1.45); 10		
		Any evening	1.08 (0.81–1.44); 164		
		Only evening	1.21 (0.9–1.64); 148		
		OR Duration (years) of any overnight work with > 1 shift/wk		Same as above	
		< 1 shift/wk	1; 469		
		< 8 yr	0.74 (0.32–1.68); 11		
		≥ 8 yr	0.32 (0.12–0.83); 6		
		OR Duration (years) of any evening work with > 1 shift/wk		Same as above	
		< 1 shift/wk	1; 356		
		< 5 yr	0.91 (0.6–1.38); 51		
		≥ 5 yr	1.24 (0.86–1.8); 79		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Papantoniou *et al.* 2015 Case-control Spain **Enrollment or follow-up:** 2008–2013	**Population:** MCC-Spain population-based Cases: 1708; Controls: 1778 **Exposure assessment method:** questionnaire	**OR Type of shift**		Age, study center, education, menopausal status, family history of breast cancer, BMI, Smoking status, OC use, leisure time physical activity, alcohol consumption	**Exposure information:** Partly or entirely working midnight–6:00 AM at least 3 nights/month; duration and cumulative frequency. **Strengths:** Large population-based case-control study; detailed exposure assessment including differentiation of rotating and permanent night work; duration and frequency of night shifts. Detailed analysis used to control multiple potential confounders. **Limitations:** Some attrition in control recruitment **Additional results:** - **Confidence in evidence:** Some evidence
		Never night work	1; 1,438		
		Ever night work	1.18 (0.97–1.43); 270		
		Permanent night work	1.19 (0.89–1.6); 114		
		Rotating night work	1.17 (0.91–1.51); 156		
		OR Excluding housewives and rotating shift workers without night shift		Same as above	
		Never shift work	1; 1,190		
		Permanent night work	1.13 (0.84–1.51); 114		
		Rotating night work	1.11 (0.86–1.43); 156		
		OR Cumulative years of total night work		Same as above	
		Never shift work	1; 1,438		
		1–4 yr	1.21 (0.83–1.76); 67		
		5–14 yr	1.13 (0.83–1.53); 103		
		≥ 15 yr	1.21 (0.89–1.65); 97		
		OR Cumulative years of permanent night work		Same as above	
		Never night work	1; 1,438		
		1–4 yr	1 (0.59–1.66); 32		
		5–14 yr	1.17 (0.74–1.87); 46		
		≥ 15 yr	1.49 (0.88–2.53); 34		
		Trend-test *P*-value = 0.109			
		OR Cumulative years of rotating night work		Same as above	
		Never night work	1; 1,438		
		1–4 yr	1.58 (0.94–2.66); 40		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		5–14 yr	0.96 (0.65–1.41); 56		
		≥ 15 yr	1.22 (0.82–1.81); 59		
		Trend-test *P*-value = 0.369			
		OR Cumulative number of total night shifts		Same as above	
		Never night work	1; 1,438		
		36–599	1.15 (0.8–1.64); 62		
		600–1,799	1.2 (0.85–1.7); 53		
		≥ 1,800	1.18 (0.83–1.69); 56		
		Trend-test *P*-value = 0.248			
		OR Cumulative number of permanent night shifts		Same as above	
		Never night work	1; 1,438		
		36–599	0.96 (0.5–1.85); 14		
		600–1,799	1.15 (0.65–2.04); 16		
		≥1,800	1.48 (0.81–2.68); 20		
		Trend-test *P*-value = 0.149			
		OR Cumulative number of rotating night shifts		Same as above	
		Never night work	1; 1,438		
		36–599	1.34 (0.77–1.67); 14		
		600–1,799	1.32 (0.83–2.08); 16		
		≥ 1,800	1.08 (0.66–1.79); 20		
		Trend-test *P*-value = 0.519			
		OR Morning chronotype: Type of work		Same as above	
		Never night work	1; 425		
		Ever night work	1.17 (0.83–1.65); 89		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Permanent night work	1.26 (0.76–2.09); 37		
		Rotating night work	1.11 (0.71–1.74); 52		
		OR Morning chronotype: Night work cumulative duration and # of shifts		Same as above	
		Never night work	1; 425		
		1–4 yr	2.09 (1.03–4.22); 24		
		5–14 yr	1.14 (0.66–1.98); 32		
		≥ 15 yr	0.91 (0.54–1.51); 31		
		36–599 shifts	2.1 (1–4.42); 23		
		600–1,799 shifts	1 (0.57–1.8); 19		
		≥ 1,800 shifts	0.9 (0.5–1.59); 17		
		OR Evening chronotype: Type of shift		Same as above	
		Never night work	1; 275		
		Ever night work	1.27 (0.81–2); 56		
		Permanent night work	1.11 (0.59–2.12); 25		
		Rotating night work	1.43 (0.79–2.59); 31		
		OR Evening chronotype: Night work cumulative duration and # of shifts		Same as above	
		Never night work	1; 275		
		1–4 yr	0.95 (0.44–2.03); 13		
		5–14 yr	1.17 (0.55–2.48); 20		
		≥ 15 yr	1.76 (0.85–3.67); 23		
		36–599 shifts	0.8 (0.37–1.72); 9		
		600–1,799 shifts	1.9 (0.86–4.22); 14		
		≥ 1,800 shifts	1.38 (0.59–3.24); 10		
		OR Night shift and menopausal status		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Premenopausal: Never	1; 552		
		Premenopausal: Ever	1.33 (0.98–1.79); 140		
		Postmenopausal: Never	1; 1037		
		Postmenopausal: Ever	1.08 (0.82–1.42); 130		
		OR Night shift and first full-time pregnancy		Same as above	
		1st exposure before first full-term pregnancy	1.25 (0.93–1.67); 130		
		1st exposure after first full-term pregnancy	1.14 (0.81–1.6); 81		
		OR Subtypes: Premenopausal		Same as above	
		ER+	1.38 (1–1.89); 552		
		ER-	1.01 (0.56–1.82); 103		
		PR+	1.44 (1.05–1.99); 498		
		PR-	0.9 (0.54–1.51); 154		
		ER+/PR+	1.44 (1.04–1.98); 485		
		ER+/PR-	0.87 (0.4–1.89); 61		
		ER-/PR+	2.56 (0.49–13.29); 9		
		ER-/PR-	0.91 (0.48–1.72); 93		
		Her2 nue+	1.56 (0.94–2.59); 116		
		Her2 nue-	1.25 (0.9–1.73); 501		
		Invasive	1.35 (0.99–1.83); 607		
		In situ	1.37 (0.67–2.79); 58		
		I–II grade	1.27 (0.88–1.81); 359		
		III–IV grade	0.86 (0.51–1.45); 159		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Ductal	1.37 (1–1.89); 524		
		Lobular	1.74 (0.82–3.7); 46		
		OR Postmenopausal: Subtypes		Same as above	
		ER+	1.05 (0.78–1.41); 791		
		ER-	1.2 (0.75–1.94); 181		
		PR+	0.95 (0.7–1.31); 652		
		PR-	1.43 (0.99–2.1); 309		
		ER+/PR+	0.94 (0.68–1.29); 640		
		ER+/PR-	1.81 (1.11–2.95); 138		
		ER-/PR+	1.15 (0.18–7.32); 10		
		ER-/PR-	1.2 (0.73–1.97); 169		
		Her2 nue+	1.07 (0.65–1.79); 174		
		Her2 nue-	1.1 (0.82–1.48); 733		
		Invasive	1.15 (0.87–1.53); 1,470		
		In situ	0.68 (0.35–1.34); 170		
		I–II grade	0.9 (0.64–1.27); 540		
		III–IV grade	1.65 (1.07–2.54); 200		
		Ductal	1.1 (0.82–1.47); 741		
		Lobular	1.62 (0.8–3.28); 65		
Pesch *et al.* 2010 Case-control Bonn, Germany Enrollment or follow-up: 2000–2004	Population: GENICA Study Cases: 857; Controls: 892 Exposure assessment method: interview	**OR Cumulative number of night shifts (adjusted PR not bootstrap)**		Family history of breast cancer, use of post menopausal hormones, number of mammograms, age	**Exposure information:** Night work: Ever working midnight to 5:00 AM full time ≥1 year; duration and cumulative number of shifts. **Strengths:** Large population based case-control study with precise definition of night work; assessed both
		Never worked at night	1; 698		
		Ever worked at night	1.01 (0.68–1.5); 55		
		< 807 (total)	0.66 (0.4–1.11); 25		
		≥ 807 (total)	1.78 (0.89–3.58); 23		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		< 1056 (≥ 3/mo)	0.8 (0.47–1.36); 25		intensity and duration and timing of shift work. **Limitations:** Low prevalence of shift work and long term night shift work limited the power of the study to detect an effect. **Additional results:** - **Confidence in evidence:** Some evidence
		≥ 1056 (≥ 3/mo)	1.66 (0.8–3.46); 20		
		OR Duration (years) of night work (adj. OR not boot strap)		Same as above	
		0–4 yr	0.64 (0.34–1.24); 15		
		5–9 yr	0.93 (0.41–2.15); 11		
		10–19 yr	0.91 (0.38–2.18); 10		
		≥ 20 yr	2.49 (0.87–7.18); 12		
		OR Age (years) at 1st night shift (adj OR not bootstrap)		Same as above	
		< 20 yr	0.53 (0.28–1.03); 14		
		20–29 yr	1.51 (0.8–2.83); 25		
		30–39 yr	1.25 (0.38–4.15); 6		
		≥ 40 yr	0.98 (0.19–5.09); 3		
		OR Years since last night shift (adjusted OR not bootstrap)		Same as above	
		Currently working night shifts	1.1 (0.51–2.38); 14		
		1–9 yr	1.04 (0.31–3.53); 6		
		10–19 yr	1.69 (0.69–4.14); 13		
		≥ 20 yr	0.62 (0.33–1.19); 15		
		OR Postmenopausal women: Cumulative number of night shifts		Same as above	
		Employed, but never in shiftwork	1; 510		
		< 807 nights	0.65 (0.34–1.23); 16		
		≥ 807 nights	2.29 (0.91–5.78); 14		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		< 1,056 and > 3/month	0.71 (0.39–1.36); 16		
		≥ 1,056 and > 3/month	2.09 (0.76–5.78); 11		
		OR Postmenopausal women: Duration (years) of night shift work		Same as above	
		Employed, but never in shiftwork	1; 510		
		> 0–< 5 yr	0.46 (0.21–1.03); 9		
		5–9 yr	1.54 (0.48–4.97); 7		
		10–19 yr	1.45 (0.38–5.57); 5		
		≥ 20 yr	2.6 (0.89–8.57); 9		
		OR Postmenopausal women: Years since last night shift		Same as above	
		Employed, but never in shiftwork	1; 510		
		Current night work	1.76 (0.48–6.31); 6		
		1–9 yr	0.84 (0.16–4.39); 3		
		10–19 yr	1.91 (0.55–6.67); 7		
		≥ 20 yr	0.71 (0.36–1.4); 14		
Rabstein *et al.* 2013 Case-control Bonn, Germany **Enrollment or follow-up:** 2000–2004	**Population:** GENICA Study Cases: 857; Controls: 892 **Exposure assessment method:** questionnaire	**OR ER positive: Cumulative # of night shifts**		Age, family history of breast cancer, use of post menopausal hormones, number of mammograms	**Exposure information:** Night work: Ever working midnight to 5:00 AM full time ≥1 year; duration and cumulative number of shifts. **Strengths:** Large population-based case-control study with detailed analysis by breast cancer subtypes. **Limitations:** Low prevalence of long term night shift work for subtypes. The study had limited power to assess the association between night shift work and
		Never worked at night	1; 539		
		Ever worked at night	0.98 (0.63–1.5); 39		
		< 807 total shifts	0.66 (0.37–1.16); 18		
		≥ 807 total shifts	1.56 (0.73–3.33); 15		
		< 1,056 (≥ 3/mo)	0.74 (0.41–1.36); 17		
		≥ 1,056 (≥ 3/mo)	1.46 (0.65–3.28); 13		
		OR ER positive: Duration (years) of night shifts		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		> 1–< 5 yr	0.58 (0.27–1.22); 10		estrogen receptor status. **Additional results:** - **Confidence in evidence:** Some evidence
		5–< 10 yr	0.96 (0.39–2.4); 8		
		10–19 yr	1.04 (0.41–2.64); 8		
		≥ 20 yr	1.81 (0.56–5.83); 7		
		OR ER negative: Cumulative # of night shifts		Age, family history of breast cancer, use of post menopausal hormones, number of mammograms	
		Never worked at night	1; 134		
		Ever worked at night	1.16 (0.62–2.18); 14		
		< 807 (total)	0.71 (0.29–1.75); 6		
		≥ 807 (total)	2.34 (0.89–6.14); 7		
		< 1,056 (≥ 3/mo)	1.02 (0.44–2.4); 7		
		≥ 1,056 (≥ 3/mo)	2.11 (0.76–5.9); 6		
		OR ER negative: Duration (years) of night shift		Same as above	
		> 1–< 5 yr	0.89 (0.3–2.64); 4		
		5 – < 10 yr	0.98 (0.26–3.64); 3		
		10–19 yr	0.58 (0.1–2.72); 2		
		≥ 20 yr	4.73 (1.22–18.36); 4		
Wang *et al.* 2015 Case-control Guangzhou, China **Enrollment or follow-up:** 2010–2012	**Population:** Hospital based case-control study in women 22–85 years of age. Cases: 661; Controls: 714 **Exposure assessment method:** questionnaire	**OR Ever worked night shift: All women and menopausal status**		Age, education, age at menarche, menopausal status, parity, physical activity, breastfeeding, family history of breast cancer, BMI, sleep duration	**Exposure information:** Ever/never worked night shifts **Strengths:** Large, young cohort of premenopausal women with a range of occupations; controls for a range of breast cancer risk factors. **Limitations:**. Hospital-based case-control study may be subject to selection bias, limited exposure assessment, and low sensitivity; traditional risk factors for breast cancer did not vary by case status.
		Never worked nights	1; 443		
		All	1.37 (1.07–1.74); 218		
		Premenopausal	1.47 (1.07–2.01); 144		
		Postmenopausal	1.17 (0.77–1.8); 74		
		OR Ever night work: ER/PR/HER2 status		Same as above	
		Never worked nights	1; NR		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		HER2-	1.39 (1.05–1.83); 146		**Additional results:** Combined effect of nightwork and no daytime napping or longer sleep duration is greater than their independent effects. Interaction p < 0.054. Combined effect of nightwork and no daytime napping or longer sleep duration is greater than their independent effects. Interaction p < 0.009 for long duration (0.473 for short duration). **Confidence in evidence:** Some evidence
		HER2+/equivocal	1.35 (0.94–1.94); 66		
		ER-	1.1 (0.74–1.62); 53		
		ER+	1.48 (1.13–1.93); 160		
		PR-	1.34 (0.93–1.93); 66		
		PR+	1.39 (1.05–1.82); 147		
		Localized: OR Ever night work: Clinical stage		Same as above	
		Never	1; NR		
		Localized	1.47 (1.09–1.99); 120		
		Regional/distant	1.22 (0.89–1.67); 89		
		OR Night shift work and daytime napping		Same as above	
		No nightwork and never daytime napping	1; 179		
		No nightwork and ever daytime napping	1.01 (0.75–1.33); 260		
		Ever nightwork and never daytime napping	1; 113		
		Ever nightwork and ever daytime napping	0.62 (0.4–0.95); 1.04		
		Trend-test *P*-value <.054			
		OR Night shiftwork and sleep duration (hours/night)		Same as above	
		No nightwork and 6.1–8.9 hr/night	1; 289		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		No nightwork and short duration (≤ 6.0 hr/night)	1.41 (0.94–2.11); 69		
		No nightwork and long duration (≥ 9.0 hr/night)	1.16 (0.81–1.67); 79		
		Ever nightwork and 6.1–8.9 hr/night	1; 47		
		Ever nightwork and short duration (≤ 6.0 hr/night)	2.08 (1.18–3.64); 119		
		Ever nightwork and long duration (≥ 9.0 hr/night)	3.22 (1.72–6.04); 49		
		Trend-test *P*-value < 0.009			

References

1. Åkerstedt T, Knutsson A, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. 2015. Night work and breast cancer in women: a Swedish cohort study. *BMJ Open* 5(4): e008127. (Supported by the AFA Insurance Company. Authors affiliated with Karolinska Institutet, Sweden; Stockholm University, Sweden; Mid Sweden University, Sweden; Radboud University, Netherlands.)

2. Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, Guénel P. 2016. Night work and breast cancer risk defined by human epidermal growth factor receptor-2 (HER2) and hormone receptor status: A population-based case-control study in France. *Chronobiol Int* 33(6): 783-787. (Supported by the Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [ANSES], the Agence Nationale de la Recherche [ANR]; Fondation de France, the Institut National du Cancer [INCA], and the Ligue contre le Cancer. Authors affiliated with INSERM, France; Centre Georges-François Leclerc, France; Centre Eugène Marquis, France.)

3. Cordina-Duverger E, Menegaux F, Popa A, Rabstein S, Harth V, Pesch B, Brüning T, Fritschi L, Glass DC, Heyworth JS, Erren TC, Castaño-Vinyals G, Papantoniou K, Espinosa A, Kogevinas M, Grundy A, Spinelli JJ, Aronson KJ, Guénel P. 2018. Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol*. (Support not reported. Authors affiliated with INSERM, France; Institute of the Ruhr-Universität Bochum, Germany; University Medical Center Hamburg-Eppendorf, Germany; Curtin University, Australia; Monash University, Australia; University of Western Australia, Australia; University of Cologne, Germany; CREAL, Spain; IMIM, Spain; Universitat Pompeu Fabra, Spain; CIBERESP, Spain; Medical University of Vienna, Austria; CRCHUM, Canada; Universite´ de Montréal, Canada; BC Cancer, Canada; University of British Columbia, Canada; Queen's University, Canada.)

4. Davis S, Mirick DK, Stevens RG. 2001. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 93(20): 1557-1562. (Supported by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Connecticut Health Center, CT.)

5. Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, Boyle T, El-Zaemey S, Rogers P, Peters S, Slevin T, D'Orsogna A, de Vocht F, Vermeulen R, Heyworth JS. 2013. The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer* 109(9): 2472-2480. (Supported by the National Health and Medical Research Council Australia, the Cancer Council Western Australia, the University of Western Australia, and the Lions Cancer Institute. Authors affiliated with University of Western Australia, Australia; University of Cologne, Germany; Monash University, Australia; Cancer Council Western Australia, Australia; Health Consumer Representative, Australia; University of Manchester, UK; Utrecht University, Netherlands.)

6. Grundy A, Richardson H, Burstyn I, Lohrisch C, SenGupta SK, Lai AS, Lee D, Spinelli JJ, Aronson KJ. 2013. Increased risk of breast cancer associated with long-term shift work in Canada. *Occup Environ Med* 70(12): 831-838. (Supported by the Canadian Institutes of Health Research. Authors affiliated with Queen's University, Canada; Drexel University, PA; British Columbia Cancer Agency, Canada; University of British Columbia, Canada.)

7. Gu F, Han J, Laden F, Pan A, Caporaso NE, Stampfer MJ, Kawachi I, Rexrode KM, Willett WC, Hankinson SE, Speizer FE, Schernhammer ES. 2015. Total and cause-specific mortality of U.S. nurses working rotating night shifts. *Am J Prev Med* 48(3): 241-252. (Supported by NCI, NIH Heart, Lung and Blood Institute, and the CDC/The National Institute for Occupational Safety and Health. Authors affiliated with NCI, MD; Brigham and Women's Hospital, MA; Harvard Medical School, MA; University of Massachusetts, MA; Indiana University, IN; National University of Singapore, Singapore; National University Health System, Singapore; Applied Cancer Research–Institution for Translational Research Vienna, Austria.)

8. Hansen J. 2001. Increased breast cancer risk among women who work predominantly at night. *Epidemiology* 12(1): 74-77. (Support not reported. Author affiliated with Danish Cancer Society, Denmark.)

9. Hansen J, Lassen CF. 2012. Nested case-control study of night shift work and breast cancer risk among women in the Danish military. *Occup Environ Med* 69(8): 551-556. (Supported by the Danish Ministry of Defence. Authors affiliated with Danish Cancer Society, Denmark.)

10. Hansen J, Stevens RG. 2012. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. *Eur J Cancer* 48(11): 1722-1729. (Supported by the Danish Cancer Society and from the National Programme of Environmental Health Research. Authors affiliated with Danish Cancer Society, Denmark; University of Connecticut Health Center, CT.)

11. Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ. 2017. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 43(2): 117-126. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Illinois at Chicago School of Public Health, IL; Danish Cancer Society, Denmark.)

12. Knutsson A, Alfredsson L, Karlsson B, Åkerstedt T, Fransson EI, Westerholm P, Westerlund H. 2013. Breast cancer among shift workers: results of the WOLF longitudinal cohort study. *Scand J Work Environ Health* 39(2): 170-177. (Support not reported. Authors affiliated with Mid Sweden University, Sweden; Karolinska Institutet, Sweden; Norrlands University Hospital, Sweden; Stockholm University, Sweden; Jönköping University, Sweden; Uppsala University, Sweden.)

13. Koppes LL, Geuskens GA, Pronk A, Vermeulen RC, de Vroome EM. 2014. Night work and breast cancer risk in a general population prospective cohort study in The Netherlands. *Eur J Epidemiol* 29(8): 577-584. (Supported by the Dutch Ministry of

Social Affairs and Employment. Authors affiliated with Netherlands Organization for Applied Scientific Research, Netherlands; Utrecht University, Netherlands.)

14. Li W, Ray RM, Thomas DB, Davis S, Yost M, Breslow N, Gao DL, Fitzgibbons ED, Camp JE, Wong E, Wernli KJ, Checkoway H. 2015. Shift work and breast cancer among women textile workers in Shanghai, China. *Cancer Causes Control* 26(1): 143-150. (Supported by NIOSH, NCI, and NIH. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; Zhong Shan Hospital Branch, China; Group Health Research Institute, WA; University of California - San Diego, CA.)

15. Lie JA, Kjuus H, Zienolddiny S, Haugen A, Stevens RG, Kjaerheim K. 2011. Night work and breast cancer risk among Norwegian nurses: assessment by different exposure metrics. *Am J Epidemiol* 173(11): 1272-1279. (Supported by the Research Council of Norway, the South-Eastern Norway Regional Health Authority, and the Norwegian Cancer Society. Authors affiliated with National Institute of Occupational Health, Norway; University of Connecticut Health Center, CT; Cancer Registry of Norway, Norway.)

16. Lie JA, Kjuus H, Zienolddiny S, Haugen A, Kjaerheim K. 2013. Breast cancer among nurses: is the intensity of night work related to hormone receptor status? *Am J Epidemiol* 178(1): 110-117. (Supported by the Research Council of Norway, the South-Eastern Norway Regional Health Authority, the Norwegian Cancer Society, and the "Raagholtstiftelsen" foundation. Authors affiliated with National Institute of Occupational Health, Norway; Cancer Registry of Norway, Norway.)

17. Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, Kerbrat P, Fevotte J, Guenel P. 2013. Night work and breast cancer: a population-based case-control study in France (the CECILE study). *Int J Cancer* 132(4): 924-931. (Supported by the Agence Nationale de securite sanitaire de l'alimentation, de l'environnement et du travail [ANSES], the Agence Nationale de la Recherche [ANR], the Fondation de France, the Institut National du Cancer [INCA]; Ligue contre le Cancer Grand Ouest, and the Association pour le recherche contre le cancer [ARC]. Authors affiliated with INSERM, France; Univ Paris-Sud, France; Center Georges-Francois Leclerc, France; Center Eugene Marquis, France; Institut de Veille Sanitaire [InVS], France.)

18. O'Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, Gammon MD, Leske MC, for the Electromagnetic Fields Breast Cancer on Long Island Study Group. 2006. Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol* 164(4): 358-366. (Supported by NCI and NIEHS. Authors affiliated with Stony Brook University, NY; University of Connecticut Health Center, CT; University of North Carolina at Chapel Hill, NC.)

19. Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Ardanaz E, Altzibar JM, Sanchez VM, Gomez-Acebo I, Llorca J, Munoz D, Tardon A, Peiro R, Marcos-Gragera R, Pollan M, Kogevinas M. 2015. Breast cancer risk and night shift work in a case-control study in a Spanish population. *Eur J Epidemiol*. (Supported by the ''Accion Transversal del Cancer,'' approved on the Spanish Ministry Council on the 11th

October 2007, by the Instituto de Salud Carlos III-FEDER, the Fundacio´n Marque´s de Valdecilla, the ICGC International Cancer Genome Consortium CLL, the Spanish Ministerio de Economía y Competitividad, the Red Temática de Investigación del Cáncer, the Junta de Castilla y León, the the Consejería de Salud of the Junta de Andalucía, the Conselleria de Sanitat of the Generalitat Valenciana, the Recercaixa, the European Commission, the Spanish Association Against Cancer, the Scientific Foundation, the Catalan Government DURSI Grant and a predoctoral Grant PFIS. Authors affiliated with Centre for Research in Environmental Epidemiology, Spain; IMIM [Hospital del Mar Medical Research Institute], Spain; Universitat Pompeu Fabra, Spain; Carlos III Health Institute, Spain; Cancer Epidemiology Research Group, Spain; Instituto de Salud Publica de Navarra, Spain; Basque Regional Health Department, Spain; Universidad de León, Spain; University of Cantabria, Spain; IDIVAL, Spain; Universidad de Huelva, Spain; Universidad de Oviedo, Spain; Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana, Spain; Girona Biomedical Research Institute, Spain; CIBER Epidemiologıía y Salud Pública, Spain; National School of Public Health, Greece.)

20. Pesch B, Harth V, Rabstein S, Baisch C, Schiffermann M, Pallapies D, Bonberg N, Heinze E, Spickenheuer A, Justenhoven C, Brauch H, Hamann U, Ko Y, Straif K, Brüning T. 2010. Night work and breast cancer - results from the German GENICA study. *Scand J Work Environ Health* 36(2): 134-141. (Supported by the German Federal Ministry of Education and Research, the Research Institute of Occupational Medicine of the German Social Accident Insurance, the Robert Bosch Foundation of Medical Research, the Evangelische Kliniken Bonn GmbH, and the Deutsches Krebsforschungszentrum. Authors affiliated with Ruhr University Bochum, Germany; Evangelische Kliniken Bonn gGmbH, Germany; University Tübingen, Germany; Deutsches Krebsforschungszentrum, Germany; IARC, France.)

21. Pronk A, Ji BT, Shu XO, Xue S, Yang G, Li HL, Rothman N, Gao YT, Zheng W, Chow WH. 2010. Night-shift work and breast cancer risk in a cohort of Chinese women. *Am J Epidemiol* 171(9): 953-959. (Supoprted by NIH. Authors affiliated with NCI. MD; Vanderbilt University School of Medicine, TN; Shanghai Cancer Institute, China.)

22. Rabstein S, Harth V, Pesch B, Pallapies D, Lotz A, Justenhoven C, Baisch C, Schiffermann M, Haas S, Fischer HP, Heinze E, Pierl C, Brauch H, Hamann U, Ko Y, Bruning T, Consortium G. 2013. Night work and breast cancer estrogen receptor status--results from the German GENICA study. *Scand J Work Environ Health* 39(5): 448-455. (Supported by the German Federal Ministry of Education and Research, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Ruhr-University Bochum, the Robert Bosch Foundation, Stuttgart, EvangelischeKliniken Bonn GmbH, and the Deutsches Krebsforschungszentrum. Authors affiliated with Institute of the Ruhr-Universität Bochum, Germany; University Medical Centre Hamburg-Eppendorf, Germany; Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Germany; University of Tübingen, Germany; Medical Faculty of the University of Bonn, Germany; Deutsches Krebsforschungszentrum, Germany; Evangelische Kliniken Bonn gGmbH, Germany.)

23. Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, Colditz GA. 2001. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst* 93(20): 1563-1568. (Supported by NCI, NIH, and the Austrian Federal Ministry of Education, Science and Culture. Authors affiliated with Harvard Medical School, MA; Brigham and Women's Hospital, MA; Harvard Center for Cancer Prevention, MA; Dana-Faber/Harvard Cancer Center, MA.)

24. Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. 2006. Night work and risk of breast cancer. *Epidemiology* 17(1): 108-111. (Support not reported. Authors affiliated with Harvard Medical School, MA; LBI-ACR VIEnna & ACR-ITR VIEnna, Austria.)

25. Schwartzbaum J, Ahlbom A, Feychting M. 2007. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 33(5): 336-343. (Supported by the Swedish Council for Working Life. Authors affiliated with Ohio State University, OH; Karolinska Institutet, Sweden.)

26. Travis RC, Balkwill A, Fensom GK, Appleby PN, Reeves GK, Wang XS, Roddam AW, Gathani T, Peto R, Green J, Key TJ, Beral V. 2016. Night shift work and breast cancer incidence: Three prospective studies and meta-analysis of published studies. *J Natl Cancer Inst* 108(12): djw169. (Supported by the UK Health and Safety Executive, Cancer Research UK, and the Medical Research Council. Authors affiliated with University of Oxford, UK; GlaxoSmithKline R&D, UK; Oxford University Hospitals NHS Trust, UK.)

27. Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. 1996. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control* 7(2): 197-204. (Support not reported. Authors affiliated with Cancer Registry of Norway, Norway; Radiation Protection Authority, Norway; University of Oslo, Norway.)

28. Vistisen HT, Garde AH, Frydenberg M, Christiansen P, Hansen AM, Andersen J, Bonde JP, Kolstad HA. 2017. Short-term effects of night shift work on breast cancer risk: a cohort study of payroll data. *Scand J Work Environ Health* 43(1): 59-67. (Supported by the Danish Work Environment Research Fund and NordForsk, Nordic Program on Health and Welfare. Authors affiliated with Aarhus University Hospital, Denmark; National Research Centre for the Working Environment, Denmark; Aarhus University, Denmark; Danish Breast Cancer Corporative Group, Denmark; University of Copenhagen, Denmark; Danish Cancer Society Research Center, Denmark; Bispebjerg University Hospital, Denmark.)

29. Wang P, Ren FM, Lin Y, Su FX, Jia WH, Su XF, Tang LY, Ren ZF. 2015. Night-shift work, sleep duration, daytime napping, and breast cancer risk. *Sleep Med* 16(4): 462-468. (Supported by the National Natural Science Foundation of China and the Guangdong Provincial Natural Science Foundation. Authors affiliated with Sun Yat-sen University, China; Chinese University of Hong Kong, China; CUHK Shenzhen Research Institute, China.)

30. Wegrzyn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, Laden F, Willett WC, Hankinson SE, Schernhammer ES. 2017. Rotating night shift work and risk of breast cancer in the nurses' health studies. *Am J Epidemiol*. (Supported by the CDC,

NIOSH, and NIH. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; Harvard T.H. Chan School of Public Health, MA; University of Massachusetts, MA; University of Connecticut Health Center, CT; Medical University of Vienna, Austria; Applied Cancer Research-Institution for Translational Research Vienna, Austria.)

National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night

Appendix C: Light at Night, Transmeridian Travel and Breast Cancer

November 2020

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

List of Tables

Appendix C. Light at Night (LAN) and Transmeridian Travel and Breast Cancer – Quality rankings and results.

Appendix C includes the rationales for quality rankings of studies of breast cancer and light at night reported in Section 3.3, Table 3-9. The rationales for the quality ratings of indoor and outdoor studies of breast cancer and light at night are shown in Tables C-1a-f. Results for the indoor and outdoor studies of breast cancer and light at night are shown in Appendix C: Table 2.

Appendix C also includes rationales for quality rankings of studies of breast cancer and transmeridian travel reported in Section 3.4, Table 3-13. The rationales for these rankings are shown in Appendix C: Table C-5. Results of the breast cancer and transmeridian travel studies are shown in Appendix C: Table C-6.

Table C-1a: Breast cancer and lighting at night (LAN) – Indoor and Outdoor: Selection bias rationale

Reference	Selection bias rating
Indoor lighting	
Davis *et al.* 2001a	+++ ↔ Cases and controls were selected from the same population by similar methods and criteria. No evidence that selection of the subjects was related to both exposure and disease.
Fritschi *et al.* 2013	++ ↔ Cases and controls selected from same population with similar criteria. No evidence that selection was related to both exposure and disease. However, due to low response rates, sensitivity analyses were conducted to examine what level of selection bias (Lash *et al.* 2009) would hide a real effect of 1.5 for ever working nights, resulting in that conclusion that it is unlikely that such bias could account for this size effect. There were some differences in age and residential remoteness between those who participated and those who did not for cases and differences in age for controls. If LAN is related to environmental light, differences in cases and controls in environmental light may be unmeasured.
Garcia-Saenz *et al.* 2018	++ ↔ Cases and controls were selected from the same underlying population to ensure that they were comparable. There is no evidence that selection of the subjects was related to both exposure and disease; however, attrition bias is possible since recruitment differed between cases and controls with only 52% of the controls responding. Calls were made repeatedly at different times during the day to avoid missing night shift workers.
Hurley *et al.* 2014	+++ ↓ The cohort is clearly defined and includes the relevant eposed and nonexposed for a specific period/location with no evidence that follow-up differed between exposed and non-exposed subjects. No discussion of healthy worker effect/healthy worker survival effect (HWE/HWSE), however, residential light and light in the sleeping area are not likely to be related to employment.
Johns *et al.* 2018	+++ ↔ The cohort is clearly defined and includes the relevant exposed, non-exposed for a specific time period/location, with no evidence that follow-up differed between exposed and non-exposed. No evidence of HWE.

Reference	Selection bias rating
Keshet-Sitton *et al.* 2016	+ ↑ Cases and controls might not have been selected from the same population. Slightly more controls lived in rural areas and significantly more were non-native born than cases. "For neighborhood (friend) controls to satisfy the study base principle, one must consider the base as divided into geographically defined strata, with controls representing the entire person-time of the area from which cases arise. Use of neighborhood controls in a study with a secondary base may not satisfy the principle" (Wacholder *et al.* 1992). There is not enough information about the criteria for selection of controls in terms of their residences; controls were matched to cases after their "selection." That more cases were native Israelis spoke to the issue that there may be cultural differences in exposure preferences or residential preference in areas with bright lights at night. For example, if cases lived in areas with more light than controls, or for various reasons used more/brighter light at night in their homes than immigrant controls, the odds ratio (OR) would be biased away from the null.
Kloog *et al.* 2011	++ ↔ Cases and controls were selected from the same population by similar criteria. No evidence that selection of the subjects was related to both exposure and disease. Evidence of attrition bias due to low response rates in the controls.
Li *et al.* 2010	+++ ↔ Cases and controls selected from the same population by similar methods and criteria. No evidence that selection of subjects related to both exposure and disease.
O'Leary *et al.* 2006	++ ↔ Cases and controls were initially selected from the same population by similar methods and criteria. There is no evidence that selection of the subjects was related to both exposure and disease. The second set of cases and controls were selected from the first based on their residential stability. These cases and controls differed from the full set of cases and controls – they were older, postmenopausal, white, parous, heavier, ever users of alcohol and hormone replacement therapy (HRT), and less likely to have more than a high school degree or to have breastfed. Cases and controls in the study subset were interviewed twice – the first time with participants in the larger study, then for a second time, on average 202-239 days later, focusing on questions involving light at night and shift work. While no data are available to determine how lighting differs between the two populations because these questions were only asked in the second interview, there is little reason to believe that differential selection bias would be introduced. Because of the two-phase study design, attrition particularly in the controls was significant suggesting some selection bias in an unknown direction.
White *et al.* 2017	+++ ↔ The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location), with no evidence that follow-up differed between exposed and non-exposed subjects. There is no evidence of HWE or HWSE as this is not an occupational cohort and women currently working shifts were excluded from the analysis. The mean age of the cohort is about 55 making it somewhat "older," and questions about LAN at baseline were asked in relation to habits in the past year. Six blind women were excluded.

Reference	Selection bias rating
Outdoor lighting	
Bauer *et al.* 2013	+ ⬇ It is not clear that lung cancer cases are the appropriate comparison group, as 5 studies have found lung cancer related to shift work (Parent *et al.* 2012, Schernhammer *et al.* 2013, Gu *et al.* 2014, Yong *et al.* 2014, Kwon *et al.* 2015); two of the studies were in females. If so, the estimate could be biased towards the null. Also, almost 20% of addresses were removed because of non-geocodable addresses which are more likely in rural areas. For the black/white analysis, there are many rural Georgia counties with > 50% blacks, and if they have less precise addresses, a bias towards the null would be likely particularly in the black/white analysis. These counties may also have fewer diagnosed cases as they are far from urban centers.
Garcia-Saenz *et al.* 2018	++ ↔ Cases and controls were selected from the same underlying population to ensure that they were comparable. There is no evidence that selection of the subjects was related to both exposure and disease; however, attrition bias is possible since recruitment differed between cases and controls with only 52% of the controls responding. Calls were made repeatedly at different times during the day to avoid missing night shift workers.
Hurley *et al.* 2014	+++⬇ The cohort is clearly defined and includes the relevant eposed and nonexposed for a specific period/location with no evidence that follow-up differed between exposed and non-exposed subjects. No discussion of HWE/HWSE; however, residential light and light in the sleeping area are not likely to be related to employment.
James *et al.* 2017	+++ ↔ The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location), with no evidence that follow-up differed between exposed and non-exposed subjects. Minimal HWSE, as young women were recruited into the cohort. Small amount of missing information from the cohort; but as only 85% of addresses could be geocoded, there was a loss of some addresses of some nurses which may differ in urban/nonurban characteristics and LAN exposure; likely to have a small impact.
Keshet-Sitton *et al.* 2016	+ ⬆ Cases and controls might not have been selected from the same population. Slightly More controls lived in rural areas and significantly more were non-native born than cases. "For neighborhood (friend) controls to satisfy the study base principle, one must consider the base as divided into geographically defined strata, with controls representing the entire person-time of the area from which cases arise. Use of neighborhood controls in a study with a secondary base may not satisfy the principle" (Wacholder *et al.* 1992). There is not enough information about the criteria for selection of controls in terms of their residences; controls were matched to cases after their "selection." That more cases were native Israelis spoke to the issue that there may be cultural differences in exposure preferences or residential preference in areas with bright lights at night. For example, if cases lived in areas with more light than controls, or for various reasons used more/brighter light at night in their homes than immigrant controls, the OR would be biased away from the null.

Table C-1b: Breast cancer and lighting at night (LAN) – Indoor and Outdoor: Exposure assessment rationale

Reference	Exposure Assessment rating
Indoor lighting	
Davis *et al.* 2001a	++ ⬇ Exposure assessment methods have ability to distinguish women based on their own subjective assessment with high, medium, or low exposure to light in the residential area, and % of night with light on. No other information about light exposure from outside sources, and the "unexposed" may not be truly unexposed. Recall bias likely to be minimal as the hypothesis for light at night and cancer was not well publicized at the time of the study.
Fritschi *et al.* 2013	+ ⬇ Exposure assessment methods go beyond shiftwork studies by ascertaining level of light at the workplace. However, those with medium and high exposure were contrasted with those with unknown LAN work exposure, but who sleep in lighted rooms during the day, which calls into question the actual contrast. Unclear how different light levels at different jobs was handled. Exposure assessment methods have ability to distinguish women with high or low exposure to light from lighting in the workplace only, but not exposure from other sources, including use of electronic devices, TV, outside lighting, daylight, or residential lighting at home, nor information on amount, spectrum, timing or duration of lighting. Qualitative measures of ability to read, etc. are insufficient to classify exposure. Recall bias in this case-control study cannot be completely excluded, even though shift work and light were not the focus of the interview.
Garcia-Saenz *et al.* 2018	++ ⬇ The exposure assessment methods have moderate sensitivity and specificity with respect to level of exposure. Allows for discrimination between exposed and unexposed. However, no measure of direct light.
Hurley *et al.* 2014	++ ⬇ Exposure assessment methods for indoor light are sensitive and specific for exposure in the year before diagnosis as both frequency and duration of bright light in the sleeping area was assessed. No information on other sources of indoor light was collected (e.g., TV, electronic devices), nor any information on intensity, wavelength, and timing in the evening.
Johns *et al.* 2018	+ ⬇ The exposure assessment methods have low sensitivity and specificity with respect to ever-exposure, exposure level, timing, or other metrics of light at night. The question of the alignment of definitions used and lighting levels sufficient for circadian disruption and cancer are questionable. For some, the quality of recall about exposure at age 20 may have been 60+ years ago, and would be questionable.
Keshet-Sitton *et al.* 2016	++ ⬇ Self-reported exposure to light 10–15 years ago may be susceptible to non-differential memory bias; type of light was measured using pictures for reference which helps provide information about the intensity of lighting. Several different proxies included which allowed for assessment of various levels of light.
Kloog *et al.* 2011	++ ⬆ Exposure assessment methods have moderate sensitivity and specificity; includes information about levels of light and light from multiple sources at night.

Reference	Exposure Assessment rating
Li *et al.* 2010	+ ⬇ Exposure assessment methods were limited to measuring residential lighting at night or while sleeping and do not refer to other sources of light, e.g., lighting at work. For residential exposure the assessment method allows for some discrimination between exposed and non-exposed as electronic sources and use of shades from street lighting is incorporated. No attempt was made to combine exposures to all of these sources of light at night.
O'Leary *et al.* 2006	+ ⬇ Exposure assessment methods have ability to distinguish women with high or low exposure to light from lighting in the residential area only, but not exposure from other sources, including electronic devices, TV, outside lighting, daylight, or shiftwork, nor information on amount, spectrum, timing or duration of lighting. Because LAN was defined so narrowly, it is not known whether the "unexposed" were truly unexposed. Recall bias may be possible given this subset of subjects was selected for a second interview for electromagnetic measurements and light at night which took place on average 200 days later.
White *et al.* 2017	+ ⬇ The exposure assessment methods have poor sensitivity and specificity for classifying overall exposure to light at night and are limited to light in the sleeping area at night with no information on exposure or duration of exposure to light prior to bedtime or during sleep. There is no information regarding outdoor lighting exposure.
Outdoor lighting	
Bauer *et al.* 2013	+ ⬇ Exposure assessment methods have strengths and weaknesses: the validation substudy suggests that the Defense Meteorological Satellite Program-Operation Linescan System (DMSP-OLS) satellite images are highly correlated with daysimeter readings which measure circadian relevant light; however, the personal exposure to measured light is ill-defined outside of the residential address. No additional information about where subjects may have spent most of their time during the day or evening is provided. In addition, no information on length of residency at the address that was geocoded, meaning exposure is not certain.
Garcia-Saenz *et al.* 2018	+++ ⬇ The exposure assessment methods have good sensitivity and specificity with respect to level of exposure, allowing for discrimination between exposed and unexposed along relevant axis (melatonin suppression).
Hurley *et al.* 2014	++ ⬇ Exposure assessment methods for outdoor light; the satellite imagery used was the best available at the time, however, the available images for just one year (2006) were not congruent with baseline addresses (1995–1996). an examination of the low-dynamic range data showed that light levels were relatively similar. Also, data from other addresses of individuals who moved was not incorporated into the overall analysis, although sensitivity analyses were performed limiting analysis to those who were residentially stable. In addition, there is disagreement over whether satellite images measure light relevant for circadian disruption (CD).

Reference	Exposure Assessment rating
James *et al.* 2017	++ ⬇ The exposure assessment methods have good relative sensitivity and specificity, leading to reliable classification (or discrimination) as all addresses starting at baseline throughout follow-up were incorporated. Broad range of exposure levels compared to previous studies (48 states); that is, highest levels are much higher than in other studies. Past addresses were not geocoded, so if early exposure to outdoor LAN is associated with breast cancer, this wouldn't have been captured. Also, shift workers, who have the most extreme light at night, were included in the analysis to capture indoor light at night at work. However, DMSP output from the satellite may not strictly correlate with the restricted portion of the spectrum that is circadian disruptive, thus while the exposure assessment was superior to many, it is still a question of whether this is the appropriate exposure proxy (as these images capture only a fraction of the light from the earth, but represent relative levels of nighttime illumination at ground level (Hsu et al. 2015). In addition, details about other indoor light exposures were not measured.
Keshet-Sitton *et al.* 2016	+ ⬇ Self-reported exposure to light 10–15 years ago may be susceptible to non-differential memory bias; exposure to strong outdoor source of LAN does not account for type of LAN or source.

Table C-1c: Breast cancer and lighting at night (LAN) – Indoor and Outdoor: Outcome assessment rationale

Reference	Outcome assessment rating
Indoor lighting	
Davis *et al.* 2001a	++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnoses were conducted independent of exposure status. No cancer subtypes analyzed.
Fritschi *et al.* 2013	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnoses were conducted independent of exposure status.
Garcia-Saenz *et al.* 2018	+++ ↔ Diagnoses appear to have been conducted independent of exposure assessment; cases were histologically verified.
Hurley *et al.* 2014	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects; follow-up and diagnosis were conducted independent of exposure status. Subtypes also evaluated, although small numbers of exposed precluded analysis of subtypes.
Johns *et al.* 2018	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnosis were conducted independent of exposure status.
Keshet-Sitton *et al.* 2016	+ ⬇ Outcome methods were not sufficiently detailed to determine how breast cancer cases were defined (e.g., ICD codes); whether they are prevalent or incident cases; and if these included breast cancer *in situ*. No diagnostic criteria described
Kloog *et al.* 2011	++ ⬇ Cases could be included if breast cancer in non-index breast, meaning that some of the "controls" were in fact cases. Thus, outcome methods did not clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. While there was information on human epidermal growth factor receptor 2 (HER2) status, this was not included in analysis.
Li *et al.* 2010	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Histologically confirmed cases and potential non-cases from surgeries performed. Estrogen receptor/progesterone receptor (ER/PR) status was also determined.
O'Leary *et al.* 2006	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis was conducted independent of exposure assessment.
White *et al.* 2017	++ ⬇ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status; not all cases were verified by pathology.
Outdoor lighting	
Bauer *et al.* 2013	+++ ⬇ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status. However, use of lung cancer cases as controls may bias results towards the null if LAN is related to lung cancer.

Reference	Outcome assessment rating
Garcia-Saenz *et al.* 2018	+++ ↔ Diagnoses appear to have been conducted independent of exposure assessment. Cases were histologically verified.
Hurley *et al.* 2014	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnosis were conducted independent of exposure status. Subtypes also evaluated, although small numbers of exposed precluded analysis of subtypes.
James *et al.* 2017	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.
Keshet-Sitton *et al.* 2016	+ ⬇ Outcome methods are not sufficiently detailed to determine how breast cancer cases were defined (e.g., ICD codes); whether they are prevalent or incident cases; and if these included breast cancer *in situ*. No diagnostic criteria described

Table C-1d: Breast cancer and lighting at night (LAN) – Indoor and outdoor: Sensitivity rationale

Reference	Sensitivity rating
Indoor lighting	
Davis *et al.* 2001a	++ ⬇ Sufficient numbers of exposed cases; exposure levels were able to distinguish women at various levels of light exposure, but not to other sources of light. Whether LAN in the 10 years prior to diagnosis is the relevant window of exposure is not known; no lagged analyses were performed.
Fritschi *et al.* 2013	++ ⬇ The study does not have enough information on all sources of exposure to light determine who actually had "high" or "low" exposure to light. Authors conducted lagged analyses to exposure that occurred in the windows of time > 30 years, 20–30 years, 10–20 years, and ≤ 10 years before recruitment compared with those who were unexposed during each window of time.
Garcia-Saenz *et al.* 2018	++ ⬇ The study has an adequate number of exposed subjects (N = 211 including both dim light and quite illuminated); but small numbers (31 cases) for highest level of illumination.
Hurley *et al.* 2014	++ ⬇ The study has ability to distinguish levels of exposure, but there is a small number of exposed subjects with high indoor bright light exposure at night. There is adequate duration of follow-up. WIndow of exposure (past year) may not be adequate to assess exposure.
Johns *et al.* 2018	+ ⬇ Substantial numbers of exposed, but questions did not categorize individuals into groups which may have been highly exposed to circadian effective light.
Keshet-Sitton *et al.* 2016	++ ⬇ The study has a small number of cases. The window of exposure is reasonable. Some information available to assess levels of light.
Kloog *et al.* 2011	++ ⬇ The study has adequate number of exposed subjects at high levels as defined by this protocol. As exposure is considered "current" there is no accounting for latency period, and assumes that the most recent, current exposure is the relevant window of exposure. No consideration that cases may change their behaviors with respect to night lighting, thereby violating the temporality criteria.
Li *et al.* 2010	+ ⬇ Small to adequate number of exposed subjects with poorly defined exposure levels; no information on duration, and window of exposure is set *a priori* (past 10 years). Given that cases (72%) and controls (60%) are primarily over the age of 50, if this exposure period (10 years prior) is not relevant, it may not be possible to detect an effect.
O'Leary *et al.* 2006	+ ⬇ The study had an adequate number of exposed subjects with substantial exposure as defined in this study to light in the sleeping area at night; however, because the definition of exposure was so limited, it is not clear that these individuals were highly exposed, or that unexposed were truly unexposed. Also, the window of exposure may not have been adequate as only the last 5 years prior to the reference date was measured in this older population. No analyses of night workers and light was possible given the small number of night workers; and analyses by cancer subtypes were not possible given the small numbers.

Reference	Sensitivity rating
White *et al.* 2017	+ ⬇ If LAN in the sleeping area at a particular time in life is related to breast cancer, this study would not capture early exposures, either in adolescence or in young adulthood. Light at night prior to sleeping not captured; duration of light being on not captured. No outside LAN captured.
Outdoor lighting	
Bauer *et al.* 2013	+ ⬇ Limited exposure range and highest levels are quite low in Georgia compared to other similar studies. Window of exposure variable for each woman.
Garcia-Saenz *et al.* 2018	++ ↔ The study has an adequate number of exposed subjects in the third tertile (N = 126 for visual light; N =138 for dim light). However, the very top 5%–10% were not noted. LAN not measured/relevant for younger ages.
Hurley *et al.* 2014	+ ⬇ Window of early exposure was excluded as data were only examined for the follow-up period when the average age was older. the available images (2006) were not congruent with baseline addresses (1995–1996), although limiting analysis to those who did not move did not change results, and ranking of LAN values were stable over the time in the study area.
James *et al.* 2017	++ ⬇ Missing window of exposure prior to about age 33 in this young cohort of women may decrease sensitivity if early LAN exposure is the most relevant.
Keshet-Sitton *et al.* 2016	++ ⬇ The study has a small number of cases. The window of exposure is reasonable. Can't separate highly and lower exposed individuals by source or other characteristics of LAN.

Table C-1e: Breast cancer and lighting at night (LAN) – Indoor and outdoor: Confounding rationale

Reference	Confounding rating
Indoor lighting	
Davis *et al.* 2001a	Breast: ++ ↑ Did not control for socioeconomic status (SES); shift work was not taken into consideration in analysis (6% of population had a history of night work).
Fritschi *et al.* 2013	Breast: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them.
Garcia-Saenz *et al.* 2018	Breast: +++ ↔ The study models were adjusted *a priori* for base level variables and an additional set. Reproductive variables not included in final model.
Hurley *et al.* 2014	Breast: ++ ↓ Variables in the pathway and family history of breast cancer, breastfeeding, physical activity, were unrelated to indoor LAN and including them in the final model is likely to have lowered the risk estimate; no information was included on shift work.
Johns *et al.* 2018	Breast: ++ ↓ Variables in the pathway were included in the model and were likely to have lowered the risk estimate.
Keshet-Sitton *et al.* 2016	Breast: ++ ↓ The study measured relevant potential confounders and used appropriate analyses to address them. Addition of variables in the pathway and unrelated to LAN in the model, however, was likely to bias results towards the null.
Kloog *et al.* 2011	Breast: ++ ↔ The study measured relevant potential confounders, and included them in models, but did not show differences in alcohol, education, ethnicity, or parity by case-control status.
Li *et al.* 2010	Breast: ++ ↑ SES not controlled.
O'Leary *et al.* 2006	Breast: ++ ↑ Did not take 7.6% of shift workers into account in this analysis, even though the authors had data on both shift work and LAN.
White *et al.* 2017	Breast: +++ ↔ None
Outdoor lighting	
Bauer *et al.* 2013	Breast: + ↑ The study measured relevant potential confounders on an individual or county-wide basis with the exception of alcohol consumption, but it is likely there is residual confounding remaining as a result of the lack of individual level data for parity and education.
Garcia-Saenz *et al.* 2018	Breast: +++ ↔ Models were adjusted *a priori* for base level variables and an additional set. None included reproductive variables.
Hurley *et al.* 2014	Breast: ++ ↓ Variables in the pathway, family history of breast cancer, breastfeeding history, physical activity, were unrelated to outdoor LAN and including them is likely to have lowered the risk estimate; no information on shift work.

Reference	Confounding rating
James *et al.* 2017	Breast: ++ ↔ Other factors associated with outdoor LAN may not be fully controlled by population density and air pollution and could explain the relationship between LAN and breast cancer; alternatively, factors unrelated to LAN but included in the model may reduce the estimates of the effect.
Keshet-Sitton *et al.* 2016	Breast: ++ ↓ The study measured relevant potential confounders and used appropriate analyses to address them. Addition of variables in the pathway and unrelated to LAN in the model, however, was likely to bias results towards the null.

Table C-1f: Breast cancer and lighting at night (LAN) – Indoor and outdoor: Analysis and selective reporting rationale

Reference	Analysis rating	Selective reporting rating
Indoor lighting		
Davis *et al.* 2001a	+++ ↔ Study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Fritschi *et al.* 2013	++ ↔ The study used relevant data and appropriate assumptions and methods of analysis. Amount of light was controlled for; and lagged analyses were conducted. However, for the LAN analysis, restricting the questions only to shiftworkers limited the utility of this information.	+++ ↔ No evidence that selective reporting of data or analyses compromised the interpretation of the study.
Garcia-Saenz *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis	+++ ↔ No evidence that reporting of data or analyses were limited to only a subset of the data collected
Hurley *et al.* 2014	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Johns *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of data or analyses were limited to only a subset of the data collected
Keshet-Sitton *et al.* 2016	+++ ↔ The study used relevant data and methods.	++ ↔ Reporting of the data were limited to statistical results, and no numbers of exposed cases or controls were reported.
Kloog *et al.* 2011	++ ↔ The analysis did not use relevant available data in their methods; that is, it was not possible to determine results for different levels of light notwithstanding the fact that data were available. Relevant data would have included information on time periods or duration, but these variables were not available.	++ ↔ Reporting didn't clearly indicate number of cases or relationships between covariates or levels of lighting effect even though they had the data.
Li *et al.* 2010	++ ↓ The study used relevant data and appropriate assumptions and methods of analysis, but stopped short of combining various indices of light at night exposure.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
O'Leary *et al.* 2006	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.

Reference	Analysis rating	Selective reporting rating
White *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Outdoor lighting		
Bauer *et al.* 2013	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of data or analyses were limited to only a subset of the data that were collected.
Garcia-Saenz *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of data or analyses were limited to only a subset of the data collected.
Hurley *et al.* 2014	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
James *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis. In particular, LAN analyses were both controlled for and stratified by shift work.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Keshet-Sitton *et al.* 2016	+++ ↔ The study used relevant data and methods.	++ ↔ Reporting of the data was limited to statistical results, and no numbers of exposed cases or controls were reported.

Table C-2: Breast cancer and light at night (LAN) study results – Indoor and outdoor

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Indoor lighting studies					
Davis *et al.* 2001b Case-control Seattle, WA **Enrollment or follow-up:** 1992–1995	**Population:** Cases: 813; Controls: 793 **Exposure assessment method:** questionnaire	**OR Ambient light levels**		Parity, family history of breast cancer, oral contraceptive (OC) use, sse of hormone replacement therapy (HRT) discontinued < 5 years, age.	**Exposure information:** Bedroom light: self-reported ambient light level of bedroom at night, number of times per night turning on light, and percentage of night light was on. Non-peak sleep (not sleeping during nocturnal melatonin peak (going to sleep after 2:00 AM, rising before 1:00 AM, not sleeping): ever non-peak sleep, number nights/week, or number of years of non-peak sleep during 10 years prior to diagnosis. **Strengths:** Population-based case-control study with good response rates; early study conducted prior to concerns about light at night and breast cancer likely to introduce little recall bias; exposure assessment good for nonpeak sleep and adequate for light in the sleeping area. **Limitations:** Other sources of light in the sleeping area or prior to bedtime are not known; likely that unexposed were not completely unexposed. **Additional results:** - **Confidence in evidence:** Strong to moderate evidence (highest self-reported ambient light level (elevated, but not significant); frequent non-peak sleep.
		Darkest	1; 94		
		Some light	1 (0.7–1.4); 633		
		Lightest	1.4 (0.8–2.6); 35		
		Continuous levels of light	1.1 (0.9–1.2); 762		
		OR Frequency (# times/night) of light turned on during night		Same as above	
		Reference	1; 429		
		< 0.3	0.8 (0.6–1.2); 67		
		0.3–0.8	1.1 (0.8–1.5); 94		
		0.8–1.3	1.1 (0.8–1.6); 93		
		≥ 1.3	1 (0.7–1.4); 80		
		Continuous number of times	1.03 (0.9–1.18); 763		
		OR Percentage of night with light on		Same as above	
		Reference	1; 435		
		< 0.4	1 (0.7–1.4); 86		
		0.4–0.9	0.9 (0.6–1.2); 76		
		0.9–2.9	1 (0.7–1.4); 79		
		≥ 2.9	1 (0.7–1.4); 86		
		Continuous percentage	0.99 (0.97–1.02); 762		
		OR Frequency (nights/week) of non-peak sleep		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Reference	1; 665		
		< 0.6	1 (0.5–1.8); 22		
		0.6–1.2	1.1 (0.6–2.1); 23		
		1.2–2.6	1 (0.5–1.9); 20		
		≥ 2.6	1.7 (1–3.1); 33		
		Continuous nights per week	1.14 (1.01–1.28); 763		
		Trend-test *P*-value = 0.03			
		OR Ever or duration (years) of non-peak sleep ≥ 3 nights/wk		Same as above	
		No	1; 682		
		Yes	1.4 (1–2); 81		
		< 1	1.2 (0.6–2.3); 19		
		1.0–3.0	1.4 (0.7–2.8); 20		
		3.0–4.6	0.6 (0.3–1.5); 9		
		≥ 4.6	2.3 (1.2–4.2); 33		
		Continuous number of years Trend-test P-value = 0.01	1.09 (1.02–1.18); 763		
Fritschi *et al.* 2013 Case-control Western Australia **Enrollment or follow-up:** May 2009 –	**Population:** Cases: 1,202; Controls: 1,785 **Exposure assessment method:** questionnaire	**OR LAN during night shift work: level of exposure**		Age	**Exposure information:** Self-reported levels of light at work or while sleeping during the day; number of years exposed to high (enough light to read) or medium (enough light to see but not enough to read) light.
		Never exposed	1; 947		
		Ever exposed	1.15 (0.96–1.38); 253		
		Low levels	0; 0		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
January 2011		Medium levels	1.06 (0.82–1.37); 110		**Strengths:** Large population based-study which measured self-reported LAN during night work. **Limitations:** Low response rate, particularly among controls. Exposure limited and non-exposure ill-defined. Potential for attrition bias. **Additional results:** - **Confidence in evidence:** Some evidence (reading easily at night at work [elevated, not significant]; < 10 or 10–19 years sleeping with medium/high light [elevated, not significant]).
		High levels	1.25 (0.98–1.59); 143		
		< 10 years (medium/high levels)	1.25 (0.99–1.57); 153		
		10–19 years (medium/high levels)	1.21 (0.86–1.7); 65		
		≥ 20 years (medium/high levels)	0.84 (0.55–1.28); 35		
		Premenopausal	1.1 (0.78–1.55); 92		
		Postmenopausal	1.17 (0.94–1.45); 196		
Garcia-Saenz *et al.* 2018 Case-control Spain **Enrollment or follow-up:** 2008–2013	**Population:** Cases: 380; Controls: 490 **Exposure assessment method:** Interview	**OR Indoor LAN (base model)**		Age, center, educational level, menopausal status	**Exposure information:** 4 levels of self-reported LAN in the bedroom while sleeping atatat the age of 40: total darkness, almost dark, dim light, and quite illuminated. **Strengths:** Strong design and analysis. **Limitations:** Potential selection bias due to attrition in controls; exposure assessment restricted to self-reported data on light levels in the sleeping area based on one self-reported measurement at the age of 40. **Additional results:** Fully adjusted model point estimates for exposure levels were null and non-significant. Chronotype showed no clear pattern; no correlation found between indoor and outdoor ALAN values; nor between outdoor ALAN visual and melatonin index. **Confidence in evidence:**
		Total darkness	-		
		Almost dark	0.88 (0.55–1.41); 119		
		Dim light	1.26 (0.78–2.03); 180		
		Quite illuminated	1.08 (0.57–2.02); 31		
		OR Indoor LAN (fully adjusted model)		Age, center, educational level, menopausal status, socioeconomic status (SES), body mass index (BMI), tobacco, family history of breast cancer, chronotype, adjustment for outdoor LAN, urban vulnerability index (UVI)	
		Total darkness	-		
		Almost dark	0.73 (0.44–1.21); 118		
		Dim light	1.01 (0.6–1.69); 178		
		Quite illuminated	0.77 (0.39–1.51); 31		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		OR Indoor LAN (base model) and morning chronotype		Age, center, educational level, menopausal status	No evidence
		Total darkness	1; 17		
		Dim light	1.67 (0.8–3.46); 85		
		Quite illuminated	1.29 (0.47–3.53); 11		
		OR Indoor LAN (base model) and evening chronotype		Age, center, educational level, menopausal status	
		Total darkness	1; 10		
		Dim light	0.65 (0.17–2.55); 27		
		Quite illuminated	1.2 (0.23–6.28); 7		
Hurley *et al.* 2014 Cohort California **Enrollment or follow-up:** 1995–1996	**Population:** California Teachers Study 106,731 **Exposure assessment method:** questionnaire	**HR Use of Indoor LAN: Combined hrs/ night, frequency (night/wk) and duration (months)**		Age, race/birthplace, family history of breast cancer, age at menarche, pregnancy history, breastfeeding history, physical activity, strenuous, BMI, alcohol consumption, menopausal status + hormone replacement therapy, smoking status, smoking pack years, neighborhood SES, urbanization.	**Exposure information:** Indoor users of LAN: heavy users (≥ 10 months for ≥ 5 days/week/≥ 7 hours/night); light users (0–-3 months, 1–3 days/week/1–2 hours/night); medium users: all other combinations of duration/frequency. **Strengths:** Large defined cohort of teachers with well-defined information on covariates; specific information on frequency and duration of bright light at night in the sleeping area. **Limitations:** Limited data on sources of LAN in the indoor environment leading to potential misclassification of exposure; window of most relevant exposure may not be adequate. **Additional results:** - **Confidence in evidence:** Some evidence (highest self-reported ambient level of light [not significant]).
		No use of LAN	1; 4,869		
		Any use of LAN	1.03 (0.9–1.18); 226		
		Light user	1.17 (0.87–1.57); 45		
		Medium user	0.99 (0.82–1.2); 109		
		Heavy user	1.13 (0.84–1.52); 44		
		Trend-test *P*-value = 0.53			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Johns *et al*. 2018 Cohort United Kingdom **Enrollment or follow-up:** 2003–2012	**Population:** UK Generations Study 105,866 **Exposure assessment method:** questionnaire	**HR LAN and Night waking, All women, year before recruitment**		Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, menopausal status, age at menopause, BMI-premenopausal, BMI-post-menopausal, alcohol consumption, smoking, physical activity.	**Exposure information:** Self-reported LAN in the sleeping area: light enough to read (high), light enough to see across room but not read (medium) and too dark to see your hand or wear a mask (low) during year prior to recruitment and at age 20. **Strengths:** Large national prospective study, comprehensive assessment of breast cancer risk factors, high follow-up rates. **Limitations:** Limited exposure assessment in relation to LAN metrics, and precision of metric chosen. Concern as to whether "high" light represents light sufficient to result in circadian disruption and cancer. **Additional results:** - **Confidence in evidence:** No evidence
		Low	1; 416		
		Medium	1 (0.89–1.12); 847		
		High	1.01 (0.88–1.15); 512		
		No night waking	1; 939		
		Yes night waking	1.01 (0.92–1.12); 674		
		HR LAN and Night Waking, Post-menopausal women, year before recruitment		Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, menopausal status, age at menopausse, BMI, premenopausal, BMI, post-menopausal, alcohol consumption, smoking, physical activity.	
		Low	1; 271		
		Medium	1.05 (0.91–1.22); 521		
		High	1 (0.85–1.18); 293		
		No night waking	1; 527		
		Night waking	0.96 (0.85–1.1); 427		
		HR LAN and Night Waking, Premenopausal women, year before recruitment		Age, benign breast disease, family	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Low	1; 145	history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity.	
		Medium	0.91 (0.74–1.1); 326		
		High	1 (0.81–1.24); 219		
		No night waking	1; 412		
		Night waking	1.1 (0.93–1.29); 247		
		HR LAN and night waking, All women, age 20		Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity, BMI- post-menopausal, menopausal status, age at menopause	
		Low	1; 452		
		Medium	1.02 (0.9–1.16); 846		
		High	1 (0.88–1.15); 540		
		No night waking	1; 1450		
		Night waking	0.85 (0.7–1.04); 103		
		HR LAN and Night Waking, Post-menopausal women, age 20		Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity,	
		Low	1; 227		
		Medium	1.11 (0.95–1.29); 525		
		High	1.04 (0.88–1.24); 302		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		No night waking	1; 857	breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity, BMI-post-menopausal, menopausal status, age at menopause	
		Night waking	0.96 (0.73–1.27); 53		
		HR LAN and Night Waking, Pre-menopausal women, age 20		Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal, alcohol consumption, smoking, physical activity	
		Low	1; 125		
		Medium	0.88 (0.71–1.08); 321		
		High	0.91 (0.73–1.13); 238		
		No night waking	1; 593		
		Night waking	0.74 (0.55–0.99); 50		
		HR ER positive tumor, High LAN or waking at night		Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal,	
		All, high LAN, year before recruitment	0.98 (0.84–1.14); 391		
		All, waking, year before recruitment	1.01 (0.9–1.13); 524		
		All high LAN, at age 20	1 (0.86–1.17); 409		
		All, waking, at age 20	0.82 (0.65–1.04); 77		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Postmenopausal, high LAN, year before recruitment	0.97 (0.81–1.17); 226	alcohol consumption, smoking, physical activity.	
		Postmenopausal, waking, year before recruitment	0.96 (0.83–1.11); 336		
		Postmenopausal, high LAN, at age 20	1 (0.82–1.22); 224		
		Postmenopausal, waking, at age 20	0.95 (0.69–1.3); 41		
		Premenopausal, high LAN, year before recruit	0.97 (0.76–1.24); 165		
		Premenopausal, waking, year before recruitment	1.09 (0.91–1.31); 188		
		Premenopausal, high LAN, at age 20	0.97 (0.76–1.25); 185		
		Premenopausal, waking, at age 20	0.69 (0.49–0.97); 36		
		HR ER negative tumor, High LAN or waking at night		Age, benign breast disease, family history of breast cancer, SES score, age at menarche, age at first birth, parity, breastfeeding duration, OC use, HRT, BMI-premenopausal,	
		All, high LAN, year before recruitment	1.16 (0.82–1.65); 77		
		All, waking, year before recruitment	1.01 (0.78–1.32); 100		
		All, high LAN, at age 20	0.94 (0.67–1.32); 84		
		All, waking, at age 20	0.82 (0.49–1.4); 15		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Postmenopausal, high LAN, year before recruitment	1.23 (0.79–1.92); 46	alcohol consumption, smoking, physical activity.	
		Postmenopausal, waking, year before recruitment	0.9 (0.64–1.26); 61		
		Postmenopausal, high LAN, at age 20	1.17 (0.76–1.8); 53		
		Postmenopausal, waking, at age 20	0.72 (0.32–1.63); 6		
		Premenopausal, high LAN, year before recruitment	1.04 (0.59–1.85); 31		
		Premenopausal, waking, year before recruitment	1.24 (0.82–1.86); 39		
		Premenopausal, high LAN, at age 20	0.64 (0.37–1.11); 31		
		Premenopausal, waking, at age 20	0.91 (0.45–1.82); 9		
Keshet-Sitton *et al.* 2016 Case-control Israel **Enrollment or follow-up:** 2010–2014	**Population:** Cases: 93; Controls: 185 **Exposure assessment method:** Questionnaire	**OR Light before sleep**			**Exposure information:** Self-reported light intensity, light use before or during sleep, light from outside. **Strengths:** Multiple metrics of exposure to light at night **Limitations:** Potential selection bias in this case-control study supported by the fact that breast cancer risk factors were unrelated to case-status; likely non-differential exposure misclassification, lack of information on numbers of participants at different levels of exposure.
		Reading with bed light	0.81 (0.67–0.97); NR		
		Reading with room light	0.96; NR		
		OR LAN (indoor) use during sleep in bedroom			
		Turning lights on	0.88; NR		
		Dim light	0.89; NR		
		Sleep with light on (reading intensity)	0.96; NR		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		TV on most of night	1.26; NR		**Additional results:** - **Confidence in evidence:** Some evidence (subjective level of lighting, continuous [not significant]).
		Falling asleep with TV on	0.84; NR		
		OR LAN levels and type of light			
		Subjective light intensity	1.21; NR		
		Bedroom illumination LWL/SWL	1.35; NR		
		Bed light illumination long-wavelength light (LWL)/short-wavelength light (SWL)	1.56; NR		
Kloog *et al.* 2011 Case-control Israel **Enrollment or follow-up:** 2006–2008	**Population:** Cases: 794; Controls: 885 **Exposure assessment method:** questionnaire	**OR Sources of light during sleep hours**		Education, ethnicity, parity, alcohol consumption	**Exposure information:** Presence of several inside sources of lighting (e.g., bedlight, TV). Self-reported levels of light in the sleeping area (dark, low, average, and high (all lights on)) **Strengths:** Large, population-based study of breast cancer. Multiple exposure metrics and ability to
		Bedroom light intensity (1-4)	1.22 (1.118–1.311); 425		
		Bedroom shutters, open	0.818 (0.663–1.008); 527		
		TV on while sleeping	0.914 (0.725–1.151); 180		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *P*-value = 0.001			differentiate high and low exposed individuals. **Limitations:** Low response rates in controls; exposure assessment is limited to current time period which may violate temporality criteria that exposure precede disease; no data to assess latency, and assumes that current exposure is the relevant time window. **Additional results:** - **Confidence in evidence:** Evidence (subjective level of lighting, continuous)
Li *et al.* 2010 Case-control Connecticut, U.S.A. **Enrollment or follow-up:** 1994–1997	**Population:** Cases: 363; Controls: 356 **Exposure assessment method:** Questionnaire	**OR Premenopausal women: Indoor LAN during sleep**		Age, race, BMI, age at menarche, family history of breast cancer, age at first birth, breastfeeding duration, cigarette smoking, alcohol drinking.	**Exposure information:** LAN in the sleeping area at night (e.g., keeping light on while sleeping, sleeping during night or day, clock radio, TV, hall light) **Strengths:** Well-conducted population-based case-control study of breast cancer with information on subtypes. **Limitations:** Small sample size, weak exposure assessment limited to broad questions about bedroom lighting and sleeping during the day/night. Assumes current exposure is relevant window of exposure. **Additional results:** - **Confidence in evidence:** Evidence (turns on light when waking; daylight or sleeping during the day); some evidence among post-menopausal women (light from outside (shades up) while sleeping)
		No lights	1; 67		
		Lights on	1.1 (0.4–3.6); 7		
		No other light sources	1; 13		
		Other light sources (e.g TV, hall light)	1.1 (0.5–2.5); 61		
		OR Premenopausal women: Timing of sleep		Same as above	
		Night	1; 71		
		Day	0.9 (0.2–3.9); 3		
		OR Premenopausal women: Outdoor LAN during sleep		Same as above	
		Shades down	1; 62		
		Shades up	0.7 (0.3–1.5); 12		
		No street/exterior light	1; 42		
		Street or exterior lighting	1 (0.5–1.8); 32		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		OR Post menopausal women: Indoor LAN during sleep		Same as above	
		No lights	1; 263		
		Lights on	1.4 (0.7–2.7); 26		
		No other light sources	1; 45		
		Other LAN sources (e.g., TV)	1.1 (0.6–1.7); 244		
		OR Post menopausal women: Timing of sleep		Same as above	
		Night	1; 280		
		Day	1.4 (0.5–4.3); 9		
		OR Post menopausal women: Outdoor LAN during sleep		Same as above	
		Shades down	1; 215		
		Shades up	1.2 (0.8–1.9); 74		
		No outside street or exterior lighting	1; 180		
		Street or exterior lighting	1.1 (0.8–1.7); 109		
O'Leary *et al.* 2006 Case-control Long Island, NY **Enrollment or follow-up:** August 1996–June 1997	**Population:** Electromagnetic fields and breast cancer on Long Island study Cases: 487; Controls: 509 **Exposure assessment method:** Questionnaire	**OR Frequency of lights on during sleep hours**		Parity, family history of breast cancer, education, benign breast disease, age at reference date	**Exposure information:** Frequency of turning lights on during sleep hours per night and per week. **Strengths:** Overall large sample size and analytic control for potential confounders. **Limitations:** Highly selected population-based on long-term residence; retrospective assessment of exposure in a delayed second interview creating opportunities for recall bias; exposure to light at night was
		< 1/mo or never	1; 311		
		1–3/mo	0.98 (0.66–1.44); 66		
		1/wk	0.71 (0.43–1.16); 31		
		2–4/wk	0.99 (0.67–1.48); 63		
		≥ 5/wk	1.12 (0.8–1.57); 105		
		OR Frequency of lights on when waking: Highly exposed (lights ≥ 1 or 2 per week)		Parity, family history of breast cancer,	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		1–3/mo or never (ref)	1; 377	education, benign breast disease, age at reference date	limited to the past 5 years in this somewhat older subset of participants. **Additional results:** - **Confidence in evidence:** Strong to moderate evidence (waking ≥ 2/week and turning on light ≥ 2/night; and waking ≥ 1/week and turning on light ≥ 2/night (not significant).
		1/wk: 1/night	0.88 (0.67–1.16); 145		
		1/wk: ≥ 2/night	1.46 (0.92–2.32); 53		
		2/wk: 1/night	0.91 (0.67–1.24); 116		
		2/wk: ≥ 2/night	1.65 (1.02–2.69); 51		
		Non-peak sleep: OR		Parity, family history of breast cancer, education, benign breast disease, age at reference date	
		No	1; 556		
		Yes	0.83 (0.44–1.57); 19		
White *et al.* 2017 Cohort Continental U.S.A. and Puerto Rico **Enrollment or follow-up:** 2003–2009	**Population:** The Sister Study 50,884 **Exposure assessment method:** questionnaire	**HR Sleep: Frequency of waking up**		Race, education, income, marital status, HRT use, OC use, alcohol consumption, age at menarche, parity, age at first birth, age at menopause, pack years of smoking, physical activity	**Exposure information:** Frequency of waking (daily, weekly); and yes/no about turning on light/TV in sleeping area **Strengths:** Large sample size allowed consideration of ER status, excluded shift workers **Limitations:** Light at night prior to sleeping and duration of time that lights are on not captured. Assumes window of exposure is the relevant time window. **Additional results:** - **Confidence in evidence:** No evidence
		< 1 month	1; 151		
		1–3 days/month	0.98 (0.78–1.23); 163		
		≥ 1 / week	0.92 (0.76–1.1); 612		
		Most or every night	1.05 (0.88–1.24); 1809		
		HR Sleep: Number of times waking up/night		Same as above	
		Never	1; 50		
		1	1.08 (0.81–1.44); 1538		
		2	1.14 (0.85–1.53); 743		
		≥ 3	1.13 (0.83–1.53); 400		
		HR LAN during sleep: All women		Same as above	
		No LAN	1; 486		
		Daylight	0.87 (0.66–1.15); 65		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Light/TV in room	1.09 (0.93–1.26); 336		
		Light outside room	1.01 (0.9–1.13); 936		
		Nightlight	0.97 (0.87–1.08); 1762		
		HR LAN during sleep: ER+		Same as above	
		No LAN	1; 264		
		Daylight	1.05 (0.74–1.5); 41		
		Light/TV in room	1.2 (0.97–1.47); 178		
		Light outside room	1.11 (0.96–1.3); 543		
		Nightlight	1.07 (0.93–1.23); 1028		
		HR Turns lights on when waking up		Same as above	
		No	1; NR		
		Turn lights on	1.07 (0.95–1.21); 320		
		Lights already on	0.86 (0.52–1.4); 18		
Outdoor lighting studies					
Bauer *et al.* 2013 Case-control Georgia, U.S.A. **Enrollment or**	**Population:** Cases: 33,503; Lung cancer controls: 14,314 **Exposure assessment method:**	**OR Outdoor LAN level**			
		Low	1; 27,121	Race, tumor grade and stage, year of diagnosis, age at	**Exposure information:** Range of LAN levels = 0 to 63 watts per steradian cm^2. Low = 0–20 watts per steradian cm^2; medium
		Medium	1.06 (0.97–1.16); 5,974		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
follow-up: 2000–2007	Environmental monitoring	High	1.12 (1.04–1.2); 9,659	diagnosis, Metropolitan Statistical Area (MSA) (county level), MSA population mobility (county level), birth/1,000 women ages 15–50 (county level), prevalence of cigarette smoking at county level	= 21–41 watts per steradian cm^2; and high = 41-63 watts per steradian cm^2. **Strengths:** Large population-based study of LAN; satellite measurements of LAN and cancer registry data based on individual level data. A substudy validation of ground level measurements of circadian-relevant light spectrum and satellite images strengthens this study. **Limitations:** Lung cancer controls may not be an appropriate choice as LAN has been found to be related to lung cancer in some studies. Potential selection bias due to large percentage of non-geocodable addresses; window of exposure varies for each woman; and changes of addresses over time are not incorporated. Further, DMSP data is the low-intensity data so range of exposure is narrow and low. County level covariates rather than individual level covariates increased likelihood of uncontrolled confounding. **Additional results:** - **Confidence in evidence:** Evidence
		OR Outdoor LAN level: White women		Same as above	
		Low	1; 8,367		
		Medium	1.07 (0.97–1.17); 4,912		
		High	1.13 (1.05–1.22); 18,359		
		OR Outdoor LAN level: Black women		Same as above	
		Low	1; 1,240		
		Medium	1.04 (0.78–1.38); 991		
		High	1.02 (0.82–1.28); 8,230		
Garcia-Saenz *et al.* 2018 Case-control Spain **Enrollment or follow-up:** 2008-2013	**Population:** Cases: 380; Controls: 490 **Exposure assessment method:** environmental monitoring	**OR Outdoor LAN - visual light (base model)**		Age, center, education, menopausal status	**Exposure information:** LAN from photos with 3 spectral bands from the International Space Station (ISS) 2012–13. Visual light average for cases = 0.034; blue light average for cases = 0.155. **Strengths:** Strong design and analysis and exposure assessment.
		1st tertile: 0.009–0.046 (reference)	1; 133		
		2nd tertile: 0.046–0.071	0.86 (0.6–1.21); 121		
		3rd tertile: 0.071–0.226	0.86 (0.59–1.26); 126		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		OR Outdoor LAN - visual light (adjusted model)		Age, center, education, menopausal status, SES, urban vulnerability index (UVI), BMI, tobacco, family history of breast cancer, chronotype, indoor light.	**Limitations:** Potential selection bias due to attrition in controls; exposure at young age not captured. **Additional results:** No correlation between outdoor and indoor lighting for breast cancer; also no correlation between blue light and visual spectrum light. **Confidence in evidence:** Strong to moderate evidence
		1st tertile: 0.009–0.046 (reference)	1; 132		
		2nd tertile: 0.046–0.071	0.87 (0.6–1.24); 121		
		3rd tertile: 0.071–0.226	0.81 (0.54–1.2); 123		
		OR Outdoor LAN - blue light (base model)		Age, center, education, menopausal status.	
		1st tertile: 0.041–0.128 (reference)	1; 126		
		2nd tertile: 0.128–0.163	0.8 (0.56–1.15); 116		
		3rd tertile: 0.163–0.407	1.16 (0.81–1.66); 138		
		OR Outdoor LAN - blue light (adjusted model)		Age, center, education, menopausal status, SES, urban vulnerability index (UVI), BMI, tobacco, family history of breast cancer, chronotype, indoor light.	
		1st tertile: 0.041–0.128 (reference)	1; 124		
		2nd tertile: 0.128–0.163	0.91 (0.62–1.32); 114		
		3rd tertile: 0.163–0.407	1.47 (1–2.17); 138		
		OR Outdoor LAN - MSI, ER+ PR+ and HER2-		Age, center, education, menopausal status.	
		1st tertile	1; 84		
		2nd tertile	0.86 (0.6–1.28); 82		
		3rd tertile	1.26 (0.8–1.88); 101		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		OR Outdoor LAN - MSI, HER2+		Age, center, education, menopausal status.	
		1st tertile	1; 18		
		2nd tertile	0.8 (0.4–1.65); 19		
		3rd tertile	0.99 (0.5–2.07); 20		
		OR Outdoor LAN - MSI, Triple negative		Age, center, education, menopausal status.	
		1st tertile	1; 13		
		2nd tertile	0.59 (0.2–1.6); 7		
		3rd tertile	0.64 (0.2–1.8); 6		
Hurley *et al.* 2014 Cohort California **Enrollment or follow-up:** 1995–1996	**Population:** California Teachers Study 106,731 **Exposure assessment method:** Environmental monitoring	**HR All women: outdoor light levels (quintiles)**		Age, race/birthplace, family history of breast cancer, age at menarche, pregnancy history, breastfeeding history, physical activity (strenuous) BMI, alcohol consumption, menopausal status + HRT, smoking status, smoking pack years, neighborhood SES, urbanization	**Exposure information:** Average annual 2006 DMSP satellite night time radiance value assigned to residence at baseline. **Strengths:** Large defined cohort of teachers with full information on potential confounders. **Limitations:** Window of outdoor light exposure limited to older ages; potential misalignment of satellite data and residential addresses. **Additional results:** - **Confidence in evidence:** Some evidence
		1 (lowest)	1; 1006		
		2	1.05 (0.95–1.16); 1029		
		3	1.06 (0.95–1.17); 1010		
		4	1.05 (0.95–1.17); 1009		
		5 (hightest)	1.12 (1–1.26); 1041		
		Trend-test *P*-value = .0.06			
		HR Premenopausal women BMI < 25: Outdoor LAN levels (quintiles)		Same as above	
		1 (lowest)	1; 142		
		2	1.33 (1.03–1.73); 175		
		3	1.37 (1.05–1.8); 167		
		4	1.3 (0.98–1.72); 151		
		5 (highest)	1.56 (1.16–2.08); 167		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *P*-value = 0.02			
		HR Premenopausal women BMI ≥ 25: Quintiles of outdoor LAN		Same as above	
		1 (lowest)	1; 87		
		2	0.94 (0.67–1.33); 86		
		3	0.92 (0.64–1.32); 83		
		4	0.91 (0.62–1.32); 80		
		5 (highest)	1.06 (0.72–1.56); 98		
		Trend-test *P*-value = 0.59			
		HR Postmenopausal women BMI <25: Outdoor LAN (quintiles)		Same as above	
		1(lowest)	1; 341		
		2	0.94 (0.79–1.12); 322		
		3	0.95 (0.8–1.14); 324		
		4	1.03 (0.86–1.24); 352		
		5 (highest)	0.98 (0.8–1.18); 326		
		Trend-test *P*-value = 0.82			
		HR Postmenopausal women BMI ≥ 25: Outdoor LAN (quintiles)		Same as above	
		1 (lowest)	1; 271		
		2	1.06 (0.87–1.28); 273		
		3	1.07 (0.87–1.31); 277		
		4	1.02 (0.82–1.25); 272		
		5 (highest)	1.11 (0.89–1.39); 295		
		Trend-test *P*-value: 0.44			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
James *et al.* 2017 Cohort 48 states in continental U.S.A **Enrollment or follow-up:** 1989–2013; followup 1989–2013	**Population:** Nurses Health Study II. 109,672 **Exposure assessment method:** Environmental monitoring	**HR Cumulative average LAN: Quintiles (median nW/cm²/sr)**		Benign breast disease, family history of breast cancer, age at menarche, parity and age at first birth, height, white race, BMI, BMI at age 18, OC use, mammography screening, menopausal status, smoking status, alternative healthy eating index (AHEI), physical activity, marital status, living alone, personal income, shift work after 1989, region, PM2.5, census-tract median home value, income, population density.	**Exposure information:** Cumulative LAN exposure based on time-varying satellite data for a composite of persistent nighttime illumination at ~ 1 km2 scale for each residence during follow-up. Quintiles with medians 4.3, 12.4, 22.9, 37.2, and 64 nW/cm2/sr. **Strengths:** Large established cohort of young nurses with shift work exposure; examination of impact of shift work on LAN estimates; inclusion of time-varying information on addresses throughout follow-up. **Limitations:** Satellite images of visual light may not be the most relevant proxy for circadian disruption; missing measurement of LAN during window of early exposure and from indoor sources. While air pollution and population density were controlled, cannot rule out the possibility that other factors correlated with outdoor LAN may explain the observed association of LAN and breast cancer risk; many variables included in model which may not be associated with LAN that may reduce the estimate of effect. **Additional results:** Continuous LAN 1.06 (95% CI = 0.99–1.13) for ER+; Continuous LAN 0.98 (95% CI = 0.85–1.13) for ER-; p for heterogeneity for ER+/ER-, *P* = 0.33. **Confidence in evidence:** Some evidence
		Quintile 1 (4.3)	1; 571		
		Quintile 2 (12.4)	1.05 (0.94–1.18); 715		
		Quintile 3 (22.9)	1.01 (0.9–1.13); 710		
		Quintile 4 (37.2n)	1.08 (0.97–1.22); 776		
		Quintile 5 (64.0)	1.14 (1.01–1.29); 777		
		Continuous LAN (per interquartile range [IQR], 31.6, increase)	1.05 (1–1.11); NR		
		Trend-test *P*-value = 0.02			
		HR Cumulative average LAN: Premenopausal women		Same as above except menopausal status	
		Quintile 1	1; 282		
		Quintile 2	1.02 (0.87–1.19); 367		
		Quintile 3	1.08 (0.92–1.26); 415		
		Quintile 4	1.12 (0.96–1.31); 447		
		Quintile 5	1.2 (1.02–1.41); 462		
		Continuous LAN (per IQR increase)	1.07 (1.01–1.14); NR		
		HR Cumulative average LAN: Postmenopausal women		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Quintile 1	1; 223		
		Quintile 2	0.96 (0.8–1.16); 242		
		Quintile 3	0.92 (0.77–1.11); 229		
		Quintile 4	0.99 (0.82–1.19); 248		
		Quintile 5	0.95 (0.78–1.15); 230		
		Continuous LAN (per IQR increase)	1 (0.91–1.09); NR		
		HR No shift work since 1989		Same as above except shift work status, menopausal status.	
		Quintile 1	1; 386		
		Quintile 2	0.98 (0.86–1.13); 469		
		Quintile 3	0.96 (0.84–1.1); 472		
		Quintile 4	1.01 (0.88–1.16); 515		
		Quintile 5	1.04 (0.9–1.2); 511		
		Continuous LAN (per IQR increase)	1.03 (0.97–1.09); NR		
		HR Cumulative average: Any shift work since 1989		Same as above	
		Quintile 1	1; 185		
		Quintile 2	1.18 (0.98–1.43); 246		
		Quintile 3	1.09 (0.9–1.32); 238		
		Quintile 4	1.19 (0.98–1.44); 261		
		Quintile 5	1.29 (1.06–1.56); 266		
		Continuous LAN (per IQR increase)	1.09 (1.01–1.18); NR		
		HR ER positive tumor		Same as above	
		Quintile 1	1; 325		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Quintile 2	1.13 (0.97–1.3); 434		
		Quintile 3	1.08 (0.93–1.26); 433		
		Quintile 4	1.16 (1–1.35); 476		
		Quintile 5	1.2 (1.02–1.4); 469		
		Continuous LAN (per IQR increase)	1.06 (0.99–1.13); NR		
		Trend-test *P*-value = 0.06			
		HR ER negative tumor		Same as above	
		Quintile 1	1; 96		
		Quintile 2	0.92 (0.69–1.23); 105		
		Quintile 3	0.8 (0.59–1.08); 95		
		Quintile 4	0.93 (0.7–1.25); 111		
		Quintile 5	0.94 (0.69–1.29); 105		
		Continuous LAN (per IQR increase)	0.98 (0.85–1.13); NR		
		Trend-test *P*-value = 0.86			
		HR Continuous cumulative average exposure (per IQR increase): smoking status		Same as above except smoking status, shift work after 1989.	
		Non smokers	1 (0.94–1.07); NR		
		Past smokers	1.1 (1.01–1.19); NR		
		Current smokers	1.21 (1.07–1.37); NR		
Keshet-Sitton *et al.* 2016 Case-Control Israel **Enrollment or follow-up:**	**Population:** Cases: 93; Controls: 185 **Exposure assessment method:** questionnaire	**OR Outdoor LAN sources**			**Exposure information:** Strong residential LAN source near sleeping area **Strengths:** Population-based case-control study with specific metric of exposure to light at night from external source. **Limitations:**
		Closed shutters during sleep	0.82 (0.68–0.99); NR		
		Residing near strong LAN sources	1.52 (1.1–2.12); NR		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
2010-2014		Outdoor light penetrating during sleep	0.96; NR		Breast cancer risk factors were unrelated to case-status, supporting potential selection bias; likely non-differential exposure misclassification, lack of information on source of external light. **Additional results:** - **Confidence in evidence:** Some evidence - residing near strong ambient source of LAN.

Table C-3a. Breast cancer and transmeridian travel: Selection bias rationale

Reference	Selection bias rating
Linnersjö *et al.* 2003	++ ↔ Cases and controls selected from the cohort based on similar criteria; this young cohort was well defined (age at start < 30 years of age) with 5% of person-years among 60+ year olds. SIR overall was 1.01 for women (95% CI = 0.78–1.24) indicating no healthy worker effect (HWE) (SIR for breast cancer was 1.3 (95% CI = 0.85–1.74)). 8% were lost due to migration.
Pinkerton *et al.* 2016	++ ↓ The cohort from which this nested study was composed is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location); there is no evidence of HWE as participants had 37% increased breast cancer risk compared to U.S. population. The original cohort (9,617) was reduced to the analysis incidence cohort (6,093) or 64.4% of original mortality cohort. Proxies responding for deceased individuals had lower response rates (41%/46%), but participants had longer employment histories with Pan Am than the initial mortality cohort, thus the remaining women constitute a survivor cohort.
Pukkala *et al.* 2012	+++ ↔ Included most of the certified cabin crew in four countries; no incomplete follow-up.
Reynolds *et al.* 2002	++ ↔ Union files only available for one year, thus age, sex, and residential distributions had to be estimated for earlier time periods based on data from a single time period and assumptions of workforce profile stability and no information on race/ethnicity on non-cases. SIRs and proportional incidence ratios (PIRs) were similar, suggesting that little bias was introduced as a result of having data from only one period of time.
Schubauer-Berigan *et al.* 2015	++ ↓ The cohort is clearly defined (e.g., includes the relevant exposed, nonexposed, or referent group for a specific time period/location); there is no evidence of HWE as participants had 37% increased breast cancer risk compared to U.S. population. The original cohort (9,617) was reduced to the analysis incidence cohort (6,093) or 64.4% of original mortality cohort. Proxies responding for deceased individuals had lower response rates (41%/46%), but participants had longer employment histories with Pan Am than the initial mortality cohort, thus the remaining women are a survivor cohort.

Table C-3b. Breast cancer and transmeridian travel: Exposure assessment rationale

Reference	Exposure assessment rating
Linnersjö *et al.* 2003	++ ⬇ Exposure assessment methods have moderate sensitivity and specificity, leading to reliable discrimination between exposed and unexposed. Block hours in long-distance flights may or may not adequately estimate times zones crossed.
Pinkerton *et al.* 2016	++ ↔ The exposure assessment methods have moderate sensitivity and specificity, leading to some misclassification with respect to circadian disruption (CD) exposure metrics. Not all members had individual flight records; no records were available to back up self-reported time zones or radiation so these may be quite imprecise which could result in non-differential misclassification, although in this retrospective analysis, recall bias should be considered.
Pukkala *et al.* 2012	++ ⬇ Exposure assessment methods have moderate sensitivity and specificity crossing time zones. Women classified as unexposed or less exposed may have been more exposed since transmeridian flights with stopovers were counted as separate segments. No information on turnover rates (long stayovers or short stayovers), repeated jet lags, irregular night shift work, and associated sleep loss. Assumptions of similar route distribution may have misclassified exposure, but likely in the null direction.
Reynolds *et al.* 2002	++ ⬇ The exposure assessment methods have moderate sensitivity to differentiate exposed and unexposed. However, union records were limited and flight information based on only one point in time. Transmeridian flights are not clearly defined, only international flights; however, duration and age at entry were available.
Schubauer-Berigan *et al.* 2015	++ ↔ The exposure assessment methods have moderate sensitivity and specificity, leading to some misclassification with respect to CD exposure metrics. Not all members had individual flight records; no records to back up self-reported time zones or radiation so these may be quite imprecise and could result in non-differential misclassification, although in this retrospective analysis, recall bias should be considered.

Table C-3c. Breast cancer and transmeridian travel: Outcome assessment rationale

Reference	Outcome assessment rating
Linnersjö *et al.* 2003	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects; follow-up and diagnoses are conducted independent of exposure.
Pinkerton *et al.* 2016	++ ⬇ Includes prevalent cases in the population denominator.
Pukkala *et al.* 2012	+++ ↔ Complete record linkage in 4 countries. Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.
Reynolds *et al.* 2002	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.
Schubauer-Berigan *et al.* 2015	++ ⬇ Prevalent cases in denominator and second primaries in numerator increased population rates by 3.5% which would introduce bias towards the null.

Table C-3d. Breast cancer and transmeridian travel: Sensitivity rationale

Reference	Sensitivity rating
Linnersjö *et al.* 2003	++ ⬇ The study has a moderate level of sensitivity in that it is not clear if those classified as highly exposed actually crossed time zones; small numbers of exposed cases decreased power to detect an effect.
Pinkerton *et al.* 2016	++ ⬇ The study has highly correlated exposure metrics, flight data (domicile averages applied to individuals) likely contributed to high correlations between metrics and inability to detect an effect (however in studies of pilots with individual level data on cumulative cosmic dose and times zones, high correlations also exist); small numbers in certain relevant analytic subsets; adequate duration of follow-up for latency.
Pukkala *et al.* 2012	++ ⬇ Adequate sensitivity as 40% had at least 150 flights across 6 or more time zones.
Reynolds *et al.* 2002	++ ⬇ Use of the three metrics allowed differentiation of those at risk; numbers were adequate and follow-up was adequate.
Schubauer-Berigan *et al.* 2015	++ ⬇ The study has highly correlated exposure metrics, flight data (domicile averages applied to individuals) likely contributed to high correlations between metrics and inability to detect an effect (however in studies of pilots with individual level data on cumulative cosmic dose and times zones, high correlations also exist); small numbers in certain relevant analytic subsets; adequate duration of follow-up for latency.

Table C-3e. Breast cancer and transmeridian travel: Confounding rationale

Reference	Confounding rating
Linnersjö *et al.* 2003	Breast: + ⬆ An external source of information about potential confounders (limited to reproductive variables parity and age at first full-term pregnancy) was used to estimate that an excess breast cancer incidence of 10% would be expected rather than 1.3 observed. In addition, alcohol, socioeconomic status (SES), were not controlled.
Pinkerton *et al.* 2016	Breast: +++ ⬆ Indirect adjustments for parity and age at first birth suggest that the two factors in combination could have explained the excess risk observed. No adjustments were made for SES or alcohol consumption.
Pukkala *et al.* 2012	Breast: ++ ⬆ The study did not control for all potential confounders including SES, age.
Reynolds *et al.* 2002	Breast: + ⬆ The study did not control for potential confounders including alcohol consumption, parity. No measures of radiation dose were evaluated.
Schubauer-Berigan *et al.* 2015	Breast: ++ ⬆ Indirect adjustments made for independent effects of parity and age at first birth suggest that the two factors in combination could have explained the excess risk observed. No adjustments were made for SES or alcohol consumption.

Table C-3f. Breast cancer and transmeridian travel: Analysis and selective reporting rationale

Reference	Analysis rating	Selective reporting rating
Linnersjö *et al.* 2003	+++ ↔ The study used relevant data and appropriate methods of analysis.	+++ ↔ No evidence that selective reporting of the data or analyses was limited to a subset of the data.
Pinkerton *et al.* 2016	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis. Multiple sensitivity analyses performed: alternative lag periods were considered, exclusion of data from proxies, exclusion of those with multiple diagnostic x-rays or radiation prior to diagnosis; surgical menopause time dependent term.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Pukkala *et al.* 2012	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	++ ↔ No indication that reporting was selective; however, results were less than adequately presented so that the number of cases in various categories were not shown.
Reynolds *et al.* 2002	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Schubauer-Berigan *et al.* 2015	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis. Conducted multiple analyses with different lag windows.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.

Table C-4. Breast cancer and transmeridian travel study results

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Linnersjö *et al.* 2003 Nested case-control Sweden **Enrollment or follow-up:** 1957–1994	**Population:** Crew from the Swedish Scandinavian Airline System (SAS) Cases: 48; Controls: 174 **Exposure assessment method:** Company records	**OR > 10,000 total block hours**			**Exposure information:** 10,000+ block hours; high altitutde, long-distance flight duty; and 5,000+ block hours in high altitude long distance flights. **Strengths:** Administrative flight records available particularly on types of high-altitude long-duration flights; young exposed population. **Limitations:** Exposure assessment does not clearly differentiate cases highly exposed to multiple time zones; and the small numbers of cases led to inadequate power to detect an effect; no control for alcohol. **Additional results:** Comparator is female Swedish population. **Confidence in evidence:** Some evidence (high altitude, long duration flights)
		< 10,000 block hours	1; NR		
		> 10,000 block hours	1.14 (0.15–8.48); 3		
		OR High altitude, long distance flight duty			
		Never	1; NR		
		Ever	1.79 (0.31–10.45); 14		
		OR > 5,000 block hours in high altitude, long distance flights			
		Never	1; NR		
		Ever	3.27 (0.54–19.7); 5		
		SIR External evaluation - Employment duration (years)			
		< 10 yr	1.36 (0.72–2.32); 13		
		10–19 yr	1.26 (0.67–2.15); 13		
		20+ yr	1.39 (0.56–2.86); 7		
Pinkerton *et al.* 2016 Nested case-control U.S.A. **Enrollment or follow-up:** 2002–2005	**Population:** Pan American World Airways (Pan Am) flight attendants Cases: 344; Controls: 5,749 **Exposure assessment method:** questionnaire	**eRR Excess RR for 10-year lagged cumulative standard sleep interval (SSI)**			**Exposure information:** Absorbed dose 10 mGy increase; SSI 2,000 hour increase; time zones crossed (per 4,600 increase in zones crossed). **Strengths:** Largest cohort of flight attendants with individual self-reported data; long follow-up; evaluated working during the standard sleep interval or circadian night; medical record follow-back and registry linkage for diagnosis verification; use of objective external sources to derive exposure
		Per 2,000 hour increase of SSI, parity 0,1,2	-0.039 (-0.15–0.14); NR		
		Per 2,000 hour increase of SSI, Parity = 3+	0.99 (-0.041–4.3); NR		
		Trend-test *p*-value: .06			
		eRR Excess RR for 10-year lagged cumulative time zones crossed			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Per 4,600 increase of time zones crossed, Parity = 0, 1, 2	-0.0017 (-0.12–0.18); NR		metrics for time zones crossed. Detailed and sensitive analysis and treatment of potential confounding and effect modification. **Limitations:** Low cumulative exposure, potential exposure misclassification, potential recall bias, relatively low participation. **Additional results:** **Confidence in evidence:** Some evidence based on women of 3+ parity
		Per 4,600 increase of time zones crossed, Parity = 3+	1.5 (0.14–6.2); NR		
		Trend-test *P*-value = 0.02			
Pinkerton *et al.* 2012 Cohort U.S.A. **Enrollment or follow-up:** 2002–2005	**Population:** Pan American World Airways (Pan Am) flight attendants 11,311 **Exposure assessment method:** company records	**SRR Standard sleep interval (SSI) (hours)**			**Exposure information:** Duration of employment; standard sleep interval; time zones crossed **Strengths:** Largest cohort of flight attendants with individual self-reported data; long follow-up; evaluated working during standard sleep interval or circadian night; medical record follow-back and registry linkage for diagnosis verification; use of objective external sources to derive exposure metrics for time zones crossed and working during the standard sleep interval. **Limitations:** Low sensitivity due to mortality outcome; limited duration of employment; likely that there is some exposure misclassification; highly correlated exposure metrics. **Additional results:** - **Confidence in evidence:** Supporting evidence
		0 to < 318	1; 69		
		318 to < 792	1 (0.69–1.45); 69		
		792 to < 1,435	1.41 (0.98–2.05); 67		
		1,435 to < 2,642	1.13 (0.78–1.63); 70		
		≥ 2,642	0.93 (0.64–1.36); 68		
		SRR Employment duration (days)			
		0 to < 731	1; 68		
		731 to < 1,614	0.78 (0.54–1.12); 68		
		1614 to < 2,831	1.02 (0.71–1.48); 69		
		2,831 to < 5,369	0.96 (0.65–1.41); 70		
		≥ 5,369	0.74 (0.51–1.08); 68		
		SRR time zones crossed			
		0 to < 724	1; 69		
		724 to < 1,716	0.94 (0.66–1.36); 70		
		1716 to < 3,201	1.17 (0.81–1.68); 67		
		3201 to < 6,399	1.01 (0.69–1.47); 68		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		≥ 6,399	0.87 (0.6–1.26); 69		
Pukkala *et al.* 2012 Nested case-control Nordic countries **Enrollment or follow-up:** 1953–2005	**Population:** Nordic airline cabin crew from Sweden, Norway, Finland, and Iceland. **Exposure assessment method:** Company records	**OR RIsk per 100 flights crossing 6+ times zones**		Parity, age	**Exposure information:** 100+ flights crossing 6+ time zones. **Strengths:** Large study with decades of population-based registration of incident cancer. Exposure assessment based on time zones crossed. **Limitations:** Exposure assessment may have been diluted due to the nature of company records on flights. **Additional results:** Similar results for those crossing 4+ or 5+ time zones. Also adjusted for age at first live birth which was similar in cases and non-cases. **Confidence in evidence:** No evidence
		Per 100 crossings of 6+ times zones	0.92 (0.77–1.11); NR		
Reynolds *et al.* 2002 Cohort California, U.S.A. **Enrollment or follow-up:** 1988–1995	**Population:** California flight attendants. 44,021 **Exposure assessment method:** Company records	**SIR Domestic vs. International flights**			**Exposure information:** Domestic vs. international assignments; age starting employment < 25; employment duration 15+ years. **Strengths:** Largest flight attendant union, and largest population-based cancer registry, PIR and SIRs similar in magnitude, information on employment duration, age started and assignment on international flights.
		Domestic	1.21 (0.8–1.75); 28		
		International	1.79 (1.21–2.54); 31		
		SIR Employment duration (years)			
		≥ 15 yr	1.57 (1.16–2.08); 49		
		< 15 yr	0.96 (0.48–1.73); 11		
		SIR Age at entry			
		< 25 yr of age	1.72 (1.23–2.34); 41		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		≥ 25 yr of age	1.09 (0.65–1.7); 19		**Limitations:** No control for confounders; exposure assessment based on one point in time, and does not indicate transmeridian crossing, only international flights. **Additional results:** - **Confidence in evidence:** Evidence
Schubauer-Berigan *et al.* 2015 Cohort U.S.A. **Enrollment or follow-up:** 2002–2005	**Population:** Pan American World Airways (Pan Am) flight attendants 6,093 **Exposure assessment method:** questionnaire	**SRR Standard sleep interval (SSI) (hours)**			**Exposure information:** > 933.9 time zones crossed; > 395 hours working during standard sleep interval (night work) (Grajewski *et al.* 2003; Waters *et al.* 2009) based on all airline jobs; > 853 days employment duration. **Strengths:** Largest cohort of flight attendants with individual self-reported data; long follow-up; evaluated working at night; medical record follow-back and registry linkage for diagnosis verification; use of objective external sources to derive exposure metrics for time zones crossed. **Limitations:** Selected participants employed longer with company so likely survivor cohort; Correlated exposure metrics; no airline history of flights so time zone metrics were calculated; low cumulative exposure, potential exposure misclassification, potential recall bias, relatively low participation. Prevalent cases in population denominator. No direct control for potential confounders or effect modifiers.
		0 to < 318	1; 69		
		318 to < 792	1 (0.69–1.45); 69		
		792 to < 1,435	1.41 (0.98–2.05); 67		
		1435 to < 2,642	1.13 (0.78–1.63); 70		
		≥ 2,642	0.93 (0.64–1.36); 68		
		SRR Employment duration (days)			
		0 to < 731	1; 68		
		731 to < 1,614	0.78 (0.54–1.12); 68		
		1,614 to < 2,831	1.02 (0.71–1.48); 69		
		2,831 to < 5,369	0.96 (0.65–1.41); 70		
		≥ 5,369	0.74 (0.51–1.08); 68		
		SRR time zones crossed			
		0 to < 724	1; 69		
		724 to < 1,716	0.94 (0.66–1.36); 70		
		1716 to < 3,201	1.17 (0.81–1.68); 67		
		3201 to < 6,399	1.01 (0.69–1.47); 68		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		≥ 6,399	0.87 (0.6–1.26); 69		**Additional results:** - **Confidence in evidence:** Some evidence

References

1. Bauer SE, Wagner SE, Burch J, Bayakly R, Vena JE. 2013. A case-referent study: light at night and breast cancer risk in Georgia. *Int J Health Geogr* 12: 23. (Supported by the Georgia Cancer Coalition. Authors affiliated with University of Georgia, GA; University of South Carolina, SC; Georgia Comprehensive Cancer Registry, GA.)

2. Davis S, Kaune WT, Mirick DK, Chen C, Stevens RG. 2001a. Residential magnetic fields, light-at-night, and nocturnal urinary 6-sulfatoxymelatonin concentration in women. *Am J Epidemiol* 154(7): 591-600. (Supported by the Electric Power Research Institute. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Washington, WA; EM Factors, WA; University of Connecticut Health Center, CT.)

3. Davis S, Mirick DK, Stevens RG. 2001b. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 93(20): 1557-1562. (Supported by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; University of Connecticut Health Center, CT.)

4. Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, Boyle T, El-Zaemey S, Rogers P, Peters S, Slevin T, D'Orsogna A, de Vocht F, Vermeulen R, Heyworth JS. 2013. The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer* 109(9): 2472-2480. (Supported by the National Health and Medical Research Council Australia, the Cancer Council Western Australia, the University of Western Australia, and the Lions Cancer Institute. Authors affiliated with University of Western Australia, Australia; University of Cologne, Germany; Monash University, Australia; Cancer Council Western Australia, Australia; Health Consumer Representative, Australia; University of Manchester, UK; Utrecht University, Netherlands.)

5. Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, Amiano P, Martín Sánchez V, Guevara M, Capelo R, Tardón A, Peiró-Perez R, Jiménez-Moleón JJ, Roca-Barceló A, Pérez-Gómez B, Dierssen-Sotos T, Fernández-Villa T, Moreno-Iribas C, Moreno V, García-Pérez J, Castaño-Vinyals G, Pollán M, Aubé M, Kogevinas M. 2018. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain Study). *Environ Health Perspect* 126(4): 047011. (Supported by the Accion Transversal del Cancer, Instituto de Salud Carlos III-FEDER, the Fundación Marqués de Valdecilla, the ICGC International Cancer Genome Consortium CLL, MINECO, RTICC, the Junta de Castillay León, Consejería de Salud of the Junta de Andalucía, the Conselleria de Sanitat of the Generalitat Valenciana, the Regional Government of the Basque Country, the Consejería de Sanidad de la Región de Murcia, the European Commission, AECC, the Catalan Government– Agency for Management of University and Research, the Fundación Caja de Ahorros de Asturias, the University of Oviedo, CERCA, the STARS4ALL project, the European Union, and the Cities at Night project. Authors affiliated with Barcelona Institute for Global Health, Spain; CIBER, Spain, CIBERESP, Spain; IAA, Spain; CSIC,

Spain; Universidad Complutense de Madrid, Spain; Cégep de Sherbrooke, Canada; University Exeter, UK; IMIM, Spain; National Centre for Epidemiology, Spain; IDIVAL, Spain; Health Department of Basque Region, Spain; University of León, Spain; IdiSNA, Spain; CYSMA, Spain; IUOPA, Spain; FISABIO, Spain; University of Granada, Spain; ibs.GRANADA, Spain; Autonomous Government of Catalonia, Spain; REDISSEC, Spain; IDIBELL, Spain; University of Barcelona, Spain.)

6. Gu F, Han JL, Hankinson S, Schernhammer E, Nurses' Hlth Study G. 2014. Rotating night shift work and cancer mortality in the nurses' health study. *Cancer Research* 74(19): 2.

7. Hurley S, Goldberg D, Nelson D, Hertz A, Horn-Ross PL, Bernstein L, Reynolds P. 2014. Light at night and breast cancer risk among California teachers. *Epidemiology* 25(5): 697-706. (Supported by the Regents of the University of California, California Breast Cancer Research Program and the National Cancer Institute. Authors affiliated with Cancer Prevention Institute of California, CA; Beckman Research Institute, CA; Stanford University School of Medicine, CA.)

8. James P, Bertrand KA, Hart JE, Schernhammer ES, Tamimi RM, Laden F. 2017. Outdoor light at night and breast cancer incidence in the Nurses' Health Study II. *Environ Health Perspect* 125(8): 087010. (Supported by the Harvard National Heart, Lung, and Blood Institute, NIH, NCI, and the Susan G. Komen for the Cure® organization. Authors affiliated with Harvard T. H. Chan School of Public Health, MA; Brigham and Women's Hospital and Harvard Medical School, MA; Boston University, MA; Medical University of Vienna, Austria; University of California Los Angeles, CA.)

9. Johns LE, Jones ME, Schoemaker MJ, McFadden E, Ashworth A, Swerdlow AJ. 2018. Domestic light at night and breast cancer risk: a prospective analysis of 105 000 UK women in the Generations Study. *Br J Cancer* 118(4): 600-606. (Supported by Breast Cancer Now, The Institute of Cancer Research, and NHS. Authors affiliated with Institute of Cancer Research, UK; Breast Cancer Now Research Centre, UK.)

10. Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A. 2016. Can avoiding light at night reduce the risk of breast cancer? *Integr Cancer Ther* 15(2): 145-152. (No financial support received. Authors affiliated with University of Haifa, Israel; Poria Medical Center, Israel; Soroka University Medical Center, Israel.)

11. Kloog I, Portnov BA, Rennert HS, Haim A. 2011. Does the modern urbanized sleeping habitat pose a breast cancer risk? *Chronobiol Int* 28(1): 76-80. (Support not reported. Authors affiliated with University of Haifa, Israel; Technion–Israel Institute of Technology and Clalit Health Services National Cancer Control Center, Israel; Harvard School of Public Health, MA.)

12. Kwon P, Lundin J, Li W, Ray R, Littell C, Gao D, Thomas DB, Checkoway H. 2015. Night shift work and lung cancer risk among female textile workers in Shanghai, China. *J Occup Environ Hyg* 12(5): 334-341. (Supported by NIH. Authors affiliated with Bassett Army Community Hospital, Alaska; University of Washington, WA; Fred Hutchinson

Cancer Research Center, WA; Walter Reed Army Institute of Research, MD; Fudan University, China; University of California San Diego, CA.)

13. Lash TL, Fox MP, Fink AK. 2009. *Applying Quantitative Bias Analysis to Epidemiologic Data*, New York, NY: Springer-Verlag. 192 pp.

14. Li Q, Zheng T, Holford TR, Boyle P, Zhang Y, Dai M. 2010. Light at night and breast cancer risk: results from a population-based case-control study in Connecticut, USA. *Cancer Causes Control* 21(12): 2281-2285. (Supported by the National Cancer Institute/National Institute of Environmental Health Science. Authors affiliated with Huazhong University of Science and Technology, China; Yale School of Public Health, CT; International Prevention Research Institute, France; Chinese Academy of Medical Sciences, China.)

15. Linnersjö A, Hammar N, Dammström BG, Johansson M, Eliasch H. 2003. Cancer incidence in airline cabin crew: experience from Sweden. *Occup Environ Med* 60(11): 810-814. (Supported by the Swedish Council for Work Life Research. Authors affiliated with Stockholm Center of Public Health, Sweden; Swedish SAS, Sweden; Swedish Air Force, Sweden.)

16. O'Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, Gammon MD, Leske MC, for the Electromagnetic Fields Breast Cancer on Long Island Study Group. 2006. Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol* 164(4): 358-366. (Supported by NCI and NIEHS. Authors affiliated with Stony Brook University, NY; University of Connecticut Health Center, CT; University of North Carolina at Chapel Hill, NC.)

17. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. 2012. Night work and the risk of cancer among men. *Am J Epidemiol* 176(9): 751-759. (Supported by the Health Canada, the National Cancer Institute of Canada, the Institut de recherche en santé et sécurité au travail du Québec, the Fonds de la recherche en santé du Québec, and the Canadian Institutes of Health Research. Authors affiliated with INRS, Canada; University of Quebec, Canada; CRCHUM, Canada; University of Montreal, Canada.)

18. Pinkerton LE, Waters MA, Hein MJ, Zivkovich Z, Schubauer-Berigan MK, Grajewski B. 2012. Cause-specific mortality among a cohort of U.S. flight attendants. *Am J Ind Med* 55(1): 25-36. (Supported by the Office of Women's Health of the U.S. Department of Health and Human Services. Authors affiliated with NIOSH, OH.)

19. Pinkerton LE, Hein MJ, Anderson JL, Little MP, Sigurdson AJ, Schubauer-Berigan MK. 2016. Breast cancer incidence among female flight attendants: exposure-response analyses. *Scand J Work Environ Health* 42(6): 538-546. (Supported by NCI, USDHHS, and NIOSH. Authors affiliated with NIOSH, OH; CACI, Inc., OH; NCI, MD.)

20. Pukkala E, Helminen M, Haldorsen T, Hammar N, Kojo K, Linnersjö A, Rafnsson V, Tulinius H, Tveten U, Auvinen A. 2012. Cancer incidence among Nordic airline cabin crew. *Int J Cancer* 131(12): 2886-2897. (Supported by the Nordic Cancer Union. Authors affiliated with Finnish Cancer Registry, Finland; University of Tampere, Finland; Cancer Registry of Norway, Norway; Karolinska Institutet, Sweden; STUK-Radiation and

Nuclear Safety Authority, Finland; University of Iceland, Iceland; Icelandic Cancer Registry, Iceland; Institute for Energy Technology, Norway.)

21. Reynolds P, Cone J, Layefsky M, Goldberg DE, Hurley S. 2002. Cancer incidence in California flight attendants (United States). *Cancer Causes Control* 13(4): 317-324. (Supported by the California Breast Cancer Research Program. Authors affiliated with California Department of Health Services, CA; Public Health Institute, CA.)

22. Schernhammer ES, Feskanich D, Liang G, Han J. 2013. Rotating night-shift work and lung cancer risk among female nurses in the United States. *Am J Epidemiol* 178(9): 1434-1441. (Supported by NIH. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; ACR-ITR, Austria; LBI-ACR, Austria; Southeast University, China; Tianjin Medical University Cancer Institute and Hospital, China.)

23. Schubauer-Berigan MK, Anderson JL, Hein MJ, Little MP, Sigurdson AJ, Pinkerton LE. 2015. Breast cancer incidence in a cohort of U.S. flight attendants. *Am J Ind Med* 58(3): 252-266. (Supported by the National Cancer Institute and the Office of Women's Health of the U.S. Department of Health and Human Services. Authors affiliated with NIOSH, OH; NCI, MD.)

24. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. 1992. Selection of controls in case-control studies. II. Types of controls. *Am J Epidemiol* 135(9): 1029-1041. (Support not reported. Authors affiliated with NCI, MD; University of Minnesota, MN.)

25. White AJ, Weinberg CR, Park YM, D'Aloisio AA, Vogtmann E, Nichols HB, Sandler DP. 2017. Sleep characteristics, light at night and breast cancer risk in a prospective cohort. *Int J Cancer* 141(11): 2204-2214. (Supported by NIH. Authors affiliated with NIEHS, NC; NIH, NC; Social & Scientific Systems, Inc., NC; University of North Carolina, NC.)

26. Yong M, Blettner M, Emrich K, Nasterlack M, Oberlinner C, Hammer GP. 2014. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. *Scand J Work Environ Health* 40(5): 502-510. (Supported by the Deutsche Gesetzliche Unfallversicherung. Authors affiliated with BASF SE, Germany; Johannes Gutenberg University Mainz, Germany; Laboratoire National de Santé, Luxembourg.)

National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night

Appendix D: Night Shift Work and Prostate Cancer

November 2020

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

List of Tables

Appendix D: Prostate Cancer Studies Tables

Appendix D encompasses tables related to human studies on shift work exposure and risk of prostate cancer. Tables D-1a to D-1f provide ratings and the rationales for the domains of study quality and study sensitivity. Table D-2 gives detailed results for each evaluated epidemiological study.

Table D-1a. Evaluation of selection bias in human prostate cancer studies.

Reference	Selection Bias rating
Åkerstedt *et al.* 2017	++ ⬇ The cohort is clearly defined, and no evidence suggests follow-up differed by exposure status. The study did not account for HWE due to lack of information on work history on this older population.
Behrens *et al.* 2017	++ ⬇ The cohort is clearly defined for a specific time period and geographic location. No evidence that follow-up differed by exposure status. Higher prostate cancer risk in individuals lost to follow-up may be due to shift work and may be biasing results toward the null. To account for HWE, shift work information was censored after baseline questionnaires.
Dickerman *et al.* 2016	+++ ⬇ The prospective cohort is clearly defined as to its source and population, and given it is not an occupational cohort is not susceptible to HWSE. The authors were interested in the influence of midlife circadian-related exposures on prostate cancer risk and mortality later in life; thus, the mean age of the cohort at baseline questionnaire (mean age 40) ignores any effect from early life exposures and early prostate cancer.
Gapstur *et al.* 2014	+++ ⬇ The cohort is clearly defined with a relevant exposed, non-exposed and referent group, and no evidence that follow-up differed between the groups. General population cohort so less concern with HWSE, however, this is still a survival cohort.
Hammer *et al.* 2015	++ ⬇ The cohort is clearly defined and includes the relevant exposed and unexposed populations for a specific time period and location. HWE may be induced through ongoing selection based on health-related criteria into, or out of, shift or day work. To correct a potential on-going selection due to differentially declining health status, the authors included a term for employment duration in regression models as a proxy for work-related health effects.
Kubo *et al.* 2006	++ ⬇ The cohort is clearly defined with no evidence that follow-up differed between exposed and non-exposed subjects. There is no discussion of healthy worker effect (HWE) or healthy worker survivor effect (HWSE) in this cohort of survivors.
Kubo *et al.* 2011	+ ↔ Cohort is selected from a larger cohort to avoid selection bias by potential for prostate cancer screening (recent prostate-specific antigen [PSA] screening in health checkups). Follow-up significantly differed between unexposed and exposed subjects because shift workers entered the database earlier. HWSE is also possible if previous shift workers with prostate cancer symptoms were more likely to become day workers, die, or be excluded.

Reference	Selection Bias rating
Schwartzbaum *et al.* 2007	++ ⬇ Only an external analysis was conducted. No evidence of HWE, as the overall SIR for all cancers was approaching unity. HWSE is still possible and may bias results toward the null.
Conlon *et al.* 2007	++ ↔ Cases and controls were selected from same population; however, low response rates, especially in controls, may have produced a non-representative control group; unrealistically high proportion of controls and cases who normally worked rotating shifts (44% and 49% respectively); and insufficient information to evaluate impact of differential screening of cases and controls.
Papantoniou *et al.* 2015	++ ↔ Cases and controls were selected from the same general population with controls being randomly selected. Lower response rate by controls may be related to ongoing shift work at night, which may impact the directionality of selection bias in either direction.
Parent *et al.* 2012	+++ ↔ Cases and controls selected from the same population using similar criteria; no evidence that selection of subjects was related to both exposure and disease. Distribution of occupations of controls was comparable to distribution in the Canadian censuses, and percentage of those who were shift workers (14.5%) was similar to the general male population.
Tse *et al.* 2017	++ ↔ Cases and controls were selected from the same population using similar methods and criteria. There is no evidence that selection was related to both exposure and disease. Cases ages were similarly distributed to the Hong Kong Cancer Registry. Hospital controls (i.e. colorectal and pancreatic diseases) may not have been an appropriate comparator group and may have biased results toward the null.
Wendeu-Foyet *et al.* 2018	+++ ↔ Differences in controls was minimized by socioeconomic status (SES) matching, and expected and realized recruitment of cases were similar. Proportion of night shift workers in study population was similar to general French population.

Table D-1b. Evaluation of exposure assessment methods in human prostate cancer studies

Reference	Exposure Assessment rating
Åkerstedt *et al.* 2017	+ ⬇ Exposure assessment methods were less than ideal; the singular question used to determine exposure status is subject to exposure misclassification. For those considered unexposed, it is unknown what type of work patterns they engaged in (day/shift/evening). Night work was not clearly defined. If the unexposed were actually exposed, this will bias results toward the null.
Behrens *et al.* 2017	+++ ⬇ The exposure assessment methods have good sensitivity and specificity, leading to reliable classification with respect to ever/never exposure, shift and night work, exposure duration, and time-to-event. Although 18% of participants had less-detailed shift-work information, results from sensitivity analysis excluding these participants did not see a change in risk estimates.
Dickerman *et al.* 2016	0 ⬇ Critical concern for exposure assessment methods, as current night work exposure is captured without additional information on prior work history.
Gapstur *et al.* 2014	0 ⬇ Critical concern for exposure assessment methods, as current night work exposure is captured without additional information on prior work history.
Hammer *et al.* 2015	+ ⬇ Detailed information on shift work schedule and intensity were used. Years of shift work were also captured, but not prior to 1995. Exposure status prior to 1995 was estimated to be misclassified for both unexposed (1.2%–3.1%) and exposed (9.8%–13.4%) participants based on a sensitivity analysis of 300 participants. Validation study revealed the likelihood of misclassification impacting results was low; however, potential differential misclassification for exposed subjects will bias results toward the null.
Kubo *et al.* 2006	+ ⬇ Exposure methods are not able to discriminate well between exposed and unexposed. Restricting the question about shift work to the longest held type of schedule with no information on duration or intensity or timing of this longest schedule, the length and timing of other schedules is unknown both for the exposed and unexposed, thus rendering overall exposure incomplete.
Kubo *et al.* 2011	++ ↔ Exposure assessment methods have good sensitivity and specificity for discriminating ever-exposure and exposure level within this highly selected group. No measure of duration was included. Work schedules were recorded at the time of annual health checkups, so any short-term rearrangements were missed.
Schwartzbaum *et al.* 2007	0 ⬇ Night shift work was determined according to percentage of those in each job category reporting shift work in a survey independent of the study cohort. Given the lack of individual-level data on exposure, participants categorized as unexposed are more likely to have been misclassified.
Conlon *et al.* 2007	++ ⬇ Exposure assessment methods are clearly defined and reflect information about rotating shift work, duration and timing (age started and years since stopped). Given the large difference in response rates, there is some likelihood of recall bias.

Reference	Exposure Assessment rating
Papantoniou *et al.* 2015	++ ⬇ Exposure assessment methods were sufficient to differentiate exposed and unexposed with respect to ever-exposure, duration, and frequency. However, there was a higher percentage of cases with missing information on cumulative frequency.
Parent *et al.* 2012	++ ⬇ Exposure methods reliably discriminate between ever and never exposed. However, no information was gathered on frequency or types of shifts, direction or rate of shift rotation. Timing of shift work was collected but crudely divided as recent (within past 20 years), or distant past (20+ years ago) exposure.
Tse *et al.* 2017	+ ⬇ The exposure methods reliably distinguish between ever and never exposure to shift work. No information was given on exposure level, timing, intensity, or types of shift work schedules. Potential for recall bias.
Wendeu-Foyet *et al.* 2018	+++ ↔ Exposure assessment methods were sufficient to differentiate between exposed and unexposed.

Table D-1c. Evaluation of outcome assessment in human prostate cancer studies.

Reference	Outcome Assessment rating
Åkerstedt *et al.* 2017	+++ ↔ Outcome methods distinguish between diseased and non-diseased using either a physician-diagnosed registry or a cause of death standardized register. Prostate specific antigen (PSA), staging, or other specific outcome data were not reported.
Behrens *et al.* 2017	++ ↔ Outcome methods distinguish between diseased and non-diseased in the cohort. Follow-up and diagnoses were conducted independent of exposure status. Self-reported prostate cancer data were used in this study, which is subject to misclassification. No information was provided on tumor stage or grade.
Dickerman *et al.* 2016	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects; follow-up and diagnosis conducted independent of exposure status.
Gapstur *et al.* 2014	++ ↔ Outcome methods distinguish between subjects with and without prostate cancer deaths; follow up and diagnoses appear to be conducted independent of exposure. no information on screening differences.
Hammer *et al.* 2015	++ ↓ Outcome methods distinguish between diseased and non-diseased subjects, and follow-up was conducted independent of exposure classification; however, given the development of the registry (only 80% complete), some cases may have been missed, although it is likely that this is non-differential, leading to a bias towards the null.
Kubo *et al.* 2006	++ ↔ Cancer registry linkage should provide adequate data to distinguish diseased and non-diseased; however, for prostate cancer, there is variability in diagnosis, thus more information regarding the classification of malignant tumors, would have been desirable. Follow-up and diagnosis were conducted independent of exposure status.
Kubo *et al.* 2011	+ ↓ Information about outcome methods are not sufficient to determine how the disease classification was made, only that disease classification was noted in health insurance records. If this was incomplete, a bias towards the null would be likely; outcome methods only explored company records, not national or regional death records.
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Conlon *et al.* 2007	++ ↔ Outcome methods distinguish overall diseased and non-diseased subjects, but lack of information on stage and screening limit the usefulness of this prostate cancer study; diagnoses conducted independent of exposure.
Papantoniou *et al.* 2015	+++ ↔ Histopathological confirmation of prostate cancer with accompanying clinical information (i.e., PSA, Gleason scores) for cases distinguishes between diseased and non-diseased subjects. Diagnosis was conducted prior to the determination of exposure status.
Parent *et al.* 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis conducted independent of exposure status.

Reference	Outcome Assessment rating
Tse *et al.* 2017	+++ ⬇ Outcome methods distinguish between prostate and non-prostate cancers. Tumor grade, stage, and PSA scores were also collected.
Wendeu-Foyet *et al.* 2018	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects.

Table D-1d. Evaluation of study sensitivity in human prostate cancer studies.

Reference	Sensitivity rating
Åkerstedt *et al.* 2017	+ ⬇ The study has an intermediate size of exposed cases and a small number with a long duration. Apart from ever- and duration of exposure, no information was provided further characterizing type and timing exposure. Follow-up on this older cohort was short.
Behrens *et al.* 2017	++ ⬇ Small number of exposed cases. Study had good sensitivity regarding ever- exposure, shift vs. night work, duration of exposure, time-to-event, stratification by preferred midpoint of sleep, and vitamin D status. No information on shift schedules.
Dickerman *et al.* 2016	+ ⬇ Exposure level limited to current job at prospective period in order to look at night work exposure in midlife. The study has an adequate number of incident cases exposed to rotating work. No information on level, duration, or intensity. Follow-up is adequate to detect prostate cancer, particularly in this older population (mean age at entry was 40).
Gapstur *et al.* 2014	+ ⬇ The study has an adequate number of deaths but with unknown exposure level, duration, or timing; and follow-up was adequate (up to 28 years). Insensitive to any relationship of early exposure and prostate cancer, or to duration or frequency of shift work.
Hammer *et al.* 2015	+ ↔ Adequate number of exposed subjects; workers were an average ~50 years of age at end of follow-up, so relatively young for a study of prostate cancer. Elevated SIRs for both shift and day workers compared to the population may indicate detection bias in this population. No information level, duration, or range.
Kubo *et al.* 2006	+ ⬇ The study has a very small number of exposed subjects with unknown exposure level (e.g., level, duration, or timing); duration of follow-up is inadequate. Young cohort followed for only 8 years.
Kubo *et al.* 2011	+ ⬇ The study has a very small number of exposed cases with substantial duration, and cancer was not assessed in a window when prostate cancer is common.
Schwartzbaum *et al.* 2007	+ ↔ Adequately long follow-up period for incident prostate cancer. Large number of exposed cases for men. However, poor categorization of level, duration, and range of exposure to shift work due to the nature of non-specific registries.
Conlon *et al.* 2007	++ ↔ The study has an adequate number of exposed subjects with substantial exposure (30+ years), but little information on frequency or type of rotation.
Papantoniou *et al.* 2015	++ ⬇ The study has an adequate number of exposed subjects with substantial frequency, duration, and variability of shift work. Additionally, the study was able to examine chronotype and severity of disease. There is potential for inadequate latency duration for the development of prostate cancer given the range in age (27-85 years old) of cases and controls.

Reference	Sensitivity rating
Parent *et al.* 2012	++ ⬇ The study has a moderate number of exposed prostate cancer cases, but no information on intensity/frequency or pattern of exposure (e.g., type of shifts); or screening information.
Tse *et al.* 2017	+ ↔ The study has a small number of ever-exposed prostate cancer cases. Apart from ever vs. never exposure, no information was given on level, type, duration, frequency, or other metrics associated with shift work.
Wendeu-Foyet *et al.* 2018	+++ ↔ Moderate-to-large number of exposed prostate cancer cases. Study was highly sensitive and examined shift work exposure and prostate cancer aggressiveness via numerous metrics.

Table D-1e. Evaluation of potential for confounding bias for human prostate cancer studies.

Reference	Confounding rating
Åkerstedt *et al.* 2017	Prostate: +++ ↔ The study measured relevant potential confounders and used appropriate analysis to address them.
Behrens *et al.* 2017	Prostate: +++ ↔ The study measured relevant potential confounders and used appropriate analysis to address them. Study presented multiple models to allow for parsimonious and full models.
Dickerman *et al.* 2016	Prostate: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them.
Gapstur *et al.* 2014	Prostate: ++ ↓ Potential confounders were measured and presented either as age or multivariate adjustments. Employment status (present in the cohort or left) is a potential confounder in this study, but not measurable.
Hammer *et al.* 2015	Prostate: +++ ↔ The study measured relevant potential confounders (age and job level which varied between exposed and non-exposed) and used appropriate analyses to address them.
Kubo *et al.* 2006	Prostate: +++ ↔ The study measured all relevant potential confounders and also ran models with dietary variables including meat consumption (not shown in paper). For rotating shift work, the model with just age yielded equivalent results to the full model.
Kubo *et al.* 2011	Prostate: +++ ↔ The study measured all relevant potential confounders (e.g., age).
Schwartzbaum *et al.* 2007	Prostate: +++ ↔ The study measured all relevant potential confounders and appropriate analyses to address them.
Conlon *et al.* 2007	Prostate: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them
Papantoniou *et al.* 2015	Prostate: +++ ↔ The study measured all releveant potential confounders and used appropriate analyses to address them.
Parent *et al.* 2012	Prostate: ++ ↓ The study measured all relevant potential confounders and used appropriate analyses to address them; however, model possibly over-controlled for variables not related to prostate cancer (e.g., smoking, physical activity, education, farming, alcohol, body mass index [BMI] that may bias estimates toward the null.
Tse *et al.* 2017	Prostate: +++ ↔ The study measured relevant potential confounders and used appropriate analysis to address them. Study used a parsimonious "base" model to increase statistical power.
Wendeu-Foyet *et al.* 2018	Prostate: +++ ↔ The study measured all releveant potential confounders and used appropriate analyses to address them.

Table D-1f. Evaluation of analysis and selective reporting for human prostate cancer studies.

Reference	Analysis rating	Selective Reporting rating
Åkerstedt *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of the data collected.
Behrens *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Dickerman *et al.* 2016	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of data or analyses were limited to only a subset of the data collected.
Gapstur *et al.* 2014	+++ ↓ The study used relevant data and appropriate assumptions and methods of analysis	+++ ↔ No evidence that reporting of the data were limited to a subset of the data collected.
Hammer *et al.* 2015	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Kubo *et al.* 2006	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that selective reporting of data or analyses were limited to subsets of the data collected.
Kubo *et al.* 2011	+ ↑ The study used relevant data but choice of model may not have been ideal, as the hazard ratio (HR) and odds ratio (OR) are equal for short follow-up periods, but the ORs increases in magnitude compared with the HR when the follow-up is extended as in this study. The use of logistic regression in studies with long follow-up time instead of the Cox proportional hazards models tends to bias results away from the null.	++ ↔ Reporting of data were limited to a subset of the data that were collected. While this may have been to test a 3-shift system against no shifts, no data on 2-shift systems were shown.
Schwartzbaum *et al.* 2007	++ ↔ Study used relevant data, had appropriate assumptions and used adequate methods for an external analysis (SIR).	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Conlon *et al.* 2007	++ ↔ The study used relevant data; however, assumptions and methods of analysis unclear.	+++ ↔ No evidence that reporting of the data were limited to a subset of the data collected.
Papantoniou *et al.* 2015	+++ ↔	+++ ↔

Reference	Analysis rating	Selective Reporting rating
	The study used relevant data, appropriate assumptions and methods for analysis.	No evidence that reporting of the data or analyses were limited to a subset of the data collected.
Parent *et al.* 2012	+++ ↔ Study used relevant data, and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Tse *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Wendeu-Foyet *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.

Table D-2. Evidence from epidemiological cohort and case-control studies on prostate cancer and exposure to night shift work

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Åkerstedt *et al.* 2017 Cohort Sweden **Enrollment or follow-up:** 1998–2003; follow-up until 12/31/2010	**Population:** Swedish Twin Registry (STR) Cohort 12 ,322 men **Exposure assessment method:** questionnaire	**HR Ever and duration of night work: complete follow-up**		Age, education, tobacco consumption, BMI, having children, coffee consumption, previous cancer	**Exposure information:** Night shift work 1–45 years; night not defined. **Strengths:** Data linkage study from a unique twin cohort of men. **Limitations:** Poor exposure characterization can lead to substantial misclassification. No information on timing of exposure. Moderate number of exposed cases. Longer duration of follow-up after baseline is desired considering mortality data was used. **Additional results:** Results from unadjusted models and models restricting follow-up to 60 years old were similar to adjusted models. **Confidence in evidence:** Null
		0 yr (Reference)	-		
		Ever	0.91 (0.74–1.12); 160		
		1–5 yr	0.86 (0.63–1.17); 55		
		6–10 yr	1.09 (0.74–1.61); 31		
		11–20 yr	1.12 (0.78–1.63); 38		
		21–45 yr	0.72 (0.5–1.05); 36		
Behrens *et al.* 2017 Cohort Ruhr area, Germany **Enrollment or follow-up:** 2000–2003	**Population:** Heinz-Noxdorf Recall (HNR) Cohort Study 1,757 men **Exposure assessment method:** questionnaire	**HR Ever and duration of shift work**		Age at event, smoking status, family history of prostate cancer, education, income	**Exposure information:** Ever exposure and duration, stratified by night and shift work, preferred midpoint of sleep, and vitamin D status **Strengths:** Good sensitivity regarding duration of exposure. Examined night and shift work separately. Unique consideration of sleep preferences and vitamin D status as modifying factors. Had both baseline and follow-up information. Exposure categorized by time of day.
		Never/<1 yr (Reference)	-		
		Ever: 1+ yr	2.29 (1.43–3.67); 38		
		1–<10 yr	1.87 (0.99–3.55); 13		
		10–<20 yr	2.18 (1.01–4.72); 8		
		20+ yr	3.08 (1.67–5.69); 17		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *p*-value: 0.0001			**Limitations:** Small number of exposed cases. Potential for recall bias given retrospective analysis. Higher prostate cancer risk not included in the cohort. **Additional results:** - **Confidence in evidence:** Evidence
		HR Ever and duration of night work		Same as above	
		0-<1 yr (Reference)	-		
		Ever: 1+ yr	2.27 (1.42–3.64); 32		
		1–<10 yr	1.72 (0.88–3.35); 11		
		10–<20 yr	1.68 (0.66–4.26); 5		
		20+ yr	3.76 (2.04–6.93); 16		
		Trend-test *p*-value: <0.0001			
		HR Ever exposure to night shift work among early sleepers		Same as above	
		0-<1 yr (Reference)	-		
		Ever night work (1+ years)	6.43 (1.81–22.8); 7		
		HR Ever exposure to night shift work among intermediate sleepers		Same as above	
		0-<1 yr (Reference)	-		
		Ever night work (1+ years)	2.3 (1.22–4.35); 18		
		HR Ever exposure to night shift work among late sleepers		Same as above	
		0-<1 yr (Reference)	-		
		Ever night work	1.42 (0.33–6.2); 3		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		(1+ years)			
Dickerman *et al.* 2016 Cohort Finland **Enrollment or follow-up:** 1981-2012	**Population:** Older Finnish Twin Cohort study 11,370 male twins **Exposure assessment method:** questionnaire	**Incidence: HR Type of shift work**		Age, education, BMI, physical activity, social status, smoking status, alcohol consumption, snoring, zygosity	**Exposure information:** Rotating shift pattern of morning, evening or night in 2- or 3-shift patterns; fixed nights **Strengths:** Prospective population-based design, long duration of follow-up, complete outcome data from registry linkage, high initial question response rate, use of within-family analysis with a twin-co-twin design. Information on chronotype incorporated. **Limitations:** Definition of shift work is limited to current job and metrics limited in order to restrict study to exposures during midlife. **Additional results:** Age-adjusted results are similar in models examining prostate cancer incidence and mortality **Confidence in evidence:** No confidence, not included in the assessment.
		Day (Reference)	-		
		Night	0.5 (0.1–1.9); 2		
		Rotating	1 (0.7–1.2); 80		
		Mortality: HR Type of shift work		Same as above	
		Day (Reference)	-		
		Rotating	0.8 (0.3–1.5); 11		
		Incidence: HR Shift type and chronotype			
		Day, definite morning chronotype (Reference)	-		
		Rotating, definite morning chronotype	1 (0.7–1.5); 26		
		Rotating, somewhat morning chronotype	0.5 (0.3–1); 12		
		Rotating, somewhat evening chronotype	1.5 (1–2.2); 29		
		Rotating, definite evening chronotype	1.5 (0.8–2.9); 10		
Gapstur *et al.* 2014 Cohort	**Population:** American Cancer Society II (ACS-II) Study	**HR Ever rotating and permanent night shift work**		Age, race, education, BMI, smoking status,	**Exposure information:** Fixed nights (started work 9 PM-12 AM), fixed day (started working 6AM- 10AM),
		Fixed day	-		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
50 states in the U.S. **Enrollment or follow-up:** 1982-2010	305,057 men **Exposure assessment method:** questionnaire	(Reference)		family history of prostate cancer, painful/frequent urination	fixed afternoon/evening (started work 2pm - 4pm); rotating (not clearly defined) **Strengths:** Prospective design, large, nationwide sample of employed men, ability to adjust for potential confounders. **Limitations:** Exposure information limited to current employment at baseline thus adds information only for midlife exposures on later prostate cancer. **Additional results:** Age-adjusted estimates are similar **Confidence in evidence:** No confidence, not included in the assessment.
		Rotating	1.08 (0.95–1.22); 268		
		Fixed night	0.72 (0.44–1.18); 16		
Hammer *et al.* 2015 Cohort Germany **Enrollment or follow-up:** 1995–2005; follow-up: 2000–2009	**Population:** Male chemical production workers in Rhineland-Palatinate Germany 27,828 employed men **Exposure assessment method:** company records	**Internal analysis: HR (RR)**		Age	**Exposure information:** Ever worked forward rotating shift work pattern: either 3 x 12 hours (day, off, night) or 4 x 12 (day, off, off, night) **Strengths:** Large retrospective cohort with adequate number of cases based on personnel records, with balanced numbers of daytime and shift workers from the same parts of the company and with the same working conditions, thus comparable in terms of risk profile, age, and SES. **Limitations:** Limited follow-up due to availability of data at cancer registry; exposure assessment does not include lifetime exposure to shift work; cancer case reporting is somewhat less than complete; and stage was
		Daytime (Reference)	-		
		Rotating (all stages)	0.93 (0.73–1.18); 146		
		Stage T1	1.26 (0.44–3.86); 10		
		Stage T2	0.84 (0.62–1.15); 84		
		Stage T3	0.9 (0.53–1.52); 32		
		Stage T4	1.36 (0.25–6.18); 3		
		Stage T Unknown	1.42 (0.64–3.19); 17		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
					incomplete for 25%– 30% of subjects. This was a young cohort to detect prostate cancer; potential detection bias for external analysis. **Additional results:** Sensitivity analyses controlled for smoking, type of job (manual or professional), and/or duration of employment (<20 vs. >20 years) in models; risk estimates did not greatly differ. **Confidence in evidence:** Null
Kubo *et al.* 2006 Cohort Japan **Enrollment or follow-up:** 1988–1990	**Population:** Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk 14,052 men **Exposure assessment method:** questionnaire	**RR (Hazard ratio) Ever rotating and permanent night shift work** Daytime (Reference) Rotating Fixed night	 - 3 (1.2–7.7); 7 2.3 (0.6–9.2); 3	Age, study area, BMI, smoking, alcohol consumption, job type, physical activity at work, workplace, perceived stress, education, marital status, family history of prostate cancer	**Exposure information:** Rotating and fixed night work, not defined **Strengths:** Nationwide sample of workers, complete collection of potential confounders. **Limitations:** Incomplete exposure histories leading to likely misclassification; short follow-up time for prostate cancer; no discussion of the impact of healthy worker survivor effect (HWSE) on this restricted set of current workers; low statistical power. **Additional results:** Authors states similar findings found in additional analysis using data for an additional 15,906 working men aged 40–79 years with 55 total cases of prostate cancer; although the number of exposed cases were not reported. Author could not provide additional information upon follow-up. **Confidence in evidence:** Some evidence

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Kubo *et al.* 2011 Cohort Japan **Enrollment or follow-up:** Records from 2006–2008	**Population:** Industry-based retrospective manufacturing cohort 4,995 male workers **Exposure assessment method:** company records	**RR Ever worked rotating shifts**		Age, BMI, alcohol consumption, exercise, marital status, smoking status	**Exposure information:** Ever exposure (counterclockwise 3-shift system for 80%+ of career, vs. day workers) **Strengths:** High-quality long-term work schedule information from industry records; annual health records from the same health plan and annual prostate-specific antigen (PSA) exams. Homogeneity in socioeconomic status (SES) and healthcare access. **Limitations:** Small number of exposed cases; follow-up did not extend past the age of 65 years when prostate cancer is common; analytic method may not have been appropriate; highly selected group of survivors with no information on HWSE. **Additional results:** Estimates from age-adjusted model are similar **Confidence in evidence:** Inconclusive
		Daytime (Reference)	-		
		Rotating	1.79 (0.57–5.68); 4		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Schwartzbaum *et al.* 2007 Cohort Sweden **Enrollment or follow-up:** enrollment: 1977-1981; follow-up: 1971-1989	**Population:** Swedish working men registered in 1960 and 1970 census data. 2,101,126 men **Exposure assessment method:** JEM	**SIR Ever worked night shift by census period**		Age, socioeconomic status, occupational position, county of residence	**Exposure information:** Workplace (aggregate-level) either had a rotating schedule or had work hours between 1-4 AM **Strengths:** Large number of exposed cases in a nationwide cohort of men in diverse industries followed for 19 years. **Limitations:** Aggregate exposure data, lack of data on potential confounders or co-exposures. **Additional results:** Similar results seen when restricted to participants in 1960 and 1970 census **Confidence in evidence:** No confidence, not included in the assessment.
		1970	1.04 (0.99–1.1); 1319		
Conlon *et al.* 2007 Case-Control Northeastern Ontario, Canada **Enrollment or follow-up:** 1995–1998	**Population:** Population based case-control study Cases: 760; Controls: 1,632 **Exposure assessment method:** questionnaire	**OR Ever and duration of full-time rotating shift work**		Age, family history of prostate cancer	**Exposure information:** Ever rotating shift work; duration of full-time rotating work; age first began working full time rotating shift; age working fulll-time rotating shift; years since full-time rotating shift **Strengths:** Large population-based case-control study with adequate numbers of cases working rotating shifts. **Limitations:** Poor response rates especially in the controls, suggesting some attrition bias, lack of information on grade of prostate cancer or screening information, potential recall bias; and little information on stage or grade of cancer.
		No (Reference)	-		
		Yes (Ever)	1.19 (1–1.42); 369		
		≤ 7 yr	1.44 (1.1–1.87); 115		
		> 7–22 yr	1.14 (0.86–1.52); 87		
		> 22–34 yr	0.93 (0.7–1.23); 81		
		>34 yr	1.3 (0.97–1.74); 86		
		Trend-test *p*-value: 0.42			
		OR Age at first full-time rotating shift work		Same as above	
		No (Reference)	-		
		11–19 yr	1.04 (0.79–1.36);		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
			98		**Additional results:** - **Confidence in evidence:** Some evidence
		20–22 yr	1.11 (0.81–1.52); 67		
		23–29 yr	1.38 (1.05–1.8); 107		
		≥ 30 yr	1.13 (0.94–1.65); 97		
		Trend-test *p*-value: 0.05			
		OR Years since working full-time rotating shift work (latency)		Same as above	
		No (Reference)	-		
		1–36 yr	1.17 (0.88–1.56); 93		
		21–30 yr	1.34 (1.01–1.76); 100		
		31–40 yr	1.13 (0.85–1.5); 86		
		41–50 yr	1.11 (0.82–1.49); 89		
		Trend-test *p*-value: 0.16			
Papantoniou *et al.* 2015 Case-Control Spain **Enrollment or follow-up:** 2008–2013	**Population:** MCC-Spain Cases: 1,095; Controls: 1,388 **Exposure assessment method:** questionnaire	**OR Ever exposure to night shift work by shift work type**		Age, study center, education, physical activity over the past decade, past sun exposure, daily meat consumption, smoking status, family history of prostate cancer	**Exposure information:** Partly or entirely working midnight-6:00 AM, 3+ nights/month **Strengths:** Large population-based case-control study; detailed exposure assessment including differentiation of rotating and permanent night work; duration and frequency of night shifts. Investigated effect modification by chronotype and cancer severity. **Limitations:**
		Never (Reference)	-		
		Permanent and rotating	1.14 (0.94–1.37); 362		
		Permanent only	1.1 (0.85–1.43); 158		
		Rotating only	1.16 (0.92–1.46); 206		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		OR Lifetime cumulative duration of night work: Permanent and rotating		Same as above	Low response rate in controls, potential for recall bias; large proportion of missing data for shiftwork frequency. **Additional results:** When examining cumulative frequency of night shifts in morning chronotype individuals, risk of prostate cancer increased by tertile of cumulative frequency, but no significant trend was seen (P = 0.11). Results were similar when examining cumulative frequency for evening chronotype Results generally similar when examining cumulative frequency for high risk cancer. Also similar results seen when Gleason score was used to categorize severity (high risk = Gleason score >7). **Confidence in evidence:** Evidence
		Never (Reference)	-		
		≤ 10 yr	1.1 (0.83–1.45); 128		
		11–27 yr	0.94 (0.69–1.27); 92		
		≥ 28 yr	1.38 (1.05–1.81); 138		
		Trend-test *p*-value: 0.047			
		OR Cumulative duration of night work: Permanent only		Same as above	
		Never (Reference)	-		
		≤ 10 yr	1.07 (0.75–1.51); 75		
		11–27 yr	1.01 (0.65–1.56); 41		
		≥ 28 yr	1.4 (0.83–2.37); 36		
		Trend-test *p*-value: 0.251			
		OR Cumulative duration of night work: Rotating only		Same as above	
		Never (Reference)	-		
		≤ 10 yr	1.21 (0.85–1.74); 73		
		11–27 yr	0.84 (0.56–1.26); 47		
		≥ 28 yr	1.37 (0.97–1.94); 85		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *p*-value: 0.158			
		OR Cumulative frequency of night shifts: Permanent and rotating		Same as above	
		Never (Reference)	-		
		≤ 1,152 nights	1.03 (0.75–1.42); 85		
		1,153–2,856 nights	1.09 (0.78–1.52); 71		
		≥ 2,857 nights	1.3 (0.97–1.74); 100		
		Trend-test *p*-value: 0.084			
		OR Type and cumulative duration of night work: Morning chronotype		Same as above	
		Never (Reference)	-		
		Permanent and rotating	1.14 (0.87–1.51); 152		
		Permanent only	1.19 (0.8–1.76); 67		
		Rotating only	1.12 (0.8–1.56); 85		
		1-10 yr	0.95 (0.63–1.43); 51		
		11-27 yr	0.9 (0.57–1.4); 39		
		≥ 28 yr	1.79 (1.16–2.76); 61		
		Trend-test *p*-value: 0.017			
		OR Type and cumulative duration of night work: Evening chronotype		Same as above	
		Never (Reference)	-		
		Permanent and	1.5 (0.85–2.66); 49		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		rotating			
		Permanent only	1.57 (0.76–3.27); 24		
		Rotating only	1.44 (0.7–2.93); 25		
		≤ 10 yr	1.92 (0.8–4.54); 19		
		11-27 yr	1.3 (0.55–3.07); 14		
		≥ 28 yr	1.33 (0.56–3.16); 16		
		Trend-test *p*-value: 0.619			
		OR Type and cumulative duration of night work: High risk cancer		Same as above	
		Never (Reference)	-		
		Permanent and rotating	1.4 (1.05–1.86); 106		
		Permanent only	1.35 (0.91–1.99); 44		
		Rotating only	1.44 (1.02–2.03); 62		
		≤ 10 yr	1.32 (0.86–2.02); 35		
		11-27 yr	1.26 (0.8–1.98); 30		
		≥ 28 yr	1.63 (1.08–2.45); 40		
		Trend-test *p*-value: 0.027			
Parent *et al.* 2012 Case-Control Montreal,	**Population:** Population based occupational case-control study	**OR Ever and duration of night work**		Age, ancestry, education, family income, respondent status,	**Exposure information:** Ever, cumulative duration, and timing of night work (worked from 1:00 AM–2:00 AM for 6+ months)
		Never (Reference)	-		
		Ever	2.77 (1.96–3.92); 132		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Canada **Enrollment or follow-up:** 1979–1985	Cases: 400; Controls: 512 **Exposure assessment method:** questionnaire	<5 yr	3.13 (1.98–4.95); 68	smoking, alcohol, BMI, occupational physical activity, farming	**Strengths:** Possible to compare risks across cancer sites; complete population-based case ascertainment system; histologic confirmation of primary cancers; large number of cases; nighttime definition likely to encompass a period pertinent to the hypothetical mechanism of carcinogenesis. **Limitations:** No screening, grade or severity information about prostate cancer; approximately 18% of cases contributed information through proxies. **Additional results:** - **Confidence in evidence:** Evidence
		5–10 yr	2.11 (1.11–3.99); 27		
		≥ 10 yr	2.68 (1.45–4.95); 36		
		OR Timing of night work		Same as above	
		Never (Reference)	-		
		Recent: ≤ 20 yr ago	3.17 (1.89–5.31); 55		
		Distant: > 20 yr ago	3.01 (1.83–4.93); 57		
Tse *et al.* 2017 Case-Control Hong Kong, China **Enrollment or follow-up:** 2011–2016	**Population:** Hospital-based case-control study from Prince of Wales Hospital Cases: 431; Controls: 402 **Exposure assessment method:** questionnaire	**OR Ever exposure to night shift work**		Age, marital status, unemployment status, family history of prostate cancer, consumption of deep fried food, consumption of pickled vegetables, green tea drinking habits, cumulative BPA index	**Exposure information:** Ever worked nights (at least 1 hour from 1:00 AM–5:00 AM for more than 1x/month for >1 year) **Strengths:** Moderate-sized case-control study from the same population. Explicit definition of night work exposure. **Limitations:** Low number of exposed cases. Only categorized shift work as ever exposure, limited sensitivity. **Additional results:** Base model had similar results. **Confidence in evidence:** Some evidence
		Never (Reference)	-		
		Ever	1.76 (1.07–2.89); 58		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Wendeu-Foyet *et al.* 2018 Case-Control France **Enrollment or follow-up:** 2012–2013	**Population:** Epidemiology of Prostate Cancer (EPICAP) study Cases: 818; Controls: 875 **Exposure assessment method:** interview	**OR Ever night work: permanent and rotating**		Age, family history of prostate cancer, race, education level	**Exposure information:** Ever worked, shift type (permanent or rotating), duration, number of consecutive nights worked, night shift length, cumulative frequency, shift timing, rotation type, shift rotation speed, sleep duration, chronotype. **Strengths:** Large-size case-control study from the same population. Highly sensitive study with numerous metrics to capture shift work exposure. **Limitations:** Potential for recall bias. **Additional results:** Rotating shifts did not see a significant increased risk or trend with duration. Frequency of rotating shifts were not associated with a significant increased risk or trend. Shift length >10 hours was associated with elevated prostate cancer for permanent or rotating night shift (OR = 1.57, 95% CI = 0.79 to 1.19). Duration of 20+ years and either 6+ nights or 10+ hour shift length increased the risk of prostate cancer for permanent night work. 10+ hour shift length and either 1314 cumulative nights worked or 6+ nights consecutively worked increased the risk of prostate cancer, particularly for permanent night shift workers. For permanent shift workers, working 6+ consecutive permanent night shifts, >10 hours shift length, and a combination of
		Never (Reference)	-		
		Ever	0.97 (0.79–1.19); 286		
		Ever permanent night work	1.04 (0.82–1.32); 210		
		Ever rotating night work	0.81 (0.59–1.16); 84		
		OR Total duration of permanent night work		Same as above	
		Never (Reference)	-		
		<10 yr	0.91 (0.62–1.38); 54		
		10-19 yr	1.17 (0.76–1.83); 48		
		20-29 yr	0.87 (0.56–1.37); 39		
		30+ yr	1.22 (0.83–1.79); 69		
		Trend-test *p*-value: 0.26			
		OR Lifetime frequency of permanent night work		Same as above	
		Never (Reference)	-		
		< 1,314 nights	1.05 (0.76–1.46); 90		
		1,314+ nights	1.03 (0.77–1.38); 120		
		Trend-test *p*-value: 0.89			
		OR Number of consecutive permanent		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		nights worked			longest duration, consecutive nights, shift length, and frequency of night work was associated was associated with increased risk of aggressive prostate cancer (Gleason score 7+). Results did not hold for non-aggressive prostate cancer or for rotating shift work. **Confidence in evidence:** Some evidence
		Never (Reference)	-		
		< 6 nights	1.01 (0.74–1.39); 95		
		6+ nights	1.33 (0.95–1.87); 93		
		Trend-test *p*-value: 0.25			
		OR Permanent night shift length (hours)		Same as above	
		Never (Reference)	-		
		< 8 hr	0.32 (0.16–0.64); 11		
		8–10 hr	0.86 (0.48–1.53); 23		
		> 10 hr	1.88 (1.08–3.26); 38		
		Trend-test *p*-value: 0.29			
		OR Duration (years) and number of consecutive permanent nights		Same as above	
		Never (Reference)	-		
		<20 yr & <6 nights	1.06 (0.71–1.58); 57		
		<20 yr & 6+ nights	1.21 (0.74–2); 35		
		20+ yr & <6 nights	0.91 (0.57–1.46); 38		
		20+ yr & 6+ nights	1.42 (0.92–2.18); 58		
		OR Ever and duration of permanent night work: Gleason score 7+		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Never (Reference)	-		
		Ever	1.41 (0.98–2.04); 58		
		< 20 yr	1.09 (0.66–1.81); 23		
		20+ yr	1.76 (1.13–2.75); 35		
		Trend-test *p*-value: 0.003			

References

1. Åkerstedt T, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. 2017. Night work and prostate cancer in men: a Swedish prospective cohort study. *BMJ Open* 7(6): e015751. (Supported by the AFA Insurance Company. Authors affiliated with Karolinska Institutet, Sweden; Stockholm University, Sweden; Radboud University, Netherlands.)

2. Behrens T, Rabstein S, Wichert K, Erbel R, Eisele L, Arendt M, Dragano N, Brüning T, Jöckel KH. 2017. Shift work and the incidence of prostate cancer: a 10-year follow-up of a German population-based cohort study. *Scand J Work Environ Health* 43(6): 560-568. (Supported by the German Social Accident Insurance, the Heinz Nixdorf Foundation, the German Ministry of Education and Science, the Kulturstiftung Essen, and the German Research Foundation. Authors affiliated with Institute of the Ruhr-Universität Bochum, Germany; University Hospital of Essen, Germany; Heinrich Heine University, Getmany.)

3. Conlon M, Lightfoot N, Kreiger N. 2007. Rotating shift work and risk of prostate cancer. *Epidemiology* 18(1): 182-183. (Support not reported. Authors affiliated with Sudbury Regional Hospital, Canada; Ontario School of Medicine, Canada; University of Toronto, Canada.)

4. Dickerman BA, Markt SC, Koskenvuo M, Hublin C, Pukkala E, Mucci LA, Kaprio J. 2016. Sleep disruption, chronotype, shift work, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. *Cancer Causes Control* 27(11): 1361-1370. (Suppored by NCI, NIH, and the Academy of Finland. Authors affiliated with Harvard T.H. Chan School of Public Health, MA; University of Helsinki, Finland; Finnish Institute of Occupational Health, Finland; Finnish Cancer Registry, Finland; University of Tampere, Finland; National Institute for Health and Welfare, Finland.)

5. Gapstur SM, Diver WR, Stevens VL, Carter BD, Teras LR, Jacobs EJ. 2014. Work schedule, sleep duration, insomnia, and risk of fatal prostate cancer. *Am J Prev Med* 46(3 Suppl 1): S26-33. (Supported by the American Cancer Society. Authors affiliated with American Cancer Society, GA.)

6. Hammer GP, Emrich K, Nasterlack M, Blettner M, Yong M. 2015. Shift work and prostate cancer incidence in industrial workers: A historical cohort study in a German chemical company. *Dtsch Arztebl Int* 112(27-28): 463-470. (Supported by the German Social Accident Insurance. Authors affiliated with Johannes Gutenberg University, Germany; Laboratoire National de Santé, Luxembourg; Occupational Medicine and Health Protection, BASF SE, Germany.)

7. Kubo T, Ozasa K, Mikami K, Wakai K, Fujino Y, Watanabe Y, Miki T, Nakao M, Hayashi K, Suzuki K, Mori M, Washio M, Sakauchi F, Ito Y, Yoshimura T, Tamakoshi A. 2006. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. *Am J Epidemiol* 164(6): 549-555. (Supported by the Ministry of Education, Science, Sports and Culture of Japan. Authors affiliated with University of Occupational and Environmental Health, Japan; Kyoto Prefectural University of Medicine, Japan; Aichi Cancer Center Research Institute, Japan; Fukuoka Institute of Occupational Health, Japan; Meiji University of Oriental

Medicine, Japan; Fujita Health University School of Health Sciences, Japan; Sapporo Medical University School of Medicine, Japan; Nagoya University Graduate School of Medicine, Japan; Fukuoka Institute of Health and Environmental Sciences, Japan.)

8. Kubo T, Oyama I, Nakamura T, Kunimoto M, Kadowaki K, Otomo H, Fujino Y, Fujimoto N, Matsumoto T, Matsuda S. 2011. Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. *Int J Urol* 18(3): 206-211. (Supported by KAKENHI, the the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Occupational Health Promotion Foundation, Japan. Authors affiliated with University of Occupational and Environmental Health, Japan; Asahi Kasei Nobeoka Office Health Care Center, Japan; Asahi Kasei Chemicals Mizushima Works Health Care Center, Japan.)

9. Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Burgos J, Gomez-Acebo I, Llorca J, Peiro R, Jimenez-Moleon JJ, Arredondo F, Tardon A, Pollan M, Kogevinas M. 2015. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. *Int J Cancer* 137(5): 1147-1157. (Supported by the "Accion Transversal del Cancer," Spanish Ministry Council, the Instituto de Salud Carlos III-FEDER, and a predoctoral grant PFIS. Authors affiliated with Centre for Research in Environmental Epidemiology [CREAL], Spain; IMIM [Hospital Del Mar Medical Research Institute], Spain; Universitat Pompeu Fabra [UPF], Spain; CIBER Epidemiologıa Y Salud Publica, Spain; Carlos III Health Institute, Spain; Cancer Epidemiology Research Group, Spain; Hospital Ramon Y Cajal, Spain; Instituto Ramon Y Cajal De Investigacion Sanitaria, Spain; Universidad De Alcala De Henares, Spain; University of Cantabria, Spain; IDIVAL, Spain; Fundacion Para El Fomento De La Investigacion Sanitaria Y Biomedica De La Comunidad Valenciana, Spain; Hospitales Universitarios De Granada/Universidad De Granada, Spain; Hospital Infanta Elena, Spain; Universidad De Huelva, Spain; Universidad De Oviedo, Spain; National School of Public Health, Greece.)

10. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. 2012. Night work and the risk of cancer among men. *Am J Epidemiol* 176(9): 751-759. (Supported by the Health Canada, the National Cancer Institute of Canada, the Institut de recherche en santé et sécurité au travail du Québec, the Fonds de la recherche en santé du Québec, and the Canadian Institutes of Health Research. Authors affiliated with INRS, Canada.)

11. Schwartzbaum J, Ahlbom A, Feychting M. 2007. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 33(5): 336-343. (Supported by the Swedish Council for Working Life. Authors affiliated with Ohio State University, OH; Karolinska Institutet, Sweden.)

12. Tse LA, Lee PMY, Ho WM, Lam AT, Lee MK, Ng SSM, He Y, Leung KS, Hartle JC, Hu H, Kan H, Wang F, Ng CF. 2017. Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. *Environ Int* 107: 1-7. (Supported by the Health and Medical Research Fund, Hong Kong Special Administrative Region, China. Authors affiliated with Chinese University of Hong Kong, China; Prince of Wales Hospital, China; Guilin Medical College, China; Hong Kong Polytechnic University, China; San Jose State University, CA; University of Toronto, Canada; Fudan University, China.)

13. Wendeu-Foyet MG, Bayon V, Cénée S, Trétarre B, Rébillard X, Cancel-Tassin G, Cussenot O, Lamy PJ, Faraut B, Kheder SB, Léger D, Menegaux F. 2018. Night work and prostate cancer risk: Results from the EPICAP study. *OEM* 75(8): 573-581. (Supported by the Institut National du Cancer, Fondation ARC, the Ligue nationale contre le cancer, the Ligue contre le cancer du Val-de-Marne, Fondation de France, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [ANSES], and Paris-Sud University. Authors affiliated with INSERM, France; Hôtel Dieu, France; VIFASOM, France; Hérault Cancer Registry, France; Clinique Beau Soleil, France; Hopital Tenon, France; Sorbonne Université, France; Imagenome, France.)

National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night

Appendix E: Night Shift Work and Colorectal Cancer

November 2020

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

List of Tables

Appendix E: Colorectal Cancer Studies Tables

Appendix E encompasses tables related to human studies on shift work exposure and risk of colorectal cancer. Tables E-1a to E-1f provide ratings and the rationales for the domains of study quality and study sensitivity. Table E-2 gives detailed results for each evaluated epidemiological study.

Table E-1a. Evaluation of selection bias in human colorectal cancer studies.

Reference	Selection Bias rating
Jørgensen *et al.* 2017	+ ⬇ The cohort was clearly defined by exposure status for a specific time period and location. Follow-up did not differ by exposure status. Left truncation is an issue in this older survivor cohort. Authors indicated most nurses have to participate in rotating shift work early in their careers, and this is a >44 year old cohort, so selection of exposure status may not be appropriate. Mortality analysis is likely to miss about 1/3 of cases having longer survival and later death, likely resulting in non-differential (not related to exposure status) misclassification, loss of power, and an underestimation of the risk estimate.
Papantoniou *et al.* 2018	++ ⬇ The cohort is clearly defined with no evidence that follow-up differed between exposed and non-exposed subjects. Together, the two cohorts cover broad windows of exposure for women of different ages; however, analysis was done separately for each cohort. For NHS2, women are less likely to be selected out due to inability to adapt to shift work. For NHS, there is a higher likelihood of HWE given it is an older population.
Schwartzbaum *et al.* 2007	++ ↔ Only an external analysis was conducted. No evidence of HWE, as the overall SIR for all cancers was approaching unity. HWSE is still possible and may bias results toward the null.
Yong *et al.* 2014	++ ⬇ The cohort is clearly defined and includes the relevant exposed and unexposed populations for a specific time period and location. Healthy worker effect (HWE) is possible, as cancer incidence was higher among shift workers and lower among day workers, compared to the general population. There was also no consideration of HWSE in this occupational cohort. In Hammer *et al.* (2015), a validation analysis of the same cohort reported no change in day to shift work for 893 (97%) of the employees, and there was little movement between shifts in this company suggesting HWSE was minimized.
Papantoniou *et al.* 2017	++ ↔ Cases and controls were selected from the same population by similar criteria. No evidence that the selection of the subjects was related to both exposure and disease. However, the very low response rates for controls raises the question of potential selection bias with unknown direction of effect. Subjects working at night, especially permanent night workers, might have been more likely to be at home during the day when phone calls were performed and, if so, they might have been overrepresented among controls.
Parent *et al.* 2012	+++ ↔ Cases and controls selected from the same population using similar criteria;

Reference	Selection Bias rating
	no evidence that selection of subjects was related to both exposure and disease. Distribution of occupations of controls was comparable to distribution in the Canadian censuses, and percentage of those who were shift workers (14.5%) was similar to the general male population.
Walasa *et al.* 2018	++ ↔ Cases and controls were selected from the same population using similar criteria. There was no evidence that selection of subjects was related to both exposure and disease. Poor response rates in both cases and controls may lead to selection bias, although rates are comparably low in both groups. The prevalence of ever graveyard shift in the study (20%) was similar to current shift work in Australia (16% of employed persons, Australian Bureau of Statistics 2013).

Table E-1b. Evaluation of exposure assessment methods in human colorectal cancer studies.

Reference	Exposure Assessment rating
Jørgensen *et al.* 2017	0 ⬇ Current information on work status at baseline only. No information on past employment status casting doubt on those classified as unexposed. No data on duration of shift schedule and shift work intensity lead to a less sensitive exposure categorization. Furthermore, authors mention the high likelihood of exposure misclassification for nurses whose training involves shift work early in their career.
Papantoniou *et al.* 2018	++ ⬇ The exposure assessment methods have moderate to good sensitivity and specificity for NHS-2, but poorer sensitivity and specificity for NHS. No information on frequency or intensity was provided. NHS: the shift work question was asked at baseline. No data on permanent or less frequent rotating night shift work was collected.
Schwartzbaum *et al.* 2007	0 ⬇ Night shift work was determined according to percentage of those in each job category reporting shift work in a survey independent of the study cohort. Given the lack of individual-level data on exposure, participants categorized as unexposed are more likely to have been misclassified.
Yong *et al.* 2014	+ ⬇ Detailed information on shift work schedule and intensity was examined. Years of shift work was also captured, but not prior to 1995. Exposure status prior to 1995 was estimated to be misclassified for both unexposed (1.2%–3.1%) and exposed (9.8%–13.4%) participants based on a sensitivity analysis of 300 participants. Validation study revealed the likelihood of misclassification impacting results was low; however, potential differential misclassification for exposed subjects will bias results toward the null.
Papantoniou *et al.* 2017	++ ⬇ Exposure assessment methods have good sensitivity and specificity leading to reliable classification of exposure. Recall bias may have been introduced into assessment of exposure frequency which had a high degree of missing values (35% of shift workers) compared to duration (< 1% missing), perhaps explaining the differential risk observed across groups with increasing rotating night shift work intensity.
Parent *et al.* 2012	++ ⬇ Exposure methods reliably discriminate between ever and never exposed. However, no information was gathered on frequency (exposure-level) or types of shifts (fixed or rotating), direction or rate of shift rotation. Timing of shift work was collected but crudely divided as recent (within past 20 years), or distant past (20+ years ago) exposure.
Walasa *et al.* 2018	+ ↔ Characterization of graveyard, early-morning, and phase shift exposures were conducted via a group-level job exposure matrix (JEM), and therefore, is subject to exposure misclassification.

Table E-1c. Evaluation of outcome assessment in human colorectal cancer studies.

Reference	Outcome Assessment rating
Jørgensen *et al.* 2017	++ ⬇ Reported causes of death were not histologically-confirmed, rather only based on physician report from death records.
Papantoniou *et al.* 2018	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status. Pathology confirmation of cause of death in 98% of cases, although all cases were included in analysis. No subtypes ascertained.
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Yong *et al.* 2014	++ ⬇ Outcome methods distinguish between diseased and non-diseased subjects, and follow-up was conducted independent of exposure classification; however, given the development of the registry, some cases may have been missed, although it is likely that this is non-differential, leading to a bias towards the null.
Papantoniou *et al.* 2017	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis was conducted independent of exposure.
Parent *et al.* 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis conducted independent of exposure status.
Walasa *et al.* 2018	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis was conducted independent of exposure status.

Table E-1d. Evaluation of study sensitivity for human colorectal cancer studies.

Reference	Sensitivity rating
Jørgensen *et al.* 2017	+ ⬇ Small number of CRC mortality cases. Poor sensitivity of exposure status due to lack of level, duration, or range of exposure. Adequately long follow-up duration.
Papantoniou *et al.* 2018	+++ ↔ The study has an adequate number of exposed subjects, and adequate (N=98) to small (N=15) number of women with 15+ years of exposure in NHS and NHS-2, respectively. Both cohorts only measure ever and duration of exposure. NHS examined CRC subsite.
Schwartzbaum *et al.* 2007	+ ↔ Adequate number of exposed cases for males but not females, and no information about intensity or duration. Adequate duration of follow-up.
Yong *et al.* 2014	+ ↔ The study has a small-to-moderate number of exposed colorectal subjects, but no information on level, duration, or range, and exposure variation is essentially flat across the exposed. Latency follow-up was adequate.
Papantoniou *et al.* 2017	++ ↔ The study has an adequate number of exposed subjects with substantial exposure (duration and timing of exposure). However, no information on type of schedule or intensity of exposure.
Parent *et al.* 2012	++ ⬇ The study has a moderate-to-large number of exposed colon and rectal cancer cases, but no information on intensity/frequency or pattern of exposure (e.g., type of shifts); or screening information.
Walasa *et al.* 2018	++ ↔ There was a small-to-moderate number of exposed cases for graveyard shift workers. Numerous shift work variables were appropriately examined, although not on shift work intensity due to reliance on JEM.

Table E-1e. Evaluation of potential for confounding bias in human colorectal cancer studies.

Reference	Confounding rating
Jørgensen *et al.* 2017	+++ ⬇ The study measured all relevant confounders and used appropriate analyses to address them. The addition of all possible confounders may attenuate results and widen confidence in the estimates.
Papantoniou *et al.* 2018	+++ ↔ The study measured all relevant confounders and used appropriate analyses to address them. The addition of all possible confounders may attenuate results and widen confidence in the estimates.
Schwartzbaum *et al.* 2007	+ ⬆ The study did not measure potential confounders such as alcohol, red meat consumption and BMI.
Yong *et al.* 2014	+ ⬇ The study did not measure potential confounders such as alcohol consumption, red meat consumption; job level can stand as a proxy for physical exercise, although there is no dietary or body mass index (BMI) information.
Papantoniou *et al.* 2017	++ ⬇ The study measured all relevant potential confounders and used appropriate analyses to address them. The addition of all possible confounders may have attenuated results and widened confidence in the estimates.
Parent *et al.* 2012	++ ⬇ The study measured all relevant potential confounders with the exception of red meat. Additional factors such as smoking and beta carotene may have reduced effect estimates.
Walasa *et al.* 2018	++ ↔ The study measured most of the relevant potential confounders and used appropriate analyses to address them, but did not account for BMI and red meat consumption in the main analyses.

Table E-1f. Evaluation of analysis and selective reporting for human colorectal cancer studies.

Reference	Analysis rating	Selective Reporting rating
Jørgensen *et al.* 2017	++ ⬇ Inclusion of multiple covariates not related to the exposure and outcome of interest may have attenuated results and widened confidence intervals.	+++ ↔ No evidence that data or analysis was limited to a subset of data.
Papantoniou *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence suggests analysis was limited to only a subset of the data that were collected.
Schwartzbaum *et al.* 2007	++ ↔ Study used relevant data, had appropriate assumptions and used adequate methods for an external analysis (SIR).	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Yong *et al.* 2014	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the collected data.
Papantoniou *et al.* 2017	+++ ↔ Study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Parent *et al.* 2012	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of data collected.
Walasa *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.

Table E-2. Evidence from epidemiological cohort and case-control studies on colorectal cancer and exposure to night shift work.

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Jørgensen *et al.* 2017 Cohort Denmark **Enrollment or follow-up:** 1993-2013	**Population:** Danish Nurses Cohort (DNC) 28,731 women **Exposure assessment method:** questionnaire	**HR Ever evening, night, and rotating shift work**		Age, smoking status, pack years, physical activity, BMI, alcohol consumption, diet (veggies, fruit, meat), pre-existing disease (hypertension, diabetes, MI), self-reported health, stressful work environment, marital status, use of HRT, OC use	**Exposure information:** Ever evening, night, rotating shifts **Strengths:** Nationwide prospective cohort of female nurses with detailed information on work schedules at baseline, and potential confounders. **Limitations:** Small numbers of colorectal cancer deaths, no information on duration or intensity, type of rotations, or past information on night work. No cancer validation. **Additional results:** Unadjusted estimates are similar to adjusted estimates (night shifts have a higher magnitude of effect but still non-significant). **Confidence in evidence:** No confidence; not included in assessment.
		Day	-		
		Night	1.02 (0.5–2.11); 9		
		Rotating	0.83 (0.5–1.36); 20		
Papantoniou *et al.* 2018 Cohort 11 U.S. states **Enrollment or follow-up:** NHS: 1976 (enrolled), 1988-2012 (follow-up); NHS-2: 1989 (enrolled), 1989-2013 (follow-up)	**Population:** Nurses in Nurses Health Study NHS and NHS-2 NHS: 77,349 women; NHS-2: 113,371 women **Exposure assessment method:** questionnaire	**HR (RR) NHS: Duration (years) of rotating shift work, baseline**		Age, height, BMI, education level, menopausal status, menopausal hormone therapy, family history of colorectal cancer, alcohol consumption, physical activity, Smoking status, colonoscopy/sigmoidoscopy in previous 2 years, current regular aspirin/NSAIDS use, daily energy intake, red or processed meat intake, folate consumption	**Exposure information:** Ever and duration of rotating shift work **Strengths:** Utilization of two cohorts with long follow up time; complete information on potential confounders; ability to analyze by subtype; ability to compare two similar, but age differentiated cohorts. **Limitations:** Potential misclassification of unexposed potentially including permanent night workers and non-shift workers as most women exposed to some light at night. Small number of NHS2 women exposed for 15+years; no information on intensity or pattern of nightshift work most
		Never (Reference)	-		
		1–14 yrs	1.04 (0.94–1.16); 800		
		≥ 15 yrs	1.15 (0.95–1.39); 143		
		HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Never (Reference)	-		disruptive to circadian rhythms. **Additional results:** For NHS, a base model adjusted for age and follow-up cycle only had a significant RR of 1.34 (95%CI = 1.02 to 1.76) for nurses working 20-29 years rotating night shift work. For NHS2, baseline rotating night shift work history showed generally similar nonsignificant risk estimates by duration of exposure. **Confidence in evidence:** Some evidence (Will delete this, but my call for some evidence is that you see significant RR for 15+ years for baseline NHS cohort (1.60, 95%CI: 1.09, 2.34). Thoughts? Should this be considered null?)
		1–2 yr	1.04 (0.91–1.19); 346		
		3–4 yr	1.05 (0.91–1.22); 269		
		5–9 yr	1.06 (0.87–1.3); 112		
		10–14 yr	1.01 (0.79–1.29); 73		
		15–19 yr	1.02 (0.75–1.39); 45		
		20–29 yr	1.26 (0.96–1.65); 59		
		≥ 30 yr	1.17 (0.84–1.63); 39		
		Trend-test *p*-value: 0.14			
		HR (RR) NHS2: Duration (years) of rotating shift work, updated		Same as above	
		Never (Reference)	-		
		1–4 yr	0.77 (0.62–0.95); 187		
		5–9 yr	0.9 (0.66–1.21); 60		
		10–14 yr	1 (0.66–1.51); 27		
		≥ 15 yr	0.96 (0.56–1.64); 15		
		Trend-test *p*-value: 0.88			
		HR (RR) NHS2: Duration (years) of rotating shift work, updated		Same as above	
		Never (Reference)	-		
		1-14	0.81 (0.66–0.99); 274		
		15+	0.96 (0.56–1.64); 15		
		Combined proximal and distal colon: HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	
		Never (Reference)	-		
		1–14 yr	1.02 (0.9–1.16); 542		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		≥ 15 yr	1.09 (0.87–1.37); 93		
		Trend-test *p*-value: 0.62			
		Proximal colon: HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	
		Never (Reference)	-		
		1–14 yr	0.98 (0.83–1.14); 347		
		≥ 15 yr	1 (0.75–1.34); 57		
		Trend-test *p*-value: 0.90			
		Distal colon: HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	
		Never (Reference)	-		
		1–14 yr	1.12 (0.9–1.4); 195		
		≥ 15 yr	1.27 (0.87–1.85); 36		
		Trend-test *p*-value: 0.32			
		Rectum only: HR (RR) NHS: Duration of rotating shift work			
		Never (Reference)	-		
		1–14 yr	1.05 (0.82–1.34); 156		
		≥ 15 yr	1.6 (1.09–2.34); 36		
		Trend-test p-value: 0.02			
Schwartzbaum *et al.* 2007 Cohort Sweden **Enrollment or follow-up:**	**Population:** Swedish working women registered in 1960 and 1970 census data. 1,148,661 female workers and 2,102,126 male workers	**Colon only; Females: SIR Ever worked night shift by census period**		Age, socioeconomic status, occupational position, county of residence	**Exposure information:** Workplace (aggregate-level) either had a rotating schedule or had work hours between 1-4 AM **Strengths:** Nationwide cohort of men and women in
		1970	0.94 (0.54–1.52); 16		
		Colon only; Males: SIR Ever worked night shift by census period		Same as above	
		1970	1.03 (0.94–1.13); 449		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
1977-1981 (enrollment); 1971-1989 (follow-up)	**Exposure assessment method:** JEM	**Rectum only; Females: SIR Ever worked night shift by census period**		Same as above	diverse industries followed for 19 years. **Limitations:** In men, adequate number of exposed cases of colon and rectal cancer; in women, very small number of colon cancer cases. Aggregate exposure data, lack of data on potential confounders or co-exposures such as diet and alcohol use. **Additional results:** Risk estimates for female colon cancer using the 1960 and 1970 census were on 3 cases, with a low risk and imprecise confidence estimates (SIR: 0.42, 95% CI 0.09-1.23). Other risk estimates reported had similar results when restricted to participants in 1960 & 1970 censuses. **Confidence in evidence:** No confidence, not included in the assessment.
		1970	0.46 (0.12–1.17); 4		
		Rectum only; Males: SIR Ever worked night shift by census period		Same as above	
		1970	1.02 (0.91–1.13); 326		
Yong *et al.* 2014 Cohort Germany **Enrollment or follow-up:** 2000–2009	**Population:** Male chemical production workers in Rhineland-Palatinate Germany 27,828 men **Exposure assessment**	**HR (RR) Internal analysis: rotating shift work**		Age, job level, smoking, employment duration	**Exposure information:** Ever worked forward rotating shift work pattern: either 3 x 12 hours (day, off, night) or 4 x 12 hours (day, off, off, night) **Strengths:** Large retrospective cohort with adequate
		Rotating	1.33 (0.86–2.06); NR		
		SIR External analysis: ever rotating shift work		Age, calendar year	
		Rotating	1.08 (0.84–1.36); 68		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
	method: company records	Ratio of rotating vs. day	1.24 (0.88–1.77); NR		number of cases. Attempts to estimate bias from lack of exposure data. **Limitations:** Exposure data did not encompass all employment history. No variation in exposure metrics beyond ever exposure; duration crudely estimated and not used in analysis; only 80% estimated completeness of cancer case reporting; potential confounders not controlled; HWE is evident. **Additional results:** - **Confidence in evidence:** Some evidence
Papantoniou *et al.* 2017 Case-Control Spain **Enrollment or follow-up:** 2008–2013	**Population:** MCC-Spain Cases: 1626 men and women; Controls: 3378 men and women **Exposure assessment method:** questionnaire	**OR Ever rotating and night shift work**		Age, center, education, BMI, smoking status, physical activity, leisure, alcohol consumption, past, total energy intake gms/day, red meat consumption gms/day, sleep duration hrs/day, NSAIDs, family history of colorectal cancer, sex	**Exposure information:** Ever shift work, lifetime cumulative duration, age of first shift work exposure, years since last exposure. **Strengths:** Large, representative population based case-control study of histologically confirmed tumors, large number of exposed cases with long duration of rotating shift work; and control for potential confounders. **Limitations:** Low response rate in controls, potential for recall bias. Large proportion of missing data for shift work frequency. **Additional results:** When restricted to permanent night shift work for cumulative duration, there was no increased risk of colorectal cancer incidence by quartile or fixed category, both in base and full models. For age at first permanent shift work, results
		Never (Reference)	-		
		Rotating	1.22 (1.04–1.43); 426		
		Permanent night	0.79 (0.62–1); 129		
		OR Cumulative duration of rotating shift work: quartiles and fixed categories		Same as above	
		Never (Reference)	-		
		<8 years	1.14 (0.85–1.51); 89		
		8-19 years	1.12 (0.84–1.49); 87		
		20-34 years	1.38 (1.06–1.81); 119		
		35+ years	1.36 (1.02–1.79); 127		
		<15 years	1.19 (0.95–1.49); 147		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		15+ years	1.28 (1.06–1.56); 274		were reaching unity and non-significant when stratifying by age at first permanent shift work. **Confidence in evidence:** Evidence
		Trend-test *p*-value: 0.005 (quartiles)			
		OR Age at first rotating shift work		Same as above	
		Never (Reference)	-		
		<25 years	1.24 (0.99–1.56); 166		
		25+ years	0.95 (0.72–1.25); 99		
		OR Years since stopped rotating night shift work		Same as above	
		Never (Reference)	-		
		<15 years	1.12 (0.83–1.52); 89		
		15+ years	0.97 (0.76–1.24); 136		
		Colon only: OR Ever rotating and permanent night shift work		Same as above	
		Never (Reference)	-		
		Rotating	1.22 (1.02–1.46); 282		
		Permanent night	0.79 (0.6–1.11); 83		
		Rectum only: OR Ever rotating and permanent night shift work		Same as above	
		Never (Reference)	-		
		Rotating	1.26 (0.99–1.58); 143		
		Permanent night	0.76 (0.53–1.11); 42		
Parent *et al.* 2012 Case-Control Montreal, Canada **Enrollment or follow-up:** 1979–1985	**Population:** Montreal population based occupational case-control study of cancer in men 35-70 years of age. Cases: 439; Controls: 512 **Exposure assessment**	**Colon only: OR Ever, duration, and timing of night shift work**		Age, ancestry, education, family income, respondent status, smoking, BMI, alcohol, beta carotene, occupational exposure to aromatic amines	**Exposure information:** Ever, cumulative duration, and timing of night work (worked from 1:00 AM – 2:00 AM for 6+ months) **Strengths:** Possible to compare risks across cancer sites; complete population-based case-ascertainment
		Never (Reference)	-		
		Ever (6+ months)	2.03 (1.43–2.89); 110		
		6 months - < 5 years	2.32 (1.47–3.68); 61		
		5-10 years	1.43 (0.73–2.8); 20		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
	method: questionnaire	10+ years	2.11 (1.13–3.94); 29		system; histologic confirmation of primary cancers; large number of cases; detailed lifetime occupational histories; information on potential covariates; night definition likely to encompass a period pertinent to the hypothetical mechanism of carcinogenesis. **Limitations:** No screening, grade or severity information about colorectal cancer; approximately 18% of cases contributed information through proxies. **Additional results:** - **Confidence in evidence:** Evidence
		≤ 20 years ago	2.5 (1.51–4.14); 53		
		< 20 years ago	2.08 (1.24–3.47); 45		
		Rectum only: OR Ever, duration, and timing of night shift work		Same as above	
		Never (Reference)	-		
		Ever (6+ months)	2.09 (1.4–3.14); 58		
		6 months - < 5 years	2.58 (1.53–4.33); 35		
		5-10 years	1.42 (0.64–3.18); 10		
		10+ years	1.67 (0.77–3.61); 12		
		≤ 20 years ago worked nights	2.27 (1.27–4.05); 25		
		20+ years ago worked nights	2.35 (1.32–4.02); 26		
Walasa *et al.* 2018 Case-Control Australia **Enrollment or follow-up:** 2005–2007	**Population:** Western Australia Bowel Health Study (WABOHS). Cases: 350; Controls: 410 **Exposure assessment method:** JEM	**Colorectal (Female): OR Ever and duration of graveyard shift work**		Age group, education level, socioeconomic status, lifetime cigarette smoking, alcohol intake 10 years ago	**Exposure information:** Ever and duration of graveyard and early shifts, LAN, phase shift, poor diet, physical inactivity, sleep disturbance, vitamin D status; CRC, colon, and rectal cancers **Strengths:** Good sensitivity in regard to shift work characterization. Use of JEM allowed for standardized exposure definitions. **Limitations:** Poor response rates in cases and controls. Poor exposure characterization based on group-level information. In women, there was a small-to-moderate number of exposed cases. **Additional results:**
		Never (Reference)	-		
		Ever (0.1+ years)	1.06 (0.73–1.54); 73		
		> 0 - <7.5 yeras	1.17 (0.73–1.88); 40		
		7.5+ years	0.95 (0.57–1.58); 33		
		Colorectal (Female): OR Ever and duration of shift work involving light at night (LAN)		Same as above	
		0 (Reference)	-		
		Ever (0.1+ years)	1.02 (0.7–1.48); 70		
		> 0 - <7.5 years	1.12 (0.69–1.81); 38		
		7.5+ years	0.91 (0.55–1.53); 32		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Colorectal (Female): OR Ever and duration of phase shift work		Same as above	Age-adjusted only model results and results when examining graveyard shift work and colon cancer only were similar. Graveyard shift exposure and rectal cancer was elevated but n.s. [OR: 1.38 (95% CI 0.81 - 2.33)]. Similar elevated risks were seen in shorter and longer durations. Ever exposure to shift work involving LAN and rectal cancer had an elevated but n.s. OR: 1.40 (95% CI: 0.83 - 2.38). Ever exposure to phase shift work and rectal cancer was elevated but n.s. [OR: 1.40 (95% CI: 0.82-2.38)]. **Confidence in evidence:** Null
		Never (Reference)	-		
		Ever (0.1+ years)	1 (0.69–1.45); 69		
		> 0 - <7.5 yeras	1.09 (0.68–1.76); 38		
		7.5+ years	0.89 (0.53–1.51); 31		

References

1. Australian Bureau of Statistics. 2013. *Working Time Arrangements, Australia*. https://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/6342.0.

2. Hammer GP, Emrich K, Nasterlack M, Blettner M, Yong M. 2015. Shift work and prostate cancer incidence in industrial workers: A historical cohort study in a German chemical company. *Dtsch Arztebl Int* 112(27-28): 463-470. (Supported by the German Social Accident Insurance. Authors affiliated with Johannes Gutenberg University, Germany; Laboratoire National de Santé, Luxembourg; Occupational Medicine and Health Protection, BASF SE, Germany.)

3. Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ. 2017. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 43(2): 117-126. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Illinois at Chicago School of Public Health, IL; Danish Cancer Society, Denmark.)

4. Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Alonso-Aguado MH, Martin V, Aragonés N, Pérez-Gómez B, Pozo BM, Gómez-Acebo I, Ardanaz E, Altzibar JM, Peiro R, Tardon A, Lorca JA, Chirlaque MD, García-Palomo A, Jimenez-Moleon JJ, Ierssen T, Ederra M, Amiano P, Pollan M, Moreno V, Kogevinas M. 2017. Shift work and colorectal cancer risk in the MCC-Spain case-control study. *Scand J Work Environ Health* 43(3): 250-259. (Supported by the "Accion Transversal del Cancer", approved on the Spanish Ministry Council on 11 October 2007, by the Instituto de Salud Carlos III-FEDER, by the Fundación Marqués de Valdecilla, by the ICGC International Cancer Genome Consortium CLL [The ICGC CLL-Genome Project is funded by Spanish Ministerio de Economía y Competitividad [MINECO] through the Instituto de Salud Carlos III [ISCIII] and Red Temática de Investigación del Cáncer [RTICC] del ISCIII], by the Junta de Castilla y León, by the Consejería de Salud of the Junta de Andalucía, by the Conselleria de Sanitat of the Generalitat Valenciana, by the Recercaixa, by the European Commission grants, by the Spanish Association Against Cancer [AECC] Scientific Foundation, by the Catalan Government DURSI grant, by a predoctoral grant PFIS, by FEDER, by the European Commission, by the the Catalan Government DURSI, and by the Canadian Institutes of Health Research. Authors affiliated with CREAL, Spain; Medical University of Vienna, Austria; IMIM, Spain; Universitat Pompeu Fabra, Spain; University of Ottawa, Canada; IDIBELL, Spain; Hospitalet de Llobregat, Spain; Universidad de León, Spain; Carlos III Health Institute, Spain; IIS Puerta de Hierro, Spain; Complejo Hospitales Universitarios de Granada, Spain; University of Cantabria, Spain; Instituto de Salud Publica de Navarra, Spain; Navarra Institute for Health Research, Spain; Public Health Division of Gipuzkoa, Spain; Biodonostia Research Institute, Spain; FISABIO, Spain; Universidad de Oviedo, Spain; CYSMA, Spain; Universidad de Huelva, Spain; IMIB-Arrixaca, Spain; Universidad Murcia, Spain; Universidad de Granada, Spain; University of Barcelona, Spain; CIBERESP, Spain.)

5. Papantoniou K, Devore EE, Massa J, Strohmaier S, Vetter C, Yang L, Shi Y, Giovannucci E, Speizer F, Schernhammer ES. 2018. Rotating night shift work and

colorectal cancer risk in the Nurses' Health Studies. *Int J Cancer* 143(11): 2709-2717. (Supported by CDC/NIOSH and NIH. Authors affiliated with Medical University of Vienna, Austria; Brigham and Women's Hospital, MA: Harvard Medical School, MA; Harvard T. H. Chan School of Public Health, MA; University of Colorado, CO; Chinese PLA General Hospital, China.)

6. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. 2012. Night work and the risk of cancer among men. *Am J Epidemiol* 176(9): 751-759. (Supported by the Health Canada, the National Cancer Institute of Canada, the Institut de recherche en santé et sécurité au travail du Québec, the Fonds de la recherche en santé du Québec, and the Canadian Institutes of Health Research. Authors affiliated with INRS, Canada; University of Quebec, Canada; CRCHUM, Canada; University of Montreal, Canada.)

7. Schwartzbaum J, Ahlbom A, Feychting M. 2007. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 33(5): 336-343. (Supported by the Swedish Council for Working Life. Authors affiliated with Ohio State University, OH; Karolinska Institutet, Sweden.)

8. Walasa WM, Carey RN, Si S, Fritschi L, Heyworth JS, Fernandez RC, Boyle T. 2018. Association between shiftwork and the risk of colorectal cancer in females: a population-based case-control study. *Occup Environ Med* 75: 344-350. (Supported by the Australian National Health and Medical Research Council, the University of Adelaide, NHMRC, Canadian Institutes of Health Research, and the Cancer Council Western Australia. Authors affiliated with Curtin University, Australia; University of Western Australia, Australia; University of Adelaide, Australia; University of South Australia, Australia.)

9. Yong M, Blettner M, Emrich K, Nasterlack M, Oberlinner C, Hammer GP. 2014. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. *Scand J Work Environ Health* 40(5): 502-510. (Supported by the Deutsche Gesetzliche Unfallversicherung. Authors affiliated with BASF SE, Germany; Johannes Gutenberg University Mainz, Germany; Laboratoire National de Santé, Luxembourg.)

National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night

Appendix F: Night Shift Work and Female Hormonal Cancer

November 2020

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

List of Tables

Appendix F: Female Hormonal Cancer Studies Tables

Appendix F encompasses tables related to human studies on shift work exposure and risk of female hormonal cancers, which include ovarian and endometrial cancers. Tables F-1a to F-1f provide ratings and the rationales for the domains of study quality and study sensitivity. Table F-2 gives detailed results for each evaluated epidemiological study.

Table F-1a. Evaluation of selection bias in female hormonal cancer studies.

Reference	Selection Bias rating
Carter *et al.* 2014	+++ ↔ The cohort is clearly defined by exposure status for a specific time period and location. Follow-up did not differ by exposure status.
Jørgensen *et al.* 2017	+ ↓ The cohort was clearly defined by exposed/non-exposed for a specific time period and location. Follow-up did not differ by exposure status. Left truncation is an issue in this older survivor cohort. Authors indicated most nurses have to participate in rotating shift work early in their careers, and this is a >44 yr old cohort, so selection of exposure status may not be appropriate. Mortality analysis is likely to miss about 1/3 of cases having longer survival and later death, likely resulting in non-differential (not related to exposure status) misclassification, loss of power, and an underestimation of the risk estimate.
Poole *et al.* 2011	+++ ↓ The cohort is clearly defined with no evidence that follow-up differed between exposed and non-exposed subjects. Given that this is a combination of Nurses' Health Study (NHS) and NHS-2, women are less likely to be selected out due to inability to adapt to shift work.
Schwartzbaum *et al.* 2007	++ ↔ Only an external analysis was conducted. No evidence of HWE, as the overall SIR for all cancers was approaching unity. HWSE is still possible and may bias results toward the null.
Bhatti *et al.* 2013	+++ ↔ Cases and controls were selected from the same population using similar criteria. No evidence that selection of subjects was related to both exposure and disease. Known predictors of ovarian cancer in evidence in this population. Response rate was relatively high.
Viswanathan *et al.* 2007	++ ↓ The cohort is clearly defined by exposure status for a specific time period/location, with no evidence that follow-up differed between exposed and non-exposed subjects. There is no discussion of healthy worker survivor effect (HWSE) in this occupational cohort, although this is an older survivor cohort. If early exposure for long durations is a risk factor for colorectal cancer, this cohort would likely not be able to detect it.

Table F-1b. Evaluation of exposure assessment methods in female hormonal cancer studies.

Reference	Exposure Assessment rating
Carter *et al.* 2014	0 ⬇ Exposure assessment methods have poor sensitivity and specificity leading to questionable classification of the unexposed. With no information on previous lifetime job history, it cannot be certain that those not currently working night shifts, never did so. No information on exposure level/frequency was available.
Jørgensen *et al.* 2017	0 ⬇ Current information on work status at baseline only. No information on past employment status casting doubt on those classified as unexposed. No data on duration of shift schedule and shift work intensity lead to a less sensitive exposure categorization. Furthermore, authors mention the high likelihood of exposure misclassification for nurses whose training involves shift work early in their career.
Poole *et al.* 2011	++ ⬇ The exposure assessment methods have less than moderate sensitivity and specificity with respect to rotating shifts, and have poor sensitivity in relation to ever worked nights. For NHS nurses, the shiftwork question was only asked once and not updated; however, sensitivity analysis indicated this would lead to a small misclassification of exposure. No data on permanent or less frequent rotating night shift work was collected; however, sensitivity analyses indicated that the effects of such bias were likely to be small. These issues would have biased results towards the null. Data on exposure was collected prior to diagnosis of cancer thus avoiding recall bias.
Schwartzbaum *et al.* 2007	0 ⬇ Night shift work was determined according to percentage of those in each job category reporting shift work in a survey independent of the study cohort. Given the lack of individual-level data on exposure, participants categorized as unexposed are more likely to have been misclassified.
Bhatti *et al.* 2013	++ ⬇ The exposure methods have moderate sensitivity and specificity for distinguishing by exposure status. Starting at age 25 may have eliminated some with shift work early in their careers, meaning that the unexposed may not have been truly unexposed.
Viswanathan *et al.* 2007	++ ⬇ The exposure assessment methods have less than ideal sensitivity and specificity with respect to rotating shifts, and have poor sensitivity in relation to ever working nights. Nurses working permanent night shifts may have misinterpreted the question and not classified themselves as working rotations, but rather as non-rotation workers, or did not answer the question. This would have biased results towards the null. Data on exposure was collected prior to diagnosis of cancer thus avoiding recall bias.

Table F-1c. Evaluation of outcome assessment in female hormonal cancer studies.

Reference	Outcome Assessment rating
Carter *et al.* 2014	++ ↔ Outcome methods distinguish between diseased and non-diseased subjects. However, as ovarian cancer is typically considered a heterogenous mix of tumor types, having no information on tumor type is less than ideal. Follow-up and diagnoses are conducted independently of one another.
Jørgensen *et al.* 2017	++ ↓ Reported causes of death were not histologically-confirmed, rather only based on physician report from death records.
Poole *et al.* 2011	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Bhatti *et al.* 2013	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects; subtypes and grade of tumors are reported, and cases were histologically verified.
Viswanathan *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.

Table F-1d. Evaluation of study sensitivity in female hormonal cancer studies.

Reference	Sensitivity rating
Carter *et al.* 2014	+ ⬇ Adequate number of currently exposed subjects, but total exposure is unknown for these subjects and for the unexposed. Sufficient latency to detect cases.
Jørgensen *et al.* 2017	+ ⬇ Small number of night and rotating shift ovarian cancer cases. Poor sensitivity of exposure status due to lack of level, duration, or range of exposure. Adequately long follow-up duration.
Poole *et al.* 2011	++ ⬇ The study had a large number of exposed cases, but inadequate number in the younger cohort to capture effect from longer durations; intensity/level of exposure not addressed.
Schwartzbaum *et al.* 2007	+ ⬇ Study has very small number of ever exposed ovarian cancer cases. No information about intensity or duration. Adequate duration of follow-up.
Bhatti *et al.* 2013	++ ⬇ The study has adequate number of exposed cases ever working nights, and information on cumulative work/years of night shifts (short durations), but no information on intensity or type of shift rotations was available.
Viswanathan *et al.* 2007	++ ⬇ The study had adequate numbers of exposed endometrial cancer cases and information on duration; but intensity/level of exposure not addressed.

Table F-1e. Evaluation of the potential for confounding bias in female hormonal cancer studies.

Reference	Confounding rating
Carter *et al.* 2014	+++ ↔ The study controlled for many potential confounders as well as age alone. The multivariable control while including many variables of no consequence to Ovarian cancer, were not materially different from the model controlling for age alone.
Jørgensen *et al.* 2017	+++ ↔ The study measured all relevant confounders and used appropriate analyses to address them. The addition of all possible confounders may attenuate results and widen confidence in the estimates.
Poole *et al.* 2011	+++ ↔ The study measured all relevant potential confounders and used appropriate analyses.
Schwartzbaum *et al.* 2007	+ ↑ The study did not measure potential confounders such as parity, smoking, or OC use.
Bhatti *et al.* 2013	+++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them.
Viswanathan *et al.* 2007	++ ↓ Models may have over-controlled by including variables in the pathway in the model: age at menarche and menopause, diabetes, hypertension, and body mass index (BMI).

Table F-1f. Evaluation of analysis and selective reporting in female hormonal cancer studies.

Reference	Analysis rating	Selective Reporting rating
Carter *et al.* 2014	+++ ↔ The study used relevant data and assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited only to a subset of the data collected.
Jørgensen *et al.* 2017	++ ↓ Inclusion of multiple covariates not related to the exposure and outcome of interest may have attenuated results and widened confidence intervals.	+++ ↔ There isn't any evidence that data or analysis was limited to a subset of data.
Poole *et al.* 2011	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.
Schwartzbaum *et al.* 2007	++ ↔ Study used relevant data, had appropriate assumptions and used adequate methods for an external analysis (SIR).	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Bhatti *et al.* 2013	++ ↓ The study used relevant data and appropriate assumptions and methods of analysis; however, "never" exposed were not consistently defined throughout the analysis, as in some analyses, exposed women with fewer night shifts were included in the "unexposed" category, biasing these analyses towards the null.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of the data.
Viswanathan *et al.* 2007	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.

Table F-2. Evidence from epidemiological cohort and case-control studies on female hormonal cancer and exposure to night shift work

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Ovarian Cancer					
Carter *et al.* 2014 Cohort U.S. **Enrollment or follow-up:** 1982-2010	**Population:** Cancer Prevention Study II (CPS-II) cohort 161,004 employed women **Exposure assessment method:** questionnaire	**RR Ever worked rotating, fixed evening or night shifts**		Age, OC use, age at menarche, age at menopause, tubal ligation, parity, HRT use, race, family history of breast/ovarian ca, exercise, BMI, height	**Exposure information:** Fixed day, rotating shift workers, fixed aft/evening workers, fixed night workers. **Strengths:** Large prospective population based study of fatal ovarian cancer. **Limitations:** Exposure classification based only on current job; ovarian cancer based on fatal cases with no differentiation by type. **Additional results:** Results from age-adjusted model are similar to fully-adjusted model. **Confidence in evidence:** No confidence; not included in assessment.
		Fixed day (Reference)	-		
		Rotating	1.27 (1.03–1.56); 101		
		Fixed afternoon/evening	0.62 (0.34–1.12); 11		
		Fixed night	1.12 (0.67–1.87); 15		
Jørgensen *et al.* 2017 Cohort Denmark **Enrollment or follow-up:** 1993-2013	**Population:** Danish Nurses Cohort (DNC) 28,731 women **Exposure assessment method:** questionnaire	**HR Ever day, night, and rotating shifts**		Age, smoking status, pack years, physical activity, BMI, alcohol consumption, diet (veggies, fruit, meat), pre-existing disease (hypertension, diabetes, MI), self-reported health, stressful work enviornment, marital status, parity, age at first birth, use of HRT, OC use	**Exposure information:** Ever evening, night, rotating shifts **Strengths:** Nationwide prospective cohort of female nurses with detailed information on work schedules at baseline, and potential confounders. **Limitations:** Small numbers of ovarian cancer deaths, no information on duration or intensity, type of rotations, or past information on night work. No cancer validation. **Additional results:** Age-adjusted model results are similar to adjusted model results. **Confidence in evidence:** No confidence, not included in the assessment
		Day (Reference)	-		
		Night	0.63 (0.22–1.78); 4		
		Rotating	0.64 (0.35–1.16); 13		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Poole *et al*. 2011 Cohort 11 U.S. states **Enrollment or follow-up:** NHS: 1976 (enrolled), 1988–2008 (follow-up); NHS-2 1989–2007	**Population:** Nurses' Health Study (NHS and NHS-2) 181,548 women (NHS = 68,999; NHS-2 = 112,549) **Exposure assessment method:** questionnaire	**HR NHS & NHS-2: Duration of rotating night shift work**		Age, OC duration, parity, BMI, smoking status, tubal ligation history, menopausal status, fam hx ovarian ca, breastfeeding duration, cohort	**Exposure information:** Ever and duration of rotating shift work **Strengths:** Large number of ovarian cancer cases in a large prospective study of nurses with well-documented follow-up procedures and outcome definitions, with adequate data on potential confounders. Analyses to address healthy worker survival were conducted. **Limitations:** Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed in NHS. **Additional results:** Multivariate adjusted: Combined NHS and NHS-2 cohorts. Hazard ratio (HR) for age-adjusted model was similar for combined. **Confidence in evidence:** Some evidence
		None (Reference)	-		
		1–2 yr	1.07 (0.89–1.29); 197		
		3–5 yr	0.9 (0.72–1.13); 115		
		6–9 yr	0.92 (0.68–1.25); 51		
		10–14 yr	1.14 (0.81–1.6); 39		
		15–19 yr	1.28 (0.84–1.94); 24		
		20+ yr	0.8 (0.51–1.23); 22		
		Trend-test *p*-value: 0.74			
		HR NHS: Duration of rotating night shift work		Same as above	
		None (Reference)	-		
		1-2 years	1.2 (0.97–1.49); 143		
		3-5 years	0.95 (0.73–1.23); 80		
		6-9 years	0.96 (0.67–1.4); 33		
		10-14 years	1.06 (0.7–1.62); 25		
		15-19 years	1.3 (0.81–2.1); 19		
		20+ years	0.88 (0.56–1.37); 22		
		Trend-test *p*-value: 0.84			
		HR NHS2: Duration of rotating night shift work		Same as above	
		None (Reference)	-		
		1-2 years	0.8 (0.56–1.14); 54		
		3-5 years	0.79 (0.52–1.18); 35		
		6-9 years	0.8 (0.47–1.35); 18		
		10-14 years	1.25 (0.7–2.24); 14		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		15-19 years	1.21 (0.48–3.02); 5		
		Trend-test *p*-value: 0.78			
Schwartzbaum *et al.* 2007 Cohort Sweden **Enrollment or follow-up:** 1977-1981 (enrollment); 1971-1989 (follow-up)	**Population:** Swedish working women registered in 1960 and 1970 census data. 1,148,661 female workers **Exposure assessment method:** JEM	**SIR Ever worked night shift by census period**		Age, socioeconomic status, occupational position, county of residence	**Exposure information:** Workplace (aggregate-level) either had a rotating schedule or had work hours between 1-4 AM **Strengths:** Nationwide cohort of women in diverse industries followed for 19 years. **Limitations:** Very small number of ovarian cancer cases. Aggregate exposure data, lack of data on potential confounders or co-exposures such as smoking and diet. **Additional results:** - **Confidence in evidence:** No confidence, not included in the assessment.
		1970	0.8 (0.45–1.32); 15		
		1960 and 1970	1.13 (0.49–2.23); 8		
Bhatti *et al.* 2013 Case-Control Western Washington State U.S. **Enrollment or follow-up:** 2002–2009	**Population:** Population-based case control study Cases: 1,490 (1,101 invasive, 389 borderline); Controls: 1,832 **Exposure assessment method:** questionnaire	**Invasive tumors: OR Ever and cumulative duration of night shift work**		Age, county, reference year, OC duration, parity, BMI at age 30	**Exposure information:** Ever and cumulative night shift work years **Strengths:** Large population-based study of ovarian cancer, and subtypes; comprehensive data on nightshift schedules, complete data on confounders, and high participation rates. **Limitations:** Exposure assessment metrics did not adequately capture features of night shift work that could could help evaluate levels or intensity of circadian disruption. **Additional results:** - **Confidence in evidence:** Evidence
		Never (Reference)	-		
		Ever	1.24 (1.04–1.49); 293		
		4 mo–1 nightshift work-years	1.03 (0.72–1.47); 55		
		>1–3 nightshift work-years	1.13 (0.82–1.54); 75		
		>3 –7 nightshift work-years	1.95 (1.41–2.68); 94		
		>7 nightshift work-years	1.02 (0.74–1.42); 68		
		Borderline tumors: OR Ever and cumulative duration of night shift work		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Never (Reference)	-		
		Ever	1.48 (1.15–1.9); 126		
		4 months - 1 year	1.44 (0.9–2.29); 27		
		>1 - 3 years	1.33 (0.87–2.02); 35		
		>3 - 7 years	2.37 (1.57–3.57); 44		
		>7 years	0.97 (0.58–1.61); 20		
Endometrial cancer					
Viswanathan *et al.* 2007 Cohort 11 U.S. states **Enrollment or follow-up:** NHS: 1976 (enrolled); 1988–2004 (follow-up)	**Population:** Nurses' Health Study (NHS) 53,487 women **Exposure assessment method:** questionnaire	**RR Duration of rotating night shift work**		Age, age at menarche, age at menopause, parity, BMI, OC duration, HRT duration, hypertension, diabetes, park-years of smoking	**Exposure information:** Women who had never worked rotating shifts accounted for 40.4% of person-years of follow-up; 1–14 years = 52.2%; 15–29 years = 5.6%; 30+ years =1.8%. **Strengths:** Large prospective study of nurses with well documented follow-up procedures and outcome definitions, with adequate data on potential confounders. **Limitations:** Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed. No analyses on HWSE in this occupational cohort. **Additional results:** Results similar in age-adjusted model **Confidence in evidence:** Evidence
		Never (Reference)	-		
		1–9 yr	0.89 (0.74–1.08); 224		
		10–19 yr	1.06 (0.76–1.49); 43		
		20+ yr	1.47 (1.03–2.1); 38		
		Trend-test *p*-value: 0.04			

References

1. Bhatti P, Cushing-Haugen KL, Wicklund KG, Doherty JA, Rossing MA. 2013. Nightshift work and risk of ovarian cancer. *Occup Environ Med* 70(4): 231-237. (Supported by the US National Cancer Institute. Authors affiliated with Fred Hutchinson Cancer Research Center, WA; Geisel School of Medicine at Dartmouth, NH.)

2. Carter BD, Diver WR, Hildebrand JS, Patel AV, Gapstur SM. 2014. Circadian disruption and fatal ovarian cancer. *Am J Prev Med* 46(3 Suppl 1): S34-S41. (Supported by the American Cancer Society. Authors affiliated with American Cancer Society, GA.)

3. Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ. 2017. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 43(2): 117-126. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Illinois at Chicago School of Public Health, IL; Danish Cancer Society, Denmark.)

4. Poole EM, Schernhammer ES, Tworoger SS. 2011. Rotating night shift work and risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 20(5): 934-938. (Supported by NCI. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA: Harvard School of Public Health, MA: LBI-ACR & ACR-ITR VIEnna/CEADDP, Austria.)

5. Schwartzbaum J, Ahlbom A, Feychting M. 2007. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 33(5): 336-343. (Supported by the Swedish Council for Working Life. Authors affiliated with Ohio State University, OH; Karolinska Institutet, Sweden.)

6. Viswanathan AN, Hankinson SE, Schernhammer ES. 2007. Night shift work and the risk of endometrial cancer. *Cancer Res* 67(21): 10618-10622. (Supported by NIH. Authors affiliated with Harvard Medical School, MA; Brigham and Women’s Hospital, MA; Applied Cancer Research-Institute for Translational Research Vienna, Austria.)

National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night

Appendix G: Night Shift Work and Lung Cancer

November 2020

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

List of Tables

Appendix G: Lung Cancer Studies Tables

Appendix G encompasses tables related to human studies on shift work exposure and risk of lung cancer. Tables G-1a to G-1f provide ratings and the rationales for the domains of study quality and study sensitivity. Table G-2 gives detailed results for each evaluated epidemiological study.

Table G-1a. Evaluation of selection bias in lung cancer studies

Reference	Selection Bias rating
Jørgensen *et al.* 2017	+ ⬇ The cohort was clearly defined by exposed/non-exposed for a specific time period and location. Follow-up did not differ by exposure status. Left truncation is an issue in this older survivor cohort. Authors indicated most nurses have to participate in rotating shift work early in their careers, and this is a >44 yr old cohort, so selection of exposure status may not be appropriate. Mortality analysis is likely to miss about 1/3 of cases having longer survival and later death, likely resulting in non-differential (not related to exposure status) misclassification, loss of power, and an underestimation of the risk estimate.
Schernhammer *et al.* 2013	++ ⬇ Cohort is defined by exposure status for a specific time period and location, and follow-up does not appear to differ among exposed and unexposed. Healthy worker survivor effect (HSWE) and left truncation were possible, but stratification by duration of employment helps to mitigate those potential impacts. HWE is also possible given the healthier nurse population.
Schwartzbaum *et al.* 2007	++ ⬇ Only an external analysis was conducted. No evidence of HWE, as the overall SIR for all cancers was approaching unity. HWSE is still possible and may bias results toward the null.
Taylor and Pocock 1972	++ ⬇ Cohort is clearly defined by exposure status for a specified time period and location. Follow-up did not differ between exposed and unexposed. Healthy worker effect (HWE0 was not accounted for in analyses, although mortality rates of cohort were comparable to greater population. Since only workers from large companies with health pre-screening requirements were chosen, selection bias may be present and may non-differentially bias results toward the null.
Yong *et al.* 2014	++ ⬇ The cohort is clearly defined and includes the relevant exposed and unexposed populations for a specific time period and location. Evidence of HWE, as cancer incidence was higher among shift workers and lower among day workers, compared to the general population. There was also no consideration of HWSE in this occupational cohort. In Hammer *et al.* (2015), a validation analysis of the same cohort reported no change in day to shift work for 893 (97%) of the employees, and there was little movement between shifts in this company suggesting HWSE is minimized.
Kwon *et al.* 2015	++ ↔ Cases and sub-cohort (case-cohort study) were chosen from the same cohort by similar methods and criteria, and cohort was clearly defined by exposure status. No evidence that follow-up differed by exposure status. HWE is

Reference	Selection Bias rating
	possible in this study, considering exposed population would need to be healthier in order to work nights.
Parent *et al.* 2012	+++ ↔ Cases and controls selected from the same population using similar criteria; no evidence that selection of subjects was related to both exposure and disease. Distribution of occupations of controls was comparable to distribution in the Canadian censuses, and percentage of those who were shift workers (14.5%) was similar to the general male population.

Table G-1b. Evaluation of exposure assessment methods in lung cancer studies

Reference	Exposure Assessment rating
Jørgensen *et al.* 2017	0 ⬆ Current information on work status at baseline only. No information on past employment status casting doubt on those classified as unexposed. No data on duration of shift schedule and shift work intensity lead to a less sensitive exposure categorization. Furthermore, authors mention the high likelihood of exposure misclassification for nurses whose training involves shift work early in their career.
Schernhammer *et al.* 2013	++ ⬇ Study adequately captures shift schedule and years of shift schedule, but not shift intensity. Exposure may have been misclassified, resulting in bias toward the null due to the nature of the questions asked, (i.e. permanent night work may not have been considered to be rotating.
Schwartzbaum *et al.* 2007	0 ⬇ Night shift work was determined according to percentage of those in each job category reporting shift work in a survey independent of the study cohort. Given the lack of individual-level data on exposure, participants categorized as unexposed are more likely to have been misclassified.
Taylor and Pocock 1972	++ ⬇ Exposure assessment allows for discrimination between exposed and unexposed populations. Shift schedule (day, shift, ex-shift), duration (10+ years vs. <10 years), and shift intensity (day, 3-week rotating, rapid rotating, alternate night/day, double days, etc.) were all captured, but not all quantified in final models. Any exposure misclassification is likely non-differential and will bias toward the null.
Yong *et al.* 2014	+ ⬇ Detailed information on shift work schedule and intensity were used. Years of shift work was also captured, but not prior to 1995. Exposure status prior to 1995 was estimated to be misclassified for both unexposed (1.2%–3.1%) and exposed (9.8%–13.4%) participants based on a sensitivity analysis of 300 participants. Validation study revealed the likelihood of misclassification impacting results was low; however, potential differential misclassification for exposed subjects will bias results toward the null.
Kwon *et al.* 2015	++ ⬌ Exposure to shift work was characterized by cumulative years and nights worked, but not by shift schedule or shift intensity. Exposure was not based at an individual-level and relied on a job exposure matrix (JEM), although strict regulations standardized schedules.
Parent *et al.* 2012	++ ⬌ Exposure methods reliably discriminate between ever and never exposed. However, no information was gathered on frequency (exposure-level) or types of shifts (fixed or rotating), direction or rate of shift rotation. Timing of shift work was collected but crudely divided as recent (within past 20 years), or distant past (20+ years ago) exposure.

Table G-1c. Evaluation of outcome assessment in lung cancer studies

Reference	Outcome Assessment rating
Jørgensen *et al.* 2017	++ ⬇ Reported causes of death were not histologically-confirmed, rather only based on physician report from death records.
Schernhammer *et al.* 2013	+++ ↔ Outcome methods distinguish between diseased and non-diseased subjects; medically confirmed. Furthermore, lung cancer subtypes were examined
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Taylor and Pocock 1972	+++ ↔ Outcome methods distinguish between diseased and non-diseased based on the use of death certificates. Unknown who did follow-up ICD-coding or who determined cancer status.
Yong *et al.* 2014	++ ⬇ Outcome methods distinguish between diseased and non-diseased subjects, and follow-up was conducted independent of exposure classification; however, given the development of the registry, some cases may have been missed, although it is likely that this is non-differential misclassification, leading to a bias towards the null.
Kwon *et al.* 2015	++ ⬇ Outcome methods distinguish between diseased and non-diseased subjects. Follow-up and diagnosis were independent of exposure. Disease diagnoses were not histologically confirmed, nor were any lung cancer subtypes examined, so there is potential for outcome misclassification.
Parent *et al.* 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis conducted independent of exposure status.

Table G-1d. Evaluation of study sensitivity in lung cancer studies

Reference	Sensitivity rating
Jørgensen *et al.* 2017	+ ⬇ Small number of night and rotating shift lung cancer cases. Poor sensitivity of exposure status due to lack of level, duration, or range of exposure. Adequate follow-up duration.
Schernhammer *et al.* 2013	++ ⬇ The study has a large number of exposed lung cancer cases. Study has a substantial duration of exposure; however, it does not capture level or range of shift work.
Schwartzbaum *et al.* 2007	+ ↔ In men, adequate number of exposed cases of lung/trachea cancer; in women, very small number of cancer cases. Poor categorization of level, duration, and range of exposure to shift work due to the nature of non-specific registries.
Taylor and Pocock 1972	+ ⬇ The study has a substantial number of exposed subjects and a small number of cases with an adequate follow-up duration. For lung cancer, only day, shift, and ex-shift workers were compared for their observed vs. expected mortality, which provides little information on the magnitude of exposure and no information of duration and range of shift work exposure.
Yong *et al.* 2014	+ ⬇ The study had a small-to-moderate number of lung cancer cases. No information on level, duration, or range, and exposure variation is essentially flat across the exposed. Latency follow-up is adequate.
Kwon *et al.* 2015	++ ↔ Study had a large number of exposed cases, a substantial stratification by cumulative years/nights, and accounted for follow-up using 10- and 20-year lag stratification. The study, however, did not measure shift intensity or shift schedules.
Parent *et al.* 2012	++ ⬇ The study has a large number of exposed lung cancer cases, but no information on intensity/frequency or pattern of exposure (e.g., type of shifts); or screening information.

Table G-1e. Evaluation of the potential for confounding bias in lung cancer studies

Reference	Confounding rating
Jørgensen *et al.* 2017	Lung: +++ ↔ Study measured all relevant potential confounders.
Schernhammer *et al.* 2013	Lung: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them. Various iterations of models controlling for different subsets of potential confounders were presented.
Schwartzbaum *et al.* 2007	Lung: + ↔ The study did not measure relevant lung cancer confounders such as smoking.
Taylor and Pocock 1972	Lung: + ↔ The study did not measure potential confounders including smoking. Lung cancer rates were similar to the external population across all work types, and therefore, not indicative of unmeasured confounding in the population.
Yong *et al.* 2014	Lung: ++ ↔ The study did not measure potential confounders relevant to the chemical industry.
Kwon *et al.* 2015	Lung: +++ ↔ The study adequately measured potential confounders and controlled for them in their analysis, including accounting for latency using lag models.
Parent *et al.* 2012	Lung: +++ ↔ The study adequately measured potential confounders and controlled for them in their analysis.

Table G-1f. Evaluation of analysis and selective reporting in lung cancer studies

Reference	Analysis rating	Selective Reporting rating
Jørgensen *et al.* 2017	++ ⬇ Inclusion of multiple covariates not related to the exposure and outcome of interest may have attenuated results and widened confidence intervals.	+++ ↔ There isn't any evidence that data or analysis was limited to a subset of data.
Schernhammer *et al.* 2013	+++ ↔ Study used relevant data, appropriate assumptions, and appropriate analytical methods.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the collected data.
Schwartzbaum *et al.* 2007	++ ↔ Study used relevant data, had appropriate assumptions and used adequate methods for an external analysis (SIR).	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Taylor and Pocock 1972	+ ↔ Study used relevant data and appropriate assumptions, but an standardized mortality ratio (SMR) would have been more appropriate to determine the magnitude of lung cancer mortality in the sample vs. the population.	+++ ↔ No evidence that reporting was limited to a subset of data, but reporting of analytical results were limited.
Yong *et al.* 2014	+++ ↔ The study used relevant available data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the collected data.
Kwon *et al.* 2015	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis, although unclear why a case-cohort was chosen over a nested case-control study.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of data collected.
Parent *et al.* 2012	+++ ↔ Study used relevant data, appropriate assumptions, and valid methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of data collected.

Table G-2. Evidence from epidemiological cohort and case-control studies on lung cancer and exposure to night shift work

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Jørgensen *et al.* 2017 Cohort Denmark **Enrollment or follow-up:** 1993-2013	**Population:** Danish Nurse Cohort 18 015 **Exposure assessment method:** questionnaire	**HR Ever exposure by night and rotating shift work**		Age, smoking status, pack years, physical activity, BMI, alcohol consumption, diet (veggies, fruit, meat), pre-existing disease (hypertension, diabetes, MI), self-reported health, stressful work environment, marital status, parity, use of HRT, OC use	**Exposure information:** Day, evening, night, rotating shifts **Strengths:** Nationwide prospective cohort of female nurses with detailed information on work schedules at baseline, and potential confounders. **Limitations:** Small numbers of lung cancer deaths, no information on duration or intensity, type of rotations, or past information on shiftwork. No cancer validation. **Additional results:** - **Confidence in evidence:** No confidence, not included in the assessment
		Day (Reference)	-		
		Night	1.09 (0.65–1.82); 19		
		Rotating	0.96 (0.65–1.42); 33		
Schernhammer *et al.* 2013 Cohort 11 U.S. states **Enrollment or follow-up:** Enrolled 1976; followed 1988–2008	**Population:** Nurses' Health Study - US 78,612 women **Exposure assessment method:** questionnaire	**RR All women: duration of rotating shift work**		Age, Smoking status, age started smoking, # cigarettes smoked / day, time since quitting among past smokers, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them	**Exposure information:** Ever and duration of rotating shift work **Strengths:** Large prospective study of nurses with well documented follow-up procedures and outcome definitions including lung cancer subtypes, and adequate control for potential confounders. **Limitations:** Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed. No analyses on healthy worker survival in this occupational cohort. **Additional results:** Age/time-period adjusted model and model excluding diet variables saw similar results. age-adjusted model only had similar results similar results in age- and time-adjusted model
		0 (Reference)	-		
		1–5 yr	1.03 (0.91–1.16); 572		
		6–14 yr	0.96 (0.81–1.14); 177		
		15+ yr	1.28 (1.07–1.53); 164		
		Trend-test *p*-value: 0.03			
		RR Former smokers: duration of rotating shift work		Age, age started smoking, time since	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		0 (Reference)	-	quitting among past smokers, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them, menopausal status, HRT use, OC use	only Results from base model similar to full model Base models are similar to full model Base models show a stronger relationship with increased duration (15+ years) and a positive dose-response trend, but no accounting for smoking. For the 6-14 year and 15+ year categories, base models (not adjusting for smoking), reveal stronger point estimates and a stronger dose-response relationship. **Confidence in evidence:** Evidence
		1–5 yr	0.99 (0.83–1.16); 292		
		6–14 yr	0.86 (0.66–1.1); 78		
		15+ yr	1.06 (0.81–1.38); 68		
		Trend-test *p*-value: 0.92			
		RR Current smokers, duration of rotating shift work		Age, age started smoking, time since quitting among past smokers, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them, menopausal status, HRT use, OC use, # cigarettes smoked / day	
		0 (Reference)	-		
		1–5 yr	1.01 (0.82–1.24); 203		
		6–14 yr	1.16 (0.89–1.52); 84		
		15+ yr	1.61 (1.21–2.13); 80		
		Trend-test *p*-value: 0.0006			
		RR Never smokers, duration of rotating shift work		Age, fruit intake, vegetable intake, bmi,	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		0 (Reference)	-	yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them	
		1–5 yr	1.19 (0.82–1.73); 63		
		6–14 yr	0.75 (0.39–1.45); 11		
		15+ yr	1 (0.51–1.94); 11		
		Trend-test *p*-value: 0.65			
		Adenocarcinoma: RR Duration of rotating shift work		Age, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them, age started smoking, time since quitting among past smokers, # cigarettes smoked / day in current smokers, menopausal status, HRT use, OC use	
		Never (Reference)	-		
		1–5 yr	1.03 (0.87–1.24); 263		
		6–14 yr	0.92 (0.71–1.2); 74		
		15+ yr	0.91 (0.67–1.24); 50		
		Trend-test *p*-value: 0.4			
		Squamous-cell carcinoma: RR Duration of rotating night shift work		Same as above	
		Never (Reference)	-		
		1–5 yr	0.96 (0.69–1.33); 75		
		6–14 yr	1.01 (0.64–1.6); 25		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		15+ yr	1.45 (0.92–2.3); 26		
		Trend-test *p*-value: 0.13			
		Small cell/oat cell: RR Duration of rotating night shift work		Same as above	
		Never (Reference)	-		
		1–5 yr	1.11 (0.79–1.57); 73		
		6–14 yr	1.4 (0.91–2.15); 34		
		15+ yr	1.56 (0.99–2.47); 29		
		Trend-test *p*-value: 0.03			
		RR Current smokers with 15+ years shift work		Same as above	
		Adenocarcinoma	1.22 (0.74–2.01); NR		
		Small-cell carcinoma	1.57 (0.85–2.89); NR		
		Squamous-cell carcinoma	1.48 (0.68–3.23); NR		
		RR Past smokers with 15+ years shift work		Same as above	
		Adenocarcinoma	0.78 (0.5–1.22); 340		
		Small-cell carcinoma	1.78 (0.82–3.86); 72		
		Squamous-cell carcinoma	1.4 (0.75–2.62); 114		
Schwartzbaum *et al.* 2007 Cohort **Enrollment or follow-up:** 1977-1981 (enrollment);	**Population:** Swedish working women registered in 1960 and 1970 census data. 1,148,661 female workers and 2 102 126 male workers **Exposure assessment method:** JEM	**Female: SIR Working in industries with 40% workers on night or rotating shift: Time period**		Age, socioeconomic status, occupational position, county of residence	**Exposure information:** Workplace had rotating schedule or work between 1 and 4 AM **Strengths:** Nationwide cohort of men and women in diverse industries followed for 19 years. **Limitations:** In men, adequate number of exposed cases of
		1970	1.13 (0.62–1.89); 14		
		1960 and 1970	1.28 (0.47–2.79); 6		
		Males: SIR Working in industries with 40% workers on night or rotating shift: Time period		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
1971-1989 (follow-up)		1970	0.95 (0.88–1.02); 706		lung/trachea cancer; in women, very small number of cancer cases. Aggregate exposure data, lack of data on potential confounders or co-exposures such as smoking status. **Additional results:** - **Confidence in evidence:** No confidence, not included in the assessment.
		1960 and 1970	0.9 (0.82–0.99); 397		
Taylor and Pocock 1972 Cohort England and Wales **Enrollment or follow-up:** Employed on 1/1/1956, followed 1956–1968	**Population:** None 8,603 manual workers **Exposure assessment method:** company records	**SIR Type of work**			**Exposure information:** Shift work for 10 years **Strengths:** Company records from 10 diverse companies across the country provided reliable information about shiftwork. **Limitations:** Cancer was not confirmed; exposure metrics were insufficiently detailed for lung cancer; and follow-up was relatively short. Furthermore, no information of potential confounders, including smoking. **Additional results:** - **Confidence in evidence:** Inadequate
		Day	1.09 (0.8–1.33); 95		
		Shift	1.11 (0.9–1.36); 94		
		Ex-shift	1.15 (0.6–1.97); 13		
Yong *et al.* 2014 Cohort Germany **Enrollment or follow-up:** 2000–2009	**Population:** Male chemical production workers in Rhineland-Palatinate Germany 27,828 men **Exposure assessment method:** company records	**SIR External analysis: day vs. rotating shift work**		Age, calendar year	**Exposure information:** Ever worked forward rotating shift work pattern: either 3 x12 hours (day, off, night) or 4 x12 hours (day, off, off, night) **Strengths:** Large retrospective cohort with adequate number of cases. **Limitations:** Exposure data did not encompass all employment
		Day	0.48 (0.34–0.66); 39		
		Rotating	0.7 (0.51–0.94); 46		
		Ratio of rotating shift vs.day	1.46 (0.93–2.3); NR		
		HR (RR) Internal analysis: day vs. rotating shift work		Age, job level, smoking, employment	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Day	1; NR	duration	history; no variation in exposure metrics beyond ever exposure; duration crudely estimated and not used in analysis; only 80% estimated completeness of cancer case reporting; potential confounders not controlled; HWE is evident. **Additional results:** - **Confidence in evidence:** Null evidence
		Rotating	0.93 (0.54–1.63); NR		
Kwon *et al.* 2015 Nested Case-Control Shanghai, China **Enrollment or follow-up:** 1989–1991	**Population:** Female textile workers cohort form Shanghai, China Cases: 1,451; Controls: 3,020 **Exposure assessment method:** JEM	**HR (RR) All women, no lag: Duration of rotating night shift work**		Age, smoking status, parity, endotoxin	**Exposure information:** Ever/never worked rotating night shifts; # of nights worked and years duration **Strengths:** Large, well defined occupational cohort with low rates of smoking, with sufficient number of lung cancer cases; work histories complete for all women; detailed shift work information for each job including several metrics; data on potential confounders available. **Limitations:** Night shift work was embedded within rotating shift work patterns, with no assigned jobs being exclusively night shift. No detail about rotation schedules or intensity of shift work. Exposure status was collected as an aggregate at the factory level. ICD-9 codes are prone to non-differential misclassification if confirmatory data is not available. **Additional results:** Results from unadjusted model are similar **Confidence in evidence:** Null
		Zero (Reference)	-		
		>0 - 17.1 yr	0.76 (0.62–0.93); 259		
		>17.1 yrs –≤ 24.9 yr	0.89 (0.72–1.09); 261		
		>24.9 yrs–≤ 30.6 yr	0.94 (0.76–1.17); 259		
		> 30.6 yr	0.82 (0.66–1.02); 261		
		Trend-test *p*-value: 0.294			
Parent *et al.* 2012	**Population:**	**OR Ever and duration of night shift work**		Age, ancestry,	**Exposure information:**

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Case-Control Montreal, Canada **Enrollment or follow-up:** 1979–1985	Montreal population based occupational case-control study of cancer in men 35-70 years of age. Cases: 761; Controls: 512 **Exposure assessment method:** questionnaire	Never (Reference)	-	education, family income, respondent status, smoking, beta carotene, occupational exposure to asbestos and silica	Ever, cumulative duration, and timing of night work (worked from 1:00 AM–2:00 AM for 6+ months) **Strengths:** Possible to compare risks across cancer sites; complete population-based case-ascertainment system; histologic confirmation of primary cancers; detailed lifetime occupational histories; information on potential covariates; nighttime definition likely to encompass a period pertinent to the hypothetical mechanism of carcinogenesis. **Limitations:** No screening, grade or severity information about prostate cancer; approximately 18% of cases contributed information through proxies. **Additional results:** - **Confidence in evidence:** Evidence
		Ever (6+ months)	1.76 (1.25–2.47); 216		
		<5 yr	1.93 (1.22–3.03); 110		
		5–10 yr	1.51 (0.8–2.85); 52		
		10+ yr	1.67 (0.9–3.09); 54		
		Worked nights in past 20 years	1.76 (1.07–2.89); 91		
		Worked nights more than 20 years ago	1.88 (1.13–3.14); 79		
		OR Ever night work: Lung cancer subtypes		Same as above	
		Squamous-cell carcinoma	1.91 (1.27–2.87); NR		
		Small-cell carcinoma	1.62 (1.25–2.47); NR		
		Adenocarcinoma	1.46 (0.86–2.5); NR		

References

1. Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ. 2017. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 43(2): 117-126. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Illinois at Chicago School of Public Health, IL; Danish Cancer Society, Denmark.)

2. Kwon P, Lundin J, Li W, Ray R, Littell C, Gao D, Thomas DB, Checkoway H. 2015. Night shift work and lung cancer risk among female textile workers in Shanghai, China. *J Occup Environ Hyg* 12(5): 334-341. (Supported by NIH. Authors affiliated with Bassett Army Community Hospital, Alaska; University of Washington, WA; Fred Hutchinson Cancer Research Center, WA; Walter Reed Army Institute of Research, MD; Fudan University, China; University of California San Diego, CA.)

3. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. 2012. Night work and the risk of cancer among men. *Am J Epidemiol* 176(9): 751-759. (Supported by the Health Canada, the National Cancer Institute of Canada, the Institut de recherche en santé et sécurité au travail du Québec, the Fonds de la recherche en santé du Québec, and the Canadian Institutes of Health Research. Authors affiliated with INRS, Canada.)

4. Schernhammer ES, Feskanich D, Liang G, Han J. 2013. Rotating night-shift work and lung cancer risk among female nurses in the United States. *Am J Epidemiol* 178(9): 1434-1441. (Supported by NIH. Authors affiliated with Brigham and Women's Hospital, MA; Harvard Medical School, MA; ACR-ITR, Austria; LBI-ACR, Austria; Southeast University, China; Tianjin Medical University Cancer Institute and Hospital, China.)

5. Schwartzbaum J, Ahlbom A, Feychting M. 2007. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 33(5): 336-343. (Supported by the Swedish Council for Working Life. Authors affiliated with Ohio State University, OH; Karolinska Institutet, Sweden.)

6. Taylor PJ, Pocock SJ. 1972. Mortality of shift and day workers 1956-68. *Br J Ind Med* 29(2): 201-207. (Support not reported. Authors affiliated with London School of Hygiene and Tropical Medicine,UK.)

7. Yong M, Blettner M, Emrich K, Nasterlack M, Oberlinner C, Hammer GP. 2014. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. *Scand J Work Environ Health* 40(5): 502-510. (Supported by the Deutsche Gesetzliche Unfallversicherung. Authors affiliated with BASF SE, Germany; Johannes Gutenberg University Mainz, Germany; Laboratoire National de Santé, Luxembourg.)

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
P.O. Box 12233, MD K2-14
Research Triangle Park, NC 27709