National Toxicology Program
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Draft Report on Carcinogens Monograph on Night Shift Work and Light at Night

Peer Review Draft

Running title: Draft RoC Monograph on Night Shift Work and Light at Night

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Office of the Report on Carcinogens
Division of the National Toxicology Program
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Foreword

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens* and (ii) to which a significant number of persons residing in the United States are exposed. The NTP, with assistance from other Federal health and regulatory agencies and nongovernmental institutions, prepares the report for the Secretary, Department of HHS. The most recent RoC, the 14th Edition (2016), is available at http://ntp.niehs.nih.gov/go/roc.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (http://ntp.niehs.nih.gov/go/rocprocess) with multiple opportunities for scientific and public input and using established listing criteria (http://ntp.niehs.nih.gov/go/15209). A list of substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing http://ntp.niehs.nih.gov/go/37893.

Objectives and Methods

Objective and scope

Modern electric 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 monograph is to reach a preliminary listing recommendation for night shift work and exposure to LAN for the RoC 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 6:00 AM and 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). Several of these characteristics such as LAN, sleep disturbances, and changes in meal timing are related to circadian disruption.
- LAN refers to exposure to light during the biological night which is the time when the circadian clock promotes sleep.

Human cancer studies of transmeridian travel were also reviewed as this involves exposure to both LAN and shift work; however, no overall preliminary recommendation was made for this exposure scenario.

As circadian disruption is a key intermediate in the pathway between exposure and potential cancer, this monograph reviews studies evaluating exposure and circadian disruption and studies on circadian disruption and cancer. 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).

Monograph 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

Evidence stream	Exposure (intermediate)	Comparison group	Cancer outcome or effect
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
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 of 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

Evidence stream	Exposure (intermediate)	Comparison group	Cancer outcome or effect
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.

Methods for developing the RoC monograph

Process leading to the selection of night shift work and light at night for review

Light at night (LAN) was nominated for review for the Report on Carcinogens (RoC) by several individuals based in part on the International Agency for Research on Cancer (IARC) conclusions that shift work involving circadian disruption is probably carcinogenic to humans (IARC 2012). Thus, the NTP broadened its consideration of LAN to consider shift work and circadian disruption. As per the process for preparation of the RoC, the Office of the RoC (ORoC) released for public comment a draft concept document, "Shift Work at Night, Light at Night, and Circadian Disruption," which outlined the rationale and proposed the approach for the review. The ORoC also presented the draft concept document to the NTP Board of Scientific Counselors (BSC) at its meeting on June 25, 2013, which provided opportunity for written and oral public comments. After the meeting, the concept was finalized, and shift work at night, light at night, and circadian disruption was approved by the NTP Director as a topic for review. The concept document is available on the RoC website (https://ntp.niehs.nih.gov/go/41532).

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. 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 RoC monograph on exposures related to modern lighting practices for public input on the NTP webpage (https://ntp.niehs.nih.gov/go/41532) prior to the release of the draft monograph.

Monograph development

This monograph evaluates the available, relevant scientific information and assesses its quality, applies the RoC listing criteria to the scientific information, and recommends a RoC listing status. The monograph also includes a draft profile containing the NTP's preliminary listing

recommendation for night shift work and LAN, a summary of the scientific evidence considered key to reaching that recommendation, data on exposure to night shift work and LAN, and Federal regulations and guidelines to reduce exposure.

The process of applying the RoC listing criteria to the body of evidence includes assessing the level of evidence from cancer studies of night shift work and LAN in humans. The scientific information must come from publicly available sources. 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. As circadian disruption is a key intermediate in the cancer process, the document also reviews (1) studies of LAN and shift work and biomarkers of circadian disruption and (2) studies of circadian disruption (primary 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:

- Introduction 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 Preliminary Listing Recommendations (Section 7).

The appendices in the RoC Monograph 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 monograph 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?
- Should night shift work be listed in the RoC?
  - If so, how should it be defined?
  - Can we define the underlying exposures related to circadian disruption?
- Should LAN be listed in the RoC?
  - 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 acts through mechanisms indicating they would likely cause cancer in humans?

Methods for preparing the monograph

The methods for preparing the RoC monograph on night shift work and LAN are described in the RoC 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. See the Handbook for Preparing RoC Monographs (hereinafter referred to as RoC Handbook) for a detailed description of methods.

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, 660 references were selected for final inclusion in the monograph. Literature searches are updated on a monthly basis.

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 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 evaluation and preliminary listing recommendation. The cancer hazard assessment involves the 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 preliminary listing recommendations are 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 monograph to provide transparency for the decision-making process for reaching a listing recommendation for LAN and night shift.

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.

Collaborators, Contributors and Acknowledgments

Collaborators

Role	Collaborator	Affiliation
Co-project leads Responsible for execution and coordination of project activities, including conception, design, planning, conduct, or technical review of cancer hazard evaluation.	Ruth M. Lunn, DrPH Pamela J. Schwingl, PhD	NIEHS, DNTP, ORoC ILS
RoC 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 Mehta, MPH	ILS ILS NIEHS, DNTP, ORoC NIEHS, DNTP, ORoC

Contributors

Role	Contributor	Affiliation
Provided technical assistance with the monograph preparation	Whitney Arroyave, PhD Andrew Ewens, PhD Alton Peters, MS	ILS ILS ILS
Technical Advisors Provided critical review of specific sections of the monograph	David Blask, PhD, MD Marianna 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 the monograph	John Bucher, PhD (Chair) Windy A. Boyd, PhD Tania Carreón-Valencia, PhD Claire Caruso, PhD, RN Suzanne Fenton, PhD Gopi Gadupudi, PhD Stephanie Holmgren, MSLS, MBA Christina Lawson, PhD Scott Masten, PhD Arun Pandiri, PhD Leslie Reinlib, PhD Amy Wang, PhD, BVM Alexandra White, PhD	NIEHS, DNTP NIEHS, DNTP NIOSH NIOSH NIEHS, DNTP NIEHS, DNTP NIEHS, DNTP NIOSH NIEHS, DNTP NIEHS, DNTP NIEHS, DERT NIEHS, DNTP NIEHS, DIR

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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

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ORoC = Office of the Report on Carcinogens, DNTP, NIEHS.

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1 Introduction 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 and 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 monograph is to evaluate the relationship between two exposures related to modern electric 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 electrical 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 regulation and 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 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, and melatonin. These are briefly discussed below.

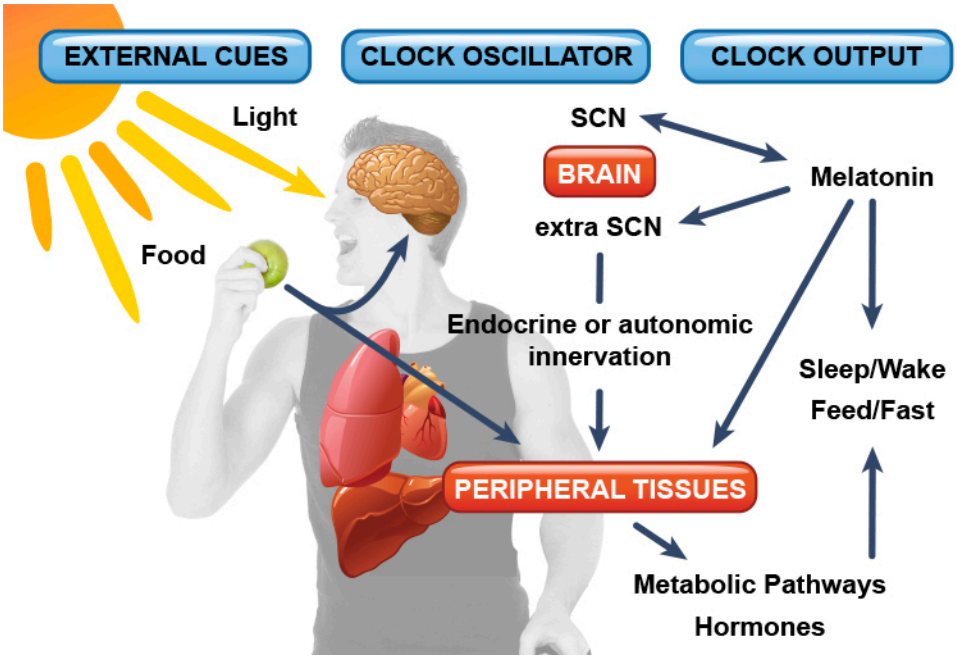

Figure 1-1. Regulation of circadian rhythms by internal and external cues

Light is the primary regulator of the master circadian clock found in the suprachiasmatic nucleus (SCN) of the brain. The SCN sends endocrine and neural signals to a variety of peripheral tissues to temporally coordinate their physiology and metabolism. The SCN also sends a signal to the pineal gland to produce the hormone melatonin during darkness at night. Melatonin can then convey signals back to the SCN, other parts of the brain, and peripheral tissues to help coordinate physiological functions and behaviors to approximate 24-hour days.
Source: Lunn *et al.* (2017) (used with permission, license number 4260831046002).

As illustrated in Figure 1-1, the circadian system is organized in a hierarchical manner consisting of a master oscillator, the bilaterally paired SCN of the hypothalamus, and downstream peripheral oscillators in the brain and other tissues (Lunn *et al.* 2017). The SCN synchronizes cellular oscillators or clocks in the brain and peripheral organs and tissues via humoral, endocrine, and neural signals. 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 (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 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. Some of the more obvious circadian rhythms include the sleep/wake and feeding/fasting cycles. 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 (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). Phase information transmitted from the SCN to the rest of the brain and body allows organisms to control circadian rhythms in behavior, physiology, endocrinology, and metabolism in anticipation of cyclic changes in their environment (Buhr and Takahashi 2013). In addition to the daily light-dark cycle, the time pattern of food intake is also recognized as an important non-photic zeitgeber for peripheral clocks and at times may become dominant (see Figure 1-1) (Haus and Smolensky 2013, Asher and Sassone-Corsi 2015).

1.1.1 Role of melatonin

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) and 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 (Chowdhury *et al.* 2008, Slominski *et al.* 2008). 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).

Melatonin-binding receptors. These include membrane receptors (MT1, MT2), cytosolic receptors (MT3) and nuclear receptors (RORα, RORα2, RZRα, RZRß) and 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 a vital 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, Reiter *et al.* 2014, Smolensky *et al.* 2015).

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) and brain and muscle aryl hydrocarbon receptor nuclear translocator [ARNT]-

like (BMAL1) (Ko and Takahashi 2006, Haus and Smolensky 2013). CLOCK 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. 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. This small number of core clock genes controls expression of thousands of genes (estimated at about 2% to 10% of the genome in mammals), including cell-cycle regulation, DNA damage response, and energy metabolism cycles (Haus and Smolensky 2013, Stevens *et al.* 2014, Panda 2016). 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.

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	*Clock*	CLOCK	Positive component of the feedback loop: CLOCK/BMAL1 complex initiates transcription of *Per, Cry*, *Rev-erbα*, and numerous other genes
Brain and muscle ARNT-like protein 1	*Bmal1*	BMAL	
Period	*Per1, 2, and 3*	PER1, 2, and 3	Negative component of the feedback loop: PER/CRY complex translocates to the nucleus and inhibits CLOCK:BMAL1
Cryptochrome	*Cry 1 and 2*	CRY1 and 2	
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	Postranslational 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

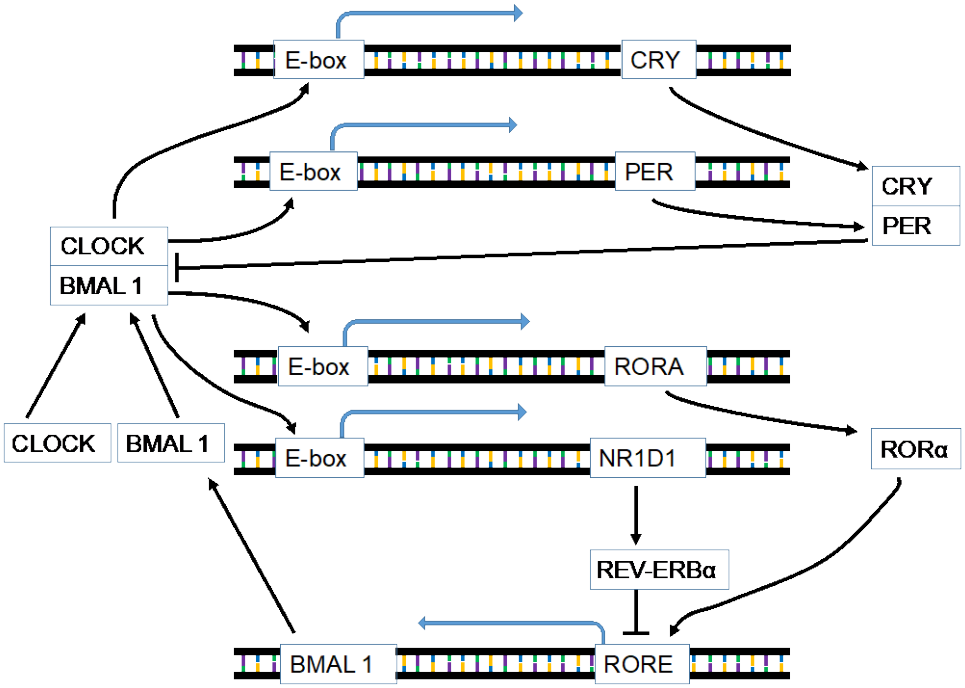

Figure 1-2. Core circadian machinery transcription-translation regulatory feedback loops

Adapted from Salavaty 2015.

1.1.3 Circadian disruption

Circadian disruption occurs when the daily circadian rhythms 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, persistent 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 affects the circadian system by changing the levels and timing of nighttime melatonin production and by inducing phase shifts (advances or delays). 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 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 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 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 (i.e., sanctioned by national or international standard-setting bodies) function characterizing the spectral sensitivity of the human circadian system is currently available, but circadian system spectral sensitivity functions and one mathematical model have been proposed (Gall and Bieske 2004, Rea *et al.* 2005, Andersen *et al.* 2012, Lucas *et al.* 2014).

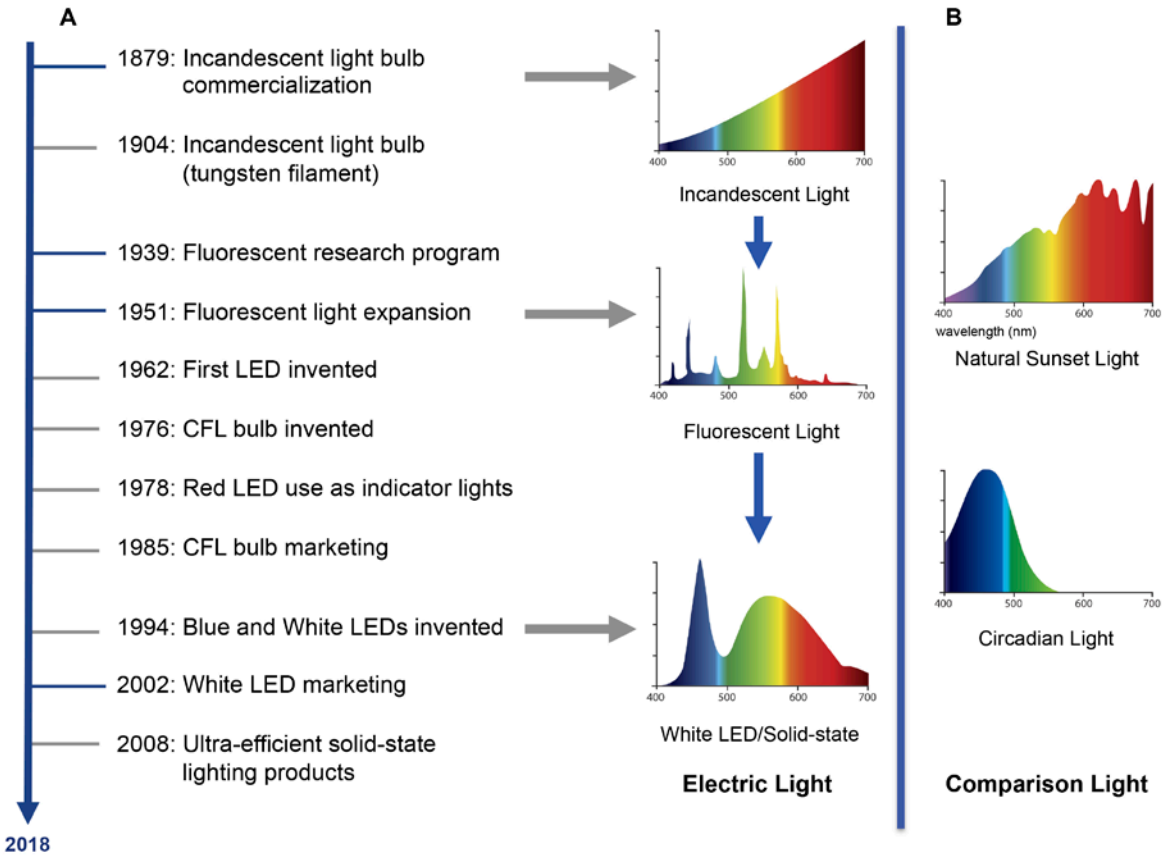

Figure 1-3. Technology advances in lighting over time have led to lighting with higher levels of short wavelengths

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 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, such as organic LEDs (OLEDs) and 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]NR = 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

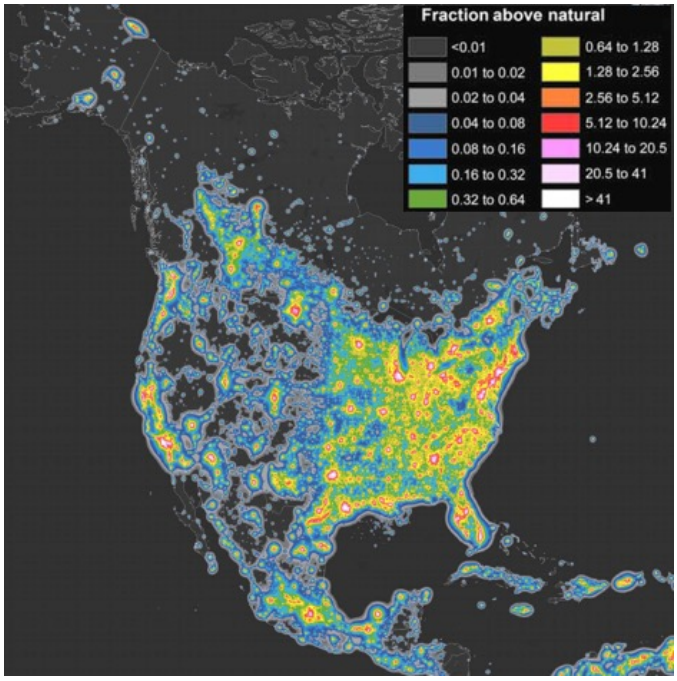

Figure 1-4. Map of North America's artificial sky brightness as a ratio to the natural sky brightness

Source: Falchi *et al.* 2016.

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."

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 daily and night hours (ILO 2004). 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) (IARC 2010). Table 1-3 summarizes general types of shift work and related shift scheduling criteria that have been applied or described in epidemiological studies (see Section 3).

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 (but can range from 6 hours to 12 hours)
Speed of rotation	Number of consecutive days worked before changing shift • Fast (e.g., change daily; change every 2, 3, or 4 days) • Intermediate (e.g., weekly change) • Slow (e.g., change 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 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).

Shift scheduling has steadily changed from weekly or bi-weekly slow-rotation systems to schedules with increased rotation speeds (e.g., change daily or every 2 or 3 days) as slower-rotating shift schedules can foster higher phase shifts and circadian disruption (Costa *et al.* 2010, Neil-Sztramko *et al.* 2014). 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.

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 (e.g., night, evening, or rotating). 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 (evening, night, or rotating shift, or some other schedule) 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).

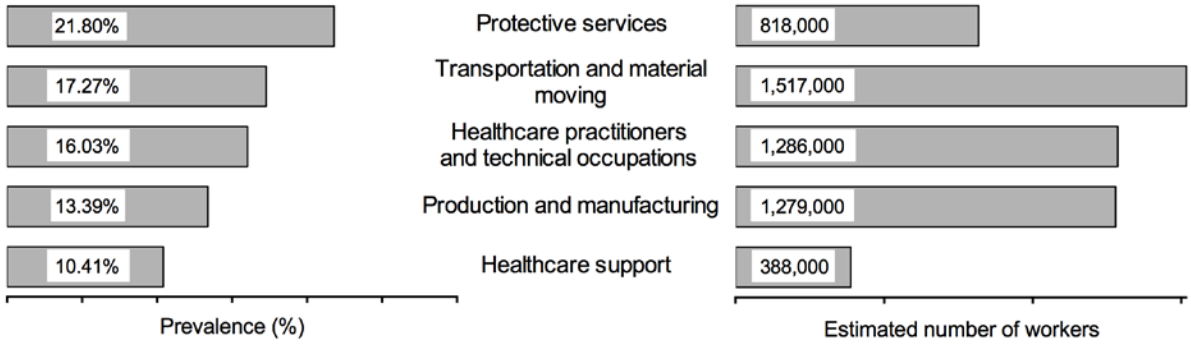

Figure 1-5. Prevalence and estimated numbers of U.S. workers who frequently work night shifts

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 exposures (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 dayworkers 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

Study population (N)	Measured personal light exposure[a] (lux[b, c])	Reference
U.S. non-rotating shift workers Medical device manufacturing facility (N = 32)	427[d]	Burch *et al.* 2005
Canadian rotating shift workers Telecommunications center (N = 10)	72.5[e]	Dumont *et al.* 2012
Canadian rotating shift nurses (N = 31)	7.02[f]	Grundy *et al.* 2009
Canadian rotating shift nurses (N = 123)	37.2[g]	Grundy *et al.* 2011
Spanish permanent night shift workers Various occupations (N = 72)	38[h]	Papantoniou *et al.* 2014

[a]Mean, unless noted otherwise.
[b]To approximate eye-level exposure, subjects in 3 studies (Grundy *et al.* 2009, Grundy *et al.* 2011, Dumont *et al.* 2012) wore light intensity loggers around their necks, and participants in Papantoniou *et al.* 2014 wore light intensity loggers at shoulder level. Subjects in Burch *et al.* 2005 wore light intensity loggers on their non-dominant wrist.
[c]Lux is a photometric unit that takes into account the sensitivity of the human visual system to different wavelengths; therefore, lux is not an ideal metric for the sensitivity of the human circadian system to different wavelengths.
[d]24-hour time-weighted average ambient light exposure for third shift (10:00 PM to 6:00 AM) workers.
[e]Median light exposure during night shift.
[f]Mean light intensity exposure from midnight to 5:00 AM (lumens/m^2) (1 lumen/m^2 = 1 lux)
[g]Maximum value on night shift from midnight to 5:00 AM.
[h]Median LAN exposure from midnight to 5:00 AM (interquartile range = 26) which was mostly generated from overhead fluorescent lamps; mean light exposures ranged from 15 to 246 lux.

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, 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 dayworkers 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 (NHS2) reported more physical activity than participants in the older cohort (NHS), and in both cohorts, activity levels in rotating workers were higher than in dayworkers. Neil-Sztramko *et al.* (2016) reported that although shift workers had less sedentary time than dayworkers, 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 (Rose *et al.* 1999) can produce

desynchronization between an individual's circadian rhythms and destination day-night cycles. 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 (BLS 2017b, a). The U.S. Department of Transportation reported that approximately 117 million total passengers traveled on transmeridian flights in 2017 [destinations to Europe [65 million], Far East [34 million], Middle East [10 million], Africa [2 million], 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 people could have been affected by transmeridian travel 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 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") (Rutters *et al.* 2014, McMahon *et al.* 2018, Uzoigwe and Sanchez Franco 2018). As discussed in Section 2.1.4, the sleep-wake cycle and the circadian system are linked with each other. Social jet lag symptoms are similar to jet lag symptoms except they are more chronic in nature. Over two-thirds of the general population could be affected by social jet lag (up to 2 hours shift between week days and weekends), and adolescents can have even higher social jet lag (≥ 2 hours) (see Table 1-5) (Roenneberg 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 1hour 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 via humoral, endocrine, and neural signals. Melatonin, a tryptophan derivative primarily synthesized in the pineal gland, serves as both an output and input factor to the circadian system and it regulates expression of circadian oscillator genes (i.e., core clock genes) in central and peripheral tissues. The core clock genes include *Clock*, *Bmal1*, *Per1, 2*, and *3*, and *Cry1* and *2*). These and a few other core clock genes control expression of thousands of

other genes, estimated to make up 2% to 10% of the genome 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 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 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

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 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, 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.

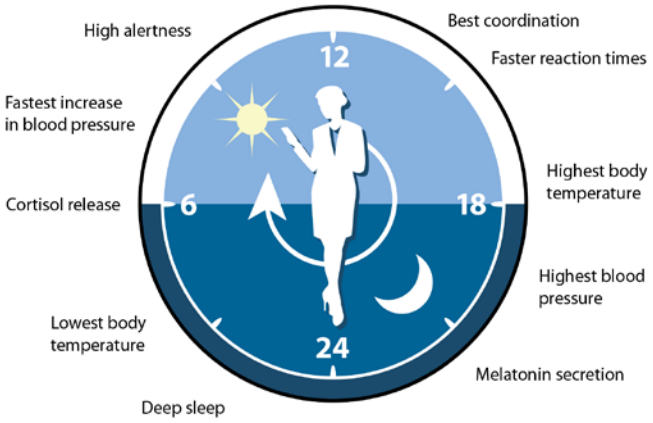

Figure 2-1. The circadian clock

Figure adapted from Nobel Prize 2017, with permission.

2.1.1 Melatonin

Melatonin is thought to be a main synchronizer between the master and peripheral clocks and regulates the sleep-wake cycle by chemically causing drowsiness and lowering the body temperature and is suppressed by LAN. Melatonin (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). 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).

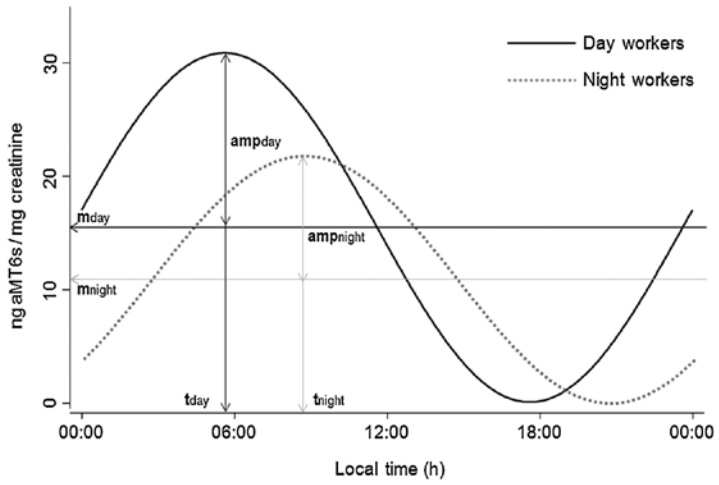

Figure 2-2. Cosinor modeling of melatonin metabolite (aMT6s) production over time for day and night workers

Source: Papantoniou *et al.* 2014

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. 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) (see Figure 2-2).

2.1.2 Clock 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).

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).

2.1.4 Sleep

Sleep is regulated by an interaction between (1) the homeostatic process, which corresponds to the rhythms of sleep pressure (sleep pressure 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 affects 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

Night time melatonin suppression can occur after exposure to light with wavelengths from 420 to 600 nm (Brainard *et al.* 2001); however, short-wavelength 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.

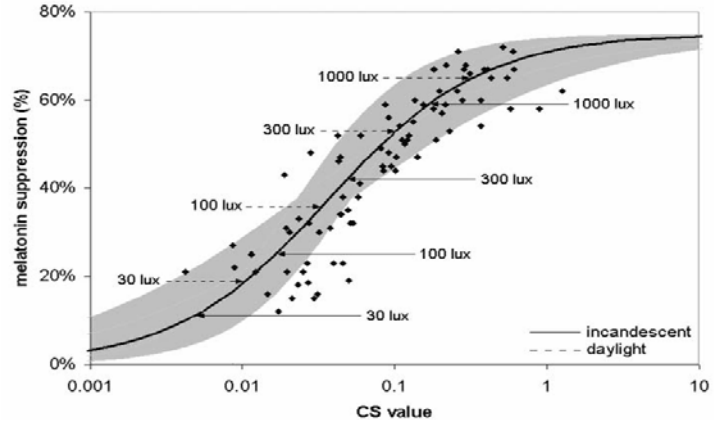

Figure 2-3. Human nocturnal melatonin suppression as a function of circadian light stimulus

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 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 (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 as 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 greatest circadian senstivity is for the youngest children. 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. Some studies suggest that morning types and evening types experience different light profiles; morning types may spend more time exposed to sunlight (bright light and less exposure to light in the evening than evening type); exposure to bright light during the day may increase the amplitude of the light:dark cycle (difference between daylight and night time 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, thus, without proper entrainment, these subjects will continue to advance their circadian phase progressively every day. When these subjects were exposed to light close to the DLMO, it produced a phase delay and may 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 as a stronger association between exposure to LAN was observed when subjects were exposed to electronics using blue light goggles (Figueiro *et al.* 2011, Wood *et al.* 2013), computer screens with short wave lengths (Green *et al.* 2017), and 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 day-time 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-back lit screen	LED vs. non-LED ↓ nighttime salivary melatonin
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 years	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	Self-luminous devices starting 3 hr prior to bedtime 1st night orange goggles (“dark”) – 2nd night: 1 hr orange googles + 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 each exposure	Melatonin measured at 3 time points

Study	Study design/population	Exposure	Results
		Light intensity: low (LI): vs. high (HI) Wave length: short (SWL) vs. Long Four conditions LI/SWL, HI/SLW, LI/LWL, HL/LSW	SWL: Greatest melatonin suppression irrespective of intensity
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 form 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 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 in 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

Study	Study design/population	Exposure	Results
			(mainly computers) 3 hr prior to bedtime ↓ exposure to blue light during the day
Wood *et al.* 2013	Random cross-over 13 volunteers Aged 18.9 ± 5.2 yr	1–2 hr exposure to tablets at night Highest brightness + blue light goggles + orange light goggles	Tablets vs. dark control ↓ 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; LED = light emitting diode.

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 levels were lower among participants who turned on lights during sleep interruption but not among participants with sleep interruptions without lights on or with other measures of bedroom light (e.g., light outside the bedroom, electronic or TV use (Hersh *et al.* 2015). Levallois *et al.* (2001) reported that nocturnal urinary melatonin levels were somewhat lower (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 may 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., they 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. 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) (Chen *et al.* 2005). A study in adult volunteers using lower doses and shorter duration of monochromatic light (12.1 μW/cm^2 for 460 nm and 10.05 μW/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 melatonin suppression is dose-dependent but that 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.* 2013a, 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 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.* 2013a, 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. Results varied by light source and intensity, tissues, species, and the specific genes or proteins studied.

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 24:0[a]	Proteins: CLOCK, BMAL1, CRY1 Skin	CLOCK, CRY1: no effect BMAL1: increased
Fonken *et al.* 2013a	Swiss Weber mice (M)	14:10 (150:0): C 14:10 (150:5)	*Genes: Clock, Bmal1, Per1, Per2,*	Hypothalamus/SCN

Reference	Species (Sex)	Light exposure day:night hr (day:night lux)	Endpoint Clock genes and proteins Tissue(s)	Results (gene/protein expression)
			Cry1, *Cry2*, *Rev-erbα*	*Clock*, *Bmal1*, *Cry1*, *Rev-erbα*: no effect
			Proteins: CLOCK, BMAL, PER1, PER2	*Per1*, *Per2*, *Cry2*: reduced CLOCK, BMAL: no effect PER1, PER2: reduced
			Hypothalamus/SCN, hippocampus, liver, fat	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 on clockwise or counterclockwise 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 working (or counterclockwise) 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 6 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.* 2016a). 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 nightshift 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 less readily adapted 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 nightwork (see Section 1).

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, studies that compared melatonin levels at multiple time periods, such as those using cosinor analysis of mesor (average levels), amplitude (fluctuation), acrophase (timing of peak melatonin production) in night shift vs. day shift workers, or studies comparing nighttime melatonin in night shift workers after night work to levels in day shift workers after night time sleep are the most 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 nightshift 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, 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.

- 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 urinary 6-sulphatoxymelatonin (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 among hospital workers who worked ≥ 3 consecutive nights compared to 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, 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 night time sleep after working days and during daytime sleep after working nights, but not in nighttime melatonin levels after working night shift or during night time 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%) ($P = 0.01$). 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 the 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 age 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	Convenience sample ages ≥ 19 yr, working ≥ 20 hr/week. 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 Night shift higher average light exposure than day off or day-shift work Small numbers of participants
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 Alterations in 17-β-estradiol levels but not clock gene expression Adjusted for potential confounders

Study Country (Year or years of exposure)	Population	Methods: Timing	Results	Comments
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 and 17-β-estradiol levels Adjusted for potential confounders
Burch *et al.* 2005 United States (2001–2002)	Medical device manufacturing unit; 171 workers 3 non-rotating shifts: Day, swing (2:00 PM–10:00 PM), and night (10:00 PM–6:00 AM)	UaMT6s (creatine 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 322 work days and 301 off day	Salivary melatonin 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	NSW vs. DWS ↓ 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)	Light measured using a light logger. On work days, LAN higher for NSW than DWS; light during 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

Study Country (Year or years of exposure)	Population	Methods: Timing	Results	Comments
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 versus 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 hours or during work time
Hansen 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
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

Study Country (Year or years of exposure)	Population	Methods: Timing	Results	Comments
Schernhammer *et al.* 2004 United States NHS (1989–1990); NHS2 (1996–1999)	Nurse's Health Study (NHS and NHS2) NHS: 633 controls from previous study of endogenous hormones and breast cancer risk (postmenopausal) NHS2: 113 randomly selected cancer-free participants (premenopausal)	NHS and NHS2 - plasma hormone samples available; spot morning urine sampled 7 to 9 days prior to expected next menstrual cycle NHS2: UaMT6s (creatinine adjusted) (repeated)	Shift work premenopausal: inverse association with increasing numbers of nights worked within 2 weeks of urine collection and urinary melatonin level	Same study population as cancer studies Repeat melatonin measure (3 samples per woman, 80 women): ICC = 0.72 Estradiol bioavailability: decreased with increasing quartiles of urinary melatonin (inverse association). Adjusted for potential confounders
Song *et al.* 2016 Korea (NR)	100 female nighttime 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 73 DSW (54 healthcare workers & 19 teachers)	UaMT6s Collected over a 24-hr period the 2nd day or 2nd night shift	NSW compared to DSW ↓ average UaMT6s (mesor) ↓ UaMT6s fluctuation (amplitude) Later time of peak UaMT6s (acrophase)	Forward rotating: 2 or 4 morning shifts, 2 afternoon shifts, 2 night shifts, 2 off days NSW also higher estradiol and progesterone levels than DSW
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)	Chronotype Differences in UaMT6s (mesor) between NSW and DSW were more pronounced among later chronotypes and among shift workers working ≥ 3 consecutive nights

Study Country (Year or years of exposure)	Population	Methods: Timing	Results	Comments
			Within participant comparison of rotating workers: Night vs. day shift ↓ average UaMT6s (mesor) Earlier time of peak UaMT6s (acrophase)	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** Greatest ↓ melatonin levels Greatest phase shift	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
Night shift vs. day shift in rotating night shift worker				
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	UaMT6s ↓ after night shift than day shift Salivary melatonin No alteration in timing of peak salivary melatonin	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

Study Country (Year or years of exposure)	Population	Methods: Timing	Results	Comments
		for those working 2nd consecutive day shift Salivary melatonin 4 samples over 24 hours	levels (peak still occurred at night regardless of shift) **Light intensity**: significant inverse relationship Salivary melatonin: all subjects combined UaMT6s levels: NSW Lower levels during day sleep and peak at night during work	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 Canada (2008–2009)	123 rotating nurses aged 30–65 yr); DD, NN, 5 days off Participated in the study twice (after night and day) in summer and winter 118 1st season; 96 2nd season	UaMT6s 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 hours	UaMT6s No differences between night and day shift ≥ 20 years shift work associated with increase in peak and possibly change in melatonin levels **Light intensity**: small inverse relationship Peak and change in melatonin levels and light observed in night work group	Same population sources as Grundy *et al.* 2009 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 years); 724 provided morning samples 354 currently rotating NSW Currently DSW	UaMT6s Morning samples for analysis of NSW Evening samples used for between subject variability	Current NSW vs. DSW Similar morning UaMT6s ↓ (P = 0.06) morning UaMT6s for working ≥ 8 night shifts/month in total and premenopausal women	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

Study Country (Year or years of exposure)	Population	Methods: Timing	Results	Comments
			↓ morning UaMT6s for working ≥ 10 hr/night Combined DSW and NSW No trend with duration, total hours, or cumulative number of night shifts	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
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

D = day; DSW = day shift workers; ICC = intraclass correlation coefficient. JEM = job exposure matrix; N = night; NSW = night shift workers; UaMT6s = Urinary 6-sulphatoxymelatonin.

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; thus, 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
Field studies				
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 years)	*BMAL1, CLOCK, CRY1, CRY2, PER1, PER2,* and *PER3*	↑ *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

Study	Population	Methods: Timing	Results	Comments
	92 current NSW and 92 current DSW All workers had previously worked rotating NSW	Blood morning after night work (average 7:15 AM) or before day work (average 8:30 AM)	Lifetime duration of night shift work among NSW but not DSW	*PER2* and *PER 3* down regulated in late vs. early morning 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

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, Wu *et al.* 2010, Wu *et al.* 2012). 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 that 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).

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)	12L:12D: 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)	12L:12D: 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)	12L:12D: 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)	12L:12D: 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)	12L:12D: 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
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)	12L:12D: 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

Reference	Species (Sex)	Exposure	Clock gene(s)/ proteins Tissue(s)	Results
Salgado-Delgado *et al.* 2010	Wistar rats (M)	12L:12D: 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)	12L:12D: C Simulated night work (active for 8 hr 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)	12L:12D: 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 hypothalamus 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, 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 their 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 and hormone expression patterns 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 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 also can cause circadian disruption. 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 human breast cancer evaluation in relation to these exposure scenarios are provided in Appendix A (literature search strings) and the Electric Light at Night protocol. 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 discussion of the key issues regarding each exposure scenario. Sections 3.2 through 3.4 assess the available epidemiologic literature for each exposure scenario in relation to breast cancer. Each section begins with a discussion of the key issues to be addressed in the evaluation for that exposure scenario.

Sections 3.3 through 3.5 include the following elements of the cancer hazard evaluation

- Description of the study methods and characteristics
- Evaluation of study quality
- Cancer hazard assessment: Synthesis of the evidence across studies

3.1 Overview of breast cancer epidemiology

Female breast cancer is the most common cancer in the United States, accounting for 15% of all new U.S. cancer cases. The age-adjusted annual breast cancer rates per 100,000 women in the United States from 2010 to 2014 (SEER 2018) were approximately 124.9 for incidence and 21.2 for mortality, with a five-year survival rate of 89.7%. 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. The length of time between biological initiation and diagnosis of breast cancer (latency) was recently estimated to be approximately 16.3 years (Nadler and Zurbenko 2014). 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).

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 induces terminal differentiation of many cells, thereby reducing the number of stem cells at risk for malignant transformation (Institute of Medicine 2012). Early-onset breast cancer is more likely to be associated with increased familial risk, low body mass, early age at menarche, heavy alcohol consumption, high intake of red meat, low physical activity, low intake of fruits and vegetables, recent oral contraceptive use, early childbearing, and multiparity (Althuis *et al.* 2003, Cho *et al.* 2006, Harris *et al.* 2017). Breast cancer arising in women under the age of 35 is characterized by a more aggressive phenotype and a higher percentage of ER-negative or PR-negative tumors, higher rates of Her2/neu over-expression, and a trend toward shorter disease-free survival; age at diagnosis is a powerful independent predictor of recurrence risk and survival (Anders *et al.* 2008, Anders *et al.* 2009).

3.2 Night shift work

None of the shift-work studies measured circadian disruption directly; however, persistent exposures to night shift work — such as frequent, long-term, or timing of exposure to light at night during susceptible hormonal stages (e.g., at a younger age) — are likely to be the best surrogates for night work related to circadian disruption. In general, the adequacy of the 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 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 nine 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, especially of exposure, and lack of control for potential confounders (Datta *et al.* 2014). Studies are listed in the 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 chronologically) 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 identical. 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	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, frequency, 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.* 2006)	**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	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	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	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 NHS Central Registers invasive breast cancer incidence or death	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	Questionnaire Metrics: current work at night; usually or always Night work: midnight–6:00 AM 3.6% current night work
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	Questionnaire 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

Reference	Population	Outcome and sources(s)	Exposure assessment and information
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	Company records, 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 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	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 questionnaire, 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
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/week held in 1960 and 1970 Metrics: ever worked in occupation-industry combo. with 70% shift workers or worked in occupational-industry combo. with ≤ 30% shift workers 0.06% exposed

Reference	Population	Outcome and sources(s)	Exposure assessment and information
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.

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).

Enrollment into the studies spanned four decades starting in 1961 (Tynes *et al.* 1996, Schwartzbaum *et al.* 2007) and ending in 2012 (Vistisen *et al.* 2017), decades during which typical shift-work schedules changed considerably (see Section 1). The proportion of women exposed to night work in these populations also varied considerably, from 0.06% (Schwartzbaum *et al.* 2007) to 67% of women ever working nights (Li *et al.* 2015). Those studies with the highest proportion of night workers were studies of nurses (Wegrzyn *et al.* 2017) and other occupational cohorts (Tynes *et al.* 1996, Pronk *et al.* 2010, Li *et al.* 2015).

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 or left-truncation bias. In general, 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 the oldest cohorts including primarily postmenopausal women (Pronk *et al.* 2010, Travis *et al.* 2016, Wegrzyn *et al.* 2017 NHS, Jørgensen *et al.* 2017) and the youngest cohorts including primarily premenopausal women (Tynes *et al.* 1996, Knutsson *et al.* 2013, Koppes *et al.* 2014, Vistisen *et al.* 2017, Wegrzyn *et al.* 2017, (NHS2). 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.

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 most persistent exposures and those with weaker exposures. 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 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 four studies did not specify which hours in the night were worked (Koppes *et al.* 2014, 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 the 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 were 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 to be 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 were able to report 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). 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 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. The definition of the unexposed "day workers" used by Vistisen *et al.* (2017) (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, frequency, 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 frequency of night work (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 confounding bias resulting from inadequate inclusion of potential confounding factors 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 was 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 were not considered in the NHS and NHS2 studies of nurses (Wegrzyn *et al.* 2017); such effects could bias the effect away from the null if large numbers of nurses were exposed to 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. While most studies included family history, BMI, and age at menarche, inclusion of these variables in the final models when unrelated to exposure resulted in a lower rating for confounding methods. 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 frequency) (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. Two cohort studies had moderate utility for the evaluation (Knutsson *et al.* 2013, Li *et al.* 2015). 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	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility
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 about bias and for study quality rating: Equal column width for types of bias does not imply that they have equal weight: Scoring system: +++ = 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: Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low 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-controls 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 cases 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	Questionnaire, all jobs held ≥ 6 mo (≥ 12 mo in Spain). Metrics: ever/never, duration of night work, night shift length, no. shifts/week, no. night hours/week, 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

Reference	Population	Breast cancer incidence source(s)	Exposure assessment and information
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	Questionnaire, all jobs held ≥ 1 yr Metrics: ever/never, frequency, duration, rotating, permanent night work Night shift: ≥ 1 year, midnight–6:00 AM for ≥ 3/mo (overnight, late evening [ending after midnight] and early morning [starting before 6:00 AM]). 13.3% ever nights; 5.9% ≥ 15 yr
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	Questionnaire, ever worked nights ≥ 6 mo ≥ 1/wk Metrics: ever/never; night work + sleep duration + daytime napping Night shift: ≥ 6 mo ≥ 1/wk, midnight–6:00 AM 37.6% ever nights
Fritschi *et al.* 2013, Fritschi *et al.* 2017	**BCEES study** Population-based Enrolled 2009–2011 30% premenopausal 1,202 cases 1,785 controls	Western Australia Cancer Registry	Mailed questionnaire, 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	Questionnaire, all jobs ≥ 6 mo Metrics: duration, % evenings/nights (20%, 40%, 60%, 80%, 100%), 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	Questionnaire, 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

Reference	Population	Breast cancer incidence source(s)	Exposure assessment and information
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	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
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	Questionnaire, 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	Questionnaire, 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

Reference	Population	Breast cancer incidence source(s)	Exposure assessment and information
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	Questionnaire, 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
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	Questionnaire, 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 the most persistent exposures and those with weaker exposures. 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 to be 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 of 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 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 in order to classify those with the most persistent exposures (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, 2017) 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.* (2017) 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 senstivity 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 exposed cases were included, and multiple levels of various exposure metrics across night workers enabled better differentiation of those with persistent exposure.

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 exposure to 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	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility
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 about bias and for study quality rating: Equal column width for types of bias does not imply that they have equal weight: Scoring system: +++ = 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: Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low 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 level of 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?

Moderate to strong evidence: Elevated risk estimates of "persistent exposure" found for several analyses of different exposure metrics, exposure-response relationships, or effect modification reported 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 "persistent exposure" 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.

Eight 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, Yuan *et al.* 2018), as well as a qualitative review of seven of these (Pahwa *et al.* 2018). Four of the five 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; three of four 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). 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.

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 exposure to 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 exposure to night work — that is, exposure proxies for shift work related to circadian disruption, including 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 and 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

Citatio	Ever/never	Duration n	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.

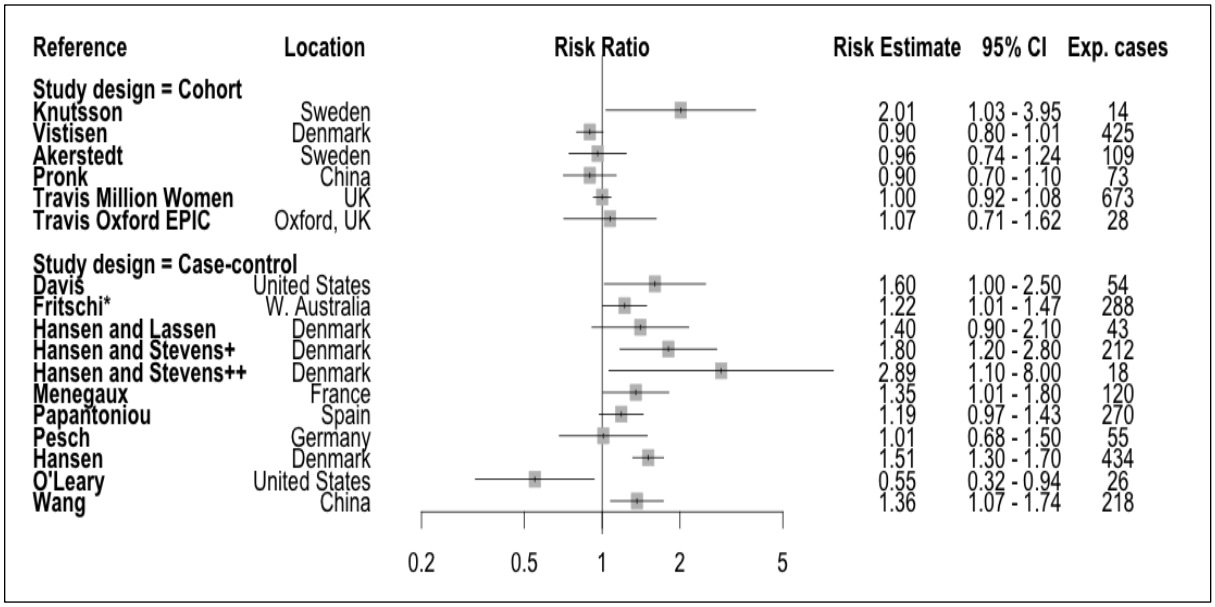

Figure 3-1. Breast cancer risk by "ever night work" by study design

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.

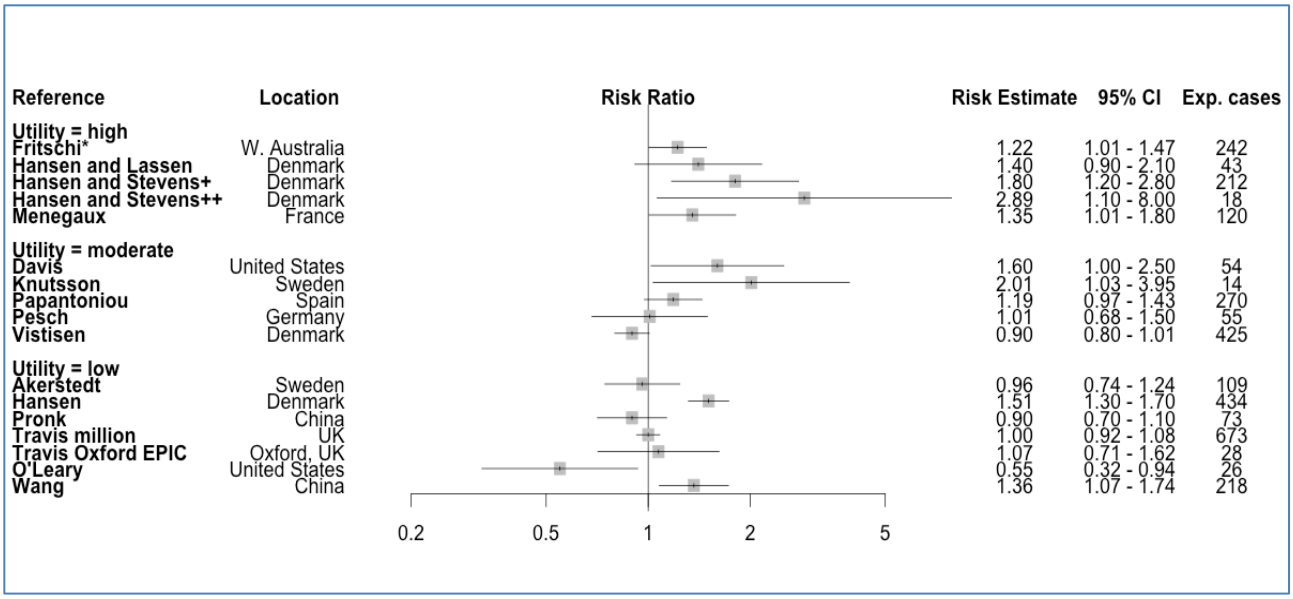

Figure 3-2. Breast cancer risk by "ever night work" by study utility

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, respectively. 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).

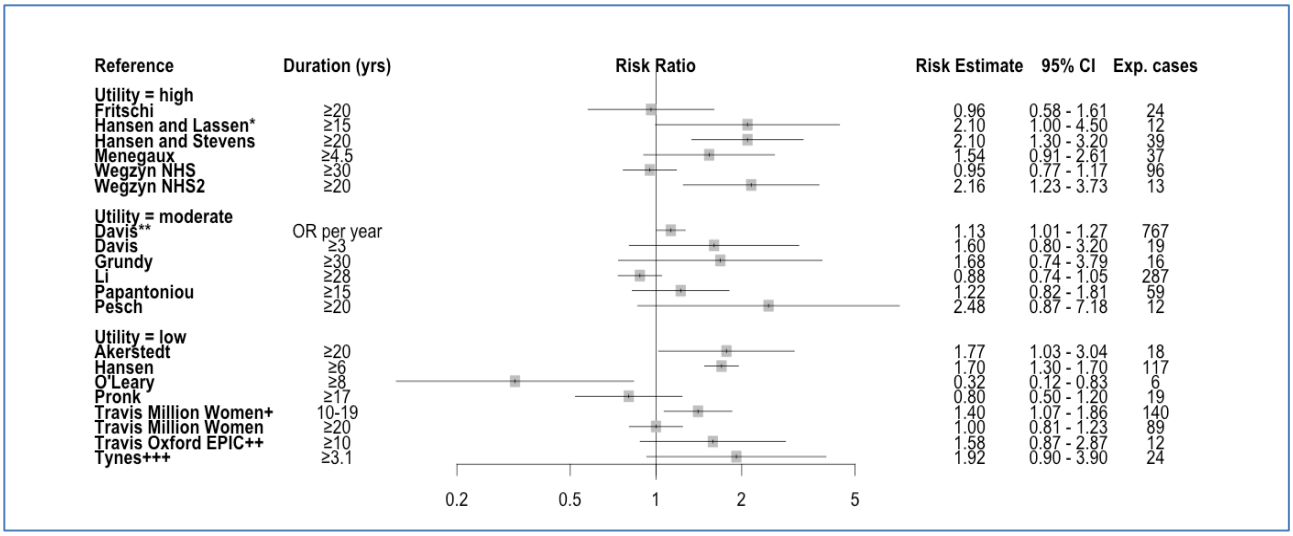

Figure 3-3. Breast cancer risk by longest reported duration of night work by study utility

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 were reported of 77% 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 of night work

Results from nine high- and moderate-utility studies suggested that breast cancer risk was associated with high frequency or intensity of night work, regardless of duration. Frequency of night work in these studies was defined in two ways: as the cumulative number of night shifts or day-night rotations (Pesch *et al.* 2010, Pronk *et al.* 2010, Lie *et al.* 2011, Hansen and Lassen

2012, Hansen and Stevens 2012, Li *et al.* 2015, Papantoniou *et al.* 2015a) and as the minimum average number of nights or hours per week or month (Davis *et al.* 2001b, Pronk *et al.* 2010, Lie *et al.* 2011, Menegaux *et al.* 2013). Two studies (Pronk *et al.* 2010, Lie *et al.* 2011) reported estimates for both the minimum average number of nights and the cumulative number of night shifts (Figure 3-4); Papantoniou reported both overall cumulative number of night shifts as well as the number of cumulative night shifts among permanent night workers.

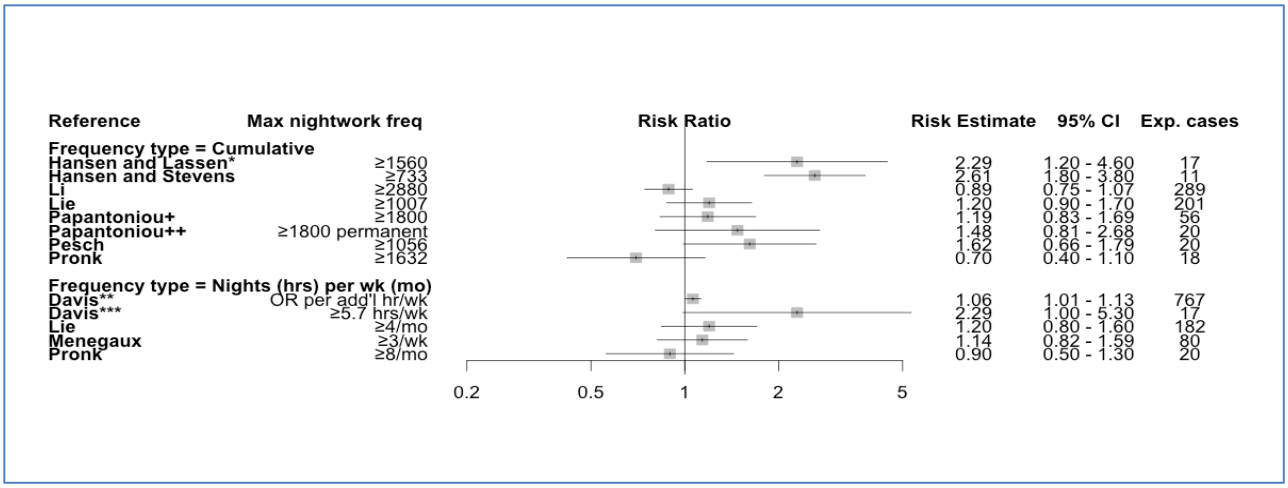

Figure 3-4. Breast cancer risk by maximum frequency per unit time or maximum cumulative night shifts

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 cumulative number of all night shifts.
++Refers to cumulative number of permanent night shifts only.

Among the six high- or moderate-utility studies reporting on the cumulative 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). Pesch *et al.* reported a non-significant 61% excess risk among those with the highest frequency of night work, and estimates reported by Lie *et al.* and Papantonoiou *et al.* were close to unity. Null results were reported from the Li *et al.* study which had the highest cumulative number of shifts. Pronk *et al.* (2010), a low-utility study, found no association between frequency of night work and breast cancer risk, nor any other metric of circadian disruption.

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 reported the highest intensity (≥ 3 nights per week) with an excess non-statistically significant risk of 14%. Lie *et al.* reported a non-significant elevated risk of 20% for working ≥ 4 nights/month.

Combined measures of duration and frequency

Four high- or moderate-utility studies reported measures of frequency explicitly combined with long duration of shift work (Lie *et al.* 2011, Hansen and Lassen 2012, Grundy *et al.* 2013a, Menegaux *et al.* 2013) (Figure 3-5). Hansen and Lassen reported a statistically significant doubling of risk for women with at least three night shifts per week for at least 6 years (P_{trend} = 0.02). Menegaux *et al.* (2013) reported an association with breast cancer (OR = 2.0, 95% CI = 1.26 to 3.45) for the lowest frequency category (< 3 nights per week) combined with the longest work duration category (≥ 4.5 years) but not for the highest frequency category (≥ 3 nights per week) combined with the longest duration category (≥ 4.5 years). Lie *et al.* (2011) found elevated risks of breast cancer among nurses working 5 to 7 consecutive night shifts for at least 5 years. Grundy *et al.* (2013a) reported doubled risks for 100% evenings or nights combined for durations of 15 to 30 years and at least 30 years, however, only estimates of 50% or 80% evening/nights for at least 30 years were statistically significant (Figure 3-5).

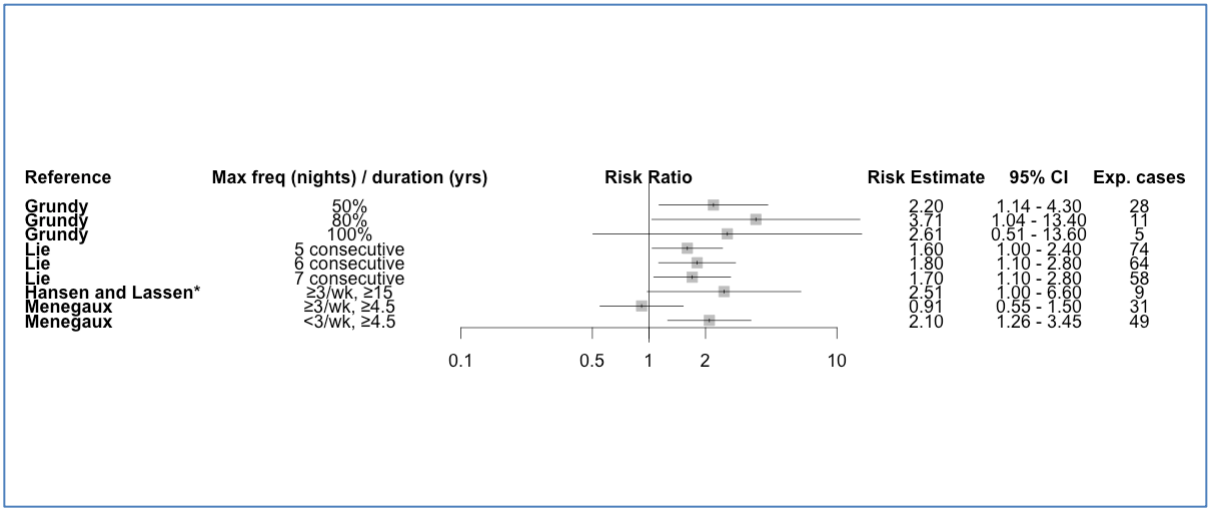

Figure 3-5. Breast cancer risk by maximum frequency of night work and duration

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 — 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 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 (NHS). 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/week &	
≥ 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 hour 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/week 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 hour shift	0.90 (0.55–1.48)
		≤ 2 yr[c]	1.58 (0.68–3.64)

[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 work 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), and no association 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: Receptor status

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).

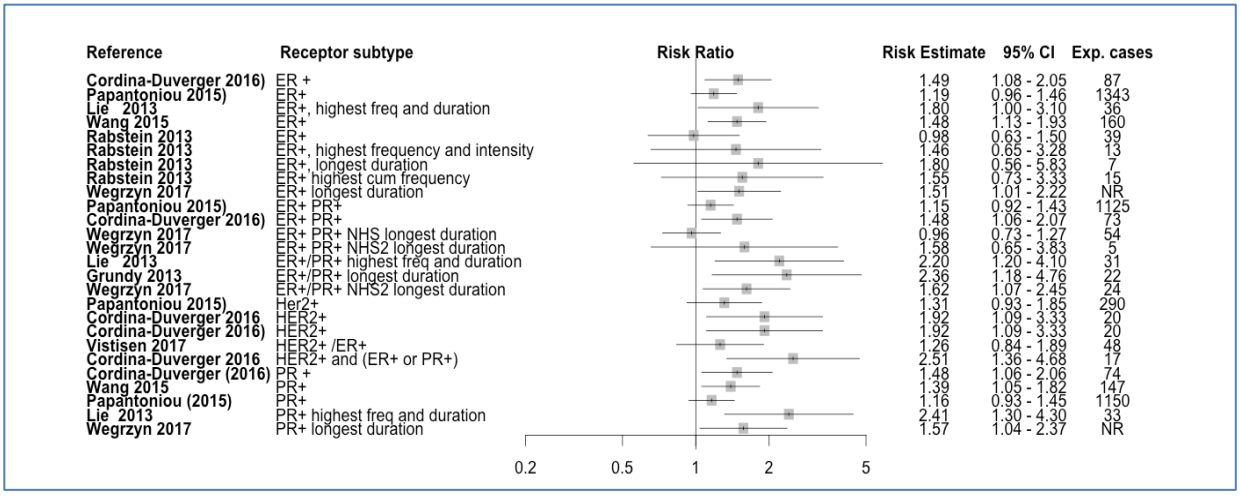

Figure 3-6. Risk of receptor-positive breast cancer and night work, all women

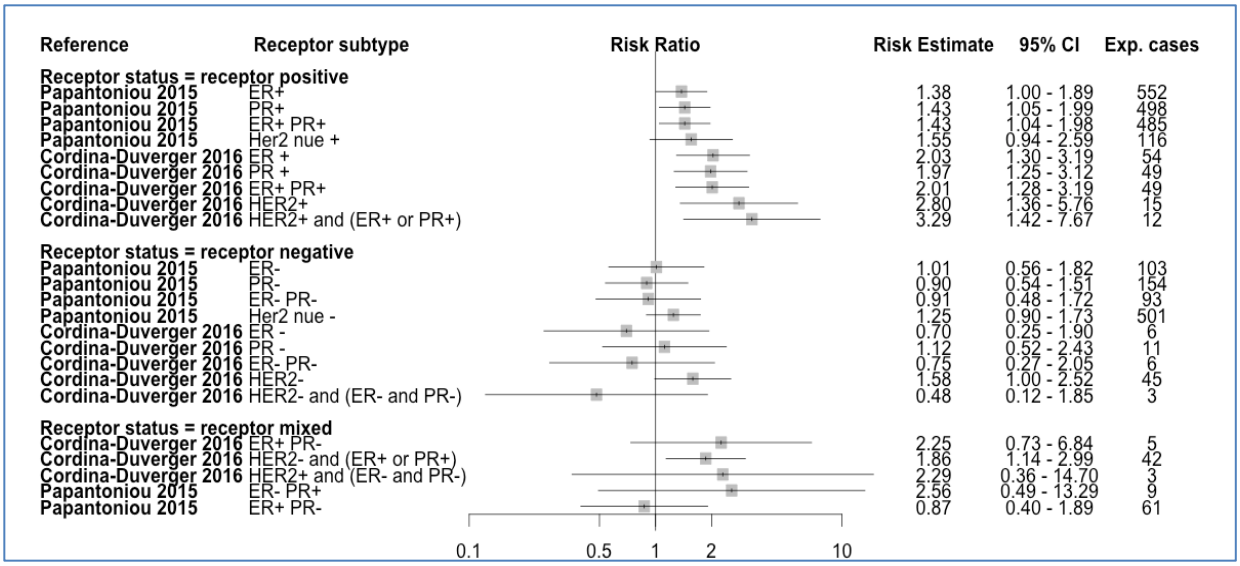

Figure 3-7. Risk of breast-cancer and night work by receptor subtypes, premenopausal women

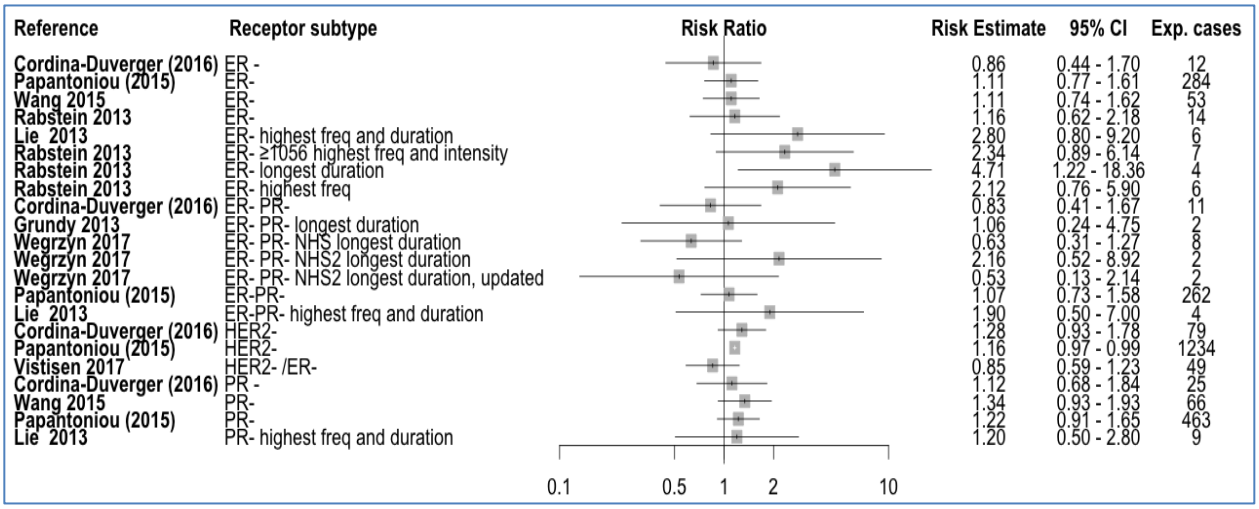

Figure 3-8. Risk of receptor-negative breast cancer subtypes and night work, all women

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

Seven studies included nurses and health professionals exclusively (Lie *et al.* 2011, Hansen and Stevens 2012, Vistisen *et al.* 2017, Wegrzyn *et al.* 2017) or as an analytic subpopulation (Grundy *et al.* 2013a, Travis *et al.* 2016 Million Women Cohort). However, 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. Some of the strongest findings were reported in studies of nurses, who may be exposed to various workplace carcinogens, which left uncontrolled would bias findings away from the null. No study of nurses took co-exposures into account. However, not all studies of nurses or health professionals found evidence for an association, and elevated risks were reported in several general populations of women.

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, however, 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. 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. However, recall bias, although not a likely explanation for these results, cannot be completely ruled out.

Elevated risks due to confounding by factors related to both breast cancer and night work should be considered as an explanation for the findings. 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), and socioeconomic backgrounds, factors related to breast cancer risk. Overall, most studies controlled for all such risk factors, and adjustments made no material difference in any of the studies reporting both crude and adjusted estimates.

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	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

Reference	Population	Breast cancer incidence sources	Exposure information and assessment
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	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	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	Outdoor LAN, satellite imagery data, DMSP-OLS Metrics: low (0–20 nW·sr−1/cm2) medium (21–41 nW·sr−1/cm2 high (> 41 nW·sr−1/cm2) 59.7% with high LAN levels LAN range = 0 to 63 nW·sr−1/cm2
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 questionnaire 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

Reference	Population	Breast cancer incidence sources	Exposure information and assessment
Johns *et al.* 2018	**Generations Study UK** 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 and sleep patterns 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, 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, 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 artificial LAN 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, 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
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

Reference	Population	Breast cancer incidence sources	Exposure information and assessment
Kloog *et al.* 2011	**Northern Israel** Population 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** 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, telephone 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; EBCLIS = Electromagnetic Fields and Breast Cancer on Long Island Study; LAN = light at night: MCC = Multi Center Case-Control-Study, Spain.

Four studies of LAN focused on outdoor LAN: two cohort studies (Hurley *et al.* 2014, James *et al.* 2017), one case-control study (Garcia-Saenz *et al.* 2018), and one case-referent study (Bauer *et al.* 2013). Ten studies (two cohort studies and eight case-control studies) focused on indoor LAN, specifically LAN in the sleeping area; two of these reported on both indoor and outdoor LAN (Hurley *et al.* 2014, 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). A small pilot case-control study of sleep in darkness and breast cancer risk in India was not included in the evaluation because of inadequate reporting to assess the quality of the exposure assessment and other study elements and lack of consideration of potential confounders (Datta *et al.* 2014).

3.3.2 Study quality evaluation

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) studies 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 may be minimal. Being far from urban centers, these counties may 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 some attrition bias; however, the authors adjusted for individual and area-based socioeconomic status to take into account, in part, a potential bias from differential participation among cases and controls.

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., LAN that causes circadian disruption), and second, how precisely the proxy was measured. Outdoor LAN measurements derived from satellite imagery data from the U.S. Defense Meteorological Satellite Program (DMSP; NOAA 2015) were used in three of the four studies. Whether satellite imagery data is an appropriate surrogate for exposure to light that causes circadian disruption remains a question. (See Section 2 for studies on melatonin suppression.)

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 may 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 of 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 [SD] = 14). In addition, the range of exposure levels was attenuated by the 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.

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 may 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 may 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.

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 high utility; however, among these, the Garcia-Saenz study had the highest rating for exposure assessment based on the application of the MSI index. Bauer *et al.* (2013) had low overall utility.

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

Citation	Selection	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility
Outdoor LAN								
Garcia-Saenz *et al.* 2018	++	+++	+++	+++	+++	+++	++	+++
James *et al.* 2017	+++	++	+++	++	+++	+++	++	+++
Hurley *et al.* 2014 (Outdoor)	+++	++	+++	++	+++	+++	+	+++
Bauer *et al.* 2013	+	+	+++	+	+++	+++	+	+
Indoor LAN								
Garcia-Saenz *et al.* 2018	++	++	+++	+++	+++	+++	++	++
Johns *et al.* 2018	+++	+	+++	++	+++	+++	+	+
White *et al.* 2017	+++	+	++	+++	+++	+++	+	+
Keshet-Sitton *et al.* 2016	+	++	+	++	+++	++	++	++
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 about bias and for study quality rating: Equal column width for types of bias does not imply that they have equal weight: Scoring system: +++ = 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: Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low utility; + = low utility; 0 = inadequate utility.

Indoor LAN studies

Selection

The Keshet-Sitton *et al.* (2016) study raised serious concerns about selection bias. The case and control subjects may not have been selected from the same population, as the control subjects were friends 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. Attrition in the case-control studies (O'Leary *et al.* 2006, Kloog *et al.* 2011, Fritschi *et al.* 2013, Garcia-Saenz *et al.* 2018) may also have introduced moderate selection bias.

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 which 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 among individuals with high and low exposure would be available for each analysis. 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, what was considered to be a "high" subjective level may have varied among 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 may have been low. Recall bias may 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

Based on the questions asked, the level of light exposure in the sleeping area was generally quite low, and the information presented in the studies made it difficult to assess whether light levels and type of LAN were sufficient to suppress melatonin. Furthermore, very few women reported exposure to high levels of LAN. In most studies, little information was available to capture variation in exposure, such as the length of time lights were on when the women were awake or asleep (with eyes closed), actual light levels, or type of LAN. 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 four 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 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 (Table 3-10).

Outdoor environmental LAN

Overall, all four studies of outdoor environmental LAN suggested that outdoor LAN modestly increased the risk of breast cancer. The three high-utility studies (Hurley *et al.* 2014, James *et al.* 2017, Garcia-Saenz *et al.* 2018) provided moderate to strong evidence of an effect, and the one low-utility study (Bauer *et al.* 2013) provided some evidence of an effect. The primary sources of heterogeneity were the exposure assessment methods used. In addition, potential selection and confounding biases were likely in Bauer *et al.* (2013).

The four studies reported statistically significant excess risks of breast cancer among women in the highest LAN exposure category (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 top 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). Hurley *et al.* (2014) found that the excess risk of LAN exposure was confined to premenopausal women with BMI under 25 kg/m^2 (HR = 1.56, 95% CI = 1.16 to 2.08; P_{trend} = 0.02), although the interaction between menopausal status and BMI was not statistically significant.

In the NHS2 study by James *et al.* (2017), the relationship between LAN and breast cancer was stronger in shift workers (HR = 1.09; 95% CI = 1.01 to 1.18 per interquartile range [IQR] increase) than the total population (HR = 1.06, 95% CI = 1.00 to 1.13 per IQR increase) and attenuated in the overall population when shift workers were removed (HR = 1.03, 95% CI = 0.97 to 1.09 per IQR increase). The effect modification, however, was not statistically significant. Similarly, the main analysis of the population studied by Garcia-Saenz *et al.* (2018) did not include shift workers; however, when they were included in sensitivity analysis, the risk of breast cancer in the highest exposure category was reduced to OR = 1.29 (95% CI = 0.91 to 1.83) and no longer statistically significant.

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 *et al.* (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.

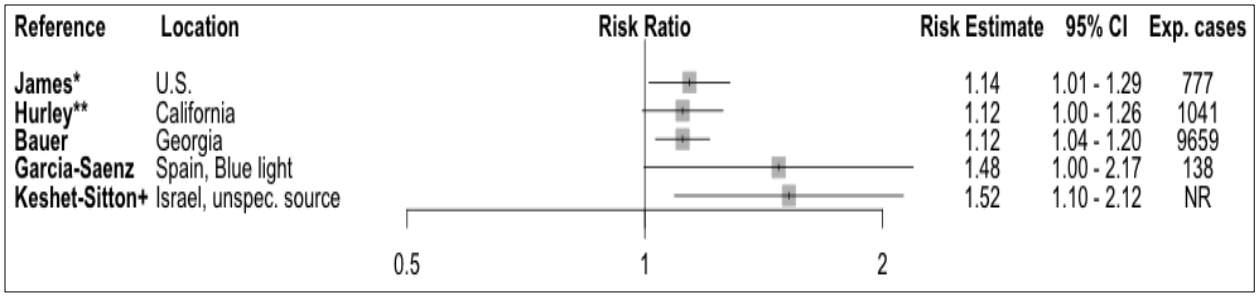

Figure 3-9. Risk of breast cancer and light at night (LAN)

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

Indoor LAN

Overall, there was weak evidence of increased breast cancer risk among women with the highest exposure to LAN in the sleeping area. Of the indoor LAN studies, three of the five studies with moderate utility provided evidence (moderate to strong or some evidence) of an association; and two of the five low utility studies provided evidence or 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[c] sig						
Light from the outside (~< 1 lux)			≤ 1	≤ 1[f] sig			≤ 1	1.2 ns		
Resides near strong outside ambient LAN				1.52 sig						
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, three found evidence or some evidence of breast cancer being associated with the highest self-reported ambient light level (40% statistically significant excess risk; Davis *et al.* 2001b), subjective light level (22% statistically significant excess risk [Kloog *et al.* 2011]), or living near a strong source of artificial LAN (52% excess risk; Keshet-Sitton *et al.* 2016). In addition, a significant 70% excess risk of breast cancer was associated with frequent non-peak sleep (Davis *et al.* 2001b). 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.

Among the low-utility studies, one study indicated evidence of an effect (O'Leary *et al.* 2006), and reported 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. Some evidence was reported by Fritschi *et al.* (2013), who 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. 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. The results from the Li *et al.* (2010) study were inconclusive.

Key issues

The major predictor of heterogeneity across indoor LAN studies was the varied metrics used to measure indoor LAN, making it difficult to compare studies. It also is not known whether the low light exposure levels and the light spectra used in the sleeping areas in indoor studies were sufficient to disrupt circadian rhythms. However, for both outdoor and indoor LAN, the question of whether the measured proxies were actually measuring exposure to light that causes circadian disruption remains unanswered. Casting further doubt on the relevance of light levels estimated from satellite imagery alone, Rea *et al.* (2011) found no correlation between satellite imagery output and light at the level of the bedroom window or outdoor light and personal exposure measured with a Daysimeter (Rea *et al.* 2008). 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 LAN may directly contribute to breast cancer risk. To understand the association between LAN and breast cancer, additional studies measuring not only the intensities but the spectral characteristics of indoor and outdoor LAN would be helpful.

Chance, bias, or confounding

Alternative explanations for the evidence in the outdoor LAN studies cannot be completely ruled out. Errors in processing satellite data may have affected the results, but the fact that all four studies found an elevated risk argues against this possibility.

James *et al.* (2017) adjusted for air pollution and population density, but other factors related to both breast cancer and LAN (Rybnikova *et al.* 2015) could potentially explain the observed association.

Alternative explanations for the evidence found in the indoor LAN studies could not be ruled out, either. Given the imprecision of many of the exposure metrics, chance or misclassification bias are plausible explanations for these results. Furthermore, none of these studies considered LAN during the evening. In addition, the many different metrics used across studies were not examined in relation to one another, limiting interpretation of how they relate to one another. Although some studies asked about shades or curtains to block light from outside, none presented the 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	Same as Schubauer-Berigan *et al.* 2015 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	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

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 passing ≥ 6 time zones Exposed: 100+ flights passing ≥ 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 Study quality : Transmeridian travel

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	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility
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 about bias and for study quality rating: Equal column width for types of bias does not imply that they have equal weight: Scoring system: +++ = 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: Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low 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). 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 (total time from flight departure to arrival, including time on the ground) 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. 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 the two circadian rhythm disruption metrics that were robust to multiple model assumptions. In addition, a non-statistically significant positive trend was observed for hours spent traveling during the standard sleep interval among women who first gave birth between age 25 and 29. The high correlation among exposure metrics made it impossible to assess whether radiation and circadian disruption were independently associated with breast cancer. The authors suggested that because the findings for absorbed doses of cosmic radiation among high-parity women were unexpected, the results in this subgroup were likely due to circadian disruption. 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 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 and 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 may 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 preliminary 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 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 inadequate to evaluate the roles of LAN, sleep disturbances, or other factors in breast cancer carcinogenicity. In general, lifestyle behaviors 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.

There is limited evidence for the carcinogenicity of LAN from studies in humans. Consistent evidence of an increased risk of breast cancer from living in areas with high exposure to LAN as measured using satellite imagery data is evident in the four epidemiologic studies, including one study which was able to measure circadian-effective light. 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.

The database was inadequate to evaluate breast carcinogenicity of LAN exposure in the bedroom or sleeping areas. The studies 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 for specific metrics of LAN and an increased breast cancer risk, overall, the evidence across studies was inconsistent.

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), and female hormonal cancers (i.e., ovarian and endometrial, 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., LAN, transmeridian travel, geographical coordinates) (Section 4.6).

Twenty-five (25) 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-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 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” exposures 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 subtype and gender for colorectal cancer.

4.1 Prostate cancer

Prostate cancer is the third most common cancer in the United States, representing almost 10% of all incident cancers. Approximately 161,360 incident prostate cancer cases and 26,730 prostate cancer deaths have been predicted for 2017 in the United States (Howlader *et al.* 2017). Prostate cancer has a high survival rate, with 98.5% of men living past five years from diagnosis.

As prostate cancer is not immediately fatal, the use of mortality data in studies will 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). A study by Yong *et al.* (2014a) 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, 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 Prospective Cohort Study** 1988–1990 (enrollment) 14,052 working men (population based)	Incidence 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 4,995 working men (specific manufacturing corporation)	Incident prostate cancer Health insurance records	Company records *Night work;* continuous counter-clockwise 3-shift rotation system *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)	Fatal prostate cancer Underlying cause of death Personal inquiries and verification using death	Mailed questionnaire *Night work:* not defined for rotating shifts, fixed night started work from 9:00 PM–midnight

Reference	Population	Outcome and source(s)	Exposure assessment and information
	305,057 employed men (population based)	certificates/national registry	*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)	Incidence prostate cancer; type of cancer Rhineland-Palatinate Cancer Registry	Company records *Night work:* forward rotating system: one 12-hour shift (6:00 AM–6:00 PM), 24 hours off, 12-hour (6:00 PM–6:00 AM), and another 48 hours 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	Mailed 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 stud**y 2000–2011 (enrollment and follow-up period) 1,757 men residing in highly-industrial 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
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	Mailed questionnaire *Night work*: rotating full-time (not defined) *Metrics:* ever worked, duration, age at first shift work, and years since full-time rotating shiftwork

Reference	Population	Outcome and source(s)	Exposure assessment and information
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 Quebec Tumor Registry	In-person questionnaire *Night work*: included work between 1:00 AM–2:00 AM for ≥ 6 months *Metrics:* Ever, cumulative duration, and night work ≤ 20 years or ≥ 20 years 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/month *Metrics*: Ever worked shifts (≥ 1 year), type of shift, 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 year)
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 hours or 3 nights/month for > 1 year *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

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 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 except for overall study utility and study findings 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	Exposure	Outcome	Confounding methods	Adequacy of analysis	Selective reporting	Sensitivity	Utility
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 quality rating: Scoring system: +++ = 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. Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low 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% 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 weaker 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 or 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 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% and 11.6%, respectively, for day and 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-analyses approach informative and thus did not include its own meta-analyses and nor 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 does not include 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 lifetime shifts 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 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 for studies of night work and prostate cancer

Study utility or informativeness	Level of evidence	Cohort studies	Case-control studies
Moderate or high: 5 studies	Moderate to strong evidence: 3 studies	Behrens *et al.* 2017	Papantoniou *et al.* 2015b Parent *et al.* 2012
	Some evidence: 2 studies		Conlon *et al.* 2007 Wendeu-Foyet *et al.* 2018
Low[a]: 5 studies	Some evidence: 2 studies	Kubo *et al.* 2006	Tse *et al.* 2017
	Null evidence: 2 studies	Hammer *et al.* 2015 Åkerstedt *et al.* 2017	
	Inconclusive: 1 study	Kubo *et al.* 2011	

[a]Mainly due to low sensitivity or bias towards the null.

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.

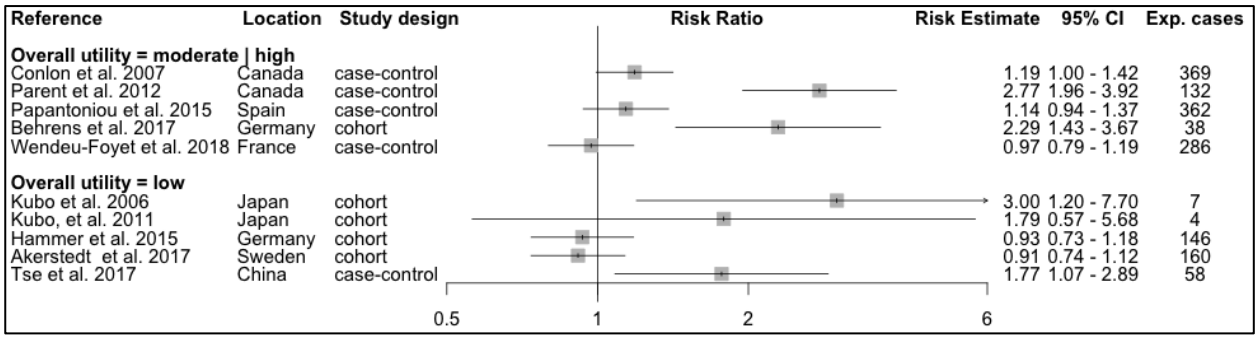

Figure 4-1. Forest plot of human studies on the risk of prostate cancer from ever-exposure to night work; stratified by study utility

*Note: Plotted confidence intervals (CI) are standardized and estimated based on software package, and therefore, may slightly differ 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 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 (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 risk. Papantoniou *et al.* (2015b) observed an increased risk of prostate cancer among those working rotating nights with the highest cumulative frequency (≥ 2,857 rotating night shifts; OR = 1.32, 95% CI = 0.99 to 1.77). Wendeu-Foyet *et al.* (2018) did not see a difference by cumulative frequency for overall, permanent, or rotating night shift work; however, a positive association was observed with combined exposure metrics. A significant 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 significant decreased risk of prostate cancer for shift lengths less than 8 hours (OR = 0.32, 95% CI = 0.16 to 0.34) and a significant increased risk with greater than 10 hours (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).

Though 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.

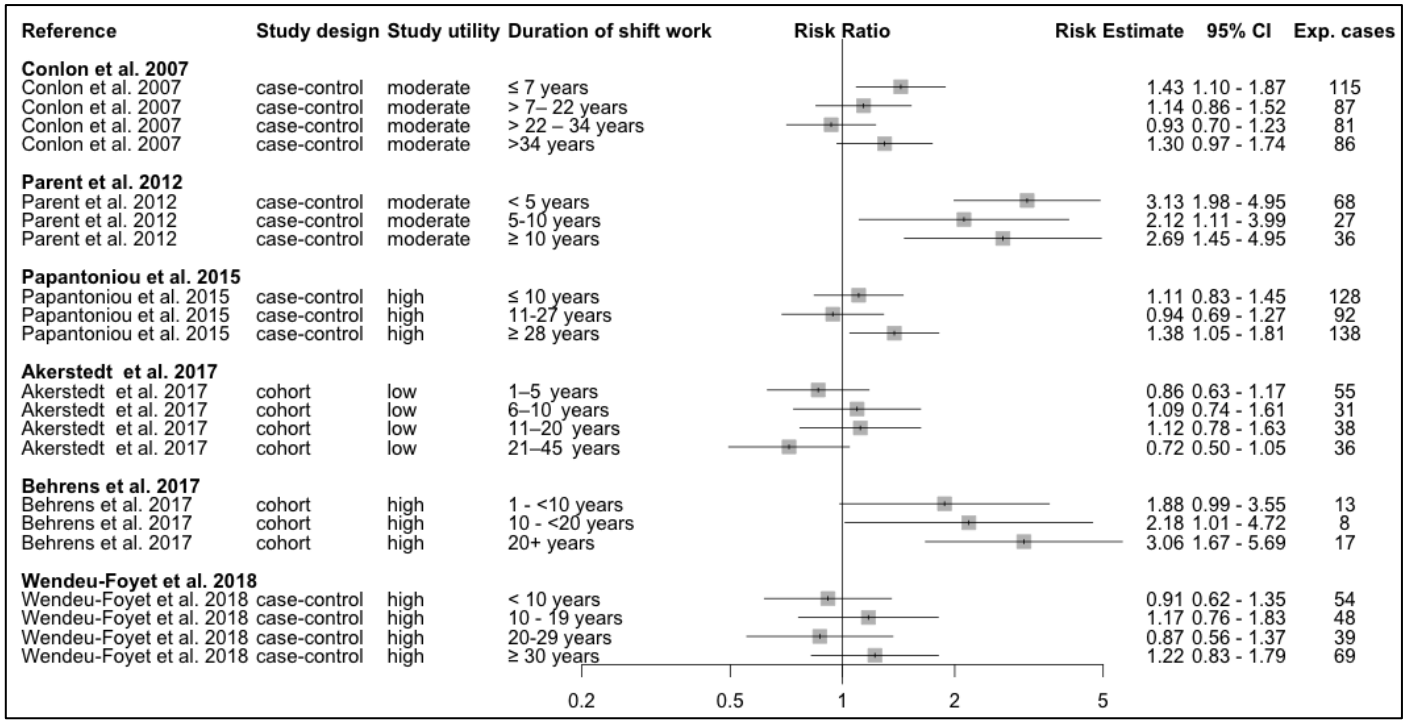

Figure 4-2. Forest plot of human studies on the risk of prostate cancer by cumulative duration of night work

*Note: Plotted confidence intervals (CI) are standardized and estimated based on software package, and therefore, may slightly differ 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, only three studies 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), greater than 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 or 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. There is a greater likelihood that findings were biased due to exposure misclassification. 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.

4.2 Colorectal cancer

In 2017, there were predicted to be an estimated 135,430 new colon and rectum cancer cases 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

eligible 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). One 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. Most studies combined colon and rectal cancers, with Parent *et al.* (2012), Schwartzbaum *et al.* (2007), Walasa *et al.* (2018), 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 mortality 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	Mailed questionnaire *Night work*: undefined time for ≥ 3 rotating night shfit/month *Metrics*: Ever worked rotating night shifts (≥ 1 year), 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 cancer. See Table 4-1	See Table 4–1
Yong *et al.* 2014a	**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-hour shift (6:00 AM–6:00 PM), 24 hours off, 12-hour shift (6:00 PM–6:00 AM), and another 48 hours 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	Mailed questionnaire *Night work*: 11:00 PM–7:00 AM Metric fixed nights), rotating shifts include day (7:00 AM–3:00 PM) and evening (3:00 PM–midnight) *Metrics*: current type of shift work (fixed night 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/month Exposed: Worked night shifts ≥ 1 year (at least 1 hour from midnight-6:00 AM for ≥ 3 nights/month) *Metrics*: Ever worked shifts (≥ 1 year), type of shift, cumulative duration, age at first shift work, shift work ≤ 15 years or ≥ 15 years 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 and 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

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	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility
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 quality rating: Scoring system: +++ = 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. Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low 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 be engaged in shift work long enough to see an effect.

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 rated as having a critical concern for exposure misclassification. Exposure misclassification issues with the JEM in Schwartzbaum *et al.* (2007) are explained in greater detail in Section 4.1, and were therefore rated as having critical concern. Walasa *et al.* (2018) also used a JEM which 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 on lifetime occupational history.

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.

Overall study utility

The study of the NHS and NHS2 cohorts (Papantoniou *et al.* 2018)case-control studies in Canada (Parent *et al.* 2012) and Spain (Papantoniou *et al.* 2017) were considerate to be informative for the evaluation (high or moderate utility). 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-analyses approach informative and thus did not include its own meta-analyses 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. A meta-analysis by Yuan *et al.* (2018) found a significant increased aggregate risk estimate of all digestive cancers, including colorectal cancer, in women overall, and when analyzing female nurses who worked long durations of night shift work. The utility of these analyses 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 significant 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-significant increased association of colorectal cancer with having ever worked rotating night shift work in both internal and external analyses (2014a), suggesting that there is some evidence of an association. 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

Study utility or informativeness	Level of evidence	Cohort studies	Case-control studies
Moderate or high: 3 studies	Moderate to strong evidence: 2 studies		Parent *et al.* 2012 Papantoniou *et al.* 2017
	Some evidence: 1 study	Papantoniou *et al.* 2018	
Low: 2 studies	Some evidence: 1 study	Yong *et al.* 2014a	
	Inconclusive: 1 study		Walasa *et al.* 2018

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-significant increased risk of rectal cancer for ever having worked graveyard shifts (0.1+ months). The NHS/NHS2 study did not report on ever exposure.

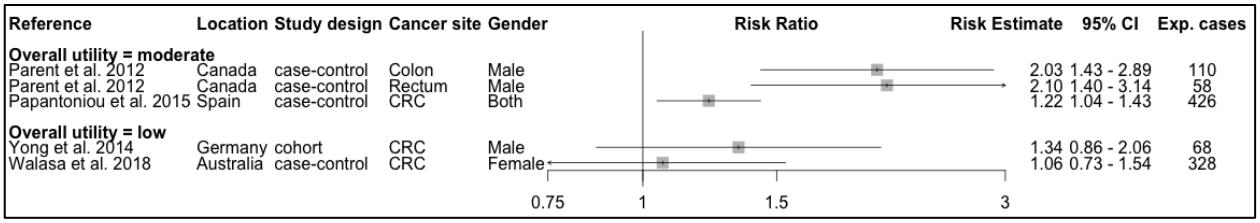

Figure 4-3. Forest plot of human studies on the risk of colon, rectal, and colorectal (CRC) cancers from ever exposure to night work; stratified by study utility

*Note: Plotted confidence intervals (CI) are standardized and estimated based on software package, and therefore, may slightly differ 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 CRC risk was seen in nurses working 10 to 14 years (RR = 1.15, 95% CI = 0.73 to 1.81); however, this estimate 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. 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, 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-significant 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.

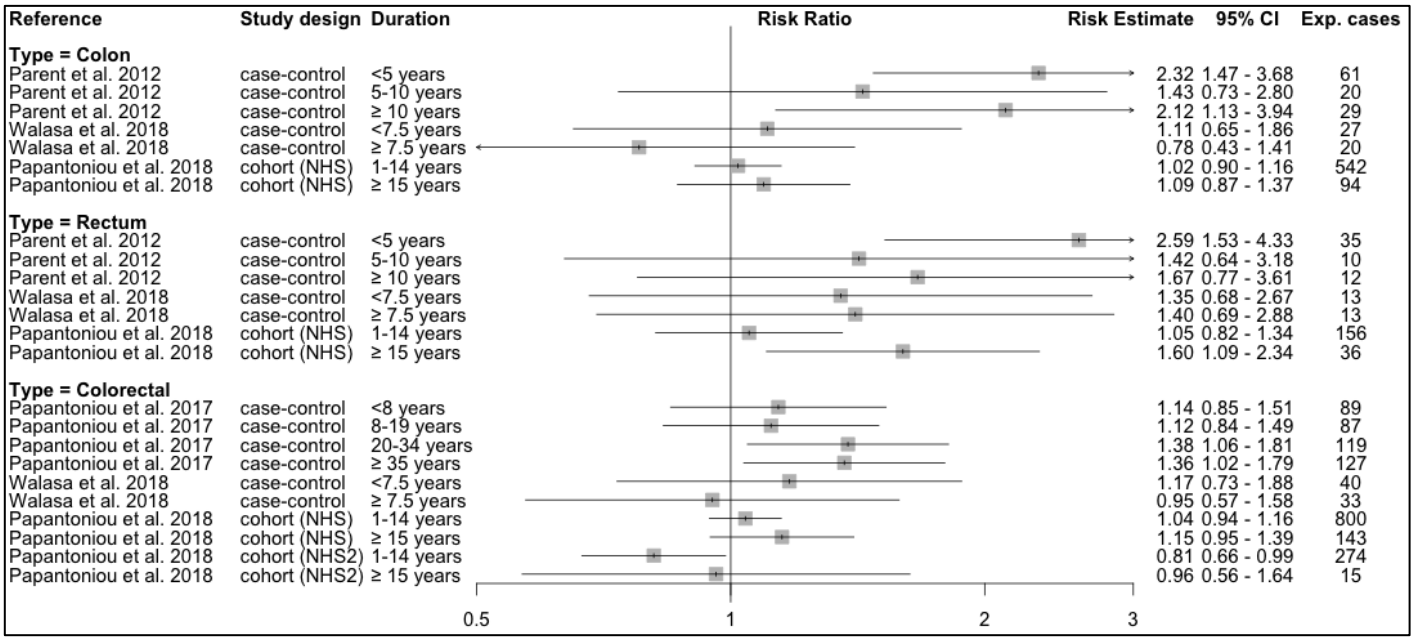

Figure 4-4. Forest plot of human studies on the risk of colon, rectal, and colorectal cancer and lifetime duration of shift work exposure; stratified by cancer type

*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, a 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).

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. When examining the association between shift work exposure and risk of colorectal cancer by gender (i.e., male, female, both), no effect modification is apparent. 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 body mass index (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 away from the null. 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, and 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 not necessarily related to colorectal cancer or 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 (NHS). 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	Mailed questionnaires *Night work*: undefined time for ≥ 3 rotating nights month *Metrics*: Ever worked rotating night shifts (≥ 1 year), 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 (ACS) cohort** 1982 (enrollment) to 2010 (follow-up) 161,004 employed women (general population)	Fatal ovarian cancer Biennial death certificate and automatic linkages with NDI	Mailed 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 nightshift 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	Mailed 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/month *Metrics*: Ever worked rotating night shifts (≥ 1 year), duration of rotating night work

NDI = National Death Index.

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	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility
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 quality: Scoring system: +++ = 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. Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low 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) study may not be as susceptible to this bias, as younger women from the NHS2 cohort were included in the study population. Minimal concern was seen 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 were rated as having a 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 cohort (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 duration of exposure-response relationship. 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; as well as three cohort studies of fatal lung cancer (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. 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 bronchus 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 months 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	**US Nurses' Health Study cohorts (NHS/NHS2)** 1976 (enrolled), 1988 (exposure collection) 1988-2008 (follow-up) N = 78,612 women	Incident lung cancer, including histology subtypes Self-report, next of kin, postal service, death registry	Mailed questionnaires *Night work*: undefined time for ≥ 3 nights/month in addition to days/evenings in that month. *Metrics*: Worked rotating night shifts (≥ 1 year) by duration of rotating night work
Gu *et al.* 2015 (supporting study)	NHS (1988) Follow-up 1988–2010 74,862 female nurses	Fatal lung cancer, underlying causes Next of kin, postal authorities, death registry	
Yong *et al.* 2014a	**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 4-1 400 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

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 NHS cohort (Schernhammer *et al.* 2003, Gu *et al.* 2015); 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 healthy-worker survivor effect (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	Exposure	Outcome	Confounding	Analysis	Selective reporting	Sensitivity	Utility
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 quality rating: Scoring system: +++ = 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. Scoring system: ++++ = high utility; +++ = moderate utility; ++ = moderate/low 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 and selected findings are graphed in the forest plots below.

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 and nor include the published meta-analyses in the cancer hazard assessment. One meta-analysis by Yuan *et al.* (2018) found a significant risk of lung cancer among female nurses who worked long durations of night shift work; however, the

utility of this analysis was limited by inclusion of studies with poorly characterized exposure to shift work. 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 Inconclusive	Yong *et al.* 2014a 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 nonsignificant 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.

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 significant 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 frequency of shift work (i.e., cumulative nights of shift work).

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. A meta-analysis by Yuan *et al.* (2018) found a significant increased risk of skin cancer in women who worked a longer duration of night shifts.

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 significant 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).

Three studies were identified that evaluated position in a time zone and cancer risk. Circadian misalignment may be more severe in western part of a time zone because people living in the western part of 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, colorectal, 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 cancer 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 preliminary 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, 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.

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 the results of studies that examine 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. Some of these studies also measured markers of circadian disruption, such as activity, body temperature, and estrus cycling in females. Serum levels of melatonin or 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 and 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 do not support 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 endogenous melatonin production. Melatonin deficient mice are nocturnal and have a circadian pattern similar to melatonin-proficient mice, 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. 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). 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.

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). In addition, not only LAN, but also the wavelength of light during the daytime can affect nighttime melatonin production (Dauchy *et al.* 2013a, Dauchy *et al.* 2013b). The human exposures most relevant are those involving dim or intermittent LAN or simulating shift work or chronic jet lag. 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 that are exposed to constant bright lights during night shifts and sleep during daylight hours.

5.1 Animal models of LAN or other relevant light exposures

The effects of different light schedules on tumor formation and growth were compared in rodents exposed to dim or bright LAN, intermittent light pulses during the dark phase, light:dark (LD) cycles other than 12:12 hours LD (such as 8:16 hours LD), or 24-hour light (LL) or dark (DD) schedules. The studies reviewed are organized by animal model type (Sections 5.1.1 to 5.1.3) and summarized in Table 5-1. In addition, two studies evaluated exposure to daytime blue light and tumor growth (Section 5.1.4)

5.1.1 Chemical 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. In some of the studies, the animals were acclimated to a standard LD cycle, exposure groups 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 continuous light (LL) or LD were injected with dimethylbenzanthracene (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: 12:12 LD, LL (300 lux), 12:12 LD with exposure to 300 lux for 30 minutes after 6 hours of dark, and 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 reports (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; endogenous 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 serum melatonin levels initially decreased with LAN, but at study end were 3-fold higher than LD levels.	
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; melatonin serum 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		
DEN: GST-P liver foci Wistar rats[c] (Isobe *et al.* 2008)	Preneoplastic GST-P liver foci greater in LD group than LL group		

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
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			
MCF7 breast cancer RNU rats[c] (Blask *et al.* 2003, Blask *et al.* 2005, Blask *et al.* 2014, Dauchy *et al.* 2014)		*Tumors*: growth dependent on LAN intensity; MCF-7 cells grew faster with dim LAN than with LD (4 out of 4 studies); Perfusion with human blood: high proliferation with daytime or LAN collected blood, decreased proliferation with night collected blood (Blask *et al.* 2005). Serum levels of melatonin measured in all 4 studies. *Co-exposure*: exogenous melatonin decreased MCF-7 growth (Blask *et al.* 2014)	
Hepatoma Buffalo rats[a]		*Tumors:* growth dependent on LAN intensity (4 out of 4 studies). Perfusion with human blood: high proliferation with	

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
(Dauchy *et al.* 1997, Dauchy *et al.* 1999, Blask *et al.* 2005, Dauchy *et al.* 2011)		daytime or LAN-exposed collected blood; decreased proliferation with night-collected blood (Blask *et al.* 2005). Serum levels of melatonin measured in all 4 studies.	
Murine mammary-gland cancer cells Balb/c mice[b] (Schwimmer *et al.* 2014)		LAN 30 min after 7 hr dark phase; group had sign. larger tumors than 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] (Lang *et al.* 2003, Otálora *et al.* 2008)	*Tumors:* sign. increase in tumor weight *Co-exposure*: melatonin exposure decreased tumor weight (Otálora *et al.* 2008)		*Tumors*: sign. smaller tumor volume in the 6:18 LD group, intermediate in 12:12 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. 18:6 LD and 6:18 LD.
Murine prostate cancer cells C57BL/6 mice[b] (Haim *et al.* 2010)			Sign. larger tumors with 16:8 LD long day exposure vs 8:16 LD short day.
Rat C6 glioma cells Wistar rats (Guerrero-Vargas *et al.* 2017)	*Tumors:* sign. increase in tumor volume		
Spontaneous tumors			
Lung adenocarcinoma, leukemia/lymphoma, CBA mice[a]	Sign. increase in lung adenocarcinoma and leukemia/lymphoma with LL		

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
(Anisimov *et al.* 2004)			
Mammary tumors (*Her-2/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 mRNA expression by 2.5 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 conditions (NL) 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 natural light conditions (NL) 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.		

LD = light:dark; LL = 24-hour light; 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 and 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.

In 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 continuous light (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 given DEN or saline injections after acclimatization to 12:12 LD, continuous dark (DD), or continuous light (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

continuous light (LL), continuous dark (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).

5.1.2 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. 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). 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-light-at-night group had faster tumor growth, as measured by tumor weight, than did the 12:12 LD control group. 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 tumor incidences were significantly greater in the long- and short-day groups than in the 12:12 LD group. 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 (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 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.

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 day time (12 hour dark:12 hour light schedule using blue-tinted cages) compared to nude mice housed in clear cages (12 hour light:12 hours dark cycle).

5.1.3 Spontaneous tumor formation

In general, of the five studies reviewed in this section, continuous light exposure in mice and rats resulted in four of the studies reporting a decrease in tumor latency and life span compared with exposure to a standard 12:12 LD cycle; one study reported an increase in tumor latency with continuous light exposure. 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 HER-2/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 latency and greater tumor multiplicity (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.

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. 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 than 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).

5.1.4 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).

5.2 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. The studies are organized by animal model (Sections 5.1 to 5.3) and summarized in Table 5-2.

5.2.1 Chemical 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 *N*-nitroso-*N*-methylurea (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).

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 (Fang *et al.* 2017)		CJL exposure advanced mammary tumor onset, increased tumor multiplicity, and significantly increased tumor burden per animal than LD
K-rasG12D; p53-/- : lung tumors **K-ras LSL-**G12D/+; p53flox/flox transgenic mice (Papagiannakopoulos *et al.* 2016).		CJL increased lung tumor burden (tumor area/lung area) compared to LD
Xenografts/tumor growth		
Ehrlich carcinoma or sarcoma Sprague-Dawley rats[a] (Li and Xu 1997)	Light-inverted group had shorter survival and greater tumor growth	
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
Pancreatic adenocarcinoma B6D2F1 mice[c] (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 and sign. increase in metastases to lung

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)
Rat mammary gland adenocarcinoma Fischer 344 rats[a] (Logan *et al.* 2012)		CJL promoted mammary adenocarcinoma incidence and multiplicity in the lung with i.v. 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[c] (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 has 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.

[a]Melatonin proficient.
[b]Melatonin deficient.
[c]Not determined.

5.2.2 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 injected with Ehrlich carcinoma or sarcoma cells and 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).

5.2.3 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, increased body weight gain, longer period of inactivity, and lower food consumption. The total number of tumors did not differ between the groups; both developed mammary-gland carcinoma and fibrosarcoma or carcinosarcoma.

In both sexes of C57BL6/6J mice, a CJL model (weekly alteration 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). 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.

5.3 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.

Studies on the growth of injected tumor cells and some initiation-promotion studies for the most part 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, cervix, skin, colon, 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 and less proliferation with blood collected at nighttime. 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.

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.

Exposure of rodents injected with tumor cells and exposed to conditions to simulate CJL resulted in faster tumor growth and lower survival than in 12:12 LD control groups, 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 i.v. injection of mammary gland adenocarcinoma cells (see Section 5.2 and Table 5-2). Types of tumors included Ehrlich carcinoma or sarcoma, 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.

These studies provide strong evidence that LAN, CJL, or shift work can, through circadian disruption, promote tumor growth and decrease tumor latency. In contrast, exposure to blue light during the daytime has the opposite effect (i.e., slower tumor growth and longer tumor latency) suggesting that total light exposure is important in circadian regulation and carcinogenicity. In the studies of light exposure (during the night or daytime), melatonin was shown to play a role in carcinogenicity (see Section 6.2.1). What is less certain is whether and how these factors affect spontaneous initiation of carcinogenesis. Spontaneous tumor formation with LAN studies were of limited utility and there were only one CJL and one shift-work study. The CJL study found an increase in liver tumor incidence, and the shift-work study found shortened tumor latency, but no change in tumor incidences. 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 night shift workers (especially those with "persistent" exposure with respect to timing, duration, or frequency of shift work) are at risk for breast cancer, and to a lesser degree, prostate cancer (see Sections 3 and 4). Some human studies have also found an association with environmental exposure to LAN (outdoor or indoor) and increased breast cancer risk. Studies in experimental animals demonstrate that exposure to dim light during the biological night or phase shifts in the light-dark cycle promote tumor growth and development (Section 5).

Persistent night shift work can constitute extreme exposure to LAN (Lunn *et al.* 2017). Both LAN and night shift work suppress melatonin secretion in a dose-dependent manner (see Section 2). In addition to melatonin suppression, LAN, night shift work, and transmeridian travel (i.e., jet lag) 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). Re-entrainment to a new light-dark cycle (e.g., following transmeridian travel) occurs gradually over several days to several weeks depending on the tissue and cell types. Phase advance of the light-dark cycle, induced by earlier timing of light exposure, produces a more prolonged period of desynchronization within the SCN than phase delay. This effect is also dependent upon the spectrum, brightness, and duration of the light source.

This section reviews the mechanistic and other relevant data associated with night shift work and LAN (or light during the biological night). Other conditions that contribute to circadian disruption and are often associated with LAN and/or shift work (i.e., reduced exposure to sunlight, vitamin D deficiency, sleep deprivation, and meal timing) are also reviewed.

The mechanistic links between LAN- and shift work-related exposures, circadian disruption, and cancer have been extensively investigated but remain uncertain. Key mechanistic questions evaluated in the monograph include the following:

- What are the key risk factors and mechanistic issues related to breast cancer (Section 6.1)?
- Are the mechanistic data consistent with the observations in humans with respect to breast cancer subtypes and timing of exposure (Section 6.1)?
- What are the proposed mechanisms that link LAN or shift work exposure and cancer (Section 6.2)?
- What biological effects are caused by LAN and night shift work (Section 6.3)?
- Are the biological effects consistent with the key events in the proposed mechanisms (Sections 6.2 and 6.3)?
- Do exposures other than LAN and shift work contribute to circadian disruption (Section 6.4)?

6.1 Overview of breast cancer carcinogenicity

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 principle 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 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, PR, 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 in 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 LAN and shift work exposure and breast cancer

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 LAN during susceptible hormonal stages (e.g., working shifts at early ages and/or prior to the first full-term pregnancy) are 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 Proposed mechanisms

Two related mechanisms that address potential links between night shift work, LAN and cancer are the melatonin hypothesis and the LAN or circadian disruption theory. Section 2 provided evidence that both night shift work and LAN suppress melatonin production and cause other types of circadian disruption.

6.2.1 Melatonin hypothesis

Melatonin has a prominent role in circadian biology and mediates its effects through receptor-mediated and receptor-independent pathways. Electric power 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 (Stevens 1987, Stevens *et al.* 1992). 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).

The melatonin hypothesis lead to several predictions that cover a diverse set of populations including: (1) non-day shift workers would have a higher risk, (2) blind women would have a lower risk, (3) sleep duration as a surrogate for hours of darkness would be inversely associated with risk, (4) light levels in bedrooms at night would be associated with risk, (5) indigenous populations in the northern latitudes would have a lower risk, and (6) population level studies would show associations of community light levels and breast cancer incidence. Epidemiological studies are generally consistent with these predictions (Stevens 2009a). Since the publication of the melatonin hypothesis, numerous epidemiologic and experimental studies have investigated the association of melatonin levels and cancer risk or the effects of melatonin on tumor growth and survival. Findings from these studies are presented below.

Human studies of melatonin suppression and breast cancer and prostate cancer

Overall, available data for breast cancer 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) suggest that melatonin levels are inversely associated with breast cancer risks among postmenopausal women. However, additional data are needed to address some of the important inconsistencies found across studies and for premenopausal women. 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. Data from pre- and post-menopausal women are available from each cohort (Figure 6-1). 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 since samples were collected.

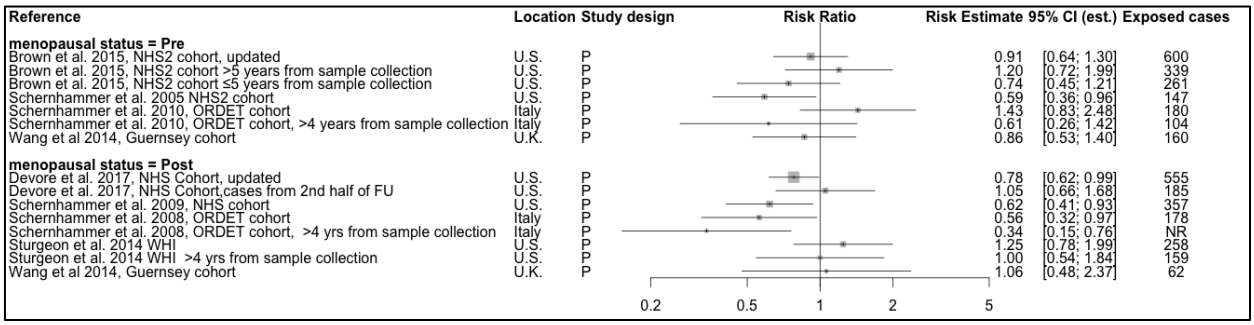

Figure 6-1. Relationship of urinary melatonin levels (top quartile vs. bottom quartile) and risk of breast cancer

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 on 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 to LAN-induced cancers because melatonin levels would not be suppressed by LAN exposure (Feychting *et al.* 1998, Stevens 2009a). 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). Individuals with severe visual impairment includes those 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-significant 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 be dependent 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 a discussion of LAN effects on tumor growth).

LAN studies (see Section 5 for details on the cancer effects): LAN, including dim LAN as low as 0.2 lux, exposure 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. 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., blood collected from human volunteers during the night or rat blood enriched with synthetic melatonin) (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 total light exposure (i.e., timing, intensity, duration, and spectral properties) throughout the day are 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 when perfused with melatonin-enriched rat blood (Blask *et al.* 1999). An *in vitro* study also reported that melatonin added to the culture medium at physiological concentrations reduced the invasiveness of MCF-7 cells (Cos *et al.* 1998).

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 involved in multiple tumor defense mechanisms and may offer some protection against all the biological effects that are considered to be hallmarks of cancer (Erren 2005, Hill *et al.* 2015). 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). The data also suggest that LAN-induced melatonin suppression can cause global DNA hypomethylation by inhibiting DNA methyltransferase (Zubidat and Haim 2017).

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, 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 also represses metastasis in human breast cancer cells by inhibiting epithelial to mesenchymal cell transition via regulation of GSK3ß and RSK2 (Mao *et al.* 2012, Mao *et al.* 2016b). 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, extracellular signal-regulated kinase (ERK 1/2), protein kinase B (Akt) activation, and [3H]-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 17-ß-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

Mechanism	Pathway	Key Events: Cellular/Molecular Effects	Outcome
Prevention of circadian disruption	Clock genes and epigenetic pathways	↓ Abnormal epigenetic modifications ↓ Dysfunctional clock genes (SCN and peripheral)	↑ Internal clock synchronization ↑ Oncostatic activity – multiple tumor types

Sources: Mediavilla *et al.* 2010, Srinivasan *et al.* 2011, Zubidat and Haim 2017.
↓ = decreases, ↑ = increases.

6.2.2 Circadian disruption theory

The melatonin hypothesis was later expanded to the LAN or circadian disruption theory after recognizing that other mechanisms and biological rhythms, in addition to melatonin suppression, are affected by LAN (Stevens 2009b). These include altered clock gene function and expression and desynchronization of the master clock from the peripheral clocks. Circadian disruption, as used in this monograph, was defined in Section 2. Disruption of the clock regulatory loops, mutations, deregulated expression, and translocations of core clock genes are frequently observed in human breast, prostate and other cancers while expression of some clock genes have been linked to prognosis (Davis and Mirick 2006, Cadenas *et al.* 2014, Karantanos *et al.* 2014, Mazzoccoli *et al.* 2014, Altman 2016, Reszka and Przybek 2016).

Although direct mechanistic links between shift work, LAN, circadian disruption, and cancer have not been established (Figueiro 2017), epidemiological and experimental studies have identified several plausible modes of action and measured several biological effects or key events and pathways that are associated with the hallmarks of cancer (Hanahan and Weinberg 2011) and/or the characteristics of carcinogens (Smith *et al.* 2016). Cancerous tissues differ substantially from normal cells in their metabolism and growth characteristics (Hanahan and Weinberg 2000, 2011). These fundamental differences reflect a series of disrupted regulatory circuits and gene expression patterns (including the core clock genes, oncogenes and tumor suppressor genes) that are under circadian control (Greene 2012, Altman 2016). For example, studies in humans show that sympathetic nervous system (SNS) signaling is deregulated during shift work (Adams *et al.* 1998) and studies in mice show that jet lag desynchronizes the central clock-SNS-peripheral clock axis, inhibits the ATM-p53 tumor suppressor pathway, and activates the *c-Myc* oncogene (Lee *et al.* 2010). Consequently, 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). Much of the current knowledge on the role of clock genes has been derived from genetic models in rodents, polymorphism studies in humans, and *in vivo* and *in vitro* gene expression studies.

Genetic models in experimental animals

Clock gene suppression or knockouts and mutations in mice are associated with a cancer prone phenotype, accelerated growth of tumors, and other effects that may contribute to carcinogenesis (e.g., immune deficiencies, chronic inflammation, metabolic disorders, obesity, and premature aging) (Fu *et al.* 2002, Antoch *et al.* 2008, Lee *et al.* 2010, Kettner *et al.* 2014). Mice with germline *Per2* (*Per2*$^{m/m}$) and *Bmal1* (*Bmal1*$^{-/-}$) loss of function mutations had accelerated lung tumor growth and progression and decreased survival (Papagiannakopoulos *et al.* 2016). Downregulation of the *Bmal1* gene in mice inoculated with C26 mouse colon cancer cells also accelerated tumor growth *in vivo* and accelerated proliferation of C26 cells *in vitro* (Zeng *et al.* 2010). *Per2* inactivation accelerated intestinal and colon tumorigenesis in mice while downregulation of *PER2* enhanced proliferation of two human colon cancer cell lines *in vitro* (Wood *et al.* 2008). *Cry1, Cry2, and Per2* mutant mice developed four to eight-fold more DEN-induced liver and bile duct tumors than wildtype mice (Mteyrek *et al.* 2016, Mteyrek *et al.* 2017). Mice deficient in *Bmal1, Per1* and/or *Per2, Cry1* and/or *Cry2* were prone to spontaneous tumors (lymphoma, liver, and ovarian) or radiation-induced lymphoma development (Lee *et al.*

2010). Fu *et al.* (2002) also showed that *Per2* mutant mice develop a cancer-prone phenotype and are more sensitive to γ radiation.

Clock gene effects

The core DNA-binding transcription factors, CLOCK and BMAL1, control the expression of approximately 10% of transcripts in the human genome in a tissue- and time-specific manner (Masri *et al.* 2015). The central clock in the SCN regulates cell proliferation and apoptosis in peripheral tissues at the systemic level through the sympathetic branch of the autonomic nervous system, and the neuroendocrine system (e.g., hypothalamic-pituitary-adrenal axis [HPA] and the hypothalamic-pituitary-gonadal axis [HPG]) (Fu and Lee 2003). Estrogens and glucocorticoids produced by the HPA and HPG are known to control cell proliferation and apoptosis in peripheral tissues. The SNS innervates all peripheral organs and controls the circadian rhythm of diverse cellular processes and signaling pathways in peripheral tissues (Kettner *et al.* 2014). SNS signaling plays an important role in cell cycle progression by activating *Ap1*, *Per1,* and *Per2* genes and ATM-p53 signaling in mice (Lee *et al.* 2010). Deregulated SNS signaling can result in uncontrolled cell proliferation and contribute to tumor initiation. Observations in experimental animals show that circadian disruption by LAN or simulated chronic jet lag accelerates tumor growth (see Section 5). 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, circadian control of cell cycle gene expression in peripheral tissues and cell proliferation signaling pathways are regulated by both the positive and negative feedback loops of the molecular clock (Fu and Kettner 2013). Genes involved in cell cycle regulation, DNA damage checkpoints and apoptosis that are under circadian control include proto-oncogenes (e.g., *Ras, c-Myc*, *Mdm2*, *ß-catenin*), tumor suppressor genes (e.g., *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 and Kettner 2013). The CLOCK-BMAL1 heterodimer directly regulates genes that play an essential role in cell cycle control, including blocking *c-Myc* overexpression (Sahar and Sassone-Corsi 2007, Lee *et al.* 2010). Papagiannakopoulos *et al.* (2016) reported that *Per2* and *Bmal1* had important roles as tumor suppressors in mouse models of lung adenocarcinoma. Circadian rhythm disruption of these core circadian clock genes by simulated jet lag or in genetically engineered mutant mice resulted in increased c-Myc expression, enhanced tumor growth, and metabolic dysregulation. 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 (Chen-Goodspeed and Lee 2007). *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). 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).

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.

A simplified model of circadian clock control of cell growth regulation is shown in Figure 6-2.

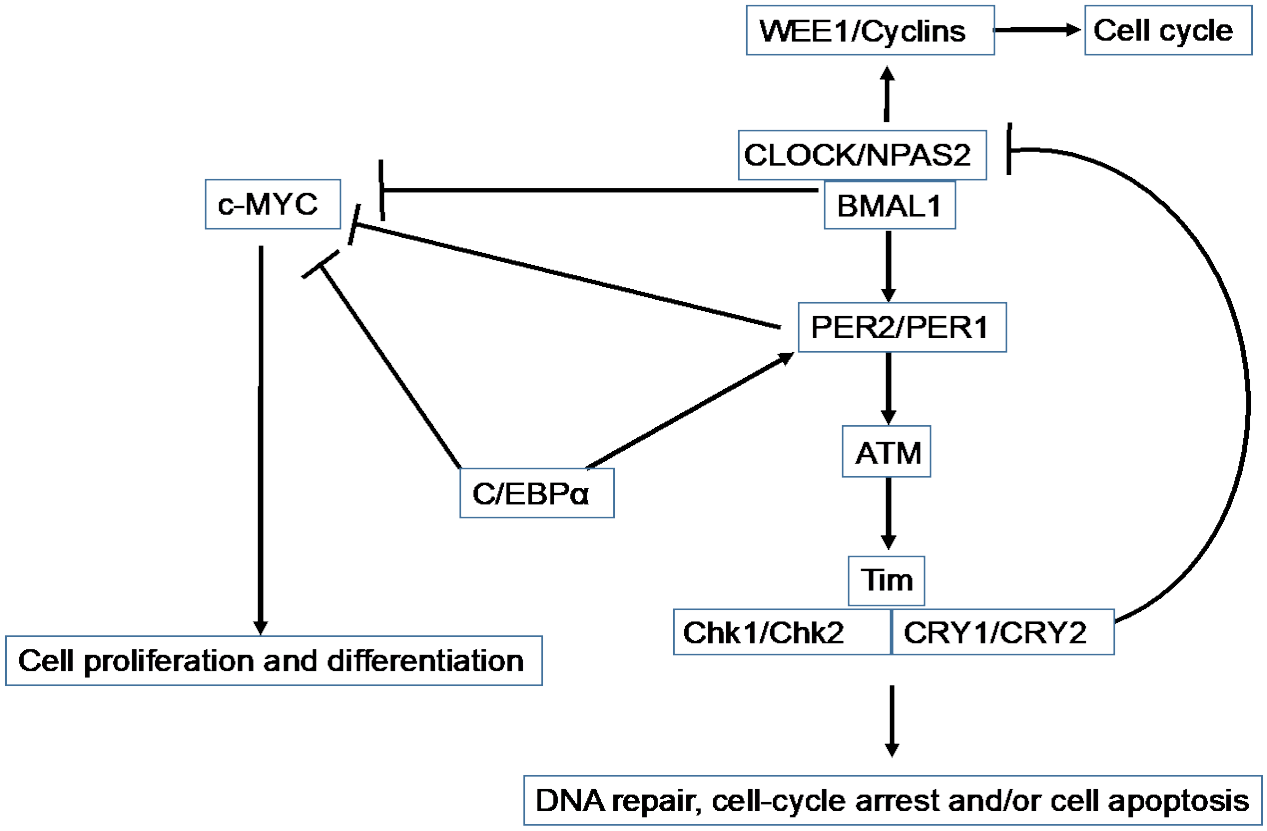

Figure 6-2. Proposed model of cell growth regulation by the circadian clock

The circadian clock controls the cell growth by regulating transcripts of cell cycle proteins (Cyclins, WEE1, and c-MYC) and cell cycle checkpoint pathways (ATM-Chk1/Chk2). This complex can, in turn, interact with CRY1/CRY2, which serves as a negative regulator of the circadian transcriptional complex activity (NPAS2/BMAL1 or CLOCK/BMAL1). In addition to the clock transcription complex, the Per1/Per2 promoter activities can also be regulated by C/EBPαs (adapted from Chen-Goodspeed and Lee 2007).

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 4 clock genes (*Clock*, *RorA*, *RorB*, 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 LAN or shift work exposure.

6.3 LAN and shift work studies: Biological effects related to cancer

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 is limited data on the genotoxic effects of LAN or shift work 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. Molecular links between circadian clock proteins and DNA damage response have been established (Collis and Boulton 2007). As discussed in Section 6.2, melatonin and the core clock genes have important roles in regulating cell cycle control and DNA damage repair. The expression levels of all DNA repair pathways exhibit circadian rhythms with significant temporal differences in repair capacity (Vaskova *et al.* 2011, Palombo *et al.* 2015). Thus, one of the expected consequences of circadian disruption is altered DNA repair.

Animal studies of LAN and shift work

Experimental animal studies support a link between LAN exposure or simulated jet lag and inhibition of DNA repair, genomic instability, and 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. Simulated jet lag also disrupted circadian expression of DNA damage response and repair genes in rats and accelerated mammary tumorigenesis (Fang *et al.* 2017). 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 controls (Frajacomo *et al.* 2015).

Studies in shift workers

A few studies in humans also provide evidence that night shift work is associated with decreased DNA repair. Urine samples collected during night sleep from 217 day shift workers and during both day and night sleep (on their first day off) periods for 223 night shift workers were analyzed for 8-hydroxydeoxyguanosine (8-OH-dG) and 6-sulfatoxymelatonin. Night shift workers exhibited a reduced capacity to repair oxidative DNA damage based on significantly lower urinary clearance of 8-OH-dG during their day sleep periods compared to their night sleep periods or compared to day shift workers (Bhatti *et al.* 2016, 2017). Urinary levels of 6-sulfatoxymelatonin were lowest in night shift workers during their day sleep periods and were positively correlated with clearance of 8-OH-dG. These data are consistent with melatonin's antioxidant properties and stimulation of DNA excision repair. 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 shift workers compared to a control group. *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 is frequently 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 intensive night work schedules (i.e., working 6 consecutive nights for more than 5 years) was associated with decreased telomere length and increased breast cancer risk (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 but the relationship was not statistically significant. However, sleep duration was positively associated with telomere length (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. Thus, telomere shortening may be a contributing factor to increased breast cancer risk associated with the duration and intensity of night shift work (see Section 3).

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. This effect was abolished by addition of a melatonin receptor antagonist. *In situ* perfusion of PC3 human prostate cancer xenografts in nude rats with melatonin-rich human blood (but not melatonin-poor blood) 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 misregulation 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., histone acetyltransferases (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 $NAD^{\pm}$-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 LAN or shift work

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 6-2.

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 with (1) 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) 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. miR-219 dampens cancer cell sensitivity to apoptosis and 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 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 difference 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 are involved in regulating defense mechanisms against viruses and tumors. Thus, circadian disruption by LAN and/or shift work 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).

Table 6-2. 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 Demark	Diet, Cancer and Health Cohort Long term shift workers ages 50–64 yr **Analyses** Specific genes: 19 shift workers; 98 day workers 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* **S**ignificant 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
Jacobs *et al.* 2013	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	

Reference Location	Population/exposure	DNA methylation	Results	Comments and gene effects
Shi *et al.* 2013	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 in MCF-7 breast adenocarcinoma cells** 319 mRNAs differentially expressed transcripts	Hypermethylation may dampens cancer cell 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	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 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.
Bhatti *et al.* 2015	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 7,173 CpG islands in 3,769 genes. 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.

Reference Location	Population/exposure	DNA methylation	Results	Comments and gene effects
Adams *et al.* 2017	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
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* for medium exposure to shift work No significant effects for other night work exposure categories **Case-case analysis: Ref 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.

Reference Location	Population/exposure	DNA methylation	Results	Comments and gene effects
Peplonska *et al.* 2017 Lodz, Poland,	Nurses and midwives Cross-section study Fast rotating forward shift workers ages 40–60 years. 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). LAN or jet lag 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 LAN and shift work

Three LAN exposure studies and one simulated jet lag study reported evidence of oxidative stress in rodents. 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 other 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). Kishi and Sunagawa (2011) reported that experimental jet lag in wild type and hypertensive rats increased blood pressure and SNS activity via oxidative stress.

Studies in shift workers

Several studies have reported 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). Results from Gromadzinska *et al.* (2013) were less clear. This study reported significantly higher red blood cell glutathione peroxidase (GSH-Px) activity in nurses working night shifts compared to day shift nurses. This effect was positively associated with the number of night shifts worked per month. However, plasma GSH-Px activity was lower in shift workers (postmenopausal nurses only). Significantly lower levels of vitamins A and E were found in premenopausal women working night shifts but 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 (Faraut *et al.* 2013, Cermakian *et al.* 2014). Thus, it is not surprising that studies of shift workers or experimental animals exposed to LAN or jet lag 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.

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 lipopolysaccharide (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.

Rodents subjected to various chronic jet lag protocols showed evidence of circadian disruption and altered immune and inflammatory responses (Castanon-Cervantes *et al.* 2010, Wu *et al.* 2010, Logan *et al.* 2012, Guerrero-Vargas *et al.* 2015). 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 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). 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).

Studies in shift workers

Human studies are generally consistent with the studies in rodents also showing 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 the 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 in 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 1779 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 LAN, shift work, and jet lag may contribute to inflammation and an altered immune response in humans and experimental animals; 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

Obesity and metabolic syndrome, are recognized risk factors for some cancers and are often associated with long-term shift work and circadian disruption in humans (Renehan *et al.* 2015, Arnold *et al.* 2016, Zubidat and Haim 2017). 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 induced spontaneous hepatocellular carcinomas in wild-type mice. The reported mechanism of liver carcinogenesis involves circadian disruption, global liver metabolic dysfunction, non-alcoholic fatty liver disease, steatohepatitis, fibrosis, and hepatocellular carcinoma development). The importance of the circadian system in maintaining metabolic homeostasis is further supported by circadian mutant mouse models (Rudic *et al.* 2004, Turek *et al.* 2005, Fonken and Nelson 2014, Kettner *et al.* 2015). 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).

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).

Rodent studies of exposure to LAN

Various LAN protocols induced or promoted tumor growth in rodents (see Section 5). Several of these studies also 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.* 2015c, 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. These effects could be mediated by melatonin-induced changes in hormone levels (see Section 6.2).

Eight of nine published studies measuring estrogen levels in shift workers (Schernhammer *et al.* 2004, Nagata *et al.* 2008, Langley *et al.* 2012, Bracci *et al.* 2013, Bracci *et al.* 2014, Gómez-Acebo *et al.* 2015, Papantoniou *et al.* 2015c, Peplonska *et al.* 2016) reported higher levels of various estrogen metabolites in shift workers compared to day workers. In addition, the highest estrogen levels were reported among women with the longest shift work duration (Schernhammer *et al.* 2004, Langley *et al.* 2012, Peplonska *et al.* 2016). 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. In the studies measuring melatonin, melatonin levels were unrelated to reproductive hormone levels.

All three studies that investigated progesterone levels in shift workers (Langley *et al.* 2012, Gómez-Acebo *et al.* 2015, Papantoniou *et al.* 2015c) reported higher progesterone levels or total progestogens in night workers compared to day workers. Langley *et al.* also reported increasing progesterone levels with increasing duration of shift work.

Seven of twelve studies conducted primarily in larger populations measuring prolactin levels in shift workers reported no relationship between night work and prolactin levels (Spiegel *et al.* 1996, Aktan *et al.* 1997, Axelsson *et al.* 2003, Schernhammer *et al.* 2004, Korompeli *et al.* 2009, Langley *et al.* 2012, Bukowska *et al.* 2015). Five small studies reported some difference in prolactin levels (generally lower levels) or altered rhythms in shift workers (Aulitzky *et al.* 1984, Touitou *et al.* 1990, Miyauchi *et al.* 1992, Costa *et al.* 1997, Weibel and Brandenberger 1998).

Six studies in populations which varied by gender, menopausal and occupational status investigated testosterone or androgens in shift workers with differing results. Of the two studies in premenopausal women (Schernhammer *et al.* 2004, Papantoniou *et al.* 2015c), only Papantoniou *et al.* reported significantly elevated testosterone and 3α,5α-androstanediol levels in night workers compared with day workers; no differences were found between postmenopausal women with and without a history of night shift work (Nagata *et al.* 2008). One study of male oil refinery workers working a fast-forward shift system found decreased levels of testosterone in night workers compared to controls (Touitou *et al.* 1990), while a study of male police officers reported no differences in testosterone levels among those working 2, 4, or 7 consecutive nights with a corresponding number of consecutive recovery days (Jensen *et al.* 2016b).

6.4 Other mechanisms associated with LAN and shift work

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 factors contribute to circadian disruption including: reduced sunlight exposure, vitamin D deficiency, sleep deprivation, and meal timing (Costa *et al.* 2010, Asher and Sassone-Corsi 2015, Smolensky *et al.* 2015, Figueiro 2017, Zubidat and Haim 2017). 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). As discussed in Section 2, total light exposure (too much LAN and not enough sunlight) affects melatonin suppression and circadian disruption. 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 shiftwork carcinogenicity is inconclusive. Two studies did not find that night shift work was associated with an increased 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 (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) in some studies, 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

LAN, shift work, and social jet lag misalign 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 shiftwork-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 and 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). 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 that took a short nap during night shift work had significantly lower 17-ß-estradiol levels compared to night-shift nurses that 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.* 2017). 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 (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 LAN, shift work, and/or jet lag induces circadian disruption as evidenced by melatonin suppression and altered clock gene expression. Shift work is the best studied LAN-associated exposure in humans and represents extensive LAN exposure conditions. These studies suggest an increased risk of breast cancer in women, and to a lesser degree, an increased risk of prostate cancer in men. 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 to accelerated tumor growth.

The proposed mechanisms linking LAN/shift work, circadian disruption, and cancer focus on the biological properties of melatonin (i.e., melatonin hypothesis) and the role of the circadian system and clock genes (circadian disruption theory) in maintaining cellular and tissue homeostasis. There is substantial experimental evidence that melatonin and the circadian system protect against tumor development and progression and affect mechanisms and pathways that are relevant to most, if not all, the hallmarks of cancer. 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 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 mechanisms are not well understood, it is clear the possible modes of action are complex and multifactorial. In addition to the complex interactions of melatonin, the central clock, and the peripheral clock and clock-controlled genes, interactions also occur with other factors that are associated with LAN and shift work that mitigate or exacerbate circadian disruption. These include sleep and sleep deprivation, vitamin D, and lifestyle factors (i.e., smoking, drinking, meal timing, 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 have been investigated in humans and/or human cancer cell lines and are relevant to humans.

7 Evidence Integration and Preliminary Listing Recommendations

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 6:00 AM and 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).
- 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 monograph is to define exposure to (1) LAN and (2) night shift work in ways that are supported by the scientific evidence and to reach a preliminary RoC listing recommendation 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 preliminary listing recommendations (Section 7.4). Because the data on transmeridian travel were inadequate for evaluation, no overall preliminary recommendation was made for this exposure scenario.

7.1 Methods for evidence integration

The cancer hazard assessment integrates relevant evidence across many studies 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 listing recommendation 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 the preliminary listing recommendation (see Table 7-1). The level-of-evidence conclusions from studies in humans and the preliminary listing recommendations 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 a key step in the carcinogenicity pathway and 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.* 2016a), 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. In general, night shift workers at highest risk for breast cancer are those who started working before age 30 and worked at least 3 times/week and for durations lasting 10 or more years; however, the exact conditions may depend on a combination of these conditions. 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 simulated shift work decreased the latency of mammary gland tumors in a cancer-prone mouse model (Van Dycke *et al.* 2015), as well as 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). Although the data from the cancer epidemiology studies are strong, they are not considered sufficient because of the (1) low sensitivity of most cohort studies to assess persistent night shift work conditions, (2) the possibility, albeit low, of differential recall biases in the case-control studies) and (3) the possibility of co-exposure to other carcinogens in the occupational cohorts of nurses or in other specific industries. 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).

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 melatonin suppression and clock-gene desynchrony, play 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 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 play 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 associated with carcinogenicity (e.g., decreased DNA repair, increased oxidative stress, increased inflammation, altered circulating levels of estrogen and progesterone, and epigenetic changes that modify the expression of core clock genes or clock-controlled genes). A strength of the database is that several of the animal cancer studies (involving exposure to LAN or simulated shift work) also measured some biological effects associated with cancer (e.g., DNA damage repair), thus providing links between exposure, intermediate biological effects, and cancer. Moreover, the biological effects observed in night shift workers 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 melatonin suppression and circadian clock gene deregulation 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.

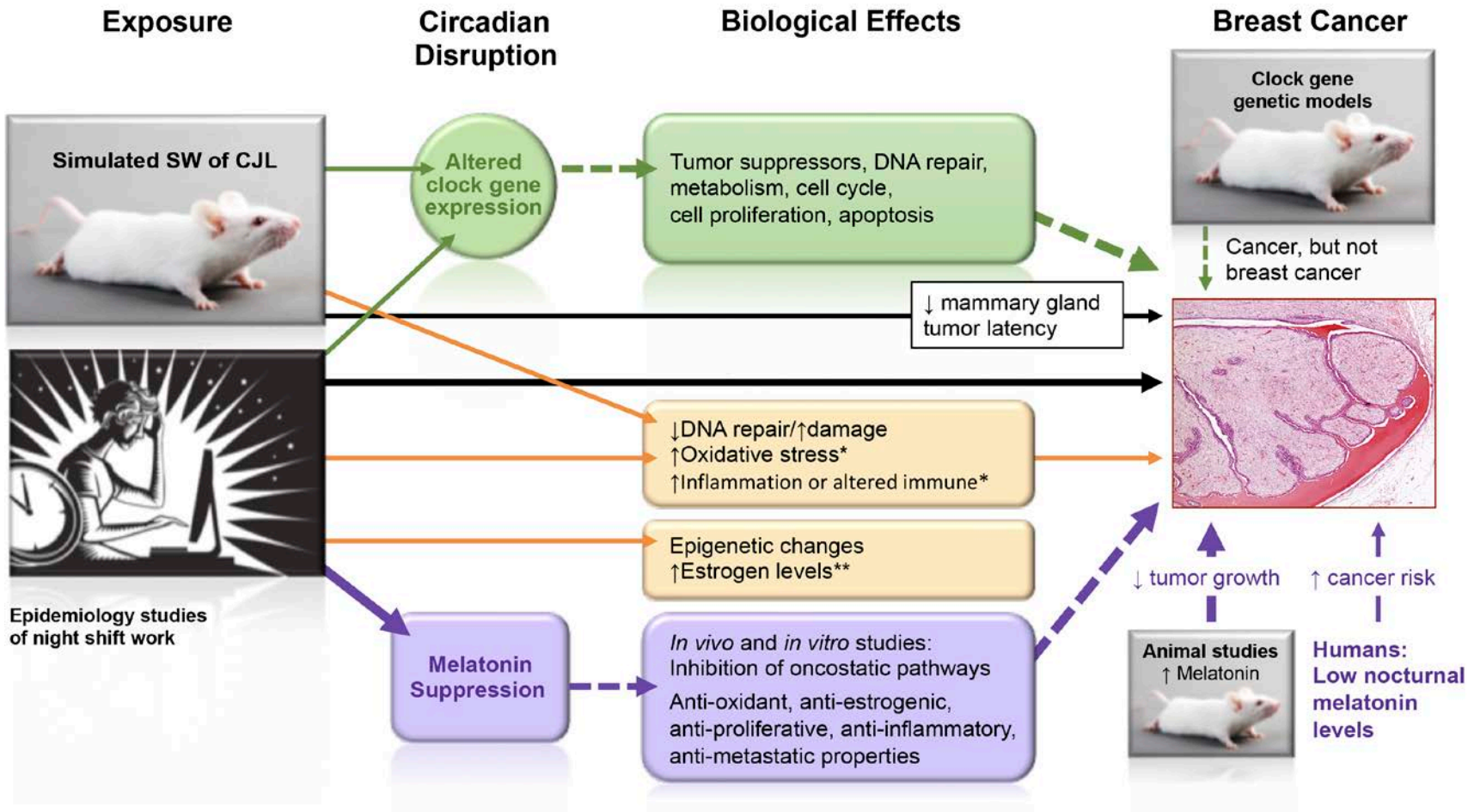

Figure 7-1. Integration of evidence from studies relevant to night shift work and breast cancer

Evidence from studies in humans and experimental animals for the relationship between night shift work and biomarkers of circadian disruption, biological effects related to carcinogenicity, 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 humans and animals provide strong evidence that LAN promotes breast cancer proliferation and growth (see Section 5 and Table 7-2), causes biological effects that are 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 from LAN exposure to circadian disruption to biological effects to 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, cervix (human), 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 (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 strong evidence for an indirect role of altered clock-gene expression in LAN-induced carcinogenicity. 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 affects) that are associated with carcinogenicity, including some that are consistent with development of hormone-receptor-related breast cancer (e.g., altered estrogen levels or function). 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 melatonin suppression and the circadian disruption theory (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). 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; however, 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 direct link to LAN exposure. Despite their limitations, the results of the human studies are consistent with the strong data from mechanistic and animal cancer studies of LAN exposure. The database for LAN exposure in bedrooms or sleeping areas 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 capture these characteristics; therefore, the recommended listing is for “certain lighting practices that cause circadian disruption.”

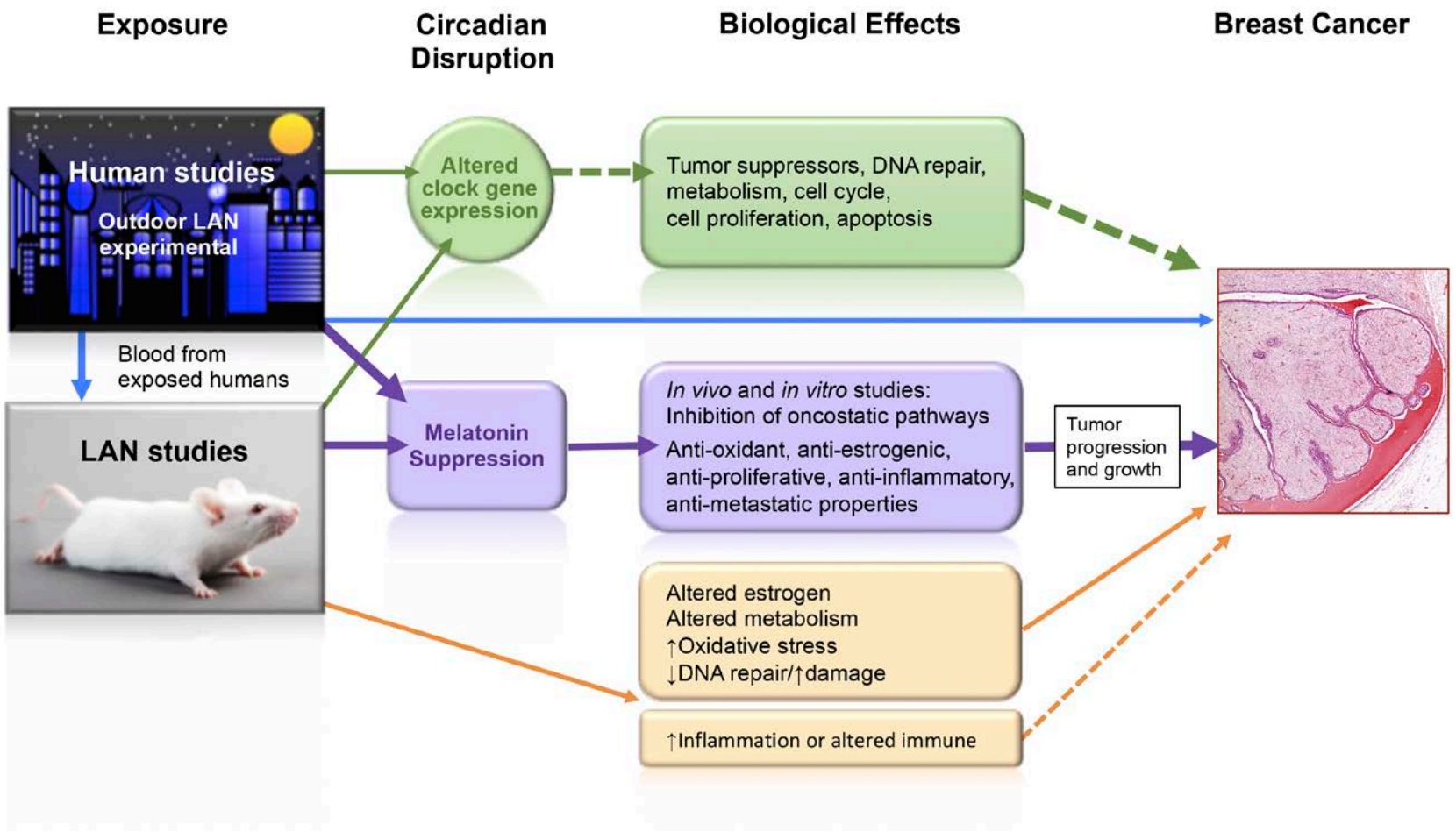

Figure 7-2. Integration of evidence from studies relevant to LAN and breast cancer

Evidence from studies in humans and experimental animals for the relationship between LAN and biomarkers of circadian disruption, biological effects related to carcinogenicity, 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 preliminary listing recommendations

Table 7-1 summarizes the evidence supporting the preliminary listing recommendations. Tables 7-2 and 7-3 summarize in more detail the key evidence from human and animal cancer studies

Persistent night shift work — i.e., frequent and long-term night shift work, especially beginning in early adulthood – that causes circadian disruption is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

- This conclusion is based on the collective body of evidence from cancer epidemiological studies and mechanistic studies in humans and in experimental animals. Human epidemiological studies provide 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 general, 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.

Certain lighting conditions — i.e., excessive LAN exposure combined with insufficient daylight exposure — that cause circadian disruption are *reasonably anticipated to be a human carcinogen.*

- This conclusion is based on strong evidence that LAN acts through mechanisms that are likely to cause cancer in humans and limited evidence of the carcinogenicity of LAN from studies 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 and may increase breast cancer risk.
- 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 biological effects that are consistent with several of 10 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	***Known to be a human carcinogen*** *Persistent night shift that causes circadian disruption* Sufficient evidence of carcinogenicity of 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** 4 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	Limited evidence that outdoor LAN causes breast cancer risk (few studies) Inconsistent evidence that indoor light is associated with increased breast cancer risk and inadequate information on relative light levels across studies 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	***Reasonably anticipated to be a human carcinogen*** *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 Limited evidence for carcinogenicity of LAN from studies 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* Potential for differential recall bias is minimal but cannot be completely ruled out **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, although potential confounding by unmeasured occupational co-exposure may be possible in some studies Patterns of exposure: highest risk found for persistent exposure (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.

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
Night shift work	Prostate cancer	10 studies of independent populations 5 cohort studies 5 case-control studies	**Strength** Controlled for known risk factors for prostate cancer **Limitations** Non-differential exposure misclassification Low sensitivity	Adequacy of the database: 5 informative studies; potential biases in low-quality studies are most likely towards the null 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

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
Simulated shift work or jet lag	Mammary-gland tumors	**Experimental animals (mice)** 2 studies **Shift work** Transgenic mouse (p53R270H[a]/+ WAPCre conditional mutant); melatonin deficient Inverted LD cycle **Jet lagged model** Female C3(1)/Tag transgenic mice Advance light onset by 12 hours, followed by a 12-hour LD cycle for seven days.	**Strengths** 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	Simulated shift work or jet lag decreased latency to mammary-gland tumor development or increased multiplicity 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** Studies of spontaneous tumors were of limited utility because of poor reporting; pathology methods were unclear, especially for looking at specific tumor types Other studies looked only at tumor progression, growth, latency	Consistent evidence of tumor promotion and growth Tumors: liver, Ehrlich carcinoma or sarcoma, 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)**	**Strengths** Outdoor light studies higher quality than indoor studies	Strongest evidence is for outdoor light or living near a strong LAN source; however, it is not clear whether LAN was a proxy for other activities; 1 study found an

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
		2 cohort studies, 1 case referent study, and 1 case-control study of outdoor light 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	**Limitations** Non-differential misclassification in exposure assessment, especially for indoor light studies Potential confounding from lifestyle factors	increased risk of breast cancer from exposure to blue light, suggesting a direct role of LAN Inconsistent across studies of indoor light; somewhat more consistent for measures of presumed higher exposure 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 methods were unclear, especially for looking at specific tumor types Other studies looked only at tumor progression, growth, latency	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: mammary gland, human breast, liver, lung, skin, peripheral nervous system and kidney, prostate, human cervix, glioma

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
				Some evidence that continuous light or long light days (natural lighting conditions of NW Russia) increased spontaneous tumors or decreased latency of several types 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	Studies in experimental animals	**Strengths** Evaluated role of melatonin in LAN-induced tumors	Co-exposure to melatonin restored mammary-gland tumor inhibitory activity in initiation-promotion studies of continuous light

Exposure	Outcome or effect	Evidence stream/approach	Strengths & limitations	Assessment of the evidence
	breast cancer or mammary-gland tumors	Light initiation-promotion studies ± melatonin Dim light human cancer xenograft or implant studies ± melatonin Human blood from women exposed to LAN	Human relevance **Limitations** Measured only tumor progression and growth	Co-exposure to melatonin restored human breast cancer inhibitory activity in xenograft studies of dim light or blood from women exposed to LAN
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 hypothesis	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	Cancer	Molecular epidemiology studies of clock gene expression in night shift workers Experimental animal studies of simulated shift work or jet lag and clock-gene expression; one was a carcinogenicity study 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 is 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	Strong (although indirect) evidence that altered clock-gene expression plays 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	Circadian clock is regulated at the epigenetic level Some studies in shift workers have found effect modification of clock-gene polymorphisms for both breast and prostate cancer	
Night-shift work	Biological effects related to cancer	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 and progesterone 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	Biological effects related to cancer	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

Abbreviations

ACF	aberrant colon crypt foci
ACS	American Cancer Prevention Study II
Akt	protein kinase B
ALAN	artificial light at night
AMOLED	active-matrix 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 LEDs
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

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.

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.

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.

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.

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).

Section 2 –

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 or 6:00 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.

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

Draft Report on Carcinogens Monograph on Night Shift Work and Light at Night

Draft Substance Profiles

August 24, 2018

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

Modern Lighting Practices That Cause Circadian Disruption

Introduction

The invention of electric light facilitated the transformation from 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 can potentially result in daily physiological and behavioral cycles (known as "circadian rhythms") becoming misaligned with external stimuli (a phenomenon known as "circadian disruption") or with each other. The circadian rhythms affected can include processes and behaviors such as sleep-wake cycles, eating schedules, and body temperature fluctuations, among others.

Two exposure scenarios related to modern lighting practices and circadian disruption are listed in the Report on Carcinogens:

1. Persistent night shift work (i.e., frequent and long-term, especially beginning in early adulthood) that causes circadian disruption.
2. Certain lighting conditions (i.e., excessive LAN exposure combined with insufficient daylight exposure) that cause circadian disruption.

This introduction discusses circadian biology, circadian disruption, and the association of circadian disruption with cancer, all of which are common to both listings, and is followed by the two substance profiles, which provide specific information for each exposure scenario.

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 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 is needed to make the internal clock match the 24-hour day (i.e., to "entrain" the clock). The major external signal that entrains the master clock to the 24-hour day is the light-dark cycle. The master clock is located in the suprachiasmatic nucleus (SCN) of the brain. A protein photoreceptor (melanopsin) in specialized cells of the eye (retinal ganglion cells) detects the light and relays the light signal to the SCN, which then sends signals to a large network of peripheral clocks, located in almost every cell of

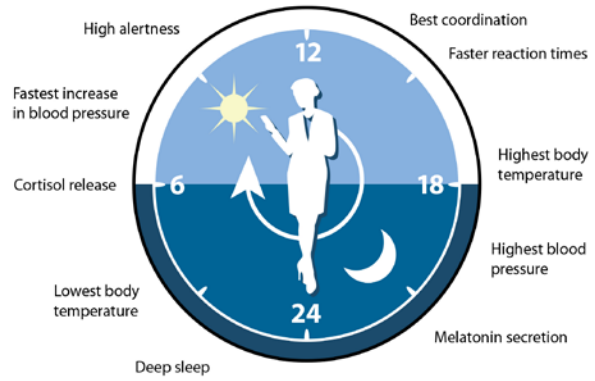

Figure 1. The circadian clock
Peaks in selected circadian rhythms and body temperature are shown across the 24 hour day.
Figure adapted from Nobel Prize 2017, with permission.

the body, to keep daily rhythms synchronized. Light that is effective in entraining the master clock is known as "circadian light." Other 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 through a series of positive and negative feedback loops and are responsible for generating the circadian rhythms of thousands of clock-controlled genes (Fu and Kettner 2013).

The SCN also sends a signal to the pineal gland in the brain to produce and secrete the hormone melatonin during darkness at night. Melatonin, in turn, conveys signals back to the SCN, to other parts of the brain, and to peripheral tissues to help coordinate physiological functions and behaviors to align with 24-hour days. In normally entrained individuals, levels of melatonin in the blood plasma are low during the day, start to increase in the evening (about 6:00 PM to 8:00 PM), peak in the middle of the biological night (midnight to 5:00 AM), and then decrease rapidly. Melatonin also regulates the sleep-wake cycle, causing drowsiness, and lowers the body temperature.

Circadian disruption occurs when this time structure becomes 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) (Zubidat and Haim 2017). Exposure to light affects the circadian system by changing the levels and timing of nighttime melatonin 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 shift. 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 shift. Circadian disruption occurs during the period of adaptation to the new work schedule or time change; however, few shift workers ever completely adapt their circadian rhythms to their new sleep schedule. The extent of the disruption depends on many factors, such as the direction of the phase shift, the type of work schedule, number of hours advanced or delayed and individual susceptibility (Arendt 2010, Stevens *et al.* 2011, Bonde *et al.* 2012, Haus and Smolensky 2013). Other characteristics of shift work, such as changes in meal timing and sleep disturbances, can also lead to circadian disruption, which can result in adverse health effects, including cancer (Smolensky *et al.* 2016).

Circadian Disruption and Cancer

The Melatonin Hypothesis

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. Because melatonin has anti-cancer properties and can suppress mammary-gland tumor growth in experimental animals, Stevens and colleagues (1992) hypothesized that the increasing breast-cancer incidence in many high-income countries might

be related in part to the increasing prevalence of light exposure at night, which is a hallmark of industrialization. Studies of cancer in night shift workers exposed to LAN were conducted to initially test this hypothesis and are discussed in the profile on Persistent Night Shift Work That Causes Circadian Disruption.

There is strong evidence that naturally occurring melatonin inhibits tumor growth in experimental animals (Mirick and Davis 2008) by protecting against biological events known to be related to cancer (Erren 2005, Hill *et al.* 2015). These protective effects, which affect all stages of cancer development and progression, include, at least (1) decreasing the levels and adverse effects of oxygen radicals, estrogens, and metabolism of fatty acids, (2) enhancing the immune system, (3) regulating the cell cycle to inhibit tumor growth by inhibiting cell proliferation and causing damaged cells to undergo programmed death (apoptosis), and (4) protecting against effects related to the spread of cancer cells to other organs (angiogenesis and metastasis) (Blask *et al.* 2002, Mediavilla *et al.* 2010, Srinivasan *et al.* 2011, Hardeland 2014, Gurer-Orhan and Suzen 2015, Haim and Zubidat 2015). Some of these effects are especially important for hormone-related cancers, such as breast cancer.

Melatonin is also important in preventing circadian disruption by regulating clock-gene expression and synchronization of the internal clocks. 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 mechanisms (i.e., mechanisms that do not involve changes to the DNA sequence, but regulate gene expression by processes such as adding methyl groups to DNA or causing changes in histones [proteins associated with DNA in the cell nuclei]). Studies of melatonin levels in humans, including those with normal sight and those with impaired vision (who are less sensitive to light-induced melatonin suppression) provide some support for the association between lower levels of melatonin at night and increased risk of breast cancer (NTP 2018).

Circadian Disruption Theory

Research since the melatonin hypothesis was proposed suggests that LAN causes other types of circadian disruption, in addition to suppressing nighttime melatonin levels, that may be linked to cancer. LAN causes phase shifts in the expression of clock genes in the master clock and peripheral clocks and in the circadian rhythms controlled by these genes, which can also result in a lack of coordination of circadian rhythms with each other and with the external environment. The evidence suggests that circadian disruption is an independent risk factor for cancer, and that tumor suppression is controlled, in part, by clock genes. This conclusion is based on the following lines of evidence: (1) disruption of clock-gene regulation occurs in human breast, prostate, and other cancers, and altered expression of some clock genes has been linked to tumor prognosis (Davis and Mirick 2006, Cadenas *et al.* 2014, Karantanos *et al.* 2014, Mazzoccoli *et al.* 2014, Altman 2016, Reszka and Przybek 2016), (2) animals in which expression of clock genes has been altered or inactivated show increased tumor growth or susceptibility to carcinogens (Fu *et al.* 2002, Wood *et al.* 2008, Lee *et al.* 2010, Zeng *et al.* 2010, Mteyrek *et al.* 2016, Mteyrek *et al.* 2017), (3) genes related to carcinogenicity (e.g., genes that control tumor suppression, DNA damage response, cell-cycle regulation, or glucose metabolism) are under circadian control, and (4) polymorphisms in clock genes (alternative forms of the genes) have been reported to be associated with increased breast-cancer risk (reviewed by Benna *et al.* 2017,

Reszka *et al.* 2017). Thus, a properly functioning circadian system plays an important role in preventing cancer formation and suppressing tumor growth (reviewed in NTP 2018).

Persistent Night Shift Work That Causes Circadian Disruption

CAS No.: none assigned

Known to be a human carcinogen[1]

Carcinogenicity

Persistent night shift work — i.e., frequent and long-term night shift work, especially beginning in early adulthood — that causes circadian disruption is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. This conclusion is based on the collective body of evidence from cancer epidemiological studies and mechanistic studies in humans and in experimental animals. Human epidemiological studies provide 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 the cancer pathway. In general, female night shift workers found to have elevated risk for breast cancer in the epidemiology studies are those who started working before age 30 and worked at least 3 times/week for 10 or more years; however, the exact conditions (e.g., duration) may depend on the specific combination of these metrics (e.g., duration may be longer if frequency is less).

Night shift work is typically defined as working at least 3 hours between midnight and 6:00 AM on a fixed (e.g., always working nights) or rotating (e.g., working evenings and days in addition to nights on a revolving basis) schedule. It is complex exposure scenario that includes exposure to electric LAN, sleep disturbances, or changes in meal timing, as well as other potential exposures (e.g., social stressors, lifestyle behaviors, decreased exposure to sunlight, and lower vitamin D levels). Most, but not all, of these exposures can lead to circadian disruption.

Epidemiological Cancer Studies in Humans

There is strong, but not 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 (well-designed and well-conducted studies capable of detecting an effect).

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 that may be related to workplace stress, such as smoking and alcohol consumption, parity or age at first full-term pregnancy, 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 all of the excess risk. Therefore, the exposure scenario that best fits the available epidemiological evidence is "persistent night shift work."

[1]NTP's preliminary listing recommendation.

Breast cancer

The conclusion that persistent night shift work increases the risk of breast cancer was based on an assessment of 21 studies, including 9 cohort studies and 12 case-control studies (see Table 1). These studies included women from specific populations (e.g., nurses, textile workers, etc.) as well as 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 higher 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 are 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. (See Human Cancer Studies: Breast Cancer for more information on the methods used to evaluate study quality and utility and how this was used in the cancer hazard assessment).

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 of different occupations and geographical locations, which helps to minimize concerns that chance or bias 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. Table 1 groups studies 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 asterisks indicate the strength of the association; tan indicates a null or negative association.

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. A pooled analysis of 5 case-control studies, which were conducted in Australia, Canada, and Europe using the same definition of night shift work (Cordina-Duverger *et al.* 2018), found a doubled risk of breast cancer among premenopausal women who had worked at least 3 nights per week for at least 10 years, at least 10-hour shifts, or within the last 2 years. Among postmenopausal women, evidence for an association with breast-cancer risk was weak. These findings are supported by the results of the two Nurses' Health Study cohorts, which used 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). A doubled risk of breast cancer was found in the younger cohort among women who had worked at least 3 shifts per month for at least 20 years, which was further increased when observations were restricted to the first 10 years of follow-up when the cohort was younger; no overall increased risk was observed in the older cohort except for a small, non-significantly elevated risk found during the first 10 years of follow-up when this cohort was younger. An increased risk of breast cancer was found in some cohorts of older women who had worked nights for many years; however, in most cases, the age when they started working nights was not known. The finding of an association of breast cancer

with more recent exposure (e.g., occurring in women still working or who recently worked night shifts) may suggest that night shift work acts to promote tumor growth and is 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.

Although the data from the cancer epidemiology studies are strong, they are not sufficient by themselves, because of (1) the low sensitivity of most cohort studies to assess metrics of persistent night shift work conditions, (2) the possibility, albeit slight, that case subjects may have remembered working night shifts better than did control subjects, thus creating a potential bias towards a false-positive result in the case-control studies, and (3) the possibility of co-exposure to other carcinogens in the occupational cohorts of nurses or in other specific industries. 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 of 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	++		+	
UK EPIC Oxford Travis *et al.* 2016	Cohort	Null	++[e]			
Million Women Study Travis *et al.* 2016	Cohort	Null	++[e]			
Tynes *et al.* 1996	Cohort		+++*		++	
Hansen 2001	Case-control	++	++		–	
Wang *et al.* 2015	Case-control	++			+	++
No evidence of 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)					

Number of + and shade of blue indicate the strength of the association with darker color and higher number of +s having the strongest association. The strength was based on the magnitude of the risk estimate and statistical significance or magnitude of the 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 ten studies included in the evaluation found that 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) and/or working night shift for a long duration (as shown in Figure 2 below) were associated with an increased risk of prostate cancer (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 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 were evaluated. (See Human Cancer Studies: Other Cancers for more information on the methods used to evaluate study quality and utility and how this was used in the cancer hazard assessment).

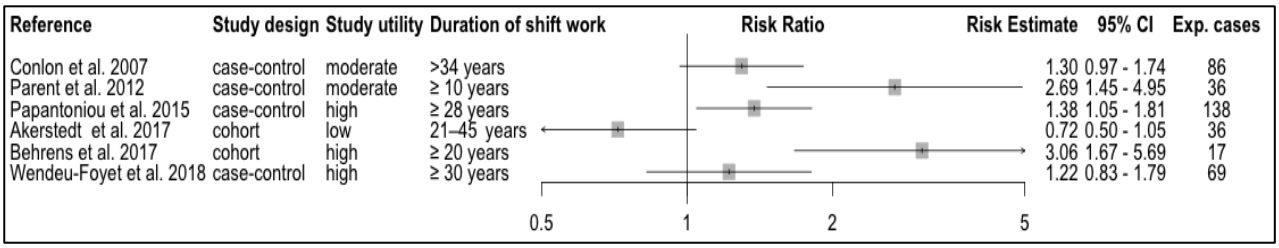

Figure 2. Forest plot of human studies on the risk of prostate cancer by lifetime duration of night shift work

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 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 (e.g., anti-cancer properties of melatonin on circadian clock genes) and cancer (see the Introduction). Because of the complex interactions and overlapping effects of LAN-induced melatonin suppression, circadian disruption, sleep deprivation, change in meal-timing, 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 (see Certain Lighting Conditions That Cause Circadian Disruption substance profile) and simulated shift

work or chronic jet lag (e.g., mimicking travel across several time zones) promotes tumor growth, supporting 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). A study using a strain of mice that is highly susceptible to mammary-gland tumors (i.e., that has a high background incidence of tumors) found that the mice exposed to simulated shift work developed mammary-gland tumors earlier than did the control-group mice (Van Dycke *et al.* 2015). 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). Three studies in mice found that simulated shift work or chronic jet lag promoted the growth of (1) mammary gland tumors initiated by co-exposure to a mammary-gland carcinogen (*N*-nitroso-*N*-methylurea) (Fang *et al.* 2017), (2) liver tumors initiated by co-exposure to a liver tumor carcinogen (diethylnitrosamine) (Filipski *et al.* 2009), and (3) lung tumors promoted by manipulating genes to make the mouse more susceptible to lung tumors (Papagiannakopoulos *et al.* 2016). Several studies in mice and rats found that simulated shift work or chronic jet lag enhanced the growth of cancer cells or tissue from the pancreas (Filipski *et al.* 2006), bone (osteosarcoma) (Filipski *et al.* 2004, Filipski *et al.* 2005, Filipski *et al.* 2006), lung (Wu *et al.* 2012), mammary tumor cells (Logan *et al.* 2012), immune system (plasmacytoma) (Wu *et al.* 1988), and abdominal fluid (Ehrlich sarcoma or carcinoma) (Li and Xu 1997) when implanted into host mice.

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 the Introduction). 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 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 so it parallels 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 studies of both rotating and night shift workers found that circadian rhythms of melatonin and cortisol levels and heart rate are not adapted to night work up to three consecutive night shifts (Jensen *et al.* 2016).

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. The timing of peak melatonin levels, which represents a change in the timing of the central clock (Arendt 2010), differed between night shift and day shift workers in some studies (Papantoniou *et al.* 2014, Gómez-Acebo *et al.* 2015, Leung *et al.* 2016). 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; however, only a few studies have measured both light and melatonin, and they have 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 causes several other biological effects that are related to carcinogenicity (e.g., decreased DNA repair, increased oxidative stress, increased inflammation or altered immune responses, altered circulating levels of estrogen and progesterone, 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 LAN 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. Overall, these data provide strong support for a role for melatonin suppression and desynchronization of the circadian clock genes (e.g., altered clock genes and lack of synergy of peripheral and central clock genes) in causing breast cancer in night shift workers.

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 6:00 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. Schedules can also vary in the number of consecutive days before shift changes; fast schedules change every 2, 3, or 4 days (IARC 2010, Stevens *et al.* 2011, Vermeulen 2016). 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). Intermediate rotating schedules (changing weekly) or slow rotating schedules (changing every 15 to 30 days) are other types of a rotating schedule. Persistent night shift work refers to frequent of long-term or working a large number of night shifts over a lifetime, especially in early adulthood.

Exposure

Over 10 million adults in the U.S. (7% of the working population) frequently work night shifts (defined as 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 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. Over half of these night shift workers are employed in the following types of occupations: (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 the Figure 3).

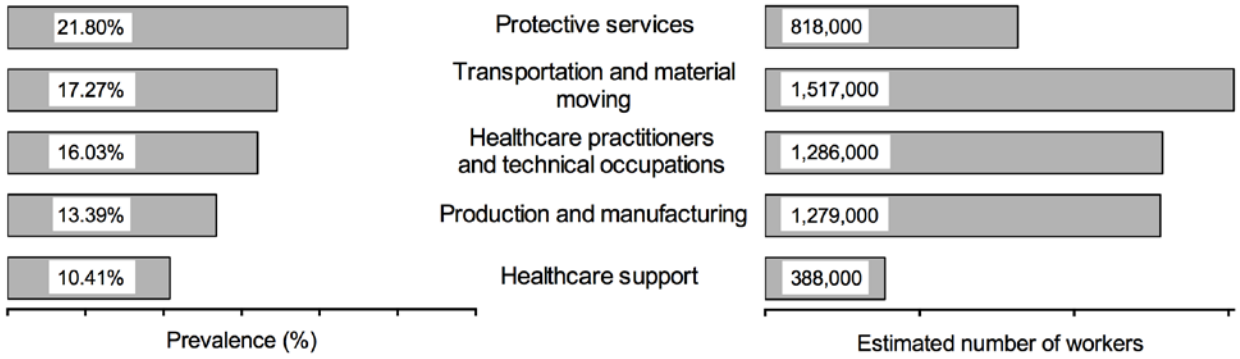

Figure 3. Prevalence and estimated numbers of U.S. workers who frequently work night shifts

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.

The percentage of U.S. workers working any type of non-day shift (including night, evening, or afternoon shifts) is at least 14%, and shift work may have increased in the last 10 years, based on estimates from various sources. The latest data (2004) from the U.S. Bureau of Labor Statistics (based on a sample of 10,189 workers) estimated that approximately 15 million U.S. workers (14.8% of the labor force) worked alternative shifts (evening, night, rotating, or split shifts or an employer-arranged irregular schedule) (BLS 2004, 2005, McMenamin 2007). Data from the 2015 National Health Interview Survey – Occupational Health Supplements survey (based on 19,456 adults) indicated that 27% of U.S. adults work evening, night, or rotating shifts, or some other non-day schedule (CDC 2015).

Transmeridian travel (crossing multiple time zones) and social jet lag represent a type of phase shift and can lead to circadian disruption. The U.S. Department of Transportation reported that approximately 117 million total passengers traveled on transmeridian flights in 2017. Social jet lag is 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") (Rutters *et al.* 2014, McMahon *et al.* 2018, Uzoigwe and Sanchez Franco 2018). Several studies have shown that over two-thirds of the general population could be affected by social jet lag (up to 2 hours difference in waking time between weekdays and

weekends), and adolescents can have even higher social jet lag (≥ 2 hours) (Roenneberg *et al.* 2012, Rutters *et al.* 2014, Malone *et al.* 2016, Koopman *et al.* 2017, McMahon *et al.* 2018).

Regulations

Federal Aviation Administration (FAA)

Flight crew member daily flight time hours are limited to 8 hours (for flight crew member report times between 12:00 midnight and 4:59 AM or between 8:00 PM and 11:59 PM) or 9 hours (for report times between 5:00 AM and 7:59 PM) for operations conducted with the minimum required flight crew (i.e., un-augmented operations).

Flight crew member duty hours are limited to 9 to 11 hours for flight crew member report times between 10:00 PM and 4:59 AM based on number of flight segments for un-augmented operations.

Flight crew member duty hours are limited to 13 to 18.5 hours for flight crew members reporting between 12:00 midnight and 5:59 AM or to 13 to 17 hours for report times between 5:00 PM and 11:59 PM based on number of pilots and type of aircraft rest facility when a crew has more than the minimum required flight crew, which allows a crew member to be replaced by another qualified crew member for in-flight rest (i.e., augmented operations).

Flight crew members are limited to working 3 consecutive flight duty periods that infringe on the window of circadian low or to working up to 5 consecutive flight duty periods that infringe upon the window of circadian low if they are provided an opportunity to rest at least 2 hours in a suitable accommodation during each of the 5 night-time flight duty periods. (A circadian low is defined as a period of maximum sleepiness that occurs between 2:00 AM and 5:59 AM during a physiological night [a physiological night's rest is 10 hours of rest encompassing the hours of 1:00 AM to 7:00 AM]).

Federal Railroad Administration (FRA)

When a commuter or intercity rail passenger transportation employee has at least 1 on-duty period that requires the employee to be on duty for any period of time between 8:01 PM on a calendar day and 3:59 AM on the next calendar day (i.e., a Type 2 assignment), the employee must have at least 24 consecutive hours off duty prior to initiating the next on-duty period based on a series of up to 14 consecutive calendar days.

Nuclear Regulatory Commission (NRC)

Fitness-for-duty program training for nuclear facility workers must include knowledge of the contributors to worker fatigue, circadian variations in alertness and performance, indications and risk factors for common sleep disorders, shift-work strategies for obtaining adequate rest, and the effective use of fatigue countermeasures.

Certain Lighting Conditions That Cause Circadian Disruption

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen[2]

Carcinogenicity

Certain lighting conditions — i.e., excessive exposure to electric LAN combined with insufficient daylight exposure — that cause circadian disruption are *reasonably anticipated to be a human carcinogen*. This conclusion is based on strong evidence that LAN acts through mechanisms that are likely to cause cancer in humans and limited evidence of the carcinogenicity of LAN from studies 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. In addition, LAN causes biological effects that are characteristics of recognized carcinogens. Studies in humans show that LAN causes melatonin suppression and may increase breast cancer risk. 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 characteristics related to electric light that are most likely to cause circadian disruption include a combination of shorter wavelengths (e.g., blue light), longer duration, higher light intensity or levels, and exposure to electric light during the biological night. The exact conditions (e.g., duration) depends 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. (See "Characteristics of Certain Lighting Conditions" for more information on the lighting characteristics.)

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 Introduction).

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 (dimethyl-benz[*a*]anthracene and *N*-methyl-*N*-nitrosourea) 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 (as summarized in Table 2). In addition, exposure of rats to seasonal lighting for Northern latitudes (i.e., a maximum of

[2]NTP preliminary listing recommendation.

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 2 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 (human), 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 2). 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) and one study found a decrease in tumor growth with LAN exposure (Isobe *et al.* 2008).

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 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 2. 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

Tumor type	Constant light	Dim LAN	Altered L-D cycle	References
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 cycle = light-dark cycle; ↑ = statistically significant increase; Empty cells = not tested; PNS = peripheral nervous system; xenograft = 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 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 Introduction).

Experimental studies in humans provide evidence that electrical 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. A potential threshold for melatonin suppression (about 15% melatonin suppression) would be about 30 lux of white light at the cornea for 60 minutes. 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 induced a greater degree of

melatonin suppression in teens (aged 15 to 17 years) (~25%) 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 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; and see Circadian Disruption, Light at Night, and Night Shift Work).

LAN causes biological effects in experimental animals (e.g., decreased DNA repair, increased oxidative stress, increased inflammation, altered metabolism, and altered estrogen levels) similar to those induced by known human carcinogens and also consistent with effects mediated by low melatonin levels or deregulation of core clock genes (see Mechanisms and Other Relevant Data). 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 are exposed to LAN, supporting the conclusion that exposure to certain lighting conditions is reasonably anticipated to cause cancer in humans.

Epidemiological Cancer Studies in Humans

Epidemiological studies provided consistent evidence of an increased risk of breast cancer among women living in areas with high exposure to LAN. LAN was measured using satellite imagery data. 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). Two studies found evidence to suggest that breast-cancer risk increases with increasing LAN exposure, and the increased risk was observed mainly in premenopausal women (Hurley *et al.* 2014, James *et al.* 2017) (see Figure 4). 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 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. However, the Spanish case-control study (Garcia-Saenz *et al.* 2018) found an increased risk of breast cancer from living at residences with increased exposure to outdoor light in the blue spectrum but not outdoor light in the overall visible spectrum, suggesting a direct link to LAN exposure.

The database was inadequate to evaluate the risk of breast cancer due to LAN exposure in bedrooms or sleeping areas. The studies 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 (see Other Human Cancer Studies).

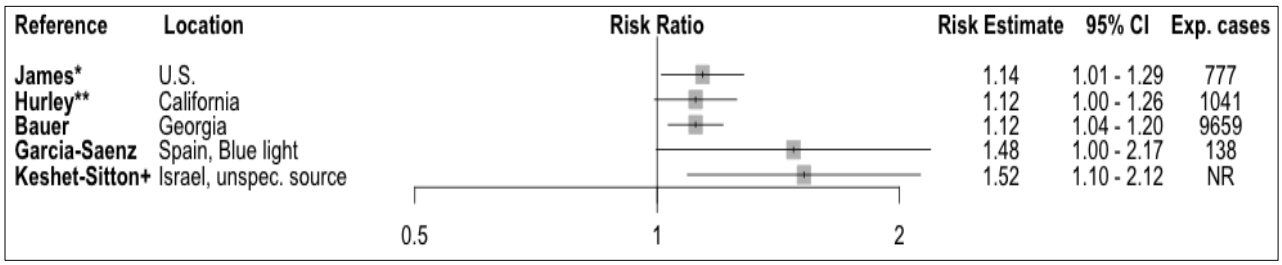

Figure 4. The risk of breast cancer in women exposed to light at night

*Trend test $P = 0.02$; **Trend test $P = 0.06$.

+Unspecified outdoor source of LAN.

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 electrical 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

"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 5 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. (See Studies of LAN and circadian disruption-related cancer for more information.)

Natural and electric light

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). Natural light, which includes a broad range of wavelengths ranging from ~380 nanometers (nm) to 780 nm, comes directly from the sun, scattered and reflected by the atmosphere, or reflected by the moon. The outdoor light level is about 10,000 lux on a clear day, but bright sunlight can be as much as 10 times higher at 100,000 lux (NOAO 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).

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 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 5).

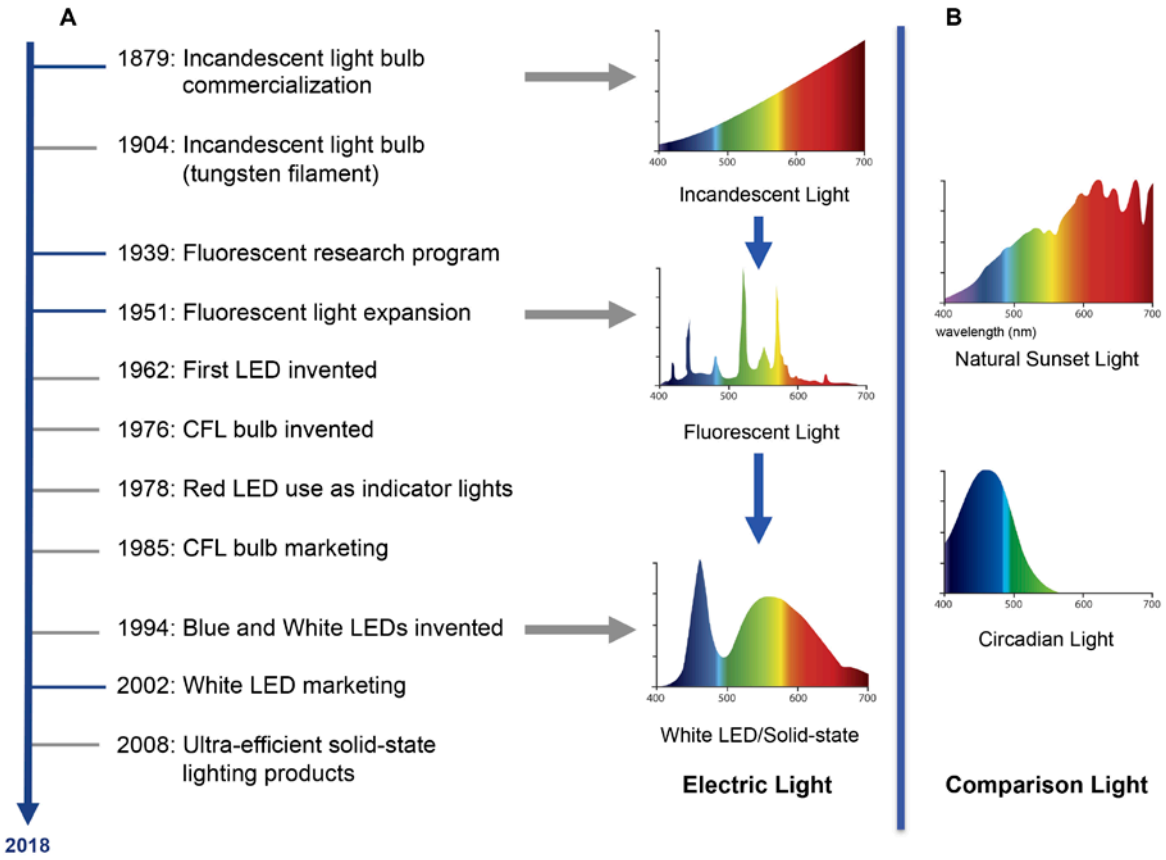

Figure 5. Technological advances in lighting over time have led to lighting with higher levels of short wavelengths

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.

Human Exposure

A significant number of U.S. residents are exposed to aberrant lighting conditions resulting from electrical LAN from outdoor lights, indoor lights at home and at work, and use of self-luminous electronic devices and insufficient natural light during the day.

Indoor light

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). 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). Further, use of LED lighting for indoor

commercial and residential applications (e.g., recessed downlights in offices and kitchens) is rapidly increasing (DOE 2018). These sources generally have a different range of wavelengths compared with natural light (see figure above). 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).

Outdoor light

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). Major sources of light for these uses 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). The use of LED lights outdoors is increasing rapidly (NOAO 2018). In 2016, satellite imaging data of the Earth at night (see figure) 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.

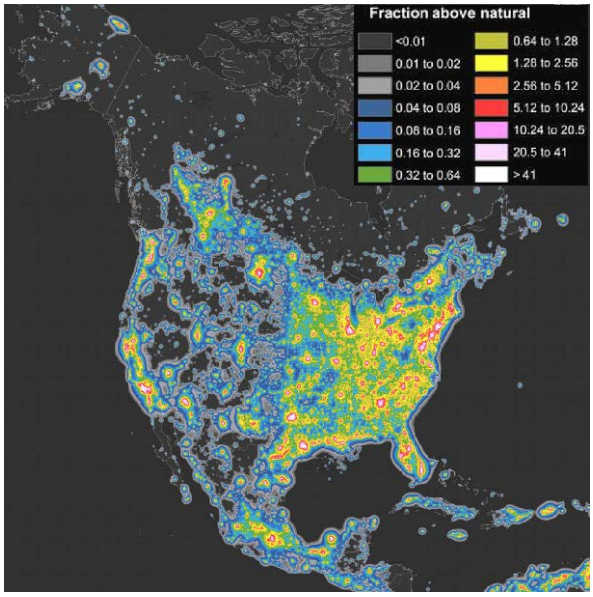

Figure 6. Map of North America's artificial sky brightness, in twofold increasing steps, as a ratio to the natural sky brightness
Source: Falchi *et al.* 2016.

Regulations

No regulations specific to reduction of exposure to certain lighting conditions were identified.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

In occupational settings where conflicting lighting needs exist (e.g., night work at a hospital), lighting should be optimized to provide low-intensity, blue wavelength-depleted light (e.g., in hospital patient bedrooms) or high intensity, blue wavelength-enriched light (e.g., at nurse

stations) as appropriate. ACGIH published a Notice of Intent to Establish entitled "Statement on the Occupational Health Aspects of New Lighting Technologies – Circadian, Neuroendocrine, and Neurobehavioral Effects of Light" containing this guidance in 2018.

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