National Toxicology Program
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Summary of NTP Cancer Hazard Conclusions

Exposure Circumstances That Cause Circadian Disruption:

Persistent Night Shift Work
Certain Lighting Conditions

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

About This Report

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This document provides a brief summary of the scientific evidence supporting NTP's cancer hazard assessments conclusions for two exposure scenarios that can lead to circadian disruption: persistent night shift work and certain lighting conditions. The full report, National Toxicology Program Cancer Hazard Assessment on Night Shift Work and Light at Night is available at https://ntp.niehs.nih.gov/go/NSW_LAN.

The Collaborators are listed below, for a complete list of contributors and the peer review panel, as well as information on the peer review, please see the full report.

Collaborators

Role	Collaborator	Affiliation
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NTP 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, DrPH	ILS ILS NIEHS, DNTP NIEHS, DNTP

Introduction

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

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

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

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

Part 1: Circadian Rhythms, Circadian Disruption, and Cancer

The Biology of Circadian Rhythms and Their Disruption

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

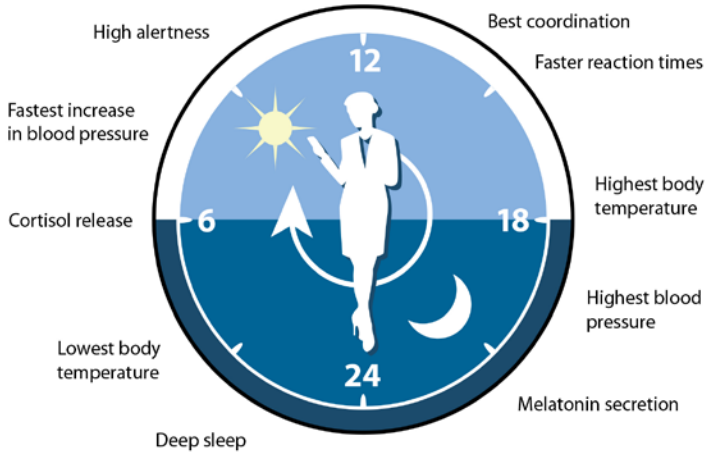

Figure 1. The circadian clock
Peaks in selected circadian rhythms and body temperature are shown across the 24-hour day.
Figure adapted from Nobel Prize 2017, with permission.

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

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

Circadian Disruption and Cancer

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

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

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

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

Part 2: Persistent Night Shift Work

Characteristics of Night Shift Work

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

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

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

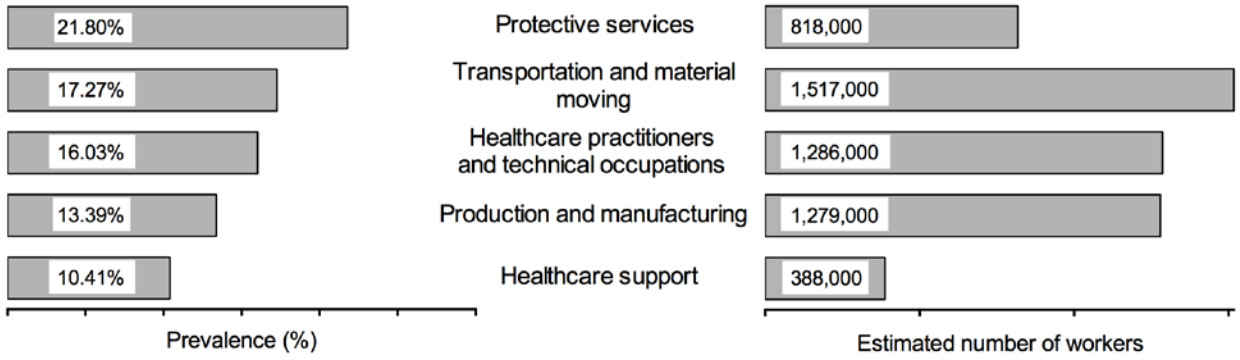

Figure 2. Prevalence and estimated numbers of U.S. workers who frequently work night shifts

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

Cancer Hazard Assessment Conclusions

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

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

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

Epidemiological Cancer Studies in Humans

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

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

Female breast cancer

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

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

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

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

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

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

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

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

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

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

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

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

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

[d]Cumulative number of night shifts.

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

[f]Ever exposed to phase-shift work.

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

Prostate cancer

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

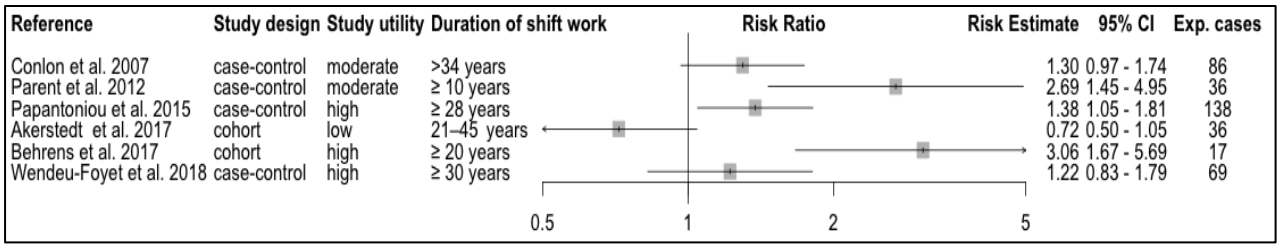

Figure 3. Forest plot of human studies on the risk of prostate cancer by cumulative duration of night shift work

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

Studies on Mechanisms of Carcinogenesis and Other Relevant Data

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

Studies in experimental animals

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

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

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

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

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

Studies of night shift work and cancer related to circadian disruption

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

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

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

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

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

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

Part 3: Certain Lighting Conditions

Characteristics of Certain Lighting Conditions

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

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

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

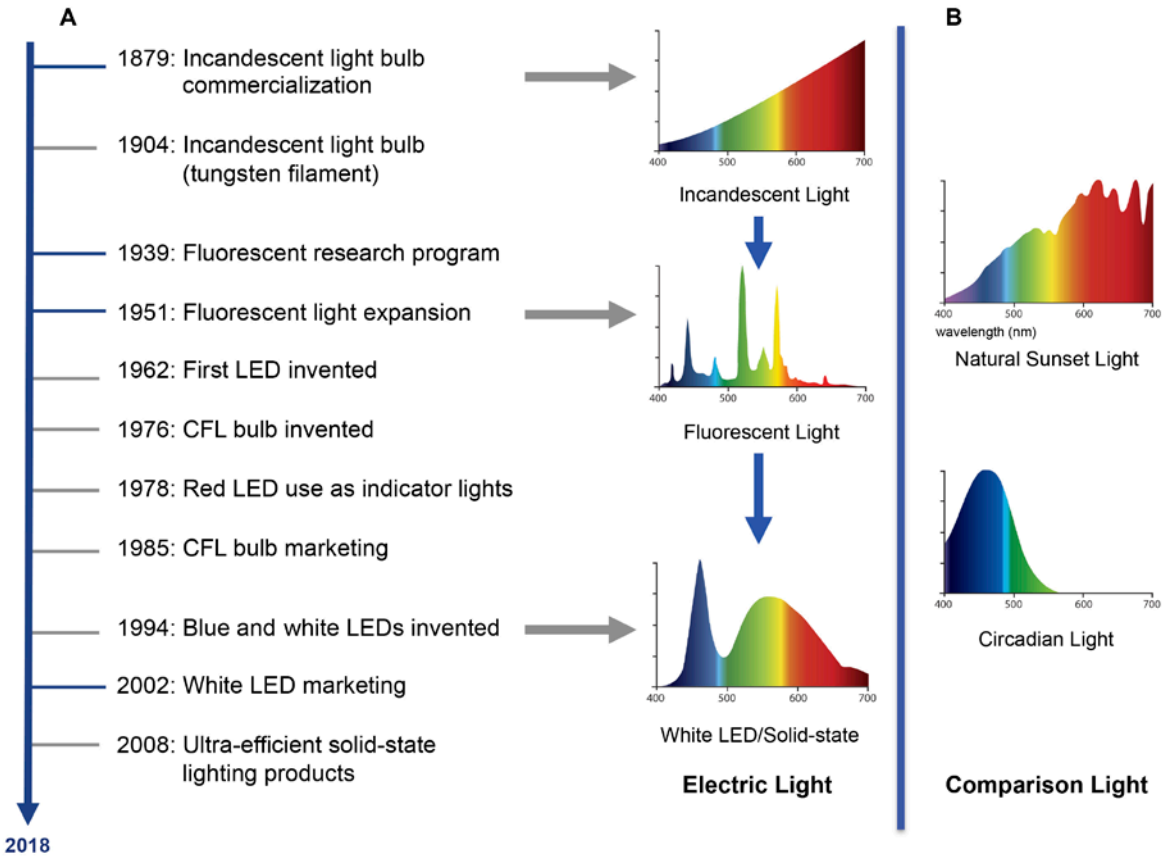

Figure 4. Technological advances in lighting over time have led to lighting with higher levels of short wavelengths

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

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

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

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

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

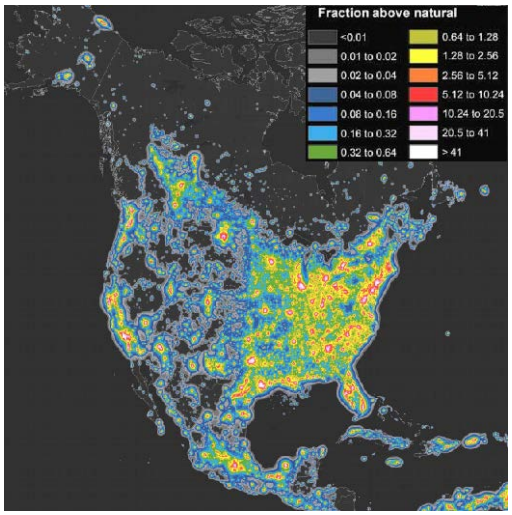

Figure 5. Map of North America's artificial sky brightness, in twofold increasing steps, as a ratio to the natural sky brightness

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

Cancer Hazard Assessment Conclusions

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

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

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

Studies on Mechanisms of Carcinogenesis and Other Relevant Data

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

Cancer studies in experimental animals

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

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

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

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

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

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

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

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

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

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

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

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

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

Epidemiological Cancer Studies in Humans

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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