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Does Current Scientific Evidence Support a Link Between Light at Night and Breast Cancer Among Female Night-Shift Nurses?:

Review of Evidence and Implications for Occupational and Environmental Health Nurses

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Abstract

Breast cancer is increasingly prevalent in industrialized regions of the world, and exposure to light at night (LAN) has been proposed as a potential risk factor. Epidemiological observations have documented an increased breast cancer risk among female night-shift workers, and strong experimental evidence for this relationship has also been found in rodent models. Indirect support for the LAN hypothesis comes from studies involving blind women, sleep duration, bedroom light levels, and community nighttime light levels. This article reviews the literature, discusses possible mechanisms of action, and provides recommendations for occupational health nursing research, practice, and education. Research is needed to further explore the relationship between exposure to LAN and breast cancer risk and elucidate the mechanisms underlying this relationship before interventions can be designed for prevention and mitigation of breast cancer.

Breast cancer is a leading cause of cancer incidence and death among women around the world (World Health Organization, 2011). For unknown reasons, the incidence of breast cancer is increasing worldwide, with the highest prevalence in developed countries (Kamangar, Dores, & Anderson, 2006). Parkin (2004) reported a five- to ten-fold higher risk of breast cancer in the industrialized countries of North America, Europe, and Australia compared to developing countries in Africa and parts of Asia. Analysis reveals that less than 50% of the international variation in breast cancer risk can be accounted for by known risk factors, such as family history of breast cancer, reproductive factors (e.g., early menarche, low parity, late age at first childbirth, late menopause), and modifiable lifestyle factors (e.g., alcohol use, overweight and obesity, physical inactivity) (Madigan, Ziegler, Benichou, Bryne, & Hoover, 1995; Nagata, Kawakami, & Shimizu, 1997).

Westernized regions of the world are increasingly becoming 24-hour-a-day societies in which citizens are exposed to more artificial light during the night in their homes and

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especially in their workplaces (Stevens, 2006). The International Agency for Research on Cancer (IARC) has recently categorized shift work involving circadian disruption as "probably carcinogenic to humans (Group 2A)" on the basis of limited human evidence and sufficient experimental animal evidence (IARC, 2007). In developed countries, approximately 20% of the population works shifts (IARC, 2007). During the past few decades, a growing number of women in developed countries have entered the work force, but few studies to date have assessed how occupational exposures may be increasing breast cancer risk among working women. However, it has recently been hypothesized that exposure to light at night (LAN) among night-shift workers may increase breast cancer risk. This theory has been supported by epidemiological observations of increased breast cancer risk among female night-shift workers and strong experimental evidence in rodent models (Blask et al., 2005; Hansen & Stevens, 2011; Lie, Roessink, & Kjaerheim, 2006; Schernhammer, Kroenke, Laden, & Hankinson, 2006; Schernhammer et al., 2001). Additionally, indirect support for the LAN hypothesis has come from studies involving blind women, sleep duration, bedroom light levels, and community nighttime light levels (Flynn-Evans, Stevens, Tabandeh, Schernhammer, & Lockley, 2009; Kakizaki et al., 2008; Kloog, Haim, Stevens, Barchana, & Portnov, 2008; Kloog, Portnov, Rennert, & Haim, 2011; Pukkala, Ojamo, Rudanko, Stevens, & Verkasalo, 2006; Wu et al., 2008).

Because both breast cancer and night-shift work are prevalent and increasing in modern societies, exposure to LAN may be a significant public health concern. This article focuses on implications of this association by examining the risk of breast cancer among night-shift nurses. The purpose of this article is to (1) review empirical evidence of the link between LAN and breast cancer, (2) discuss possible mechanisms of action, and (3) recommend future nursing research and changes in practice and education. The possible identification of LAN as a modifiable risk factor carries important implications for risk prevention and possible treatment.

METHODS

Three online databases, CINAHL, PubMed Plus, and PsycINFO, were used to identify articles examining the impact of LAN exposure on breast cancer risk among female night-shift nurses. The following limits were placed on all searches: (1) English language, (2) human studies, and (3) research articles published after 2001. The search terms included light at night, shift work, night shift, and breast cancer. A total of 11 epidemiological studies meeting the inclusion criteria were identified (Table; www.healio.com/AAOHN). Eight were case-controlled studies and three were cohort studies. The reference lists at the end of these articles were reviewed and review articles were studied to develop a broader understanding of occupational exposure to LAN and breast cancer.

LAN AND BREAST CANCER AMONG FEMALE NIGHT-SHIFT NURSES

Duration of Shift Work

Studies have reported a dose-dependent relationship between increased breast cancer risk and increased years and hours per week of night-shift work (Davis, Mirick, & Stevens, 2001; Pesch et al., 2010). In a large-scale study of Norwegian nurses (*N* = 43,835), a significant increased risk for breast cancer was found among nurses who had worked nights for 30 or more years compared to nurses who did not work night shifts after graduation from nursing school (odds ratio [OR] = 2.21, 95% confidence interval [CI] = 1.10–4.45; *p* = .01) (Lie, Roessink, & Kjaerheim, 2006). Schernhammer et al. (2006) similarly reported a modestly elevated risk of breast cancer after longer periods of rotating night work in a prospective cohort of 116,671 female nurses in the United States. Women who reported more than 20 years of rotating night-shift work were at a higher relative risk (RR) for breast cancer than women who never worked rotating night shifts (RR = 1.79, 95% CI = 1.06–3.01) (Schernhammer et al., 2006). Similarly, Schernhammer et al. (2001) used data from the Nurses' Health Study, in which 78,562 female U.S. nurses responded to a questionnaire regarding their history of rotating night shift work, to conduct a prospective cohort study. This large cohort was followed from 1988 through 1998, during which time 2,411 cases of breast cancer were diagnosed. Compared to women who had never worked night shifts, nurses who had participated in night-shift work for between 1 and 29 years showed an 8% increase in RR of breast cancer and nurses who worked 30 years or more on rotating night shift showed a 36% increase in RR (*p* = .02).

Day vs. Permanent Night vs. Rotating Shift Work

Patterns of night-shift work may also be a significant variable. Nurses who work rotating shifts after midnight have been shown to have a significantly increased risk (OR = 1.8, 95% CI = 1.2–2.8) for breast cancer relative to nurses who work permanent day shifts (Hansen & Stevens, 2011). However, no significant difference in breast cancer incidence has been found between nurses who work evenings and those who work permanent day shift (Hansen & Stevens, 2011). Of all rotating shift patterns investigated by Hansen and Stevens (2011), the highest breast cancer risk (OR = 2.6, 95% CI = 1.8–3.8) was observed for long-term day-night rotating shifts. In a study assessing the impact of the number of consecutive night shifts on breast cancer risk among 49,402 Norwegian nurses, researchers found a nonsignificant increased risk of breast cancer for nurses who worked at least 5 years with four or more (OR = 1.4) and five or more (OR = 1.6) consecutive night shifts per month (Lie et al., 2011). However, a significantly increased risk of breast cancer was observed for nurses who worked at least 5 years with six or more consecutive night shifts per month (OR = 1.8), suggesting that risk may be proportional to number of consecutive night shifts worked (Lie et al., 2011).

LAN, Melatonin Levels, and Shift Work

Some have suggested that melatonin may play a role in the relationship between LAN and cancer (Hansen, 2001; Travis, Allen, Fentiman, & Key, 2004). Grundy, Tranmer, Richardson, Graham, and Aronson (2011) recently examined the influence of exposure to LAN on melatonin levels among 123 rotating-shift nurses (two 12-hour days, two 12-hour nights, and 5 days off) and reported that although mean light exposure was significantly higher for nurses working at night ($p < .0001$), both peak melatonin levels ($p = .65$) and the daily change in melatonin levels ($p = .80$) were similar across day and night shifts. In this study, light exposure was not strongly associated with suppressed melatonin production among nurses on a rapidly rotating shift pattern. In a study assessing the associations among exposure to LAN (based on data on sleeping habits and history of night-shift work), 6-

sulfatoxymelatonin (the primary metabolite of melatonin in urine), and serum concentrations of estrogen among postmenopausal Japanese women, Nagata et al. (2008) found exposure to LAN to be significantly associated with increased serum estrogen levels and decreased urinary 6-sulfatoxymelatonin levels, but not estrogen and melatonin metabolite levels. Although this investigation points to LAN as a potential risk factor for breast cancer, the role of melatonin as a mediator between LAN and serum estrogen levels was unclear.

Despite the presence of supportive data, direct evidence for the LAN hypothesis has not been consistent. Some studies suggest no association between breast cancer risk and frequency, duration, or cumulative amount of night-shift work, with one reporting that female night-shift workers are at a *lower* risk for breast cancer than female non-shift workers (O'Leary et al., 2006; Pesch et al., 2010; Pronk et al., 2010). Inconsistent findings across the current body of evidence may be due, in part, to variations in study design, definitions of shift work, potential recall bias, and incomplete adjustment for confounding factors (Table; www.healio.com/AAOHN).

INDIRECT EVIDENCE

The LAN hypothesis is difficult to test because almost everyone in the modern world uses artificial light to shorten the daily dark period; an appropriate comparison group is challenging to create. Indirect support for the LAN hypothesis has therefore been derived from human studies of blind women, sleep duration, bedroom light levels, and community nighttime light levels. Although not necessarily generalizable to humans, compelling evidence from rodent studies provides grounding for further investigation of the LAN hypothesis in humans.

Blind Women

Several U.S. and European studies have supported a lower risk of breast cancer among visually impaired women compared to sighted women, with risk decreasing by degree of visual impairment in an inverse dose-response relationship (Flynn-Evans et al., 2009; Pukkala et al., 2006). Specifically, blind women with no perception of light have been shown to have a lower risk of breast cancer compared to blind women with light perception (Flynn-Evans et al., 2009). Although it may be speculated that this lower risk is related to mechanisms impacted by ocular light perception (i.e., melatonin signal, circadian synchronization), research is needed to clarify the relationship between the physiological implications of light perception among the blind and breast cancer risk.

Sleep Duration

Sleep duration has been hypothesized to be inversely related to breast cancer risk, possibly due to extended exposure to darkness and thereby greater melatonin production in those who sleep for longer durations (Kakizaki et al., 2008; Verkasalo et al., 2005; Wu et al., 2008). Numerous studies have reported an inverse association between sleep duration and breast cancer risk (Kakizaki et al., 2008; Wu et al., 2008). A prospective cohort study of women in Finland found this relationship to be an inverse dose-response (Verkasalo et al., 2005). However, in another report on sleep duration and breast cancer risk in the Nurses' Health

Study I, researchers found no overall association, with a modest increased risk in those who reported 9 or more hours of sleep compared to those who reported 7 hours of sleep (Pinheiro, Schernhammer, Tworoger, & Michels, 2006).

Although melatonin levels have been reported to be 42% higher among women who sleep 9 or more hours compared to women who sleep 6 or fewer hours, a recent study conducted among female rotating-shift nurses did not find sleep duration to be correlated with urinary melatonin levels, suggesting that these levels may not be the best surrogate for melatonin production (Grundy et al., 2009; Wu et al., 2008). Additionally, self-report may make study results vulnerable to recall bias and limit their ability to accurately assess sleep duration and exposure to complete darkness at night.

Bedroom Light Levels

Several studies have addressed the possibility that chronic exposure to low-level LAN in the sleeping environment may increase breast cancer risk. Kloog et al. (2011) reported a significant association between exposure to LAN in individuals' sleeping habitats and increased breast cancer risk ($p < .001$). Li et al. (2010) found a similar, although nonsignificant, trend toward increased risk of breast cancer among postmenopausal women who kept the lights on while sleeping (OR = 1.4), mainly slept during the daytime (OR = 1.4), and did not draw curtains while sleeping at night (OR = 1.2). O'Leary et al. (2006) reported an increased risk of breast cancer among women who frequently turned on lights two or more times per night (OR = 1.65) compared to those who rarely turned on lights. Although Davis et al. (2001) reported that breast cancer risk did not increase with sleep interrupted by turning on a light, they found that the risk was highest among individuals with the brightest bedrooms. It remains unclear whether low-level light can substantially impact nocturnal melatonin production, highlighting the need for further experimental studies.

Community Nighttime Light Levels

The association between breast cancer incidence and community nighttime light levels has been assessed at the population level. Researchers reported that breast cancer incidence across 147 Israeli communities was significantly associated with satellite data of nocturnal community light levels, with a 73% higher incidence in the highest LAN intensity communities compared to the lowest (Kloog et al., 2008). Some of the same researchers conducted a later study investigating whether country-level LAN was associated with breast cancer incidence, finding a 30% to 50% higher risk of breast cancer in the highest LAN-exposed countries compared to the lowest LAN-exposed countries (Kloog, Stevens, Haim, & Portnov, 2010). These findings support the coherence of existing individual findings with population trends. However, satellite images may not yield precise values for exposure to LAN at eye level.

Animal Studies

A strong rodent model supports the LAN hypothesis. Research demonstrates that exposure to LAN can accelerate tumor growth in vivo (Blask, Dauchy, Sauer, Krause, & Brainard, 2003; Wu et al., 2011). Studies have demonstrated that rodent exposure to as little as 0.2 lux of LAN can disrupt host circadian rhythms in non-tumor-bearing rats and stimulate the metabolism and proliferation of human cancer xenografts in rats (Dauchy et al., 2010; Dauchy, Sauer, Blask, & Vaughan, 1997). For comparative purposes, normative light levels are defined as follows (Higgins, Winkelman, Lipson, Guo, & Rodgers, 2007):

- Full daylight, outdoors but indirect sunlight = 10,000 to 20,000 lux
- Overcast day = 1,000 lux
- Indoor office light = 100 to 300 lux
- Twilight = 10 lux
- Full moon = 0.1 lux

As another point of reference, the mean light level of acute care hospital floors has been reported to be approximately 70 lux (Higgins et al., 2007). Regarding the mechanism potentially underlying this interaction, it has been demonstrated that pinealectomy in rats boosts tumor growth (the pineal gland is responsible for the production and secretion of melatonin) while exogenous melatonin administration exerts oncostatic effects (Grant, Melan, Latimer, & Witt-Enderby, 2009; Tamarkin et al., 1981). In further support of this melatonin-associated mechanism of action, Blask et al. (2005) designed an innovative study in which a human-derived tumor was implanted into a rat and perfused with human blood from women under one of three conditions (i.e., during the day, during the night in darkness, and during the night after exposure to LAN) to experimentally determine, as close as ethically possible, the effects of exposure to LAN on breast cancer growth in women. The melatonin-rich blood obtained in the dark of night significantly slowed tumor growth, but the melatonin-deficient blood obtained during the day and following exposure to LAN did not (Blask et al., 2005).

MECHANISMS OF ACTION

A variety of potential mechanisms of action have been proposed to explain the association among shift work, exposure to LAN, and breast cancer, including melatonin suppression, phase shift, sleep disruption, lifestyle factors (i.e., poor diet and exercise, higher body mass index), and lower vitamin D levels (Figure). As research on the detrimental effects of exposure to LAN on breast cancer risk continues, elucidating all potential mechanisms for this effect will be crucial in developing risk reduction and prevention strategies as well as treatment interventions.

Melatonin Suppression

Exposure to LAN during night-shift work may influence breast cancer risk by suppressing melatonin release and thereby diminishing the anti-carcinogenic effects of this circadian hormone. Melatonin is produced and secreted by the pineal gland. The release of melatonin is regulated by environmental light levels such that production is suppressed by light and restored by darkness (Blask, Dauchy, Brainard, & Hanifin, 2009). Melatonin levels begin to rise around 9:00 p.m., reach a peak around 3:00 am, and decrease thereafter until dawn. In addition to playing a significant role in regulating the circadian sleep-wake cycle, melatonin also possesses oncostatic potential via the inhibition of tumor development and reduction in levels of reproductive hormones implicated in cancer development (Grant et al., 2009).

The normal nocturnal melatonin signal has been shown to directly inhibit human breast cancer growth, but this effect is extinguished when darkness is interrupted by even short-term exposure to LAN (Blask et al., 2005, 2009). In fact, the effects of exposure to LAN on tumor growth have been shown to be *intensity dependent* in both laboratory and population studies. Blask et al. (2005) demonstrated that exposure of rat hepatoma and human breast cancer xenograft to increasing intensities of white fluorescent light during the night results in a dose-dependent suppression of nocturnal melatonin blood levels and stimulation of tumor growth. Similarly, a recent population study analyzed the co-distribution of LAN and breast cancer rates using satellite images of various LAN intensities across 147 Israeli communities. The researchers found a significant, positive correlation between LAN intensity and breast cancer rates, with a 73% higher incidence of breast cancer among communities exposed to the highest-intensity LAN compared to those exposed to the lowest-intensity LAN (Kloog et al., 2008).

Melatonin also normally reduces estrogen activity through indirect neuroendocrine mechanisms and direct cellular action (Cos et al., 2006). Because lifetime estrogen burden is thought to be a major determinant of breast cancer risk, it has been hypothesized that LAN-induced melatonin suppression can increase estrogen production and thereby increase breast cancer risk (Feigelson & Henderson, 1996).

Phase Shift

Many cellular, tissue, and organ processes in the human body are conducted in a rhythmic fashion, synchronized to the sleep-wake cycle governed by the circadian clock in the suprachiasmatic nuclei of the brain. Normal temporal coordination and interaction among the circadian release of melatonin, the sleep-wake cycle, and the immune system minimizes runaway, asynchronous cell proliferation characteristic of malignant tumors (Fu & Lee, 2003). However, phase shift, which can occur when an individual works at unusual times, may confuse the body's master clock and have a desynchronizing effect that promotes the growth and development of cancer.

Clock genes, which are responsible for the generation and regulation of circadian rhythms, can act as tumor suppressors. Both in vitro and in vivo laboratory studies have demonstrated links between alterations in clock gene expression and tumor induction and growth (Kuo et al., 2009; Yang et al., 2009). Epidemiological studies have demonstrated an association between clock gene polymorphisms and breast cancer (Hoffman et al., 2010; Zhu et al., 2008). Additional research is warranted to further explore the mechanism by which variations in clock gene expression may contribute to the development and progression of cancer and to further examine the impact of shift work on clock gene polymorphisms and gene expression linked to cancer.

Sleep Disruption

Sleep disruption is common among shift workers. Human epidemiological studies have demonstrated an inverse relationship between sleep duration and breast cancer risk (Kakizaki et al., 2008; Verkasalo et al., 2005; Wu et al., 2008). This finding is particularly pertinent to nurses, as mean sleep duration for nurses working during the day (8.27 hours) has been reported as significantly longer than for nurses working at night (4.78 hours) ($p < .0001$) (Grundy et al., 2009). Proposed mechanisms for this association are rooted in inadequate or frequently disturbed sleep giving rise to suppressed melatonin production, suppressed immune surveillance and altered immune function (e.g., cytokine balance shifts in which more cancer-stimulatory cytokines are produced), and increased metabolic pathways that lead to obesity (e.g., altered glucose metabolism, increased appetite, and lower energy expenditure) (Costa, Haus, & Stevens, 2010; Knutson, Spiegel, Penev, & Van Cauter, 2007). The melatonin suppression theory applies to sleep deprivation accompanied by exposure to LAN, as sleep deprivation alone does not suppress melatonin production; as long as an individual remains in complete darkness, melatonin production should not be affected. The strongest evidence for sleep deprivation's detrimental effects on breast cancer risk is rooted in the immune function hypothesis. However, the epidemiological evidence overall is rather limited and inconclusive because poor sleep is difficult to measure and can occur in the context of a myriad of other factors (e.g., increased stress, changes in hormones, poor eating habits) that could potentially affect health status. More animal and large-scale prospective cohort studies should be conducted to further investigate the relationship between sleep duration and breast cancer risk. To explore the effects of sleep deprivation and isolate the most influential mechanism of action in this relationship, the effects of sleep disruption in the absence of LAN or melatonin suppression on breast cancer risk should be considered specifically.

Lifestyle Factors

Some evidence exists that shift workers are more likely than non-shift workers to engage in lifestyle factors known to be associated with increased risk of cancer (e.g., poor diet, physical inactivity, and tobacco use) (Puttonen, Härmä, & Hublin, 2010). Regarding diet, night-shift workers may eat high-energy-dense foods in an effort to stay awake, or they may not eat enough due to lack of time, access, or hunger due to timing that is in conflict with the sleep-wake cycle. In terms of physical inactivity, night-shift workers may have lower levels of recreational physical activity than the general population because they are working through the night and may be sleeping through much of the day.

Low Vitamin D

Shift workers may have lower vitamin D levels because they have less opportunity to spend time outside in sunlight. Both animal and human studies have found sun exposure to be protective against several cancers, including breast cancer (Rhee, Coebergh, & Vries, 2009). Evidence suggests that efforts to improve vitamin D status, through sun exposure or supplementation, could reduce cancer incidence and mortality (Garland et al., 2006; Lappe, Travers-Gustafson, Davies, Recker, & Heaney, 2007). Although a theoretical rationale exists for an association among shift work, decreased sun exposure, and increased cancer risk, no published studies of sun exposure or vitamin D in night-shift workers were identified.

RECOMMENDATIONS AND IMPLICATIONS

Implications for Research

Due to the limited evidence and lack of consensus on the effects of exposure to LAN on breast cancer risk, no definite recommendations can be made. Additional well-designed human studies are required before a definite conclusion can be drawn about the effects of shift work and exposure to LAN on breast cancer. Specifically, because the exact mechanisms of this interaction remain unclear, it is difficult to determine the best metric for measuring exposure dose. Many of the proposed mechanisms are intertwined with one another (e.g., phase shift and LAN suppressing melatonin production and disrupting sleep). Additional biologically targeted investigations are needed to determine the relative contributions of LAN-induced melatonin suppression, phase shifts, sleep disruption, and immune impairment to breast cancer risk. This would involve conducting further epidemiological studies to measure precise light exposure at eye level, analyzing the effects of this exposure on melatonin fluctuations among shift workers, and assessing, as directly as possible, the effects of a human chronodisrupted melatonin signal on human breast cancer growth and development. Better understanding of the specific characteristics of light wavelength, intensity, timing, and duration that most disrupt circadian rhythm and impact breast cancer risk could permit more targeted interventions. In addressing the other potential mechanisms of action, future studies could investigate the association between shift work and clock gene polymorphism or gene expression linked to breast cancer, the relationship between sleep quantity and quality and breast cancer, and the interaction among sun exposure, vitamin D levels, and breast cancer risk among shift workers. By clarifying the exact role of shift work and exposure to LAN in the etiology of breast cancer development and growth, future studies might identify the “at-risk group” and lead to the development of effective interventions for mitigation.

In addition to clarifying the mechanism of action, future studies should address several other gaps in the current literature. First, because the presence of confounding variables remains a limitation of many studies included in this review, future studies should control for reproductive history, family history of breast cancer, use of oral contraceptives and hormone replacement therapy, socioeconomic class, alcohol consumption, and tobacco use. Second, because assessment of exposure to LAN has been varied and limited (e.g., use of self-reports, satellite photometry), future studies should investigate more precise measurements of LAN exposure at eye level. For a recent study, a sample of women wore Daysimeters, small, head-worn devices developed by the Lighting Research Center capable of recording photometric measurements at the cornea. After these measurements were compared to photometric measurements taken at women’s bedroom windows, the researchers concluded that satellite photometry was unrelated to personal light exposures (Rea, Brons, & Figueiro, 2011). Research shows that wrist-level monitoring (Actiwatch-L) provides an adequate estimate of light exposure for in-hospital circadian studies (Jardim et al., 2011). Third, the retrospective design of some of the reviewed studies is susceptible to recall bias about prior sleeping habits and shift work; future researchers should limit the potential for recall bias when designing studies. Fourth, because definitions of shift work have been inconsistent and broad across studies, the exact at-risk group remains uncertain (e.g., those working permanent vs. rotating night shifts). An IARC working group recently suggested that particular domains of occupational history be captured in future studies of shift work and cancer: (1) shift system (start time of shift, duration of shift, rotating or permanent, speed and direction of a rotating system, regular or irregular); (2) years on a particular non-day-shift schedule and cumulative lifetime exposure to that shift system; and (3) shift intensity, including time off between successive workdays (Stevens et al., 2011). Although the health of workers on different shift patterns that include night work has been compared to that of workers who do not work shifts, future studies may consider comparing the risk estimates of working permanent night shifts versus rotating shifts. Finally, ethical considerations regarding chronically exposing women to LAN in a controlled, laboratory setting to determine the direct effects on breast cancer risk must be addressed. However, unique experimental approaches that avoid ethical challenges have been implemented in which tissue-isolated tumors in situ were perfused with melatonin-rich or melatonin-deficient (after exposure to LAN) whole blood collected from female volunteers to directly assess the effects of a chronodisrupted human melatonin signal on the growth activity of human breast cancer xenografts (Blask et al., 2005).

Implications for Practice and Education

In modern 24-hour society, it is unlikely that shift work will be eliminated, regardless of the health effects associated with this work practice. However, certain aspects of shift work and individual susceptibility can be targeted for prevention. Mounting evidence may ultimately pave the way for changes in the workplace. If the evidence supporting a link between exposure to LAN and increased breast cancer risk accrues to the point of consensus, the scientific, lighting, and architectural communities may begin collaborating to develop new lighting technologies that minimize circadian disruption while maintaining visual efficiency. Additionally, if the evidence points to specific aspects of shift work responsible for this relationship (e.g., rotating vs. permanent night shifts), health care institutions could work with occupational health nurses to implement new shift-work policies.

In the meantime, individuals can implement strategies to reduce the potential for circadian disruption. Non-night-shift workers could extend their daily dark period, appreciate nocturnal awakening in the dark, and use dim red light for nighttime necessities (Stevens, 2009). Many shift workers, such as night-shift nurses, cannot realistically reduce or avoid exposure to LAN in their work environments. However, until widespread environmental lighting changes are made, certain measures can be taken to maximize melatonin production and reduce the risk of breast cancer. Recent evidence supports the use of optical filter lenses that block short-wavelength light from reaching the retina as a cost-effective and practical strategy for addressing the problem of increased breast cancer risk among night-shift workers (Kayumov, Lowe, Rahman, Casper, & Shapiro, 2007). Because short-wavelength blue light (470 to 525 nm) is primarily responsible for melatonin suppression, using amber glasses to block these blue rays from reaching the eyes may restore melatonin flow (Alpert, Carome, Kubulins, & Hansler, 2009; Kayumov et al., 2007). However, future studies are warranted to provide additional evidence that wearing amber glasses increases both the duration and the quantity of melatonin and decreases breast cancer risk. Other studies have demonstrated that significant phase shifts can be produced in night-shift workers with modifications to daytime light exposure, with no nighttime intervention (Dumont, Blais, Roy, & Paquet, 2009). Evidence on the use of melatonin supplementation is currently inconclusive. Although some studies have shown nocturnal melatonin supplementation to be effective in inhibiting the growth of existing tumors, a bolus of exogenous melatonin in a tumor-free individual may result in a phase shift that contributes to circadian disruption rather than alleviates it (Blask, 2009; Stevens, 2006). Others have therefore suggested the potential value of circadian-timed melatonin supplementation as a preventive or therapeutic agent (Blask, 2009).

Finally, the role of education should not be discounted in possibly mitigating the LAN–breast cancer association. Night-shift nurses should be educated, until the exact mechanism is clarified, on strategies to increase the duration and quality of sleep, promote healthy diets and active lifestyles, and encourage adequate sun exposure. Also, the importance of routine breast cancer screening must be emphasized.

CONCLUSION

Although the number of epidemiological studies is somewhat limited, evidence suggests that exposure to LAN during night-shift work may increase breast cancer risk. Research is needed to clarify the association among exposure to LAN, night-shift work, and breast cancer risk as well as identify the mechanisms underlying this relationship before prevention and mitigation interventions can be designed. In today's modern society, it is unlikely that shift work will be eliminated, regardless of the health effects associated with such practice. However, certain aspects of shift work and individual susceptibility may be addressed for risk reduction and prevention. Until more definitive evidence is available to stimulate occupational changes (e.g., the development of new lighting technologies and shift-work policies), individuals can implement simple lifestyle changes to reduce their potential for circadian disruption.

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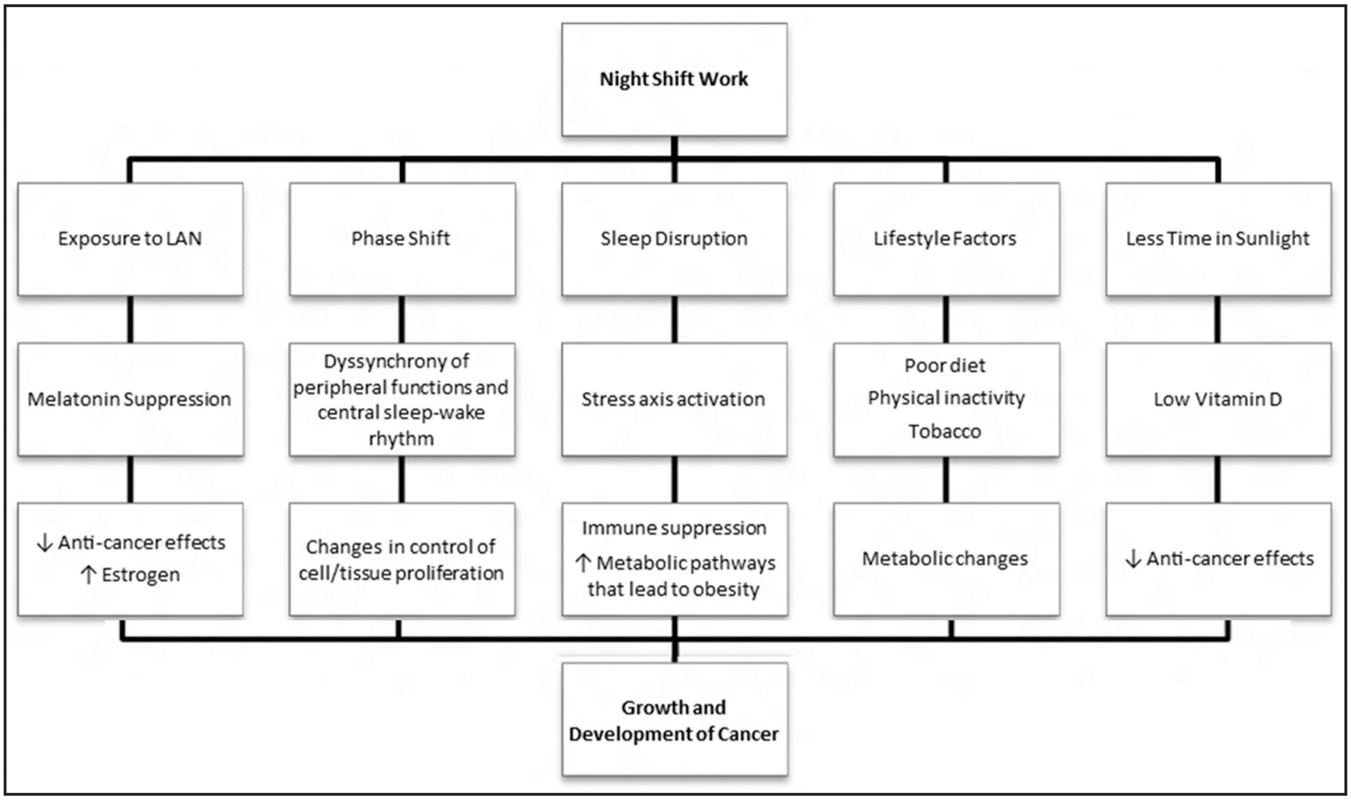

Figure.

Potential mechanisms mediating the relationship between night-shift work and cancer. LAN = light at night.

Table 1

Study Characteristics of Night Shift Nurse Studies

Reference	Purpose	Sample	Exposure Assessment	Shift Definition	Adjustment for Confounders	Major Findings	Strengths and Limitations
Davis, Mirick, & Stevens (2001)	To investigate whether the risk of breast cancer is associated with exposure to LAN as characterized by sleep habits, bedroom lighting environment, and shift work in the 10 years before diagnosis and/ or residential exposure to power frequency magnetic fields.	Case patients (n = 813), aged 20–74 years, diagnosed from November 1992 through March 1995. Control subjects (n = 793), aged 20–74 years, identified by random-digit dialing.	In-person Interview of sleeping habits, bedroom light exposure, lifetime occupational history	Graveyard shift work = 19:00 – 09:00	Parity Family history of breast caner (mother or sister) Oral Contraceptive use (ever) Recent (<5 years) discontinued use of hormone replacement therapy	- Increased breast cancer risk among subjects who frequently did not sleep during the period of the night when melatonin levels are typically at their highest (OR=1.14 for each night per week; 95% CI=1.0–1.28) - Risk did not increase with interrupted sleep accompanied by turning on a light. - Increased risk (nonsignificant) among subjects with the brightest bedrooms (OR=1.4; 95% CI=0.8–2.6). - Graveyard shift work (defined as beginning work after 7:00 PM and leaving work before 9:00 AM) was associated with increased breast cancer risk in a dose-dependent fashion (increased risk with increased years of working at least one graveyard shift per week [OR=1.13 for each year; 95% CI=1.01–1.27] and hours/week [OR=1.06 for each additional hour per week; 95% CI=1.01–1.13]).	*Strengths:* Detailed collection of data on exposure, including sleep patterns, bedroom environment, shift work *Limitations:* Potential selection bias (random-digit dialing), Details of prior sleep habits dependent on subject recall, Analyses regarding "nonpeak" sleep and graveyard shift work limited to 10 years before diagnosis, Definition of nonpeak sleep based on the assumption that the time period between 1:00 AM and 2:00 AM is the portion of the night when melatonin levels are highest
Grundy, Tranmer, Richardson, Graham, & Aronson (2011)	To examine the influence of nighttime light expo sure and shift work history on melatonin levels among rotating shift nurses.	123 nurses working a rotating shift schedule (two 12-hour days, two 12-hour nights, and five days off) were recruited and participated on a day	Nurses wore a Stow-Away light data logger over each 48-hour study period. Provided two urine and four saliva samples over a 24-hour period.	Not defined	Age BMI Total years of shift work Lifestyle characteristics (tobacco) Pack-years smoking Lifetime alcohol consumption	- Mean light exposure was significantly higher (p<0.0001) when nurses were working at night, although peak melatonin levels (p=0.65) and the daily change in melatonin levels (p=0.80) were similar across day/night shifts.	*Strengths:* Objective measures of light intensity and melatonin, Investigation of a commonly worked shift schedule *Limitations:* Investigation of single shift schedule limits

Reference	Purpose	Sample	Exposure Assessment	Shift Definition	Adjustment for Confounders	Major Findings	Strengths and Limitations
		and night shift in both the summer and winter seasons.			patterns Reproductive characteristics (age at menarche, ever pregnant, number of pregnancies, number of days since last menstrual period, menopausal status) Season Regular use of antidepressants, beta-blockers, hormone replacement therapy, or migraine medications Use of NSAIDs, sedatives, or oral contraceptives during the 24 hours of melatonin assessment Number of alcoholic and caffeinated beverages consumed and smoking behavior during the 24 hours of melatonin assessment Sleep duration and wearing a mask for daytime sleep	- Multivariate analysis did not show an association between light exposure and melatonin levels when data from both shifts was combined; however, when data from the night shift was considered alone, a statistically significant inverse relationship between light and change in melatonin was observed (p=0.04).	generalizability to other patterns of shift work, Light loggers worn around neck (potential small difference between logger-measured light intensity and actual intensity perceived at retina)
Hansen & Stevens (2011)	To investigate the association between breast cancer in Danish nurses and the length and frequency of work in various shift systems (including day, permanent night and rotating between day, evening and night).	267 cases of primary breast cancer as identified through the nationwide Danish Cancer Registry. 1035 control nurses.	Structured telephone interview on occupational history, hours of sleep on a normal day at time of interview and 10 years previously, and known/potential breast cancer risk	Day work: 06:00 or 07:00 to 15:00 or 16:00 Evening work: 15:00 or 16:00 to 23:00 or 24:00 Night Work: 23:00 or 24:00 to 07:00 or 08:00	Breast cancer in mother or sister Use of hormone replacement therapy Lifetime cumulative months of breastfeeding Age at first child birth Age at menarche Menstrual regularity Weight fluctuations	- Nurses who worked rotating shifts after midnight had a significantly increased OR (1.8; 95% CI 1.2–2.8) for breast cancer compared to nurses with permanent day work. - No association found among nurses with evening work and no night work (OR=0.9; 95% CI 0.4–1.9). - Nurses with periods of permanent night shift in	*Strengths:* Nationwide group of nurses with similar shift systems, High rates of participation for cases and controls, Analysis of risk according to different shift systems, *Limitations:* Major overlaps between different shift systems, Small reference group

Reference	Purpose	Sample	Exposure Assessment	Shift Definition	Adjustment for Confounders	Major Findings	Strengths and Limitations
			factors		Menstrual status	addition to rotating night and day shifts experienced an OR of 2.9 (95% CI 1.1–8.0). - For nurses working after midnight compared to nurses never ending work before midnight, OR in the third tertile of cumulative number of shifts was 2.2 (95% CI 1.5–3.2). - Of all the different rotating shift patterns, the highest OR (2.6; 95% CI 1.8–3.8) was observed for long-term day-night rotating shifts.	with permanent daytime work, Potential recall bias
Lie, Roessink, & Kjaerheim (2006)	To evaluate the role of night work as a potential occupational risk factor for breast cancer among Norwegian nurses.	537 breast cancer cases and 1:4 matched controls. Nested within cohort of 44, 835 Norwegian nurses educated between 1914 and 1980, as identified through Norwegian Board of Health's registry of nurses.	Total work history reconstructed from occupational information for nurses from Norwegian Board of Health's registry and census data from 1960, 1970, and 1980	Not defined	Fertility factors (age at birth of first child, number of children) Total employment time as a nurse	- Adjusted OR of breast cancer among nurses who worked nights for 30 or more years was 2.21 (95% CI 1.10–4.45) compared with those who did not work nights after graduation from nursing school (p(trend) = 0.01).	*Strengths:* Based on large cohort, Compulsory reporting of all cancer cases to the National Cancer Registry, Info about work and reproductive history from independent sources and before cancer diagnosis *Limitations:* Nurse registry included info on individual work history but not on night work, Assignment of night work was made by evaluating every registered job for each individual nurse as including night work or not, based on workplace info, Impossible to form a reference group of never exposed women as all Norwegian nurses

Reference	Purpose	Sample	Exposure Assessment	Shift Definition	Adjustment for Confounders	Major Findings	Strengths and Limitations
							were working nights during the three years of education
Lie, Kjuus, Zienolddiny, Haugen, Stevens, & Kjærheim (2011)	To assess the impact of number of consecutive night shifts on breast cancer risk among Norwegian nurses.	699 breast cancer cases and 895 controls. Nested within cohort of 49,402 Norwegian female nurses who graduated from a 3-year nursing school between 1914 and 1985	Structured telephone interview on lifetime occupational history and known/potential breast cancer risk factors	Night shift: lasted from at least 00:00 until 06:00, although the shift may start earlier or end later	Age at menarche Parity Breast cancer in mother or sister Use of oral contraceptives Recent hormonal treatment BMI at age 18 and at time of diagnosis Weight gain >10 kg from age 18 years to diagnosis Age at diagnosis Period of diagnosis Alcohol and tobacco use Duration of daily, occupational exposure to x-rays	- No increase of breast cancer risk was found after long duration of work by nurses working ≥3 night shifts per month. - Small, non-significant increased risk observed for exposure to ≥30 years in hospitals or other institutions (OR=1.1), ≥12 years in schedules including night work (OR=1.3), ≥1,007 night shifts during the lifetime (OR=1.2), and lifetime average number of ≥4 night shifts per month (OR = 1.2). - Non-significant increased risk of breast cancer observed in nurses who worked ≥5 years with ≥4 (OR=1.4) and ≥5 (OR=1.6) consecutive night shifts. - Significantly increased risk in nurses who worked ≥5 years with ≥6 consecutive night shifts (OR = 1.8, 95% CI 1.1–2.8).	*Strengths:* Based on large cohort, Compulsory reporting of all cancer cases to the National Cancer Registry, Large number of breast cancer cases *Limitations:* Potential selection bias (living, prevalent cases), Potential recall bias, Potential confounder: ionizing radiation.
Nagata, Nagao, Yamamoto, Shibuya, Kashiki, & Shimizu (2008)	To assess associations among concentrations of serum estrogen and androgen and the principal metabolite of melatonin in urine, 6-sulfatoxymelatonin, and exposure to light at night based on info on the sleeping habits and history of graveyard-shift work among postmenopausal	206 postmenopausal Japanese women	Self-administered qestionnaire of known/potential breast cancer risk factors Second questionnaire 3 years later on sleep habits and history of night-shift work	Not defined	Age BMI Smoking status Alcohol intake	- Serum estradiol level significantly higher in women who were not asleep at or after 01:00 those who were asleep after controlling for covariates. - Significantly increased estrogen levels were observed in women who had worked graveyard shift. - Urinary 6-sulfatoxymelatonin was lower in women who were not asleep at or after 01:00	*Strengths:* Evaluated the Interrelationships between estrogen, melatonin, and exposure to LAN among postmenopausal women *Limitations:* Few subjects who had worked the graveyard shift, Few women who were not asleep at or after 01:00, Low

Reference	Purpose	Sample	Exposure Assessment	Shift Definition	Adjustment for Confounders	Major Findings	Strengths and Limitations
	Japanese women.		Blood and urine samples			on weekends than those who were asleep at this time, but the difference was of borderline significance (p=0.08). - No significant association between urinary 6-sulfatoxymelatonin and any serum hormone levels.	response rate, Potential recall bias of sleeping habits
O'Leary *et al.* (2006)	To evaluate the association between breast cancer and circadian disruption.	576 women with breast cancer diagnosed from August 1996 to June 1997 and 585 population-based controls aged <75 years and living in the same Long Island, New York home for ≥ 15 years	Telephone interview and self-administered questionnaire on occupational history since age 16 (including frequency, duration, type of shift work), and residential LAN exposure (sleep hours, frequency of turning on lights during night, length of time light was on) Blood and urine samples	Evening shift: afternoon up to 02:00 Overnight shift: 19:00 to next morning	Age Parity Education Family history of breast cancer (mother, sister, or daughter) History of benign breast disease BMI	- Breast cancer risk was not associated with overall shift work (OR=1.04, 95% CI=0.79–1.38) or evening shift work (OR=1.08, 95% CI=0.81–1.44) - Female night shift workers were in fact at a *lower* risk than female non-shift workers (OR=0.55, 95% CI=0.32–0.94) - Women who frequently turned on lights at home during sleep hours (≥2x/ week and ≥2x/night) had increased risk (OR=1.65, 95% CI 1.02–2.69).	*Strengths:* Large sample size, Analytic control for potential confounders *Limitations:* Recall bias, Study population of long-term residents (compared to non-long-term residents) was reported as more likely to be older, post-menopausal, Caucasian, parous, heavier, have a history of alcohol use, have a history of hormone replacement therapy and were less likely to have more than a high school education and to have ever lactated
Pesch *et al.* (2010)	To investigate the association between night work and breast cancer risk in a German population-based case-control study known as GENICA (Gene ENvironment interaction and breast CAncer).	1749 women (857 breast cancer cases and 892 controls)	Telephone interview on shift work	Night shift: 24:00–5:00	Menopausal status Education Breast cancer in mother or sister Parity Age at first birth Duration of oral contraceptive and hormone therapy use BMI Smoking Number of mammograms until two years before interview Lifetime breastfeeding in	- Having ever done night shift work was not associated with elevated breast cancer risk (OR=0.96, 95% CI 0.67–1.38) as compared to women who worked day shifts only (OR=0.91, 95% CI 0.55–1.49) - Participating in night shift work for ≥20 years was associated with a modestly increased, but not significant, breast cancer risk (OR=2.48, 95% CI 0.62–9.99)	*Strengths:* Large sample size, Analytic control for potential confounders *Limitations:* Low prevalence of night work (especially long-term night work) in the study population, Retrospective assessment of shift work

Reference	Purpose	Sample	Exposure Assessment	Shift Definition	Adjustment for Confounders	Major Findings	Strengths and Limitations
					months		
Pronk *et al*. (2010)	To assess the association between shift work and breast cancer risk in a population-based prospective cohort study of over 70,000 women in Shanghai, China, who provided information on lifetime occupational history and nightshift work.	73,049 women (40–0 years) (n=717 breast cancer cases)	In-person interviews on lifetime occupational history and known/potential breast cancer risk factors Annual record linkage to Shanghai Cancer Registry and Shanghai vital statistics database	Night shift: starting work after 22:00 at least three times a month for over one year	Age Education Family history of breast cancer Number of pregnancies Age at first birth Physical activity Age at menarche Menopausal status BMI Caloric intake	- Breast cancer risk was not associated with ever working the night shift on the basis of the job exposure matrix (adjusted hazard ratio = 1.0, 95% CI 0.9–1.2) or self-reported history of night-shift work (adjusted hazard ratio = 0.9, 95% CI 0.7–1.1). - Risk was not associated with frequency, duration, or cumulative amount of night-shift work.	*Strengths:* Large prospective cohort study, High response rate, Stable job histories among the sample minimizing recall bias, Complementary sources of data on shift work (occupational history using a job exposure matrix and self-report) *Limitations:* Did not capture data on certain aspects of night shift work, such as rotating versus permanent shifts.
Schernhammer, Kroenke, Laden, & Hankinson (2006)	To study the relation between rotating night shift work and breast cancer risk in a cohort of premenopausal nurses.	115, 022 female, U.S. registered nurses from Nurses' Health Study II pospective cohort	Self-reported duration of rotating and permanent night shifts, one-timed assessment in 1989; biannual update	Rotating night shift: at least three nights per month in addition to days or evenings in that month	Age Age at menarche Parity Age at first birth BMI Family history of breast cancer Benign breast disease Alcohol Consumption Oral contraceptive use Smoking status Menopausal Status Age at menopause Physical activity Postmenopausal hormone use	- Women who reported >20 years of rotating night shift work experienced an elevated relative risk of breast cancer compared with women who did not report any rotating night shift work (multivariate RR 1.79; 95% CI 1.06–3.01). - No increase in risk associated with fewer years of rotating night work.	*Strengths:* Large prospective cohort study, Updated info o night shift work *Limitations:* Self-reported duration of rotating night shifts, Uncontrolled confounding (socioeconomic status, lifestyle differences), Few women had worked rotating night shifts for ≥ 20 years
Schernhammer *et al*. (2001)	To evaluate the relationship between night work, as a surrogate for exposure to LAN, and breast cancer risk in a large prospective cohort of premenopausal and postmenopausal	78, 562 female registered nurses 30–55 years old and living in 11 U.S. states who were enrolled in the Nurses' Health Study.	Self-reported life time years on rotating night shifts, one-timed assessment in 1988	Rotating night shift: at least three nights per month in addition to days or evenings in that month	Age Age at menarche Age at menopause Parity Age at first birth Weight change between age 18 years and menopause for menopausal	- Moderate increase in breast cancer risk among the women who worked 1–14 years (RR=1.08, 95% CI 0.99–1.18) or 15–29 years (RR=1.08, 95% CI 0.90–1.30) on rotating night shifts.	*Strengths:* Large prospective cohort study, Analytic control for potential confounders *Limitations:* Uncontrolled confounding (hormone

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Reference	Purpose	Sample	Exposure Assessment	Shift Definition	Adjustment for Confounders	Major Findings	Strengths and Limitations
	women.				women only BMI at age 18 Current alcohol consumption Oral contraceptive use Postmenopausal hormone use Menopausal status Benign breast disease Family history of breast cancer	- Risk further increased among women who worked 30 or more years on the night shift (RR=1.36, 95% CI 1.04–1.78). - Test for trend was statistically significant (p=0.02).	levels, stress), Potential misclassification (some nurses may not have classified themselves as never-rotating workers instead of as working on rotating shifts, because they may have perceived permanent night work as non-rotating instead of rotating night work)