

CANCER

Light-at-night, circadian disruption and breast cancer: assessment of existing evidence

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Background Breast cancer incidence is increasing globally for largely unknown reasons. The possibility that a portion of the breast cancer burden might be explained by the introduction and increasing use of electricity to light the night was suggested >20 years ago.

Methods The theory is based on nocturnal light-induced disruption of circadian rhythms, notably reduction of melatonin synthesis. It has formed the basis for a series of predictions including that non-day shift work would increase risk, blind women would be at lower risk, long sleep duration would lower risk and community nighttime light level would co-distribute with breast cancer incidence on the population level.

Results Accumulation of epidemiological evidence has accelerated in recent years, reflected in an International Agency for Research on Cancer (IARC) classification of shift work as a probable human carcinogen (2A). There is also a strong rodent model in support of the light-at-night (LAN) idea.

Conclusion If a consensus eventually emerges that LAN does increase risk, then the mechanisms for the effect are important to elucidate for intervention and mitigation. The basic understanding of phototransduction for the circadian system, and of the molecular genetics of circadian rhythm generation are both advancing rapidly, and will provide for the development of lighting technologies at home and at work that minimize circadian disruption, while maintaining visual efficiency and aesthetics. In the interim, there are strategies now available to reduce the potential for circadian disruption, which include extending the daily dark period, appreciate nocturnal awakening in the dark, using dim red light for nighttime necessities, and unless recommended by a physician, not taking melatonin tablets.

Keywords Breast cancer, circadian disruption, light-at-night, melatonin, clock

Introduction

Humans have evolved for many millions of years on Earth with a reliable daily cycle of 12 h of bright full-spectrum light, and 12 h of dark (season and latitude permitting). In fact, this cycle has been a major formative factor for all life on the planet for >3 billion years (or perhaps >4 billion years;¹). Although humans

figured out fire 250 000 years ago, and began using candles 5000 years ago, it has only been since the advent of electric lighting 130 years ago that the masses of people have begun to have the dark period dramatically eroded. Most people born in large cities have never seen the Milky Way. In addition to the loss of the starry night, electric light has extended the lighted period at home well into the night for recreation and social activities, and allowed for large numbers of people to work at night. The benefits of electricity and electric lighting are myriad, and these have changed human society much for the better in

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many ways. However, it is becoming increasingly recognized that there may also be adverse effects on human health (as well as on many other life forms²), and that the indiscriminate use of lighting might in some respects be a detriment.

Breast cancer

Breast cancer is the leading cause of cancer incidence and of death from cancer among women globally.^{3,4} There is also a large international variation in incidence with the highest risk in the most industrialized regions and lowest in the least industrialized.⁵ Based on considerable epidemiological and animal evidence, it is believed that lifetime burden of oestrogen is the major determinant of breast cancer risk.^{6,7} However, there is not scientific consensus on what personal or demographic factors are affecting oestrogen levels in such a way that can explain the bulk of the variations in risk within and across societies. It may turn out that it is the sum of many factors such as exercise, alcohol and reproductive events including breastfeeding, but at the moment this is not yet clear.

Some of the international variation is due to differences in known risk factors, but analyses expressly designed to determine the proportion of breast cancer cases explained by known risk factors have yielded estimates that are <50%.⁸ Nagata *et al.*⁹ examined time trends in four reproductive factors in Japan and concluded that <40% of the increased breast cancer incidence from 1959 to 1987 could be accounted for by the risk factors. Hahn and Moolgavkar¹⁰ analysed proportions of nulliparous women, and decade of first birth in Connecticut by cohorts born from 1855 to 1945, and concluded that these childbearing changes did not predict changes in breast cancer incidence. Hsieh *et al.*¹¹ conducted an analysis of a large international case-control study representing study centres from the range of variation in risk. They concluded that the known risk factors when applied to control women could explain only a 'small fraction' of the difference in risk between Boston and Tokyo.

This lack of consensus on what are the major causes of the international differences in risk of breast cancer, and the rising risks within countries, is in stark contrast to most other common cancers. There is scientific consensus that the bulk of lung cancer cases is explained by smoking, of liver cancer by hepatitis viruses and aflatoxin, of cervical cancer by human papilloma virus, of stomach cancer by *Helicobacter pylori* and much of colon cancer by family history, physical activity and diet. For breast cancer there is no consensus on the major causes, and it thus remains a mystery.

Light-at-night theory

The light-at-night (LAN) theory states that the introduction and increasing use of electricity to light

the night accounts for some of the international differences in risk of breast cancer, and for a portion of the rising risk worldwide. In the original publication,¹² the postulated biological mechanism was that electric LAN would lower melatonin production by the pineal gland, and that this suppression of melatonin might then lead to increased breast cancer risk by leading to increased oestrogen production.¹³ Three cohort studies have examined the association of pre-diagnosis urinary 6-sulphatoxymelatonin and risk; one found no association,¹⁴ whereas two reported a significant inverse association.^{15,16} Subsequently, other mechanisms in addition to melatonin suppression have received scrutiny including alteration of clock gene functioning and desynchronization of the master clock in the suprachiasmatic nuclei from the peripheral clocks in tissue.^{17,18} This might, for example, lead to untoward effects on cell cycle regulation in mammary tissue.¹⁹

The LAN theory is easy to state but difficult to assess scientifically. Virtually no sighted person in the modern world does not use electric light to reduce the length of the natural daily dark period. This is also increasingly true in the developing world. Finding appropriate comparison groups is difficult. Therefore a series of predictions have been made to test the theory including: (i) non-day shift workers would be at higher risk; (ii) blind women would be at lower risk; (iii) sleep duration, as a surrogate for hours of dark, would be inversely associated with risk; (iv) light level in bedrooms at night would be directly associated with risk; and (v) population level studies would show associations of community light level and breast cancer incidence.

Epidemiologic predictions

Shift work

The role of shift work in cancer risk has recently been reviewed by the International Agency for Research on Cancer, which concluded 'shift-work that involves circadian disruption is probably carcinogenic to humans (Group 2A)'.²⁰ The first studies of shift work and breast cancer were designed expressly to test the LAN theory. A case-control study published in 2001 was designed in the early 1990s to test the LAN idea for breast cancer causation.²¹ In addition, the idea was communicated by a letter to the Nurses' Health Study (NHS) in 1987 (RG Stevens to WC Willett), and thereby was included in the 1988 NHS I questionnaire, and the inaugural 1989 questionnaire for the NHS II. This question directly resulted in the reports in 2001 on NHS I²² and 2006 on NHS II,²³ both of which found elevated risk in rotating shift workers. Other studies have confirmed the finding of an association of non-day shift work and risk of breast cancer in women,²⁴⁻²⁶ whereas two have not; one was a well-conducted case-control study,²⁷ and

the other suffered from a debilitating level of exposure misclassification and can be ignored.²⁸ Kolstad²⁹ provides a recent and detailed review of the existing studies of shift work and breast cancer.

In addition to the studies of shift-work occupation, studies of female flight attendants have reported elevated breast cancer risk.³⁰ Flight attendants have work schedules that run counter to their endogenous circadian rhythm, and these studies were included in the IARC evaluation.

It is important to note that for these studies of shift work the comparison women who work 'day shift' are doing so in modern societies in which electric lighting is used to diminish the daily dark period for everyone. Therefore, IF shift work does increase risk, and IF it is due to LAN, THEN the estimates of effect are a minimum in terms of the probable total societal impact.

Blind women

Hahn³¹ reasoned that if LAN increased risk then profoundly blind women should be at lower risk because they have little or no opportunity for light during the night to dampen their natural endogenous melatonin rhythm. It has been reported in four separate US and European studies that the incidence of breast cancer is lower in women who are visually impaired compared with the sighted population.³¹⁻³⁴ Hahn³¹ analysed over 100 000 records from the National Hospital Discharge Survey and found that 0.26% of women with primary diagnoses of stroke or cardiovascular disease were blind, whereas only 0.15% of those with a primary diagnosis of breast cancer were also blind. In a prospective study in Sweden, Feychting *et al.*³² found a lower risk for all cancers combined among blind persons, including breast cancer in women. Pukkala *et al.*³³ also found lower breast cancer risk in blind women in Finland although risk for other cancers was higher, in contrast with the Swedish findings. An extension of the latter study refined the definition of visual impairment to include five categories from moderately low vision to total blindness.³⁵ From 1983 to 1996, there were 124 cases of breast cancer among approximately 11 000 women with some degree of visual impairment. The Standardized Incidence Ratio declined from 1.05 in women with 'moderately low vision' to 0.47 in totally blind women; the decrease was monotonic and statistically significant. A study of approximately 15 000 Norwegian visually impaired women also found a lower risk of breast cancer in blind women 0.64 [confidence interval (CI): 0.21-1.49] in those who became blind before 65.³⁴

Sleep duration

Based on the idea that sleep duration would be a surrogate for hours of exposure to dark each night, and thereby a greater melatonin production, Verkasalo *et al.*³⁶ predicted that sleep duration

would be inversely associated with breast cancer risk. This prediction was tested in a cohort study of women in Finland. Sleep duration, other sleep variables and breast cancer risk factors were assessed by self-administered questionnaires in 1975 and in 1981. Breast cancer incidence data for years 1976-96 was obtained from the Finnish Cancer Registry. Hazard ratios (HRs) and 95% CIs were obtained from Cox proportional hazards models adjusting for potential confounders. Analysis restricted to 7396 women (146 cases) whose sleep duration in 1975 and 1981 were in the same duration group (stable sleepers) yielded HRs of 1.10 (CI: 0.59-2.05) for ≤ 6 h, 1.0 for 7-8 h and 0.28 (CI: 0.09-0.88) for ≥ 9 h, with a decreasing trend ($P=0.03$).

The use of self-report for sleep duration may be of only limited value in estimating the association of actual sleep duration and breast cancer risk, and by extension of whether sleep duration accurately reflects hours of exposure to dark at night. Self-report of sleep duration (subjective measure) has been compared with sleep as assessed by actigraphy (objective measure) in a large sample of adults and found to be moderately correlated (0.47) but generally to overestimate the objective measure;³⁷ this bias also varied by several demographic variables. A detailed analysis of reported sleep characteristics and objective measures of sleep and circadian phase in blind persons found that self-report was well correlated with duration but not with number of nocturnal awakenings or naps.³⁸ In this study, there was good agreement between actigraphy and self-report on circadian phase as measured by urinary 6-sulphatoxymelatonin.

Since this Finnish study appeared, three more studies have been published. Pinheiro *et al.*³⁹ reported on sleep duration and breast cancer risk in the Nurses' Health Study I, and found no overall association. Among women reporting the same sleep duration on questionnaires from 1986 and 2000, there was a modest increased risk in the 9+ h sleepers compared with the 7-h sleepers. The latest cohort study comes from the Singapore Chinese Health Study. Wu *et al.*⁴⁰ reported that among approximately 33 500 women the relative risk for the groups ≤ 6 h, 7, 8, ≥ 9 were 1.0 (ref), 1.03, 0.90, 0.81 ($P=0.2$); the inverse association was statistically significant among post-menopausal women.

Finally, a case-control study by McElroy *et al.*⁴¹ also reported a small positive association of sleeping ≥ 9 h compared with sleeping 7 h. This study, however, suffers from the potential for recall bias, and the fact that early disease may have affected sleep duration, because the sleep duration question focused on only 2 years prior to diagnosis.

Light in the bedroom at night

Davis *et al.*²¹ asked cases and controls what was the ambient light level in the bedroom after lights out for sleep using a subjective scale (total dark, see hand

in front of face, see across the room); this yielded a non-significant odds ratio of 1.4 for the highest light level compared with total dark. O'Leary *et al.*²⁷ asked about how often lights were turned on at night and reported significantly elevated risk for women turning on lights two or more times per night compared with very rarely. These studies attempted to address an important possibility that chronic low-level LAN might increase risk. It is not clear whether very low-level light can have any meaningful impact on nocturnal melatonin production, and these studies, although well conducted by excellent researchers, are weak and preliminary evidence at best; although the case-control design may be good for accurate recall of night work occupation, it may be highly flawed for prior history of 'light level in bedroom'. However, these two studies do highlight a need for more experimental studies of chronic low-level light on melatonin production.⁴²

Northern latitudes

Erren and Piekarski⁴³ predicted that if LAN increased breast cancer risk by reduction in melatonin production, then indigenous populations in the Arctic should be at lower risk. The Sami live in the far north of Europe. Investigations of cancer incidence in the Sami have reported a lower risk than expected in Finland⁴⁴ and Norway;⁴⁵ in Sweden a lower risk was reported for 'reindeer herding' Sami, but not 'non-reindeer herding' Sami.⁴⁶ The incidence in the population of native Alaskans who self-report as 'Indian' now exceeds that of white women in the USA,⁴⁷ although historically it was much lower; mortality among Alaskan native peoples (Eskimo, Indian and Aleut) from breast cancer has tripled since 1969 for unknown reasons. However, in Greenland,⁴⁸ Inuit never living in Denmark have much lower risk than expected based on Danish incidence rates (SIR = 0.4). There may be many reasons for these generally lower risks of breast cancer in far-north indigenous people, but they are also consistent with Erren and Piekarski's prediction.

Population level

An important aspect to the assessment of causation from epidemiological studies is the coherence of studies in specific subpopulations with the co-distribution in time and space of the exposure of interest with the disease outcome in the entire population.^{49,50} Mounting evidence supports an association of non-day shift work and breast cancer risk; several studies report lower risk in blind women; long sleep duration is associated with reduced risk in two of three prospective studies; and two studies have reported some association of bedroom light level and risk. However, on the population level, is nighttime light level of communities associated with breast cancer incidence in those communities?

The first analysis to test this prediction was that of Kloog *et al.*⁵¹ from Israel. They combined into regression models breast cancer incidence in 147 communities with satellite data on nocturnal illumination from the same communities, as well as information on per capita income, population density, birth rate and ethnic makeup. They also modelled lung cancer incidence as a 'negative control' as a test of the specificity of their method. Nocturnal community light level was significantly associated with breast cancer incidence, and from the model, the highest LAN intensity community had a 73% higher incidence than the lowest. There was no association of LAN and lung cancer incidence. This result is a necessary but not sufficient condition for causality.

Clock genes

The core clock apparatus consists of nine genes so far identified^{52,53} (though there are undoubtedly more to be discovered⁵⁴), yet directly controls a large part of the genome.⁵⁵ In particular, the clock work and cell cycle regulatory system appear to be intertwined.⁵⁶ An obvious question is whether variants in any of the clock genes are associated with risk of breast cancer;^{57,58} a question first addressed by Zhu *et al.*⁵⁹ who reported an association of a length polymorphism in *Per3* and risk. It is too soon to say how fruitful this line of inquiry will be.

Circadian phototransduction

In 2002, Berson *et al.*⁶⁰ reported the identification of an intrinsically photosensitive retinal ganglion cell in rats. This exciting finding was the first new report of a photosensitive cell in the retina in 150 years. These have also been identified in humans,⁶¹ and are believed to have primary responsibility for signalling to the circadian system whether it is day or night.⁶² The photopigment for this ipRGC is melanopsin,⁶³ which has a structure that is more like that of invertebrate opsins than that of the visual opsins in mammals.⁶²

The wavelength of maximum efficiency for suppression of melatonin production at night in humans⁶⁴ and for phase resetting the circadian system⁶⁵ is 460–480 nm. However, photons across the spectrum can also do so given adequate intensity.⁶⁶ There are several aspects of light suppression of melatonin that are pertinent to consideration of potential adverse health effects. Bright light suppresses melatonin in anyone.⁶⁷ There is a dose-response.⁶⁴ Some people are more sensitive than others.⁶⁸ Eye colour may affect sensitivity.⁶⁹ Previous light history alters nighttime sensitivity to LAN.^{42,70} Women may in general be more sensitive than men⁷¹.

Animal models

Research on light and cancer in rodents has its roots in the 1960s⁷²⁻⁷⁴. Many laboratories have investigated various aspects of the effect of constant illumination on cancer in rodents, but only very recently has work begun with direct relevance to humans. Blask *et al.*⁷⁵ conducted a study that is as close as ethically possible to determine experimentally whether light exposure at night increases the growth of breast cancer in women. They grew MCF7 cells in nude mice to obtain a human-derived tumour, which they then implanted into a nude rat. This remarkable technique^{76,77} allows for one artery into and one vein from the growing human-derived tumour. These tumours were then directly infused with blood taken from young women under three different conditions: during the day, at night in the dark, at night after bright light exposure to the women. As predicted, the melatonin-rich blood taken during the night dramatically slowed the growth activity of the MCF7 xenograft, whereas the melatonin-depleted blood taken during the day, and at night after bright light exposure, did not slow the growth activity of the tumour at all.

Another avenue of investigation is on the effects of altered light exposure very early in life on mammary tissue development. Shah *et al.*⁷⁸ found that constant light beginning *in utero* increased terminal end bud concentration in mammary tissue of Sprague-Dawley rats by early adulthood; this increased proliferative state increased susceptibility to carcinogen later in the life of the animal. Anderson *et al.*⁷⁹ conducted similar experiments but began constant light exposure at age 26 days; they found that this exposure had the opposite effect in speeding terminal differentiation and rendering the mammary tissue refractory to malignant transformation. This is an understudied area that deserves much more attention given the idea that early experience may have a large effect on lifetime risk of breast cancer.⁸⁰

Other common diseases of modern life

Based on similar reasoning to that for breast cancer, it was proposed that risk of prostate cancer might also be raised by exposure to LAN.^{81,82} Two studies of shift workers, (^{83,84} and one of sleep duration⁸⁵) support this prediction. There is also provocative epidemiological evidence on shift workers for an effect on endometriosis,⁸⁶ endometrial cancer⁸⁷ and colon cancer.⁸⁸ In addition, other common chronic diseases such as heart disease,⁸⁹ diabetes, obesity⁹⁰ and mood disorders⁹¹ may be exacerbated by LAN. Finally, the role of circadian timing of treatment for cancer,^{92,93} including breast cancer, may also be influenced by the lighted environment of patients.

Discussion

Lighting of the night sky is as important an Earth issue as global warming. The level of impact on life on the planet, on energy consumption and on human health (not to mention aesthetics) is only now beginning to be appreciated. Of the many potential adverse effects from LAN and circadian disruption on human health, the most evidence to date is on breast cancer. No single study can prove cause and effect, as neither can a group of studies of only one of the factors cited above. However, taken together, the epidemiologic and basic science evidence may lead to a 'proof' of causality (i.e. a consensus of experts). If so, then there would be an opportunity for the architectural and lighting communities, working with the scientific community, to develop new lighting technologies that better accommodate the circadian system both at night and during the day inside buildings.^{57,94}

The quality of light during the day and night could also affect breast cancer risk by other mechanisms that are not incompatible with an effect on circadian rhythms or melatonin production. LAN may also disrupt cortisol rhythms, and that may affect breast cancer risk and/or prognosis.⁹⁵ A robust circadian rhythm relies on a dark night and a bright day. The idea that lack of sunlight on the skin and consequent inadequate vitamin D production could increase breast cancer risk⁹⁶ might therefore be somewhat difficult to disentangle from an effect on melatonin production. It is reasonable to suspect that non-day shift workers get less sunshine than day-workers, although how much less in the modern world is not clear⁹⁷. For lack of sunshine to be a confounder of the shift work and breast cancer association however, it would have to be a very strong risk factor and be tightly correlated with shift work.⁹⁸ For the study of breast cancer in Israel,⁵¹ sun exposure is most assuredly not a confounder.

Understanding mechanisms is a lesser imperative for some risk factors such as smoking and lung cancer because smokers should be helped to quit (although understanding mechanisms could help those many smokers who cannot quit). However, if the evidence continues to accrue to the point where a consensus emerges that LAN does increase risk of breast cancer, then it is crucial to understand the mechanisms for this effect for the purposes of intervention and mitigation. Increasing numbers of people must do shift work in modern societies, and few people will give up electric lighting at home. An understanding of what particular characteristics of wavelength, intensity, timing and duration most disrupt circadian rhythms would permit a minimization of any potential health risks.^{50,99}

At present, there are a few rudimentary suggestions that could help minimize circadian disruption, and thereby presumably any adverse health consequences of it. Consider extending the dark period at night to

9 or 10 h if possible. When awakening in the middle of the night, as most people do, stay in the dark and appreciate this period of 'quiet wakefulness'.^{100,101} Install in the bathroom for nighttime use a low-wattage light with a red bulb; the vanity lights in the typical bathroom are adequate to start lowering pineal melatonin secretion within minutes.^{102,103} Finally, unless recommended by a physician, do not take melatonin tablets. There is a case from experimental work¹⁰⁴ and clinical trials¹⁰⁵ that supplemental melatonin can slow the growth of existing tumours, and therefore benefit prognosis. However, for disease-free persons these supplements provide a bolus that spikes circulating melatonin much above the physiologically normal level, and have been shown to phase advance a human,¹⁰⁶ thereby contributing to circadian disruption instead of alleviating it.

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