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ORIGINAL PAPER

Artificial lighting in the industrialized world: circadian disruption and breast cancer

Richard G. Stevens

Abstract Breast cancer risk is high in industrialized societies, and increases as developing countries become more Westernized. The reasons are poorly understood. One possibility is circadian disruption from aspects of modern life, in particular the increasing use of electric power to light the night, and provide a sun-free environment during the day inside buildings. Circadian disruption could lead to alterations in melatonin production and in changing the molecular time of the circadian clock in the suprachiasmatic nuclei (SCN). There is evidence in humans that the endogenous melatonin rhythm is stronger for persons in a bright-day environment than in a dim-day environment; and the light intensity necessary to suppress melatonin at night continues to decline as new experiments are done. Melatonin suppression can increase breast tumorigenesis in experimental animals, and altering the endogenous clock mechanism may have downstream effects on cell cycle regulatory genes pertinent to breast tissue development and susceptibility. Therefore, maintenance of a solar day-aligned circadian rhythm in endogenous melatonin and in clock gene expression by exposure to a bright day and a dark night, may be a worthy goal. However, exogenous administration of melatonin in an attempt to achieve this goal may have an untoward effect given that pharmacologic dosing with melatonin has been shown to phase shift humans depending on the time of day it's given. Exogenous melatonin may therefore contribute to circadian disruption rather than alleviate it.

Keywords Breast cancer · Circadian disruption · Melatonin · Shift work

Introduction

There is a large variation in risk of breast cancer among societies of the world, with the relatively more industrialized showing five-fold or higher risk than the least industrialized [1]. In contrast with other common cancers which also vary across societies, the reasons for the rise in breast cancer that comes with Westernization is poorly understood. For lung cancer, the reason for it's variation is very clear: as societies pick up the habit of smoking, lung cancer incidence and death increase accordingly and dramatically; liver cancer is largely explained by endemic hepatitis virus infections, and alfatoxin; stomach cancer declines as societies refrigerate food; colon cancer is strongly influenced by red meat intake, sedentary lifestyle, and aspirin ingestion. In contrast, the majority of the variation in breast cancer risk among societies, and rising risk within societies, is unaccounted for by the established risk factors for breast cancer [2, 3]. There is increasing support for the idea that circadian disruption from aspects of modern life, especially electric lighting, is a factor in the population burden of breast cancer [4]. Studies of shift workers, as suggested by Stevens et al. [5], have reported elevated risk [6–10], and studies in blind women, as suggested by Hahn [11], have reported reduced risk [11–14]. The studies in blind women were conducted under the belief that blind

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R. G. Stevens (✉)
University of Connecticut Health Center, Farmington, CT 06030-6325, USA
e-mail: bugs@neuron.uchc.edu
Tel.: +1-860-679-5475
Fax: +1-860-679-5464

women, as opposed to sighted women, do not have the opportunity for nocturnal melatonin suppression by exposure to light during the night.

'Light-at-night' and breast cancer

Originally, it was argued that part of the rising risk of breast cancer in industrialized societies was due to increased use of electric lighting which could suppress melatonin [15]; a suppression of melatonin was hypothesized to increase estrogen [16], and thereby increase risk. This idea was based on experiments in rodents on the effects of constant light exposures on mammary tumorigenesis [e.g., 17], and on the epidemiology of breast cancer in which risk was highest in the most industrialized, and thereby most electrified, societies. However, Shah et al. [17] found no effect of constant light on plasma estradiol levels in rats, although melatonin administration lowered estradiol. It is not clear whether melatonin or light-at-night affects estrogen production in humans, the data being limited and conflicted [18–25].

Apart from effects on estrogen production, there are several mechanisms by which melatonin might affect breast cancer that have emerged (reviewed in [26]). These include direct oncostatic effects, interference with estrogen receptor function, effects on immune function, and effects on free radical biology. In particular, an effect of light at night, including dim light, on melatonin production can have profound effects on growth and progression of both transplanted liver tumors in rats [27] and transplanted human-derived breast tumors in rats by altering linoleic acid metabolism [28].

The first study of prediagnosis melatonin level did not find a difference between women who later developed breast cancer and those who did not [29]; the authors note, however, that the early studies of estrogen and breast cancer were inconsistent, and it has required a combined analysis of many studies to show that there is in fact a strong association [30]. In addition to affects on melatonin, the potential for light to alter circadian rhythm generation in the suprachiasmatic nuclei (SCN) leads to the potential for disruption of clock gene communication with cell cycle regulation in the mammary tissue [4, 31]. Disruption of cell cycle regulation and/or apoptosis opens a large new area for investigation of light effects on cancer risk.

Light and exogenous melatonin

Suppression of the normal nocturnal surge in melatonin by exposure to light at night may increase breast cancer risk by several different mechanisms [26, 28, 32–34]. (Stress and cortisol may also play a role in circadian disruption and cancer [35, 36]) Therefore, maintenance of a strong melatonin rhythm seems desirable. However, supplementation with melatonin could result in 'Circadian Disruption' itself due to the emerging understanding of the impact of exogenous melatonin on the human circadian rhythm. In fact, the circadian phase shift induced in humans by a pharmacological bolus of melatonin can be comparable to that induced by a bright light stimulus. Wirz-Justice et al. [37] conducted a study in which 9 healthy young men were subjected to one of 4 conditions: 5 mg of melatonin at 20:40 in the evening, a 3 h period of 5000 lux light beginning at 21:00, both, or neither (with placebo for the melatonin tablet). All nine subjects received all four exposure conditions. Melatonin onset was then measured the day following the treatments under a constant-routine, dim-light regime (>10 lux). Under the light-only exposure, there was a 41 min phase delay; under the melatonin-only exposure, there was a 24 min phase advance. The two together tended to cancel each other: with both exposures, dim-light melatonin onset (DLMO) was not significantly different from exposure to neither.

Before Lewy et al. [38], it was speculated that the human pineal was insensitive to light. Since that seminal work, the intensity of light at night shown experimentally to be required to lower melatonin has declined to very low levels [39].

It is also becoming clear that light level during the day can affect melatonin secretion at night [40], and also sensitivity to a light exposure at night on suppression of melatonin [41]. Hebert et al. [41] conducted an experiment in which 12 young, healthy subjects (6 male and 6 female) spent 1 week in a bright-day environment (exposed to sun) and 1 week in a dim-day environment (dark goggles worn during the day). At the end of each week, the subject's sensitivity to melatonin suppression by light in the middle of the night was assessed. On the 6th night in dim light (< 15 lux), a baseline of melatonin was determined by saliva sampling every 30 min. During the next night, the subjects were exposed to 500 lux light for 3 h beginning at 1 am. Percent light suppression was significantly greater after the dim week than after the bright week. However, there was a greater amplitude of melatonin production after the bright week than after the dim week.

Light and cancer in mice and rats

Among the first experimenters to investigate the impact of constant lighting on mammary tissue susceptibility to tumorigenesis was Jöchle [42]. He reported that C3H-A mice under constant light showed accelerated development

of spontaneous tumors, whereas C3H–HeJ mice under constant light showed delayed spontaneous mammary tumor development and a longer life span. The C3H–HeJ mouse has a degenerate retina (rd) and is visually blind. However, it has now been shown that nocturnal melatonin in the C3H/He rd mice can be suppressed by light [43].

Among the first to investigate the effect of light on chemically induced mammary tumors in rats was Khaetski [44; as described in 45] who conducted experiments in which 'outbred rats' were exposed to constant light beginning at four months of age, and given dimethylbenzanthracene (DMBA). Compared to rats on 12:12 light–dark (LD) cycle and which also received DMBA, those on constant light had reduced mammary tumor yield. In contrast, Khaetski reported that when constant light did not start until 4 weeks after DMBA administration, tumor development was accelerated compared to rats which continued on the 12:12 LD cycle.

Within the context of the conflicting early experiments in which mammary tumors were either stimulated or reduced in rodent models, the question becomes what are the factors which influence tumor yield from constant light? In the 1980s, Shah et al. [17] conducted an elegant series of experiments in which constant light and pinealectomy were used to investigate whether melatonin might explain the effect of light. They found that constant light beginning before birth significantly increased terminal end buds of the female offspring at maturity, and increased susceptibility to DMBA-induced mammary tumors. In an attempt to replicate this finding, Anderson et al. [46] obtained weanling female rats from a supplier, placed one group on constant light and the other on 8:16 light/dark regimen, and administered DMBA when the animals were 52 days of age. In contrast to Shah et al. [17], Anderson found a significant reduction in mammary tumor burden in the constant light group. They also found, unexpectedly, that 29 of the 50 rats in the constant light group showed mature milk glands in the mammary glands at age 141 days despite being virgin, whereas none of the 50 rats on LD showed any such structures.

The reason for the different tumor response appears to be due to differences in the age of the rat at first exposure to constant light which resulted in differences in mammary tissue development. This, in turn, would alter tumor susceptibility [47]. Constant light began in utero in Shah et al. [17], but began at age 26 days in Anderson et al. [46]. After a replication of these exposure conditions, Russo et al. [48] conducted a detailed histological examination of the mammary tissues, and found that light beginning at 26 days of age (LL26) produced a very different mammary gland development than light beginning in utero (LL0); among the LL26 rats, mammary gland differentiation was dramatically accelerated compared to the LL0 rats, and thereby at the age of 50–55 days were less susceptible to DMBA- induced tumorigenesis.

Another possibility is that light exposure of pregnant rats restricted to the period of gestation might increase mammary density and susceptibility to chemically induced mammary tumorigenesis of the female offspring later in their lives, even though after birth they were maintained on a 12:12 light–dark cycle. This is based on the idea that in utero exposures which alter hormones relevant to breast cancer might increase the lifetime risk of daughters [49, 50].

Shift work and diurnal preference

Shift work presents a quantifiable exposure that can result in circadian disruption. Time of day preference (or morning/evening preference; [51]) has been reported to predict tolerance to evening or graveyard shift work. Those workers who report a preference for morning being less tolerant to night work, and more likely to stop this work for medical reasons [52]. Melatonin profile has also been reported to be the best predictor of Horne-Östberg score for morningness/eveningness among the three circadian markers: rectal temperature, heart rate, and melatonin. Griefahn [53] conducted a controlled constant routine study in which 51 persons completed the Horne-Östberg questionnaire and were then kept under strict bedrest for 24 h under constant dim light. Among both women (17 subjects) and men (34 subjects), the peak melatonin during the night hours was about 4 h earlier in the morning types than evening types. In addition, the total melatonin production was greater in morning types. A possible implication of this is that shift-working women with a morning preference, or who have a genetic polymorphic variant associated with morning preference, may be at greater risk of breast cancer than women with an evening preference.

Schernhammer et al. [25] present interesting new data showing lower melatonin and higher estradiol in long-term shift working nurses compared to non-shift working nurses in the Harvard Nurses' Health Study. These data are consistent with an elevated breast cancer risk, but are not consistent with an elevated risk of colon cancer in shift workers (as these authors have also reported, [54]). Both Zhang et al., [55] and Nelson et al., [56] report higher estradiol associated with *lower* risk of colon cancer. In contrast, high estrogen (and estradiol in particular) has been convincingly associated with increased risk of breast cancer [30].

Light and alcohol interaction

An emerging area of research is focusing on effects of diet and of alcohol ingestion on circadian rhythms and on

modifying the effect of light on circadian rhythmicity. It is becoming apparent that timing of meals and alcohol ingestion can alter circadian rhythms independently of light and also affect light's ability to phase shift circadian rhythms. These ideas may have relevance to risk of breast cancer in women in the industrialized world. For those women on non-day shift work schedules, the timing and composition of meals may be an important co-factor in their risk of breast cancer [28].

Change in time of day of meals in rats can uncouple the circadian rhythm of the liver from that in the SCN [57]. Changes in circadian markers occur less rapidly in other tissues such as kidney, heart, and pancreas than in the liver [58], but eventually also become uncoupled from the SCN. Baird et al. [59] reported on experiments in which rats received ethanol injections at four times during the day: 1 am, 7 am, 1 pm, and 7 pm. Ethanol shifted circadian activity and temperature rhythms depending on the time it was administered.

Earnest and colleagues have been investigating the effects of developmental exposure to ethanol in rats. They have found that ethanol during the period of rapid brain development (postnatal days four to nine) causes permanent changes in the endogenous circadian clock of the SCN [60]. In particular, rats exposed to ethanol at ages four to nine days postnatal (corresponding to third trimester in utero exposures in humans), are more sensitivity to the phase shifting effects of a light pulse during the dark period of the circadian day [61]. Moderate to heavy alcohol consumption has been consistently associated with increased risk of breast cancer in women [62]. Stevens and Hiatt [63] suggested that alcohol ingestion may result in lowered melatonin levels which, in turn, may lead to elevated circulating estradiol concentration in blood [16]. Stevens and Hilakivi-Clarke [64] hypothesized that exposure of pregnant rats to ethanol would increase susceptibility to mammary tumorigenesis in their female offspring by raising estradiol. Hilakivi-Clarke et al. [65] have now investigated this possibility. Pregnant female Sprague–Dawley rats were pair-fed isocaloric diets containing either 16% alcohol of total energy (labeled as low), 25% alcohol (moderate) or no alcohol, from day seven to day 19 of pregnancy. These alcohol exposures generate blood alcohol levels of about 61 mg/dl (0.061%, stimulatory dose) and 96 mg/dl (0.096%, modestly intoxicating dose), respectively, and are much lower than those that induce fetal alcohol syndrome in rodent models (which is between 0.15% and 0.175%). Female rats exposed to alcohol in utero developed increased number of mammary tumors, consistent with increased presence of terminal end buds and epithelial density seen in these animals. The greatest tumor yield and greatest mammary density in the female offspring at their adulthood was in the moderate in utero alcohol group. However, for estradiol, there was an increase in pregnant rats in the lower alcohol group, but not in the moderate alcohol group. This casts doubt on the presumed estradiol-mediated mechanism for an in utero alcohol effect on mammary tissue development and breast tumorigenesis, and may indicate a role for altered circadian functioning as a mechanism.

For breast cancer in women, and the potential for exposures of pregnant women to increase risk in their daughters later in life, the role of diet and alcohol in modifying circadian rhythms and interacting with lighting is an important area of pursuit.

Early susceptibility and lifelong risk

If cancer requires two or more mutations in a cell [66, 67] as is currently believed, then the occurrence of breast cancer at a young age does not require membership in a susceptible subgroup. There will be a distribution of cases across the age spectrum even if all women were genetically identical and had similar carcinogen exposures throughout life. However, there clearly are susceptible subgroups who are indeed diagnosed with breast cancer at a younger age such as carriers of a mutant BRCA1 allele. Mutations in genes involved in fundamental processes of cell cycle regulation and apoptosis would be expected to be more strongly associated with risk in young women because these processes begin at conception. Given the emerging realization of the central role of the clock gene apparatus in gene regulation throughout the organism, there may be specific clock gene variants which also confer early susceptibility. These may both explain part of the family history effect from germ line mutation, and confer increased individual risk from sporadic mutation. In support of this possibility, Zhu et al. [68] have reported that a polymorphic variant of the Per3 gene is associated with breast cancer in young women.

Causal associations and biological mechanisms

There are two pathways to discovering causal associations: serendipity and prediction. The vast majority of causal associations have been found by the first pathway, serendipity. This has come from the astute observation of a series of cases, from ecological studies, and from large epidemiological studies examining many exposures. For example, it became clear from epidemiology that smoking 'caused' (i.e., greatly increased risk) lung cancer long before biological mechanisms were identified. There is now consensus that the observed association of smoking and lung cancer in epidemiological studies is causal; yet

there is still not consensus on exactly what mechanism(s) is operating. Many examples of this exist including consensus that the associations of HBV and liver cancer, aspirin use and colon cancer, and alcohol and breast cancer are all causal, yet for none of these is there consensus on what is the dominant mechanism. For each, much has been learned about the pathophysiology of exposure to the agent, but it is still not clear what part of this pathophysiology is most important, or whether there are other unrecognized mechanisms which account for the observed causal association.

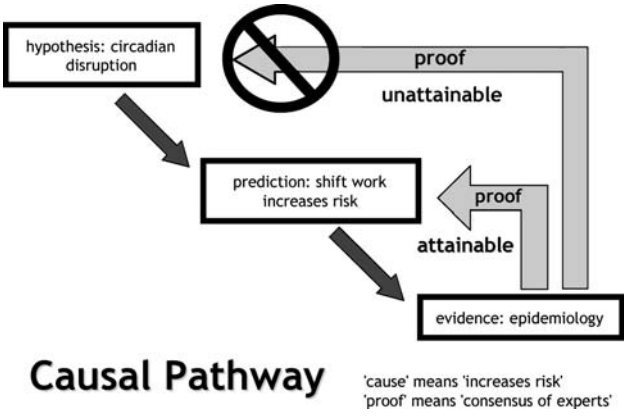
To obtain consensus that an observed association is causal requires more epidemiogical studies to eliminate chance, and then bias, as accounting for the results. At some point, it becomes clear that the exposure 'causes' the disease. Factors to consider are described by Hill [69] and include strength, consistency, dose response, reversibility, coherence, temporality, and biological plausibility. Biological plausibility, or lack of it, is weak evidence for or against the causality of an association; as Hill wrote: '…this is a feature we cannot demand.'

Strength of the association is only pertinent to a judgment of causality, not of importance. Once an association is judged to be causal, then even a very modest relative risk can be very important. For example, smoking accounts for more deaths from heart disease than from lung cancer despite the fact that the relative risk is over ten for lung cancer but less than two for heart disease.

The shift work association with breast cancer was found only after a biological mechanism was proposed and a prediction made (by letter to the Nurses' Health Study in 1987, and then published in 1992; 5). Before this association can be judged to be causal, chance and bias must be eliminated as plausible explanations. The status of this association is shown below.

It is rare for a postulated biological mechanism to lead to an epidemiological observation, as was the case for shift work and breast cancer. More typically, the epidemiological observation is made and then this leads to laboratory/basic science aimed at identification of potential biological mechanisms.

Biological plausibility plays at best a minor role in judging causality, and is not required. The value in identifying possible biological mechanisms can be for the purposes of intervention, but not always. The mechanism by which smoking causes lung cancer is irrelevant to the intervention: smokers should just quit. For shift work, however, identifying possible mechanisms would be very helpful for interventions because shift work will not go away. For shift work, a flow chart of hypothesized mechanism leading to a predicted association leading to evidence for that association is shown below.



The studies can 'prove' the predicted association to be causal, but cannot verify the originally proposed mechanism. Proof of causality is attainable, whereas proof of the mechanism is virtually unattainable. (The word 'proof' in this context can only mean a consensus of experts. In reality, proof exists only in mathematics.)

Conclusion

The topic of light, circadian disruption, and risk of breast cancer has expanded in scope dramatically in the last ten years. Since the first speculation that increasing light-at-night might be raising breast cancer risk by reducing melatonin and raising estrogen [15], many more potential mechanisms for a light effect on breast cancer have emerged [26]. The epidemiology has also advanced from the original suggestion that shift workers would be at

Reason for observed association	Status of evidence	Needed
Chance	Too few studies so far conducted to eliminate chance despite 'significance' of some of them	More studies of different types and locations
Bias	Other factors associated with shift work may be the real cause, e.g., alcohol consumption	Co-variate adjustment on all known risk factors –studies of demographics of shift workers
Causal	If chance and bias are eliminated, then the association is causal	But this does not prove the originally proposed mechanism

increased risk. This was published in 1992 [5], although it was communicated by letter to the Nurses' Health Study researchers in 1987; it was subsequently incorporated into their 1988 questionnaire, and the question formed the basis for findings from the Nurses' Health Study of increased risks of heart attack [70], breast cancer [10], and colon cancer [54] in shift working nurses. Davis et al. [9] also reported increased risk of breast cancer associated with history of shift work in a case-control study; and before either of these reports, Hansen [8, 71] reported increased risk in shift workers in a huge case-control study in Denmark. Hahn's [11] idea that another test of the 'light-at-night' hypothesis is the prediction that blind women should be at lower risk has also yielded valuable data. And now a new generation of studies can examine dietary interactions with altered light exposures (such a shift work), and focus on polymorphic variants in clock genes for possible associations with risk and/or for interactions with other factors that may disrupt circadian rhythms.

Note added in proof A study just released has reported a significant inverse relation of melatonin and breast cancer risk in the Nurses' Health Study (Schernhammer ES, Hankinson SE (2005) Urinary melatonin levels and breast cancer risk. JNCI 97:1084–7).

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