Breast Cancer and Circadian Disruption From Electric Lighting in the Modern World

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Breast cancer is the leading cause of cancer death among women worldwide, and there is only a limited explanation of why. Risk is highest in the most industrialized countries but also is rising rapidly in the developing world. Known risk factors account for only a portion of the incidence in the high-risk populations, and there has been considerable speculation and many false leads on other possibly major determinants of risk, such as dietary fat. A hallmark of industrialization is the increasing use of electricity to light the night, both within the home and without. It has only recently become clear that this evolutionarily new and, thereby, unnatural exposure can disrupt human circadian rhythmicity, of which three salient features are melatonin production, sleep, and the circadian clock. A convergence of research in cells, rodents, and humans suggests that the health consequences of circadian disruption may be substantial. An innovative experimental model has shown that light at night markedly increases the growth of human breast cancer xenografts in rats. In humans, the theory that light exposure at night increases breast cancer risk leads to specific predictions that are being tested epidemiologically: evidence has accumulated on risk in shift workers, risk in blind women, and the impact of sleep duration on risk. If electric light at night does explain a portion of the breast cancer burden, then there are practical interventions that can be implemented, including more selective use of light and the adoption of recent advances in lighting technology and application. **CA Cancer J Clin 2013;000:000-000.** © **2013 American Cancer Society.**

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Introduction

The Breast Cancer Burden

Breast cancer is the leading cause of cancer death among women worldwide.[1] Risk is highest in the economically developed societies and is increasing rapidly in those developing societies that historically showed low risk.[2] Until the 1980s, it was thought that the primary determinant of risk was a change in diet; in particular, a change from low-fat to high-fat content was extensively investigated in both rodent models and epidemiological studies. Considerable epidemiological evidence, however, has shown that fat content of adult diet has little or no effect on breast cancer risk, and the evidence for benefits of fruit and vegetable intake is weak.[3] In fact, other than alcohol intake, overall diet composition, at least in adulthood, has

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very little impact, although body mass clearly does.[4] The published analyses that have attempted to adjust for changes in known risk factors have reported that less than half the risk in high-risk societies can be accounted for by changes in the established risk factors.[5-8] Recent evidence has also implicated physical activity in risk,[9] and changes in activity as societies industrialize was not taken into account in the cited studies; however, these changes would have to be massive to explain much of the differences among societies. This stands in stark contrast to most of the major cancers for which the primary causes are known (eg, lung cancer and smoking, liver cancer and hepatitis viruses, cervical cancer and human papillomavirus, stomach cancer and *Helicobacter pylori*, skin cancer and sun exposure).

Are the differences among societies in the risk of breast cancer, and the rising trends in risk in most societies, explained by a combination of many exposures working together? Or is there a major factor that has so far been overlooked[10]?

After diet, what else changes as societies industrialize? Of course, there are many changes (eg, physical activity, hormone-replacement therapy, many aspects of diet), but a hallmark of the modern world is the increasing use of electricity to light the evening and nighttime environment. Could increased exposure to light during the dark hours, which can disrupt melatonin, circadian rhythms, and sleep, be a problem?

Circadian Rhythms

Life on Earth has adapted over 3 billion years to the 24-hour cycle of light and dark from rotation of the planet as it circles the Sun. An endogenous circadian rhythmicity in physiology has developed that enables life to anticipate the change from day to night and night to day; this is true for virtually all life forms, from cyanobacteria[11] to human beings[12] and everything in between. The circadian system of cyanobacteria has yielded invaluable insight into the circadian systems of life forms in general; it is propelled by a three-gene cluster denoted KaiA, KaiB, and KaiC, with the cyclic phosphorylation of the latter apparently driving the physiological output of the clock.[13] This three-gene cluster controls global gene expression by alteration of DNA topology and controls specific gene transcripts via a feedback loop in vivo.[11] The circadian cycle of KaiC phosphorylation and dephosphorylation can be recapitulated in vitro,[14] making it easily amenable to study. In mammals, a more complex system operates, although the three core characteristics are the same: a self-sustaining, or endogenous, ~24-hour physiological oscillation; an input mechanism to signal environmental time of day; and an output mechanism to synchronize circadian-controlled behavior, physiology, and metabolism in the rest of the organism.

Human circadian biology is complex but is also generated by an interlocking molecular genetic loop designed to maintain circadian rhythmicity in cells and tissues at approximately, but not exactly, 24 hours, even in the absence of an external time cue from the Sun. In many organisms, including humans, the primary environmental time cue used to synchronize the circadian system is the daily light-dark cycle, which, in mammals, is detected by a parallel "nonvisual" light-sensing system in the retina that is anatomically and functionally distinct from vision and is devoted to measuring both the external time of day (day vs night) and the time of year or season (duration of night).

Although managing fire became possible perhaps as long ago as 1.5 million years, and the candle was developed about 5000 years ago, it has only been since the advent of electric power a little over 100 years ago that it has become possible to pervasively and brightly light the night. Importantly as well, electric lighting as currently employed is rich in blue wavelengths, which are most effective at disrupting circadian rhythmicity; in contrast, fire light from candles and wood is rich in yellow and red, which are relatively less effective in disturbing circadian rhythms (see below).

Light, whether from the Sun or electric luminaires, is the most potent environmental exposure for functionally entraining and resetting the circadian system or for disfunctionally disrupting endogenous circadian rhythmicity.

Czeisler et al[15] conducted a landmark study designed to determine the intrinsic circadian period of humans. Eleven healthy young subjects (average age, 24 years) and 13 healthy older subjects (mean age, 67 years) were placed on a "forced desynchrony" protocol in which a 14-hour dark period was followed by a 14-hour dim light period (~15 lux). Based on measurement of melatonin, cortisol, and core body temperature, the intrinsic circadian period averaged 24.18 hours in both the young and older group, and the variance was very small in both groups. These results are important; before this work, reports of the intrinsic period ranged from 13 to 65 hours.

Circadian Rhythmicity in Physiology

In humans, the master pacemaker is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Through both neural and humoral transduction, the SCN communicates with peripheral organs and tissues to synchronize clock gene expression throughout the organism to generate endogenous circadian rhythmicity. The core circadian genetic loop consists of a remarkably small number of genes, at present believed to be about 10. Yet this core controls the expression of about 10% of the entire genome[16,17]; importantly, the gene expression under circadian control is tissue-specific, with only a minority that are common among tissues. These clock genes generate an endogenous

circadian rhythmicity in physiology, which means that, under constant dark conditions, humans will cycle intrinsically at a period slightly longer than 24 hours (by ~12 minutes on average, although the population range is from ~23.6 to 25.1 hours) for the rest of their lives.[15] While a seemingly small difference from 24 hours, the daily 12-minute synchronizing shift by light that we take for granted is essential; sun in the morning is detected by the retina, which sends this signal to the SCN, which, in turn, resets the clocks in the rest of the body. Without this resetting, we could not remain entrained to the 24-hour world. Unfortunately, this is exactly what is experienced by the majority of totally blind people, whose lack of light detection prevents a necessary resetting of their endogenous circadian clock each day to precisely 24 hours, and so it runs on a non-24-hour cycle. This can cause non-24-hour sleep-wake disorder, a highly disruptive and chronic circadian rhythm disorder characterized by cyclic episodes of good sleep, followed by poor nighttime sleep and excessive daytime napping, and then good sleep again as the internal clock runs in and out of synch with the 24-hour social day, in a never-ending cycle.[18] It is not just sleep that is affected, however; all circadian-controlled systems become desynchronized, including many hormones (eg, melatonin, cortisol, thyroid-stimulating hormone), glucose and lipid metabolism, temperature regulation, cell cycles, and more.

Haus and Smolensky[19] and Blask[20] provide succinct analyses of various potential physiological mechanisms that might link circadian disruption to cancer risk; these include consequences of melatonin suppression, disruption of sleep-wake patterns, cell cycle impairment, and altered clock gene function. In addition, the role of circadian control of steroid hormone secretion by the adrenal cortex is described by Ota et al[21]; the adrenal gland plays a crucial role in communicating the time of day information from the SCN to peripheral tissues through glucocorticoid secretion, and nocturnal light disrupts this process.

Bjarnason et al[22] demonstrated circadian expression of several circadian genes (human period circadian clock 1 [*hPer1*], human cryptochrome 1 [*hCry1*], and human brain and muscle Arnt-like protein 1 [*hBmal1*]) in oral mucosa in eight healthy, diurnally active males; expression profiles were as predicted based on rodent evidence. In addition, cell cycle markers of G and S phase were also circadian, raising the possibility that cell cycle regulation was under circadian gene control. This ground-breaking work has been followed by many new insights about the interconnections of circadian gene function and cell cycle regulation in cells and tissues in general.[23] Cell cycle regulation and loss of cell cycle control are central to our understanding of the carcinogenic process; increased normal cell turnover increases risk of mutations in general, and in tumor suppressor genes in particular, leading potentially to a transformed cell and the beginning of the path to a diagnosed cancer. Therefore, chronic disruption of clock gene expression that leads to cell cycle deregulation could provide a chronic stimulus, increasing DNA replication errors and resulting mutations. Many aspects of DNA damage response are also under circadian control,[24] thus potentially exacerbating the impact of disruption of circadian rhythmicity on cell cycle regulation and initiation of cancer. Studies in rodents and cell systems of the effect of "circadian disruption" by clock gene knockout (KO) (eg, *Per2*, *CLOCK*, *Cry1*) on cancer risk, however, are mixed.[25-28]

A further aspect of circadian impact is the investigation of a fundamental link between circadian gene expression and metabolism[29]; this connection opens a plethora of potential adverse effects of circadian disruption. In particular, CLOCK is a histone acetyltransferase (HAT) that appears to counterbalance sirtuin 1 (SIRT1), a histone deacetylase. Another clue on the circadian-metabolism connection is that the long sought ligand for nuclear receptor subfamily 1, group D, members 1 and 2 (REV-ERBα and REV-ERBβ, respectively), key elements of the circadian oscillator, is heme.[30] In our evolutionary history, what better single molecule could our endogenous circadian system use to assess the nutritional status of our mammal than heme?

Impact of Electric Light at Night on Circadian Rhythmicity

In 1980, the first clear evidence was published in *Science* that ocular exposure to bright white light during the night could suppress melatonin production in young adults.[31] Since that seminal report, great detail has emerged on the impact of wavelength, intensity, duration, and time of night on the acute suppression of melatonin production by light. Similarly, much more is understood about how light resets the timing of the circadian clock and the rhythms it controls, often measured from the timing of the melatonin rhythm but also including cortisol, core body temperature, and circadian gene expression.

Initially, it was thought that bright light, at least 2500 lux, was required for melatonin suppression in humans.[31] More recently, however, it has been shown that, under carefully controlled conditions, retinal exposure to illuminances of as low as 1 lux or less of monochromatic light at wavelength 440 to 460 (blue-appearing light) can significantly lower nocturnal melatonin,[32,33] as can <100 lux of broad-spectrum fluorescent light.[34-37] These same light levels can also elicit significant phase shifts of the circadian clock and directly enhance alertness[37-40]; approximately 100 lux exposure will cause about 50% of the maximum response. Such light exposure, when experienced in the evening at home from bedside lamps, TVs, computer screens, tablets, and other devices, causes suppression of melatonin, delays the

timing of circadian rhythms, and elevates alertness, all of which make it harder to fall asleep, make it harder to wake up in the morning, and restrict sleep.[36,41]

The physiological mechanism by which light exposure is conveyed to the circadian system is one of the more intriguing topics in modern biology[42]; a hitherto unknown intrinsically photosensitive retinal ganglion cell (ipRGC) was reported in 2002 in *Science*.[43-45] This novel photoreceptor is anatomically and functionally distinct from the rods and cones used for vision and is a more fundamental aspect of mammalian biology, having evolved before vision.[46] These ipRGCs, which represent <1% of ganglion cells, contain the photopigment melanopsin, which is maximally sensitive to blue light (λmax, ~480 nm). The cells are spread across the retina to provide a network of light detectors across the eye, which is further enhanced by the melanopsin contained in their dendritic fields, and are hardwired to areas of the brain involved in regulation of circadian rhythms and alertness.[47,48] While rods and cones play a role in light detection for the circadian system,[49,50] melanopsin is the primary photoreceptor by which light information is transduced to the circadian system.

It is now evident that, among other things, 1) bright light exposure at night suppresses melatonin in all sighted persons[31]; 2) shorter wavelength (blue) light is most effective and longer wavelength (red) is least effective in melatonin suppression, alerting the brain, and resetting the circadian pacemaker[32,40,51]; 3) there is a dose response in which, the greater intensity of the light, the greater percentage suppression of melatonin[37,52]; 4) there are differences in individual sensitivities to light-induced melatonin suppression[53-55]; and 5) characteristics of daytime lighting can alter sensitivity to light exposure during the night.[56-59] These and other properties of light that are under investigation have important implications for future research directions, design of epidemiological studies, and finally, for potential intervention and mitigation.

Sleep Disruption Versus Circadian Disruption

Adequate sleep is required for optimal cognitive function and for many other aspects of well-being that are not entirely understood. Inadequate or interrupted sleep has short-term safety consequences through increased sleepiness and potential longer term risks to chronic diseases, including cardiovascular disease, diabetes, and some cancers. Sleep is essential to health; however, it is not sufficient to synchronize the circadian clock: a strong daily cycle of light and dark is required (although, at least in mammals, the sleep-wake cycle gates light exposure to the retinae for entrainment of the circadian clock by the opening and closing of the eyes and, so, is an important practical consideration). The normal nocturnal rise in circulating melatonin is not affected by being asleep or awake but is severely attenuated by light exposure during the night.

Research on sleep and health cannot entirely separate effects of sleep duration from duration of exposure to dark, because the sleep-wake cycle gates light-dark exposure to the SCN and pineal[60]; therefore, the results of observational and laboratory experimental research are difficult to interpret. The distinction is important. A requirement for a daily and lengthy episode of darkness to maintain optimal circadian health has different implications than a requirement that one must be asleep during this entire period of dark; it may be normal to have wakeful periods in the middle of a dark night.[61]

Electric light exposure during the night can disrupt sleep as well as circadian rhythmicity. The long-term health effects of short sleep and circadian disruption are both increasingly receiving research attention.[62,63] Short or interrupted sleep has been shown in observational studies and in carefully controlled experiments to have marked impacts on markers of metabolic disorders.[64,65] Because dark and sleep are difficult to adequately disentangle in studies of diurnal animals such as humans, it is not clear whether the proximate cause of metabolic changes is sleep disruption itself, disruption of circadian physiology, and/or a direct effect of light exposure. For example, Taheri et al[66] examined sleep as determined by polysomnography in 1024 adults and found that sleep duration was significantly associated with morning levels of leptin in the blood. In the same group of subjects, however, total reported hours of sleep were more strongly associated. The mean reported sleep duration was 7.2 hours, whereas the mean of verified sleep was 6.2 hours, an entire hour shorter. Self-reported "sleep" probably relates to the number of hours between lights out in the evening and getting up in the morning, or, total hours of dark.

Another example is described by Moller-Levet et al.[67] In that experimental study, 26 subjects (12 female; mean age, 27 years) were exposed to 1 week of "sufficient sleep" and 1 week of "insufficient sleep" in a balanced cross-over design, and then a transcriptome analysis was performed; the authors reported that 711 genes were either up-regulated or down-regulated by "insufficient sleep." They also reported that restricted sleep altered melatonin by delaying its phase and blunting its amplitude. The restricted sleep protocol, however, required 18 hours of bright light (and the paper is surprising in its lack of detail on the lighting used in the experimental conditions), whereas the "control" condition required exposure to 14 hours of bright light. The authors designated the control condition as one in which there was an "opportunity" for 10 hours of sleep, and the restricted condition was the opportunity for only 6 hours. The longer lighted period for the restricted condition would be expected

to truncate melatonin production, but this does not mean that a person at home in 10 hours of dark who only actually sleeps for 6 hours has any impact on melatonin production or gene expression.

Buxton et al[68] attempted to disentangle the effects of circadian disruption from those of sleep disruption on metabolic disorders in humans. In their experiments, the combination of the two had large effects on the resting metabolic rate and plasma glucose concentrations, both in directions that would be expected to increase the risk of obesity and diabetes if maintained chronically. It is not yet clear which type of disruption, circadian or sleep, has the greater effect, or how they interact, however. Future research should attempt to distinguish the relative roles of circadian disruption, sleep disruption, melatonin suppression, or light itself on the interaction between electric lighting and adverse health effects, as these distinctions are vital to guide intervention strategies.

Animal Models of Light and Cancer

Investigation of light effects on mammary tumorigenesis in rodents began in the 1960s.[69-78] For both chemically induced and spontaneous tumors, most of these studies showed an increase in tumor incidence and number by exposure to a constantly lighted environment compared with a 24-hour alternating schedule of light and dark (eg, 24 hours of light vs 12 hours of light:12 hours of dark). Beginning in the 1980s, researchers focused more closely on the ability of melatonin to inhibit mammary carcinogenesis and on the impact of a constant light environment in animal rooms on mammary tissue development, and major effects were reported.[79,80] Because the stimulatory effects of constant light on mammary tumorigenesis mimicked the tumor-promoting effects pinealectomy, it was proposed that the light-induced suppression of melatonin production was specifically responsible for augmenting mammary carcinogenesis. At the time of these studies, light was used as a tool for melatonin suppression and, itself, was not considered as a human exposure of consequence. It is important to note that constant exposure to bright light not only suppressed melatonin synthesis in these experiments but also induced additional detrimental effects on the circadian activity of the SCN in general.

In the early 2000s Blask and colleagues began to examine the effect of various levels of light during the night on the growth of a human breast cancer xenograft in nude rats.[81,82] They predicted that nighttime light exposure would suppress melatonin and that this suppression would significantly increase an existing tumor's ability to utilize linoleic acid for its growth.[83] This prediction was based on previous work showing that nocturnal melatonin directly suppressed the growth of both estrogen receptor-positive and estrogen receptor-negative tumors and that linoleic acid, which is required for the growth of breast tumors, is also suppressed by nighttime levels of melatonin. Therefore, linoleic acid and its mitogenic metabolite can be used as markers of tumor growth rate in response to endogenous nocturnal melatonin signal and its suppression by light at night.[81-84]

Consistent with their prediction, Blask et al[81,82] found a dose-dependent suppression by nighttime fluorescent light exposure on blood melatonin levels in exposed rats, a significant increase in metabolism of linoleic acid in the human breast cancer xenografts, as well as a large increase in tumor growth rate; the estimated tumor weight (from palpation) attained 5 g at 30 days post-implantation in constant dark, whereas it attained 5 g at 15 days in the constant light condition. The dose response was dramatic; and, even at the lowest illumination level, there was a partial suppression of melatonin and a corresponding increase in tumor growth rate.

Blask et al[81] took this experimental design an important step further by perfusing the human xenografts growing in the nude rat with human blood taken from young women under three conditions: 1) during the day, 2) at night during the dark, and 3) at night after light exposure to the subject. Blood taken at night in the dark and, thus, high in melatonin, strongly inhibited the growth and metabolism of the xenografts; whereas blood taken at night from the same young women after light exposure and, thus, low in melatonin, did not slow the tumor growth at all. Moreover, the addition of melatonin to the blood taken after nighttime light exposure restored to it a strong tumor-inhibitory capacity; whereas the addition of a melatonin antagonist to the blood taken in the dark obliterated its tumor-inhibitory capability. These results clearly demonstrated that the tumor-inhibitory effect of blood taken at night was because of its melatonin content.

Other notable recent animal experiments also designed to test the idea that circadian disruption from electric light may increase cancer risk have shown that simulated jet lag stimulates cancer growth in mice[85,86]; the cell line used was Glasgow osteosarcoma. It must be noted that Filipski et al[85,86] deliberately chose a mouse strain that had a weak and inverted melatonin rhythm, with low circulating levels during the night and a daytime peak. Their goal was to identify a cancer-promoting effect of light that was not mediated by melatonin suppression.

Anticancer Mechanisms of Melatonin

There is strong experimental evidence that, in complete darkness, melatonin inhibits the growth of established, but extremely small, tumors; these tumors may never progress to become a clinically detectable neoplasm, in part because of the oncostatic effect of melatonin.[87,88] This inference is based on a series of experiments first using murine tumor

lines implanted into rats and then using human breast cancer xenografts implanted into the rat model. The theory that light at night may increase cancer risk was originally based on a light-induced suppression of melatonin.[89]

Melatonin may also aid in preventing cancer initiation as well because of its antiproliferative and antioxidant capacities, its ability to enhance immune surveillance, and its effects in modulating cellular and humoral responses and epigenetic alterations.[90-95]

Light and Breast Tissue Development

The important experiments by Blask and colleagues[81,82] focus on the growth of existing but small tumors that might never survive but for the melatonin suppression from exposure to light at night. There may be other potential mechanisms by which circadian disruption might induce cancer. Cancer development is believed to follow a multistage, or multihit, process in which an accumulation of mutations eventually results in a normal cell transforming into a malignant cell capable of growing into a clinically detectable neoplasm.[96] The mutations are believed to be essential; however, cancer-causing agents do not necessarily have to be directly mutagenic; altered growth and development of a tissue, such as breast, can have a profound impact on the chances that the essential mutations will occur over time. It is for this reason that estrogen levels, age at menarche, and child bearing are believed to play such an important role in risk of breast cancer; they all affect the normal growth and development of breast.[97]

The early experiments of Mhatre et al[79] and Shah et al[80] found that constant light had a measurable impact on breast tissue development in rats. When constant light was initiated in utero to pregnant dams,[80] tumor yield from dimethylbenzanthacene (DMBA) administration at age 55 days to the female offspring was substantially increased; the mammary tissue in exposed rats was also found to be rich in terminal end buds, the structures most susceptible to chemical mutagenesis.[79] In contrast, Anderson et al[98] initiated constant light when the female rats were 26 days old (having been on a 12:12 hour light:dark cycle until then) and found that tumor yield was actually reduced. Remarkably, Anderson et al[98] also found that the exposed rats had evidence of rapidly advanced terminal differentiation of breast tissue, and most began lactating though still virgin. This, the authors surmised, rendered their breast tissue refractory to malignant transformation by DMBA. The difference in timing of light exposure between the work of Shah et al[80] and Anderson et al[98] had a large effect on tumor yield. This area deserves vastly more investigation.

By these mechanisms, exposure to light at night early in life (even in utero from exposure of the pregnant mother[99]) may affect breast cancer risk throughout life.

Epidemiological Studies of Circadian Disruption and Breast Cancer

The first suggestion that light at night might explain a portion of the breast cancer pandemic was made in 1987.[10,100] The hypothesis was based on the idea that exposure to light at night would result in melatonin suppression, which, in turn, would increase breast cancer risk as described in the previous section. Since 1987, a series of predictions of this theory have been tested, including: that shift working women should be at higher risk[101]; blind women should be at lower risk[102]; risk would have an inverse association with sleep duration[103]; and, across societies, the incidence of breast cancer and nighttime ambient illumination, as measured by satellite image, should be correlated.[104] In general, predictions of the theory have been supported.[105]

Shift Work

The strongest evidence to date are data showing that women who work nights (shift work) are at higher risk of breast cancer. These data led the International Agency for Research on Cancer (IARC) to conclude that "shift work that includes circadian disruption is probably carcinogenic to humans (Group 2A)."[106] The American Medical Association then broadened the topic in a policy statement in 2012 on the health hazards of light at night in general.[107] Since the IARC classification, there have been more epidemiological studies in various settings and populations that have supported an association,[108-112] with one showing mixed results[113] and one that reported no association.[114] These and the previous studies are reviewed together in a meta-analysis by Jia et al,[115] who reported that, among the "high-quality studies," night work was associated with an increased risk of breast cancer (relative risk, 1.4; confidence interval, 1.13-1.73).

An issue for the interpretation and comparison of the published studies is that there has not been a uniform definition of "shift work" used across the studies. Some studies focused on rotating shifts, others on "graveyard shift," and others on any non-day shift; some studies analyzed risk according to duration in years of work, but not in the intensity (eg, the number of shifts per week or per month) over the working life, while others did examine intensity as well as duration. In 2009, the IARC convened a workshop of 23 experts in occupational medicine and epidemiology; the task was to attempt some sort of consensus on what are the most disruptive and what are the least disruptive features of non-day shift work.[116] The authors concluded that future epidemiological studies should attempt to quantify all three of these shift work features in exposure assessment: 1) shift schedule (eg, evening, night, rotating), 2) years on each shift schedule, and 3) shift intensity.

Shift work has been used as a surrogate for exposure to light at night and circadian disruption in the epidemiological studies of cancer. (This circadian disruption can include

melatonin suppression, clock gene disruption, and sleep disruption; the epidemiological studies to date cannot distinguish among these three.) The weight of evidence strongly supports a suppression of melatonin amplitude and disruption of its phase,[117-121] although not all studies have found this[122]; there is also one report that race or ethnicity may modify the impact of shift work on melatonin production.[123] If shift work is a surrogate for light at night exposure, then another important consideration in evaluation of these studies is that the comparison groups, day workers, are certainly not unexposed. Almost all persons in the modern world use electric lights in the evening and at night. The degree of melatonin suppression is a continuum, with shift workers likely to be the most suppressed and blind people the least (on average), but each and every day, people suppress their melatonin to some degree if they are not in the dark at dusk and stay there until dawn. Similarly, all people in the modern world experience some degree of circadian or sleep disruption because of electric light, and, again, the degree of disruption is distributed continually. The electric light exposures typically seen in the evening at home have strong effects on suppressing melatonin, shortening sleep, and disrupting circadian rhythmicity (see section above: "Impact of Electric Light on Circadian Rhythmicity").

Blindness

Hahn[102] published the first evidence that blind women may be at lower risk of breast cancer than sighted women. He reasoned that, if light during the night increased risk, then blind women should be at lower risk because they may have an inability to detect light and would not be inclined to use electric lighting at any time of day or night. There have been four studies since then that have each supported Hahn's prediction, albeit in small numbers of cases[105,124]; in 3 of these, the confidence interval for the reduced relative estimate for total blindness included 1.0; however, in one of these, the trend in lower risk with increasing degree of visual impairment was statistically significant. It must be noted that, on average, however, blind women have not been shown to exhibit greater 24-hour melatonin production[124]; what is different is that blind women cannot have their endogenous melatonin signal blunted or altered by electric lighting as it can be in sighted women.

Sleep Duration and Disruption

Another prediction of the theory that electric light exposure at night leads to circadian disruption and, hence, increases cancer risk is that short and/or disrupted sleep would be associated with elevated risk by exposing individuals to more light and/or suppressing melatonin to a greater extent. The first report to test this prediction was by Verkasalo et al.[103] Subsequent results have been mixed, so the evidence to date is inconclusive.[105] In particular, Girschik et al[125] reported on a case-control study of breast cancer from Australia that neither sleep duration nor sleep quality was associated with risk. However, for this particular exposure, sleep, the case-control design may be highly prone to bias, both recall bias but, more likely, bias by indication in which a development of breast cancer changes sleep habits.[126] These studies have not isolated sleep, because when sleep changes, so does light exposure, and many other metabolic changes occur. The physiological changes purported to be because of sleep restriction[64,65] may, in part, be because of light extension.

Ecological Analyses

If ocular exposure to light at night increases breast cancer risk, then communities with high levels of ambient nighttime light should be associated with higher incidence rates.[127] This was first tested by Kloog et al[104] using the Israeli National Cancer Registry and Defense Meteorological Satellite Program (DMSP) illumination data (ospo.noaa.gov/Operations/DMSP/index.html). Among 147 communities, the breast cancer incidence and the nighttime light level were significantly correlated; the highest lighted community had a 73% higher incidence compared with the lowest after controlling for demographic variables of ethnic makeup, birth rate, population density, and local income level. Lung cancer incidence was also analyzed as a "negative" control, and, in fact, there was no correlation of nighttime illumination and lung cancer incidence, as predicted.

Kloog et al[128] extended this analysis to 164 countries of the world using the GLOBOCAN 2002 database and again the DMSP database. Cancers of lung, colon, larynx, and liver were also analyzed with the expectation that they would not be correlated with nighttime illumination, and they were not. Breast cancer incidence was significantly associated with nighttime illumination, and it was estimated that the risk was 30% to 50% higher in the highest lighted countries compared with the lowest after controlling for fertility rate, per capita income, percent of urban population, and electricity consumption. In a similar approach, Bauer et al[129] conducted a case-referent analysis of geographic location of residence in the state of Georgia, USA. With breast cancer as the case and lung cancer as the referent, the odds ratio for the highest of three light level categories (constructed from the DMSP light level data) was 1.12 (confidence interval, 1.04-1.20), further supporting the association of higher levels of ambient nighttime light exposure and breast cancer risk.

Circadian Gene Polymorphisms

The initial suggestion that circadian gene polymorphisms might be related to breast cancer risk focused on CLOCK

and a possible interaction of it with cell cycle regulation, specifically cyclin D1[130]; these ideas were expanded upon a few years later.[131]

The first investigations into the effects of disruption of circadian gene function on risk were conducted by Yong Zhu and colleagues beginning with a report of a circadian gene polymorphism associated with breast cancer risk published in 2005.[132] These authors selected the variable number tandem repeat (VNTR) polymorphism in the coding region of Per3, one of the core circadian genes, because it had been previously reported to be associated with affective disorder and diurnal preference.[133] Loss of this gene has a more subtle phenotypic impact than loss of Per1 or Per2, in that Per3 KO in mice does not result in a complete loss of circadian control but, rather, results in a shortened circadian period by about 30 minutes.[134] Recently in humans, the less common 5/5 genotype was shown to be associated with self-reported sleep patterns that were different from persons with the 4/4 and 4/5 genotypes (ie, earlier wake time, bed time, and less daytime sleepiness) in a prospective study of 675 subjects aged 20 to 35 years in England.[135] The sleep assessments were based on a questionnaire. A smaller study using polysomnography on 22 healthy subjects did not show any difference in sleep behavior but did show differences in sleep architecture between 5/5 subjects compared with 4/4 subjects, such as more slow wave sleep.[136]

Zhu et al[132] reported an odds ratio of 1.7 (confidence interval, 1.0-3.0) for premenopausal women with the 5/5 or 5/4 genotype compared with the 4/4 genotype. Intriguingly, it has recently been reported that persons with the 5/5 genotype are more sensitive to the suppressive effect of blue-enriched light at night than those with the 4/4 genotype.[55] A limited number of further studies have been conducted of other circadian gene polymorphisms with mixed results.[137,138]

It is too soon to tell whether these efforts will lead to a coherent story that might result in some sort of screening or therapeutic benefit.

Circadian Gene Expression

There have been a limited number of studies showing differences in circadian gene expression in breast tumor tissue compared with surrounding normal tissue,[139] and those studies are difficult to interpret at present. Another approach has been to assess global differences in markers of circadian gene expression using peripheral blood lymphocytes (PBLs) in breast cancer cases and controls. For example, significant hypomethylation of the *CLOCK* promoter and hypermethylation of the *CRY2* promoter were found when comparing PBLs from breast cancer cases and controls.[140,141] This was followed by a study showing similar differences between day-working and night-working women in promoter methylation of these two genes,[142] which provides another possible mechanism for an increased risk in night workers. This is an exciting and emerging area of investigation.

Other epigenetic mechanisms may also connect circadian gene expression and breast cancer risk. Sahar and Sassone-Corsi[143] proposed that, because CLOCK has HAT activity, it may alter expression of cyclin D1, the gene product of which plays a critical role in cell cycle regulation and reportedly is associated with breast cancer risk.[144]

Future Directions—Intervention and Mitigation

It is now clear that electric lighting, including indoor evening light levels, has strong effects on human circadian rhythms in physiology, metabolism, and behavior. Recent experimental evidence in humans has shown, for example, that the lighting commonly used in the typical home in the evening is enough to delay melatonin onset and blunt its nocturnal peak.[36] Even the display screens of personal computers, which often emit light rich in the blue portion of the visible spectrum, can alter melatonin production in the evening.[41] It is not certain that these alterations, in fact, can increase breast cancer risk; that evidence is accumulating but is not yet conclusive. However, chronic disruption of circadian rhythmicity has the potential to yield serious long-term health consequences.

Nocturnal light exposure and circadian disruption may be particularly important for children,[145] and even exposure to the mother while pregnant may affect fetal exposure to altered hormone levels in utero. Wada et al[146] have reported one of the first studies of maternal circulating estradiol and testosterone levels; levels were higher among women who reported typically being awake at 1 AM, and there was an inverse relationship of reported sleep duration and hormone levels among these pregnant women. Much more study of the impact of the home light environment of children and pregnant women should be conducted.

An analogy exists between breast cancer in women and prostate cancer in men in the sense that both are considered primarily hormone-driven cancers, each is the most common cancer worldwide in each gender (after lung cancer in men), and for neither are there convincing explanations for their high incidence in the industrialized world. Much less research exists on circadian disruption in prostate cancer than breast cancer, but there is some limited evidence.[105] In a prospective study conducted in Iceland, Sigurdardottir et al[147] focused on sleep and found that men who reported poor-quality sleep at baseline were at about a 2-fold higher risk compared with men who reported good-quality sleep. The authors argued that disrupted and poor-quality sleep reflects circadian disruption as well. Flynn-Evans et al[148] exploited the 2005-2006 National Health and Nutrition Examination Survey (NHANES)

database for a cross-sectional study to determine whether men working non-day shifts had elevated prostate-specific antigen (PSA) levels, and they found a strong relationship. Men with PSA levels >4 ng/mL were more than twice as likely to also be non-day shift workers than men with PSA levels <4 ng/mL; men with PSA levels >10 were nearly 4 times as likely to be shift workers. The authors argue that this suggests an elevated risk of future prostate cancer.

Another area of research that demands attention is the effect of light-induced circadian disruption in breast cancer patients with respect to the progression of their disease and their responsiveness to chemotherapy, hormonal therapy, radiotherapy, and/or targeted biological therapy. For example, do breast cancer patients who are circadian disrupted exhibit increased resistance to, and toxicity from, various standard therapeutic modalities compared with "circadian-intact" patients? Many cancer patients experience circadian disruption and sleep disturbances because of the presence of disease and/or the effects of therapy in addition to an altered light exposure over the 24-hour daily cycle. Would chronic exposure of breast cancer patients to light at night throughout the course of their disease and treatment result in unnecessary treatment failures? Such treatment failures might lead to accelerated disease progression and increased morbidity/mortality, which could be avoided altogether by correcting the underlying circadian regulatory deficit by appropriate circadian-friendly lighting of their homes and, to the extent possible, in hospital. This not only might serve to slow down or even halt disease progression but conceivably could open the door for circadian-optimized cancer therapy, which might improve the chances of disease remission or even cure.

As research on a possible increase in breast cancer risk grows (and other health concerns, such as other cancers, metabolic disorders, and childhood development), so too has research on lighting technologies that remain visually effective yet support improved regulation of human circadian, neuroendocrine, and neurobehavioral systems; this research is both in photonics (ie, light-emitting materials) and in lighting applications. For example, the new solid-state lighting system being developed for installation on the International Space Station in 2015-2016, is designed to provide astronauts optimum visual support as well as improved sleep, circadian entrainment, and daytime alertness.[149] In another innovative approach, Jou et al[150] report on the development of a light-emitting diode that mimics the spectral irradiance of candle light, which would presumably have much less impact on the circadian system if used in the evening instead of a blue-enriched compact fluorescent light bulb.

An important direction for future research includes developing novel animal models and experimental strategies that can determine the relative contributions to breast cancer risk of circadian phase shifts, sleep deprivation, and nocturnal melatonin suppression within the spectrum of circadian disruption induced by light exposure at night. In particular, there is a need for extensive investigation of the impact of circadian disruption on sex hormone production, distribution, and function in humans (eg, estrogens), as these have known and strong effects on breast cancer risk. The interactions among these factors are undoubtedly complex, and parsing out their individual as well as relative contributions to breast cancer risk may be a formidable challenge—the whole, indeed, may be greater than the sum of its parts.

Lighting technology is rapidly advancing, and it could have pervasive adverse health effects if we do not understand its disruptive potential. But this same technology also allows for a more sophisticated control of lighting to much better accommodate circadian health in this increasingly lighted, industrialized world. ■

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