The Pathophysiologic Role of Disrupted Circadian and Neuroendocrine Rhythms in Breast Carcinogenesis

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Most physiological processes in the brain and body exhibit daily (circadian) rhythms coordinated by an endogenous master clock located in the suprachiasmatic nucleus of the hypothalamus that are essential for normal health and functioning. Exposure to sunlight during the day and darkness at night optimally entrains biological rhythms to promote homeostasis and human health. Unfortunately, a major consequence of the modern lifestyle is increased exposure to sun-free environments during the day and artificial lighting at night. Additionally, behavioral disruptions to circadian rhythms (ie, repeated transmeridian flights, night or rotating shift work, or sleep disturbances) have a profound influence on health and have been linked to a number of pathological conditions, including endocrine-dependent cancers. Specifically, night shift work has been identified as a significant risk factor for breast cancer in industrialized countries. Several mechanisms have been proposed by which shift work-induced circadian disruptions promote cancer. In this review, we examine the importance of the brain-body link through which circadian disruptions contribute to endocrine-dependent diseases, including breast carcinogenesis, by negatively impacting neuroendocrine and neuroimmune cells, and we consider preventive measures directed at maximizing circadian health. **(*Endocrine Reviews* 37: 450–466, 2016)**

I. Introduction

Breast cancer is the most prevalent cancer among women worldwide (1), with the highest rates found in the most industrialized countries of Europe, North America, and Australia (Figure 1A). There is a 5- to 10-fold difference in risk between these high-risk areas relative to low-risk populations, including developing countries in Africa and in parts of Asia (2–4). The incidence of breast cancer has been increasing worldwide for the last several decades, with the most pronounced increases seen in regions that, until recently, had a low risk of breast cancer. This is possibly due to the adoption of a more modern lifestyle and consequent exposure to artificial lighting (5). Migrational studies examining changes in breast cancer risk among women emigrating from low-risk areas, such as Asia, to high-risk areas, including the United States, report significant increases in breast cancer incidence after migration (6–8). Furthermore, studies comparing the risks of migrants (particularly from Asia to the United States) to the risks of their offspring report major increases in risk between first, second, and third generations, pointing to changes in lifestyle and environmental exposure rather than genetics (9). Exposure to nighttime light co-distributes with this rise in breast cancer incidence in women worldwide (10–13) with the exception of women with visual impairments (14–16), provid-

ISSN Print 0163-769X ISSN Online 1945-7189
Printed in USA

Received November 19, 2015. Accepted July 21, 2016.
First Published Online July 26, 2016

Abbreviations: AMA, American Medical Association; CCG, clock-controlled gene; ER, estrogen receptor; GR, glucocorticoid receptor; HPA, hypothalamo-pituitary-adrenal; LAN, light at night; NK, natural killer; RR, relative risk; SCN, suprachiasmatic nucleus; TTFL, transcriptional-translational feedback loop.

Figure 1.

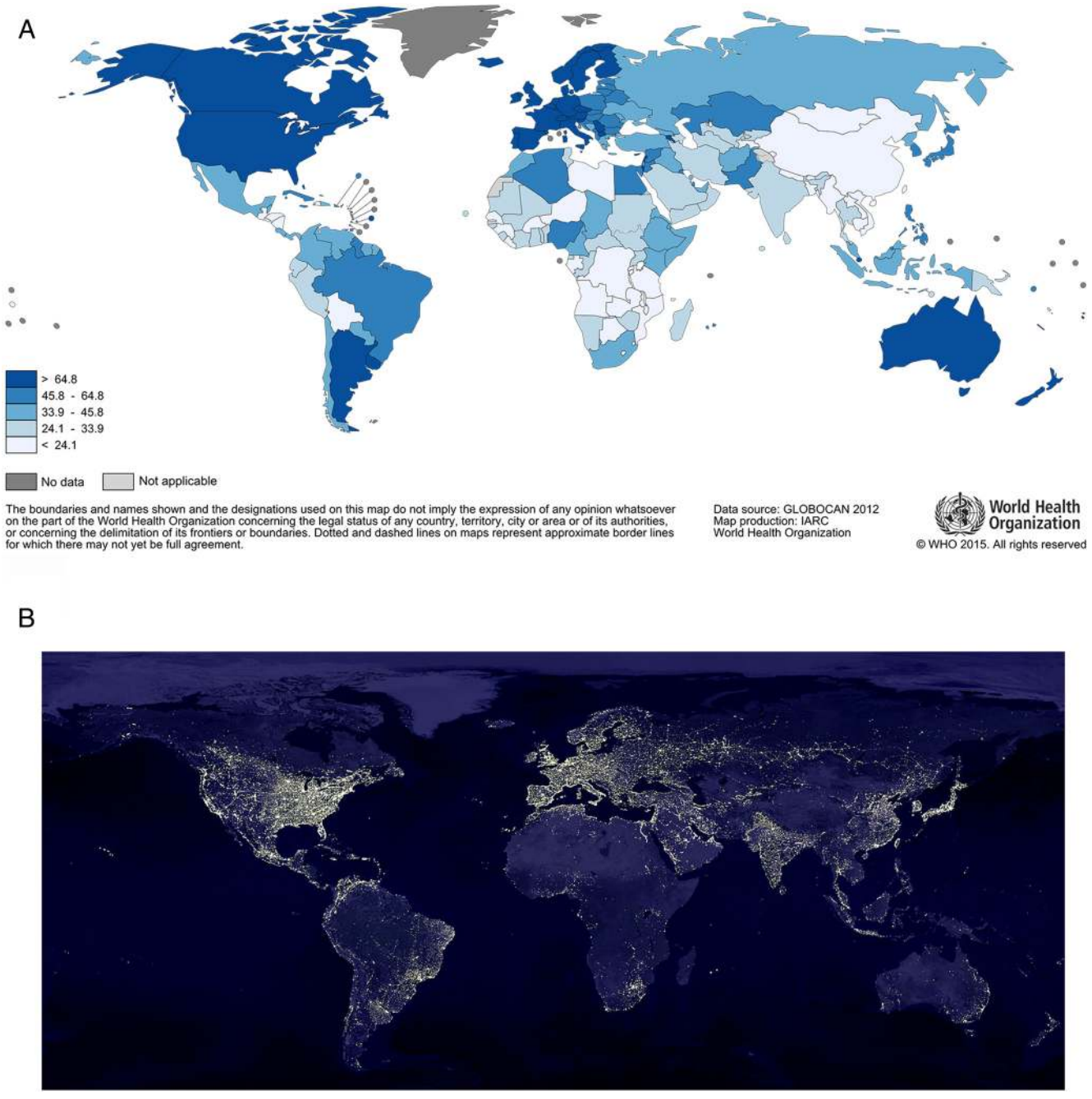

Figure 1. A, Estimated breast cancer incidence worldwide 2012. Rates are age-standardized (per 100 000). GLOBOCAN 2012, International Agency for Research on Cancer, World Health Organization. (From Ref. 203.) B, World light pollution at night. National Oceanic and Atmospheric Administration (NOAA) National Geophysical Data Center. Data were collected by the U.S. Air Force Weather Agency under the Defense Meteorological Satellite Program, 1994–1995. Data courtesy Marc Imhoff of NASA Goddard Space Flight Center and Christopher Elvidge of National Oceanic Atmospheric Administration, National Geophysical Data Center. Image by Craig Mayhew and Robert Simmon, NASA Goddard Space Flight Center.

ing further evidence that artificial light exposure negatively impacts human physiology and contributes to disease progression (Figure 1B).

Most physiological processes exhibit circadian (daily) rhythms that are essential for normal health and functioning. Circadian rhythms are coordinated by an endogenous master clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus (17, 18). Despite the critical role of the SCN in circadian functioning, it is more appropriate to conceptualize the "circadian system" as an assembly com-

prised of not only a master clock, but also a series of subordinate clocks whose phase and coordinated activity are set by the SCN. Individual cells in the SCN and subordinate systems maintain circadian timing at the cellular level through interlocking transcriptional-translational feedback loops (TTFLs) composed of clock genes and their protein products (Figure 2A) (19). In nearly every peripheral tissue examined thus far, the core clock genes are expressed in a rhythmic fashion (20). Clock genes confer circadian rhythmicity by regulating cellular functions either directly or by gating expression of other genes in local tissues. The SCN has direct access to environmental time via specialized retinal ganglion cells that transmit light information to the SCN via a direct retino-hypothalamic tract independent from the visual system (21, 22). In turn, because subordinate central and peripheral clocks do not have access to such time cues, the SCN communicates environmental information throughout the central nervous system and periphery. This communication sets extra-SCN clocks to environmental time and also synchronizes ensembles of individual cellular oscillators within a system. At the cellular, organ, and systemic levels, normal circadian rhythms are critical for appropriately guiding innumerable cellular processes, including gene expression, cell proliferation, apoptosis, hormone secretion, and immune modulation (Figure 2B).

Although circadian rhythms are generated endogenously, exposure to sunlight during the day and darkness at night optimally entrains (synchronizes) circadian rhythms to environmental time to promote homeostasis on a temporal schedule and to maximize human health. Unfortunately, a major consequence of the modern lifestyle is increased exposure to sun-free environments during the day and artificial lighting at night (23–25) (Figure 1B), which collectively and adversely impacts circadian health. Disruptions in circadian rhythms have been linked to a number of pathological conditions, including obesity (26), ulcers (27), heart disease (28), diabetes (29), sleep disturbances (30), cognitive impairment (31), and depression (32) (Figure 3).

The increased incidence of these pathologies is associated with disruptions to endocrine timing. For example, metabolic hormones such as growth hormone, melatonin, cortisol, leptin, and ghrelin are affected and governed by circadian rhythms and sleep quality. Associated with these altered patterns of hormone secretion, shift workers have an increased prevalence of obesity and a 40% increased risk of cardiovascular disease relative to daytime workers (33–36). Importantly, the observed effects of shift work on obesity may be more pronounced in female shift workers of all ages compared to men, according to a population-based study by Karlsson et al (37). Furthermore, female nurses who worked rotating night shifts for 6 years or more exhibit an increased risk of coronary heart disease after correcting for smoking, among other risk factors (38). Finally, night workers experience lower insulin sensitivity, increased triglycerides, and blunted postmeal ghrelin suppression (39).

Most relevant to the present overview, disruptions in circadian rhythms are associated with increased incidence and susceptibility to cancer. Specifically, shift work is associated with a significant increase in the incidence of solid cancers, including breast, prostate, endometrial, and colon cancers, as well as dispersed cancers including lymphomas and leukemia (40–52). In animal models, both altered light environments and targeted disruption of genes generating circadian rhythms accelerate cancer progression relative to controls (3, 53–55), providing a direct causal link between circadian biology and cancer. Collectively, these findings and others have led to the recent classification of shift work as a probable carcinogen in humans by the International Agency for Research on Cancer (56). Several mechanisms have been proposed by which shift work-induced circadian disruption promotes cancer. In this review, we examine the importance of the brain-body link through which circadian disruptions negatively impact neuroendocrine and neuroimmune functioning to promote breast carcinogenesis. Finally, we describe mitigating strategies to maximize sleep and circadian health in at-risk individuals.

II. Epidemiological Studies Linking Circadian Disruption and Breast Cancer

Whereas a woman's lifetime exposure to estrogen is believed to be a major risk factor for breast cancer development (57, 58), a number of environmental factors associated with the modern lifestyle have also been attributed to increased breast cancer prevalence. Technical advances that allow operation as a 24-hour society and convenient travel across time zones also promote prolonged and irregular exposure to light and represent potentially important and often overlooked lifestyle factors that contribute to breast cancer risk (11, 59). This exposure is particularly true in industrialized countries where shift work and night work are estimated to involve about 15–20% of the working population and in some professions, such as health workers, 30% or higher (60). Shift work, defined as any employment after 7 PM and before 9 AM, is seen in services such as healthcare, the military, and protection (eg, firefighters, police, medical personnel). Whereas some shift workers may have sleep-wake rhythms and hormonal rhythms that are out of phase with the environment, the

Figure 2.

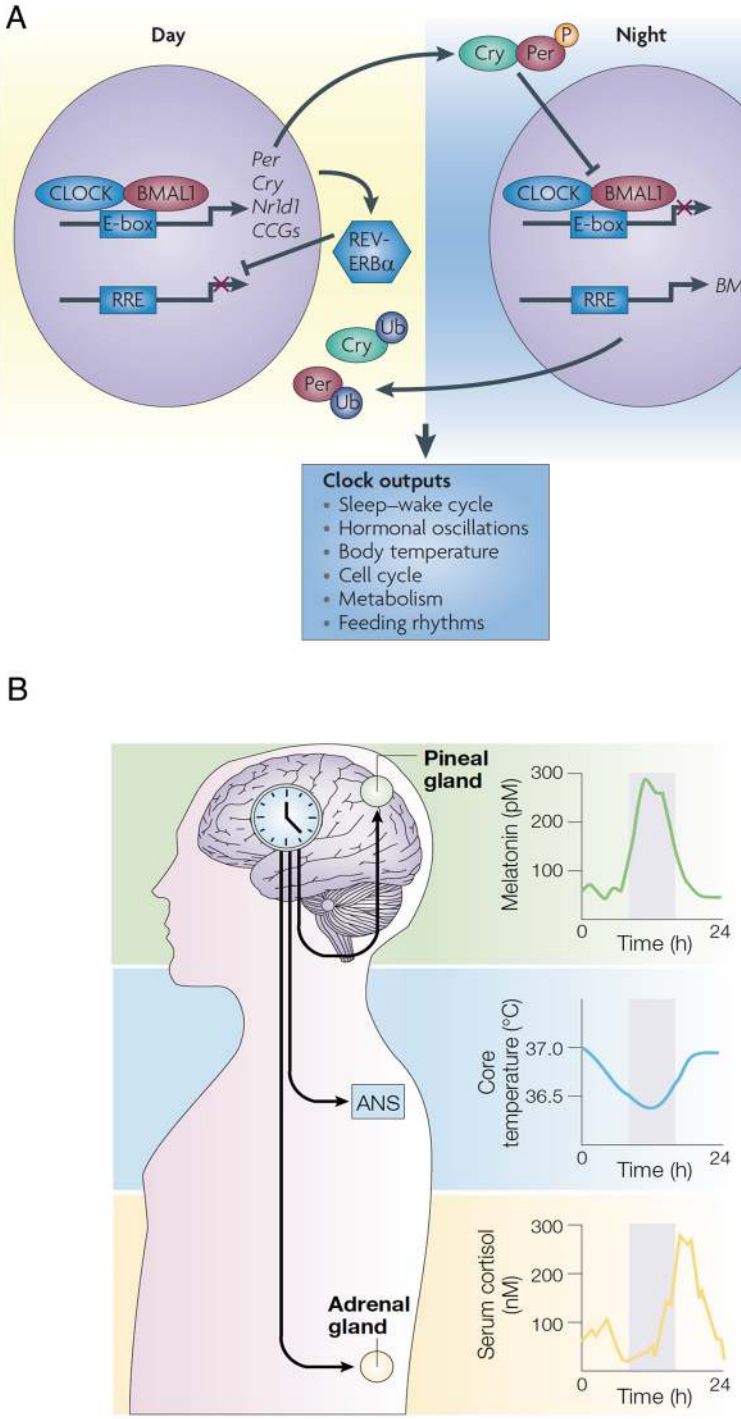

Figure 2. A, Circadian rhythm generation at the cellular level. Circadian rhythms are generated by TTFLs of the core circadian genes. CLOCK and BMAL1 increase the transcription of Period (Per), Cryptochrome (Cry), and other clock-controlled genes during the day. In the classic view, the levels of Per and Cry proteins increase during the night, after which they dimerize and translocate to the nucleus to repress CLOCK–BMAL1-mediated transcription. Per and Cry proteins are then ubiquitylated and degraded to initiate a new circadian cycle. Conversely, REV-ERBα (encoded by *Nr1d1*) protein levels are high during the day and inhibit *BMAL1* transcription at this time. At night, REV-ERBα protein levels are low, allowing *BMAL1* transcription to take place. P, Phosphorylation; RRE, REV-ERB/ROR response elements; Ub, ubiquitylation. (From Ref. 84.) B, Circadian organization at the systems level. A contemporary view of circadian organization in which a hypothalamic pacemaker, in the SCN, communicates through various neural and endocrine links to drive and/or synchronize rhythms in peripheral physiology and behavior. This ensures that as individuals progress through the regular 24-hour cycle of sleep (gray shading) and wakefulness, their metabolism is adjusted accordingly to anticipate the demands and opportunities of the solar day. ANS, Autonomic nervous system. (From Ref. 25).

Figure 3.

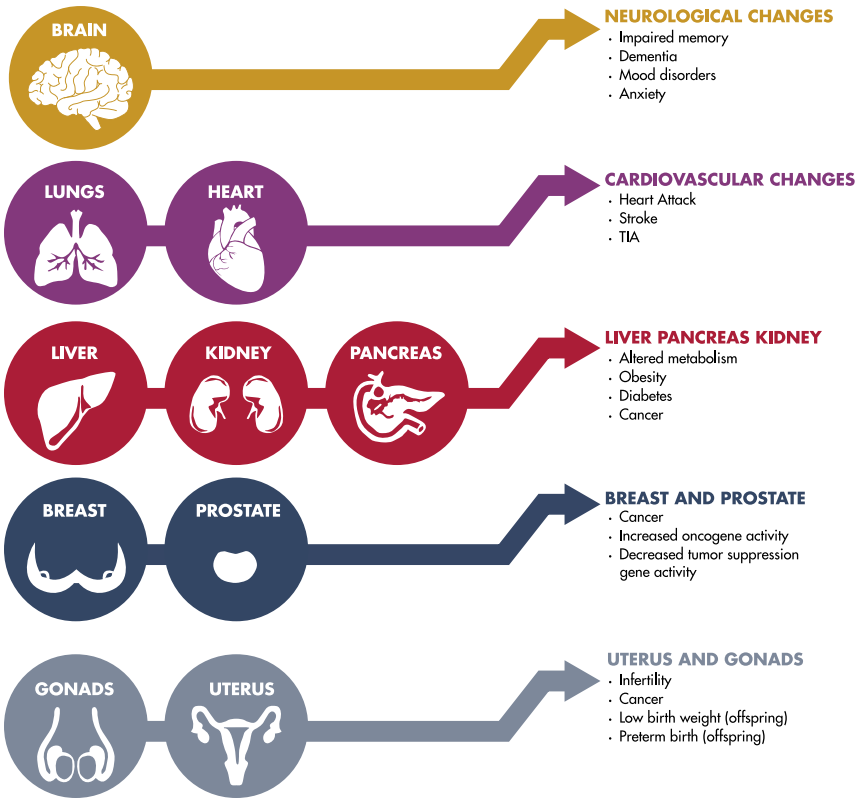

Figure 3. The pleiotropic effects of circadian disruption. Circadian disruption affects multiple organ systems. The diagram provides examples of how circadian disruption negatively impacts the brain and the digestive, cardiovascular, and reproductive systems. Although the diagram displays unidirectional effects, there are various feedback loops that exist within the system and interactions that occur between these systems. (From Ref. 204.)

majority do not display alignment of physiological rhythms with the day/night cycle different from day-working controls (61). In fact, most shift workers maintain circadian rhythms that promote sleep during the dark hours and wakefulness during the day hours, despite meeting work-related behavioral demands at night. This incongruence between physiological rhythms and behavioral demands in shift workers is believed to contribute to a myriad of health disorders (62) (Figure 3).

The importance of circadian disruption in human breast cancer was brought to public attention through several large-scale epidemiological studies demonstrating that breast cancer incidence increases significantly in women working night shifts, with greater risk the more years and hours per week worked (43, 44, 46). In one landmark prospective study, Schernhammer et al (43) uncovered a pronounced association between night work and breast cancer among 78, 562 women participating in the Nurses' Health Study. In this 10-year follow-up study, postmenopausal women who worked rotating night shifts for 30 or more years exhibited a significant increase in breast cancer risk (relative risk [RR] = 1.36) compared to nurses who never worked rotating night shifts. In the Nurses' Health Study II (46), premenopausal nurses who reported more than 20 years of rotating night shift work experienced an elevated risk of breast cancer (RR = 1.79) compared with nurses who did not report any rotating night shift work. In a related study by Davis et al (44), night work was associated with a 60% increase in breast cancer risk (RR = 1.6), with a trend toward increased risk with more hours of night work per week. Similar trends have been reported in other parts of the world, including Norway (63, 64), Germany (65), Canada (66), France (67, 68), Sweden (69), and Denmark (45, 70–72). Together, these findings point to a strong, positive association between shift work and/or nighttime light exposure and breast cancer across cultures. Risk is increased with the number of consecutive night shifts worked in addition to the number of years employed as a night-shift worker.

III. Laboratory Models Linking Circadian Disruption and Breast Cancer

Rodent models of breast cancer have provided invaluable advances in our understanding of this complex disease, affording the opportunity to test hypotheses not suitable or ethically possible in human research. Several different experimental models of breast cancer have been applied to examine the effects of circadian disruption on breast tumorigenesis, including human xenograft models, chemically induced models, and genetically engineered mouse models (ie, transgenic/knockout mice). Whereas no model can fully recapitulate human breast cancer, each has offered important insights at the molecular, cellular, and systemic levels of circadian-mediated breast tumorigenesis.

The first evidence that nocturnal illumination can affect the growth of human breast cancer cells was presented in 2003 with the finding that constant light exposure markedly increased tumor growth in MCF-7 xenografts (73). Similarly, rats exposed to constant light experience increases in 7,12-Dimethylbenz[a]anthracene (DMBA)-in-

duced mammary tumor formation and growth (74, 75). Likewise, an increase in tumor multiplicity is observed under constant light and in chronically alternating light cycles in transgenic mouse models of breast cancer including mice overexpressing the c-neu/Human Epidermal Growth Factor Receptor-2 (Her-2) oncogene that is overexpressed in 15–20% of human breast cancers (76, 77). Altered light environments can modify the daily rhythmic expression patterns of circadian and cancer-related gene transcripts in mouse mammary tumors, pointing to a potential mechanism driving circadian-mediated carcinogenesis (78). Finally, circadian disruption also exerts tumor-promoting effects in other cancer models, with experimental jet lag or SCN ablation accelerating malignant growth and shortening survival in two transplantable tumor models, Glasgow osteosarcoma and pancreatic adenocarcinoma (79–82).

IV. Neuroendocrine Mechanisms of Circadian Mediated Carcinogenesis

A. Glucocorticoids

Whereas numerous epidemiological (41–44) and experimental (79, 80, 83) studies point to an association between temporal disruptions and cancer, the specific mechanisms linking these events remain less well specified. Because the SCN communicates to the periphery via neural and hormonal pathways to coordinate peripheral clocks (84, 85), alterations in neuroendocrine pathways induced by circadian insults likely contribute to tumor development (Figure 4). Circulating levels of glucocorticoids, for example, display circadian rhythmicity and are potent mediators of circadian clock entrainment in peripheral tissues (86). Likewise, insults to the circadian system (eg, jet lag, shift work) result in activation of the stress axis and increased plasma glucocorticoid concentrations (87–89). Numerous studies link stress hormones to a higher incidence, progression, and recurrence of breast cancer (90, 91), pointing to a likely link between circadian disruption and carcinogenesis. For example, a meta-analysis of primary breast tumor gene expression demonstrated that high levels of glucocorticoid receptor (GR) expression in estrogen receptor (ER)-negative tumors significantly correlate with shorter, relapse-free survival (92). Furthermore, gene expression analysis in these tumors revealed a direct transcriptional role for GR through differential activation of GR target genes involved in several cancer-related pathways, including epithelial-to-mesenchymal transition, cell adhesion, and cell survival. Analogous findings are observed in animal studies in which increased endogenous glucocorticoid exposure is associated with increased tumor growth in ER-negative breast tumors, whereas pretreatment with a synthetic glucocorticoid (dexamethasone) inhibits tumor cell apoptosis induced by the chemotherapeutic agent paclitaxel (92–94). With regard to human breast cancer treatment, glucocorticoids have also been shown to contribute to a decrease in tumor cell apoptosis while increasing tumor cell survival and chemotherapeutic resistance (95, 96).

Cancer patients sometimes exhibit attenuated (low amplitude or flattened) circadian rhythms (84, 97, 98) asso-

Figure 4.

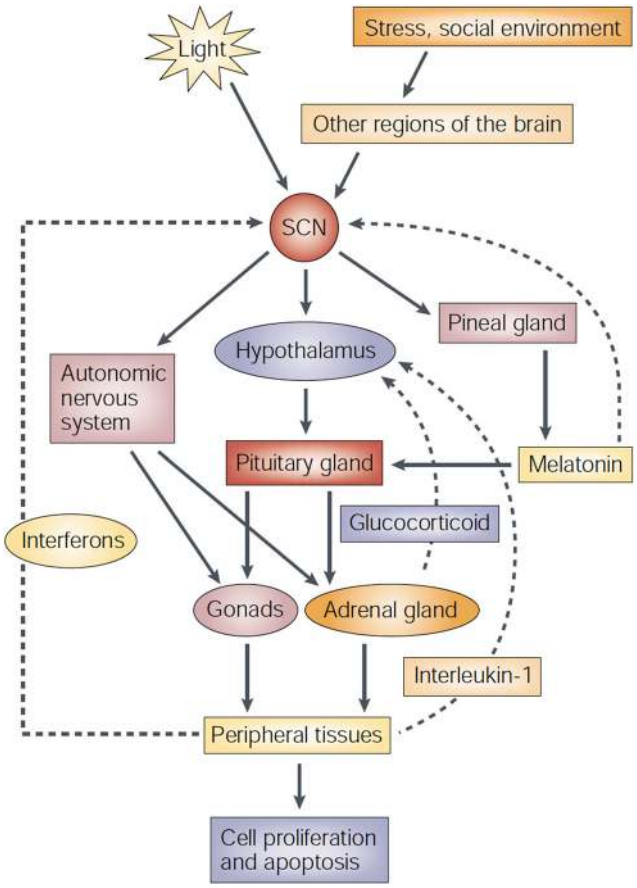

Figure 4. Circadian control of cell proliferation and apoptosis at the systemic level. Light and other environmental cues reach the SCN through various input pathways. The SCN clock synchronizes with the environment to generate endogenous rhythms, which are transmitted through output pathways to peripheral tissues. Representative output pathways, such as the autonomic nervous system (ANS) and the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary adrenal (HPA) axes, are shown. The pineal gland and peripheral tissues can also feed back to SCN or HPA axes through the production of melatonin to regulate homeostasis. Melatonin binds to receptors on SCN neurons to induce phase shifts (202, 205). The adrenal glands produce glucocorticoids, which have negative feedback on the hypothalamus to terminate the release of corticotropin-releasing hormone (CRH) (205). The products of immune activity, such as interferon-α and -γ and interleukin-1, can also modulate the activity of SCN, as well as the HPA axis (206, 207). Feedback pathways are indicated by dashed lines. (From Ref. 85.)

ciated with cancer-related distress (99) and the quality of circadian rhythms among cancer patients has been shown to be a predictor of patient survival in some studies (100–102). Specifically, abnormal cortisol rhythms are associated with a 2-fold risk of mortality in patients with metastatic breast cancer compared to patients with a normal cortisol pattern (90). This interaction between the circadian system and cancer may lead to a self-perpetuating feedback loop where disruptions in circadian function induce alterations in endocrine functioning that promote cancer development, and in turn, the development of cancer may promote disruptions in circadian function leading to further progression of the disease. As a result, developing pharmacological, behavioral, and environmental strategies (described below) to maximize circadian health represents an important variable to consider when treating cancer patients.

B. Gonadal steroids

In addition to glucocorticoids, gonadal hormones also participate in this circadian feedback loop, with altered daily patterns in estrogen signaling being a common feature in breast cancer patients. Circulating estradiol and the ER expression exhibit a circadian pattern (103, 104), and estrogen signaling differentially regulates the circadian clock in the brain, breast, and other peripheral tissues (105). Specifically, estrogen regulates the expression of several core clock genes, including *Bmal1* (106), *Per1* (105, 107), *Per2* (105, 106, 108), and *Clock* (109). Importantly, these genes are differentially affected by estrogen signaling in both ERα-positive and ERα-negative breast cancer cells (106, 108, 109), implicating canonical ER pathways as well as alternative mechanisms for estrogen-induced regulation of clock genes. These findings also provide mechanistic insights at the molecular level whereby the mammary circadian clock is linked to estrogen activity.

C. Melatonin

Melatonin disruption was first suggested to play a role in human breast cancer in 1978 when it was hypothesized that reduced pineal function and resulting decreased melatonin secretion lead to the development of breast tumors (110). Since that time, numerous studies have explored the association between melatonin disruption, estrogen signaling, and breast cancer (111–116), although clinical investigations clarifying the protective role of melatonin in women are lacking.

Epidemiological studies indicate that women with visual impairments are less likely to develop breast cancer (14, 16, 117, 118). The circadian synthesis of melatonin is regulated by the SCN, with melatonin being secreted only in darkness and nocturnal secretion being suppressed in (sighted) individuals exposed to light at night (LAN). This suppression occurs in a dose-dependent manner, with brighter light resulting in greater suppression of melatonin. Furthermore, blue light (460–480 nm) is more disruptive than red light (620–750 nm) (119). Not surprisingly, disruptions in the pattern of melatonin secretion are observed in individuals with sleep disorders and chronic jet lag (120). Similar alterations in circulating and urinary melatonin levels have been observed in women working night shifts, and these disruptions are associated with increased breast cancer risk (120–126). Importantly, low levels of melatonin secretion and excretion are observed in women with breast cancer (127, 128). Specifically, the nocturnal peak in melatonin is significantly reduced in patients with breast cancer and is inversely correlated with tumor size (128). Given the protective role of melatonin in breast cancer development and progression (129–135), it is important to develop strategies for maximizing daily rhythms of this hormone in women from at-risk populations and those currently fighting the disease.

In experimental rodent models of breast cancer, light exposure at night promotes tumor growth, and exogenous melatonin reverses this effect, providing direct evidence for correlational observations in women (136). Additionally, early in vivo studies revealed that pinealectomy or exposure to photoperiods that suppress melatonin results in higher tumor incidence, growth rate, and multiplicity (137–140). By the 21st century, the availability of xenograft models of breast cancer allowed researchers to examine the inhibitory effects of physiological levels of melatonin on the growth of human breast cancer in nude rats. When nude rats bearing human breast cancer xenografts were exposed to constant light, a dose-dependent reduction in blood melatonin levels was observed concomitant with an increase in tumor growth (73, 134). To further these studies, Blask et al (134) used an innovative approach to establish the inhibitory effects of human nocturnal melatonin on the growth of human breast cancer by perfusing xenografts growing in situ with blood collected from human female subjects at various times of day or after LAN exposure. It was found that the melatonin-rich, nocturnal blood collected at night significantly inhibited the proliferative activity and the growth of human breast cancer xenografts in rats compared to xenografts perfused with melatonin-depleted blood collected during the day or after LAN (134). These early mechanistic studies paved the way for more recent investigations demonstrating that, in addition to decreasing tumor cell proliferation and size, melatonin also inhibits angiogenesis and increases tumor cell sensitivity to tamoxifen therapy (132, 133) and doxorubicin (141) in human xenograft models of breast cancer.

These observations in xenografts are further supported by studies involving transgenic and transplantable mouse models of breast cancer where melatonin reduces the incidence and size of spontaneous mammary tumors in transgenic mice (76, 77, 130, 131, 135) and slows the proliferation of 4T1 tumor transplants in BALB/c mice (129).

Melatonin's pleiotropic oncostatic effects on breast cancer range from regulating the expression and transactivation of nuclear receptors, transcription factors, and coregulatory proteins to antioxidant activity, immunomodulation, and enzyme regulation. Specifically, melatonin inhibits the expression and/or phospho-activation of numerous kinases, transcription factors, and coregulators, which are known to drive breast cancer promotion and/or progression (142, 143). Collectively, these melatonin-mediated mechanisms result in suppression of cell proliferation (144–147).

Melatonin also blocks the mitogenic effects of estradiol in vitro by down-regulating ERα mRNA levels (142, 148) and in vivo by decreasing phospho-activation of ERα protein. Together, these melatonin-mediated effects result in the suppression of estrogen-induced transcriptional activity of ERα in human breast cancer cell lines. The down-regulation of estrogen signaling exerted by physiological concentrations of melatonin subsequently leads to alterations in the transcriptional regulation of a number of downstream ER gene targets, including antiapoptotic targets Bcl-2, TGF-α, and Bax (112, 114). Melatonin also acts as a selective estrogen enzyme modulator by inhibiting the aromatase pathway in ER-positive MCF-7 human breast cancer cells and in 7,12-Dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumor tissue (113, 149).

Although some ERα-negative breast cancer cell lines are unresponsive to the antiproliferative effects of melatonin, a number of studies report inhibitory growth effects in ERα-negative human breast tumors through immunomodulatory and alternative mechanisms involving cell cycle arrest (112, 146). For example, melatonin suppresses tumor cell cAMP formation, leading to a decrease in linoleic acid uptake and its metabolism to the mitogenic signaling molecule 13-hydroxyoctadecadenoic acid (150). Linoleic acid activates the epidermal growth factor receptor pathway, resulting in activation of p38MAPK-induced cell proliferation and cell survival pathways. Thus, melatonin-induced inhibition of linoleic acid uptake and metabolism attenuates the epidermal growth factor receptor signaling pathway, diminishing tumor growth (147). In vitro studies further demonstrate that melatonin inhibits breast cancer cell invasion and metastasis by inhibiting p38 MAPK signaling and subsequently inhibiting the expression of downstream gene targets involved in invasion including the matrix metalloproteinases 2 and 9 (151).

In addition to its antitumor effects, melatonin has been shown to have hypnotic effects under some circumstances (152), although its efficacy in treating sleep disruption has not been consistently supported (153, 154). These equivocal findings are likely due to the difficulty in estimating the precise dosage and timing of melatonin, given the high variability in concentrations of this hormone in humans and animals. Likewise, melatonin is most effective if taken at a time before endogenous melatonin production (152). Given these findings, clinical trials are currently ongoing to explore the efficacy of melatonin in the treatment of sleep disturbances and other cancer-related conditions in breast cancer patients (155–157).

Circadian disruption can lead to the temporal dysregulation of the sleep-wake cycle that can lead to sleep disturbances that, in turn, affect circadian rhythmicity. Not surprisingly, there is a high prevalence of sleep disruption in women diagnosed with breast cancer both during and after treatment (158), with nearly 80% of women experiencing insomnia, a particular sleep disruption associated with difficulty falling and/or staying asleep, waking up earlier than intended, and/or poor sleep continuity. Numerous precipitating factors contribute to the development of sleep disruption in cancer (eg, stress of the diagnosis, side effects of cancer treatments), with disruption of circadian rhythmicity likely playing a role. Importantly, recent research suggests that sleep quality, defined by sleep efficiency (the ratio of time being asleep to total time spent in bed*100%), is a significant prognostic factor in women with breast cancer. Specifically, women with advanced disease who experience better sleep efficiency (≥85%) and less sleep disruption have significantly lower mortality compared to women with less efficient sleep (159).

V. Neuroimmune Mechanisms

Circadian-mediated alterations in circulating levels of melatonin and cortisol are in a position to have direct immunomodulatory effects impacting antitumor immunity. The activation of lymphocytes and macrophages by melatonin may provide one explanation for its anticancer effects in ERα-negative and ERα-positive breast cancer cell lines. Through its immune-enhancing properties, melatonin supports T-helper cell responses by stimulation of IL-2, IL-10, and interferon-γ secretion (160). Not only can the release of cytokines from T-helper cells activate antigen-specific cytotoxic T-cell responses, but cytokines can also directly kill tumor cells through activation of death receptors on the tumor cell surface (161). Furthermore,

exogenous melatonin administration increases nonspecific immune responses by stimulating monocyte and natural killer (NK) cell production in both the spleen and bone marrow (162). NK cells play an important role in immunosurveillance, the process by which cancer cells are detected and eliminated by the immune system.

The immunomodulatory activities of glucocorticoids have been well established and exploited for many decades in the treatment of inflammatory conditions. Glucocorticoids can inhibit both innate and adaptive immune responses through suppression of lymphocyte proliferation, cytokine production, and NK cell cytotoxicity (87, 163, 164). Thus, important aspects of antitumor immunity may be suppressed by circadian-mediated increases in hypothalamo-pituitary-adrenal (HPA) axis activity, a hypothesis worthy of further exploration.

In addition to affecting cancer indirectly through circadian hormonal regulation, the circadian system also plays a direct role in the regulation of both the innate and adaptive immune responses. Immune tissue and immune cells, including splenocytes, lymph nodes, and macrophages, all rhythmically express circadian clock genes (165–167). Furthermore, patterns of circadian rhythmicity have been observed in circulating white blood cells, T and B lymphocytes, and cytokines, as well as in NK cell activity (60, 168). Not surprisingly, disruptions to the circadian clock result in deficits in immune functioning; the immune response in mice lacking essential circadian clock genes is severely suppressed, and these mice develop more spontaneous and γ-radiation-induced cancers than wild-type mice (53, 169). These findings suggest that circadian regulation may be an important prerequisite for the maintenance of host defenses against cancer.

VI. Clock Genes and Carcinogenesis

At the molecular level, dysregulation of circadian gene targets involved in cell proliferation and apoptosis also represents a potential means by which insults to the circadian timing system can influence tumorigenesis. For example, the central clock synchronizes circadian rhythms of TTFLs for both mitogenic signals (eg, hormones, growth factors, neurotransmitters, cytokines) and cell cycle regulators (eg, cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors, tumor suppressors) in peripheral tissues, all of which serve to gate the timing of cell division. The SCN controls cell proliferation and apoptosis in peripheral tissues by regulating both the release of extracellular mitogenic signals and the expression of clock-controlled genes (CCGs). CCGs are genes that are rhythmically produced by the cellular clockwork but are not part of the clock mechanism. Of all the CCG targets identified to date, up to 7% have been estimated to regulate cell proliferation or apoptosis in rodents (20, 170–172), including the cell cycle genes c-Myc (G_0/G_1 transition), cyclin D1 (G_1/S transition), wee1 (G_2/M transition), P53 (G_1 and G_2 cell cycle arrest), Gadd45 (G_1/S transition), transcription factors, caspases and cytokines, as well as genes involved in modulating signal transduction pathways and proteasomal degradation (20, 53, 170–172) (Figure 5). Thus, circadian disruption may accelerate tumor progression through dysregulation of tumor cell proliferation and apoptosis.

Furthermore, in some tumor types, rhythms of cell division are autonomous to that of the host's circadian rhythms (173). For example, both in vitro and in vivo, some cancers, including breast cancer, become unresponsive to circadian regulation of cell proliferation through alterations of peripheral clock gene expression (106, 174). Genetic manipulations, including targeted gene mutations and silencing, reveal that specific core clock genes have important tumor suppressor activity; their genetic absence allows cancer cells to grow twice as fast as genetically intact tumor cells, both in vitro and in vivo (53, 55). Mice deficient in the core circadian clock genes *Bmal1*, *Cry1*, and *Cry2* or *Per1* and *Per2*, for example, exhibit increased spontaneous and γ-radiation-induced tumor development compared to wild-type control mice (53, 55).

In peripheral tissues, the *Period* genes have been given considerable attention for their putative tumor suppressor

Figure 5.

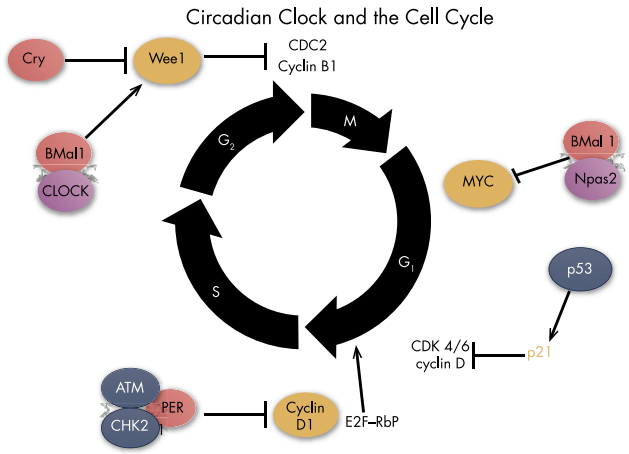

Figure 5. Circadian control of cell proliferation and apoptosis at the cellular level. Circadian clock and the cell cycle. The circadian clock is coupled to the cell cycle by clock-controlled genes that have either E-box or RAR-related orphan receptor elements in their promoters. Without detailing post-transcriptional products and downstream pathways, this figure indicates where clock-controlled genes and proteins may potentially interact with the cell cycle. (From Ref. 208.)

activity. Down-regulation of *Per2* in mammary tumors significantly accelerates proliferation rates and doubles the daily amplitude of tumor growth rhythms in vivo (54). Conversely, *Per2* overexpression decreases cancer growth rates and diminishes tumor numbers while increasing cell cycle arrest and apoptosis (108, 175, 176). With regard to human breast cancer, *Per2* bears clinical significance; genome-wide searches for genetic alterations in breast cancer have revealed specific *Per2* gene mutations that are conserved across several different human breast cancers (177). In culture, *Per2* expression is reduced in human breast cancer cell lines, an observation that is common across other cancer cell types (54, 178). Likewise, in another report examining human breast tumors, *Per2* down-regulation was found in 95% of cancerous tissue compared to nearby, noncancerous breast cells (179).

Recent studies point to a negative downstream effect of the *MYC* oncogene, and the related *MYCN* gene, on cancer cell proliferation through actions on the core molecular clockwork. The MYC protein is a transcription factor that binds to E-boxes, the same binding site as the CLOCK-BMAL1 complex, providing the ability to regulate both the *Per/Cry* and *Rev-Erb/ROR* genes. *MYC* and *MYCN* overexpression dampen BMAL1 expression through an increase in *Rev-Erbα* (180). Significantly, neuroblastomas with the highest *MYCN* and *Rev-Erbα* expression are associated with the poorest prognosis (180), pointing to a potential contributory role for MYC in cancer progression through dysregulated cellular clocks. In contrast to findings obtained for neuroblastomas, treatment of breast cancer cell lines with a REV-ERB agonist led to cell cycle arrest and reduced cell proliferation, likely through suppression of cyclin A (181).

In addition to alterations in clock gene expression through the core TTFL, circadian gene expression can also be modified through epigenetic mechanisms, where methylation of the *Per* gene promoters are positively correlated with *Her2* expression in breast cancers. This association is not unique to the *Per* genes because case-controlled breast cancer studies have identified alterations in the promoter methylation of other clock genes (182, 183). Importantly, gene-specific and genome-wide analyses have revealed that long-term shift work leads to similar changes in the promoter methylation of clock genes as well as in cancer-relevant genes (184). These findings point to important circadian-mediated mechanisms of epigenetic modification in the promotion and progression of breast cancer requiring further investigation.

Genetic manipulations have also implicated *Per1* in tumor suppression. Overexpression of *Per1*, in vitro, inhibits its human cancer cell growth and increases cellular apoptosis in response to genotoxic stress (3). In contrast, down-regulation of *Per1* decreases cellular apoptosis after genotoxic stress. In a study by Yang et al (185) examining the role of *Per1* in breast cancer cell proliferation and tumor growth, the authors established that *Per1* regulates the growth of breast tumors, with two daily growth peaks that are coupled to the daily expression patterns of clock-controlled cell cycle genes. Furthermore, down-regulation of tumor *Per1* gene expression increases tumor growth, in vivo, by increasing the amplitude of these two daily tumor growth peaks. *Per1* and *Per2* have also been implicated in suppressing the proliferation of prostate (186), endometrial, and pancreatic tumorigenesis (187–189).

Whereas the *Period* genes have been reported to have important tumor suppressor activities, induction of the *Clock* gene promotes the proliferation of breast cancer cells (109, 190). The *Clock* gene is expressed at higher levels in cancerous breast tissue compared to adjacent, normal breast tissue (182). *Clock* is thought to mediate breast cancer proliferation through the regulation of ER signaling and cell cycle gene targets (191). Likewise, *Clock* promotes the proliferation of MCF-7 and T47D breast cancer cells through enhancing the transcriptional activity of ERα in these cells (190). The *CRY* clock gene also regulates cell cycle progression and inactivation mutations, or gene knockdown studies of *CRY* exert a protective effect in breast cancer cells (183, 192, 193). Finally, low expression levels of the core clock genes *Bmal1* and *Cry1* are independent prognostic factors of epithelial ovarian cancer (194), and methylation of the *Cry1* promoter is hypothesized to be involved in the development of endometrial cancers (187).

VII. Preventive Measures

Given that lifestyle changes are unavoidable in today's society, it is of vital importance that researchers within the basic, epidemiological, and applied sciences examine the potential risks associated with circadian disruption. For example, with regard to shift work, schedules that minimize circadian disruption should be implemented. As a step toward developing such approaches, a recent workshop in Copenhagen was held to examine evidence-based preventive measures to decrease the effects of night work on breast cancer (195). Several preventive recommendations for shift workers emerged from the workshop, including organizing shift schedules to minimize the associated risks. These strategies can be implemented by reducing the number of consecutive night shifts and the total number of years working night shifts. In support of this recommendation, several studies examining shift workers at a chemical site in Germany reported no in-

crease in the rates of cancer or overall mortality with a shift system that does not require more than one or two subsequent night shifts in a row (196–198). Furthermore, it is recommended that the shift system be forward-rotating, with night work following a resting period of 24–48 hours whenever possible. With regard to women workers with previous or current breast cancer, it is strongly advised that such individuals avoid working night shifts altogether.

As mentioned previously, healthier sleep efficiency and less sleep disruptions are significant prognostic factors in women with advanced breast cancer (159, 199), underscoring the importance of diagnosing and treating sleep disruption in women diagnosed with breast cancer. Whereas there are a number of effective medications for insomnia (eg, zolpidem), their long-term use in cancer patients has not been evaluated. Thus, behavioral approaches are recommended, particularly for longer durations (>6 months) of sleep disturbance. Cognitive behavioral therapy for insomnia and modified versions of this behavioral therapy have been effective in treating insomnia in women diagnosed with breast cancer during and after cancer treatment (200–202). Given the findings that report an association between poor sleep efficiency and shorter survival, early diagnosis and treatment of sleep disturbance are recommended in breast cancer patients.

Recently, the American Medical Association (AMA) also adopted a policy statement on nighttime lighting and human health (209). The America Medical Association acknowledges many of the health concerns (eg, sleep, metabolic, mood, and reproductive disorders) that are associated with circadian disruption as well as the carcinogenic potential of nighttime lighting, especially in breast cancer. The AMA further recognizes that exposure to excessive nighttime light through the extended use of electronics is especially worrisome in children and adolescents. As a result, the AMA recommends the use of dim red lighting only in the nighttime bedroom environment. The AMA also supports the need for advancements in lighting technologies both at home and at work that minimize circadian disruption while maintaining visual efficiency.

VIII. Conclusions and Considerations

Circadian rhythms are essential for normal health and functioning. Exposure to sunlight during the day and darkness at night optimally entrains biological rhythms in humans to promote homeostasis and human health. Behavioral disruptions in circadian rhythms have a profound influence on health and have been linked to the acceleration of cancer and poorer patient prognosis. Night shift work has been identified as a significant risk factor for hormone-sensitive cancers in industrialized countries, with epidemiological and experimental studies pointing to several mechanisms by which circadian disruption promotes cancer, including alterations in cell cycle gene expression and dysregulation of neuroendocrine and neuroimmune function. A greater understanding of the connections between circadian functioning and central and peripheral physiology has led to the recommendation of several preventive measures to mitigate the deleterious effects of circadian disruption on human health. These measures include optimizing shift systems and lighting technologies that allow for visual efficiency while minimizing circadian resetting. In the home environment, it is recommended to reduce unnecessary lighting and extend the dark period at night by refraining from electronic media before bedtime and using only dim red lighting in the nighttime bedroom environment (11, 26). Given the strong association between circadian physiology and cancer development, implementing strategies to reduce circadian disruption and improve sleep quality is paramount in the prevention, treatment, and survivorship of hormone-dependent cancers.

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This work was supported by National Institutes of Health Grants HD-050470 (L.J.K.), CA-181659 (O.P.) and CA-185678 (O.P.)

Disclosure Summary: The authors have nothing to disclose.

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