

Accepted Manuscript

Title: Sleep and Circadian Disruption and Incident Breast Cancer Risk: An Evidence-Based and Theoretical Review

Authors: Laura B. Samuelsson, Dana H. Bovbjerg, Kathryn A. Roecklein, Martica H. Hall



PII: S0149-7634(17)30162-8
DOI: <https://doi.org/10.1016/j.neubiorev.2017.10.011>
Reference: NBR 2972

To appear in:

Received date: 1-3-2017
Revised date: 26-9-2017
Accepted date: 11-10-2017

Please cite this article as: Samuelsson, Laura B., Bovbjerg, Dana H., Roecklein, Kathryn A., Hall, Martica H., Sleep and Circadian Disruption and Incident Breast Cancer Risk: An Evidence-Based and Theoretical Review. *Neuroscience and Biobehavioral Reviews* <https://doi.org/10.1016/j.neubiorev.2017.10.011>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Sleep and Circadian Disruption and Incident Breast Cancer Risk:**An Evidence-Based and Theoretical Review****Suggested Short Title:** Sleep and Circadian Disruption and Breast Cancer**First Author Surname:** SamuelssonLaura B. Samuelsson, MS^aDana H. Bovbjerg, PhD^{a,b,c,d}Kathryn A. Roecklein, PhD^{a,e}*Martica H. Hall, PhD^{a,b}^aDepartment of Psychology, University of Pittsburgh, Pittsburgh, PA^bDepartment of Psychiatry, University of Pittsburgh, Pittsburgh, PA^cDepartment of Behavioral & Community Health Sciences, University of Pittsburgh, Pittsburgh, PA^dBiobehavioral Oncology Program, University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA^eCenter for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA***Corresponding author:** Dr. Martica H. Hall

Western Psychiatric Institute and Clinic

3811 O'Hara Street, TDH E-1101

Pittsburgh, PA 15213

(412) 246-6431 (phone)

(412) 246-5300 (fax)

hallmh@upmc.edu

Sleep and Circadian Disruption and Breast Cancer

Funding Sources: This work was supported by the National Institute of General Medical Sciences [grant number R01GM113243] and the National Cancer Institute [grant number P30 CA047904]. The authors attest that they have no conflicts of interest.

Sleep and Circadian Disruption and Breast Cancer

Highlights

- Cancer research has focused on sleep as an outcome or symptom.
 - Evidence suggests circadian disruption leads to increased breast cancer risk.
 - Effects of sleep disruption for mammary oncogenesis are relatively unknown.
 - Sleep and interrelated circadian disruption may combine to increase risk.
- Nature and strength of combined or independent risk factors are unclear.

Abstract

Opportunities for restorative sleep and optimal sleep-wake schedules are becoming luxuries in industrialized cultures, yet accumulating research has revealed multiple adverse health effects of disruptions in sleep and circadian rhythms, including increased risk of breast cancer. The literature on breast cancer risk has focused largely on adverse effects of night shift work and exposure to light at night (LAN), without considering potential effects of associated sleep disruptions. As it stands, studies on breast cancer risk have not considered the impact of both sleep and circadian disruption, and the possible interaction of the two through bidirectional pathways, on breast cancer risk in the population at large. We review and synthesize this literature, including: 1) studies of circadian disruption and incident breast cancer; 2) evidence for bidirectional interactions between sleep and circadian systems; 3) studies of sleep and incident breast cancer; and 4) potential mechanistic pathways by which interrelated sleep and circadian disruption may contribute to the etiology of breast cancer.

Keywords: breast cancer; circadian disruption; sleep disruption; sleep; sleep duration; light at night; night shift work; LAN; mammary oncogenesis; circadian rhythms; cancer

Sleep and Circadian Disruption and Breast Cancer

Introduction

Breast cancer is the most common cancer in women and the principal cause of death from cancer among women worldwide [1]. Recently, the National Cancer Institute projected that the total number of breast cancer cases in the United States will be 50% greater by 2030 than it was in 2011 [2]. Given the increasing personal and global health burden posed by this disease, there is a need to identify potentially modifiable behavioral risk factors that may illuminate new opportunities for cancer prevention and targets for intervention.

Researchers have identified a number of risk factors for breast cancer, including penetrant gene mutations [3] and genetic polymorphisms [4], race [5], age [6], and breast density [7]. Many of the identified risk factors are non-modifiable, however, and thus far, only a small percentage of breast cancer risk has been successfully linked to genetic inheritance [8;9]. Considerable research has investigated the associations between daytime behaviors, such as alcohol consumption [10], smoking [11], diet [12], and physical activity [13], and individual risk for breast cancer. However, much less attention has been paid to the one-third of our daily experience that occurs during sleep. The research that has been conducted to date on nocturnal behaviors and incident cancer has focused largely on exposure to light at night (LAN) and night shift workers, a population with high LAN exposure. There is considerable evidence supporting a role for LAN in cancer risk, particularly in night shift workers, and this evidence has been thoroughly reviewed elsewhere [14-16]. However, we propose that the LAN model of circadian disruption for oncogenesis is incomplete without considering the contributions of a densely interrelated process: sleep.

The present review therefore builds upon the framework established in these previous models in three innovative and important ways: 1) we present converging trans-disciplinary empirical evidence to support expanding the LAN model of cancer risk to include sleep disruption, above

Sleep and Circadian Disruption and Breast Cancer

and beyond night shift work; 2) we propose that sleep disruption and circadian disruption may be risk factors for all individuals, regardless of shift work status; and 3) we focus our review specifically on incident breast cancer, given that the heterogeneity of cancers makes broader generalizations and associations challenging to support.

Three points are integral to this review: First, the theoretical mechanisms of LAN exposure for cancer risk are not limited to night shift workers. The average human in industrialized societies today is regularly exposed to a significant degree of LAN and chronodisruption, regardless of shift work status, particularly in relation to the recent surge in technological availability and nighttime use [17;18] and overall country-level LAN [19;20]. Furthermore, in all humans, changes in circadian rhythms are often accompanied by changes in sleep duration, continuity, and/or timing. Adaptive sleep behaviors and sleep-wake rhythms are foundational for maintaining optimal functioning [21], and disruptions in these systems are associated with adverse health outcomes (see [22;23] for reviews).

Second, the sleep-wake system is strongly and bidirectionally associated with the circadian system, and changes in one affect the other. For example, Borbély's [24] two-process model of sleep-wake regulation posits that periods of sleep and wakefulness are determined by the relationship between an endogenous circadian rhythm and a homeostatic sleep drive. Given the growing body of evidence supporting the carcinogenic effects of circadian desynchronization (e.g., [14;25]), the influence of the sleep-wake system on circadian functioning should not be overlooked in mechanistic models. Endogenous and exogenous cues that entrain the circadian system are necessary but insufficient for the generation of sleep periods; behavioral, psychological, and social factors also influence the availability and timing of sleep periods and thereby influence circadian rhythms.

Sleep and Circadian Disruption and Breast Cancer

Finally, sleep is a critical biobehavioral mechanism for maintaining optimal immune [26;27], cellular [28;29], metabolic [30], and endocrine [31] functioning, although many of these studies fail to account for the potentially mediating effects of concurrent changes in circadian rhythms. In turn, dysfunction in each of these neurophysiological systems is implicated in the oncogenic pathway [32]. It is therefore plausible that disruption of the sleep system may represent a direct and largely unexplored risk factor for mammary oncogenesis.

The current paper is an evidence-based review of the associations between circadian disruption, sleep disruption, and breast cancer etiology within the framework of our proposed model (Figure 1). First, we briefly review the state-of-science on circadian disruption and breast cancer risk (for a longer review, see [14]). Next, we present evidence that supports the bidirectional associations between the circadian and sleep-wake systems. Next, we review the literature on associations between sleep disruption and incident breast cancer. Finally, we explore potential mechanistic pathways linking mammary oncogenesis to circadian disruption and sleep disruption, focusing on the roles of cellular damage via oxidative stress, melatonin, inflammation, and metabolic function.

Literature Search Criteria

To be included in this review, studies had to investigate: 1) sleep disruption (“sleep”, “sleep duration”, “sleep disruption”) and/or 2) circadian disruption (“circadian rhythms”, “circadian disruption”, “circadian dysregulation”, “light at night”, “shift work”) and 3) incident breast cancer (“breast cancer risk”, “breast cancer prevalence”) and/or mechanisms implicated in mammary oncogenesis, including cellular damage, the melatonin-estrogen pathway, inflammation, and neuroendocrine and metabolic function. A literature search was conducted in PubMed and Google Scholar that included all combinations of these keywords. References of selected

Sleep and Circadian Disruption and Breast Cancer

original and review publications were reviewed for further inclusion. Abstracts and editorials were excluded.

The Circadian Disruption and Breast Cancer Pathogenesis Model

Nearly three decades ago, research demonstrated that women reporting a history of night shift work had greater risk of developing breast cancer [33]. These findings led to the consideration of light at night (LAN) as both a hallmark of industrialized countries and a plausible pathway to mammary cancer via the pineal gland and melatonin, a LAN pathway model of breast cancer pathogenesis pioneered by Richard Stevens [16;34].

Overview of the Circadian System

The circadian system is a hierarchical organization of endogenous, oscillating clocks throughout the body that are regulated by the suprachiasmatic nuclei (SCN), located in the hypothalamus [35]. The SCN receive input from what are known as *zeitgebers*, external cues that entrain the internal circadian clock in the SCN to the external 24-hour light/dark cycle. For the central clock, the most potent *zeitgeber* is light input via light sensitive cells located in the retina [36].

Importantly, the SCN has diverse projections that allow it to coordinate autonomic, neuroendocrine, and reproductive processes displaying biological rhythms throughout the body, which are implicated in mammary oncogenesis [37]. The SCN also projects to the gonadotropin-releasing hormone (GnRH) system in the hypothalamus, allowing for circadian control of the hypothalamic-pituitary-gonadal (HPG) axis [38]. Due to the diversity of SCN outputs, disruption of the SCN results in disruption of numerous coordinated systems, which is the foundational argument underlying the circadian disruption hypothesis in breast cancer.

The output of the SCN results in coordinated, endogenous biological rhythms that are entrained to the 24-hour solar light-dark cycle. Early interest in understanding how organisms are

Sleep and Circadian Disruption and Breast Cancer

entrained to the 24-hour solar light-dark cycle revealed the existence of molecular oscillators within single neurons. These “circadian clocks” are encoded by an autoregulatory transcriptional-translational feedback loop that relies on a cycle of positive and negative feedback co-regulated by CLOCK:BMAL1 heterodimers within the cell [39]. In the positive feedback loop, these heterodimers activate rhythmic transcription of core clock genes, including *Period* (*Per1* and *Per2* in humans) and *Cryptochrome* (*Cry1* and *Cry2*) genes [40]. When these PER:CRY heterodimers translocate back into the nucleus, they act on the CLOCK:BMAL1 complex to repress their own transcription. Circadian oscillation is further regulated by CLOCK:BMAL1 heterodimer transcription activation of retinoic acid-related orphan nuclear receptors (ROR), *Rev-erba* and *Rora*. REV-ERBs and RORs competitively bind to ROR response elements in the *Bmal1* promoter region to repress or activate transcription of *Bmal1*, respectively, thus feeding back on the CLOCK:BMAL1 heterodimer. These autoregulatory feedback loops constitute the circadian molecular clock and take approximately 24 hours to complete one cycle [41]. Importantly, the transcriptional factors and targets that comprise the molecular oscillator are found not only in the central nervous system but in peripheral tissues, including the breast [42]. Additionally, core clock genes regulate clock-controlled genes (CCGs), many of which are also integral cell cycle regulators implicated in tumorigenesis [43;44], including *c-Myc* [45], *Wee1* [46], and *cyclin D1* [47], although the effects of these cell cycle regulators are outside the scope of this review.

In mammals, the timing and regularity of light exposure are critical for optimal circadian rhythmicity. Prior to the invention of artificial light, environmental light exposure was confined to the day, resulting in alignment of the solar light/dark cycle and endogenous circadian rhythms. Exposure to light at night (LAN) results in misalignment between the central clock and the solar light-dark cycle, with downstream effects on neuroendocrine and behavioral processes, such as melatonin suppression [48] and sleep disruption [49]. Variability in exposure to LAN results in

Sleep and Circadian Disruption and Breast Cancer

perturbations of circadian synchrony and can alter the phase of physiological processes under circadian control, including sleep [50].

The “Light-Gated” Pathway of Circadian Disruption and Breast Cancer

Circadian disruption is hypothesized to increase risk for breast cancer via disruption of central and peripheral clocks, resulting in widespread dysregulation of clock-controlled biological processes and melatonin suppression, processes that have been thoroughly reviewed elsewhere [14]. Clock genes and circadian regulation are involved in virtually all cellular processes underlying cancer initiation, including cell cycle regulation, DNA damage and repair, cellular apoptosis and survival, and cell proliferation [51]. In order to understand why exposure to LAN can have such potent downstream—and ultimately carcinogenic—effects, it is critical to first understand circadian gating of light. In humans, synchrony between light exposure and the solar light-dark cycle is necessary for optimal expression of numerous physiological and behavioral processes. However, the roughly 24.18-hour endogenous human circadian period is slightly longer than the 24-hour solar period [50] and therefore requires “resetting” each day to in order to re-align with the solar photoperiod [52]. To achieve this, the circadian system must be highly sensitized to and able to integrate photic and temporal information in order to anticipate and adapt to environmental changes. For diurnal animals such as humans, light exposure is expected during the middle of the subjective or solar day and therefore has little effect on altering circadian rhythms. Light exposure during the solar night and near dawn or dusk, however, is a potent entrainment cue for the circadian system and is effective in phase shifting the central clock, as well as initiating a cascade of neuroendocrine processes under circadian control. This “light-gated” model of circadian disruption begins with photic initiation of the core clock transcriptional-translational feedback loop out of phase with the solar light-dark cycle, for example due to LAN exposure from shift work or during nocturnal awakenings from sleep. Light at night suppresses melatonin (N-acetyl-5-methoxytryptamine), a potent pleiotropic

Sleep and Circadian Disruption and Breast Cancer

hormone released from the pineal gland that displays a diurnal pattern with maximal expression at night [53;54]. Melatonin is both an output of the central circadian system and a key regulator of central and peripheral oscillators, including oscillators found in breast tissue [55], and has been identified as a critical modulator in breast cancer development.

The Circadian System and Melatonin

Melatonin entrains peripheral clocks to the SCN in organs that express the receptors melatonin 1 (MT1) and melatonin 2 (MT2; [56]. Suppression of melatonin is influenced by light duration, irradiance, and wavelength [57]. Melatonin suppression is dose-responsive, with maximal suppression at 3,000 lux, and wavelength-dependent, maximally affected by blue wavelength (440-460nm; [48]. Recent evidence has demonstrated that exposure to irradiance of as little as 1 lux of 440-460 wavelength light can lower melatonin expression by ~8% [58]. The low levels of light to which we are exposed in the evening, from TV, phone, and computer screens and incandescent light bulbs, are sufficient to cause phase delays in the circadian system [59;60].

Melatonin plays a regulatory role in the HPG axis, suppressing ovarian estrogen synthesis [61]. Melatonin is also a potent repressor of estrogen-induced estrogen-receptor- α (ER α) transcriptional activity [62], an action that is attenuated by LAN exposure. Elevated levels of ovarian hormones contribute to the development of breast cancers (e.g., [63;64], and high levels of endogenous estrogen are associated with increased risk of incident breast cancer in both pre- and post-menopausal women [65], respectively). These findings highlight the importance of an estrogen-suppressing mechanism such as melatonin in a model of breast cancer pathogenesis.

Classification of Light at Night and/or Shift Work as Carcinogenic to Humans

Sleep and Circadian Disruption and Breast Cancer

In 2007, the International Agency for Research on Cancer (IARC) Working Group concluded that “shift-work that involves circadian disruption is probably carcinogenic to humans” (group 2A) on the basis of “sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)” and “limited evidence in humans for the carcinogenicity of shift-work that involves night work”. In 2012, the American Medical Association House of Delegates adopted a similar policy regarding light at night. In their Executive Summary [66], the AMA report states that nighttime lighting includes “potential carcinogenic effects related to melatonin suppression, especially breast cancer”. The AMA report cites evidence from laboratory models of cancer of the role of melatonin as an anticancer and tumor suppressor agent, as well as limited epidemiological studies on LAN and/or disruption of circadian rhythm on breast cancer risk. While the IARC Working Group statement emphasizes the risks to night shift workers, the AMA statement broadens the risk to all persons exposed to nighttime lighting.

Importantly, the IARC published a follow-up paper [67] advocating a movement toward greater specificity in the definition of night shift work as a cancer risk factor. The working group identified several domains that may contribute to variability in cancer risk: “shift system”, comprised of timing of shift work, length of shift work per 24-hour period, permanent or rotating, and regularity of shift work; cumulative shift work exposure in years over the individual’s lifetime; and intensity of shift work, calculated as time off between shift work days. Significant variability in the operational definition and characterization of NSW across studies may account for some of the discrepancies in risk observed across prospective studies, as described below.

Associations among Circadian Disruption, Light at Night, Melatonin, and Breast Cancer

Melatonin: In Vivo and In Vitro Studies. Melatonin has the distinction of being the first identified nocturnal anticancer signal in humans that links the central circadian clock with breast

Sleep and Circadian Disruption and Breast Cancer

carcinogenesis [68]. Melatonin release is dependent on both the pineal gland and the SCN, with nocturnal release of this hormone gated by the SCN [69;70], suggesting that disruptions in the SCN, either via sleep and/or circadian disruption, may also alter melatonin release.

Reproductive Hormones: In Vivo and In Vitro Studies. The central circadian system exerts multiple modulatory effects on the synthesis and release of reproductive hormones via the hypothalamic-pituitary-gonadal axis and expression of hormone receptors. There is evidence that ER α expression is directly modulated by the core clock gene *Per2*, and the transcriptional capability of ER α in healthy and cancerous breast cells displays periodicity [38]. Deregulation of *Per1*, *Per2*, and *Per3* genes in breast cancer cells has also been detected [71]. Clock genes regulate the HPG axis and affect reproductive viability. *Clock* mutant mice are subfertile and have lengthened estrous cycles [72;73], and *Bmal1* knockout mice are infertile [74;75]. Furthermore, the LH surge shows a circadian release pattern in the presence of estradiol [76], while SCN lesions abolish this [77]. These data support the role of the central clock in coordinating reproductive rhythms. Mechanisms that disrupt the circadian system are therefore capable of dysregulating the HPG axis.

Case-Control and Cohort Studies. Converging evidence suggests that sources of circadian disruption, such as LAN and shift work, similarly disrupt melatonin in humans and have oncogenic effects. Blask's group [78] extended their animal research findings by testing the blood of human volunteers exposed to bright (~2,800 lux) LAN, finding that LAN abolished the tumor suppressive effects of melatonin and that these effects were restored by the addition of melatonin to the blood. In a prospective case-control study from the Nurses' Health Study cohort of 18,643 cancer-free women, those with the highest morning melatonin, as measured by levels of the primary metabolite 6-sulfatoxymelatonin (aMT6s) in first morning urine, had the lowest risk of incident breast cancer [79]. A related prospective case-control study from the Nurses'

Sleep and Circadian Disruption and Breast Cancer

Health Study II cohort of 147 women with invasive breast cancer and 291 matched controls found that women with the highest levels of aMT6s also had the lowest risk of invasive breast cancer [80]. A retrospective case-control study found that breast cancer risk was increased in women who reported frequently not sleeping during the time of night when melatonin levels peak (~1:00 a.m.) in the 10 years prior to diagnosis [81]. A meta-analysis of five prospective case-control studies indicated an overall inverse association between incident breast cancer risk and higher levels of urinary aMT6s [82].

Researchers have also investigated associations between other sources of LAN and incident breast cancer. One case-control study found that keeping the lights on while sleeping, not drawing the shades while sleeping at night, and sleeping in the daytime were all associated with slight but non-significant increases in breast cancer risk [83]. More compelling evidence for the risks of LAN comes from a case-control study of 1,679 women [84], where greater bedroom-light intensity while sleeping was associated with increased breast cancer risk (OR=1.22, 95% CI=1.12-1.31). Recently, it has been demonstrated that ipRGCs are able to receive and transmit photic input even through closed eyelids, and brief flashes of light administered to sleeping individuals induced both shifts in circadian phase and melatonin suppression [85]. It is therefore plausible that exposure to ambient bedroom LAN could induce sufficient circadian disruption to be potentially oncogenic.

There is strong evidence to suggest that women working night shifts are at increased risk for incident breast cancer. In a comparison of Danish night and day shift workers, women working night shifts had significantly decreased urinary aMT6s concentrations than day shift workers [86]. A case-control study in France found that there was an increased rate of breast cancer in women who had ever worked night shifts [87]. Women employed in night work for more than 4 years prior to their first pregnancies had the highest rates of incident breast cancer (OR=1.95,

Sleep and Circadian Disruption and Breast Cancer

95% CI=1.13-3.35). These findings corroborate a Danish nurse case-control study [88], where night shift workers had increased risk for breast cancer (OR=1.8; CI 1.2-2.8). Permanent night shift work was associated with the greatest risk. A population-based case-control study in Australia found a 22% increase in breast cancer risk with frequently rotating night shift schedules, and a trend for increased risk for women ever working 12:00-5:00 a.m. [89]. However, in a large, prospective Dutch cohort study of incident breast cancer, neither occasional nor regular night work was associated with hospital admission for breast cancer during the 7-year follow-up [90]. While these findings certainly run contrary to the previous studies, the study is limited by using hospital admission as its primary outcome measure.

Meta-Analyses. Overall, the majority of results from nine published meta-analyses of the associations between circadian disruption and incident breast cancer support the circadian disruption model of breast cancer pathogenesis (see Table 2). Eight of the meta-analyses reported an overall increased incidence of breast cancer (ranging from 5-48%) in women exposed to some form of circadian disruption, including lifetime exposure to night shift work and LAN [25;91-97]. Furthermore, six of the meta-analyses conducted sub-analyses on years and nights of exposure, with converging evidence from five of the six studies suggesting that circadian disruption is associated with increased risk in a dose-dependent manner [94-98]. Kamdar and colleagues [93] did not find that participants working 8 or more years of NSW were at greater risk for developing breast cancer compared to non-shift workers, and Jia and colleagues [92] found that women working 15 or more years of NSW were not at increased risk above and beyond women who reported ever working night shift. The most recent meta-analysis [99] which included previously unpublished data from three prospective studies along with data from 7 published studies, found no significant associations among NSW and incident breast cancer risk (RR=0.99, 95% CI=0.95-1.03). However, as with previous meta-analyses, there was significant heterogeneity in the characterization of NSW as a risk factor across the

Sleep and Circadian Disruption and Breast Cancer

included studies. Moreover, as was identified in a recently published response to the Travis et al. meta-analysis, the baseline age of women in the paper's 3 prospective studies ranged from early-50s to upper-60s with follow-up periods of only 2-3 years [99;100]. This makes it challenging to support the authors' claim that the "melatonin hypothesis" for breast cancer risk lacks merit, but gives credence to the IARC Working Group's {IARC, 2009} argument for establishing greater consistency in operationally defining NSW as a risk factor.

While the overall findings from these meta-analyses suggest that circadian disruption is a significant predictor of breast cancer, results should be interpreted with some degree of caution. As mentioned above, many of the meta-analyses combined samples potentially too heterogeneous to be included in one statistical model, including samples of mixed menopausal status or occupation, such as flight attendants, who are exposed to different circadian disruptions than other NSWs, including frequent time zone changes and increased radiation exposure, which may predispose them to increased rates of breast cancer [101]. Furthermore, latitude and season were not accounted for in these analyses, introducing error due to shortened or lengthened light-dark cycles. However, these results are promising, and suggest that circadian disruption from LAN exposure and night shift work is likely carcinogenic and in a time-dependent manner.

Sleep Disruption and Breast Cancer Oncogenesis: Expanding the Model

Bidirectional Associations among Sleep and Circadian Systems

The sleep and circadian systems are yoked, with sleep demonstrating circadian rhythmicity in all vertebrate and invertebrate species in which it has been investigated [102;103], including mature humans, who typically spontaneously enter into sleep and wake periods once per day in concordance with the solar light-dark cycle. Sleep behavior is an integrated function of both an innate homeostatic sleep drive and endogenous circadian rhythms, and changes in one system

Sleep and Circadian Disruption and Breast Cancer

effect changes in the other. Many of these effects are mediated by light, which affects sleep by synchronizing the clock via specialized light-sensitive cells in the retina that project to the SCN [104;105]. In turn, the SCN has multisynaptic projections to brain areas involved in sleep-wake regulation, including the ventrolateral preoptic (VLPO) and lateral hypothalamus (LH; [35]). These two systems are therefore inextricably linked, as demonstrated by experimental findings in animals with variants in core circadian clock genes, which show altered sleep phenotypes. For example, *Clock* mutant mice have shorter sleep periods than wild type (WT) mice [106]. Animals with double knockouts of cryptochrome 1 and 2 (*Cry1^{-/-}/Cry2^{-/-}*) exhibit changes in sleep micro- and macro-architecture, including increased non-REM (NREM) sleep [107]. *Bmal1* mutant mice show increased sleep fragmentation and duration [108]. These findings may be mediated by changes in the rhythmicity of postulated wake and sleep agents, orexin and adenosine, which appear to be under a degree of circadian regulation. Orexin activity is increased during wake periods [109;110], while adenosine is maximally expressed at night in dark conditions [111]. While they are interrelated, it is important to note that sleep and circadian rhythms are distinct processes. Experimental evidence demonstrates that the sleep-wake rhythm is preserved in the absence of the circadian clock through *Opn4*-mediated photic input that activates neurons in the VLPO [112].

Converging empirical evidence suggests that changes in sleep elicit changes in circadian rhythms. For instance, a partial sleep deprivation condition in Syrian hamsters under constant dark conditions induced large circadian phase advances of up to 4 hours, suggesting that the neurophysiological effects of sleep deprivation are sufficient to reset the circadian clock [113]. In a follow-up study, adenosine agonist administration induced dose-dependent phase shifts similar to the sleep deprivation condition [114]. Importantly, these findings were independent of light-dark effects; both the sleep deprivation and AD agonist administration conditions were sufficient to inhibit light-induced phase shifts, above and beyond resetting of the circadian clock.

Sleep and Circadian Disruption and Breast Cancer

On a molecular level, experimental sleep deprivation affects transcriptional activity of core clock genes *bmal1*, *clock*, and *cry2* [115]. Interpreting these results in the context of a human model, it is plausible that sleep deprivation may disrupt the circadian clock independently of LAN exposure, triggering the pro-oncogenic downstream effects of circadian disruption.

Systematic Review of Associations between Sleep Disruption and Incident Breast Cancer.

To date, twelve studies have been published on the relationships between one or more index of sleep and incident breast cancer, with mixed results (see Table 3). Of these, 5 were case-control studies and 7 were cohort studies; the studies were evenly split between prospective and retrospective designs.

Case-Control Studies. The findings from the case-control studies are mixed. In the earliest study, McElroy and colleagues [116] found that women reporting ≥ 9 h of sleep per night had a 6% increase in risk for every additional hour of sleep, compared to women sleeping 7.0-7.9h. This study relied on the retrospective self-report of invasive breast cancer patients and community controls. Additionally, while the authors reported that shorter sleep duration was not associated with increased risk, their cutoff of < 7 h differs from the conventional threshold of ≤ 5 h or ≤ 6 h often used in research on the health outcomes of short sleep (e.g., [117]). Fritschi and colleagues [118] created a composite variable of self-reported “sleep disturbance” that included either short (< 6 h) or long (≥ 9 h) sleep duration, poor sleep quality, and frequent difficulty falling or staying asleep. They found that greater sleep disturbance was not associated with increased incidence of breast cancer, although the odds ratio approached significance (OR=1.21, 95% CI 0.95-1.55, “ever” having sleep disruption vs. never). It is worth noting that the authors did not investigate breast cancer risk for each sleep variable separately, and they also failed to find any associations between either night shift work or LAN and breast cancer in their sample. This same group published a follow-up paper that did investigate sleep duration individually in this same case-control sample [119]; they found no associations between self-reported short (< 6 h)

Sleep and Circadian Disruption and Breast Cancer

or long (>8h) sleepers and breast cancer. Like the McElroy et al. [116] study, this study sample was a retrospective case-control examination of the self-reported sleep of women recently diagnosed with incident invasive breast cancer [119]. It is possible that the retrospective nature of the report, after first cancer diagnosis, introduces some element of reporting bias. Yet another case-control study, a nested design within the larger prospective Singapore Chinese Health Study cohort, did not find that self-reported sleep duration was associated with breast cancer risk [120]. In this study, they compared long sleepers against short sleepers; it is unclear whether conventionally short (≤ 6 h) or long (≥ 9 h) sleepers were at risk compared to average (7-8h) sleepers. Most recently, Wang and colleagues [121] found that women who reported both short (≤ 6 h) and long (≥ 9 h) habitual sleep over the past 10 years had 53% and 59% increased risk, respectively. Interestingly, this group also looked at history of night shift work and daytime napping and found that napping appeared to confer some degree of protection against breast cancer, but only in NSW. This finding of a dynamic association among shift work as a risk factor and sleep as a protective mechanism supports the importance of assessing both sleep *and* circadian variables in research studies.

The findings of the 6 published prospective cohort studies are also mixed. One study of 23,995 Japanese women found that shorter sleep duration was associated with higher risk of incident breast cancer [122]; compared to women sleeping 7h, women who reported sleeping ≤ 6 h had higher rates of incident breast cancer (HR=1.62, 95% CI=1.05-2.50), with associations most pronounced in women under 60 years, who had a 200% increase in risk (HR=2.01, CI=1.12-3.59). Two prospective, population-based cohort studies found that longer sleep duration may have a protective effect against incident breast cancer [123;124]. In a population study of Finnish women born before 1958, sleep was assessed by self-reported questionnaires administered in 1975 and 1981. Compared to women who reported habitually sleeping 7-8h, women who reported sleeping ≥ 9 h at both times had a 72% decreased risk of incident breast

Sleep and Circadian Disruption and Breast Cancer

cancer (HR=0.28, 95% CI=0.09-0.88)[120]. A study of incident breast cancer in postmenopausal women from the Singapore Chinese Health Study [124] found that women reporting ≥ 9 h of sleep showed a trend for reduced risk of incident breast cancer an average of 11 years later (RR=0.67, 95% CI=0.4-1.1, $p=0.047$) compared to <6 h sleepers. Urinary aMT6s levels were positively associated with hours of self-reported sleep ($p=0.035$) and were 42% higher in women sleeping ≥ 9 h compared to those reporting ≤ 6 h. These findings suggest that sleep duration may gate melatonin secretion; the oncostatic effect of melatonin may be one mechanism by which prolonged sleep duration protects against breast cancer.

Finally, three prospective studies found no associations between sleep duration and breast cancer [119;125;126]. The first, using prospective data from the Nurses' Health Study, found that habitual self-reported short or long sleep duration was not associated with self-reported incident breast cancer over the 16 year follow-up [125], although there was a linear trend for longer sleep duration and increasing risk ($p=.07$). More recently, Vogtmann and colleagues [126] also reported no associations between self-reported sleep duration, sleep quality, insomnia, or sleep disturbance and incident breast cancer in a sample of 110,011 postmenopausal women in the Women's Health Initiative cohort. Similar null findings were published from the Breast Cancer Detection Demonstration Project, which failed to find that self-reported short or long sleep was a risk factor in their sample [127]. Finally, one study examined self-reported daytime napping frequency in the Million Women Study [128], finding 6% increased breast cancer risk in women who napped "sometimes" and 11% increased risk in women who "usually" napped, compared to non-nappers. These data suggest that, if there is a beneficial effect to sleep, it may be optimal only when the sleep period is optimally aligned with circadian rhythms and the exogenous light-dark cycle, although further research is needed.

Sleep and Circadian Disruption and Breast Cancer

Critical factors may underlie the discrepant findings of the studies on sleep and breast cancer. First, it appears that none of these studies were specifically designed to test associations between measures of sleep and incident breast cancer, and this is reflected by the general paucity of sleep measures. Second, all studies relied on a self-reported measure of sleep, often assessed with a single question. Third, only half of these studies were able to collect data prospectively, introducing retrospective reporting bias. Fourth, there was significant heterogeneity between the samples in these studies, particularly in percentages of pre- and post-menopausal status, an independent predictor of breast cancer risk, and in types of breast cancers, which also displays great heterogeneity. Finally, very few of the studies included concurrent measures on night shift work or LAN exposure, making it difficult to determine the relative contributions of the circadian and sleep systems.

Meta-Analyses of Sleep Duration and Breast Cancer Risk

The first meta-analysis of the associations between sleep and cancer included studies examining all types of cancers [129]. Ten prospective studies were included, with a combined sample of 555,678 participants and 8,392 incident cancer cases. The authors found that neither short ($RR=1.05$, 95% $CI=0.90-1.24$) nor long ($RR=0.92$, 95% $CI=0.76-1.12$) sleep duration was associated with increased all-cancer or breast cancer risk. However, these analyses included only 3 studies of breast cancer, which have been previously discussed in this review [122;123;130].

Two more recent meta-analyses focusing exclusively on breast cancer found no evidence that sleep duration was associated with increased incidence [96;131]. Both reviewed the same six studies, all that had been published on sleep duration and breast cancer through 2013. Yang and colleagues [96] analyzed the summed relative risks across all 6 studies for 1h increase in sleep per night ($RR=1.00$, $CI=0.995-1.01$) and longest versus shortest sleepers ($RR=0.96$,

Sleep and Circadian Disruption and Breast Cancer

CI=0.77-1.19). Qin and colleagues grouped their analyses by short and long sleep versus reference, neither of which were significant predictors (RR=1.01, CI=0.90-1.14 and RR=0.95, CI=0.86-1.04, respectively). However, the discrepancy between study definitions of short and long sleep is worth noting. While Wu [120], Girschik [132], and Kakizaki [133] used a threshold of ≤ 6 h, Pinheiro [125] and McElroy [116] used ≤ 5 h and Verkasalo [123] ≤ 4 . For long sleep, most studies used a threshold of ≥ 9 h except for Girschik ([132]; ≥ 8 h) and Verkasalo ([123]; ≥ 10 h). Both meta-analyses included retrospective studies, and all studies used self-reported sleep measures, limiting our interpretability of their null findings. Well-designed, prospective studies using objective measures of sleep are needed to better address the question of whether any indices of sleep are associated with incident breast cancer.

Potentially Interrelated Mechanistic Pathways Between Circadian and Sleep Disruption and Mammary Oncogenesis

Circadian and sleep disruption may act on immunologic, molecular, cellular, neuroendocrine, and metabolic levels in ways that contribute to breast cancer development. Table 1 provides an overview of the potential mechanistic pathways, noting the strength of the experimental and/or epidemiological evidence for each pathway.

Mammary carcinogenesis begins with the mutation of a healthy cell through a process that includes alterations in cellular and immune processes, including oxidative nuclear DNA damage [134], changes in cellular apoptosis [135], and changes in innate immune function [136]. Mutated cells are able to survive in the face of compromised innate tumor suppressor mechanisms, such as inactivation of the *p53* gene [137], which can result in decreased apoptosis of aberrant cells [138]. The growth of human breast cells is regulated by steroid hormones, and the role of estrogen as an oncogenic agent is well-established [139;140]. Sleep disruption and circadian disruption negatively impact the timing and availability of melatonin, an

Sleep and Circadian Disruption and Breast Cancer

oncostatic agent and potent estrogen suppressor. Changes in the immune system also predispose the system to oncogenesis. Persistent inflammation can induce genetic instability that may lead to cell mutations. Downregulation of anti-tumor immune responses and upregulation of pro-angiogenic immune factors contribute to survival of mutated cells and tumorigenesis. Disruptions in sleep and circadian systems also affect metabolic processes and predispose the organism to increased adiposity, which is associated with increased breast cancer risk.

Inflammation and the Immune System.

Repeated disruptions of the sleep and circadian systems can affect both innate and acquired immune function. Several studies have demonstrated that a single night of sleep deprivation is associated with decreased numbers of circulating NK cells [141] and NK cytotoxicity [142]. NK cells are enhanced by cytokines such as interferon-gamma (IFN- γ) and interleukin-2 (IL-2; [136], which are also affected by sleep duration [141]. Sleep disruption may lead to a shift in cytokine production balance from Th-1 cytokines to Th-2 cytokines, including IL-10 [143], which can allow tumor cells to escape from immune surveillance [144] and which is associated with increased breast cancer risk [145]. Healthy sleep is associated with production of pre-myeloid dendritic cells, which produce IL-12 [146], a cytokine associated with the delay of tumor onset and decreased tumor multiplicity [147].

Chronic inflammation is also implicated in the oncogenic pathway, and both sleep disruption and circadian disruption have been demonstrated to have pro-inflammatory effects [148;149]. In addition, melatonin has been shown to enhance IL-2 and IL-6 production via nuclear receptor-mediated mechanisms (ROR α ; [150]). It was recently discovered that certain lymphocytes are capable of producing melatonin in a time-dependent manner [151] and, in turn, melatonin has been shown to moderate the role of many immune functions, including IL-2 production

Sleep and Circadian Disruption and Breast Cancer

[151;152]. Repeated disruptions in melatonin synthesis resulting from nightly circadian and sleep disruption may have potent negative effects on healthy immune functioning.

Sleep fragmentation is also associated with repeated transient increases in sympathetic nervous system (SNS) activation, and experimental research indicates that beta-adrenergic signaling regulates a number of cellular processes underlying oncogenesis, including compromised DNA repair and cellular immune responses [153]. Sleep disruption is associated with increased glucocorticoid production [154], and numerous studies have shown that short sleep duration [154] and sleep deprivation [155] are associated with altered cortisol profiles and elevated evening cortisol levels [156]. Glucocorticoid feedback from the adrenal cortex has suppressive effects on the amplitude of circadian rhythms within the hypothalamus and pituitary [157;158]. These studies demonstrate yet another pathway by which sleep disruption may have both direct effects on physiological processes and indirect effects via circadian disruption leading to increased risk for breast cancer.

Oxidative Stress, Reactive Oxygen Species (ROS), and DNA Damage.

Oxidative stress is known to cause DNA damage and is associated with increased breast cancer risk [159]; conversely, antioxidants reduce the amount of DNA damage. Oxidative stress-induced DNA damage may be a primary pathway by which sleep disruption may have greater direct mechanistic effects on mammary oncogenesis than circadian disruption. Sleep is theorized to have antioxidant effects, providing an opportunity for the body to remove oxidants produced during wakefulness [160;161]. Several experimental studies have demonstrated that disrupting sleep increases reactive oxygen species (ROS) [162-164]. ROS can lead to DNA damage by binding to neighboring molecules with unpaired electrons, causing strand breaks [165]. ROS formation also may be a link between sleep deprivation and circadian dysregulation. Sleep deprivation-induced ROS formation and DNA damage has been shown to phase advance

Sleep and Circadian Disruption and Breast Cancer

the mammalian circadian clock both *in vivo* and *in vitro* [166]. While the mechanism is poorly understood, this research supports one pathway by which sleep disruption may contribute to oncogenesis directly, through cellular damage, and indirectly, by disrupting the circadian system.

Oxidative stress is also as a mediator of cellular apoptosis [167]; sleep deprivation-induced oxidative stress may allow mutated cells to escape apoptosis. Circadian mechanisms are also implicated in this pathway. *In vitro* studies have shown that inhibition of *Per1* in human cancer cells blunted DNA damage-induced apoptosis [168]. Cell samples from human cancer patients show reduced *Per1* levels. Dysregulation in the clock gene *Per2*, which acts as a tumor suppressor, has been associated with increased DNA damage [169].

The circadian orphan nuclear receptor ROR α also appears to play a role in the cellular stress response and human tumorigenesis. Increase in ROR α expression inhibits cellular growth and progression, and experimental evidence testing the effects of various stressors on ROR α expression (UV light, MMS, H₂O₂) suggests that this is an adaptive response to stress [170]. Hypoxia, such as that caused by sleep disordered breathing, also increases the amount of ROR α transcripts [171]. However, transcriptional levels of ROR α have been found to be downregulated in breast cancer samples [170], indicating dysfunction in the circadian molecular oscillator.

Melatonin and Estrogen.

It has been proposed that the circadian system developed as a means of counteracting oxidative damage caused by radiation [172;173]. Melatonin is a potent free radical scavenger that impacts quinone reductases to reduce oxidative damage by ROS in tissues [174].

Sleep and Circadian Disruption and Breast Cancer

Administration of physiological levels of melatonin has been shown to induce the expression of antioxidants glutathione and glutathione-S-transferase [175].

Early *in vivo* experimental work on the role of melatonin demonstrated that animals whose melatonin production was disrupted by pineal or SCN ablation were prone to increased rates of spontaneous mammary carcinogenesis [70;176]. The most commonly used *in vivo* model of human breast cancer is a murine mammary tumor induced by 7,12-dimethylbenz[a]anthracene (DMBA), whose pathogenesis is similar to that in humans [177]. Experimental studies on the effects of constant light on DMBA-induced murine mammary tumor development demonstrate that melatonin suppression is associated with increased tumorigenesis [178] and hyperplastic processes in the mammary gland [179;180]. Conversely, rodents administered melatonin during DMBA-induced mammary tumorigenesis show decreased tumor incidence and number compared to controls [176;181], and melatonin administration to rodents with constant light-induced spontaneous mammary hyperplasia resulted in normalization of tissue [182]. In pinealectomized rats, melatonin administration inhibits mammary carcinogenesis, even in a constant illumination (LL) regimen [183].

More recently, Blask and colleagues provided compelling evidence that melatonin is the active factor in LAN-induced mammary tumorigenesis [78]. Human breast cancer xenografts in immunodeficient rats perfused with melatonin-rich blood collected at night from female subjects resulted in significantly suppressed tumor proliferative activity and linoleic acid (LA) uptake. Administration of a melatonin receptor blocker negated these effects [78]. The suppressive effects on LA uptake may be another oncostatic property of melatonin, as LA demonstrates oncogenic effects via upregulation of gene expression involved in ER α expression, G-protein signaling, and cell cycle progression [184]. However, the associations between LA and incident breast cancer remain unclear [185].

Sleep and Circadian Disruption and Breast Cancer

Mammotropic hormones, including estrogens, progesterone, and prolactin, impact breast cancer etiology [186]. Melatonin has an inhibitory effect on estrogen receptors and can counteract the tumor-promoting effects of estrogens [187]. Melatonin can down-regulate estrogen receptor- α (ER α) protein and mRNA expression in a time- and dose-dependent manner [188] and can modulate estrogen-related proteins and growth factors, including *c-myc* [189]. Melatonin administered at physiological nocturnal doses increases the expression of p53 in MCF-7 cells, a human breast cancer cell line expressing 17 β -estradiol receptors [190], inducing apoptosis [191]. Melatonin can temporarily increase the duration of the cell cycle by more than three hours and arrest progression [192]. These actions oppose the mechanisms of estradiol, which stimulates cell proliferation and cell progression [193].

Sleep also impacts hormone levels. Sleep deprivation in female rats is associated with higher levels of progesterone [194] and increased levels of prolactin [195]. Partial sleep deprivation in healthy young women results in increases in LH and estradiol [196], and elevated prolactin levels have been observed in humans following sleep deprivation nights [197]. In humans, objectively-assessed sleep duration has been shown to be inversely associated with levels of 17 β -estradiol [198]. These data suggest that repeated nightly short sleep or sleep disruption may be associated with chronically elevated estrogen levels contributing over time to breast cancer risk.

In the Wu et al. [124] study previously described, women who reported sleeping ≥ 9 h had 42% higher levels of aMT6s and decreased risk of incident breast cancer compared to women sleeping 7h. While another study found no association between hours of sleep and levels of urinary aMT6s, they did find that women awake at night had higher serum concentrations of estradiol [199].

Sleep and Circadian Disruption and Breast Cancer

Metabolic Function.

It is plausible that sleep disruption and circadian disruption may contribute to mammary oncogenesis through other physiological mechanisms. One potential pathway may be altered metabolic function. The obesogenic properties of both circadian and sleep disruption have received support from experimental and observational studies. As previously discussed, melatonin suppresses the uptake of linoleic acid, an oncogenic substance associated with rapid development of mammary tumors in mice [200]. In humans, experimental circadian misalignment and short sleep duration both result in impaired glucose tolerance and decreased leptin [201;202] and increased adiposity [203]. Meta-analysis has established short sleep duration as an independent risk factor for childhood and adult obesity [204].

Summary

Overall, the experimental data supporting a circadian and, to a lesser extent, sleep disruption model for mammary oncogenesis are promising (Table 1). Future studies are needed to prospectively, objectively, and comprehensively assess indices of sleep disruption and circadian rhythms, including melatonin, LAN exposure, shift work, and nocturnal eating, to determine the relative contributions of these disruptions to mammary oncogenesis. Forced desynchrony studies, whereby the circadian and sleep systems are effectively separated, are needed to disambiguate circadian and sleep effects on biomarkers of cancer development. Observational research that is prospective, longitudinal, and population-based is needed to determine whether sleep disruption, not just sleep duration, is prospectively associated with incident breast cancer cases. Experimental research is needed to test and refine the proposed model to better understand the potential mechanistic pathways by which sleep disruption and circadian disruption may contribute to increased risk. Finally, we must consider the real world context. Future research should seek to understand the relative and combined contributions of

Sleep and Circadian Disruption and Breast Cancer

susceptibility factors from all sources—biological, environmental, behavioral, and psychosocial—in the development of breast cancers. Ultimately, these future research questions and avenues will allow us to develop a more ecologically valid and complete understanding of risk factors for breast cancer pathogenesis from a biopsychosocial perspective.

Sleep and Circadian Disruption and Breast Cancer

Table 1.

Potential mechanistic pathways between circadian and sleep disruption and mammary oncogenesis.

Mechanistic Pathway	Evidence for Effects of Circadian Disruption	Evidence for Effects of Sleep Disruption
1. DNA DAMAGE & OXIDATIVE STRESS		
Increased oxidative stress, oxidative DNA damage	Limited	✓✓
Decreased antioxidant effects	✓	Theoretical
2. MELATONIN & ESTROGEN		
Decreased melatonin release	✓✓	Limited
Increased mammotropic hormone production and/or release	✓✓	✓
3. INFLAMMATION & IMMUNE FUNCTION		
Decreased NK cell count & cytotoxicity		✓✓
Shift to Th-2 cytokine production & tumor cell survival		✓
Decreased Th-1 cytokine production (e.g., IL-2)	✓✓	✓✓
Chronic inflammation via activation of pro-inflammatory pathways	✓	✓✓
Increased repeated SNS activation		✓✓ (especially via SDB)
Changes in glucocorticoid production & feedback	Limited	✓
4. METABOLIC FUNCTION		
Increased adiposity & obesity	✓✓	✓✓

Sleep and Circadian Disruption and Breast Cancer

Metabolic disruption (e.g. insulin, glucose, leptin, ghrelin)	✓✓	✓✓ (especially via SDB)
---	----	----------------------------

Notes: ✓✓ = strong research support; ✓ = some/mixed research support; “limited” = support from 1-2 studies; “theoretical” = no known support, compelling theoretical association; SDB = sleep disordered breathing.

Sleep and Circadian Disruption and Breast Cancer

Table 2.

Meta-analyses of circadian disruption and incident breast cancer risk.

Citation	Number of studies	Study Types	Predictor Variables	Overall Odds Ratio (OR) or Relative Risk (RR)
Megdal et al., 2005 [90]	6	4 cohort, 2 case-control	NSW	1.48 (95% CI=1.36-1.61)
Jia et al., 2013 [91]	13	5 cohort, 8 case-control	NSW	1.20 (95% CI=1.08-1.33)
Wang et al., 2013 [93]	10	3 cohort, 5 case-control	NSW	1.19 (95% CI=1.05-1.35)
Ijaz et al., 2013 [94]	12	1 cohort, 11 case-control	NSW	1.05 (95% CI=1.01-1.10) for 5-year NSW
Kamdar et al., 2013 [92]	15	5 cohort, 10 case-control	NSW	1.21 (95% CI=1.00-1.47)
Yang et al., 2014 [95]	5	5 case-control	LAN exposure	LAN: 1.17 (95% CI=1.11-1.24)
He et al., 2015 [25]	18 (n=12 NSW; n=3 LAN; n=3 NSW and LAN)	NSW: 5 cohort, 7 case-control; LAN: 3 case-control; both: 3 case-control	NSW; LAN exposure; both	NSW: 1.19 (95% CI=1.08-1.32); LAN: 1.12 (95% CI=1.119-1.121)
Lin et al., 2015 [96]	6	6 cohort	NSW	1.057 (95% CI=1.014-1.102)
Travis et al., 2017 [99]	10	3 prospective, 7 cohort	NSW	0.99 (95% CI=0.95-1.03)

Note: NSW=night shift work; LAN=light at night.

Sleep and Circadian Disruption and Breast Cancer

Table 3.
Studies of sleep disruption and incident breast cancer risk.

Citation	Study Type	Number of Participants & Cases	Sample	Sleep Variables	Incident Breast Cancer Risk	Findings
Verkasalo et al., 2005	Prospective, population-based cohort	N=12,222; Incident cases n=242	Finnish women born before 1958	Self-reported sleep duration assessed at 1975 and 1981; steady LS (≥ 9 h at both times)	HR=0.28 (95% CI 0.09-0.88) steady LS vs. steady 7-8h sleepers	LS \downarrow risk
McElroy et al., 2006	Retrospective, population-based case-control	N=9,347; BCa patients n=4,033	Invasive breast cancer patients and community controls	Self-reported sleep duration over past 2 yrs.; LS (≥ 9 h)	OR=1.13 (95% CI 0.93-1.37) LS vs. 7-8h sleepers	LS \uparrow risk (trend)
Pinheiro et al., 2006	Prospective, cohort	N=77,418; Incident cases n=4,223	Nurses' Health Study	Self-reported habitual sleep duration reported at 1986 and 2000; SS (≤ 5 h); LS (≥ 9 h); steady LS (≥ 9 h at both times)	HR=0.93 (95% CI 0.79-1.09) SS vs. 7h sleepers; HR=0.95 (95% CI 0.82-1.11) LS vs. 7h sleepers Linear trend for sleep duration as continuous variable ($p=0.07$)	\neq LS \uparrow risk (trend, continuous sleep predictor)
Kakizaki et al., 2008	Prospective, population-based cohort	N=23,995; Incident cases n=143	Ohsaki National Health Insurance Cohort Study	Self-reported habitual sleep duration; SS (≤ 6 h)	HR=1.62 (95% CI 1.05-2.50) SS vs. 7-h sleepers Linear trend for sleep duration as continuous variable ($p=0.03$)	SS \uparrow risk
Wu et al., 2008	Prospective, population-based cohort	N=33,528; Incident cases n=525	Singapore Chinese Health Study	Self-reported habitual sleep duration; LS (≥ 9 h)	RR=0.67 (95% CI 0.4-1.1) LS vs. ≤ 6 h sleepers	LS \downarrow risk
Cairns et al., 2012	Prospective, cohort	N=795,238; Incident cases n=20,058	The Million Women Study, UK	Self-reported daytime napping frequency (never, sometimes, usually)	RR=1.06 (95% CI 1.04-1.08) sometimes nap vs. never; RR=1.11 (95% CI 1.07-1.15) usually nap vs. never	Naps \uparrow risk
Fritschi et al., 2013	Retrospective, case-control	N=2,994; BCa patients n=1,205	Western Australia women	Self-reported "sleep disruption" composite measure	OR=1.21 (95% CI 0.95-1.55) "ever" sleep disruption vs. never	Sleep disruption \uparrow risk (trend)
Wu et al., 2013	Nested case-control study	N=991; BCa patients	Singapore Chinese Health	Self-reported habitual sleep duration	OR=0.89 (95% CI 0.64-1.22) LS vs. ≤ 6 h sleepers	\neq

Sleep and Circadian Disruption and Breast Cancer

		n=248	Study			
Girschik et al., 2013	Retrospective, case-control	N=2,994; BCa patients n=1,205	Breast Cancer Environment and Employment Study	Self-reported habitual sleep duration; SS (<6h); LS (>8h)	OR=1.05 (95% CI 0.82-1.33) SS vs. 7-8h sleepers; OR=1.10 (95% CI 0.87-1.39) LS vs. 7-8h sleepers	≠
Vogtmann et al., 2014	Prospective, cohort	N=110,011; Incident cases n=5,149	Women's Health Initiative	Self-reported sleep duration, sleep quality, sleep disturbance; SS (≤5h); LS (≥9h)	HR=0.95 (95% CI 0.85-1.07) SS vs. 7h sleepers; HR=1.03 (95% CI 0.90-1.18) LS vs. 7h sleepers	≠
Wang et al., 2015	Retrospective, case-control	N=1,454; BCa patients n=712	Chinese breast cancer patients and age-matched controls	Self-reported 10-year habitual sleep duration; SS (≤6h); LS (≥9h); daytime napping	OR=1.53 (95% CI 1.10-2.12) SS vs. 6.1-8.9h; OR=1.59 (95% CI 1.17-2.17) LS vs. 6.1-8.9h OR=0.57 (95% CI 0.36-0.90) napping NSW vs. non-napping NSW	SS ↑ risk LS ↑ risk Naps ↓ risk in NSW
Qian et al., 2015	Prospective, cohort	N=40,013; Incident cases n=1,846	Breast Cancer Detection Demonstration Project	Self-reported weekday and weekend sleep duration; SS (<6h); LS (≥9h)	RR=0.87 (95% CI 0.70-1.22) SS vs. 8-9h sleepers; RR=1.00 (95% CI 0.84-1.19) LS vs. 8-9h sleepers	≠

Notes: SS=short sleepers; LS=long sleepers; NSW=night shift workers. Italics indicate trend approaching statistical significance.

Sleep and Circadian Disruption and Breast Cancer

Reference List

- [1] DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin* 2014 Jan;**64**: 52-62.
- [2] Rosenberg PS, Barker KA, Anderson WF. Estrogen Receptor Status and the Future Burden of Invasive and In Situ Breast Cancers in the United States. *J Natl Cancer Inst* 2015 Sep;**107**.
- [3] Walsh MF, Nathanson KL, Couch FJ, Offit K. Genomic Biomarkers for Breast Cancer Risk. *Adv Exp Med Biol* 2016;**882**: 1-32.
- [4] Dunning AM, Healey CS, Pharoah PD, Teare MD, Ponder BA, Easton DF. A systematic review of genetic polymorphisms and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1999 Oct;**8**: 843-54.
- [5] Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, *et al.* Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J Natl Cancer Inst* 2005 Mar;**97**: 439-48.
- [6] Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, *et al.* Trends in breast cancer by race and ethnicity: update 2006. *CA Cancer J Clin* 2006 May;**56**: 168-83.
- [7] McCormack VA, dos SS, I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006 Jun;**15**: 1159-69.

Sleep and Circadian Disruption and Breast Cancer

- [8] Oldenburg RA, Meijers-Heijboer H, Cornelisse CJ, Devilee P. Genetic susceptibility for breast cancer: how many more genes to be found? *Crit Rev Oncol Hematol* 2007 Aug;**63**: 125-49.
- [9] Ghoussaini M, Pharoah PD, Easton DF. Inherited genetic susceptibility to breast cancer: the beginning of the end or the end of the beginning? *Am J Pathol* 2013 Oct;**183**: 1038-51.
- [10] Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, *et al.* Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998 Feb;**279**: 535-40.
- [11] Xue F, Willett WC, Rosner BA, Hankinson SE, Michels KB. Cigarette smoking and the incidence of breast cancer. *Arch Intern Med* 2011 Jan;**171**: 125-33.
- [12] Boyd DB. Insulin and cancer. *Integr Cancer Ther* 2003 Dec;**2**: 315-29.
- [13] Vainio H, Kaaks R, Bianchini F. Weight control and physical activity in cancer prevention: international evaluation of the evidence. *Eur J Cancer Prev* 2002 Aug;**11 Suppl 2**: S94-100.
- * [14] Haus EL, Smolensky MH. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. *Sleep Med Rev* 2013 Aug;**17**: 273-84.
- [15] Kochan DZ, Kovalchuk O. Circadian disruption and breast cancer: an epigenetic link? *Oncotarget* 2015 Jul;**6**: 16866-82.

Sleep and Circadian Disruption and Breast Cancer

- * [16] Stevens RG, Brainard GC, Blask DE, Lockley SW, Motta ME. Breast cancer and circadian disruption from electric lighting in the modern world. *CA Cancer J Clin* 2014 May;**64**: 207-18.
- [17] Vijakkhana N, Wilaisakditipakorn T, Ruedeeekhajorn K, Pruksananonda C, Chonchaiya W. Evening media exposure reduces night-time sleep. *Acta Paediatr* 2015 Mar;**104**: 306-12.
- [18] Levenson JC, Shensa A, Sidani JE, Colditz JB, Primack BA. The association between social media use and sleep disturbance among young adults. *Prev Med* 2016 Apr;**85**: 36-41.
- * [19] Kloog I, Stevens RG, Haim A, Portnov BA. Nighttime light level co-distributes with breast cancer incidence worldwide. *Cancer Causes Control* 2010 Dec;**21**: 2059-68.
- [20] Stevens RG, Zhu Y. Electric light, particularly at night, disrupts human circadian rhythmicity: is that a problem? *Philos Trans R Soc Lond B Biol Sci* 2015 May;**370**.
- [21] Buysse DJ, Soehner A, Abbott S, Kapur VK, Mahowald MW, Parker KP, *et al.* Sleep and sleep-wake disorders. In: Tasman A, Kay J, Lieberman JA, First MB, Riba MB (eds). *Psychiatry*. 4 ed. Hoboken: Wiley Blackwell; 2015. p. 1264-310.
- [22] Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011 Jun;**32**: 1484-92.
- [23] Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *J Sleep Res* 2009 Jun;**18**: 148-58.

Sleep and Circadian Disruption and Breast Cancer

- [24] Borbely AA. A two process model of sleep regulation. *Human Neurobiology* 1982;**1**: 195-204.
- [25] He C, Anand ST, Ebell MH, Vena JE, Robb SW. Circadian disrupting exposures and breast cancer risk: a meta-analysis. *Int Arch Occup Environ Health* 2015 Jul;**88**: 533-47.
- [26] Irwin M. Effects of sleep and sleep loss on immunity and cytokines. *Brain Behav Immun* 2002 Oct;**16**: 503-12.
- [27] Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. *Ann N Y Acad Sci* 2010 Apr;**1193**: 48-59.
- [28] Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev* 2006 Feb;**10**: 49-62.
- [29] Inoue S, Honda K, Komoda Y. Sleep as neuronal detoxification and restitution. *Behav Brain Res* 1995 Jul;**69**: 91-6.
- [30] Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007 Jun;**11**: 163-78.
- [31] Leproult R, Van CE. Role of sleep and sleep loss in hormonal release and metabolism. *Endocr Dev* 2010;**17**: 11-21.
- [32] Pevet P, Challet E. Melatonin: both master clock output and internal time-giver in the circadian clocks network. *J Physiol Paris* 2011 Dec;**105**: 170-82.

Sleep and Circadian Disruption and Breast Cancer

- [33] Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 1995 Nov;**87**: 1681-5.
- [34] Stevens RG, Davis S, Thomas DB, Anderson LE, Wilson BW. Electric power, pineal function, and the risk of breast cancer. *FASEB J* 1992 Feb;**6**: 853-60.
- [35] Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *J Biol Rhythms* 2006 Dec;**21**: 482-93.
- [36] Altimus CM, Guler AD, Villa KL, McNeill DS, Legates TA, Hattar S. Rods-cones and melanopsin detect light and dark to modulate sleep independent of image formation. *Proc Natl Acad Sci U S A* 2008 Dec;**105**: 19998-20003.
- [37] Kalsbeek A, Buijs RM. Output pathways of the mammalian suprachiasmatic nucleus: coding circadian time by transmitter selection and specific targeting. *Cell Tissue Res* 2002 Jul;**309**: 109-18.
- [38] Tonsfeldt KJ, Chappell PE. Clocks on top: the role of the circadian clock in the hypothalamic and pituitary regulation of endocrine physiology. *Mol Cell Endocrinol* 2012 Feb;**349**: 3-12.
- [39] Ko CH, Takahashi JS. Molecular components of the mammalian circadian clock. *Hum Mol Genet* 2006 Oct;**15 Spec No 2**: R271-R277.

Sleep and Circadian Disruption and Breast Cancer

- [40] Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature* 2002 Aug;**418**: 935-41.
- [41] Gachon F, Nagoshi E, Brown SA, Ripperger J, Schibler U. The mammalian circadian timing system: from gene expression to physiology. *Chromosoma* 2004 Sep;**113**: 103-12.
- [42] Schibler U, Sassone-Corsi P. A web of circadian pacemakers. *Cell* 2002 Dec;**111**: 919-22.
- [43] Sahar S, Sassone-Corsi P. Circadian clock and breast cancer: a molecular link. *Cell Cycle* 2007 Jun;**6**: 1329-31.
- [44] Panda S, Antoch MP, Miller BH, Su AI, Schook AB, Straume M, *et al.* Coordinated transcription of key pathways in the mouse by the circadian clock. *Cell* 2002 May;**109**: 307-20.
- [45] Lee CC. Tumor suppression by the mammalian Period genes. *Cancer Causes Control* 2006 May;**17**: 525-30.
- [46] Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, *et al.* Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 2003 Mar;**107**: 1129-34.
- [47] Roy PG, Thompson AM. Cyclin D1 and breast cancer. *Breast* 2006 Dec;**15**: 718-27.
- [48] Thapan K, Arendt J, Skene DJ. An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *J Physiol* 2001 Aug;**535**: 261-7.

Sleep and Circadian Disruption and Breast Cancer

- [49] de LL, Carter ME, Adamantidis A. Shining light on wakefulness and arousal. *Biol Psychiatry* 2012 Jun;**71**: 1046-52.
- [50] Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, *et al.* Stability, precision, and near-24-hr period of the human circadian pacemaker. *Science* 1999;**284**: 2181.
- [51] Truong T, Liqueur B, Menegaux F, Plancoulaine S, Laurent-Puig P, Mulot C, *et al.* Breast cancer risk, nightwork, and circadian clock gene polymorphisms. *Endocr Relat Cancer* 2014 Aug;**21**: 629-38.
- [52] Czeisler CA, Allan JS, Strogatz SH, Ronda JM, Sanchez R, Rios CD, *et al.* Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. *Science* 1986;**233**: 667-70.
- [53] Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, *et al.* Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* 2001 Aug;**21**: 6405-12.
- [54] Buman MP, Kline CE, Youngstedt SD, Phillips B, deMello T, Hirshkowitz M. Sitting and television viewing: novel risk factors for sleep disturbances and apnea risk? Results from the 2013 national sleep foundation sleep in America poll. *Chest* 2015 Mar;**147**: 728-34.
- [55] Stehle JH, von GC, Korf HW. Melatonin: a clock-output, a clock-input. *J Neuroendocrinol* 2003 Apr;**15**: 383-9.

Sleep and Circadian Disruption and Breast Cancer

- [56] Slominski RM, Reiter RJ, Schlabritz-Loutsevitch N, Ostrom RS, Slominski AT. Melatonin membrane receptors in peripheral tissues: distribution and functions. *Mol Cell Endocrinol* 2012 Apr;**351**: 152-66.
- [57] Reiter RJ. Action spectra, dose-response relationships, and temporal aspects of light's effects on the pineal gland. *Ann N Y Acad Sci* 1985;**453**: 215-30.
- [58] Glickman G, Levin R, Brainard GC. Ocular input for human melatonin regulation: relevance to breast cancer. *Neuro Endocrinol Lett* 2002 Jul;**23 Suppl 2**: 17-22.
- [59] Gooley JJ, Chamberlain K, Smith KA, Khalsa SB, Rajaratnam SM, Van RE, *et al.* Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *J Clin Endocrinol Metab* 2011 Mar;**96**: E463-E472.
- [60] Chellappa SL, Steiner R, Blattner P, Oelhafen P, Gotz T, Cajochen C. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *PLoS One* 2011;**6**: e16429.
- [61] Bondi CD, Alonso-Gonzalez C, Clafshenkel WP, Kotlarczyk MP, Dodda BR, Sanchez-Barcelo E, *et al.* The effect of estradiol, progesterone, and melatonin on estrous cycling and ovarian aromatase expression in intact female mice. *Eur J Obstet Gynecol Reprod Biol* 2014 Mar;**174**: 80-5.
- [62] Ram PT, Dai J, Yuan L, Dong C, Kiefer TL, Lai L, *et al.* Involvement of the mt1 melatonin receptor in human breast cancer. *Cancer Lett* 2002 May;**179**: 141-50.

Sleep and Circadian Disruption and Breast Cancer

- [63] Shafie SM, Grantham FH. Role of hormones in the growth and regression of human breast cancer cells (MCF-7) transplanted into athymic nude mice. *J Natl Cancer Inst* 1981 Jul;**67**: 51-6.
- [64] Ziegler RG, Fuhrman BJ, Moore SC, Matthews CE. Epidemiologic studies of estrogen metabolism and breast cancer. *Steroids* 2015 Jul;**99**: 67-75.
- [65] Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A, *et al.* Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol* 2013 Sep;**14**: 1009-19.
- [66] Blask DE, Brainard GC, Gibbons R, Lockley SW, Stevens RG, Motta ME. Light Pollution: Adverse Health Effects of Nighttime Lighting. *REPORT 4 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-12)AMERICAN MEDICAL ASSOCIATION* , 1-25. 2012.
- [67] Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, Castano-Vinyals G, Davis S, Frings-Dresen MH, Fritschi L, Kogevinas M, Kogi K, Lie JA, Lowden A, Peplonska B, Pesch B, Pukkala E, Schernhammer E, Travis RC, Vermeulen R, Zheng T, Coglianò V, Straif K. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occupational and environmental medicine*. 2011 Feb; **68**(2): 154-62
- [68] Blask DE. Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev* 2009 Aug;**13**: 257-64.
- [69] Pevet P, Challet E. Melatonin: both master clock output and internal time-giver in the circadian clocks network. *J Physiol Paris* 2011 Dec;**105**: 170-82.

Sleep and Circadian Disruption and Breast Cancer

- [70] Shah PN, Mhatre MC, Kothari LS. Effect of melatonin on mammary carcinogenesis in intact and pinealectomized rats in varying photoperiods. *Cancer Res* 1984 Aug;**44**: 3403-7.
- [71] Chen ST, Choo KB, Hou MF, Yeh KT, Kuo SJ, Chang JG. Deregulated expression of the PER1, PER2 and PER3 genes in breast cancers. *Carcinogenesis* 2005 Jul;**26**: 1241-6.
- [72] Chappell PE, White RS, Mellon PL. Circadian gene expression regulates pulsatile gonadotropin-releasing hormone (GnRH) secretory patterns in the hypothalamic GnRH-secreting GT1-7 cell line. *J Neurosci* 2003 Dec;**23**: 11202-13.
- [73] Miller BH, Olson SL, Turek FW, Levine JE, Horton TH, Takahashi JS. Circadian clock mutation disrupts estrous cyclicity and maintenance of pregnancy. *Curr Biol* 2004 Aug;**14**: 1367-73.
- [74] Boden MJ, Varcoe TJ, Voultsios A, Kennaway DJ. Reproductive biology of female Bmal1 null mice. *Reproduction* 2010 Jun;**139**: 1077-90.
- [75] Ratajczak CK, Boehle KL, Muglia LJ. Impaired steroidogenesis and implantation failure in Bmal1^{-/-} mice. *Endocrinology* 2009 Apr;**150**: 1879-85.
- [76] Christian CA, Mobley JL, Moenter SM. Diurnal and estradiol-dependent changes in gonadotropin-releasing hormone neuron firing activity. *Proc Natl Acad Sci U S A* 2005 Oct;**102**: 15682-7.
- [77] Schwartz WJ, Zimmerman P. Lesions of the suprachiasmatic nucleus disrupt circadian locomotor rhythms in the mouse. *Physiol Behav* 1991 Jun;**49**: 1283-7.

Sleep and Circadian Disruption and Breast Cancer

- [78] Blask DE, Brainard GC, Dauchy RT, Hanifin JP, Davidson LK, Krause JA, *et al.* Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res* 2005 Dec;**65**: 11174-84.
- [79] Schernhammer ES, Hankinson SE. Urinary melatonin levels and postmenopausal breast cancer risk in the Nurses' Health Study cohort. *Cancer Epidemiol Biomarkers Prev* 2009 Jan;**18**: 74-9.
- [80] Schernhammer ES, Hankinson SE. Urinary melatonin levels and breast cancer risk. *J Natl Cancer Inst* 2005 Jul;**97**: 1084-7.
- [81] Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst* 2001 Oct;**93**: 1557-62.
- [82] Basler M, Jetter A, Fink D, Seifert B, Kullak-Ublick GA, Trojan A. Urinary excretion of melatonin and association with breast cancer: meta-analysis and review of the literature. *Breast Care (Basel)* 2014 Jul;**9**: 182-7.
- [83] Li Q, Zheng T, Holford TR, Boyle P, Zhang Y, Dai M. Light at night and breast cancer risk: results from a population-based case-control study in Connecticut, USA. *Cancer Causes Control* 2010 Dec;**21**: 2281-5.
- [84] Kloog I, Portnov BA, Rennert HS, Haim A. Does the modern urbanized sleeping habitat pose a breast cancer risk? *Chronobiol Int* 2011 Feb;**28**: 76-80.

Sleep and Circadian Disruption and Breast Cancer

- [85] Figueiro MG, Bierman A, Rea MS. A train of blue light pulses delivered through closed eyelids suppresses melatonin and phase shifts the human circadian system. *Nat Sci Sleep* 2013;**5**: 133-41.
- [86] Marie HA, Helene GA, Hansen J. Diurnal urinary 6-sulfatoxymelatonin levels among healthy Danish nurses during work and leisure time. *Chronobiol Int* 2006;**23**: 1203-15.
- [87] Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, *et al.* Night work and breast cancer: a population-based case-control study in France (the CECILE study). *Int J Cancer* 2013 Feb;**132**: 924-31.
- [88] Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. *Eur J Cancer* 2012 Jul;**48**: 1722-9.
- [89] Smith P, Fritschi L, Reid A, Mustard C. The relationship between shift work and body mass index among Canadian nurses. *Appl Nurs Res* 2013 Feb;**26**: 24-31.
- [90] Koppes LL, Geuskens GA, Pronk A, Vermeulen RC, de Vroome EM. Night work and breast cancer risk in a general population prospective cohort study in The Netherlands. *Eur J Epidemiol* 2014 Aug;**29**: 577-84.
- [91] Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. Night work and breast cancer risk: A systematic review and meta-analysis. *Eur J Cancer* 2005 Sep;**41**: 2023-32.

Sleep and Circadian Disruption and Breast Cancer

- [92] Jia Y, Lu Y, Wu K, Lin Q, Shen W, Zhu M, *et al.* Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol* 2013 Jun;**37**: 197-206.
- [93] Kamdar BB, Tergas AI, Mateen FJ, Bhayani NH, Oh J. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2013 Feb;**138**: 291-301.
- [94] Wang F, Yeung KL, Chan WC, Kwok CC, Leung SL, Wu C, *et al.* A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. *Ann Oncol* 2013 Nov;**24**: 2724-32.
- [95] Ijaz S, Verbeek J, Seidler A, Lindbohm ML, Ojajarvi A, Orsini N, *et al.* Night-shift work and breast cancer--a systematic review and meta-analysis. *Scand J Work Environ Health* 2013 Sep;**39**: 431-47.
- [96] Yang WS, Deng Q, Fan WY, Wang WY, Wang X. Light exposure at night, sleep duration, melatonin, and breast cancer: a dose-response analysis of observational studies. *Eur J Cancer Prev* 2014 Jul;**23**: 269-76.
- [97] Lin X, Chen W, Wei F, Ying M, Wei W, Xie X. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. *Sleep Med* 2015 Nov;**16**: 1381-7.
- [98] He C, Anand ST, Ebell MH, Vena JE, Robb SW. Circadian disrupting exposures and breast cancer risk: a meta-analysis. *Int Arch Occup Environ Health* 2015 Jul;**88**: 533-47.

Sleep and Circadian Disruption and Breast Cancer

- [99] Travis RC, Balkwill A, Fensom GK, Appleby PN, Reeves GK, Wang XS, Roddam AW, Gathani T, Peto R, Green J, Key TJ, Beral V. Night Shift Work and Breast Cancer Incidence: Three Prospective Studies and Meta-analysis of Published Studies. *Journal of the National Cancer Institute*. 2016 Oct;108: 12.
- [100] Schernhammer ES. RE: Night Shift Work and Breast Cancer Incidence: Three Prospective Studies and Meta-analysis of Published Studies. *Journal of the National Cancer Institute*. 2017 Apr;109: 4.
- [101] Rafnsson V, Tulinius H, Jonasson JG, Hrafnkelsson J. Risk of breast cancer in female flight attendants: a population-based study (Iceland). *Cancer Causes Control* 2001 Feb;12: 95-101.
- [102] Siegel JM. Sleep mechanisms and phylogeny. In: Kryger MH, Roth T, Dement WC (eds). *Principles and Practices of Sleep Medicine*. Fifth ed. St. Louis: Elsevier; 2011.
- [103] Cirelli C, Bushey D. Sleep and wakefulness in *Drosophila melanogaster*. *Ann N Y Acad Sci* 2008;1129: 323-9.
- [104] Hankins MW, Peirson SN, Foster RG. Melanopsin: an exciting photopigment. *Trends Neurosci* 2008 Jan;31: 27-36.
- [105] Moore RY, Lenn NJ. A retinohypothalamic projection in the rat. *J Comp Neurol* 1972 Sep;146: 1-14.

Sleep and Circadian Disruption and Breast Cancer

- [106] Naylor E, Penev PD, Orbeta L, Janssen I, Ortiz R, Colecchia EF, *et al.* Daily social and physical activity increases slow-wave sleep and daytime neuropsychological performance in the elderly. *Sleep* 2000 Feb;**23**: 87-95.
- [107] Wisor JP, O'Hara BF, Terao A, Selby CP, Kilduff TS, Sancar A, *et al.* A role for cryptochromes in sleep regulation. *BMC Neurosci* 2002 Dec;**3**: 20.
- [108] Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, *et al.* Obesity and metabolic syndrome in circadian Clock mutant mice. *Science* 2005 May;**308**: 1043-5.
- [109] Estabrooke IV, McCarthy MT, Ko E, Chou TC, Chemelli RM, Yanagisawa M, *et al.* Fos expression in orexin neurons varies with behavioral state. *J Neurosci* 2001 Mar;**21**: 1656-62.
- [110] Espana RA, Plahn S, Berridge CW. Circadian-dependent and circadian-independent behavioral actions of hypocretin/orexin. *Brain Res* 2002 Jul;**943**: 224-36.
- [111] Ribelayga C, Mangel SC. A circadian clock and light/dark adaptation differentially regulate adenosine in the mammalian retina. *J Neurosci* 2005 Jan;**25**: 215-22.
- [112] Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, *et al.* Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry* 2008 Jan;**63**: 234-40.

Sleep and Circadian Disruption and Breast Cancer

- * [113] Antle MC, Mistlberger RE. Circadian clock resetting by sleep deprivation without exercise in the Syrian hamster. *J Neurosci* 2000 Dec;**20**: 9326-32.

- * [114] Antle MC, Steen NM, Mistlberger RE. Adenosine and caffeine modulate circadian rhythms in the Syrian hamster. *Neuroreport* 2001 Sep;**12**: 2901-5.

- [115] Wisor JP, Pasumarthi RK, Gerashchenko D, Thompson CL, Pathak S, Sancar A, *et al.* Sleep deprivation effects on circadian clock gene expression in the cerebral cortex parallel electroencephalographic differences among mouse strains. *J Neurosci* 2008 Jul;**28**: 7193-201.

- [116] McElroy JA, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, Hampton JM, Egan KM. Duration of sleep and breast cancer risk in a large population-based case-control study. *J Sleep Res* 2006 Sep;**15**: 241-9.

- [117] Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Archives of General Psychiatry* 2002 Feb;**59**: 131-6.

- [118] Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, *et al.* The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer* 2013 Oct;**109**: 2472-80.

- [119] Girschik J, Heyworth J, Fritschi L. Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. *Am J Epidemiol* 2013 Feb;**177**: 316-27.

Sleep and Circadian Disruption and Breast Cancer

- [120] Wu AH, Stanczyk FZ, Wang R, Koh WP, Yuan JM, Yu MC. Sleep duration, spot urinary 6-sulfatoxymelatonin levels and risk of breast cancer among Chinese women in Singapore. *Int J Cancer* 2013 Feb;**132**: 891-6.
- * [121] Wang P, Ren FM, Lin Y, Su FX, Jia WH, Su XF, *et al.* Night-shift work, sleep duration, daytime napping, and breast cancer risk. *Sleep Med* 2015 Apr;**16**: 462-8.
- [122] Kakizaki M, Kuriyama S, Sone T, Ohmori-Matsuda K, Hozawa A, Nakaya N, *et al.* Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study. *Br J Cancer* 2008 Nov;**99**: 1502-5.
- * [123] Verkasalo PK, Lillberg K, Stevens RG, Hublin C, Partinen M, Koskenvuo M, *et al.* Sleep duration and breast cancer: a prospective cohort study. *Cancer Res* 2005 Oct;**65**: 9595-600.
- [124] Wu AH, Wang R, Koh WP, Stanczyk FZ, Lee HP, Yu MC. Sleep duration, melatonin and breast cancer among Chinese women in Singapore. *Carcinogenesis* 2008 Jun;**29**: 1244-8.
- [125] Pinheiro SP, Schernhammer ES, Tworoger SS, Michels KB. A prospective study on habitual duration of sleep and incidence of breast cancer in a large cohort of women. *Cancer Res* 2006 May;**66**: 5521-5.
- [126] Vogtmann E, Levitan EB, Hale L, Shikany JM, Shah NA, Endeshaw Y, *et al.* Association between sleep and breast cancer incidence among postmenopausal women in the Women's Health Initiative. *Sleep* 2013 Oct;**36**: 1437-44.

Sleep and Circadian Disruption and Breast Cancer

- [127] Qian X, Brinton LA, Schairer C, Matthews CE. Sleep duration and breast cancer risk in the Breast Cancer Detection Demonstration Project follow-up cohort. *Br J Cancer* 2015 Feb;**112**: 567-71.
- [128] Cairns BJ, Travis RC, Wang XS, Reeves GK, Green J, Beral V. A short-term increase in cancer risk associated with daytime napping is likely to reflect pre-clinical disease: prospective cohort study. *Br J Cancer* 2012 Jul;**107**: 527-30.
- [129] Lu Y, Tian N, Yin J, Shi Y, Huang Z. Association between sleep duration and cancer risk: a meta-analysis of prospective cohort studies. *PLoS One* 2013;**8**: e74723.
- [130] Pinheiro SP, Schernhammer ES, Tworoger SS, Michels KB. A prospective study on habitual duration of sleep and incidence of breast cancer in a large cohort of women. *Cancer Res* 2006 May;**66**: 5521-5.
- * [131] Qin Y, Zhou Y, Zhang X, Wei X, He J. Sleep duration and breast cancer risk: a meta-analysis of observational studies. *Int J Cancer* 2014 Mar;**134**: 1166-73.
- [132] Girschik J, Heyworth J, Fritschi L. Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. *Am J Epidemiol* 2013 Feb;**177**: 316-27.
- [133] Kakizaki M, Kuriyama S, Sone T, Ohmori-Matsuda K, Hozawa A, Nakaya N, *et al.* Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study. *Br J Cancer* 2008 Nov;**99**: 1502-5.

Sleep and Circadian Disruption and Breast Cancer

- [134] Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. *J Mol Med (Berl)* 1996 Jun;**74**: 297-312.
- [135] Abedin MJ, Wang D, McDonnell MA, Lehmann U, Kelekar A. Autophagy delays apoptotic death in breast cancer cells following DNA damage. *Cell Death Differ* 2007 Mar;**14**: 500-10.
- [136] Herberman RB, Ortaldo JR. Natural killer cells: their roles in defenses against disease. *Science* 1981;**214**: 24-30.
- [137] Ozbun MA, Butel JS. Tumor suppressor p53 mutations and breast cancer: a critical analysis. *Adv Cancer Res* 1995;**66**: 71-141.
- [138] Raulet DH, Guerra N. Oncogenic stress sensed by the immune system: role of natural killer cell receptors. *Nat Rev Immunol* 2009 Aug;**9**: 568-80.
- [139] Pike MC, Spicer DV, Dahmouch L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev* 1993;**15**: 17-35.
- [140] Pietras RJ, Arboleda J, Reese DM, Wongvipat N, Pegram MD, Ramos L, *et al.* HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene* 1995 Jun;**10**: 2435-46.
- [141] Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. *Journal of Immunology* 1997 May;**158**: 4454-64.

Sleep and Circadian Disruption and Breast Cancer

- [142] Irwin M, Mascovich A, Gillin JC, Willoughby R, Pike J, Smith TL. Partial sleep deprivation reduces natural killer cell activity in humans. *Psychosomatic Medicine* 1994 Nov;**56**: 493-8.
- [143] Dimitrov S, Lange T, Tieken S, Fehm HL, Born J. Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. *Brain Behav Immun* 2004 Jul;**18**: 341-8.
- [144] Marincola FM, Jaffee EM, Hicklin DJ, Ferrone S. Escape of human solid tumors from T-cell recognition: molecular mechanisms and functional significance. *Adv Immunol* 2000;**74**: 181-273.
- [145] Langsenlehner U, Krippel P, Renner W, Yazdani-Biuki B, Eder T, Koppel H, *et al.* Interleukin-10 promoter polymorphism is associated with decreased breast cancer risk. *Breast Cancer Res Treat* 2005 Mar;**90**: 113-5.
- [146] Dimitrov S, Lange T, Nohroudi K, Born J. Number and function of circulating human antigen presenting cells regulated by sleep. *Sleep* 2007 Apr;**30**: 401-11.
- [147] Boggio K, Nicoletti G, Di CE, Cavallo F, Landuzzi L, Melani C, *et al.* Interleukin 12-mediated prevention of spontaneous mammary adenocarcinomas in two lines of Her-2/neu transgenic mice. *J Exp Med* 1998 Aug;**188**: 589-96.
- * [148] Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry* 2015 Jun.

Sleep and Circadian Disruption and Breast Cancer

- [149] Castanon-Cervantes O, Wu M, Ehlen JC, Paul K, Gamble KL, Johnson RL, *et al.* Dysregulation of inflammatory responses by chronic circadian disruption. *J Immunol* 2010 Nov;**185**: 5796-805.

- [150] Garcia-Maurino S, Pozo D, Calvo JR, Guerrero JM. Correlation between nuclear melatonin receptor expression and enhanced cytokine production in human lymphocytic and monocytic cell lines. *J Pineal Res* 2000 Oct;**29**: 129-37.

- [151] Carrillo-Vico A, Calvo JR, Abreu P, Lardone PJ, Garcia-Maurino S, Reiter RJ, *et al.* Evidence of melatonin synthesis by human lymphocytes and its physiological significance: possible role as intracrine, autocrine, and/or paracrine substance. *FASEB J* 2004 Mar;**18**: 537-9.

- [152] Carrillo-Vico A, Reiter RJ, Lardone PJ, Herrera JL, Fernandez-Montesinos R, Guerrero JM, *et al.* The modulatory role of melatonin on immune responsiveness. *Curr Opin Investig Drugs* 2006 May;**7**: 423-31.

- [153] Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer Res* 2012 Mar;**18**: 1201-6.

- [154] Spath-Schwalbe E, Scholler T, Kern W, Fehm HL, Born J. Nocturnal adrenocorticotropin and cortisol secretion depends on sleep duration and decreases in association with spontaneous awakening in the morning. *J Clin Endocrinol Metab* 1992 Dec;**75**: 1431-5.

- [155] Spath-Schwalbe E, Gofferje M, Kern W, Born J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. *Biol Psychiatry* 1991;**29**: 575-84.

Sleep and Circadian Disruption and Breast Cancer

- [156] Miller MA, Kandala NB, Kivimaki M, Kumari M, Brunner EJ, Lowe GD, *et al.* Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. *Sleep* 2009 Jul;**32**: 857-64.

- [157] Koyanagi S, Suyama H, Kuramoto Y, Matsunaga N, Takane H, Soeda S, *et al.* Glucocorticoid regulation of 24-hour oscillation in interferon receptor gene expression in mouse liver. *Endocrinology* 2006 Nov;**147**: 5034-40.

- [158] Liu RY, Unmehopa UA, Zhou JN, Swaab DF. Glucocorticoids suppress vasopressin gene expression in human suprachiasmatic nucleus. *J Steroid Biochem Mol Biol* 2006 Mar;**98**: 248-53.

- [159] Kang DH. Oxidative stress, DNA damage, and breast cancer. *AACN Clin Issues* 2002 Nov;**13**: 540-9.

- [160] Nakata A, Ikeda T, Takahashi M, Haratani T, Fujioka Y, Fukui S, *et al.* Sleep-related risk of occupational injuries in Japanese small and medium-scale enterprises. *Ind Health* 2005 Jan;**43**: 89-97.

- [161] Inoue S, Honda K, Komoda Y. Sleep as neuronal detoxification and restitution. *Behav Brain Res* 1995 Jul;**69**: 91-6.

- [162] Ramanathan L, Gulyani S, Nienhuis R, Siegel JM. Sleep deprivation decreases superoxide dismutase activity in rat hippocampus and brainstem. *Neuroreport* 2002 Aug;**13**: 1387-90.

Sleep and Circadian Disruption and Breast Cancer

- [163] Silva RH, Abilio VC, Takatsu AL, Kameda SR, Grassl C, Chehin AB, *et al.* Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice. *Neuropharmacology* 2004 May;**46**: 895-903.
- [164] Nair D, Zhang SX, Ramesh V, Hakim F, Kaushal N, Wang Y, *et al.* Sleep fragmentation induces cognitive deficits via nicotinamide adenine dinucleotide phosphate oxidase-dependent pathways in mouse. *Am J Respir Crit Care Med* 2011 Dec;**184**: 1305-12.
- [165] Boonstra J, Post JA. Molecular events associated with reactive oxygen species and cell cycle progression in mammalian cells. *Gene* 2004 Aug;**337**: 1-13.
- * [166] Oklejewicz M, Destici E, Tamanini F, Hut RA, Janssens R, van Der Horst GT. Phase resetting of the mammalian circadian clock by DNA damage. *Curr Biol* 2008 Feb;**18**: 286-91.
- [167] Buttke TM, Sandstrom PA. Oxidative stress as a mediator of apoptosis. *Immunol Today* 1994 Jan;**15**: 7-10.
- [168] Gery S, Komatsu N, Baldjyan L, Yu A, Koo D, Koeffler HP. The circadian gene *per1* plays an important role in cell growth and DNA damage control in human cancer cells. *Mol Cell* 2006 May;**22**: 375-82.
- [169] Fu L, Pelicano H, Liu J, Huang P, Lee C. The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response in vivo. *Cell* 2002 Oct;**111**: 41-50.

Sleep and Circadian Disruption and Breast Cancer

- [170] Zhu Y, McAvoy S, Kuhn R, Smith DI. RORA, a large common fragile site gene, is involved in cellular stress response. *Oncogene* 2006 May;**25**: 2901-8.
- [171] Chauvet C, Bois-Joyeux B, Berra E, Pouyssegur J, Danan JL. The gene encoding human retinoic acid-receptor-related orphan receptor alpha is a target for hypoxia-inducible factor 1. *Biochem J* 2004 Nov;**384**: 79-85.
- [172] Hardeland R, Reiter RJ, Poeggeler B, Tan DX. The significance of the metabolism of the neurohormone melatonin: antioxidative protection and formation of bioactive substances. *Neurosci Biobehav Rev* 1993;**17**: 347-57.
- [173] Reiter RJ. Interactions of the pineal hormone melatonin with oxygen-centered free radicals: a brief review. *Braz J Med Biol Res* 1993 Nov;**26**: 1141-55.
- [174] Poeggeler B, Reiter RJ, Tan DX, Chen LD, Manchester LC. Melatonin, hydroxyl radical-mediated oxidative damage, and aging: a hypothesis. *J Pineal Res* 1993 May;**14**: 151-68.
- [175] Blask DE, Wilson ST, Zalatan F. Physiological melatonin inhibition of human breast cancer cell growth in vitro: evidence for a glutathione-mediated pathway. *Cancer Res* 1997 May;**57**: 1909-14.
- [176] Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B. Melatonin inhibition and pinealectomy enhancement of 7,12-dimethylbenz(a)anthracene-induced mammary tumors in the rat. *Cancer Res* 1981 Nov;**41**: 4432-6.

Sleep and Circadian Disruption and Breast Cancer

- [177] Medina D. The mammary gland: a unique organ for the study of development and tumorigenesis. *J Mammary Gland Biol Neoplasia* 1996 Jan;**1**: 5-19.
- [178] Vinogradova IA, Anisimov VN, Bukalev AV, Semenchenko AV, Zabezhinski MA. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats. *Aging (Albany NY)* 2009 Oct;**1**: 855-65.
- [179] Ird EA. [The effect of experimental hypothyroidism on the development of mastopathia and tumors of the mammary gland in rats]. *Probl Endokrinol Gormonoter* 1966 Jan;**12**: 99-102.
- [180] Anisimov VN. [Blastomogenesis in rats with persistent estrus]. *Vopr Onkol* 1971;**17**: 67-75.
- [181] Blask DE, Hill SM, Orstead KM, Massa JS. Inhibitory effects of the pineal hormone melatonin and underfeeding during the promotional phase of 7,12-dimethylbenzanthracene-(DMBA)-induced mammary tumorigenesis. *J Neural Transm* 1986;**67**: 125-38.
- [182] Lazarev NI, Ird EA, Smirnova IO. Experimental models of endocrine gynecological diseases. *Moscow, Meditsina* 1976.
- [183] Anisimov VN. The role of pineal gland in breast cancer development. *Crit Rev Oncol Hematol* 2003 Jun;**46**: 221-34.
- [184] Blask DE, Dauchy RT, Sauer LA. Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal. *Endocrine* 2005 Jul;**27**: 179-88.

Sleep and Circadian Disruption and Breast Cancer

- [185] Zock PL, Katan MB. Linoleic acid intake and cancer risk: a review and meta-analysis. *Am J Clin Nutr* 1998 Jul;**68**: 142-53.
- [186] Adami HO, Signorello LB, Trichopoulos D. Towards an understanding of breast cancer etiology. *Semin Cancer Biol* 1998 Aug;**8**: 255-62.
- [187] Cos S, Gonzalez A, Martinez-Campa C, Mediavilla MD, Alonso-Gonzalez C, Sanchez-Barcelo EJ. Estrogen-signaling pathway: a link between breast cancer and melatonin oncostatic actions. *Cancer Detect Prev* 2006;**30**: 118-28.
- [188] Molis TM, Spriggs LL, Hill SM. Modulation of estrogen receptor mRNA expression by melatonin in MCF-7 human breast cancer cells. *Mol Endocrinol* 1994 Dec;**8**: 1681-90.
- [189] Cos S, Blask DE. Melatonin modulates growth factor activity in MCF-7 human breast cancer cells. *J Pineal Res* 1994 Aug;**17**: 25-32.
- [190] Brooks SC, Locke ER, Soule HD. Estrogen receptor in a human cell line (MCF-7) from breast carcinoma. *J Biol Chem* 1973 Sep;**248**: 6251-3.
- [191] Mediavilla MD, Cos S, Sanchez-Barcelo EJ. Melatonin increases p53 and p21WAF1 expression in MCF-7 human breast cancer cells in vitro. *Life Sci* 1999;**65**: 415-20.
- [192] Cos S, Recio J, Sanchez-Barcelo EJ. Modulation of the length of the cell cycle time of MCF-7 human breast cancer cells by melatonin. *Life Sci* 1996;**58**: 811-6.

Sleep and Circadian Disruption and Breast Cancer

- [193] Lippman M, Bolan G, Huff K. The effects of estrogens and antiestrogens on hormone-responsive human breast cancer in long-term tissue culture. *Cancer Res* 1976 Dec;**36**: 4595-601.
- [194] Antunes IB, Andersen ML, Baracat EC, Tufik S. The effects of paradoxical sleep deprivation on estrous cycles of the female rats. *Horm Behav* 2006 Apr;**49**: 433-40.
- [195] Machado RB, Tufik S, Suchecki D. Chronic stress during paradoxical sleep deprivation increases paradoxical sleep rebound: association with prolactin plasma levels and brain serotonin content. *Psychoneuroendocrinology* 2008 Oct;**33**: 1211-24.
- [196] Baumgartner A, Dietzel M, Saletu B, Wolf R, Campos-Barros A, Graf KJ, *et al*. Influence of partial sleep deprivation on the secretion of thyrotropin, thyroid hormones, growth hormone, prolactin, luteinizing hormone, follicle stimulating hormone, and estradiol in healthy young women. *Psychiatry Res* 1993 Aug;**48**: 153-78.
- [197] von TK, Norman TR, Armstrong SM. Overnight human plasma melatonin, cortisol, prolactin, TSH, under conditions of normal sleep, sleep deprivation, and sleep recovery. *J Pineal Res* 1996 Jan;**20**: 7-14.
- [198] Wang TT, Phang JM. Effects of estrogen on apoptotic pathways in human breast cancer cell line MCF-7. *Cancer Res* 1995 Jun;**55**: 2487-9.

Sleep and Circadian Disruption and Breast Cancer

- [199] Nagata C, Nagao Y, Yamamoto S, Shibuya C, Kashiki Y, Shimizu H. Light exposure at night, urinary 6-sulfatoxymelatonin, and serum estrogens and androgens in postmenopausal Japanese women. *Cancer Epidemiol Biomarkers Prev* 2008 Jun;**17**: 1418-23.
- [200] Fischer SM, Conti CJ, Locniskar M, Belury MA, Maldve RE, Lee ML, *et al*. The effect of dietary fat on the rapid development of mammary tumors induced by 7,12-dimethylbenz(a)anthracene in SENCAR mice. *Cancer Res* 1992 Feb;**52**: 662-6.
- [201] Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A* 2009 Mar;**106**: 4453-8.
- [202] Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med* 2004 Dec;**1**: e62.
- [203] Chaput JP, Despres JP, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: Results from the Quebec family study. *Obesity (Silver Spring)* 2007 Jan;**15**: 253-61.
- [204] Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, *et al*. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep* 2008 May;**31**: 619-26.

Sleep and Circadian Disruption and Breast Cancer

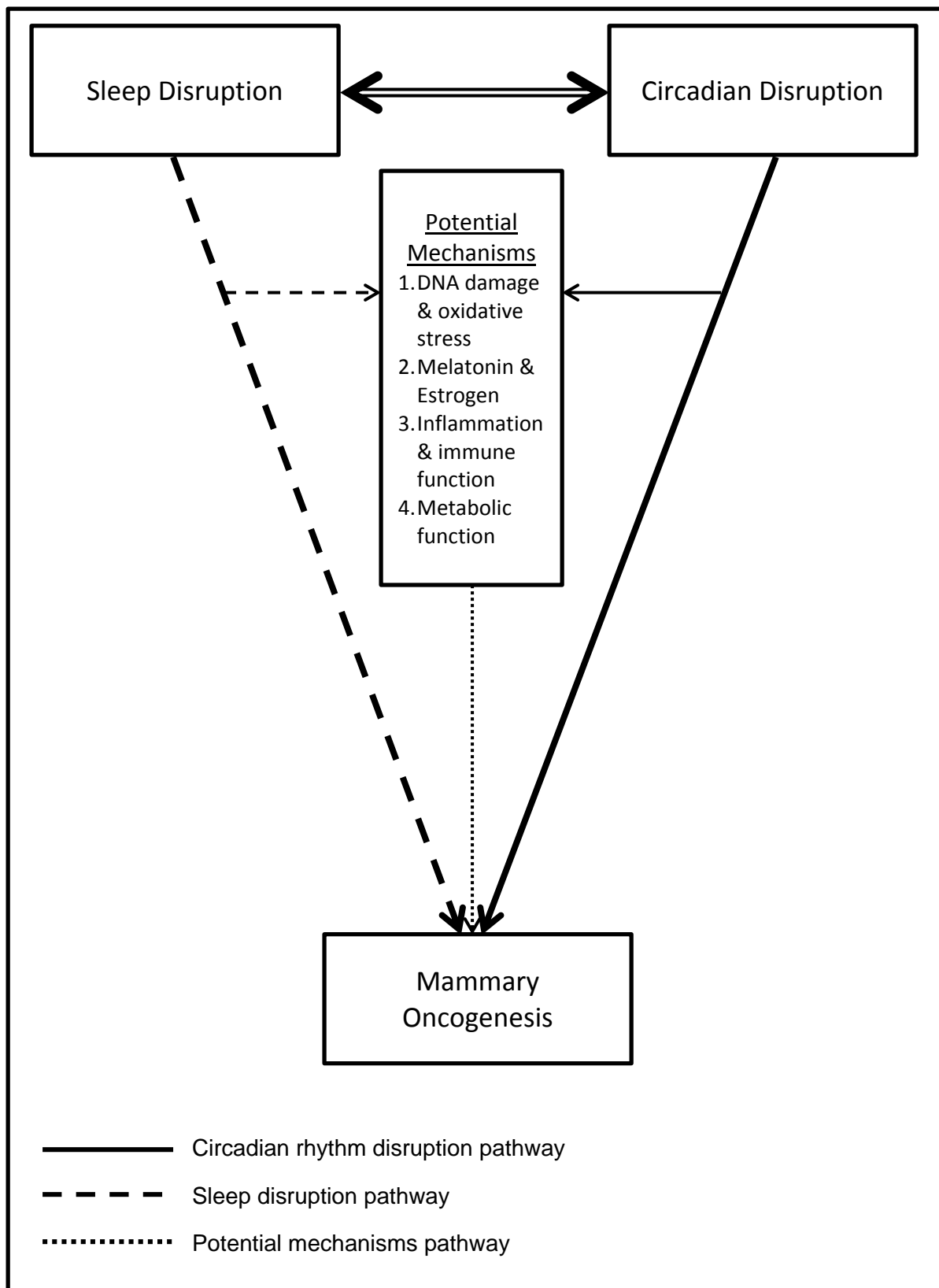


Figure 1. Biopsychosocial Model of Circadian and Sleep Disruption and Mammary Oncogenesis

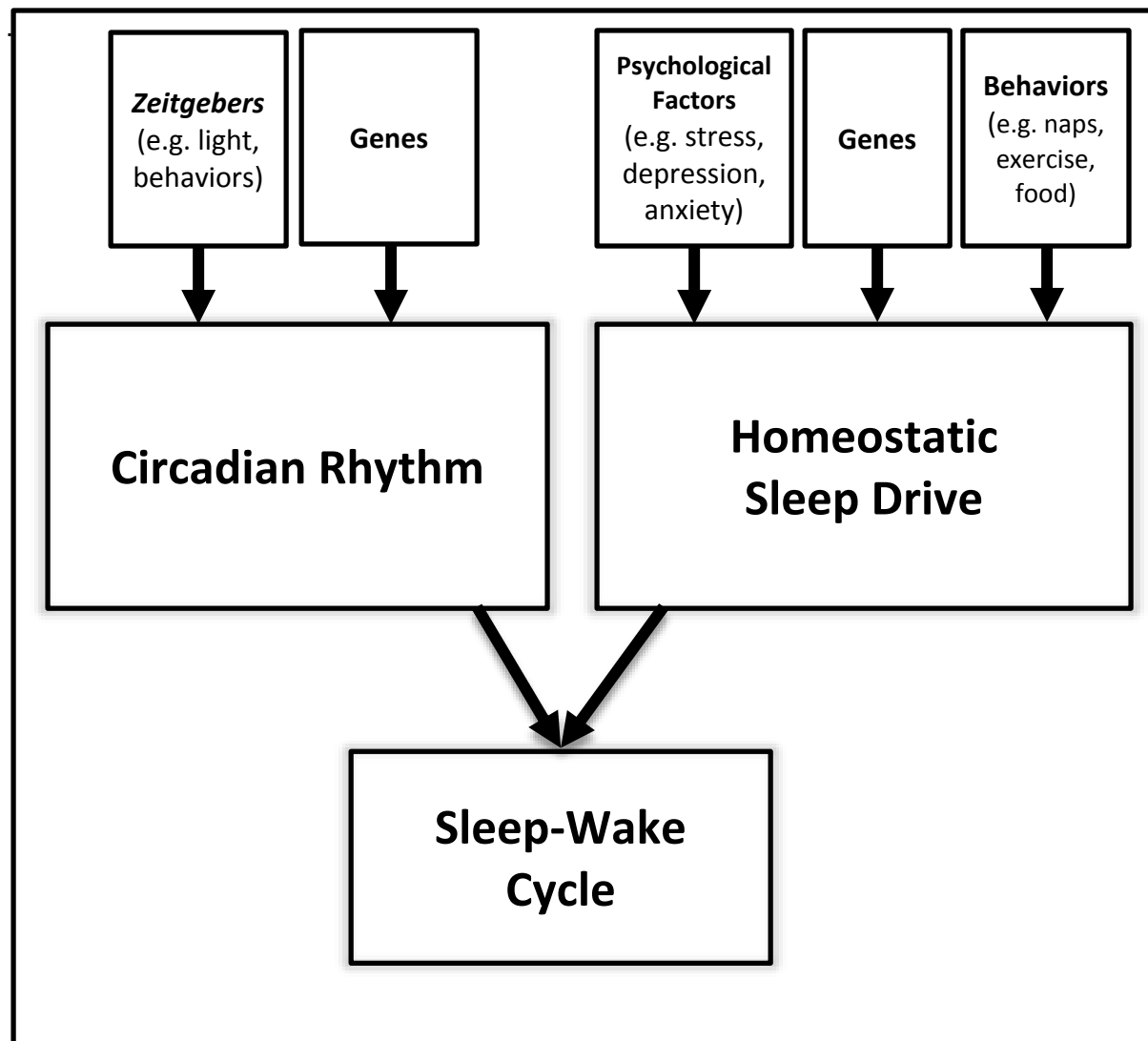


Figure 2. Two-Process Model of Sleep-Wake Cycle Regulation.