CLINICAL REVIEW

Melatonin, sleep disturbance and cancer risk

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SUMMARY

The pineal hormone melatonin is involved in the circadian regulation and facilitation of sleep, the inhibition of cancer development and growth, and the enhancement of immune function. Individuals, such as night shift workers, who are exposed to light at night on a regular basis experience biological rhythm (i.e., circadian) disruption including circadian phase shifts, nocturnal melatonin suppression, and sleep disturbances. Additionally, these individuals are not only immune suppressed, but they are also at an increased risk of developing a number of different types of cancer. There is a reciprocal interaction and regulation between sleep and the immune system quite independent of melatonin. Sleep disturbances can lead to immune suppression and a shift to the predominance in cancer-stimulatory cytokines. Some studies suggest that a shortened duration of nocturnal sleep is associated with a higher risk of breast cancer development. The relative individual contributions of sleep disturbance, circadian disruption due to light at night exposure, and related impairments of melatonin production and immune function to the initiation and promotion of cancer in high-risk individuals such as night shift workers are unknown. The mutual reinforcement of interacting circadian rhythms of melatonin production, the sleep/wake cycle and immune function may indicate a new role for undisturbed, high quality sleep, and perhaps even more importantly, uninterrupted darkness, as a previously unappreciated endogenous mechanism of cancer prevention.

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Introduction

Remarkably little is known about the actual purpose(s) of sleep even though roughly one-third of our existence on planet earth is spent asleep, primarily during the night. The 24-h sleep/wake cycle in humans is probably the most obvious manifestation of our inherent biological rhythmicity and time-keeping mechanisms.[1] Humans have evolved over millions of years such that endogenously generated daily oscillations in our physiology, metabolism and behavior are synchronized to the solar day.[2] Prior to the industrial age, humans were exposed to bright, full spectrum sunlight during the day and to complete darkness during the night (firelight, candle light, oil lamp light, gas light, moonlight and star light notwithstanding). Since the advent of electric light just a little over a 120 years ago, human daily exposure to healthful natural light and darkness has been largely compromised such that in fast-paced "24/7" westernized societies, our evolutionary heritage of bright days and dark nights has been flipped like a light switch.[3–5] Now, daytime exposure to dim indoor lighting and nighttime exposure to bright lights are increasingly the rule at home, at work and in places of leisure and entertainment. As an unforeseen consequence of these societal changes, disturbances in sleep manifested primarily as sleep deprivation and accompanying disruptions in circadian synchronization have been linked to the development of cardiovascular and gastrointestinal diseases as well as metabolic disorders such as insulin resistance, type II diabetes and obesity.[6,7] More recently, however, studies reveal that unadapted night shift workers exposed to light at night experience circadian dysregulation, including phase shifts and suppression of the chronobiotic/anticancer hormone melatonin,[a] in addition to sleep disturbances. In fact, both night and early morning shift workers sleep two or more hours less than day shift workers with accompanying reductions in sleep efficiency and quality.[8–11] In epidemiological studies it has been reported that both female and male night shift workers are at a significantly increased risk of developing a number of different malignancies including breast,[12–15] colon,[16] prostate[17] and endometrial cancer.[18] There are currently no experimental model systems that can directly address the hypothesis that sleep disturbance by itself promotes the development and growth of cancer. Therefore, this article will focus on current experimental and epidemiological evidence that indirectly supports a link between light at night-induced disturbances in physiological melatonin production, circadian/homeostatic sleep regulation and immune function and cancer.

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a See definition in the Glossary.

Nomenclature

		cAMP	cyclic adenosine monophosphate
		ERα	estrogen receptor alpha
SCN	suprachiasmatic nucleus	DNA	deoxyribonucleic acid
LA	linoleic acid	IL	interleukin
13-HODE	13-Hydroxyoctadecadienoic acid	INFα	interferon alpha
EGFR	epidermal growth factor receptor	TNFα	tumor necrosis factor alpha
MAPK	mitogen-activated protein kinase	NK	natural killer

Melatonin production, physiology and pathophysiology

Derived from the essential amino acid tryptophan, melatonin is an indoleamine[a] molecule that is found widely throughout nature. Melatonin is synthesized and immediately secreted into the blood vascular system and cerebrospinal fluid by the pineal gland[a] during the night whereas the daytime production of melatonin is virtually nil. The surge of melatonin during dark nights represents a biological timing signal that is internally driven by the activity of a central pacemaker in the suprachiasmatic nuclei[a] (SCN) of the anterior hypothalamus.[19,20] The nocturnal rhythm of melatonin production persists even in the absence of an alternating light/dark cue as a free-running circadian rhythm.[a] The nocturnal melatonin signal provides time of day information to all the cells, tissues and organs of the body and is the most stable and reliable peripheral biomarker of the timing of the central biological clock.[a] Since the duration of the melatonin surge defines the length of the biological night, the pineal gland not only acts as a clock but also as a calendar by providing an organism with information about seasonal changes in day length.[19,20] Melatonin is often referred to as the chemical expression or hormone of darkness.[21] At either physiological or pharmacological concentrations, melatonin appears to be involved in far-flung physiological and pathophysiological processes including the control of sleep, circadian rhythms, retinal physiology, seasonal reproductive cycles, cancer development and growth, immune activity, antioxidation and free radical scavenging, mitochondrial respiration, cardiovascular function, bone metabolism, intermediary metabolism and gastrointestinal physiology.[19–22]

The central circadian pacemaker or master biological clock is located in the hypothalamus and is composed of a specialized group of neurons in the SCN. The endogenous activity of this internal clock drives the complex molecular mechanisms responsible for the production of melatonin at night. In addition to the nocturnal rhythm of melatonin production, the central circadian pacemaker regulates other daily rhythms such as the sleep/wake cycle, body temperature, secretory patterns of hormones, food consumption and metabolism. The circadian timing system facilitates an organism's adaptation to changes in its environment via the temporal coordination of these and other physiological functions; the rhythmic output of melatonin every night plays a pivotal role in this biological timing mechanism.[23]

Photic signals reaching the retina of eye play an essential role in synchronizing this dynamic process. Light entering the eyes stimulates specialized photoreceptors in the retina from which neural signals are then sent not only to the primary visual system but also to non-visual centers of the brain, most particularly the SCN. During the day, light input to the SCN resets the central circadian pacemaker and thus synchronizes internal near 24-h rhythms, including the melatonin rhythm, precisely to the environmental 24-h light/dark cycle.[23] When an organism experiences a change in the timing of the ambient light/dark cycle, the central circadian pacemaker responds appropriately by advancing or delaying its own timing referred to as a phase shift. Therefore, changes in an individual's exposure to light and darkness can induce changes in the phasing of the melatonin rhythm and other circadian rhythms as are experienced during shift work, transcontinental jet travel, space flight. However, light present during darkness, provided that it is bright enough and of the proper wavelength, is detrimental to the circadian system and immediately turns off melatonin production. Although light is the most potent stimulus to the mechanisms governing internal time-keeping, much more light is actually required for circadian regulation than for vision.[23]

Following its synthesis, melatonin is immediately secreted from the pineal directly into both the bloodstream and cerebrospinal fluid of the third ventricle. The amount of melatonin produced during the night varies considerably from one individual to another and this appears to be genetically determined. The amount of melatonin produced during the night appears to be greatest around the time just before puberty with a steady decrease thereafter through middle and old age. Once it is released into the circulation, melatonin has a short half-life and it is primarily metabolized in the liver where it is converted by cytochrome P_{450} enzymes to its main metabolite, 6-sulfatoxymelatonin[a] that is excreted in the urine. Melatonin is also metabolized in a number of extrahepatic tissues, most notably the brain, by both enzymatic and non-enzymatic mechanisms.[20–22] Although the pineal gland is the primary source of melatonin release into the systemic circulation, there are a number of extrapineal sources of melatonin synthesis including the retina, gastrointestinal tract, bone marrow, circulating lymphocytes, blood platelets and skin; melatonin appears to exert a local action at these sites of production. Because of its unique molecular properties, melatonin has the capacity to pass in and out of all cellular and fluid compartments of the body with ease. In fact, the concentrations of melatonin detected in cells and tissues are orders of magnitude higher than those present in the blood circulation, indicating significant cellular/tissue uptake and storage of this molecule.[20–22] Melatonin in other body fluids such as saliva, urine, ovarian follicular fluid, breast milk and semen also exhibits a nocturnal rhythm. Due to its ability to not only produce but also take-up and store melatonin, the gastrointestinal tract contains amounts of melatonin that far exceed the levels present in the pineal gland. Bile from the liver and gall bladder contains levels of melatonin that greatly exceed those in the general blood circulation.[20–22]

Physiological or pharmacological concentrations of melatonin exert an important regulatory influence over a broad range of physiological and pathophysiological processes in both lower animals and humans. Although current knowledge of the mechanisms by which melatonin modulates these diverse processes is incomplete, specific plasma membrane-associated melatonin receptors[a] play a major role in mediating several of melatonin's actions at the cellular level. Melatonin receptors are expressed in diverse areas of the brain including the SCN as well as in several peripheral organs and tissues. Some physiological and pathophysiological situations may involve nuclear melatonin receptors whereas in other biological contexts no specific receptors appear to be required for melatonin's actions.[20–22,24,25]

Melatonin receptors mediate melatonin's ability to induce phase shifts in the firing of neurons comprising the suprachiasmatic nuclei. This action lies at the heart of melatonin's chronobiotic action, namely its ability to cause phase shifts in overt circadian

rhythms such as locomotor activity. Thus, an internal cue provided by the endogenous melatonin signal from the pineal coupled with an external cue provided by light that ultimately synchronizes the central circadian pacemaker to the 24-h period of the rest/activity cycle. Physiological nocturnal melatonin concentrations appear to facilitate sleep and may accomplish this by suppressing the circadian wakefulness-generating program through a melatonin receptor-mediated mechanism (see below). In the retina, locally synthesized melatonin, acting via melatonin receptors, is responsible for modulating certain aspects of retinal physiology.[20–22,24,25]

Other physiological and pathophysiological responses modulated by melatonin via melatonin receptor-mediated mechanisms include pituitary hormone release, testosterone production by the testes, cortisol secretion by the adrenal cortex, vascular tone, energy metabolism, fatty acid transport, immune activity, and cancer cell proliferation and tumor growth. Actions of melatonin that appear to involve nuclear receptors include stimulation of immune cells to produce biologically active substances called interleukins as well as inhibition of the proliferation of certain types of colon cancer cells.[20–22,24,25]

Melatonin and sleep

The coincidence of pineal melatonin production and the occurrence of sleep during the night indicate an important relationship between the two processes. The fact that sleep propensity during the night increases in concordance with the evening increase in blood levels of melatonin implies but does not prove the existence of a causal link.[26,27] While the occurrence of sleep is not necessary for the nocturnal production of melatonin, the presence of darkness during the night is an absolute requirement. For example, sleep deprivation in and of itself does not extinguish the nocturnal, circadian production and secretion of melatonin.[26] During sleep deprivation at night, regardless of its cause, as long as an individual is exposed to total darkness, the integrity of the nocturnal, circadian melatonin signal should remain intact. Interestingly, during sleep deprivation, fatigue actually exhibits a circadian rhythm that closely tracks the melatonin rhythm.[26]

Studies in humans under constant routine conditions have led to the definition of the so-called "biological night" that corresponds to the period during which melatonin is produced and secreted into the bloodstream. The beginning of this biological night is thus characterized by onset of the melatonin surge, an accompanying increase in sleep propensity as well as a decrease in core body temperature; the opposite occurs as the biological night and sleep end. Rising nocturnal titers of endogenous melatonin are believed to contribute significantly to the nocturnal decline in core body temperature.[26]

The inability to fall asleep during the "wake maintenance zone",[28] also called the "forbidden zone", occurs just prior to the opening of the "sleep gate".[29,30] The sleep gate is represented by the steep rise in sleepiness that occurs during the late evening that begins a period characterized by a consistently high degree of sleep propensity. The nocturnal onset of melatonin secretion predictably precedes the opening of the sleep gate by about 2 h and therefore is phase-locked to this event.[30] The onset of nocturnal melatonin release is believed by some to initiate a cascade of events culminating 1–2 h later in the opening of the sleep gate.[31] Taken together, current findings suggest that the endogenous nocturnal circadian melatonin signal is involved in the circadian rhythm of sleep propensity by turning off the circadian wakefulness-generating mechanism rather than by actively inducing sleep. In this way, the onset of melatonin secretion during the night may ensure a smooth transition between wakefulness and sleep.[31]

During sleep, the timing of sleep spindles and other electroencephalographic changes appear to correlate with the circadian melatonin rhythm.[32] Under controlled sleep laboratory conditions of constant dim light, it has been demonstrated that in a cohort of healthy habitual "long sleepers" (i.e., sleep duration > 9 h per night) versus healthy habitual "short sleepers" (i.e., sleep duration < 6 h per night), the nocturnal duration of elevated blood levels of melatonin was approximately 1 h longer while the nocturnal duration of cortisol levels was extended by 2.5 h.[33] Moreover, it was documented that switching human subjects from an 8-h night to a 14-h night was not only associated with an extension in the duration of nocturnally elevated melatonin levels but also with an increase in sleep duration from 7.3 h to 8.4 h, respectively.[34] In fact, under the conditions of a 14-h dark night, subjects initially slept for 4 h, actually woke from this first sleep and experienced a period (1–3 h) of "quiet wakefulness" followed by a lighter second sleep period of about 4 h consisting of less stage 4 (deep) and more rapid eye movement sleep.[35,36] Interestingly, this sleep pattern is apparently similar to that commonly experienced by individuals living in the preindustrial era prior to the advent of artificial light at night.[37]

Melatonin and cancer

In experimental rat models of chemical carcinogenesis the physiological melatonin signal suppresses the initiation phase of tumorigenesis. One mechanism by which this may be accomplished is via melatonin's ability to suppress the accumulation of DNA adducts (the resulting complex when chemicals bind to DNA) formed by carcinogens that cause damage to and permanent alterations in DNA (i.e., mutations and amplifications), which lead to neoplastic transformation. This may be accomplished directly via melatonin's ability to act as a potent free radical scavenger and/or through its indirect actions to detoxify carcinogens via activation of the glutathione and related antioxidative pathways. In addition to protecting cells from DNA damage, melatonin might also promote the repair of DNA once damage has occurred.[38–40]

In experimental models of neoplasia, melatonin, at nocturnal circulating concentrations, inhibits the proliferation of human cancer cell lines in vitro. This is achieved by delaying the progression of cells through a specific phase of the cell cycle. In some neoplastic cells, this indoleamine acts as a differentiating agent and diminishes their invasive/metastatic potential via alterations in adhesion molecule expression and the support of mechanisms responsible for gap junctional intercellular communication. Additional evidence supports a variety of other biochemical and molecular mechanisms of melatonin's oncostatic action at nocturnal circulating concentrations including the regulation of estrogen receptor (ERα) expression and transactivation, calcium/calmodulin activity, protein kinase C activity, cytoskeletal architecture and function, intracellular redox status, melatonin receptor-mediated signal transduction cascades, aromatase and telomerase activities, and fatty acid transport and metabolism.[38–40]

A major component of physiological melatonin's oncostatic action involves the regulation of the tumor uptake and metabolism of linoleic acid (LA),[a] an essential omega-6 polyunsaturated fatty acid. As the most prevalent polyunsaturated fatty acid in the Western diet, LA levels greatly exceed those required to prevent essential fatty acid deficiency (i.e., 1% of total calories).[41] As a potent promoter of both murine and human tumorigenesis, LA exerts actions on cancer cells that are diametrically opposed to many of the oncostatic actions of melatonin listed above. Its oncogenic effects, particularly on human breast cancer cells, are related to its ability to upregulate the expression of genes involved in estrogen receptor ERα expression, cell cycle progression, G-protein signaling, and the mitogen-activated protein kinase (MAPK) growth cascade.[39] In tissue-isolated ERα (+ and −), and human breast cancer xenografts, melatonin acts via melatonin receptors to suppress tumor cAMP formation leading to a suppression of LA uptake and its metabolism

to the mitogenic signaling molecule 13-hydroxyoctadecadienoic acid (13-HODE)[a]. Down-regulation of LA uptake and metabolism reduces the activation of the epidermal growth factor receptor (EGFR)/MAPK pathway, culminating in tumor growth inhibition.[39,40] The fact that LA up-regulates[40] whereas melatonin down-regulates transcriptional regulation of ERα in human breast cancer cells via a melatonin receptor-mediated inhibition of cAMP in these cells[42] would potentially provide ample opportunity for cross-talk among these pathways. Like rat hepatomas, human breast cancer xenografts exhibit a day–night rhythm of tumor proliferative activity, LA uptake, and metabolism and signal transduction activity that is driven by the nocturnal, circadian melatonin signal.[38,40,43]

Light at night, melatonin suppression and cancer risk

The risk of developing breast cancer is up to five times higher in industrialized nations than in underdeveloped countries. Overall, nearly 50% of breast cancers cannot be accounted for by conventional risk factors.[44,45] Westernized nations have increasingly become 24-h per day societies with greater numbers of people being exposed to more artificial light during the night both at home and particularly in the workplace.[3–6] It has been postulated that light exposure at night may represent a unique risk factor for breast cancer in industrialized societies via its ability to suppress the nocturnal production of melatonin by the pineal gland.[45] This hypothesis is based on studies showing that melatonin inhibits the development and growth of experimental models of breast cancer whereas either surgical removal of the pineal gland or exposure to constant light stimulates mammary tumorigenesis in rodents.[39] This postulate is further strengthened by recent epidemiological studies demonstrating that women working night shifts have a significantly elevated risk of breast,[12–15] endometrial[18] and colorectal cancer,[16] while male night shift workers are also at a significantly increased risk of developing prostate cancer,[17] presumably due to their increased exposure to light at night.

Recent studies from our laboratory have further clarified the relationship between circadian biology, the endogenous nocturnal melatonin signal, and suppression by light at night in humans and the growth and metabolism of human breast cancer xenografts (ERα + or −) in rats. Perfusion of tissue-isolated human breast cancer xenografts in immunodeficient, nude rats with melatonin-rich blood collected from premenopausal female subjects during the night, markedly suppresses tumor proliferative activity and LA uptake, as well as 13-HODE production, as compared with melatonin-deficient blood collected during the daytime. The addition of a melatonin receptor blocker to the melatonin-rich blood completely negated these tumor suppressive effects indicating that endogenous melatonin was the active factor.[43] The exposure of volunteers to bright, white light (i.e., 2800 lux at eye level) at night completely extinguishes the tumor inhibitory effects of blood collected during the night. The addition of a physiological nocturnal melatonin concentration to this blood perfusate completely restored its oncostatic action. This result indicated that the suppression of melatonin was responsible for the tumor-stimulatory effects of this blood perfusate following exposure to light at night.[43] Therefore, melatonin is the first soluble, nocturnal anticancer signal to be identified in humans that directly links the central circadian clock with some of the important mechanisms regulating breast carcinogenesis and possibly the progression of other malignancies. These findings also provide the first definitive nexus between the exposure of healthy premenopausal female human subjects to bright white light at night and the enhancement of human breast oncogenesis via disruption (i.e., suppression) of the circadian, oncostatic melatonin signal.[43] The suppression of circadian melatonin production by ocular exposure to bright white light at night, leading to augmented nocturnal tumor uptake of dietary LA and its conversion to

mitogenically active 13-HODE, can now be afforded serious consideration as a new risk factor for human breast cancer.[43]

The ability of light at night to stimulate human breast cancer proliferative and metabolic activities appears to be dose-dependent. For example, in female nude rats bearing ERα-human breast cancer xenografts and exposed to increasing intensities of light during the dark phase of a 12-h light/12-h dark cycle, a dose-dependent suppression of circulating melatonin levels occurred that was accompanied by a dose-dependent increase in tumor growth rates and LA metabolism.[43] A recent population study in women assessed the co-distribution of light at night with breast cancer rates using satellite images of different intensities of light at night in 147 communities in Israel.[46] This unique research strategy revealed a strong and significant positive correlation between the intensity of light at night and the breast cancer rate with a 73% higher breast cancer incidence occurring in the highest light intensity at night-exposed communities as compared to those communities with the lowest light intensity exposures at night. Whether these results correlated with a corresponding light intensity-dependent suppression of nocturnal circulating melatonin levels in these women was not ascertained in this investigation.[46] Nevertheless, this study[46] together with the nude rat experiments[43] provides strong support for an intensity-dependent effect of light at night on human female breast cancer.

The high nocturnal dietary intake of fat, particularly LA, reported for night shift workers[47,48] coupled with melatonin suppression by exposure to light at night provides a firm mechanistic basis upon which to explain, in part, the increased risk of breast cancer in some women who work night shifts for many years.[12–15] Thus, strategies to preserve the integrity of the circadian melatonin signal (i.e., avoidance of bright light at night, intelligent lighting design, circadian-timed physiological melatonin supplementation) coupled with modifications in nocturnal dietary fat intake may offer a unique approach to the prevention of breast cancer, and perhaps other melatonin-sensitive cancers, in our increasingly 24-h a day society.[5] This contention is bolstered by recent reports in premenopausal women that higher, first morning urine levels of 6-sulfatoxymelatonin[49] are associated with a significantly decreased breast cancer risk; this relationship was recently confirmed in postmenopausal women with respect to overnight urinary 6-sulfatoxymelatonin levels and breast cancer risk.[50] Interestingly, among individuals at high risk for breast cancer, plasma melatonin concentrations are independent of the degree of risk.[51] In cancer patients in general, the nocturnal amplitude of circulating melatonin levels has been reported to be reduced to various degrees.[38] In breast cancer patients in particular, nocturnal circulating levels of melatonin are negatively correlated with breast cancer ERα content while tissue levels of melatonin correlate positively with tumor ERα status and negatively with the nuclear grade and proliferative index. These findings suggest that cancer cells elaborate soluble factors that negatively feedback on the mechanisms regulating nocturnal melatonin production.[51,52]

Melatonin, sleep disturbance, immune function and cancer

The immune system is a double-edged sword in that it has both the capacity to suppress the development of malignancies via protective, immunosurveillance mechanisms and also promote cancer pathogenesis under certain circumstances. Through complex mechanisms collectively referred to as "immunosculpting", tumors may induce immune tolerance and suppression in response to immune effectors. This mechanism provides a means by which cancer cells can escape from the immunosurveillance activity of the immune system.[53]

Further adding to the complexity of the innate immune response is the endogenous pineal melatonin signal which serves as an important physiological modulator of the neuroendocrine–immune

axis via its well-known enhancement of a wide array of immune functions including the production of a variety of cytokines. In fact, there is a tight correlation between the nocturnal production of melatonin and the nocturnal rise in circulating T lymphocytes. A reduction in endogenous melatonin production leads to immune suppression that may have a stimulatory impact on the development and growth of cancer cells.[54,55] This may occur via a reduction in lymphocytes such as natural killer (NK) cells and cytotoxic tumor-infiltrating lymphocytes[54,55] as well as a decrease in the production, by circulating immune cells, of a number of cancer-inhibiting cytokines such as interleukin (IL)-2, IL-12, interferon-γ (INF-γ) (type 1 proinflammatory cytokines produced by Th-1 cells), and tumor necrosis factor (TNF)α.[56] Also at physiological nocturnal circulating concentrations, melatonin can reduce the production of IL-10, a type-2 antiinflammatory cytokine that has cancer growth promoting-activity through its immune suppressive action.[57] On the other hand, melatonin can activate human monocytes to produce IL-6, a cytokine with cancer-stimulatory activity.[58] As reviewed above, the direct oncostatic effects of the nocturnal, circadian melatonin signal on a variety of malignancies are well-established; however, the potential mechanisms by which melatonin might indirectly influence the development and growth of cancer via its immuno-modulatory actions are much less well understood.

Another route by which endogenous melatonin levels could influence the process of oncogenesis is via the synthesis and release of melatonin from human immunocompetent cells. These cells are not only equipped with the enzymatic machinery to produce substantial concentrations of melatonin but they also express membrane and nuclear melatonin receptors/binding sites that provide the substrates by which endogenous melatonin interacts with the immune system in an endocrine, intracrine, autocrine and/or paracrine manner to physiologically regulate the IL-2 and IL-2 receptor system in these cells.[54,55] Thus, in addition to melatonin of pineal gland origin, the local release of melatonin from tumor-infiltrating lymphocytes could potentially provide another direct source of oncostatic melatonin to cancer cells. Additionally, lymphocyte-derived melatonin might inhibit cancer cell proliferation by stimulating IL-2 through intracrine and/or paracrine mechanisms.

There is a reciprocal interaction and regulation between sleep and the immune system.[59] Sleep disturbances and sleep deprivation can lead to a suppression of immune function and a shift in the balance of cytokine production from a predominance of type-1 cytokines including anticancer cytokines such as IL-2 and INF-γ to type-2 cancer-stimulatory cytokines such as IL-10.[60] Conversely, as part of the humoral mechanism of sleep regulation, cytokines such as IL-1, IL-2 and TNFα enhance sleep while their levels in the brain and circulation vary with sleep.[61] As mentioned above, nocturnal physiological circulating concentrations of melatonin can stimulate the production of cytokines including IL-1 and TNFα. It is unclear whether melatonin's effects on sleep regulation are, in part, mediated via its ability to stimulate the production of these cytokines. Thus, it is conceivable that sleep disturbances have the potential to exert cancer-stimulatory influences via direct alterations in cytokine balance and/or via the circadian disruption of melatonin, in the presence of light at night, and the consequent interruption of its direct oncostatic mechanisms, or indirectly via altering the balance of cancer-inhibitory and -stimulatory cytokines.

Sleep duration and cancer risk

It is well known that fatigue and disturbances in sleep are among the most common side-effects reported by patients suffering form cancer. Sleep disorders including difficulties in sleep initiation and maintenance, poor sleep efficiency and quality, early awakening and excessive daytime sleepiness are often seen in cancer patients in response to the presence of cancer and/or to anticancer therapy.[62] On the other hand, the question of whether sleep disturbances or alterations in sleep patterns have an impact on the risk of developing clinically detectable cancer in the first place has never been addressed until recently in a series of four independent epidemiological studies. In modern 24-h a day societies the overall prevalence of sleep disturbances and daytime sleepiness has increased while the duration of sleep during each night by a number of accounts has decreased. Furthermore, exposure to artificial light at night particularly during night shift work, television and other factors has been responsible for altering our lifestyles and sleep habits. As mentioned above, most of the increase in breast cancer associated with living in modern day societies cannot be accounted for by the usual risk factors.

The first investigation into this issue was a prospective cohort study primarily designed to address the question of whether longer sleep duration was associated with lower breast cancer risk.[63] This was predicated on the notion that sleep patterns may have an impact on breast cancer risk through changes in melatonin and other hormonal rhythms. This study also addressed a possible link between sleep sufficiency and quality and breast cancer risk. The study involved a cohort of 12,222 Finish women using breast cancer incidence data for 1976–1996 from the Finish Cancer Registry linked to information about sleep duration and other sleep variables as assessed by self-administered questionnaires given in 1975 and again in 1981 (Finish Twin Cohort). Sleep duration reported in 1975 was used to predict breast cancer from 1976 to 1981 while sleep duration reported in 1981 was used to predict breast cancer from 1982 to 1996. In women who reported the same sleep duration of ≥9 h in both 1975 and 1981 there was a significant 72% reduction in breast cancer risk as compared with that in those women sleeping an average of 7–8 h. No statistically significant effects were observed for either sleep insufficiency or quality.

A similar prospective study examined the relationship between habitual sleep duration and breast cancer risk in a cohort of 35,303 Asian women aged 45–75 years, recruited as part of the Singapore Chinese Health Study and enrolled between 1993 and 1998.[64] Incident breast cancer cases were identified through the population-based cancer registry in Singapore that has been in place since 1968. Sleep duration (i.e., average number of hours in a 24-h period) in subjects was assessed via a baseline questionnaire. As an additional feature of this study, the first 278 women enrolled were also recruited to a biospecimen subcohort to examine the relationship between sleep duration and 6-sulfatoxymelatonin levels in random, single void, daytime-collected urine. While there was a trend of decreasing breast cancer risk with increasing sleep duration in all subjects, the results were statistically significant only in postmenopausal women who reported ≥9 h of sleep as compared with those women who reported ≤6 h of sleep. Interestingly, urinary 6-sulfatoxymelatonin levels in long-duration postmenopausal sleepers were 42% higher than in the short-duration sleepers. The biological significance of this finding, however, is problematic since single void urine samples were randomly collected during the daylight hours, when melatonin levels are lowest, rather than serially collected during darkness throughout the evening hours when circadian melatonin output is highest and physiologically most meaningful. Nevertheless, the results of these two prospective cohort studies provide some initial support for a decreased risk of breast cancer in long sleepers in spite of other epidemiological evidence indicating an association between long or short duration sleep and increased mortality.[65] Whether a longer duration of nocturnal melatonin secretion that presumably would occur in long sleepers (i.e., longer duration of darkness) is a biological mechanism that could explain this lower risk awaits further investigation.

Contradictory results were obtained in two other epidemiological studies that also addressed breast cancer risk as a function of sleep

duration; a prospective study of a large cohort of 77,418 women derived from the database of the Nurse's Health Study[66] and a case control study of 4033 women with invasive breast cancer versus 5314 women without breast cancer.[67] In essence, both of these studies found no evidence of a significant association between the incidence of breast cancer and sleep duration. Interestingly, these studies both determined that there was a modest trend towards increased breast cancer risk with increasing sleep duration.[67,68] The differences in the results between the two positive prospective studies and the two subsequent investigations could be due to intrinsic differences between the study populations, the number of breast cancer cases and different study designs. A major weakness of all these studies is their reliance on the study subjects' accurate recall and self-reporting of sleep habits through questionnaires rather than the documentation of sleep duration via more objective means such as wrist-actigraphy or polysomnography. It is fair to say that no definitive inferences can be drawn from these limited studies regarding whether differences in breast cancer risk can be attributed, in part, to differences in sleep duration. Clearly, more large-scale prospective cohort studies will be required in the future to help resolve the issue of sleep duration and breast cancer risk, in particular, and cancer risk, in general.

Concluding remarks

The development, growth progression and spread of cancer comprise a complex multistage process that involves intricate molecular and biochemical interactions that cause somatic cells to depart from their normally differentiated functions in situ and become transformed into rapidly proliferating tumors with the capacity for unlimited expansion and eventual invasion and metastasis into distant organs that ultimately lead to the death of the host. The environment has been implicated in the vast majority of cancers and studies reveal that environmental influences prevail in cancer etiology. Most of these studies have focused on exposures to chemical toxicants, hormones and dietary factors.[68] Recent epidemiological and basic science studies have implicated exposure to artificial light at night in the built environment in the causation of circadian disruption, particularly the suppression of nocturnal melatonin production and circadian phase shifts, as a potentially new etiologic agent in the genesis of a variety of human cancers.[12–18,43,46] In fact, the International Agency on Research on Cancer of the World Health Organization recently concluded that shift work, involving circadian disruption (ostensibly via exposure to light at night) is probably carcinogenic to humans.[69]

Since circadian disruption usually leads to disturbances in the quantity and quality of sleep or the complete disruption of sleep, it is difficult to parse out what role, if any, sleep disturbance per se may play in the etiology of cancer. Although experimentally induced circadian phase changes (i.e., SCN lesions and experimental jet lag)[70] and melatonin suppression (i.e., light at night) have been shown to promote cancer development and growth,[40] there is currently no experimental model system for testing the role of sleep and its disruption in the genesis of cancer. Sleep deprivation exacts a heavy toll on the normal activity of the neuroendocrine/pineal melatonin/immune axis which, in turn, exerts complex regulatory influences over cell proliferation and related immune surveillance mechanisms. Presently, it is impossible to determine what the relative contributions may be of sleep disturbance, circadian desynchronization due to light at night exposure, and related impairments of melatonin production and immune function to the initiation and promotion of cancer in high-risk individuals, particularly night shift workers. This begs the question of whether non-shift working individuals, who are not melatonin deficient (due to the lack of light exposure at night), but who are chronically sleep-disturbed or deprived for other reasons, are at greater risk for developing cancer? This would be possible due to the independent effects of immune suppression induced by sleep deprivation that would ostensibly occur in spite of the persistence of a circadian organized melatonin rhythm. The resolution of this issue awaits the development of an appropriate animal model in which sleep disruption can be induced without causing circadian phase shifts and/or melatonin suppression. Thus, any relationship between melatonin, sleep disturbance and cancer remains almost completely speculative at this point.

There is no doubt that our cellular, tissue and organ physiology and metabolism are organized within the framework of circadian time structure that is synchronized by regular cycles of light during the day and darkness during the night. It appears that, at least during the earlier stages of oncogenesis, cancer cells retain this temporal organization that contributes to the host/cancer balance. As malignant tumors become more advanced, however, they seem to lose this connection with internal time-keeping mechanisms tipping the host/cancer balance towards further malignant progression and the eventual death of the host.[71] The temporal organization, coordination and interactions between the circadian control of melatonin production, the sleep/wake cycle and immune function may thus minimize "runaway" cell proliferation, invasion and metastasis. The mutual reinforcement of these rhythms may indicate a unique new role for undisturbed sleep during darkness, and perhaps more importantly, uninterrupted darkness itself, as a protective mechanism against the development and growth of cancer.

Practice points

Important points to remember about melatonin, sleep disturbance and cancer are:

1. melatonin is involved in the circadian regulation and facilitation of sleep, the inhibition of cancer development and growth, and the enhancement of immune function;
2. night shift workers exposed to light at night experience biological rhythm disruption, including circadian phase shifts and melatonin suppression, and sleep disturbances;
3. sleep disturbances can lead to immune suppression and a shift to the predominance of cancer-stimulatory cytokines; and
4. the interacting circadian rhythms of melatonin, sleep/wake activity and immune function may indicate a new role for sleep in cancer prevention.

Research agenda

Future research priorities for elucidating the relationship between melatonin, sleep disturbance and cancer risk include:

1. studies to determine whether sleep disturbance due to any cause is a separate risk factor for cancer in both men and women;
2. an assessment of what aspect(s) of sleep disruption may pose the greatest risk for cancer development;
3. the development of appropriate experimental model systems to determine the role of sleep and its disruption in the etiology of cancer development and growth; and
4. a determination of the relative contributions of light at night-induced melatonin suppression, circadian phase shifts, sleep disturbance and immune impairment to cancer risk.

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Glossary

Melatonin: an indoleamine neurohormone in vertebrate species produced by the pineal gland and secreted into the bloodstream and cerebrospinal fluid during the night.

Pineal gland: a small, pea-sized and pine cone-shaped gland located deep within the middle of the human brain between the two halves of the cerebral cortex; produces the neurohormone melatonin.

Suprachiasmatic nucleus (SCN): a region in the hypothalamus of the brainstem that consists of small, bilaterally paired clusters of nerve cells that comprise the central circadian pacemaker or biological clock of the brain.

Biological clock: the mechanism within the SCN of an organism that generates repeated cycles (rhythms, oscillations) in behavioral, biochemical, metabolic and/or physiological activity that can be synchronized by environmental stimuli, primarily light.

Circadian rhythm: a self-sustained biological rhythm or oscillation of behavior, metabolism, biochemistry and/or physiology that repeats with a cycle of approximately 24 h; literally means a rhythm of about (circa) a day (dian).

Indoleamine: an aromatic heterocyclic organic compound consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring and containing an amine group.

6-Sulfatoxymelatonin: the major metabolite of melatonin resulting from the hydroxylation of melatonin followed by its sulfation in the liver; it is excreted in the urine.

Melatonin receptors: a superfamily of membrane-associated G-protein coupled receptor proteins containing seven trans-membrane domains that recognize and mediate major actions of melatonin.

Linoleic acid (LA): an omega-6 polyunsaturated fatty acid taken in through the diet that is essential for normal cellular structure and growth and used by cancer cells as a stimulatory or inhibitory growth signal; abundant in corn, cottonseed and safflower oil.

13-Hydroxyoctadecadienoic acid (13-HODE): a primarily growth stimulatory signaling molecule resulting from the metabolism of LA by 15-lipoxygenase-1 in cancer cells.