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Light at Night, Chronodisruption, Melatonin Suppression, and Cancer Risk: A Review

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ABSTRACT: Light exposure during the night is becoming progressively more common throughout the world, particularly in areas where electricity is commonly used. Also, the availability of artificial light has allowed humans to work or recreate throughout the 24-hour day. Based on photographs taken of the Earth from outer space, it is also apparent that true darkness is disappearing. For years it was assumed that polluting the daily dark period with light was inconsequential in terms of animal/human physiology. That assumption, however, has proven incorrect. Light at night has two major physiological actions, i.e., it disrupts circadian rhythms and suppresses the production of melatonin by the pineal gland. Moreover, both these changes are light intensity and wavelength dependent. Both human epidemiological and experimental studies on animals have documented that a potential negative consequence of chronodisruption and nocturnal melatonin inhibition is cancer initiation and growth. In epidemiological studies, the frequency of each of the following cancers has been reportedly increased in individuals who routinely work at night or whose circadian rhythms are disrupted for other reasons (e.g., due to jet lag): breast, prostate, endometrial, and colorectal. Likewise, in experimental animals, cancer growth is exaggerated when the animals are repeatedly phase advanced (as occurs during easterly flights) or exposed to light at night. A variety of mechanisms have been examined to explain how the suppression of melatonin exaggerates cancer risk. Mechanistically, how chronodisruption (without a consideration of melatonin suppression) would enhance cancer frequency is less clear. In addition to cancer, there may be other diseases that result from the chronic suppression of melatonin by light at night.

KEYWORDS: Melatonin, chronodisruption, light pollution, cancer, circadian rhythms

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I. INTRODUCTION

In 1996, the American Cancer Society set a goal of reducing cancer by 25% in the United States during the interval from 1992 to 2015.[1] Since then, the trends in cancer incidence have been regularly calculated from the Surveillance, Epidemiology, and End Results Registry. At the average current annual reduction in cancer incidence of 0.6% during the first half of the challenge period, the goal of a 25% reduction will fall far short of the hopes of the American Cancer Society.[2] In a 2007 evaluation of progress in this area, Sedjo and coworkers[2] emphasized the importance of continuing to reduce tobacco use and embarking on a means of decreasing the epidemic of obesity as major factors in limiting tumor incidence if the 25% goal is to be achieved or even approached. In reality, however, the difficulties in convincing individuals to refrain from tobacco use and to consume fewer calories (in a society where individuals have ready access to an overabundance of high-calorie foods, coupled with increased physical lethargy because of modern conveniences) seems to be almost insurmountable without additional, intensive, protracted education. While these two goals should continue to be strongly encouraged, it is essential that every other potential means of reducing cancer incidence also be exploited.[3]

An additional factor that should be considered as a possible contributor to an elevated cancer incidence is excessive light exposure. This is a consideration that should be taken seriously since, if it in fact impacts the onset or progression of cancer, as the epidemiological and experimental data are consistent with,[4–7] it would be an environmental perturbation that could generally be individually controlled. As innocuous as light may seem to be, when it occurs during the daily dark period it is capable of suppressing the endogenous production of the tumor-inhibiting molecule, *N*-acetyl-5-methoxytryptamine (melatonin).[8–11] In doing so, it upsets the normal physiology of the organism, which leads to a variety of alterations that may contribute to cancer cell growth.

II. LIGHT AT NIGHT, MELATONIN, AND CANCER

Bright light exposure at night as a consequence of the widespread use of artificial light sources is commonplace throughout much of the world, particularly in the well-developed countries. This excessive light pollution[12] is readily apparent when photographs are taken of Earth from space during the normal dark period. On these photographs, the location even of villages and individual residences can be identified if light is being used. Additionally, studies have shown that nighttime sky brightness is increasing at an alarming rate in countries of high population density.

Before the invention of the lightbulb by Edison in 1879, humans were exposed to only small amounts of low intensity light from candles or petroleum

lamps at night. Thereafter, growing in parallel with industrialization, the use of artificial light prolonged the "day," permitting employers to extend their work schedules well into the night and in many cases throughout the 24-hour period. It is estimated that perhaps one-fourth of the labor force of the world works during what is commonly referred to as the night shift. Furthermore, for recreational reasons, individuals are often in a brightly lit environment many hours after darkness onset.

Accompanying increased occupational and recreational light exposure at night, especially female breast cancer has steadily increased in the well-developed countries.[13–16] Because of this temporal coincidence, light at night suppresses the production of the cancer-inhibiting molecule melatonin; this drop has been incriminated as a plausible contributor to the elevated cancer risk. The justification for this speculative association certainly finds support from the substantive results of experimental and epidemiological studies.

Light at night has at least two important actions that may impact the frequency of cancer occurrence. First, it causes a disturbance of the biological clock resulting in what is referred to as chronodisruption or endocrine disruption.[7,17,18] This physiologically relevant perturbation occurs as a result of nocturnal light stimuli influencing the function of the biological clock [the suprachiasmatic nucleus (SCN) in the brain].[19] Many individuals experience consequences of these disturbances after rapid long-haul transmeridian travel; this phenomenon is known as "jet lag."

Such disturbances also occur, however, when the night is routinely interrupted by light, even in the absence of transmeridian travel.[9,20,21] During the history of the world, all organisms were exposed to regularly alternating intervals of light and darkness determined by the rising and setting of the Sun. Vertebrates, including the human, evolved a group of neurons now identified as the SCN that respond to these light/dark changes and synchronize physiological functions with the appropriate time of the day. Virtually every function in the body exhibits a 24-hour or circadian rhythm. When light is imposed at unusual times, the SCN responds and interprets the light as day and adjusts the physiology of the organism accordingly. The resulting chronodisruption has a variety of negative effects, one of which may be, over the long term, an elevated cancer initiation and progression.[18,22,23]

A second major consequence of light at night is the suppression of nocturnal melatonin production and release.[8–11,20] Melatonin is produced in the pineal gland, an end organ of the visual system,[24] in much greater abundance at night than during the day (Fig. 1). Since it is quickly released once synthesized, blood levels also exhibit a large nocturnal increase. Melatonin, referred to as the chemical expression of darkness,[26] requires uninterrupted periods of darkness, but not sleep, to manifest its normal rhythm. Thus, the extension of the "day" with artificial light impedes the normal rise in melatonin production; likewise, early morning light exposure (before sunrise) truncates melatonin synthesis and causes an ear-

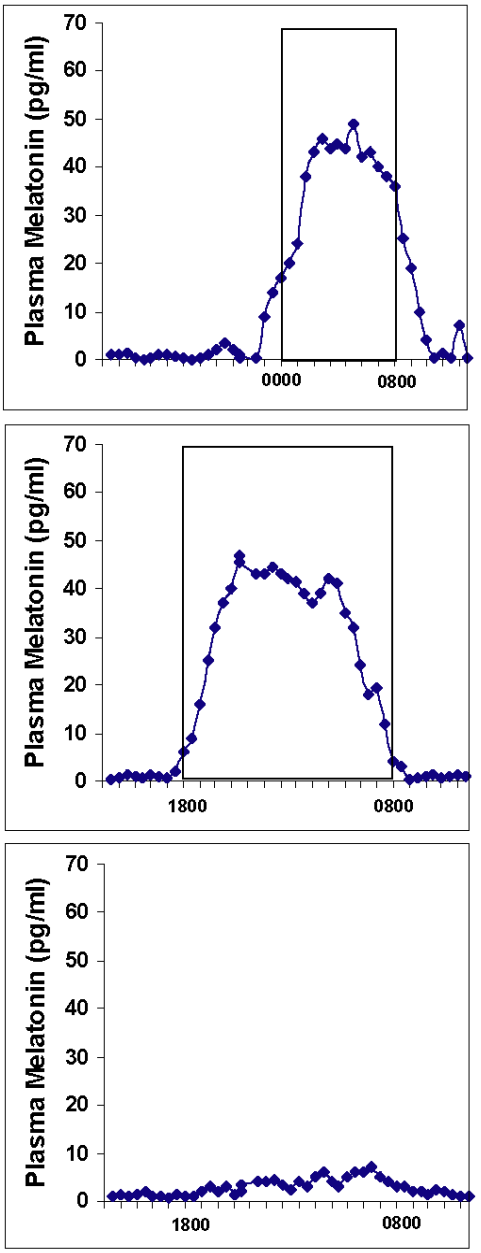

FIGURE 1. This figure illustrates that the increased duration of darkness at night is associated with a more prolonged melatonin production. In the top panel, the humans were in darkness for eight hours, i.e., light/dark cycle of 16/8, and melatonin levels were elevated throughout the dark phase. When the same group of humans was exposed to 14 hours of darkness (middle panel), blood melatonin levels remained elevated for a much longer period. Finally, under constant light conditions (light/dark 24/0; bottom panel), melatonin levels were suppressed to basal values through the 24-hour period. Figure is adapted in part from Wehr.[25]

lier than normal drop in blood levels.[27] Additionally, light exposure after darkness onset also suppresses melatonin levels, thereby limiting the total amount of this essential indoleamine produced during a given night. What this means is that modern humans are rendering themselves relatively melatonin deficient by shortening their daily dark period and, therefore, the duration of time during which melatonin can be produced. Clearly, when the environmental light/dark cycle is 12/12 (which occurs at the vernal and autumnal equinoxes), humans would normally produce melatonin for about 12 hours nightly;[28] however, when light is imposed after sunset or before dawn, the quantity of pineal melatonin is truncated at both ends, i.e., the individual is rendered relatively melatonin deficient. This becomes most severe when individuals work the night shift (Fig. 1, bottom panel).

The evidence is now compelling that melatonin is an endogenously produced oncostatic agent. This being the case, a relative deficiency of this molecule would predictably increase the risk of cancer. Both the epidemiological and experimental findings support this biologically plausible outcome.

III. EPIDEMIOLOGICAL/CLINICAL FINDINGS

In 2002, an issue of the journal *Neuroendocrinology Letters* summarized the proceedings of an international congress held in Cologne, Germany, which was convened to discuss the issue of light, endocrine disruption (chronodisruption), and cancer.[4] This publication summarized the wealth of information that had accumulated concerning light at unusual times and cancer frequency. The shortcomings of and confounders in the epidemiological studies were pointed out as well as the degree to which light pollution may actually impact cancer risk.[5,6]

In the years since this publication, the subject has matured to the extent that in a recent National Institutes of Health publication, *Science News*, an article appeared entitled "Bright Lights, Big Cancer."[29] This article focused the readers' attention on the dangers of the misuse of light at night and provided information as to how it may impact cancer initiation/progression. Likewise, the subject of light pollution and how it may predispose individuals to cancer was recently discussed by a panel of scientists convened by the World Health Organization; an outcome of this discussion was that "shift work involving circadian disruption" is a Group 2A carcinogen (probably carcinogenic to humans) according to the International Agency for Research on Cancer (IARC) and was published in *Lancet Oncology*.[30] Additionally, a summary report of a workshop organized by the National Cancer Institute was recently published; the report discusses the role of environmental light and the resulting circadian disruption in terms of their impact on not only cancer but other diseases as well.[31] It also suggested epidemiological and experimental research priorities to define the consequences of melatonin suppression and circadian disruption on the pathophysiology of disease processes in general and to identify possible mitigation to improve public health. These

publications illustrate the importance of this subject and the concern of the scientific community related to an environmental variable that was, until recently, considered innocuous in terms of human pathophysiology.

The initial studies related to cancer occurrence and irregular working hours, but particularly working at night, were descriptive in nature. Consistently, these reports generally uncovered a significant rise in the relative risk of breast cancer in female nurses,[13–16] flight attendants,[32–35] and radio and telegraph operators.[36] Furthermore, there was a suggestion of an increased likelihood of developing cancer with a longer duration of shift work.[36]

Prompted by these observations, Hansen[37] conducted a large case-controlled study to investigate whether women in Denmark who predominately worked at night exhibited an elevated likelihood of developing breast cancer. In this study with 7035 women with primary breast cancer, a 50% increase in the incidence of breast cancer in women who worked at night at least half of a year was uncovered. The association was found not to be due to confounding by age at birth of first child, number of children, or socioeconomic status, factors reported to influence breast cancer frequency. Almost simultaneously, a case-controlled study conducted in the Seattle area[38] and a cohort analysis of the data from the Nurses' Health Study,[39] a very large prospective program in the United States, revealed findings similar to those reported by Hansen.[36]

After a detailed analysis of the frequency of breast and prostate cancer in individuals from 21 studies that involved regular long-haul flight personnel and nine reports that examined cancer incidence in workers who routinely worked night shifts, Erren et al.[17] concluded that there may be up to a 70% increase in the risk of breast cancer and a 40% increase in the risk of prostate cancer as a result of these unusual work schedules. The reported rises in cancer incidence could be underestimates of the real hazard given that the control subjects or reference populations were those living "normally" and who did not engage in frequent, rapid, long-distance, transmeridian travel or in shift work. Obviously, however, the control subjects or reference populations did use artificial light that extended their days and, at least occasionally, likely interrupted their nights. Thus, they were at some times experiencing chronodisruption and were regularly relatively melatonin deficient, thereby possibly also increasing their susceptibility to cancer initiation/progression.

In addition to breast and prostate cancer, a recent report also indicates an augmentation of endometrial tumors in women who are regularly employed at night. In a large, prospective cohort investigation using data from the Nurses' Health Study, Visnanathan et al.[40] determined that women who worked rotating night shifts for long durations had a significantly elevated risk of endometrial cancer. This was only apparent in obese women, where the baseline risk of cancer was doubled; in leaner women, an increased frequency of endometrial cancer was not apparent. Mechanistically, the authors invoke the reduction in melatonin due to chronic light exposure as being contributory to the rise in endometrial

cancer. The involvement of melatonin would not be unexpected considering the multiple processes by which it interferes with the growth of cancer cells.[41–45]

Based on the above findings, an obvious prediction is that blind people who perceive less or no light visually would most probably produce more melatonin each 24-hour period and, as a result, a lower cancer risk would be expected.[46,47] In fact, consistent with this prediction, one early study in the United States[46] and four in Nordic countries[48–51] suggested a diminished risk of breast cancer in general in individuals with profound visual impairment. More recently, Pukkala and colleagues[52] reported that, as with breast cancer in women, visual impairment is also associated with a trend of reduced prostate cancer. Despite these correlations, it is not yet definitively established whether individuals who have no conscious light perception in fact produce more melatonin than those who are not visually impaired.[53] In fact, it has been shown experimentally that light induces nocturnal melatonin suppression in some totally blind individuals.[54] Considering this, some individuals in blind study populations may have essentially a normal melatonin rhythm. If so, this would tend to attenuate the hypothesized difference between cancer risks for sighted and blind individuals.

Based on the role that prolonged darkness has in promoting pineal melatonin production and release, Erren and Piekarski[55] theorized that individuals residing north of the Arctic Circle, where there are extended periods of darkness during the winter months, may have reduced levels of hormone-dependent cancers. Based on ecological data, albeit limited in scope and methodological weight, they report, in fact, that in addition to a low frequency of breast cancer[56,57] in areas north of the Arctic Circle in Alaska and Greenland, likewise prostate cancer[58–61] is also rare in circumpolar regions. In a study involving people living in Tromsø, Norway, which is inside the Arctic Circle, winter serum levels of melatonin are elevated for a longer period each day when compared to those measured in the summer.[62]

Verkasalo and coworkers[63] conducted a prospective study to determine whether the duration of sleep influences the incidence of breast cancer. One stimulus for this work was the observations of Wehr,[25,27] who showed that switching human volunteers from an eight-hour night to a 14-hour night was associated with an increase in the duration of sleep and a prolongation of elevated blood melatonin. The reader is reminded that a longer sleep period is not linked to a more prolonged period of elevated melatonin; the duration of pineal melatonin synthesis and secretion is a function of the length of the dark period and is not knowingly related to sleep duration.[28] What Verkasalo and colleagues[63] found is that the prolongation of the night sleep period was associated with a reduced breast cancer incidence. They interpreted their findings to mean that the duration of elevated melatonin, rather than an interval of sleep per se, probably accounted for the lower breast cancer risk. Likewise, in the Nurses' Health Study, no link between habitual sleep duration and the incidence of cancer was apparent.[64]

Another approach to examine the potential association between cancer risk

and the level of melatonin has been to correlate the presence of cancer or its maturational stage with circulating melatonin concentrations. A number of workers[65–69] have measured this indoleamine in the blood (or the levels of a major enzymatic metabolite, 6-hydroxymelatonin sulfate, in the urine) in tumor-bearing individuals relative to levels in age-matched, cancer-free subjects. While these studies generally confirm that individuals with cancer seem to produce less melatonin, many of the investigations are significantly handicapped by the infrequency of blood sampling, sampling at less than an optimal time, i.e., not in the middle of the night in darkness, or because of an indirect melatonin measure, i.e., 6-hydroxymelatonin sulfate, in the first morning urine void was used. There are a number of metabolites of melatonin in the urine in addition to the sulfated version of 6-hydroxymelatonin.[70] Moreover, the percentage of melatonin metabolized to 6-hydroxymelatonin in the liver may be altered in individuals suffering with cancer. Another limitation of these studies is that the observations made are only correlations; thus, no cause/effect relationship can be proven. Finally, none of these investigations determined whether melatonin levels were lower than normal in the same subjects prior to the onset of the cancer.

Of the publications in this category, the most complete study may be that of Karasek et al.[71] This group defined the serum circadian profile of melatonin in 31 patients with cervical cancer compared with those in age-matched, cancer-free individuals. The patients with cervical cancer were further subdivided into subjects with stage 0 (11 patients), stage 1 (8 patients), stage 2 (5 patients) or stage 3 (7 patients) cancer. Blood samples for melatonin measurements were drawn at

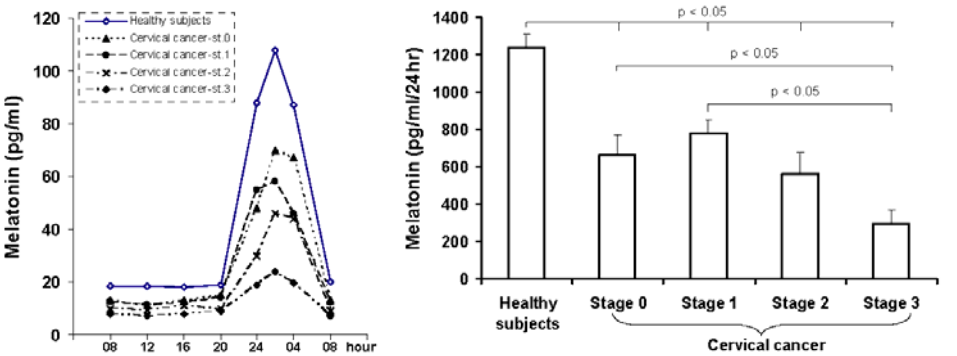

FIGURE 2. Nocturnal rises in circulating melatonin concentrations (left panel) and total melatonin generated nightly (right panel) in healthy females and those with cervical cancer (stages 0–3). There is an inverse relationship between nocturnal melatonin levels and the severity of the cancer. The implication is that cancer development could be associated with a compromised melatonin rhythm; however, observations such as these are correlations and a cause/effect relationship has not been definitively established. It is known, however, that both physiological and pharmacological concentrations of melatonin inhibit cancer growth. From Karasek et al.[71]

several times over the light/dark cycle with three samples being collected in the critical period overlapping the middle of the night (12.00; 2:00 A.M.; 4:00 A.M.). The results indicate there is an association between the stage of cervical cancer and circulating melatonin concentrations; thus, melatonin levels progressively decreased with increasing stage of cancer (Fig. 2).

This study, however, suffers from the same limitations of the others with at least three interpretations of the findings being possible: a relative melatonin deficiency increases the cancer risk; the presence of cancer inhibits melatonin production/secretion; or the observations are only coincidentally correlated and not directly related.

IV. EXPERIMENTAL FINDINGS

There are now a substantial number of experimental animal studies supporting the idea that extended light periods or regularly shifting the daily intervals of light and darkness to simulate transmeridian travel promote cancer cell growth. In these studies, it is possible that the combined effects of the suppression of the endogenous oncostatic agent, melatonin, as well as dyssynchronization of circadian rhythms, i.e., chronodisruption, contributed to tumor cell proliferation.[7,17,18]

The most intriguing and relevant studies regarding biological clock disruption due to simulated chronic experimental jet lag and cancer cell growth are those of Filipski et al.[72,73] In these investigations, mice were injected with Glasgow osteosarcoma cells and thereafter maintained either in a stable light/dark cycle of 12/12 (in hours) or they were kept under a 12/12 cycle that was phase advanced by eight hours every two days. This eight-hour phase advance is roughly equivalent to flying easterly from the mid–United States to Europe. The repeatedly phase-advanced mice, like humans under similar conditions, would experience the physiological disruption referred to as jet lag. Compared to mice maintained under a stable light/dark cycle (such as individuals who remain in the United States), the osteosarcoma tumors in the "jet lagged" mice proliferated at a significantly more rapid rate. Furthermore, when the investigators examined the neural biological clock for the expected rhythms in "clock" gene expression, they were found to be suppressed in mice subjected to repeated phase advances; conversely, the "clock" gene rhythms persisted in mice under a stable light/dark cycle. The suppression of the rhythmic nature of the biological clock and the associated severe chronodisruption that negatively impacts the physiology of many organs likely enhanced the osteosarcoma cell growth that was observed. The findings are consistent with the observations that the loss of biological rhythmicity in mice that occurs as a consequence of the electrolytic destruction of the circadian clock also leads to an enhanced growth of tumors.[74]

That repeated phase advances are severely disruptive to the physiology of organisms is supported by the recent observations of Davidson and colleagues.[75]

They found that subjecting old (27–31 months) C57BL/6 mice to chronic jet lag by repeatedly phase advancing their photoperiodic cycle (six hours every seven days) led to the premature death of mice compared to the survival of animals in a regular 12/12 light/dark environment. The survival of the mice, however, was not compromised if they were phase delayed by six hours every seven days. This latter observation was not unexpected given that the biological clock typically has an endogenous rhythm that exceeds 24 hours and, therefore, the chronodisruption and the subjective feeling of jet lag is commonly less severe when crossing numerous time zones in a westerly direction, such as occurred in those animals that were phase delayed. While the study of Davidson et al.[75] does not relate directly to cancer incidence, the results illustrate the marked metabolic disturbances that must occur during frequent phase advances of the biological clock, i.e., induced by easterly directed jet lag.

In neither the studies of Filipski et al.[72,73] nor in that of Davidson and colleagues[75] were the melatonin rhythm disturbances measured. Considering what is known about the SCN regulation of the circadian melatonin production and secretion rhythm, this cycle was surely inhibited by the repeatedly altered light/dark cycles imposed. Thus, while chronodisruption no doubt contributed to the faster than normal cancer growth as well as to premature death of mice,[76] the loss of a significant amount of melatonin also very likely predisposed the animals to accelerated cancer cell proliferation and earlier than normal death.[77]

A seminal report was published in 1997[78] that illustrates the harmful effects of either totally depriving animals of darkness or contaminating the daily interval of darkness with low-intensity light on tumor growth and metabolism. Although an early study had shown that manipulation of the light/dark cycle changed the mammary tumor response in rats treated with 9,10-dimethyl-1,2-benzanthracene,[79] the article of Dauchy et al.[78] is especially noteworthy because in this case tumor-bearing rats were either exposed to constant light or to a 12/12 light/dark cycle with the dark portion of the cycle merely being contaminated with dim light (of different intensities). Prior to these photoperiodic environments, the rats had received subcutaneous implants of Morris hepatoma 7288CTC cells. The control rats in this study received cancer implants and were exposed to a 12/12 light/dark cycle where darkness was not contaminated with light. These findings may have implications for people in urban areas where at least low-intensity light contamination of darkness is essentially universal.

The results of this investigation uncovered several predictable relationships. First, constant light exposure caused the earliest and most rapid development of palpable tumors, followed by the darkness-contaminated environment, and, finally, the rats kept in the carefully regulated light/dark cycle were the last to exhibit measurable tumors. Likewise, the rate of growth of the tumors was in direct proportion to the intensity of light contamination during the 12-hour dark period. The differences in tumor growth also were reflected in the fatty acid metabolism of the tumors. The utilization of linoleic acid, a growth factor for Morris hepa-

toma cells, as well as the intracellular production of 13-hydroxyoctadecadianoic acid (13-HODE), which induces transcription factors that stimulate cell proliferation were highly elevated in the tumors of rats kept under constant light with 13-HODE production still being well above control levels in cancers of rats kept on a light/dark cycle where darkness was contaminated with low-intensity light (Fig. 3). Furthermore, the growth and other metabolic aspects of the tumors were inversely related to the nighttime melatonin concentrations.

Collectively, the endpoints of this study argue strongly that prolonged daily light exposure, as occurs in individuals working the night shift, may exaggerate

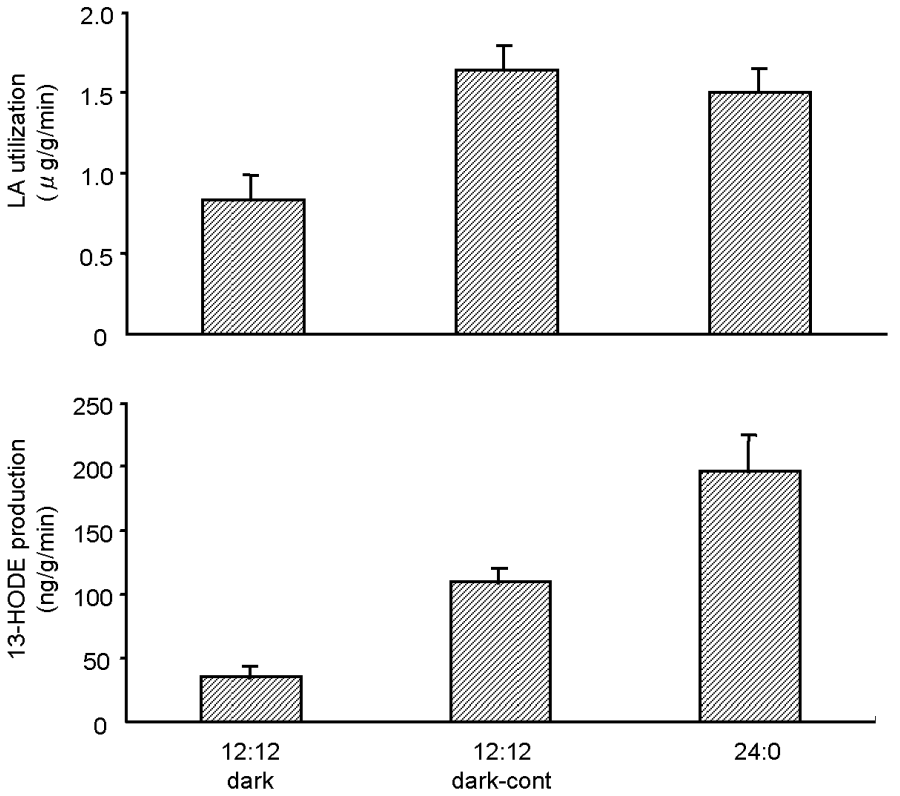

FIGURE 3. Linoleic acid uptake and its conversion to 13-hydroxy-octadecadianoic acid (13-HODE) in Morris heptoma cells growing in rats that were kept either under a light/dark cycle of 12/12, in a light/dark cycle of 12/12 where the dark period was contaminated by low-intensity light or continuous light (light/dark 24/0). Linoleic acid is a potent growth factor for these tumors and 13-HODE induces the expression of genes that stimulate tumor growth. When darkness was contaminated with light, endogenous nocturnal levels of melatonin were markedly suppressed, indicating the more rapid metabolism of the tumors in these animals was a likely consequence of the relatively melatonin deficient state. From Dauchy et al.[78]

tumor growth in humans and, furthermore, dim light at night may also be consequential in accelerating cancer progression.[78] Finally, the hastened proliferation and elevated fatty acid metabolism of tumors are likely related to the depressed melatonin rise as a result of light at night since other studies have shown that these changes can be reversed by melatonin administration.

Cos and coworkers[80] essentially confirmed the findings of Dauchy et al.[78] when they measured the growth of dimethylbenzanthracene-induced mammary tumors in rats. Animals kept under dim light (as opposed to darkness) during the daily nighttime period exhibited significantly more rapid tumor growth rates than those in animals maintained under a 12/12 light/dark cycle. The accelerated growth of tumors in the dim light–exposed rats again correlated with reduced melatonin synthesis, as evidenced by the lower excretion of 6-hydroxymelatonin sulfate in the urine. 6-Hydroxymelatonin sulfate is a major enzymatic metabolite of melatonin that is frequently used as an indirect index of the total amount of melatonin produced nightly.[81]

Perhaps the most compelling evidence that reduced circulating levels of melatonin due to nocturnal light exposure stimulates the growth and metabolic activity of tumor xenografts growing in immunocompromized animals comes from the observations of Blask et al.[82] When implanted human breast cancer or rat hepatoma tumors were perfused with daytime blood from adult women (melatonin concentration of roughly 15 mg/ml), cell proliferation (^{3}H-thymidine incorporation), cAMP levels, and lenoleic acid uptake and its metabolism to 13-HODE proceeded unabated. In contrast, when blood was collected from the same group of women at night (melatonin concentration of roughly 53 pg/ml) and perfused into the xenografts, the proliferation of the cells and their high metabolic activity were thwarted. However, when the same women were exposed to light at night to reduce their circulating melatonin levels (melatonin concentrations were roughly 28 pg/ml), their blood was incapable of suppressing any aspect of either human breast cancer or rat hepatoma cells. Clearly, the physiological nocturnal levels of melatonin in the human are sufficient to interfere with the growth and metabolic activity of cancer cells. Moreover, when nighttime blood melatonin concentrations are reduced, even if the reduction is only partial, they may be ineffective in limiting tumor growth. These findings not only have implications for the misuse of light and light pollution, but also for humans who have a genetically determined hypomelatoninemia and in the aged where endogenous melatonin synthesis normally wanes and circulating melatonin concentrations drop.[83]

V. MECHANISMS AND PERSPECTIVE

A recent meta-analysis of many of the clinical trials that used melatonin as a sole or adjuvant treatment for cancer supports the use of this agent as a therapy.[84] The authors of this survey particularly mentioned that the reduction in death, the inhibition of tumor growth, the minimal adverse effects, and the low cost of mela-

tonin suggest the indoleamine has significant potential for treating cancer. A corollary of this is that light pollution, due to its ability to restrain melatonin production, likely exaggerates cancer frequency just as the epidemiological and experimental findings discussed above reported. Thus, light at night should be classified a potential environmental carcinogen.

The plethora of mechanisms that melatonin seems to have at its disposal to limit cancer initiation, promotion, and progression is unexpectedly broad (Fig. 4).[41–45,82,85–99] Whether each of these reported courses of action are independent processes or whether they are linked into a single complex inhibitory cascade has not been satisfactorily established. Whereas it is not the purpose of this review to discuss in detail each of these mechanisms, a few with the largest amount of experimental backing will be mentioned.

Inhibition of cancer initiation by melatonin is most likely achieved by its ability to prevent an early step in the process. Due to the potent free radical scavenging activities of melatonin and its metabolites,[100–104] DNA is protected from damage due to toxins, radiation, heavy metals, etc.[105–110] Given that in excess of 50% of all cancers may be a consequence of free radical damaged DNA that goes unrepaired,[111] melatonin due to its marked protective effects at the level of the genome, could be a major process that accounts for its ability to reduce oncogenesis.

Numerous in vitro and in vivo experimental studies in animals have unequivocally documented the oncostatic actions of melatonin. This action is ac-

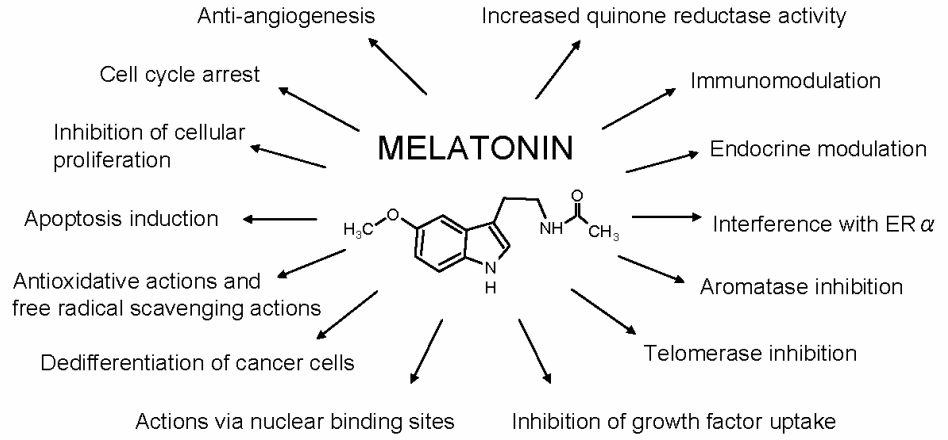

FIGURE 4. Some of the proposed actions by which melatonin either reduces cancer initiation or progression. Many of the actions overlap and the effects on cancer cells may be cell-type specific. These data have come from both in vivo and in vitro experiments. The published literature can be consulted for the details on these processes.[89–99] Some of the effects of melatonin in inhibiting cancer are indirect, e.g., via immunomodulatory effects, while others are direct, e.g., the free radical scavenging actions. Additionally, some of the actions may be receptor mediated while others are receptor independent. ERα = estrogen receptor-alpha.

complished by both physiological levels and pharmacological concentrations/doses of the indoleamine. Any suppression of total endogenous nocturnal melatonin production—e.g., by contamination of the daily dark period with artificial light (Fig. 5), a reduction in the duration of the daily dark period (as in individuals who have short daily periods of sleep), use of drugs such as β-adrenergic receptor blockers, or advanced age—would be predicted to exaggerate both cancer initiation and cancer cell growth.[45,83,113,114]

Moreover, given that melatonin and its metabolites are ubiquitously acting free radical scavengers,[98–104,115] other diseases that have oxidative damage as a basis may also be elevated in individuals exposed to an unduly large amount of inappropriately timed light over prolonged periods.[116–121] This is a conclusion also drawn by the National Cancer Institute committee that was convened to evaluate the literature related to excessive light exposure and tumor biology; thus, in addition to cancer, they cautioned that other diseases may become more common or be aggravated by excessive light exposure.[31] Of particular interest in this regard are neurodegenerative diseases since they have a free radical component.

Melatonin's primary means of indirectly influencing neoplastic growth may involve its ability to modulate the immune system and/or endocrine functions. In relation to the former, a number of cytokines are considered to be potential cancer immunotherapeutic agents. At the current time, interleukin-2 (IL-2), IL-4, IL-12, IL-24, interferon gamma (IFN- γ), granulocyte-monocyte colony stimulating factor, and tumor necrosis factor-alpha (TNF-α) are being investigated as cancer therapies.[87,88] Melatonin enhances IL-2 and IFN- γ levels.[91] Lissoni et al.[85] used concomitantly administered melatonin and IL-2, and found that this combination amplified the lymphocytic response associated with the antitumoral efficiency of IL-2. Moreover, the concurrent administration of melatonin and IL-2/IL-12 not only enhances the lymphocytosis induced by the interleukins, but also limits the toxicity of these cytokines by reducing the associated thrombocytopenia. The toxicity of another anticancer cytokine, TNF-α, may also be reduced by melatonin.[122]

One means that tumors use to evade the immune system is to suppress the Th1 response–mediated cellular immunity against cancer cells, thereby promoting the Th2 response.[123] Melatonin may effectively counteract the Th2 effect, since it increases IL-12 production by monocytes driving T-cell differentiation toward the Th1 phenotype and increasing IFN-γ production[124] while neutralizing prostaglandin E2 inhibitory actions on IL-2 levels.[125]

The endocrine effects of melatonin may also be an indirect means by which melatonin influences cancer. When light at night was first proposed to influence the likelihood of cancer frequency, it was theorized that the reduction of melatonin may be associated with increased estrogen levels, which, in turn, would enhance estrogen-dependent cancer cell growth.[126] This could be achieved intracellularly by a stimulation of the activity of aromatase, an enzyme that supports the biosynthesis of estrogen. Aromatase is abundant in breast cancer cells.

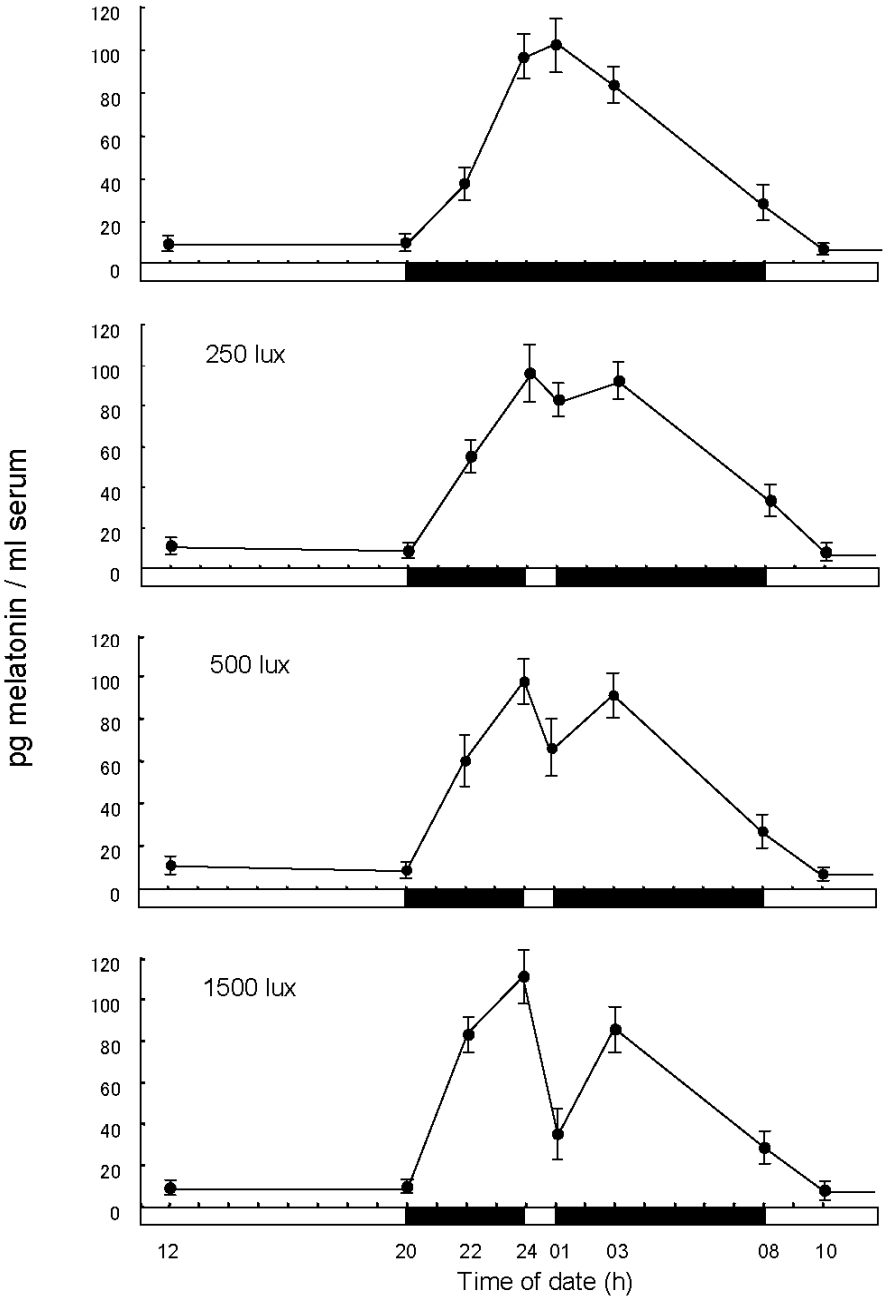

FIGURE 5. Suppression of blood melatonin levels in humans who, on different nights, were exposed to increasing white light intensities for one hour (from 12:00–01:00 A.M.). Clearly, the brighter the light, the greater the suppression of circulating melatonin concentrations. Besides the brightness of the light, the wavelength (color) of light is also important in determining inhibition of nighttime melatonin levels.[112]

Melatonin, at physiological concentrations, reduces aromatase activity and thereby inhibits estrogen production in MCF-7 estrogen-sensitive human breast cancer cells under basal conditions as well as when the enzyme is stimulated by cAMP.[94] Furthermore, melatonin downregulates aromatase expression at the transcriptional level. Thus, a deficiency in melatonin would be anticipated to elevate intracellular estrogen levels; this provides an indirect means by which light-depressed melatonin levels could stimulate neoplastic growth.

While melatonin may suppress estrogen production via inhibition of aromatase,[95] the indoleamine may also influence downstream events that allow melatonin to retard estrogen-responsive tumor growth. Melatonin is a specific inhibitor of estradiol (E2)–induced estrogen receptor-alpha (ERα) transcription while ERβ-dependent transactivation is unaffected.[92] This antiestrogen action of melatonin is theorized to be important in the oncostatic action of melatonin, especially with regard to steroid-dependent breast cancer.[93,95]

Both the immunomodulatory and the antiendocrine effects of melatonin as they relate to the inhibition of cancer are believed to be mediated by membrane receptors in the tumor cells that react to melatonin. Membrane melatonin receptors have been identified on a variety of cancer cells.[96] This information is not only germane to breast cancer but also to prostate cancer, which is likewise responsive to melatonin.[97]

As summarized in Figure 4, melatonin has a variety of direct effects on cells that may also be critical to its oncostatic actions. Some of these may rely on membrane receptors and/or nuclear binding sites for melatonin, while others may be melatonin receptor independent.[94,127,128] Certainly, these direct actions have the capability of playing fundamental and important roles in mediating cancer cell growth inhibition by melatonin. The ability of melatonin to reduce the uptake of the omega-6 fatty acid, linoleic acid, has been particularly well investigatively exploited as a means by which melatonin inhibits cancer cell proliferation. Linoleic acid is a growth factor for at least some cancer cells and its metabolic products activate genes that promote cellular proliferation.[82,86,88] Whereas some of the anticancer actions of melatonin, e.g., its antioxidative effects that reduce free radical–mediated damage to DNA, relate to reducing cancer initiation, others are concerned with promotion and progression of the growth of tumors. Thus, melatonin may also potentially reduce the likelihood of metastases since the progression of at least human breast cancer to the metastatic state relies on continued hydroxyl radical–mediated DNA damage.[129] Collectively, the observed oncostatic actions of melatonin mean that this endogenously produced indoleamine may offer protection against the six hallmarks of cancer as identified by Hanahan and Weinberg.[130] Namely, melatonin inhibits the self-sufficiency of growth signals, it elevates their sensitivity to growth-inhibitory signals, it prevents cancer cells from evading apoptosis (in fact, it induces cancer cells to undergo apoptosis[44]), and it limits the replicative potential of cancer cells while reducing persistent angiogenesis, tissue invasion, and metastatic potential.

That melatonin could act at either the level of specific receptors in the cell membrane or via cytosolic or nuclear binding sites is supported by the observation that melatonin readily enters cancer cells. Conventionally, due to its high lipid solubility, melatonin was considered to merely passively diffuse into cells. Hevia et al.,[131] however, have provided data showing that both androgen-dependent LNCap as well as androgen-independent PC-3 cultured prostate cancer cells actively take up melatonin with maximal intracellular levels being achieved in both the cytosol and nucleus within six hours after melatonin addition to the incubation medium. Inhibition of protein or RNA synthesis significantly reduced melatonin uptake as did binding of melatonin to bovine serum albumin. Given the rapid transport of melatonin into cells generally and specifically by at least some cancer cells, it is clear that the ability of melatonin to resist cell proliferation could be executed at many intracellular levels.[94]

If interference with and suppression of the endogenous melatonin rhythm is not a contributing factor to tumor progression in individuals chronically exposed to excessive light, the mechanisms whereby chronodisruption per se may initiate and/or propagate cancer cell growth is much less clear. Perhaps alterations in numerous circadian rhythms at both the organismal and cellular levels translate into a generalized metabolic imbalance that leads to an exaggerated proliferation of cancer cells. Presumably, the feeling of malaise, fatigue, and listlessness, as manifested in jet lag, are reflections of these repetitively disrupted circadian rhythms. How the chronodisrupted metabolic activity, however, would be actually translated into accelerated tumor growth remains to be unraveled. At this time, the most biologically plausible explanation for the elevated cancer risk in individuals either chronically exposed to light at night or to repeated chronodisruption is an inhibition of the endogenous cancer-inhibiting molecule, melatonin.

For decades, melatonin has been used to overcome the signs of jet lag, i.e., one of the manifestations of chronodisruption.[132] Melatonin's benefit in this case is believed to be due to its improvement and/or synchronization of a multitude of circadian rhythms at the cellular level. If the generalized chronodisruption of circadian cycles accounts, even in part, for the increased cancer risk in individuals chronically exposed to light at night, then it would seem prudent to avoid light after darkness onset where possible, particularly after going to sleep at night. Moreover, the use of melatonin to synchronize 24-hour rhythms may also be considered to reduce the likelihood of cancer in these subjects.

VI. CONCLUDING REMARKS

There is increasing epidemiological and experimental evidence that light at night has the capability of elevating cancer risk. This rise could be a result of a generalized disruption of circadian rhythms and/or a suppression of melatonin. It seems possible that both these elements are contributory to cancer initiation or progression.

There is no doubt that light exposure after darkness onset is a major feature determining the amount of melatonin produced each night by the human pineal gland. Furthermore, light at night and/or light pollution are becoming progressively more ubiquitous as the use of electricity and artificial light sources proliferate. Thus, true darkness is disappearing. Certainly, light exposure at inappropriate times, i.e., light at night, inhibits melatonin production and, as a consequence, additional metabolic disturbances seem highly likely.

Melatonin is a documented endogenous oncostatic agent while light pollution, which suppresses melatonin, seems to be associated with a rise in the risk for developing at least certain types of cancer. The mechanisms whereby melatonin stymies cancers are reported to be numerous and varied. If the rise in cancer risk seen in individuals performing night work or being repeatedly subjected to environmental time changes is not related to alterations in melatonin but rather to dysynchronization of circadian rhythms, then the mechanisms by which chronodisruption mediates a rise in cancer are less clear.

Given that exogenously administered melatonin has proven an effective treatment to alleviate short-term symptoms of chronodisruption and to inhibit cancer in numerous experiments, its use by individuals deficient in endogenous melatonin for any reason would seem conceivable or judicious. Melatonin has uncommonly low acute and chronic toxicities, has an extremely wide safety margin in terms of dose, can be administered via any of several routes including orally, is synthesized in a pharmaceutically pure form, and is inexpensive. Ultimately, melatonin should be comprehensively tested for its ability to reduce cancer risk in select populations who, because of their lifestyles, have a compromised melatonin rhythm or who are chronically dyssynchronized.

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