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Relationship Between Light and the Development and Growth of Internal Solid Cancers

A Review of Current Research and the Potential Implications for Lighting Practice

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McCLUNG LIGHTING RESEARCH FOUNDATION

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REPORT SUMMARY

Light has profound effects on human and animal biology that do not involve vision. The natural cycle of light and dark affects the daily rhythms of physiology, metabolism, and behavior; and disruptions of these rhythms caused by artificial light may have serious health consequences. This report discusses the evidence for one such possible effect: the influence of light exposure during the nighttime on the incidence and development of solid cancers.

Background

Over-exposure of the skin to the actinic radiation of the sun has long been known to induce cellular DNA damage culminating in the development of skin cancer. However, the detrimental influence of inappropriate ocular light exposure on circadian rhythm activity and its impact on health is a relatively new and emerging focus of basic and clinical research. This white paper focuses on the possible effects of light on the development and growth of internal cancers.

Objective

- To present an overview of current knowledge on the effects of light on the incidence and growth of internal, solid cancers
- To recommend directions for further research on this topic.

Approach

In research cosponsored by the McClung Foundation, the project team summarized available research results from both human and animal studies on the effect of light on the development and growth of internal, solid cancers. Their paper presents an overview of current knowledge regarding:

- The nature of the circadian system and its regulation by light
- Regulation of nighttime melatonin production by the pineal gland and the influence of light
- Basic mechanisms of development and growth of internal, solid cancers
- Basic mechanisms by which the endogenous, nocturnal melatonin signal regulates cancer development and growth
- Experimental laboratory-based evidence for the impact of light on the development and growth of internal, solid cancers, particularly in the context of population-based evidence for increased cancer risk in night shift workers.

Based on this information, the team speculated on the possible implications of current findings for lighting practice and recommended directions for future research.

Results

An increasing amount of evidence supports the hypothesis that bright light present during the dark phase of an alternating light/dark cycle stimulates the development and growth of experimental rodent tumors, especially breast cancer, either through suppression of nocturnally produced melatonin, general circadian disruption, or both. Similar findings have recently been obtained with respect to the growth and metabolism of human breast cancer in female rats. Of the 24 scientific studies reviewed for this study, 62.5% demonstrate a stimulatory effect of light during darkness on tumorigenesis, 25% show mixed and/or no effects of light, and 12.5% indicate an inhibitory effect of light during darkness on tumorigenesis. Additionally, a few studies now indicate a dose dependent relationship among light, the suppression of nocturnal melatonin production, and the stimulation of the growth of rodent liver cancer. Taken together with epidemiological evidence that shows a significant increase in the risk of certain cancers in human night shift workers, these experimental results suggest that it may be prudent to avoid prolonged exposure to bright light during the night over a period of years. However, without more detailed cancer studies, it is premature at this time to make specific recommendations to the lighting industry regarding potential changes in current standards and practices for architectural lighting. Further research is clearly needed.

EPRI Perspective

Both natural and artificial light affect human health well beyond what has been traditionally studied as vision and visual performance. Enhanced interaction between the medical research and lighting design communities will be required to bring the benefits of what is being discovered into common lighting practice. Through its Lighting Research Office (LRO), EPRI has an on-going commitment to promote research in the area of light and health. Recent EPRI publications in this area include the 5th EPRI/LRO Lighting Research Symposium - November, 2002 (EPRI report 1009370) and Lighting and Circadian Rhythms and Sleep in Older Adults (EPRI report 1007708).

Keywords

Lighting
Circadian rhythms
Cancer
Melatonin

CONTENTS

1
INTRODUCTION

When most of us think about visible light, we think about it in terms of our ability to see and interact with the world around us during both the day and night. Light is currently defined as optical radiation entering the eye that provides us with our sense of vision [1]. Although, the concept of "good" or "healthy" lighting has typically related solely to the visual system, within the past few decades it has become evident that there are profound effects of light on the biology of higher organisms, including humans that do not involve vision per se. One example of one of these so-called "non-visual" effects of light relates to the regulation of photopigment biology and vitamin D metabolism in the skin [2]. Another example is represented by the ability of light to influence daily (i.e., circadian) biological rhythms of physiology, metabolism and behavior [3] via specialized retinal photoreceptors believed to be different from the rods and cones [4]. In order for organisms to function optimally in relation to their environment, these circadian rhythms must be synchronized to the 24-hour cycles of day and night. Thus, it is not surprising that the predominant synchronizing cue for these rhythms is the natural cycle of light and dark [3].

Over-exposure of the skin to the actinic radiation of the sun has long been known to induce cellular DNA damage culminating in the development of skin cancer [2]. However, the detrimental influence of inappropriate ocular light exposure on circadian rhythm activity and its impact on health is a relatively new and emerging focus of basic and clinical research. This has been particularly evident with respect to the impact of ocular light exposure during darkness on the development and growth of cancer which was reviewed and updated at the LRO "Light and Human Health" Symposium in 2002 [5]. As a follow-up to the 2002 LRO Symposium, this white paper will focus on and highlight the research results, from both animal and human studies, that the authors believe are of most importance to the lighting industry with respect to the effects of light on the development and growth of internal, solid cancers. This white paper will present an overview of current knowledge regarding: 1) the nature of the circadian system and its regulation by light, 2) regulation of nighttime melatonin production by the pineal gland and the influence of light, 3) basic mechanisms of development and growth of internal, solid cancers, 4) basic mechanisms by which the endogenous, nocturnal melatonin signal regulates cancer development and growth, and 5) experimental laboratory-based evidence for the impact of light on the development and growth of internal, solid cancers, particularly in the context of population-based evidence for increased cancer risk in night shift workers. The final aspect of this article will be to speculate, as far as the current research data allow, as to potentially workable recommendations that might be made with regard to current lighting practices and most importantly, to make recommendations for future research.

2
REGULATION OF THE CIRCADIAN SYSTEM BY LIGHT

In humans and other mammalian species, light enters the eyes, stimulates the retina and signals are sent from the retina to the visual centers of the brain. Centuries of extensive scientific research have identified the underlying neuroanatomy and neurophysiology that support the sensory capacity of vision in humans. In 1972, it was discovered that the eyes detect environmental light and subsequent neural signals are transmitted from the retina into portions of the brain, which are not part of the visual system [6]. Figure 3-1 illustrates a simplification of the neural system that transmits information about environmental light from the retina into non-visual centers for the brain. This nerve pathway, the retinohypothalamic tract or RHT, extends from the retina into a part of the brain called the hypothalamus [6-10]. The hypothalamus is a complex neural region that controls many basic physiological functions including hormonal secretion, body temperature, metabolism and reproduction as well as higher neural functions such as memory and emotion [11,12]. Major targets of the retinal projection into the hypothalamus are the paired suprachiasmatic nuclei (SCN). These two nuclei are key components of the internal "biological clock" or circadian system. Specifically, the SCN serve as the primary central circadian oscillators which regulate daily rhythms such as the sleep-wake cycle, body temperature rhythms and 24 hour secretory patterns of hormones. The SCN modulate these diverse circadian rhythms by extensive nerve connections to many regions of the brain and spinal cord [14].

Although the neuroanatomy that supports the circadian system is largely independent of the pathways for vision and visual reflexes, there is a functional connection between the primary visual pathway and the circadian neuroanatomy by way of a projection from the intergeniculate leaflet to the SCN [9,13]. Recent studies have shown that the SCN receive input about environmental light from a specialized subset of photoreceptive retinal ganglion cells [4,14-17]]. Such photic input entrains internal near 24-hour rhythms to the environmental 24-hour light-dark cycle. Light appears to be the most potent stimulus to the internal time-keeping physiology of humans. Detection of light and darkness and its transmission to the SCN keeps rhythmic physiological and behavioral processes synchronized with the external environment. The human circadian pacemaker is exquisitely responsive to ocular light exposure, but it is well established that visual stimulation requires much less light than is required for circadian regulation [18-22]. When humans experience a change in their ambient light-dark cycle, it can induce an advance or delay of circadian rhythms. In general, light exposure during late night and early morning hours results in advancing circadian rhythms while evening light exposure induces a delay of rhythms [23-25]. Thus, changes in an individual's exposure to light and darkness can induce changes in the phases of circadian rhythms, such as that experienced during shift work, transcontinental jet travel and space flight [3,26-31].

3
REGULATION OF MELATONIN BY LIGHT

Among the many nerve pathways extending from the SCN, the tract connecting the circadian pacemaker to the pineal gland has been very well characterized as shown in Figure 3-1. After receiving signals from the retina about environmental light and darkness, the SCN transmits information sequentially to the paraventricular hypothalamus, the upper thoracic spinal cord intermediolateral cell column, the superior cervical ganglion and ultimately, the pineal gland [6-10]. By this pathway, the ambient light-dark cycle entrains the rhythmic synthesis and secretion of the pineal hormone melatonin. Numerous studies in humans and other species have demonstrated that high levels of melatonin are secreted during the night, and low levels are secreted during the day [32,33]. In addition to entraining this circadian rhythm of melatonin synthesis, unexpected exposure to light at night can elicit an acute suppression of the naturally high nighttime levels of melatonin. This rapid light-induced suppression of melatonin response has been consistently observed in many species, including humans. The light-induced melatonin suppression response has been used extensively as a tool to investigate the ocular, neural and biochemical physiology of melatonin regulation and circadian rhythms [9,27,28,34].

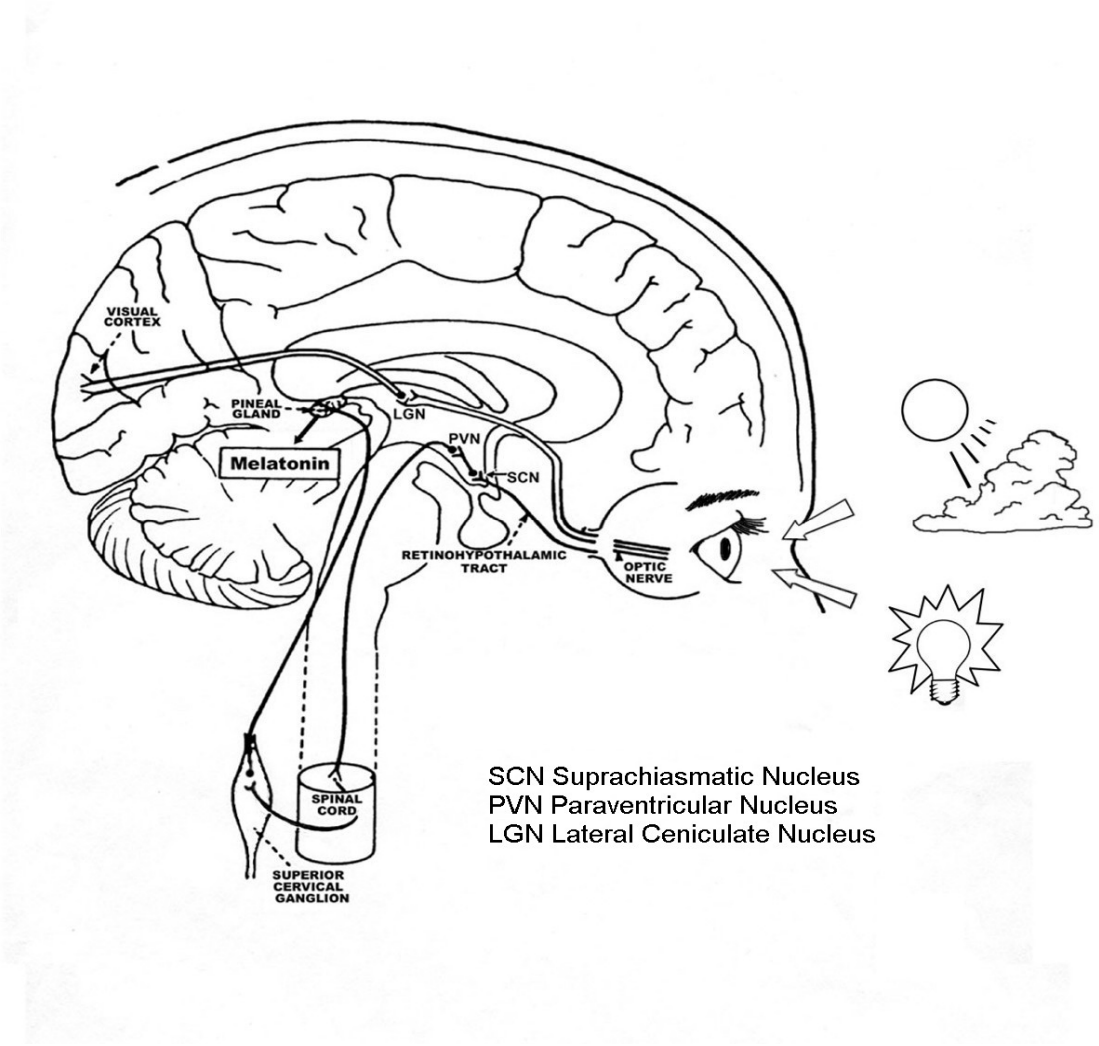

Figure 3-1

Along with circadian regulation of melatonin and acute, light-induced melatonin suppression, seasonal changes in night and day length (photoperiod) alters the duration of the elevated melatonin production. Specifically, in a number of mammalian species, the duration of high nocturnal melatonin secretion is shorter in the summer due to shortened nighttime periods. Conversely, during the winter when nights are longer, the duration of high nocturnal melatonin production is increased [32,33,35,36]. The seasonal variation in the total amount of melatonin produced relative to the photoperiod is not as easy to observe in humans living under modern, industrialized conditions. Careful, controlled laboratory studies, however, have confirmed that the human pineal gland modulates the duration of nocturnal melatonin secretion relative to photoperiod [37,38]. Overall, many studies have shown that light stimuli are the strongest and most consistent regulators of melatonin synthesis and secretion. In addition, certain drugs can powerfully impact melatonin secretion while other non-photic and non-pharmacological stimuli such as body posture and exercise may modify melatonin levels [39-41].

4
PHOTOSENSORY INPUT TO THE CIRCADIAN SYSTEM

Since environmental light is the most potent regulator of the circadian system, it is important to determine how light signals are detected for circadian and melatonin regulation. The photoreceptor physiology for circadian input has been a matter of continued debate. Earlier studies of mice that genetically lacked rod photoreceptors showed preservation of light-induced circadian responses [42,43]. Those results suggested a cone-like photoreceptor was involved in mediating light input to the circadian pathway. More recent data suggest that a novel photoreceptor system may be primarily responsible for transducing light stimuli for circadian regulation. Animal studies that support involvement of a novel photoreceptor system include light-induced circadian phase-shifting and melatonin suppression in mice that have been genetically altered so that their eyes contain no rods or cones for vision [44,45]. Furthermore, in studies on humans with complete visual blindness or humans with color vision deficits, melatonin can be suppressed by exposing the eyes to light [46,47]. Indeed, blind individuals who had no conscious light perception still detected light through their eyes for phase-shifting their circadian clock [48].

In the past three years, a series of action spectra have further supported the concept that mammals have a photoreceptor system in the eye different from the classic photopic and scotopic systems for vision. First, in normally sighted humans, a study on humans strongly indicated that the melatonin suppression response was independent of the three-cone visual system [49]. More recently, two more complete action spectra for melatonin suppression appear to be independent of the three-cone visual system and all of the individual classic visual photoreceptors [50,51]. Those studies show that the strongest light wavelengths for melatonin suppression in humans are in the blue portion of the visible spectrum. Four other recent action spectra developed in separate animal and human studies also identified the blue region of the spectrum as strongest for evoking electroretinogram B-waves in humans, pupillary constriction and circadian phase-shifting in rodless, coneless mice, and direct retinal ganglion cell response to light stimuli in rats [52-55]. When comparing the action spectra in relation to one another, it is important to consider that each examines a distinct physiological response in different mammalian species. Each of these action spectra, however, suggests that a novel photopigment mediates circadian phototransduction and other non-visual, ocular-mediated responses.

The specific biochemical identity for the photopigment(s) which supply input to the circadian system continues to be debated. The action spectra studies support the hypothesis that a vitamin A1 opsin photopigment provides the main input to the SCN [51-55]. Other investigators suggest, however, that cryptochromes [56] or combined activities of rod cells and blue cones [57] mediate circadian photoreception. Among the different photopigments which have been proposed to mediate circadian phototransduction in mammals, melanopsin is a very strong candidate. Melanopsin is a vitamin A1, opsin-based molecule localized in both the rodent and human neural retina [14,58-60]. Studies on rodents have shown that melanopsin is found in a specific subtype

of retinal ganglion cells (RCGs) which have an expansive ganglion cell dendritic net and project to the SCN and other regions of the brain [14-17, 61]. One of these studies showed that the RGCs with projections to the SCN are intrinsically responsive to light [4].

The light responses of these specific ganglion cells in rats appear to parallel those of photic entrainment and melatonin suppression, indicating that these cells are the primary photoreceptors involved in circadian regulation [4]. Recent studies of mice that have had their melanopsin gene "knocked out", however, demonstrate that although melanopsin plays a central role in phototransduction for circadian regulation and the pupillary light reflex, other photoreceptors can contribute to this light-regulated physiology when melanopsin is absent. [61-63]. Thus, there may be redundant photoreceptor inputs to the SCN. Further studies are required to determine the exact role of melanopsin in circadian phototransduction. The following section presents the growing evidence that light exposure may play a role in the development of cancer. Ultimately, it will be critical to determine if the newly discovered circadian photoreceptors also mediate the effects of light on cancer.

5
DYNAMICS OF CANCER DEVELOPMENT AND GROWTH

Normal cells that make up the tissues and organs of our developing bodies increase their number through successive rounds of cell division, also called the process of proliferation. Tissues and organs develop and grow through exquisitely controlled biochemical and molecular mechanisms that result in just the right balance between cell division, survival and death – in other words, not too much cell growth or cell loss. Cancer begins when a normal cell is transformed by a spontaneous event or more commonly by an environmental factor(s) (i.e., carcinogen) that induces a specific type of damage, called a mutation, in the genetic blueprint contained in our DNA, resulting in less controlled and more frequent cell proliferation. The process of cancer development and growth, also called carcinogenesis, is initiated in a single cell through damage to a small portion of its DNA induced by an environmental carcinogen or even a virus. Over the course of a decade or more, the altered cell and its descendants develop into what is referred to as a precancerous growth, also referred to as dysplasia. Over the next 5 to 20 years, additional mutations occur in the affected cells, resulting in changes that "turn on" the expression of cancer-promoting genes called oncogenes while simultaneously turning off the expression of tumor suppressor genes. These alterations produce further dramatic changes in cellular metabolism that lead to the accumulation of defects in cellular growth control mechanisms, to less cellular specialization and to rapid expansion of the growth into a localized, small cancer which may remain in this state, called carcinoma in situ, for many years. Under proper circumstances of stimulation by growth factors and hormones and further loss of growth inhibitory factors, the cancer takes over locally. It does this by recruiting more blood vessels, via the process of angiogenesis, thus allowing it to extend outside its local boundaries and to invade surrounding tissues. Eventually, vicious cancer cells leave the confines of the primary tumor via the circulation and spread to lymph nodes and more distant organs such as the liver, lung or bone, thus completing the process of malignancy. It is this last stage of cancer progression that often leads to the death of the host [64,65].

6
REGULATION OF CANCER DEVELOPMENT AND GROWTH BY THE NOCTURNAL, CIRCADIAN MELATONIN SIGNAL FROM THE PINEAL GLAND

The maintenance of normal cell physiology and metabolism requires that cells have the ability to detect, integrate and appropriately respond to a wide variety of external and internal signals that oscillate predictably over the 24-hour day [66]. As envoys of the external and internal environment, stimulatory and inhibitory growth factors and hormones provide temporally-coordinated inputs to normal cells that establish the proper balance between cell proliferation, survival and death in the maintenance of the normal or differentiated state, of cells in tissues and organs. As alluded to above, the characteristic uncontrolled proliferation of both precancerous and bona fide cancer cells results to a large degree from the loss of these regulatory influences and a breakdown in this balance. In fact, most types of cancer cells overproduce and/or exhibit exaggerated responses to their own growth factors, leading to a sustained, self-stimulation of their own proliferation [64,65].

The nocturnal production of melatonin, the premier circadian hormone of darkness, serves as a fundamental biological signal that literally "tells" every cell, tissue and organ of the body, including precancerous or cancer cells, about the status of the environmental photoperiod and thus the timing of the biological day. Melatonin plays an important role in a number of physiological and pathophysiological processes, including circadian rhythm regulation, seasonal reproduction immune function and tumorigenesis [67,68]. Melatonin's mechanism of action in the regulation of circadian rhythms and seasonal reproduction and many other processes including cancer, is generally thought to occur through its ability to bind to specialized cell surface proteins, called melatonin receptors that specifically recognize and respond to melatonin. Once melatonin binds to these receptor proteins it induces a change in their molecular structure that transmits a signal from the surface of the cancer cell to its interior. This signal, in turn, induces an inhibition of the production of cyclic adenosine monophosphate (cAMP), a crucial messenger molecule that influences changes in the activity of many interconnecting molecular pathways affecting a variety of cell functions [69,70]. Melatonin also modulates the internal workings of the cell by avoiding receptors all together by directly passing through the cell membrane and interacting with molecules inside the cell to effect changes in biochemical and cellular activities. For example, melatonin enters cells to act as a direct scavenger of free radical molecules and reactive oxygen species generated during cellular functions including those that cause DNA damage that may initiate the process of carcinogenesis [71].

Although some evidence suggests that melatonin may suppress cancer growth through mechanisms involving alterations to the neuroendocrine and/or immune function, the vast

majority of studies support a direct inhibitory action of melatonin on the proliferation of cancer cells themselves. These antiproliferative effects are primarily exerted over a concentration range that encompasses the levels of melatonin normally present in the blood circulation during the night. In fact, in some cancer cells, most notably human breast cancer cells, physiological nocturnal concentrations of melatonin slow down the rate of transit of cells through the cell division cycle. It accomplishes this by stimulating tumor suppressor genes, inhibiting oncogenes, and by blocking the growth-promoting actions of the ovarian hormone estrogen, the pituitary hormone prolactin and growth factors [72-75] produced by the cancer cells themselves such as epidermal growth factor (EGF) and its homologue, transforming growth factor α (TGFα) [64]. As the rate of cell division slows down, cells begin to accumulate in a quiescent phase of the cell cycle which allows them to become more differentiated (i.e., more normal). As they begin to look and act more like normal cells, they proliferate very slowly or not at all. This also increases the chances that these quiescent cells will undergo programmed cell death (i.e., apoptosis) [75]. As alluded to previously, melatonin may suppress the initiation of cancer by limiting damage to DNA caused by carcinogens in normal cells. Melatonin achieves this by directly scavenging DNA-damaging free radicals and/or by promoting the differentiated state of normal cells [71]. Finally, melatonin also slows down the spread (i.e., metastasis) of cancer cells to distant sites by minimizing their invasive properties as well as by improving their ability to communicate with one another (i.e. intercellular communication) which is a characteristic of normal, differentiated cells. As a newly acknowledged player on the ever expanding team of regulatory factors that control cell proliferation, survival, differentiation and loss, and metastasis, melatonin occupies a unique position as chronobiotic hormone (i.e., shifts the phasing of circadian rhythms) that inhibits, to one degree or another, the full range of altered cellular activities leading to cancer development and growth [72-75].

An important molecular mechanism by which melatonin specifically inhibits the proliferation of human breast cancer cells containing estrogen receptors (ERs) in the petri dish is via a melatonin receptor-mediated suppression of cAMP production, leading to an attenuation of the estrogen growth signaling pathway [76]. Another major mechanism by which the endogenous, nocturnal melatonin signal inhibits the growth of cancer in animal models is also via a melatonin receptor-mediated suppression of tumor cAMP production [77]. However, rather than affecting the estrogen response pathway, the melatonin inhibition of cAMP signaling results in a blockade in the ability of tumors to take up linoleic acid (LA), an essential dietary, omega-6 polyunsaturated fatty acid (PUFA). As the most abundant PUFA in the western diet, LA is taken up by cancer cells and metabolized, by an enzyme called 15-lipoxygenase-1, to 13-hydroxyoctadecadienoic acid (13-HODE) which is a powerful signal for LA-dependent cancer growth [78]. Once formed inside the cancer cell, 13-HODE exerts a potent stimulatory effect on the ability of EGF to stimulate DNA synthesis and cell division. By blocking the tumor uptake of LA, melatonin effectively blocks the production of the cancer growth-signaling molecule 13-HODE [77,78].

7
EFFECTS OF CONSTANT BRIGHT LIGHT ON CANCER DEVELOPMENT AND GROWTH IN EXPERIMENTAL ANIMAL MODELS OF TUMORIGENESIS

It has been known for many years that the surgical removal of the pineal gland from rodent species eliminates the expression of the nocturnal, circadian melatonin signal [32]. Similarly, the exposure of animals to constant bright light also eliminates the rhythmic melatonin signal characteristic of animals maintained on an alternating light-dark cycle [32,33,36]. Therefore, it is not surprising that exposure of animals to constant light has been used as a strategy to mimic the effects of pinealectomy in a variety of experimental situations, particularly in cancer experiments [32]. In fact, constant light exposure has often been referred to as a "functional" or "physiological" pinealectomy. While pinealectomy and constant light exposure both extinguish the circadian melatonin signal, they are not, in fact, equivalent procedures with respect to the effects they produce. For example, over time, exposure to the constant light condition causes the entire circadian system to eventually break down. This effect has been referred to as circadian disruption and represents a stressful circumstance for the organism. On the other hand, following pinealectomy, only the melatonin rhythm is obliterated, leaving the integrity of the general circadian system intact.

For the past 40 years, scientists have been interested in the effects of either pinealectomy or constant light exposure on the development and growth of cancer, particularly in experimental models of mouse and rat mammary cancer. With few exceptions, the majority of studies have demonstrated a marked stimulatory effect of either pinealectomy or constant light exposure on tumor development and growth (Table 1) [79-100]. In general, following pinealectomy or exposure to constant bright light not only do tumors appear earlier, but also a greater percentage of animals develop tumors and more tumors develop per animal as compared to control animals maintained on an alternating 12 hour light:12 hour dark cycle [79,80,82,85-87,89-93,95,98-100]. Some studies show that under the conditions of constant bright illumination (i.e., 150 lux or greater), tumors grow at a faster rate than their counterparts on diurnal lighting [91,92,98-100]. However, it is important to note that the effects of constant bright light exposure on the development of experimental cancer may depend on several factors. These include the strain of animal used as well as the timing of the initial constant light exposure in relation to reproductive status of the mouse or to the administration of a chemical carcinogen in the case of rats. For example, in some strains of mice, constant bright light exposure stimulates spontaneous mammary tumorigenesis, whereas in others it is inhibitory. The lack of a stimulatory tumor response in the latter case may be due to the presence of genetically dependent retinal degeneration in that particular mouse strain [79]. In another special, transgenic strain of mice that overexpresses an oncogene called HER-2/neu, a member of the EGF receptor family, constant light exposure fails to both increase the incidence of spontaneous mammary cancer development and stimulate tumor growth or metastasis to lungs [97]. Paradoxically, although

the number of tumors per mouse actually increased following exposure to constant light, tumors appeared significantly later than in the L:D controls. Thus, a number of genetic and epigenetic factors appear to modify the tumorigenic response to constant light exposure.

Table 1
Effects of inappropriate light exposure on the development and/or growth of various tumors in different model systems of experimental cancer. Tumor signifies a malignant (i.e., cancerous) tumor unless otherwise designated as benign. Light intensity? = light intensity not reported. In each reference box, the overall effect of light on tumorigenesis in a given study is indicated as follows: S = light is stimulatory, I = light is inhibitory; M = mixed and/or no effect of light. Types of carcinogens used in cancer studies: DMBA = dimethylbenzanthracene; NMU= nitrosomethylurea; NEU = nitrosoethylurea; DEN = diethylnitrosamine.

Tumor Type & Model System	Photoperiod & Light Exposure Conditions	Effects on Tumorigenesis	Reference
Spontaneous mammary tumors in C3H-A adult female mice (intact retinae)	Control photoperiod = 12L:12D Experimental light exposure = permanent constant light from birth to death Light intensity?	↓ Latency to tumor onset ↑ Tumor incidence ↑ Death from tumor burden	Jöchle (1964) (79) S
Spontaneous mammary tumors in C3H-HeJ adult female mice (genetic retinal degeneration)	Control photoperiod = 12L:12D Experimental light exposure = Permanent constant light from birth to death Light intensity?	↑ Latency to tumor onset ↓ Tumor incidence ↓ Death from tumor burden	Jöchle (1964) (79) I
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant light starting 7 wks prior to DMBA and continuing through tumorigenesis Light intensity?	↓ Mammary tumor incidence ↑ Ovarian tumor incidence	Khaetsky (1965) (80) M
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant light starting 4 wks after last DMBA injection and continuing through tumorigenesis Light intensity?	↓ Latency to tumor onset ↑ Tumor number and growth rate	Khaetsky (1965) (80) S

DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = Constant dark (no adaptive or control 12L:12D photoperiod), interrupted by dim light (intensity?) for animal care Experimental light exposure = Constant light starting after DMBA and continuing through tumorigenesis Light intensity?	No effects on tumor incidence or number ↑ Latency to tumor onset ↑ Incidence of fibroadenomas (benign tumors)	Jull (1966) (81) M
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant light beginning 1 wk before DMBA treatment and continuing through tumorigenesis Light intensity = 30 lumens/sq. ft Fluorescent light	↑ Tumor incidence (majority were fibroadenomas [benign tumors]); majority of tumors in control photoperiod were adenocarcinomas (malignant tumors)	Hamilton (1969) (82) S
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant darkness prior to DMBA injection and continuing through tumorigenesis	↓ Serum levels of follicle-stimulating hormone, estradiol, corticosterone ↓ Thyroid activity ↑ Latency to tumor onset ↓ Tumor incidence and number ↑ Survival	Kuralasov (1979) (83) I
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant light beginning the day of DMBA administration and continuing through tumorigenesis Light intensity? Illumination by 40-W fluorescent tubes 2 m above cages	No effect on tumor incidence ↑ Latency to tumor onset	Aubert et al. (1980) (84) M
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 10L:14D Experimental light exposure = Constant light from birth 7 wks before DMBA treatment and continuing through tumorigenesis Light intensity? Illumination	↑ Tumor incidence ↑ Tumor number ↓ Latency to tumor onset	Kothari et al. (1982) (85) S

	by 40-watt fluorescent tubes 30 cm above cages		
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 10L:14D Experimental light exposure = Constant light from birth 7 wks before DMBA treatment and continuing through tumorigenesis Light intensity? Illumination by 40 watt fluorescent bulbs 30 cm above cages	↑ Tumor incidence ↑ Tumor number ↓ Latency to tumor onset	Kothari et al. (1984) (86) S
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 10L:14D Experimental light exposure = Constant light from birth 7 wks before DMBA treatment and continuing through tumorigenesis Light intensity = 150 lux Illumination by 40-W fluorescent tubes 30 cm above cages	↑ Tumor incidence ↓ Latency to tumor onset ↑ DNA synthesis in mammary gland ↑ Terminal end buds and alveolar buds in mammary gland ↑ Plasma prolactin levels No change in plasma estradiol levels	Shah et al. (1984) (87) S
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 10L:14D Experimental light exposure = Constant light from birth 7 wks before DMBA treatment and continuing through tumorigenesis Light intensity?	No effect on tumor incidence or number ↑ Latency to tumor onset	Subramanian and Kothari (1991) (88) M
NMU-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant light or constant darkness from 4 wks of age (2 wks prior to NMU injection) and continuing through tumorigenesis Light intensity?	Constant light: ↓ nocturnal serum melatonin levels ↑ nocturnal serum prolactin levels, ↓ latency to tumor onset ↑ tumor incidence and number Constant darkness: No effect on serum melatonin or prolactin levels ↑ latency to tumor onset ↓ tumor incidence and number	Anisimov et al. (1994) (89) S
NMU-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure =	Constant light: ↓ nocturnal serum melatonin levels ↑ nocturnal serum prolactin	Anisimov et al. (1996) (90) S

	Constant light or constant darkness (3 wks prior to NMU injections) and continuing through tumorigenesis Light intensity? During constant darkness short intervals of red light exposure (light intensity?) for animal care	levels, ↓ latency to tumor onset ↑ tumor incidence ↓ life span Constant darkness: No effect on serum melatonin or prolactin levels ↑ latency to tumor onset ↓ tumor incidence no effect on life span	
Tissue-isolated transplantable rat hepatoma 7288CTC in male albino rats	Control photoperiod = 12L:12D Experimental light exposure = dim light (indirect) contamination during the dark phase of 12L:12D photoperiod or constant light 1 wk before tumor implantation and continuing through tumorigenesis Light intensity = 0.2 lux (dim light) and 810 lux (constant light) at rodent eye level Illumination by three 32-W fluorescent tubes for constant light and indirect light from light leak through door jam	↓ Nocturnal melatonin blood levels ↑ Tumor LA uptake and 13-HODE production ↓ Latency to tumor onset ↑ Tumor growth rate	Dauchy et al. (1997) (91) S

Tissue-isolated transplantable rat hepatoma 7288CTC in male albino rats	Control photoperiod = 12L:12D Experimental light exposure = dim light (direct) during the dark phase of 12L:12D photoperiod or constant light 1 wk before tumor implantation and continuing through tumorigenesis Light intensity = 0.2 lux (dim light) and 300 lux (constant light) at rodent eye level Illumination by three 32-W fluorescent tubes for constant light and two 15-W fluorescent tubes (cool white) wrapped with neutral density filters	↓ Nocturnal melatonin blood levels ↑ Tumor LA uptake and 13-HODE production ↓ Latency to tumor onset ↑ Tumor growth rate	Dauchy et al. (1999) (92) S
DEN-induced liver tumors in adult male albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant light 3 wks after DEN administration and continuing through tumorigenesis Light intensity =250 lux at cage level	↓ General circadian activity ↓ Circadian rhythm of urinary 6-sulfatoxymelatonin excretion ↑Incidence, number and size of liver tumor nodules	Van den Heiligenberg et al. (1999) (93) S
DMBA-induced mammary tumors in adult female albino rats	Control photoperiod = 8L:16D Experimental light exposure = Constant light at 26 days of age (26 days prior to DMBA) and continuing through tumorigenesis Light intensity = 120 – 250 lux at cage level	↓ Tumor incidence and number ↑ Number of rats with lactation nodules No effect on survival	Anderson et al. (2000) (94) I
Transplacental carcinogen-induced peripheral nervous system and kidney tumors in adult male and female albino rat offspring from pregnant dams treated with NEU	Control photoperiod = 12L:12D Experimental light exposure = Constant light or constant darkness from the time of NEU injection during pregnancy and continuing for 4 wks after delivery (lactation period) of offspring followed by 12L:12D through tumorigenesis and death	Constant light ↓ Latency to tumor onset Constant darkness ↑ Latency to tumor onset Constant light ↑ tumor incidence and number (majority malignant tumors) Constant darkness ↓ tumor incidence and number (except kidney tumors; majority	Behiashvilli et al. (2001) (95) S

	Light intensity?	benign tumors) Constant light ↓ survival Constant darkness ↑ survival	
NMU-induced mammary tumors in adult female pigmented rats	Control photoperiod = 12L:12D Experimental light exposure = five, 1-minute incandescent light exposures every 2 h during dark phase beginning on day of NMU injection and continuing through tumorigenesis Light intensity = 61 to 193 lux (lower to upper cage tiers) at cage floor level	No effect on tumor incidence, number or weight No effect on survival ↓ Nocturnal serum melatonin (after 1-day exposure) ↑ Nocturnal serum melatonin (after 26 wks of exposure)	Travlos et al. (2001) (96) M
Spontaneous mammary tumors in adult female albino HER-2/neu transgenic mice	Control photoperiod = 12L:12D Experimental light exposure = Constant light from 2 mos of age continuing through tumorigenesis to 11 mos of age Light intensity?	No effect on tumor incidence, size or metastasis to lungs ↑ Tumor number ↑ Latency to tumor onset	Baturin et al. (2001) (97) M
Tissue-isolated, transplantable NMU-induced mammary tumors in adult female albino rats	Control photoperiod = 12L:12D Experimental light exposure = Constant light beginning 1 wk prior to tumor implantation and continuing through tumorigenesis Light intensity = 300 lux at rodent eye level	↑ Tumor LA uptake and 13-HODE production ↓ Latency to tumor onset ↑ Tumor growth rate	Blask et al. (2002) (98) S
Tissue-isolated ER+ MCF-7 human breast cancer xenografts in adult female pigmented nude rats	Control photoperiod = 12L:12D Experimental light exposure = Tumor-bearing rats transferred from 12L:12D to constant light beginning 40 days after tumor implantation and continuing through tumorigenesis Light intensity = 300 lux at rodent eye level	↓ Nocturnal melatonin blood levels ↑ Tumor LA uptake and 13-HODE production ↑ Tumor growth rate	Blask et al. (2003) (99) S
Tissue-isolated transplantable rat hepatoma 7288CTC in male albino rats	Control photoperiod = 12L:12D Experimental light exposure = Indirect reflected light during the dark phase of 12L:12D photoperiod 2 wk before tumor implantation and	Dose-response ↓ nocturnal melatonin blood levels Dose-response ↑ tumor LA uptake and 13-HODE production Dose-response ↓ latency to	Dauchy et al. (2003) (100) S

	continuing through tumorigenesis Light intensity = 0 (complete darkness or 0 lux), 0.02, 0.05, 0.06, 0.08 or 345 μW/sq. cm (constant light or ~ 840 lux) at rodent eye level Illumination by one 32-W fluorescent tube wrapped with neutral density filters	tumor onset Dose-response ↑ tumor growth rate	

As alluded to above, in animals with chemically-induced mammary tumors a differential responsiveness to constant light exposure is predicated by the timing of the initiation of constant light exposure in relation to the onset of puberty as well as to the timing of the carcinogen administration. For example, when constant light treatment is begun approximately two months prior to multiple weekly administrations of the mammary gland carcinogen DMBA, the incidence of mammary tumor development is less than in the animals on a L:D cycle [94]. However, when constant light exposure begins a month following the last injection of DMBA, mammary tumorigenesis is stimulated as compared with L:D controls. Not only do more tumors develop per rat, but also they appear sooner following constant illumination [80]. In most of these studies, the level of light intensity was not reported and circulating melatonin levels were not measured. However, it was generally assumed that constant light-induced suppression of pineal melatonin production was responsible for its stimulatory effects on carcinogen-induced mammary carcinogenesis (Table 1). Other than constant light-induced stimulation of pituitary prolactin secretion, a hormone important for the development of experimental mammary cancer in rats [87,89,90] no assessment was made of the mechanism(s) by which constant illumination either stimulated or inhibited tumor development in these investigations.

Although constant light exposure seems to stimulate tumorigenesis in the majority of investigations (Table 1), clearly one-third of the studies conducted report either inhibitory, mixed or no effects on the development of experimental cancer. Interestingly, more consistent stimulatory actions of continuous illumination appear to occur with respect to the growth of established tumors. Moreover, mechanistic information is now available on how constant light enhances the growth of transplantable tumors. In rats bearing either tissue-isolated rat liver cancer (i.e., hepatoma) or rat mammary cancer, exposure of these animals to constant bright light (i.e., 300 lux at rodent eye level) for one week prior to tumor implantation and continuing thereafter, there is a complete absence of the nocturnal, circadian rise in circulating melatonin levels as compared with L:D controls. Moreover, not only do tumors appear much earlier as a result of constant light exposure but their average daily growth rate accelerates by a factor of 2.5- to 6-times over the average growth rate of tumors in the L:D control group. The marked increase in the rate of tumor growth results from a substantial augmentation in the rate of tumor uptake of LA and its conversion to 13-HODE as a consequence of the suppression of the circadian melatonin signal (see above) [91,92,98-100]. However, it is also possible that a dysfunction in general circadian activity, in addition to melatonin suppression, contributes to the tumorigenic effects of constant bright light exposure since complete circadian disruption occurs following several weeks of constant light exposure [101,102].

8
EPIDEMIOLOGICAL EVIDENCE THAT INDIRECTLY SUPPORTS THE LIGHT AT NIGHT HYPOTHESIS

While studies on the effects of constant light exposure in experimental models of rodent tumorigenesis have been extremely important in providing an initial biological link between light during darkness, circadian and melatonin disruption and increased carcinogenesis, there have been no similar investigations on carcinogenesis in humans. Obviously, it would be technically impossible, not to mention unethical, to expose human subjects, who either have cancer or who are at high risk for cancer, to conditions of prolonged light exposure at night for the many years that it would take for cancer to develop and grow. Population studies in night shift workers support the hypothesis of Stevens that light at night may be a significant risk factor for human breast cancer [103] and other cancers as well as a result of melatonin suppression [104]. These epidemiological studies essentially use night shift work as a surrogate for light at night, since prolonged exposure to light at night results in an increased likelihood of melatonin suppression and other types of circadian disturbances that would be a feature of this type of work. In fact, in female night shift workers (i.e., nurses) the risk of breast cancer increases up to 60% and the risk of colorectal cancer increases up to 35% with the degree of risk being directly related to the number of years of shift work [105-108]. That this increased cancer risk in shift workers may be related, at least in part, to LAN-induced melatonin suppression is supported by the fact that blind individuals, who may be protected from the melatonin-suppressive effects of light, have a substantially lower risk (i.e., up to 50%) of breast cancer with the degree of risk being inversely related to the degree of visual impairment [109-113]. The reader is encouraged to consult the individual references cited above for the details regarding the results of these important population studies.

9
EFFECTS OF CONSTANT BRIGHT LIGHT ON HUMAN BREAST CANCER GROWTH IN RATS

For the reasons cited above, testing the light at night hypothesis with regard to human carcinogenesis has eluded an experimental approach since no model system existed that would permit the examination of the effects of constant bright light suppression of the nocturnal, melatonin signal on human carcinogenesis. Recently, this problem has been partially circumvented through use of a special breed of female rat (i.e., athymic nude rat) that lacks a thymus gland. The absence of the thymus gland, an important organ of the immune system, prevents these animals from mounting an immune response against and preventing the rejection of implanted human cancer xenograft tissue [99]. Nude rats, which like all laboratory rats are nocturnally active, exhibit a robust nocturnal, circadian melatonin rhythm that is quite similar, in terms of timing, amplitude and duration, to that observed in pre- and postmenopausal healthy women. Most importantly, the melatonin signal is completely suppressible by exposure of these animals to 300 lux of constant bright light. Human breast cancer xenografts, derived from the ER+ human breast cancer cell line, MCF-7, grow quite well following their implantation into female nude rats. During a two week period following their transfer from a 12L:12D light:dark cycle (i.e., intact circadian melatonin signal) to constant bright light (i.e., 300 lux) (i.e., no melatonin signal), the average daily rate of tumor growth in constant light-exposed rats increases by 7-fold in comparison to the tumor growth rate in animals remaining on an L:D cycle. This accelerated rate of human breast cancer growth was initiated and sustained as a result of increases in the rate of tumor uptake of LA and its metabolism to 13-HODE. This augmented rate of tumor LA uptake and metabolism results from constant light-induced suppression of the circadian melatonin signal which normally drives the inhibition of these processes during the dark phase [75,77,78] (see above). Since it is likely that the function of the general circadian system is preserved in these animals over two weeks, the specific suppression of nocturnal melatonin rather than general circadian disruption is most likely responsible for accelerated tumor growth. This is the first experimental evidence to date showing a link between inappropriate exposure to continuous bright light and increased growth and fatty acid metabolism of human breast cancer. This also represents the most definitive support, thus far, for the hypothesis that light-induced suppression of nocturnal melatonin production may be a new risk factor for human breast cancer [103], particularly in night shift workers who also consume diets high in fat during the night [114].

10

EFFECTS OF LOW INTENSITY LIGHT EXPOSURE DURING DARKNESS ON CANCER GROWTH IN EXPERIMENTAL ANIMAL MODELS OF TUMORIGENESIS

As alluded to above, the ability of ocular light exposure to suppress pineal melatonin production depends on the intensity, wavelength, duration and timing of light. As important as the constant bright light studies are, they address only one aspect of the intensity issue. However, studies have demonstrated that the exposure of rats to low intensity light (i.e., 0.2 lux at rodent eye level) during the dark phase for one week prior to the implantation of tissue-isolated rat hepatomas and continuing thereafter, results in a dramatic suppression of circulating melatonin levels that is nearly as great as that induced by constant bright light [91,92]. In contrast to constant bright light exposure, general circadian function is preserved in rats exposed to 0.2 lux of light during the dark phase. However, the tumor growth rate, LA uptake and metabolism to 13-HODE are nearly as rapid as in constant light-exposed animals indicating that low intensity light-induced melatonin suppression during the dark phase, rather than general circadian disruption, is responsible for increased tumorigenesis.

Recent studies have examined the light intensity issue in greater detail by determining the effects of different light intensities during darkness on nocturnal circulating melatonin levels and the growth and LA metabolism of rat hepatoma 7288CTC [100]. Exposure of tumor-bearing rats to light intensities (at rodent eye level) ranging from complete darkness to constant bright light (345 μW/sq. cm or ~ 840 lux) results in a dose-dependent suppression of melatonin levels with a concomitant dose-related stimulation of tumor growth, LA uptake and 13-HODE production. Although preliminary, these findings represent the first evidence that stimulation of tumor growth and metabolism is dependent on the degree of the suppression of melatonin production that is, in turn, dependent upon the intensity of light present during darkness.

11
SUMMARY AND RECOMMENDATIONS REGARDING CURRENT LIGHTING PRACTICES

As reviewed above, an increasing amount of evidence more clearly supports the hypothesis that bright light present during the dark phase of an alternating light/dark cycle (i.e., constant light) stimulates the development and growth of experimental rodent tumors, especially breast cancer, either through suppression of nocturnal production melatonin, general circadian disruption or both. Similar findings have recently been obtained with respect to the growth and LA metabolism of human breast cancer in female rats (Fig. 11-1). Of the 24 scientific studies reviewed above (Table 1), 62.5% demonstrate a stimulatory effect of light during darkness on tumorigenesis, 25% show mixed and/or no effects of light while 12.5% indicate an inhibitory effect of light during darkness on tumorigenesis. Additionally, a few studies now indicate that as light intensity increases from very dim light to bright light, a dose-dependent suppression of the nocturnal, circadian melatonin signal leads to a dose-dependent stimulation of rodent liver cancer and LA metabolism. Taken together with the epidemiological evidence showing a significant increase in the risk of certain cancers in human night shift workers, these experimental results, at a minimum, provide a strong argument for prudent avoidance of prolonged exposure to bright light during the night over a period of years. Architects and engineers have traditionally designed indoor and outdoor lighting with the primary purpose of optimizing visual stimulation, maintaining visual comfort, providing an aesthetically pleasing environment and conserving energy [1,5,15]. For more than 20 years, rigorous scientific evidence has supported the concept that, separate from vision and visual reflexes, light perceived by the eye can influence human physiology, mood and behavior [3,18,26,27]. These findings could provide the basis for fundamental changes in future lighting strategies that could help foster some aspects of human health and well being. However, with respect to the process of carcinogenesis, it is premature at this time, absent additional and more detailed cancer studies, to make specific recommendations to the lighting industry regarding potential changes in current standards and practices for architectural lighting. Therefore, our major recommendation to the various constituencies of the lighting industry is that further research is needed as summarized below.

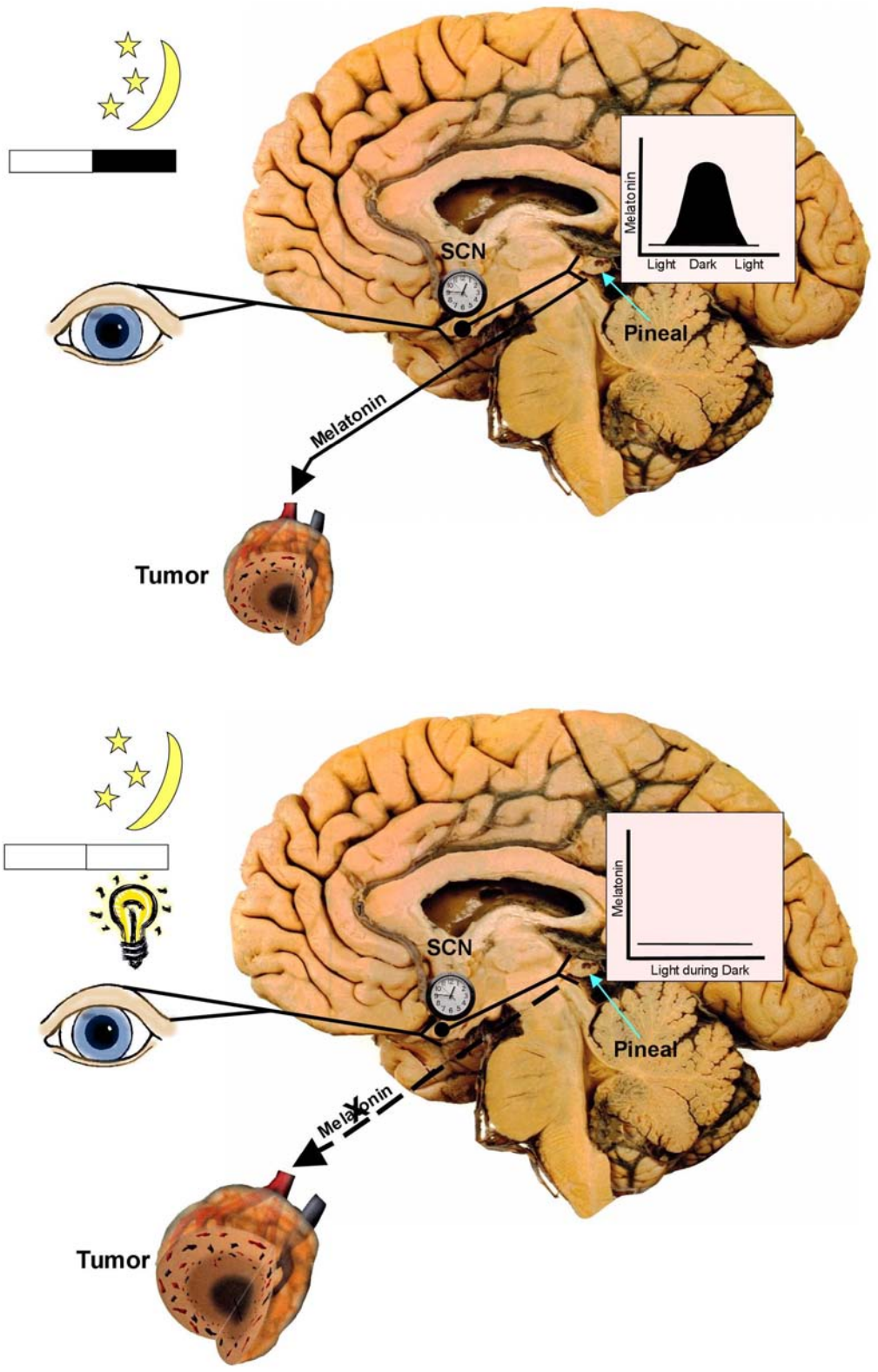
Melatonin
Light Dark Light
SCN
Pineal
Melatonin
Tumor
Melatonin
Light during Dark
SCN
Pineal
Melatonin
Tumor

Figure 11-1

12
RECOMMENDATIONS FOR FUTURE RESEARCH

In spite of the advances made over the past 40 years with respect to the effects of inappropriate exposure to light during darkness on tumorigenesis in animal models of experimental cancer we are currently just at the threshold of our understanding regarding this topic. There is no question that additional research is required to further and more precisely characterize the effects of light during darkness with respect to cancer development and growth, for a variety of different cancer types and model systems and the mechanisms mediating these effects. Such research would also be important in helping to resolve some of the conflicting results reviewed above on the effects of constant bright light exposure on tumor development and growth. For example, it will be crucial to determine the influence of exposure to different light intensities and wavelengths during darkness on tumorigenesis, including the intensities and spectra that would normally be encountered at night in both the home and workplace. Studies would also need to address the influence of both the duration and timing of light during darkness at given intensities and wavelengths on carcinogenesis, especially over long periods of time.

Studies aimed at the influence of light during darkness on tumor development will continue to be largely restricted to animal models of either spontaneous or carcinogen-induced animal tumors. However, in order to more directly and specifically relate the photobiological effects of light during darkness on human carcinogenesis, animal models accommodating the growth of transplantable xenografts of human cancers will increasingly need to be developed and used in imaginative ways. In this regard, a major challenge will be to somehow develop a model system that directly couples the assessment of the influence of light during darkness on the circadian system of the human host with human tumorigenesis in the same model system. Such an approach, if successful, would greatly minimize the need to extrapolate, as is presently the case, from light-induced circadian alterations in animal hosts bearing either animal tumors or human cancer xenografts.

Many questions remain to be answered regarding the mechanisms by which light during darkness influences tumorigenesis by way of central circadian clock/pineal melatonin output signals and their interactions at the cellular, molecular, and biochemical/metabolic level (i.e., signal transduction pathways, fatty acid metabolism, clock gene function, etc.) in both developing and established tumors. Moreover, new interactions between light during darkness and other environmental (i.e., dietary fat) [75] and genetic and epigenetic factors (i.e., clock gene polymorphisms and expression) [104] influencing carcinogenesis should be actively investigated. Finally, additional prospective epidemiological investigations that are “driven” by the results of such laboratory studies will be necessary to more accurately assess the impact of light during darkness in human populations at increased risk for developing cancer as a result of living and working in our 24-hr/day society in which artificial light at night is a prominent feature.

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REFERENCES

1. ILLUMINATING ENGINEERING SOCIETY OF NORTH AMERICA: *Lighting Handbook: Reference & Application*, Illuminating Engineering Society of North America, New York, pp. 1-989, 1993

2. HOLICK J: Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, 4th edition, Favus MJ, ed., Lippincott-Rave, Philadelphia, pp. 92-98, 1999.

3. BRAINARD G C & BERNECKER C A: Biological and behavioral effects of light in humans, *22nd Session of the International Commission on Illumination (CIE)* **1**, pp. 29-30, 1991

4. BERSON D M, DUNN F A & TAKAO M: Phototransduction by retinal ganglion cells that set the circadian clock, *Science* **295**, pp. 1070-1073, 2002

5. *Final Report of the Fifth International LRO Lighting Research Symposium: Light and Human Health*. Report No. 1009370. The Electric Power Research Institute, Palo Alto, CA, March, 2004.

6. MOORE R Y & LENN N J: A retinohypothalamic projection in the rat, *J. Comp. Neurol.* **146**, pp. 1-14, 1972

7. PICKARD G E & SILVERMAN A J: Direct retinal projections to the hypothalamus, piriform cortex, and accessory optic nuclei in the golden hamster as demonstrated by a sensitive anterograde horseradish peroxidase technique, *J. Comp. Neurol.* **196**, pp. 155-172, 1981

8. KLEIN D C, SMOOT R, WELLER J L, HIGA S, MARKEY S P, CREED G J & JACOBOWITZ D M: Lesions of the paraventricular nucleus area of the hypothalamus disrupt the suprachiasmatic spinal cord circuit in the melatonin rhythm generating system, *Brain Res. Bull.* **10**, pp. 647-652, 1983

9. KLEIN D C, MOORE R Y & REPPERT S M, eds: *Suprachiasmatic Nucleus: The Mind's Clock*, Oxford University Press, Oxford, pp. 5-456, 1991

10. ZEITZER J M, AYAS N T, SHEA S A, BROWN R & CZEISLER C A: Absence of detectable melatonin and preservation of cortisol and thyrotropin rhythms in tetraplegia, *J. Clin. Endocrinol. Metab.* **85**, pp. 2189-2196, 2000

11. MORGANE P J & PANKSEPP J, eds: *Anatomy of the Hypothalamus*, Marcel Dekker, Inc., New York, pp. 1-726, 1979

12. KANDEL E R, SCHWARTZ J H & JESSELL T M, eds: *Principles of Neural Science, Fourth Edition*, McGraw-Hill, New York, pp. 1-1414, 2000

13. MORIN L P: The circadian visual system, *Brain Res. Brain Res. Rev.* **19**, pp. 102-127, 1994

14. PROVENCIO I, RODRIGUEZ I R, JIANG G, HAYES W P, MOREIRA E F & ROLLAG M D: A novel human opsin in the inner retina, *J. Neurosci.* **20**, pp. 600-605, 2000

15. GOOLEY J J, LU J, CHOU T C, SCAMMELL T E & SAPER C B: Melanopsin in cell of origin of the retinohypothalamic tract, *Nature Neurosci.* **4**, pp. 1165, 2001

16. HATTAR S, LIAO H-W, TAKAO M, BERSON D M & YAU K-W: Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity, *Science* **295**, pp. 1065-1070, 2002

17. HANNIBAL J, HINDERSSON P, KNUDSEN S M, GEORG B & FAHRENKRUG J: The photopigment melanopsin is exclusively present in pituitary adenylate cyclase-activating polypeptide-containing retinal ganglion cells of the retinohypothalamic tract, *J. Neurosci.* **22**, pp. 1-7, 2002

18. LEWY A J, WEHR T A, GOODWIN F K, NEWSOME D A & MARKEY S P: Light suppresses melatonin secretion in humans, *Science* **210**, pp. 1267-1269, 1980

19. BRAINARD G C, LEWY A J, MENAKER M, MILLER L S, FREDRICKSON R H, WELEBER R G, CASSONE V & HUDSON D: Dose-response relationship between light irradiance and the suppression of melatonin in human volunteers, *Brain Res.* **454**, pp. 212-218, 1988

20. CZEISLER C A, ALLAN J S, STROGATZ S H, RONDA J M, SANCHEZ R, RIOS C D, FREITAG W O, RICHARDSON G S & KRONAUER R E: Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle, *Science* **233**, pp. 667-671, 1986

21. LEWY A J, SACK R L, MILLER L S & HOBAN T M: Antidepressant and circadian phase-shifting effects of light, *Science* **235**, pp. 352-354, 1987

22. ZEITZER J M, DIJK D-J, KRONAUER R E, BROWN E N & CZEISLER C A: Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression, *J. Physiol.* **526**, pp. 695-702, 2000

23. CZEISLER C A, KRONAUER R E, ALLAN J S, DUFFY J F, JEWETT M E, BROWN E N & RONDA J M: Bright light induction of strong (Type 0) resetting of the human circadian pacemaker, *Science* **244**, pp. 1328-1333, 1989

24. MINORS D S, WATERHOUSE J M & WIRZ-JUSTICE A: A human phase-response curve to light, *Neurosci. Lett.* **133**, pp. 36-40, 1991

25. KHALSA S B, JEWETT M E, CAJOCHEN C & CZEISLER C A: A phase response curve to single bright light pulses in human subjects, *J. Physiol.* **549**, pp. 945-952, 2003

26. UNITED STATES CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT: Implications for the Worker, OTA-BA-463; 1-249, 1991

27. WETTERBERG L, ed: *Light and Biological Rhythms in Man*, Pergamon Press, Stockholm, pp. 1-448, 1993

28. LAM R W, ed: *Seasonal Affective Disorder and Beyond: Light Treatment for SAD and Non-SAD Disorders*, American Psychiatric Press, Washington, D.C., pp. 1-327, 1998

29. EASTMAN C I, BOULOS Z, TERMAN M, CAMPBELL S S, DIJK D-J & LEWY A J: Light treatment for sleep disorders: consensus report. VI. shift work, *J. Biol. Rhythms* **10**, pp. 157-164, 1995

30. BOULOS Z, CAMPBELL S S, LEWY A J, TERMAN M, DIJK D-J & EASTMAN C I: Light treatment for sleep disorders: consensus report. VII. jet lag, *J. Biol. Rhythms* **10**, pp. 167-176, 1995

31. DIJK D J, NERI D F, WYATT J K, RONDA J M, RIEL E, A. R-D, HUGHES R J, ELLIOTT A R, PRISK G K, WEST J B & CZEISLER C A: Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights, *Am. J. Physiol.* **281**, pp. R1647-R1664, 2001

32. REITER R J: Pineal gland: interface between the photoperiodic environment and the endocrine system, *Trends Endocrinol. Metab.* **2**, pp. 13-19, 1991

33. ARENDT J: Melatonin and the pineal gland: influence on mammalian seasonal and circadian physiology, *Rev. Reprod.* **3**, pp. 13-22, 1998

34. BRAINARD G C, ROLLAG M D & HANIFIN J P: Photic regulation of melatonin in humans: ocular and neural signal transduction, *J. Biol. Rhythms* **12**, pp. 537-546, 1997

35. BINKLEY S, STEPHENS J L, RIEBMAN J B & REILLY K B: Regulation of pineal rhythms in chickens: photoperiod and dark-time sensitivity, *Gen. Comp. Endocrinol.* **32**, pp. 411-416, 1977

36. BRAINARD G C, RICHARDSON B A, PETTERBORG L J & REITER R J: The effect of different light intensities on pineal melatonin content, *Brain Res.* **233**, pp. 75-81, 1982

37. WEHR T A, MOUL D E, BARBATO G, GIESEN H A, SEIDEL J A, BARKER C & BENDER C: Conservation of photoperiod-responsive mechanisms in humans, *Am. J. Physiol.* **265**, pp. R846-R857, 1993

38. WEHR T A: The durations of human melatonin secretion and sleep respond to changes in daylength (photoperiod), *J. Clin. Endocrinol. Metab.* **73**, pp. 1276-1280, 1991

39. ARENDT J: Melatonin and the Mammalian Pineal Gland, Chapman and Hill, London, pp. 1-331, 1995

40. DEACON S & ARENDT J: Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans, *Brain Res.* **688**, pp. 77-85, 1995

41. BUXTON O M, L'HERMITE-BALERIAUX M, HIRSCHFELD U & VAN CAUTER E: Acute and delayed effects of exercise on human melatonin secretion, *J. Biol. Rhythms* **12**, pp. 568-574, 1997

42. FOSTER R G, PROVENCIO I, HUDSON D, FISKE S, DEGRIP W & MENAKER M: Circadian photoreception in the retinally degenerate mouse (rd/rd), *J. Comp. Physiol. [A]* **169**, pp. 39-50, 1991

43. PROVENCIO I & FOSTER R G: Circadian rhythms in mice can be regulated by photoreceptors with cone-like characteristics, *Brain Res.* **694**, pp. 183-190, 1995

44. FREEDMAN M S, LUCAS R J, SONI B, VON SCHANTZ M, MUNOZ M, DAVID-GRAY Z & FOSTER R G: Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors, *Science* **284**, pp. 502-504, 1999

45. LUCAS R J, FREEDMAN M S, MUNOZ M, GARCIA-FERNANDEZ J M & FOSTER R G: Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors, *Science* **284**, pp. 505-507, 1999

46. CZEISLER C A, SHANAHAN T L, KLERMAN E B, MARTENS H, BROTMAN D J, EMENS J S, KLEIN T & RIZZO J F, III: Suppression of melatonin secretion in some blind patients by exposure to bright light, *N. Engl. J. Med.* **332**, pp. 6-11, 1995

47. RUBERG F L, SKENE D J, HANIFIN J P, ROLLAG M D, ENGLISH J, ARENDT J & BRAINARD G C: Melatonin regulation in humans with color vision deficiencies, *J. Clin. Endocrinol. Metab.* **81**, pp. 2980-2985, 1996

48. KLERMAN E B, SHANAHAN T L, BROTMAN D J, RIMMER D W, EMENS J S, RIZZO J F & CZEISLER C A: Photic resetting of the human circadian pacemaker in the absence of conscious vision, *J. Biol. Rhythms* **17**, pp. 548-555, 2002

49. BRAINARD G C, HANIFIN J P, ROLLAG M D, GREESON J, BYRNE B, GLICKMAN G, GERNER E & SANFORD B: Human melatonin regulation is not mediated by the three cone photopic visual system, *J. Clin. Endocrinol. Metab.* **86**, pp. 433-436, 2001

50. BRAINARD G C, HANIFIN J P, GREESON J M, BYRNE B, GLICKMAN G, GERNER E & ROLLAG M D: Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor, *J. Neurosci.* **21**, pp. 6405-6412, 2001

51. THAPAN K, ARENDT J & SKENE D J: An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans, *J. Physiol.* **535**, pp. 261-267, 2001

52. HANKINS M W & LUCAS R J: The primary visual pathway in humans is regulated according to long-term light exposure through the action of a nonclassical photopigment, *Curr. Biol.* **12**, pp. 191-198, 2002

53. LUCAS R J, DOUGLAS R H & FOSTER R G: Characterization of an ocular photopigment capable of driving pupillary constriction in mice, *Nature Neurosci.* **4**, pp. 621-626, 2001

54. BERSON D M, DUNN F A & TAKAO M: Phototransduction by retinal ganglion cells that set the circadian clock, *Science* **295**, pp. 1070-1073, 2002

55. HATTAR S, LUCAS R J, MROSOVSKY N, THOMPSON S, DOUGLAS R H, HANKINS M W, LEM J, BIEL M, HOFMANN F, FOSTER R G & YAU K-W: Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice, *Nature* **424**, pp. 75-81, 2003

56. SELBY C P, THOMPSON C, SCHMITZ T M, VAN GELDER R N & SANCAR A: Functional redundancy of cryptochromes and classical photoreceptors for nonvisual ocular photoreception in mice, *Proc. Natl. Acad. Sci. U. S. A.* **97**, pp. 14697-14702, 2000

57. REA M S, BULLOUGH J D & FIGUEIRO M G: Phototransduction for human melatonin suppression, *J. Pineal Res.* **32**, pp. 209-213, 2002

58. PROVENCIO I, JIANG G, DE GRIP W J, HAYES W P & ROLLAG M D: Melanopsin: an opsin in **melanophores**, brain, and eye, *Proc. Natl. Acad. Sci. U. S. A.* **95**, pp. 340-345, 1998

59. ROLLAG M D, BERSON D M & PROVENCIO I: Melanopsin, ganglion-cell photoreceptors, and mammalian photoentrainment, *J. Biol. Rhythms* **18**, pp. 227-234, 2003

60. PROVENCIO I, ROLLAG M D & CASTRUCCI A M: Photoreceptive net in the mammalian retina, *Nature* **415**, pp. 493, 2002

61. RUBY N, BRENNAN T, XIE X, CAO V, FRANKEN P, HELLER H & O'HARA B: Role of melanopsin in circadian responses to light, *Science* **298**, pp. 2211-2213, 2002

62. PANDA S, SATO T K, CASTRUCCI A M, ROLLAG M D, DEGRIP W J, HOGENSCH J B, PROVENCIO I & KAY S A: Melanopsin (Opn4) requirement for normal light-induced circadian phase-shifting, *Science* **298**, pp. 2213-2216, 2002

63. LUCAS R J, HATTAR S, TAKAO M, BERSON D M, FOSTER R G & YAU K W: Diminished pupillary light reflex at high irradiances in melanopsin-knockout mice, *Science* **299**, pp. 245-247, 2003

64. BAST RC, KUFE DW, POLLOCK RE, WEICHSELBAUM, RR, HOLLAND JF, FREI E, eds.: *Cancer Medicine*, 5th edition, BC Decker, Hamilton, pp. 1-2546, 2000.

65. GIBBS WW: Roots of cancer, *Sci. Amer.* **289**, pp. 57-65, 2003.

66. HRUSHESKY WJM: The temporal organization of life: the impact of multifrequency non-linear biologic time structure upon the host-cancer balance. *Jpn. J. Clin. Oncol.* **30**, pp. 529-533, 2000.

67. REITER RJ: Pineal melatonin: cell biology of its synthesis and of its physiological interactions. *Endocr. Rev.* **12**, pp. 151-180 1991.

68. REITER RJ: Melatonin: a multifaceted messenger to the masses. *Lab. Med.* **25**, pp. 438-441, 1994.

69. REPPERT SM, WEAVER DR: Melatonin madness. *Cell* **83**, pp. 1059-1062, 1995.

70. LI PK, WITT-ENDERBY PA: Melatonin receptors as potential targets for drug discovery. *Drugs Future*, **25**, pp. 945-957, 2000.

71. REITER RJ: Reactive oxygen species, DNA damage, and carcinogenesis: intervention with melatonin. In :*The Pineal Gland and Cancer*; Bartsch C, Bartsch H, Blask, DE, Cardinali DP Hrushesky WJMMecke D (eds) Springer –Verlag, Berlin, pp. 442-455, 2001.

72. BLASK DE: Melatonin in Oncology. In: *Melatonin Biosynthesis, Physiological Effects, and Clinical Applications*, Yu HS, Reiter, RJ, eds., CRC Press, Boca Raton, pp. 447—475, 1993.

73. BLASK, D.E: Systemic, Cellular, and Molecular Aspects of Melatonin Action on Experimental Breast Carcinogenesis. In: *The Melatonin Hypothesis -- Breast Cancer and the Use of Electric Power*, Stevens RG,Wilson, BW, Anderson LE, eds., Battelle Press, Columbus, pp. 189-230, 1997.

74. BLASK DE: An overview of the neuroendocrine regulation of experimental tumor growth by melatonin and its analogues and the therapeutic use of melatonin in oncology. In: *The Pineal Gland and Cancer*, Bartsch C, Bartsch H, Blask, DE, Cardinali DP, Hrushesky WJM, Mecke, eds., Springer-Verlag, Berlin, pp. 309-342, 2001

75. BLASK DE, SAUER LA, DAUCHY RT: Melatonin as a chronobiotic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based cancer therapy. *Curr Top Med Chem* 2, pp. 113-132, 2002.

76. HILL SM, KEIFER T, TEPLITZKY, SPRIGGS LL, RAM P: Modulation of the estrogen response pathway in human breast cancer cells by melatonin. In: *The Pineal Gland and Cancer*, Bartsch C, Bartsch H, Blask, DE, Cardinali DP, Hrushesky WJM, Mecke D, eds., Springer-Verlag, Berlin, pp. 343-358, 2001.

77. BLASK DE, SAUER LA, DAUCHY RT, HOLOWACHUK EW, RUHOFF MS: Melatonin inhibition of cancer growth *in vivo* involves suppression of tumor fatty acid metabolism via melatonin receptor-mediated signal transduction events. *Cancer Res* 59, pp. 4693-470, 1999.

78. SAUER LA, DAUCHY RT, BLASK DE: Polyunsaturated fatty acids, melatonin, and cancer prevention. *Biochem. Pharmacol.*, **61**, pp. 1455-1462, 2001.

79. JÖCHLE W: Trends in photophysiologic concepts. *Ann. NY Aca. Sci.* 117, pp. 88-104, 1964.

80. KHAETSKY IK: Effects of hypothalamo-pituitary lesions induced by constant illumination on development of induced mammary tumors in rats. *Vopr. Exp. Oncol. (Kiev)* **1**, pp. 87-93, 1965.

81. JULL, J.W The effect of infection, hormonal environment, and genetic constitution on mammary tumor induction in rats by 7,12-dimethylbenz(a)anthracene. *Cancer Res*. **26**, pp. 2368-2373, 1966.

82. HAMILTON T: Influence of environmental light and melatonin upon mammary tumour induction. *Brit. J. Surg.* **36**, pp. 764-766, 1969.

83. KURALASOV AK: Effect of dark adaptation on carcinogenesis and efficacy of treatment on DMBA-induced mammary tumor. *Izvestia Akad Nauk Kazakh SSR, Ser Biol.* **4**, pp. 79-82, 1979.

84. AUBERT C, JANIAUD P, LECALVEZ J: Effect of pinealectomy and melatonin on mammary tumor growth in Sprague-Dawley rats under different conditions of lighting. *J. Neural Transm*. **47**, pp. 121-130, 1980.

85. KOTHARI LS, SHAH PN, MHATRE MC:Effect of continuous light on the incidence of 9,10-dimethyl1,2-benzanthracence induced mammary tumors in female Holtzman rats. *Cancer Lett.* **16**, pp. 313-317, 1982.

86. KOTHARI LS, SHAH PN, MHATRE MC: Pineal ablation in varying photoperiods and the incidence of 9,10-dimethyl-1,2-benzanthracene induced mammary cancer in rats. *Cancer Lett*. **22**, pp. 99-102, 1984.

87. SHAH PN, MHATRE MC, KOTHARI LS: Effect of melatonin on mammary carcinogenesis in intact and pinealectomized rats in varying photoperiods. *Cancer Res*. 44, pp. 3403-3407, 1984.

88. SUBRAMANIAN A, KOTHARI L: Suppressive effect by melatonin on different phases of 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced rat mammary gland carcinogenesis. *Anti-Cancer Drugs* **2**, pp.297-303, 1991.

89. ANISIMOV VN, ZHUKOVA OV, BENIASHVILI DS, BILANISHVILI VG, MENABDE M.Z: Light deprivation, electromagnetic fields and mammary carcinogenesis. In: *Advances in Pineal Research*, vol. 7, Maestroni GJM, Conti A, Reiter RJ, eds., John Libbey & Co. Ltd, London, pp. 229-234, 1994.

90. ANISIMOV VN, ZHUKOVA OV, BENIASHVILI DS, BILANISHVILI VG, MENABDE MZ, GUPTA D: Effect of the light regime and electromagnetic fields on carcinogenesis of the mammary gland in female rats. *Biophysics* **41**, pp. 817-823, 1996.

91. DAUCHY RT, BLASK DE, SAUER LA, VAUGHAN GM: Light contamination during the dark phase in 'photoperiodically-controlled' animal rooms: effect on tumor growth and metabolism in rats. *Lab. Anim. Sci.* 47, pp. 511-518, 1997.

92. DAUCHY RT, BLASK DE. SAUER LA, BRAINARD GC, KRAUSE JA: Dim light during darkness stimulates tumor progression by enhancing tumor fatty acid uptake and metabolism. *Cancer Lett*. 144, pp. 131-136, 1999.

93. VAN DEN HEILIGENBERG S, DEPRES-BUMMER P, BARBASON H, CLAUSTRAT B, REYNES M, LEVI F: The tumor promoting effect of constant light exposure on diethylnitrosamine-induced hepatocarcinogenesisin rats. *Life Sci*. 64, pp. 2523-2534, 1999.

94. ANDERSON LE, MORRIS JE, SASSER LB, STEVENS RG: Effect of constant light on DMBA mammary tumorigenesis in rats. *Cancer Lett* 148, pp. 121-126, 2000.

95. BENIASHVILI DS, BENJAMIN S, BATURIN DA, ANISIMOV VN: Effect of light/dark regimenon N-nitrosoethylurea-induced transplacental carcinogenesis in rats. *Cancer Lett*. **163**, pp. 51-57, 2001.

96. TRAVLOS GS, WILSON RE, MURRELL JA, CHIGNELL CF, BOORMAN GA: The effect of short intermittent light exposures on the melatonin circadian rhythm and NMU-induced breast cancer in female F344/N rats. *Toxicol. Pathol.* **29**, pp. 126-136, 2001.

97. BATURIN DA, ALIMOVA IN, ANISIMOV VN, POPVICH G, ZABEZHINSKI MA, PROVINCIALI M, MANCINI R, FRANCESCHI C: The effect of light regimen and melatonin on the development of spontaneous mammary tumors in HER-2/neu transgenic mice is related to a downregulation of HER-2/neu gene expression. *Neuroendocinol. Lett*. **22**, pp. 441-447, 2001.

98. BLASK DE, DAUCHY RT, SAUER LA. KRAUSE JA, BRAINARD GC: Light during darkness, melatonin suppression and cancer progression. *Neuroendocrinol. Lett*. **23**, pp. 52-56, 2002.

99. BLASK DE, DAUCHY RT, SAUER LA, KRAUSE JA, BRAINARD GC: Growth and fatty acid metabolism of human breast cancer (MCF-7) xenografts in nude rats: impact of constant light-induced nocturnal melatonin suppression. *Breast Cancer Res. Treat*. **79**, pp. 313-320, 2003.

100. DAUCHY RT, BLASK DE, BRAINARD GC, SAUER LA, LYNCH DT, DAVIDSON LK, KRAUSE JA: Low-intensity light exposure during animal room dark phase and alterations in tumor growth rate and metabolism in rats: a dose-relationship. *Cont. Top. Lab. Animal Sci*. 42, P058, p. 101, 2003.

101. CASSONE VM: The pineal gland influences rat circadian activity rhythms in constant light. *J. Biol. Rhythms* 7, pp. 27-40, 1992.

102. DEPRES-BUMMER P, LEVI F, METZGER G, TOUITOU Y: Light-induced suppression of the rat circadian system. Am. J. Physiol. 268, pp. R1111-R1116, 1995.

103. STEVENS RG: Electric power use and breast cancer: A hypothesis. *Am. J. Epidemiol*. 125, pp. 556-561, 1987.

104. STEVENS RG, REA MS: Light in the built environment: potential role of circadian disruption in endocrine disruption and breast cancer. *Cancer Causes Control* 12, pp. 279-287, 2001.

105. HANSEN J: Increased breast cancer risk among women who work predominantly at night. *Epidemiology* 12, pp. 74-77, 2001.

106. DAVIS S, MIRICK DK, STEVENS, RG: Night shift work, light at night, and risk of breast cancer. *J. Natl Cancer Inst*. 93, pp. 1557-1562, 2001.

107. SCHERNHAMMER ES, LADEN F, SPEIZER FE, WILLETT WC, HUNTER DJ, KAWACHI I, COLDITZ GA: Rotating night shifts and risk of breast cancer in women participating in the nurse's health study. *J. Natl. Cancer Inst.* 93, pp. 1563-1568, 2001.

108. SCHERNHAMMER ES, LADEN F, SPEIZER FE, WILLETT WC, HUNTER DJ, KAWACHI I, FUCHS CS, COLDITZ GA: Night –shift work and risk of colorectal cancer in the nurses' health study. J. Natl. Cancer Inst. 95, pp. 825-828, 2003.

109. HAHN RA: Profound bilateral blindness and the incidence of breast cancer. *Epidemiology* 2, pp. 208-210, 1991.

110. FEYCHTING M, ÖSTERLAND B, AHLBOM A: Reduced cancer incidence among the blind. *Epidemiology* 9, pp. 490-494, 1998.

111. PUKKALA E, VERKASALO PK, OJAMO M, RUDANKO SL: Visual impairment and cancer: a population-based cohort study in Finland. *Cancer Causes Control* 10, pp. 13-20, 1999.

112. VERKASALO P, PUKKALA E, STEVENS RG, OJAMA, RUDANKO S-L: Inverse association between breast cancer incidence and degree of visual impairment in Finland. *Br. J. Cancer* 80, pp. 1459-1460, 1999.

113. KLIUKIENE J, TYNES T, ANDERSEN A: Risk of breast cancer among Norwegian women with visual impairment. *Br. J. Cancer* **84**, pp. 397-399, 2001.

114. LENNERNAS M, AKERSTEDT T, HAMBRAEUS L: Nocturnal eating and serum cholesterol of three-shift workers. *Scand. J. Work Environ. Health* **20**, pp. 401-406, 1994.

115. COMMISSION INTERNATIONALE DE L'ECLAIRAGE: Guide on Interior Lighting, CIE Publication No. 29.2, Vienna, pp. 1-113, 1986.

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