CIRCADIAN® LIGHT

Blue Light InSight *Vol. 2*

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Less than 2% blue light content at night

LIGHT AT NIGHT

EFFECTS ON BREAST CANCER, PROSTATE AND OTHER CANCERS

SUMMARY

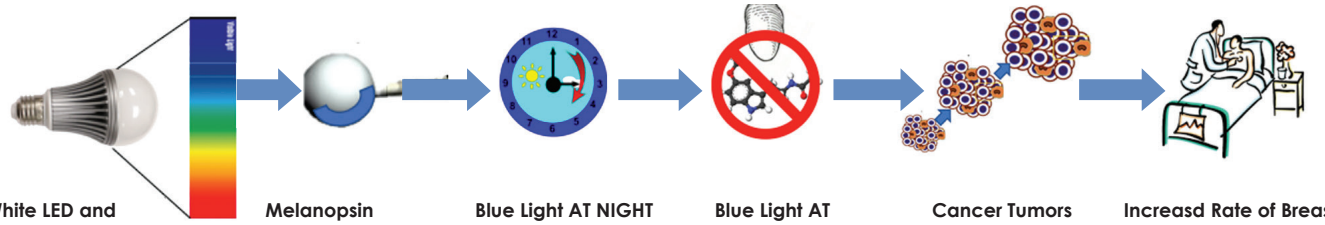
There is now substantial evidence that exposure to blue-rich light in the evening and at night increases the risk of breast cancer and prostate cancer. Because most energy efficient LEDs in the market today are rich in these blue wavelengths, the use of these LED lights at night can trigger the carcinogenic processes involved in tumor growth and cancer through:

1) Disruption of the circadian system (phase shifting and circadian misalignment),
2) Melatonin-suppression and phase shifting,
3) Accelerated unsuppressed tumor growth

Blue-rich light (including natural daylight) during the day is protective, but exposure to the same blue rich LED or florescent light during the night is harmful. To avoid this risk light fixtures need to provide blue-rich light during the day, and blue-depleted light at night.

This paper presents the scientific evidence and the lighting solutions now available.

Blue Light at Night Causal Chain: Breast and Prostate Cancer



White LED and Fluorescent Light Contains High Bio-Active Blue (430-500nm) Content

Melanopsin receptors in lower half of eye retina detect Bio-Active Blue Light

Blue Light AT NIGHT disrupts timing of Circadian Clock

Blue Light AT NIGHT suppresses Melatonin release from Pineal Gland

Cancer Tumors Grow Faster when Melatonin is suppressed

Increasd Rate of Breast Cancer and Prostate Cancer in People Working at Night

Nakamura, S (2015) Rev. Mod. Phys. 87, 1139-1151	Bailes, HJ & Lucas, RJ (2013). Proc. Roy. Soc. B. 280: 20122987, 1-9	Lockley SW, et al. (2003) J Clin Endocrinol Metab 88: 4502-4505	Brainard GC et al 2001) J.Neuroscience, 21: 6405-6412	Blask D. E. et al (2005) Cancer Res 65: 11174-11184	Hansen, J (2001) Epidemiology 12:74-77.
Stevens R et al (2014) CA Cancer J 64: 207-218	Glickman, G et al (2003) J Biol. Rhy. 18: 71-79	Rugar, M et al (2013) J Physiol. 591:353-63	West KE et al (2011) J Appl Physiol 110: 619-626,	Hill SM et al, (2015) Endocrine-Related Cancer 22, R183-R204	Kubo Tet al Am J Epidemiol (2006) 164: 549-555

Figure 1: Pathways mediating the effects of blue-rich light at night on hormone sensitive cancers

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OVERVIEW OF SCIENTIFIC EVIDENCE

Over the past twenty years substantial evidence has accumulated that links the melatonin suppression and circadian disruption caused by artificial light exposure at night (ALAN), with an increased risk of certain endocrine sensitive cancers. Because of the mounting evidence the International Agency on Research on Cancer (IARC) of the World Health Organization (WHO) conducted a comprehensive review in 2007 of the epidemiological and animal research data. Based on their analysis of the human and animal studies available at that time the IARC classified "shift work that involves circadian disruption" as "probably carcinogenic to humans" (Group 2A risk) [1].

In the ten years since the IARC report considerable further evidence has been developed to support the link between light exposure at night and certain endocrine sensitive cancers, such as breast and prostate cancer. The evidence is powerful and convincing and has come from multiple corroborating sources:

1) Breast cancer increased 32% - 58% in women regularly exposed to light at night while working night shifts based on 61 independent published studies involving a total of four million women.
2) Prostate cancer increased up to 200% in men regularly exposed to light at night while working night shifts based on multiple independent published studies.
3) Increased bedroom light levels in non-shiftworkers are associated with an increased risk of breast and prostate cancer.
4) Increasing levels of environmental light pollution at night is associated with increased incidence of breast and prostate cancers.
5) Blind women have a lower risk of breast cancer, and blind men have a lower risk of prostate cancer that is related to the degree of visual impairment.

Over the past twenty years substantial evidence has accumulated that links the melatonin suppression and circadian disruption caused by artificial light exposure at night (ALAN), with an increased risk of certain endocrine sensitive cancers.

6) A considerable body of research shows that melatonin has cancer suppressing (anti-carcinogenic) properties, and the normal rise in melatonin at night is a protective mechanism that slows or prevents the growth of cancers in humans and animals.
7) Suppressed melatonin levels in women are associated with an increased incidence of breast cancer.
8) Animal studies showing growth of implanted human breast cancer is substantially is increased by exposure to light at night, and the effect can be reversed by infusing human blood with normal nighttime melatonin levels, but not by human blood from women who have suppressed melatonin because they have been exposed to light at night.
9) Healthy human volunteers exposed to blue-rich light at night have disrupted circadian rhythms, and suppressed melatonin levels.

SCIENTIFIC LITERATURE REVIEW

Night Shift Work and Breast Cancer

The first three major epidemiological studies showing an association between night work and the incidence of breast cancer were published in 2001 [2]. Hansen showed in a study of 7,035 Danish women aged 30- 54, that they had a 50% increase risk of breast cancer if they worked predominantly at night for at least half of a year [3]. Davis et al. [4] found a 60% increased risk in women who worked overnight shifts with the risk increasing with increasing years of night shift work and increasing numbers of night shifts per week. Schernhammer et al. [5] also observed an increase in breast cancer risk among women who worked 1–14 years or 15–29 years on rotating night shifts for at least three nights per month. The risk was further increased to 36% among women who worked 30 or more years on the night shift (RR = 1.36).

Authors	Date	Population	Odds Ratio	Increased Risk
Hansen	2001	30- to 54-year old women who worked predominantly at night.	1.5	+ 50%
Davis	2001	Night shift workers, with increasing risk with years of shiftwork & hours per week of night work.	1.6	+ 60%
Schernhammer	2001	Women working 30+ years on night shift.	1.37	+ 37%
Lie et al	2011	Nurses working≥ 5 years with ≥ 6 consec-utive night shifts.	1.8	+ 80%
Yuan	2018	Meta-analysis 61 studies long-term night shiftwork 3,909,152 women.	1.32 1.58	+ 32% + 58% (nurses)

Figure 2: The increased risk of breast cancer in women exposed to light at night

Since then many other studies have confirmed the increased risk of breast cancer associated with night work cancer [6,2]. These include a meta-analysis of 61 studies, including 3.9 million participants showed a 32% increased risk of breast cancer with night work, and increased risk in other primary cancers in women [7]. Epidemiological (case-control) studies evaluating over 40,000 Norwegian nurses found an association between night work (>30 years) and increased breast cancer incidence, and suggested that the risk may be related to the number of consecutive night shifts that are worked [8,9,10].

Bedroom Light at Night and Breast Cancer Risk

Similar effects of ALAN are found in non-shiftworking populations. Several case-control studies have found an association between higher light levels in the bedroom at night and an increased risk of breast cancer, using various different methods for estimating light in the bedroom. The studies evaluated keeping lights on while sleeping, not drawing the curtains/window shades while sleeping at night, and frequently turning on lights during the sleep period [8,11,12,13].

Community Ambient Light Level and Breast Cancer Risk

Several large epidemiological studies have found an significant association between higher levels of outdoor light at night exposure and breast cancer.

- One study examined the co-distribution of light level at night and breast cancer incidence in 147 communities in Israel. The incidence in the town with the highest LAN level was 73% higher rate of breast cancer than that of the town with the lowest level [14].
- A study conducted among over 100,000 teachers, a cohort of women who do not typically work at night, provided evidence that women who live in areas with high levels of ambient light at night were at an increased risk of breast cancer not readily explained by other neighb-hood characteristics or personal breast-cancer risk factors [15].
- A study including 164 countries, using the GLOBOCAN database, found a 30–50% higher risk of breast cancer in the highest ALAN exposed countries compared to the lowest LAN exposed countries [16].
- A meta-analysis of 12 case-control and four cohort studies studying the relationship of ALAN and breast cancer found that high artificial light exposure can increase the risk of breast cancer by 17% [17].
- A similar association between ALAN exposure and breast cancer in women has been reported in other studies [18, 19].

Blind Women Have a Lower Risk of Breast Cancer

Consistent with the evidence that those who are exposed to greater levels of light exposure at night have a higher risk of breast cancer is the finding that blind women have a lower risk than sighted women. A large epidemiological study found that breast cancer risk in females decreased by degree of visual impairment, [20]. Similar findings of lower risks of breast cancer with blind women have been reported in some other smaller studies [21,22].

In summary, increased breast cancer risk is associated with a wide range of situations where women are exposed to increased levels of light at night. These include night work, higher ambient nighttime bedroom light level, and higher community nocturnal light levels, and healthy eyesight. The strongest evidence base exists for a higher risk among women with a history of working night shift work which causes circadian disruption as well as increased light exposure at night [23]. Consistent with this evidence is the finding in three prospective studies that women who sleep for the longest durations each night in the bedroom have the lowest risk of breast cancer [24,25,26].

Prostate Cancer and Light Exposure at Night

The association between prostate cancer and light exposure at night has received less attention, but there are multiple studies which have found an association between working shift work and an increased risk of prostate cancer. In 2006 Kubo and colleagues [27] conducted a prospective study of 14,052 working Japanese men and found a 200% greater risk in rotating shift workers than day workers. A similar 177% increased incidence of prostate cancer was found in a Canadian study for men who had worked nights as compared to men who have never worked at night [28] although another Canadian study found only a 40% increased risk in rotating shiftworkers as compared to day workers [29].

Authors	Date	Population	Odds Ratio	Increased Risk
Kubo et al	2006	Japanese working rotating shifts.	3.0	+ 200%
Parent et al	2012	Canadians who have worked at night.	2.7	+ 177%
Conion	2007	Canadians who began working full-time rotating shift work in their mid-20s.	1.4	+ 40%
Kim	2017	Comparison of 27 Chinese districts with high versus low levels of nocturnal lighting.	1.73	+ 73%

Figure 3: The increased risk of prostate cancer in men exposed to light at night

Bedroom light exposure in non-shiftworkers also increases prostate cancer risk. A large study including 27 districts in South Korea showed an association between light at night at home and prostate cancer [30]. The study of ALAN across 164 countries, using the GLOBOCAN database also found that the risk of prostate cancer in the highest ALAN-exposed countries was 110% higher than in the lowest ALAN exposed countries. The study found a significant positive association between exposure to ALAN, electricity consumption, and prostate cancer [31]. Another large epidemiological study evaluated the association of ALAN with all forms of cancers in 158 countries. Besides breast cancer, ALAN was significantly correlated with prostate and colorectal cancers [32].

Blind men also have a lower risk of prostate cancer. A large epidemiological study found that prostate cancer risk in men decreased by degree of visual impairment [20].

Other Cancers associated with Light Exposure at Night

There are fewer studies evaluating the relationship between shiftwork and other cancers, but a significant association has been established between working night shifts and an increased risk of colon-rectal cancer [33] extrahepatic bile duct cancer [42] and skin cancer [7].

Authors	Date	Population	Odds Ratio	Increased Risk
Schernhammer	2003	Colon rectal cancer in nurses working 3 or more night shifts a month for over 15 years	1.35	+ 35%
Lin	2015	Extrahepatic bile duct cancer in rotating shift workers.	1.93	+ 93%
Yuan	2018	Skin cancer: meta-analysis of 7 studies of long-term night shiftwork in women.	1.41	+ 41%

Mechanism of Action

Exposure to artificial light at night and, most potently blue-rich light, causes melatonin suppression and circadian disruption which in turn contribute to the increased risk on hormone sensitive cancers. We will briefly summarize some of the extensive work exploring the pathways.

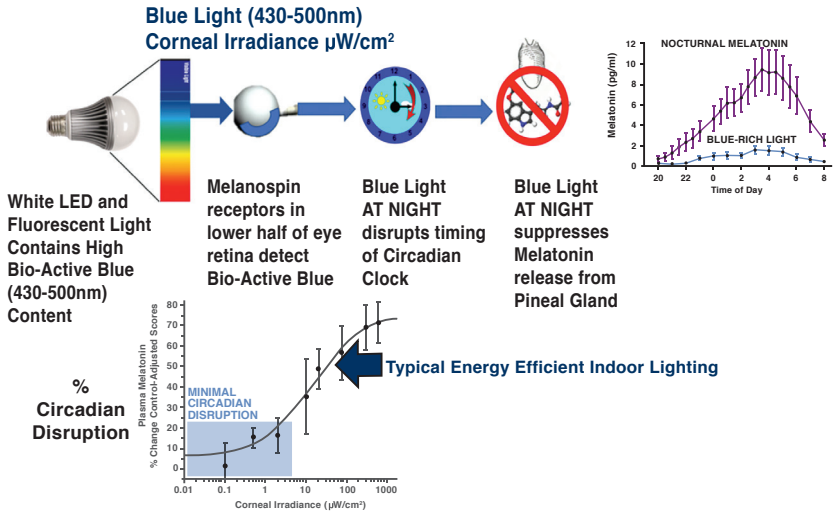

Figure 4: Mechanism of Action of Blue Light at Night on Circadian Disruption and Melatonin Suppression [42]

Melatonin Suppression

Melatonin has well established anticarcinogenic effects including inhibiting the initiation, promotion, and progression of tumors. In animal studies, removing the melatonin-producing pineal gland has been found to enhance tumor growth rodents [34], while melatonin administration has demonstrated slows tumor development.

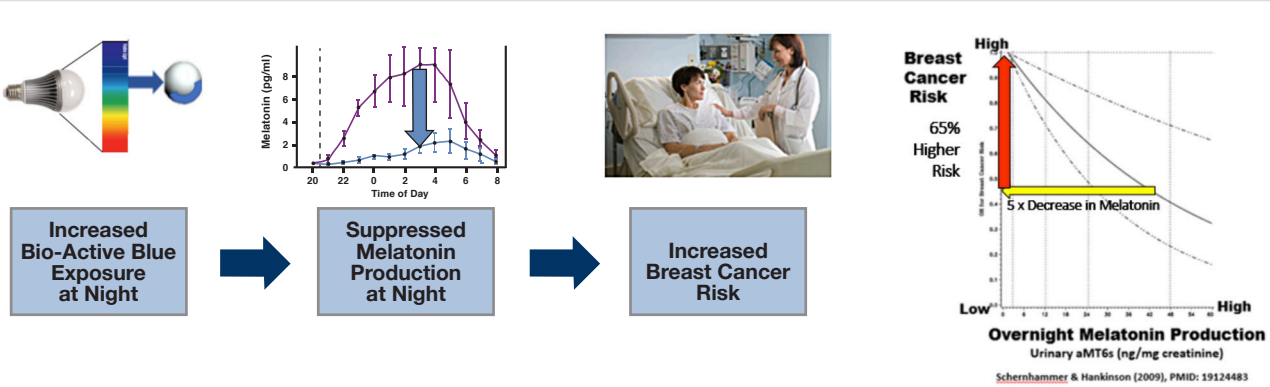

Figure 5: Relationship between Melatonin Suppression and Breast Cancer Risk

The mechanisms by which melatonin inhibits cancer growth are discussed in detail in Hill [35], and are briefly summarized here. In endocrine-dependent tumors, melatonin effects on hypothalamic centers may play an important role. Normally the surge of melatonin released at night exerts control over gonadal hormone production, and thereby have an inhibitory effect on hormone-dependent tumors. Suppression of circulating melatonin results in increased release of gonadotropins from the pituitary, which stimulates testicular testosterone or ovarian estrogen production and release.

The decrease in melatonin production results in an upregulation of the gonadal axis – as seen among female shift workers who had an increase in circulating estrogen after prolonged exposure to shift work. Prolonged exposure and/or increased cellular response to estrogens during a woman's lifetime is an important risk factor for breast cancer. Melatonin acts as a response modifier to estrogens especially estradiol. It exerts an anti-estrogenic effect and counteracts the effects of estradiol on breast cancer cell proliferation and invasiveness. Melatonin down-regulates the expression of some protein growth factors stimulated by estrogen and some growth factor receptors associated with increased malignancy in some forms of human breast cancer.

"Normally the surge of melatonin released at night exerts control over gonadal hormone production, and thereby have an inhibitory effect on hormone-dependent tumors."

In addition, melatonin modulates local estrogen biosynthesis, which is of special importance in post-menopausal breast cancer, and has oncostatic action by regulating the uptake and metabolism of linoleic acid, which is a promoter of both human and mouse breast cancer tumorigenesis via multiple pathways.

Animal studies have demonstrated the direct effect of melatonin on human breast cancer tumors using animal models. Animals exposed to constant light showed greater DNA synthesis activity in breast tissue, and higher levels of circulating prolactin. Experimental evidence suggests that light exposure during the dark cycle increases the progression of cancer [36,37,38,39,40]. Human breast cancer cells implanted In rodents grow 2-3 times faster when the animals are exposed to light at night.

The direct relevance to human breast cancer was shown by studying animals with implanted human breast cancer tumors and perfusing the animals with blood from women who were either producing melatonin in the dark at night or with melatonin-depleted blood from women exposed to light at night. The animals infused with melatonin depleted blood had faster tumor growth as compared to animals infused with blood with the normal physiologic nighttime level of melatonin [34].

In addition to its effects by acting on the hypothalamic system, melatonin also acts at the cellular level, and may protect cells from DNA damage by carcinogenic agents through its ability to act as a free radical scavenger directly or indirectly. In addition to protecting DNA by suppressing the formation and accumulation of altered DNA, melatonin may also help to promote DNA repair.

Another mechanism of action is the effect of melatonin on the immune system. Research has demonstrated that a reduction in endogenous melatonin production by pinealectomy or suppression by light during the night leads to immune suppression that may promote the establishment and growth of abnormal cell clones.

Circadian Disruption

Recent studies have focused on the role of circadian clock genes. These genes regulate cell proliferation and apoptosis (cell death) at multiple sites and by different mechanisms. Defects in some core clock genes are associated with an increased risk of developing breast, prostate and colon cancer. Endocrine target tissues, like the breast and prostate, appear to be especially prone to tumor development after circadian disruption from light at night. Repeated phase shifting leading to internal desynchronization and defects in the regulation of the circadian cell cycle; and sleep deprivation that alters the immune function [23].

Interference with Action of Cancer Drugs

Not only does light at night increase the rate of breast and prostate cancer growth, but it also interferes with medications used to control cancer. Recent research studies and clinical evidence have linked resistance to anti-estrogen drugs in breast cancer cells disturbances in nocturnal melatonin production [41].

NEW CIRCADIAN LIGHTING SOLUTIONS

To manage the risk of breast, prostate and other cancers, light fixtures should provide blue-rich light during the day and blue-depleted light at night. The key is not just to lower blue content but to make sure the lights remove enough blue at night to reduce the risk (i.e., fall within the range of minimal circadian disruption in Figure 6).

For example, CCT color tuning products that transition from 6500K during the day to 2700 K at night do not remove enough blue out of the light spectrum at night to prevent circadian disruption, melatonin suppression, and the risk of cancer (Figure 6). While these CCT color tuning products may be marketed as "circadian" they still often rely on a blue pump that can cause circadian disruption.

To address the risk of blue light, CIRCADIAN® Light has introduced fixtures that contain a light engine with both a blue-pump LEDs for daytime use as well as a patented violet-pump LED for evening and nighttime use. The "night" LED removes over 90% of the bio-active blue content to minimize circadian disruption, and provides white light with a CCT of 3200K, and CRI of 80+. To control blue light exposure 24/7, the CIRCADIAN® Light fixtures automatically switch between day and night LEDs based on location, time and season.

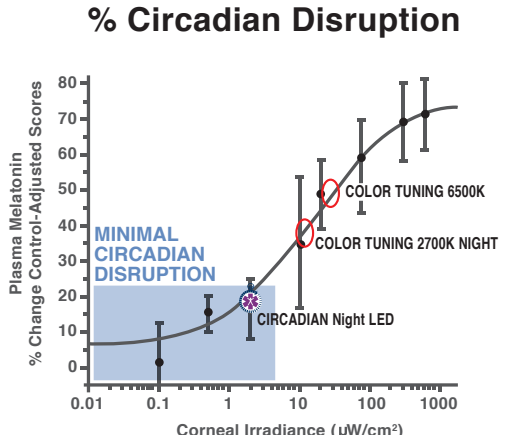

Figure 6: The relationship between the blue irradiance falling on the cornea of the eye and melatonin suppression [42] and circadian disruption by CCT color tuning lights and by CIRCADIAN Lights

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EFFECTS ON BREAST CANCER, PROSTATE AND OTHER CANCERS

ABOUT THE AUTHOR

MARTIN MOORE-EDE, M.D., Ph.D.

For over 30 years, Dr. Moore-Ede has been a leading expert on circadian clocks, and the health and safety risks faced by businesses that operate 24/7. After experiencing the challenges of fatigue as a surgeon-in-training required to work 36-hour shifts, Dr. Moore-Ede was one of the first to define the challenges of living, working, and sleeping in a 24-hours-a-day, 7-days-a-week world. As a professor at Harvard Medical School (1975–1998), he led the team that located the suprachiasmatic nucleus, the circadian biological clock in the human brain that controls the timing of sleep and wake, and pioneered research on how the human body can safely adapt to working around the clock and sustain optimum physical and mental performance.

In 1983, to implement circadian science in the workplace, Dr. Moore-Ede founded CIRCADIAN® which now helps over half of the Fortune 500 companies optimize 24/7 workforce productivity, health, and safety. In 2012, in response to the emerging evidence of the harmful effects of blue-rich LED light at night, Dr. Moore-Ede led the team that developed the first blue-depleted white LED lights for safe use at night, and established CIRCADIAN® Light, to market LED lighting systems which provide the correct blue dosage for optimal human health and safety according to the time of day, based on a comprehensive proprietary IP portfolio.

Dr. Moore-Ede graduated with a First Class Honors degree in physiology from the University of London, received his medical degrees from Guy's Hospital Medical School, and his Ph.D. in physiology from Harvard University. He has published 10 books and more than 150 scientific papers on the physiology of sleep deprivation and circadian rhythms. Dr. Moore-Ede holds multiple patents on the spectral composition of light sources, and tools for assessing and mitigating fatigue risk including the Circadian Alertness Simulator (CAS), a scientifically validated fatigue risk model. He has served on multiple national and international committees and has received numerous awards including the Bowditch Lectureship of the American Physiological Society. He is a frequent guest on television (CNN, Today Show, Good Morning America, 20:20, Dateline, Oprah Winfrey, Nova, BBC), radio (NPR Fresh Air, Connection), and print media (Wall Street Journal, New York Times, Washington Post, Time and Newsweek). He has testified before Congressional committees on multiple occasions and advised government agencies on the health and safety of the 24/7 workforce in the US, Canada, and Europe.

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