REVIEW ARTICLE

NIGHTTIME BLUE LIGHT EXPOSURE AND BREAST CANCER

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Pineal Gland

ABSTRACT:

The purpose of this article is to provide background information and the current understanding of a less familiar cause of female breast cancer; exposure to ultraviolet light at night. Breast cancer is a common disease that causes significant morbidity and mortality in women. There are several risk factors for breast cancer, most of which are genetic and environmental in nature. An often-overlooked risk factor is exposure to blue light during night shift work, which decreases melatonin production. One of the many cancer-preventing properties of melatonin is to limit estrogen production. Increased lifetime exposure to estrogen is a well-known cause of breast cancer. Awareness of nighttime blue light exposure as a breast cancer risk factor by women doing night shift work and those exposed to nighttime light via smartphones and laptops, is essential information to know so that protective measures can be taken.

INTRODUCTION

This article intends to increase awareness of night light exposure as a risk factor for female breast cancer. Breast cancer is the second most common type of cancer for women living in the United States. In 2019, it was estimated there were 268,600 new cases and 41,760 deaths due to breast cancer.[1] Although the exact cause of breast cancer is unclear, several risk factors increase the likelihood of developing the disease. The lifetime risk of an American woman getting breast cancer is around 12%. About half of all cases occur in women with no known risk factors. Commonly mentioned risk factors include increasing age, genetic mutations (i.e., BRCA1, BRCA2), family history, obesity, alcohol consumption, smoking, radiation exposure, having the first child over 30-years-old, menopause onset later in life and post-menopausal hormone therapy.[2] Another potential lesser-known risk factor is the exposure to nighttime blue light, limiting normal melatonin production by the pineal gland.[3,4] This latter risk factor is considered in this article.

METHODS

Using PubMed® and Google, a thorough search of medical literature focused on exposure to night light as a risk factor for breast cancer development and its pathophysiological basis was undertaken. Emphasis was placed on recent scientific medical discoveries to link new epidemiological findings toward trends found in the modern workplace environment and how this impacts risk factors for developing this disease. An effort to identify potential clinical solutions to these epidemiological and pathophysiological causes for breast cancer was also examined.

LITERATURE REVIEW

Pathophysiological Mechanism of Exposure to Nighttime Blue Light

An often overlooked breast cancer risk factor is nighttime exposure to short-wavelength visible light in the blue range (LAN), especially that emitted from smart devices and laptop computers.[5] Overexposure to LAN interrupts the circadian rhythm, which interferes with melatonin release by the pineal gland.[4,6] Melatonin reduces estrogen production by influencing the hypothalamus-pituitary-ovary axis. High levels of estrogen and low levels of melatonin have been implicated in the development of breast cancer.[7,8] Serum levels of melatonin and estrogen are modulated, as shown in Figure 1. In the absence of light, neurons originating in the paraventricular nucleus of the hypothalamus (PVH) send a tonic signal stimulating preganglionic sympathetic neurons in the thoracic spinal cord. These fibers synapse on postganglionic cells in the superior cervical ganglion, which then project to the pineal gland stimulating production and secretion of melatonin. Alternately, in the presence of light, a small population of photosensitive retinal ganglion cells is activated, which stimulates the suprachiasmatic nucleus of the hypothalamus (SCN). The SCN has an inhibitory effect on PVH neurons, resulting in decreased secretion of melatonin.

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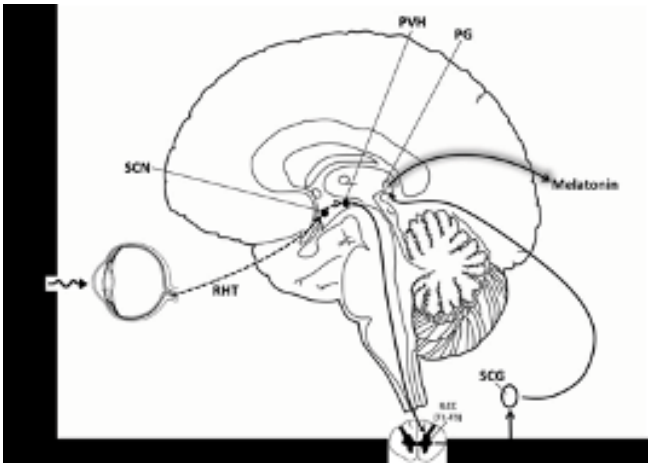
FIGURE 1:

Melatonin production pathway



Under normal (dark) conditions, the PVH sends tonic signals to the ILCC. Here, neurons ascend to the SCG, which projects to the pineal gland, where melatonin is produced and secreted (solid lines). Upon exposure to nighttime blue light, a unique subset of retinal ganglion cells is activated, which project to the SCN (via the RHT). The SCN projects too and inhibits the activity of the PVH (broken lines). RHT = retinohypothalamic tract; SCN= suprachiasmatic nucleus; PVH = paraventricular nucleus of the hypothalamus; ILCC = intermediolateral cell column; SCG = superior cervical ganglion; PG = pineal gland

Melatonin inhibits estrogen production by regulating enzymes involved in estrogen synthesis, thus acting as a selective estrogen enzyme modulator (SEEM).[9,10] The cancer-preventing effect of melatonin is due to a net reduction of estrogenic effects on breast cancer cells.[11] Estrogens are important in many aspects of malignancy; these include cell proliferation, metastasis, angiogenesis and immune evasion. Melatonin has been shown to mitigate all of these processes in the presence of estrogen.[10] Further, melatonin decreases the motility and invasive capabilities of breast cancer cells in vitro. This is due, at least in part, to melatonin's influence on certain cell surface adhesion molecules. Increased cell adhesion prevents potentially metastatic cells from becoming invasive. Estrogen has the opposite effect by downregulating adhesion molecules, thus increasing the invasive potential of the cell. It is possible that this could be another mechanism by which melatonin reduces the incidence and growth of breast cancer.[11]

Calcification of the Pineal Gland and Melatonin Production

The pineal gland is a conical organ positioned in the brain's geometric center (quadrigeminal cistern), weighing on average 150 mg. The pineal gland has a high propensity for calcification (PGC), which may begin as early as three years of age, whereas by 60 years-old, the incidence of PGC increases to greater than 70% in all populations studied worldwide.[12,13] Considering the myriad effects of melatonin on the human body, PGC's impact on melatonin production has naturally been the focus of numerous studies. Although the findings do not always agree, most evidence strongly suggests that PGC reduces melatonin levels.[14,15] Further, it has been demonstrated that PGC is correlated with an increased incidence of breast cancer in women.[16] Assessing PGC through imaging may provide additional information about preventing the development of breast cancer and/or predicting potential tumor growth post-diagnosis.

Epidemiological Linkage to Risk Factor

Many studies have focused on nighttime light exposure and the incidence of breast cancer. Female subjects assessed for breast cancer development include those who work at night in factories, as doctors, nurses and police officers. Table 1 shows that in all scenarios, these women have a higher incidence of breast cancer.[17-22] Further, women who live in areas with high levels of light (i.e., in the presence of neon and/or street lights) experience a higher likelihood of developing breast cancer. Somewhat predictably, blind women have a reduced incidence of breast cancer, presumably due to higher melatonin levels.[23,24] The literature review identified a few studies that found little or no connection between circadian rhythm disruption and breast cancer.[25,26] Investigators employing a large cohort study using serial questionnaires concluded that most populations with night light exposure histories did not experience an increased incidence of breast cancer. However, the authors did acknowledge that a small number of groups with different exposure histories did experience an increase in the development of the disease.[25]

A group of 27 scientists recently met at the International Agency for Research on Cancer to evaluate the carcinogenicity of night shift work (note that exposure to night light outside the context of shift work was not considered). The agency determined that a positive association exists between night shift work and breast cancer prevalence, although confidence in their conclusion was impacted by variation in the individual study parameters.[27,28] Additionally, other studies show as much as a 73% increase in the disease when comparing the lightest and darkest communities within a small geographic area.[29] These contradictory results are likely due to variation in the investigative designs. A major difficulty in determining the true impact of night light exposure is that authors conduct their studies using different parameters; for example, age, number of children, nulliparous or parous, length of exposure (shift length, years on the job) and light wavelength intensity may or may not be considered in a given study.

As more studies are conducted, it has become clear that other factors confound the likelihood of developing breast cancer as a function of circadian rhythm disruption. For example, flight attendants with three or more children and late-shift workers with longer periods of exposure to night light are more likely to develop breast cancer.[30] Another factor to consider is that breast maturation occurs through several stages, some of which may be more sensitive to carcinogens and/or melatonin levels. This might explain why studies have shown disparities in breast cancer incidence in younger versus older night shift workers.[31] It is especially important that women with other known risk factors (such as those with BRCA mutations) recognize the increased probability of developing breast cancer when also working late shifts.[32] Also, it is well-documented that obesity promotes the development of breast cancer.[33,34] The breast cancer risk of women classified as obese may be reduced by melatonin and through mechanisms that decrease body fat, inhibit heightened aromatase expression and counteract the oncogenic effects of

elevated leptin levels.35 Another connection is that the pineal gland volume of obese individuals is, on average, significantly smaller than that of lean subjects.36 This data implicates a mechanism that would explain how obesity, melatonin decline and breast cancer are related.

TABLE 1:[17-22]

Night shift occupation and increased incidence of breast cancer

OCCUPATION	INCREASED INCIDENCE OF BREAST CANCER
Flight attendant	32.4%
Nurses	58.0%
All night shift occupations	3-5% increased incidence/5 years

Clinical Management Strategies

Given that decreased melatonin levels are linked with a higher incidence of breast cancer, clinical avenues of management are needed to address this issue. Direct management can be made by administering melatonin to supplement deficiencies, which, in this case, might decrease the risk of breast cancer. Problematically, studies have shown tremendous variation in the quality of over-the-counter melatonin supplements that must be considered by the physician when prescribing melatonin.[37] Additionally, indirect preventive measures to lessen the incidence of breast cancer can be utilized by reducing electronic device use at night, blocking measures such as anti-blue light glasses or screen covers; and utilizing good nighttime sleep practices/hygiene to minimize blue light exposure.[4,38,39] In support of the use of blue light blocking glasses, at least one study has shown they prevent nocturnal melatonin suppression while having no adverse effects on shift work performance.[40]

CONCLUSION

Numerous studies have suggested that melatonin, naturally produced and exogenously supplied, acts as an anti-tumor agent against several cancers, including those of the breast, ovary, prostate and skin. The incidence of breast cancer increases in women who do late shift work due to exposure to nighttime blue light. This is linked to decreased melatonin production through neuronal pathways projecting to the pineal gland (the site of melatonin production). Essentially all studies reporting on the relationship between nighttime light exposure, melatonin levels and breast cancer employ methods and subjects that are considerably disparate. These discrepancies include age, genetic predisposition, a variation of nighttime light exposure (i.e., hours exposed/night, years on the job, light intensity), number of children, pre- or post-menopausal, obesity, smoking, etc. Designing and implementing a long-term study accounting for as many variables as possible would yield an enormous amount of information regarding breast cancer incidence as it is associated with the numerous combinations of risk factors.

In the clinic, we suggest that the patient's health care provider inquire about any habits that would expose her to nighttime blue light, such as employment schedule, use of technological devices, sleep environment and sleep schedule. These risk factors should be collectively considered when discussing the overall breast cancer risk with the patient. Further, alerting female patients to the unforeseen risk factor of exposure to nighttime blue light could make an important difference in many women's future health.

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