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Research

Light and breast cancer: Is there any relationship

Pushkala K[1] and Gupta P. D[2*]

[1]*S.D.N.B. Vaishnav College for Women, Chennai, India*

[2]*ManipalUniversity, Manipal, India*

Abstract

Breast cancer is the leading cause of death in women all over the world. Epidemiological survey for the incidence of breast cancer in Scandinavian countries and night shift workers provide enough evidence for the possible relation between light and hormone regulated cancers such as breast cancer and prostate cancer, may be due to disturbances in human circadian rhythm. Another evidence between the relationship of light and breast cancer comes from the visually impaired menopausal (high risk group) women; since they are less susceptible to breast cancer compared to sighted menopausal women. Comparison of the data on the incidence of breast cancer between countries closure to the poles and equator also indicates that the incidence rate is less in countries near the equator due to stable circadian rhythm (24hours light and 24 hours dark periods almost throughout the year). In India with nearly stable circadian rhythm, in the blind women model it has been shown that blind women are devoid of breast cancer. This observation indicates that an over exposure of light especially during night is a major factor responsible for the elevated incidence of breast cancer in women, thereby suggesting a relationship between an epigenetic effect of light and breast cancer risk. A possible molecular mechanism underlying this phenomenon most likely involves the production and maintenance of pineal hormone—melatonin. In blind melatonin levels are always high and stable compared to sighted women. Earlier we have shown that there is an inverse relationship between Oestrogen and melatonin. It seems that dark hours are very much essential in our daily routine.

Keywords: Scandinavian countries; Shift Workers; Blind Women Model, Photoperiod, Molecular Mechanism

Introduction

Light is essential for life; but excess of it can cause many disorders in human, other animals and even in plants. Along with the origin of earth, alternating photoperiods also emerged; in a span of 24 hours there must be a dark period followed by a light period. Before the discovery of artificial light, human body was adopted to work perfectly with circadian rhythm 12L and 12D(12hours light and 12 hours dark periods).Thus a daily circadian rhythm (sleep awake cycle) was established. And when the light disappears, humans sleep, since they are diurnal. After the discovery of electricity, human life style changed and the disturbances in circadian rhythms was linked with specific pathological disorders such as increased fatigue, digestive problems, disturbed sleep, risk of developing cancers and impaired performance at work.

Shift workers

Long-term exposure to artificial bright night light (LAN-light at night) during sleep cycle disrupts rhythmic behavior of humans. The clue for the disturbance of circadian rhythm–cancer connection was first started with by Stevens in 1987 in his study for the effect of light and extremely low frequency electric and/or magnetic (ELF) fields on pineal melatonin production, and on the relationship of melatonin to mammary carcinogenesis [1]. Later register based epidemiological study of night shift nurses who fall under three categories (namely day shift, night shift and rotating shift pattern) in the Scandinavian countries. The increased cancer risk has been reported in nurses, radio-telephone operators, flight attendants, and women employed in the enterprises, in which 60% of employees work at night [2]. Later, circadian rhythm-cancer connection has been proved from investigations involving pilots, female flight attendants and shift workers who are more likely to have disrupted circadian cycles due to abnormal working hours in different parts of the world. Stretching the day by artificial light at night disrupting the natural melatonin Oestrogen balance was linked with the increase in hormone regulated breast cancer among women [3].

Predictions were made long ago that women working a non-day shift would be at a higher risk of developing breast cancer compared to the day-working women. Night shift working pattern has also been extended recently to prostate cancer in men similar to breast cancer in women [2].

A study involving members of the Californian Teachers found an increased risk of developing breast cancer in women living in areas with the highest outdoor light at night, estimating the impact of indoor and outdoor light at night [4].

***Corresponding author:** Dr. Gupta P. D. 833, ChurukonKa Rasta, Chaura Rasta, Jaipur, India, Tel: +91 9929370150, 09460892478; E-mail: pdg2000@hotmail.com

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Polar region

Latitude plays a major role on the regulation of photoperiod on a particular place due to rotation of earth around its axis and also around the Sun. The epidemiological survey conducted in different countries indicates an alarming elevated incidence of breast cancer between countries closer to the poles or away from the equator such as North America and northern Europe compared with Asian regions suggesting that natural light is extended due to the topographical location of the countries, a major contributory factor for elevated incidence of the diseases. The lowest breast cancer mortality rates are reported in Asian regions, leading researchers to speculate that dietary, cultural, and/or environmental factors might be implicated in the etiology of the disease [5]. From the meteorological observation the circadian rhythm is deviated much form 12L and 12D in those people living in poles. Probably the melatonin level would have been maintained in the blood at a low level for most part of the 24hours day period unable to put the cancer susceptible cells insomniacs compared to the people living in countries closer to the equator.

Blind women

In the survey, out of 2060 (collected during 2006 - 2013) menopausal blind women, we found only twelve subjects were suffering with breast cancer. This study [3-8] gave a clue for the low prevalence of BC in blind menopausal women BC compared to sighted women in India [9] where stable circadian rhythm is maintained. Our study is the first of its kind considering the influence of parameters such as total blindness / partial blindness /development of blindness before menarche /after menarche /development of blindness before pre-menopause/after menopause, on the prevalence of breast cancer in blind women. Though earlier studies in Finland and Sweden [10-11] also reported low prevalence of BC in totally blind women compared to sighted women, the comparison between the incidences of BC between above mentioned parameters were wanting. Hahn indicated that, overall, women with bilateral blindness had almost half the risk of developing breast cancer compared to sighted women from a US case control study [12]. Our study showed thrice the elevated risk of developing BC, where age at onset of blindness has a profound role to play in the progression of BC. Coleman and Reiter suggested that a hypothesis could be tested that long-term blindness protects against breast cancer from long-standing register based studies of adequate quality [13]. In this study we observed postmenopausal stage of a woman has more risk of developing BC than pre-menopausal stage. Flynn-Evans et al. observed blind women with no perception of light (NPL) have a lower prevalence of breast cancer compared to blind women with light perception (LP). But they observed little difference in these associations when restricting to postmenopausal women, non-shift workers or when excluding women diagnosed with breast cancer within 2 or 4 years of onset of blindness [14].

Molecular Mechanisms

Steven W. Lockley, a chronobiologist at the University of Surrey in England, and colleagues measured melatonin in 49 blind individuals and noted that melatonin cycles in blind are predictable [15]. Blask, working is this area for a long time says, "Light at night is now clearly a risk factor for breast cancer. Breast tumors are awake during the day, and melatonin puts them to sleep at night". He added that if artificial light is added to the night environment, the cancer cells become insomniacs. Blask showed in his studies in rat, that an abnormal timing of melatonin peaks could have a powerful effect on cancer. He administered cancer-causing chemicals to rats and then over subsequent weeks, injected the animals daily with melatonin. The injections were timed to produce peaks during daylight hours, when melatonin concentrations should have been negligible. When injections were given in the mid-morning, tumors grew at the same rates seen in animals not receiving injections. However, in animals that received the hormone during the afternoon, an inhibitory effect of the hormone on tumor growth, not only in liver cancers, but also in breast cancers was observed. Human MCF-7 cell xenograft were implanted into the groins of rats and measurements were taken on the cell growth rate, the uptake of Linoleic Acid (LA- utilized by cancer cells for growth), and melatonin levels. One group of implanted rats was placed in 12L and 12Dand a second group in 24hours light 12L: 12L environments. Constant light, suppressed melatonin, increased cancer cell growth rates and increased LA uptake into cancer cells. The opposite was seen in the light-dark group. The proposed mechanism is the suppression of nocturnal melatonin by exposure to light at night (LAN) and subsequent lack of protection by melatonin on cancer cell receptor sites, which allows the uptake of LA, which in turn enhances the growth of cancer cells. Melatonin is a protective, oncostatic hormone and strong antioxidant having evolved in all plants and animals over the millennia. In vertebrates, melatonin is normally produced by the pineal gland during the early morning hours of darkness, even in nocturnal animals, and is suppressed by exposure to LAN. These findings suggest that there is a rhythm of sensitivity within tumor tissues or in cells susceptible to tumors formation and may be in people who can't perceive light, the oscillating cycle of their biological clock causes their melatonin peaks to coincide with the inhibitory period of tumor cells more often than they do in light-sensitive people. Professor Blask noted that in several laboratories working with cells and with tissues removed from animals indicates that a reduction of melatonin can alter the production of other hormones, may suppress the immune system's ability to recognize and respond to newly emerging cancers, and appears to spur the growth of at least some tumor tissues [16]. Blue and green lights appear especially effective at inhibiting melatonin synthesis in healthy young men. For some colors, "17 lux was sufficient to produce strong melatonin suppression in these men and some had full suppression with exposure to as little as 5 lux, a little more illumination than what you'd have with full moonlight. His experiments with rodents proved that tumors can grow especially rapidly when exposed to constant light, presumably due to a near-total suppression of their melatonin levels in the microenvironment [17;18].

The external light sensitive organs in human are eyes, skin and internal organs such as suprachiasmatic nucleus and pineal are the ones take part in photoreactions in the body. When light is focused

on the eye, various physical and chemical reactions are induced in the photoreceptor (specialized, light-sensitive cells) present on the retina by signal transduction pathway. The brain recognizes these changes.

Earlier we studied the effects of day light in an opthalmic rats and concluded that the mammalian eyes up serves at least two photic systems: the occipital cortex, which mediates the conscious perception of light and recognition of images and a sub cortical system that mediates light-sensitive synchronization of the circadian pace-maker [19-24].

Interaction between Pineal and Suprachiasmatic nuclei (SCN)

The details of molecular interactions between pineal and SCN has been described in the book [3], however briefly, input pathways carrying photic andnonphotic information provided by the retina, hypothalamic SCN, paraventricular nuclei,preganglionic sympathetic regions of the spinal cord, superior cervical ganglion (SCG) are given topineal gland which takes the responsibility to connect the endogenous clock to the environment.

Human biological clock is set to be prevailing in SCN which produces Serotonin, the precursor of Melatonin. The conversion of serotonin to melatonin is light dependent since, only in dark this reaction proceeds in foreword direction. The mechanism of the disease is not clearly understood, however from this data it is clear that blindness is the preventive measure of breast cancer.

Earlier in our work showed that there is an inverse relationship between melatonin and estrogen [21], a cell proliferating hormone and a quantity of this can be a cause for the proliferation of breast cells. In menopause the control of estradiol and progesterone secretion is disturbed and therefore postmenopausal women are more vulnerable to breast cancer.

As it is mentioned, that conversion of serotonin to melatonin take place in dark only, blind women maintain a constant titer of the hormone unlike the sighted women. The circadian rhythm may be intact in blind women unlike in sighted women, however the photic receptors for image formation through light are non functional. The light dependent hormone is quantitatively more in blind women and therefore as it is mentioned can regulate lower levels of estrogen even in menopausal women. It has been established that melatonin has anti-cancerous activity. From our studies it emerges that blind menopausal women may serve a model for understanding regulation of breast cancer in relation to melatonin, light, estrogen and other hormones.

Conclusions

Three different epidemiological surveys for breast cancer incidence, namely,

1. blind menopausal women

2. population on polar region, and

3. night shift workers

univocally showed the same thing that more exposer with light raises incident of breast cancer. This may be due to lower levels of melatonin in the blood because serotonin is not able to get converted in melatonin and whole hormonal milieu changes. Prolonged exposer of light not only changes melatonin levels in the body but may also bring about mutation in the genes that may also be responsible for higher incidence of cancers.

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