Increased Incidence of Breast Cancer Due to Long Exposure of Light

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Abstract: The disturbed circadian rhythm due to long exposure to varied photo periods or to artificial light during night time (LAN) results in hormonal imbalance. The epidemiological survey indicates a clear difference in the incidence of breast cancer (BC) in countries closer to the poles and to the equator. Long-term exposure to LAN during sleep cycle is found to be the root cause of many health problems. Light dependent conversion of melatonin from serotonin plays a major role in cancer development. In rat model it is shown that levels of melatonin are always inversely proportional to oestradiol in the blood. Melatonin decreases the formation of oestrogens (mitogenic hormone) from androgens via aromatise inhibition. In a pilot study we have shown that in menopausal blind (risk age for BC) women the prevalence of BC is very low (1:169; Risk Rate (RR); Cumulative Risk (CR)35-64 age), compared to sighted women (1:78; CR, 35 - 64 age). Data was collected from a total of 2060 blind subjects (18.8% being <40 years of age and 81.2% above 40 years). Partially blind subjects have 11% greater risk of developing BC than those who are totally blind (RR=1.106; 95% CI=.352 to 3.472). Other established risk factors for BC are ineffective in blind. The blind women model (proposed in this study) suggests that dark hours are essential in our daily routine. By management of proper circadian rhythms better management of various endocrine diseases including hormone dependent cancers can be achieved.

Keywords: Blind women model, low incidence, photoperiod, melatonin, epidemiology.

INTRODUCTION

Biological activities are regulated by the daily light–dark cycle. The exposure of light to human beings works in two different ways; the image formation and regulation of circadian rhythm. The light which is received through eyes performs both the functions whereas when received through the skin is involved only in regulation of circadian rhythm.

The exposure of electric light at night was anticipated to be one of the important factors for rising of BC worldwide. The negative impact due to disruption of circadian rhythms in night shift workers is also well studied. Disturbance of circadian rhythm was linked with specific pathological disorders such as increased fatigue, digestive problems, disturbed sleep, risk of developing cancers and impaired performance at work. 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 [1].

Register based epidemiological studies and a few experimental data indicate that shift working pattern might lead to circadian disruption, including disruption in the melatonin conversion. Relatively a few epidemiological studies have been carried out in this area (15 studies including 8 cohort and 7 case-control studies).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]. Several studies [3-9] revealed a clear association between night shift work and increased incidence of BC in Scandinavian countries, focusing our attention towards “Light at Night” (LAN) as a potential “carcinogen” linking with reduced secretion of light sensitive melatonin (anti-cancerous) and progression of BC [10]. 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 [11].

Melatonin, "hormone of the darkness," has also been attributed for its potential as anti-carcinogenic and anti-oxidative properties, in addition to its involvement in circadian rhythm regulation, sleep, hormonal expression of darkness, seasonal reproduction, retinal physiology, efficacy as a potent antioxidant, free-radical scavenging, cardiovascular regulation, immune activity and metabolism of lipid and glucose. Risk of developing BC increased in women who worked night shifts for more than five years especially those who are regularly engaged in night work for at least four years prior to their first pregnancy, before their mammary systems had fully differentiated [12]. Earlier studies were done to understand how imbalance of natural

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melatonin- oestrogen by artificial light at night could be linked with the increase in hormone regulated BC among women [13-17]. Blast *et al.* [18] have established that increase in melatonin levels causes the suppression of tumour growth in-vivo in nude mice model. High levels of melatonin at night with its antagonistic activity to the hormones of the reproductive system regulates both pituitary and ovarian hormones and suppressing the local production of oestrogen resulting from the conversion of androgens into oestrogen in the breast tumour cells [19, 20]. Therefore, it is not surprising that disruption of melatonin titre by circadian rhythms may be well associated with several diseases, particularly hormone regulated cancers such as breast and prostate cancers.

The use of excess or obtrusive artificial and/or natural light (sunlight only in certain regions of the globe) has many environmental impacts on biological and ecological systems as well. Latitude plays a major role on the photoperiod of a place. When viewed from a global perspective, BC mortality rates reveal interesting features and trends that may not be discerned from national or regional data alone. From the literature survey we found a several-fold difference in the BC incidence between countries closer to the poles than to the equator which experience 12 hours day light and 12 hours night light (Table **1**).

In polar region however, the strength of the Zeitgeber (time giver) is greatly reduced around summer and winter solstices (continuous light or continuous darkness). Melatonin level would have been maintained in the blood at a low level for most part of the day in people unable to put the cancer susceptible cells to sleep. These observations suggests that natural light is extended due to the topographical location of the countries which could disturb the circadian rhythm, due to varied photo periods / exposure of artificial light during night time to extend the day resulting in hormonal imbalance, a major contributory factor for elevated incidence of the diseases.

With this background knowledge we developed a "blind women model" to prove how the long exposure of (Natural/artificial) light a "chronodisruptor" disturbing the natural melatonin-oestrogen balance could be a major cause for increasing rate of hormone regulated BC throughout the world. On comparison it is observed that blind women maintain a high melatonin titre and a constant circadian rhythm unlike the sighted women, however the photic receptors for image formation through light are non functional in blind women. The literature survey showed very scanty information on the prevalence of breast cancer in blind women worldwide. The first preliminary evidence linking light to cancer in people emerged from the register based studies. Hahn computed the incidence of this malignancy in blind and sighted women and discussed the connection between light and melatonin in visually impaired women [21]. As early as 1990, scientists reasoned that anybody whose eye cannot detect light should be resistant to oestrogen generated tumours. This angle of discussion paved way for the epidemiologist to reason that people whose eyes cannot detect light should be resistant to tumour growth. Subsequently, studies based on cancer registry in Sweden and Finland supported melatonin hypothesis [22, 23]. 50% decreased risk of the disease and an inverse association between BC incidence and degree of visual impairment was also recorded [23]. Similarly, Kliukiene found only 5 subjects suffering from BC among 15,412 visually impaired subjects in blind registry in Norway [24]. Pukkala *et al.* added to the suggestive epidemiological evidence for the 40% decreased risk of hormone related cancers in people with visual impairment and consequently established a

Table 1: A Comparison of Incidence of BC in the Populations Living in Countries Closer to Poles and Equatorial Regions Respectively

S. No.	Name of the country			
	Towards poles	Incidence rate / 10,0000	Towards Equator	Incidence rate / 10,0000♀
1	Alaska	125	Magnolia	7
2	Belgium	109.2	Bhutan	7
3	Denmark	101.1	E Asia	18
4	France	99.7	S C Asia	18
5	Netherlands	98.5	Indonesia	18.6

Table showing the high incidence of BC in the countries closer to poles compared to equatorial region with disturbed circadian rhythm due to a long exposure of Natural and /or artificial light.

relationship between exposure of visible light at night and BC risk in Finland. The hypothesis is further advanced that blindness from an early age may lead to a further reduced risk of BC through altered patterns of melatonin secretion by the pineal gland [25]. The effect of age at onset, duration and degree of blindness could also be assessed after adjustment for known risk factors for BC [26]. India is the home to one of the world's largest population (12 million suffering from visual impairment, Census of India, 2001). The literature survey did not show any published data on blindness adult menopausal women suffering from BC in India. We were interested to have data on BC among Blind menopausal women in the Indian population to compare with sighted menopausal women. Therefore, a pilot epidemiological survey was undertaken to establish the prevalence of BC among visually impaired menopausal women in India located in the equatorial region with 12hours day and 12 hours night.

MATERIALS AND METHODS

India lies to the north of the equator, 6°44' and 35°30' North Latitude, 68°7' to 97°25' East Longitude with a total area of 3,287,240 square kilometres. From Indian subcontinent we have selected 2 provinces namely Gujarat (North- West) and Tamil Nadu (South-East) quite different culturally and in food habits. The following blind menopausal subjects were included in the present study, since national registry for the blind is not available:

1. Madras Metropolitan Tumor Registry (MMTR).
2. Tamil Nadu Governmental rehabilitation centers.
3. Tamil Nadu Non-governmental rehabilitation centers.
4. Gujarat Governmental rehabilitation centers.
5. Gujarat Non-governmental rehabilitation centers.

In the present study, data were obtained from personal communication with the study population of women as well as from the cancer registry. For ascertaining the degree of visual impairment (total blindness and partial blindness) a manual of classification of impairments, disabilities and handicaps, WHO Geneva, [27] was used. The data on the risk of developing cancer among normally sighted women was procured as curtsey from MMTR 2003 - 2005 for comparison [28]. Only blind women menopausal age (30 – 40 years) and post menopausal age as above 40 years (risk age) were considered for the present study. Women with menstrual cycle after 40 years were also included as pre-menopausal stage. Statistical software Epi - Info [29] was used to analyze the data.

RESULTS

In the survey out of 2060 (collected during 2006 - 2013) menopausal blind women, it was found that only twelve subjects were suffering from breast cancer. The ratio of "well established" high risk factors for prevalence of BC such as, obesity, problem in breast tissue, nulliparity, not breast fed, age of the first pregnancy (above 35 years of age), age of onset of blindness (before or after menarche), family history of any cancer, and those already suffering from other types of cancers were also considered for the analysis to find how many are at risk of developing BC in addition to their age (Figure **1**).

Among the study subjects 4% were obese, 11.27% suffer from other problems in the breast tissue. 33.8 % did not feed their children and 14.22% show nulliparity. 12.25% had the first child above 35 years old (late pregnancy) and 8.2 % have family history of cancer. In addition, suspected risk factors such as late menopause (16.2%), partial blindness (39.6 %) and age of onset of blindness (after menarche) (8.67%) were also recorded. Even though these risk factors were observed, among the study group only twelve had breast cancer including partially blind women

Statistical Analyses

Relative risk (RR) was used as a measure of association between risk factors and susceptibility to develop BC in women; the RR was defined as the ratio of the risk of developing a disease among those exposed to a specified risk to those not exposed to this risk. The 95% confidence intervals (CI) for these relative risks were also calculated. The risk ratio or relative risk (RR) is used to find the association between a disease and a possible risk factor. The susceptibility to develop the disease among women who are more than > 40 years of age is almost thrice than < 40 years (RR = 2.55; 95% CI = 0.33 to19.7). Statistical analyses of the data also provide enough evidence that partially blind women had 9 % greater risk of BC compared to totally blind women (RR = 1.09; 95% CI = 0.347 to 3.422) in this study. Similarly postmenopausal stage of a woman has more risk of developing BC than pre-menopausal stage (RR = 1.43; 95% CI = 0.186, 11.08). Information on the age at

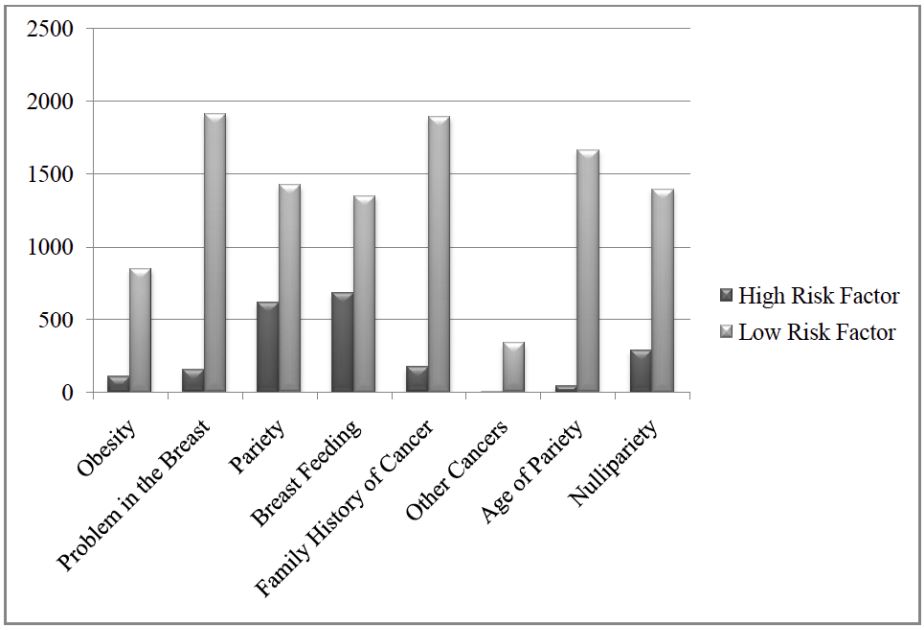

Figure 1: Prevailing ratio of established risk factors observed among study subjects.

Figure **1** showing the prevailing ratios of established risk factors observed among study subjects. X axis represents population (no of persons) and the Y axis represents the risk factors (High: obese, problem in the breast, no parity, not breast fed, having family history of cancer, prevalence of other cancers and Low: no problem in the breast, parity, breast fed, no family history of cancer, absence of other cancers) for developing BC.

which the blind subjects lost their vision was available for only 42% in our study group. Vision loss after menarche is thrice the risk of developing the disease (RR = 0.935; 95% CI = 0.125 to 7.315) (Table **2**).

The intervals for these relative risks give a very wide range of possible values for the corresponding risk ratio. This may be due to the small sample size and the rarity of breast cancer among blind women.

DISCUSSION

As far as BC is concerned, scenario is changing very fast. Studies indicate that due to changing life style in India increasing rate of BC is quite alarming. Now, it is second most common malignancy in Indian women [30]. Currently, India reports roughly 100, 000 new BC cases annually though, a significant regional variations in incidence rates persists. The overall rate is now estimated at 80 new cases per 100, 000 subject per year [31]. According to an Indian health News report one in 22 women in India are likely to suffer from breast cancer during their lifetime, while the figure is definitely more in America with one in eight being a victim of this cancer. BC incidence had zoomed by 200% since 1982 and has become the leading cause of death in women all over the world. According to the report of World Health Organization (WHO) 519, 000 deaths occur every year worldwide (WHO, 2009).

This epidemiological study is the first attempt to collect scientific data on blind menopausal women with respect to BC and compared to sighted women. We did a pilot study [32-36] which gave a clue for the low prevalence of BC in blind menopausal women. No other study has been carried out in India located in the equatorial region earlier to find the prevalence or incidence rate of BC in blind women. The present study also has taken into consideration of the ethnicity and food habits of the study population.

In the present study, blind menopausal women have shown the risk of developing breast cancer in life time is very much lower (1:169; n = 2060) since, only twelve suffered from the disease among our study group. However, Shantha *et al*. showed the risk of developing BC among sighted women in Chennai is 1:78 (Cumulative Risk 35-64 age) [37]. Feychting *et al.* supported melatonin hypothesis with the cohort study consisting of 1, 567 totally blind and 13, 292 severely visually impaired subjects from Swedish cancer registry and found that blind people have a lower incidence of cancer [22]. Similarly, Verkasalo *et al.* also found 50% decrease in the risk of developing the disease in blinds and an inverse association between BC incidence and degree of visual impairment from cancer registry in Finland [23]. The health survey data from the cancer registry of Norwegian government had approximately

Table 2: Analysis of Risk Factors for Developing BC Observed in 12 Blind Subjects

Characteristics		Cancer		Total	Relative risk	95% Confidence interval
		Present (12)	Absent			
Age (in years)	<=40	1	387	388 (18.8%)	2.563	0.330-19.911
	>40	11	1661	1672 (81.2%)		
Menopause	pre menopause	1	237	238 (11.6%)	1.440	0.185-11.2
	Menopause	11	1811	1822 (88.4%)		
Breastfed	Not breastfed	5	682	687	0.714	0.226-2.257
	Breastfed	7	1338	1345		
Age of blindness	Vision loss before menarche	11	779	790	0.935	0.125-7.315
	Vision loss after menarche	1	74	75		
Type of blindness	Total	7	1232	1239	1.09	0.345-3.448
	Partial	5	807	812		
Family History of cancer	No cancer	11	1876	1887	0.979	0.129-7.53
	cancer	1	168	169		

15, 412 visually impaired entries. Among them only 5 subjects suffered from diseases [24]. Subsequently, Pukkala *et al.* from a cohort study consisting of people with visual impairment identified from Finnish cancer registry for years 1983 - 2003 added to the suggestive epidemiological evidence for the decreased risk of hormone related cancers in people with visual impairment [25, 38]. The cohort consisted of 17, 557 of persons with visual impairment (11, 147 women, 6,410 men) showing only 184 cases of BC, which represented a 40% decrease in the risk of developing BC and established a relationship between visible light at night and BC. Due to the topographical location of India (being close to the equator), almost 12 hours light and dark cycle persists, unlike the Scandinavian countries, having long day / night due to the location close to the poles. Though image forming photic receptors are absent in blinds, photic receptors for synchronization of circadian rhythms are present to maintain a natural and normal circadian rhythm and so they enjoy less susceptibility to develop BC due to lack of cones in their retina [39].

In the Indian scenario circadian rhythms are more stable than Scandinavian countries and this could be the major reason for the very low prevalence of BC reported compared to the Scandinavian countries in this study. Other reasons for low prevalence of the disease in Indian blind population may be due to their abstinence from smoking [40], alcohol and under taking vigorous physical activity compared to Scandinavian population [41]. In the present investigation among our study group 33.8% did not feed their children and 14.22% showed nulliparity, 12.25% had their first child above 35 years old (late pregnancy) showing that they fall under "well established" risk factors [42-44] for developing BC however, these risk factors did not show much effect on blind population, nevertheless these account for 50 – 55% of the BC risk among Western populations.

Similarly, single women and nulliparous married women were prone to the disease approximately 1.4 times more than that of married women with children. The data showed that, women who breast fed their infants had a 17% lower risk of BC compared to women who did not breast feed the child [45]. Women whose first child was born before they were 20 had approximately less than 50% risk of developing BC than women whose first child birth was at the age above 30 [46]. Among the study subjects 8.2% have family history of cancer. Altogether, about 20 to 30% of women with BC have a family member with this disease [41, 47]. In addition, suspected risk factors such as, obesity (4%), other problems in the breast tissue (11.27%), late menopause (16.2%), partial blindness (39.6%) and age at onset of blindness (after menarche) (8.67%) were also recorded.

It is surprising that the above discussed risk factors seem to be either non operative or suppressed in blind menopausal women to develop the disease. However in the twelve breast cancer cases the risk factors such as nulliparity, not breast fed, early menarche and partial blindness (case-I) could be the contributory

factor of the cancer susceptibility genes such as P^{53}, BRCA I and BRCA II etc. [45].

CONCLUSION

From this study it emerges that blind menopausal women may serve as a model for understanding the regulation of hormone dependent cancer in relation to melatonin, estrogen and long exposure of light. For the first time using blind menopausal women model we have proved that light is a major culprit, responsible for the elevated incidence of BC in women. The result of the present study is a additional epidemiological evidence suggesting a relationship between visible light exposure and BC risk, taking into consideration of in the BC incidence in polar regions and among shift workers. However, little is known about possible molecular mechanisms underlying this clock cancer connection. So, further study at the molecular level is very essential to confirm the reason for the very low prevalence of BC.

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