RESEARCH ARTICLE

Association of Breast Cancer with Sleep Pattern - A Pilot Case Control Study in a Regional Cancer Centre in South Asia

Karabi Datta[1]*, Asoke Roy[2], Durgaprasad Nanda[3], Ila Das[4], Subhas Guha[1], Dipanwita Ghosh[2], Samar Sikdar[2], Jaydip Biswas[5]

Abstract

The rising trend of breast cancer both in developed and developing countries is a real threat challenging all efforts to screening, prevention and treatment aspects to reduce its impact. In spite of modern preventive strategies, the upward trend of breast cancer has become a matter of great concern in both developed and developing countries. Chittaranjan National Cancer Institute is a premier regional cancer institute in eastern region of India catering to a large number of cancer patients every year. A pilot case control study of fifty breast cancer patients and 100 matched controls was conducted during 2013 to evaluate the effects of habitual factors like working in night shift, not having adequate sleep, and not sleeping in total darkness on breast cancer of women. The study revealed that not sleeping in total darkness was associated with higher odds of outcome of breast cancer of women. This positive correlation can play a vital role in formulation of preventive strategies through life style modification.

Keywords: Light at night - melatonin - circadian rhythm - night shift work - breast cancer - Indians

Asian Pac J Cancer Prev, **15 (20)**, 8641-8645

Introduction

U.S. Cancer Statistics Working Group (2013) shows that in 2010. 206,966 women and 2,039 men in the United States were diagnosed with breast cancer and 40,996 women and 439 men in the United States died from breast cancer. Incidence counts cover about 97% of the U.S. population; death counts cover about 100% of the U.S. population.

Farley et al. (2010) find cancer of the breast in women is a major health burden worldwide. It is the most common cause of cancer among women in both high-resource and low-resource settings, and is responsible for over one million of the estimated 10 million neoplasm diagnosed worldwide each year in both sexes. It is also the primary cause of cancer death among women globally, responsible for about 375,000 deaths in the year 2000.

Ferlay et al. (2010) showed that in 2008 in 40 European countries, the most common cancers were colorectal cancers (13.6% of the total) followed by breast cancer (13.1%), lung cancer (12.2%).The most common causes of death from cancer were lung cancer (19.9% of the total), colorectal cancer (12.3%), breast cancer (7.5%) Up-to-date statistics on cancer occurrence and outcome are essential for the planning and evaluation of programmes for cancer control.

Three-year Report of Population Based Cancer Registries (2009-2011) shows among Indian women breast cancer incidence is increasing and Age Adjusted Rate varies at different regions. During the period 2009-2011, in India Age Adjusted Rate was recorded to be 32.6 in Chennai, 32.2in Delhi, 31.0 in Mumbai, 36.6 in Bangalore, 22.10 In Bhopal, 27.5 in Ahmadabad Urban and 26.1 in Kolkata.

Nandakumar et al. (2010) showed that in the year 2007, there have been an estimated 82,000 new cases of cancer breast in India. The data collected over the years from five urban population based cancer registries namely Bangalore, Bhopal, Chennai, Delhi and Mumbai, under National Cancer Registry Programme (NCRP) have shown a statistical rising trend in the incidence rate of breast cancer. In hospital-based cancer registries, cancer of the breast is the leading site of cancer in Mumbai and Thiruvananthapuram, second leading site in Bangalore, Dibrugarh and Chennai. Rajesh Dikshit et al. (2012) showed that for women aged 30-69 years, one of the three most common fatal cancers was breast cancer-10% (19,900).

In past many case control and cohort studies were undertaken to find out risk factors of breast cancer of which some were related with life style modification. A case control study by Datta and Jaydip Biswas (2009) related the different factors associated with breast cancer in Eastern India. Higher risk was found to be associated

*[1]Department of Epidemiology Biostatistics, [2]Department of Pathology and Cancer Screening, [3]Department of Surgical Oncology, [4]Depart of Cancer Chemoprevention, [5]Director, Chittaranjan National Cancer Institute, Kolkata, India *For correspondence: karabi_bhanja@yahoo.co.in*

with higher standard of living, higher consumption of deep fried food, higher BMI, higher per capita protein and fat consumption per week.

Kruk and Marchlewicz (2013) showed in a Case-Control study that a diet characterized by a high consumption of animal fat is associated with a higher breast cancer risk in sedentary women, while consumption of plant fat products may reduce risk in the same group. Shamsi et al. (2013) in a Case-Control study in Karachi, Pakistan showed that positive family history of breast cancer, single marital status, older age at menopause were risk factor for breast cancer. Jiang et al. (2013) did a case-control study with 669 cases and 682 controls and found out that relationship between breast cancer and abortions may depend on menopausal status and induced abortion may play an important role in the development of breast cancer in Jiangsu' women of China.

Ramchandra Kamath et al. (2013) conducted a case control study at Shirdi Sai Baba Cancer Hospital and Research Center, Manipal, Udupi District with 188 participants. The women with more than 7 to 12 years of education had 4.84 times risk of breast cancer (OR 4.84 CI 1.51-15.46) as compared with the illiterate women. The adjusted risk of breast cancer was more among the women who had non vegetarian diet (OR 2.80, CI 1.15-6.81) as compared with the vegetarian women. A case–control study of female breast cancer was conducted by Qian Li et al. (2010) in Connecticut with a total of 363 incident breast cancer cases and 356 age frequency-matched controls using a standardized, structured questionnaire to obtain information on sleeping patterns and bedroom light environment. It showed non-significantly increased risk of breast cancer among postmenopausal women for those keeping lights on while sleeping (OR=1.4, 95%CI 0.7, 2.7), those who reported mainly sleeping in the daytime (OR=1.4, 95%CI 0.5, 4.3), and those not drawing the curtains/window shades while sleeping at night .(OR=1.2, 95%CI 0.8, 1.9)

In order to reduce the incidence of breast Cancer in this region, it was therefore of interest to investigate the specific risk factors related to life style. The objective of the present study, therefore, is to identify and wherever possible, quantify the important modifiable risk factors attributable to breast cancers. The study is the first of its kind where an attempt has been made to correlate sleep pattern and shift work with Breast cancer in Eastern India.

Materials and Methods

A pilot Case Control study was conducted in Chittaranjan National Cancer Institute, Kolkata, India during the period 2013 to evaluate the effects of multiple explanatory factors on a binary outcome variable, i.e., effects of habitual factors like working in night shift, not having adequate sleep, not sleeping in total darkness on breast cancer of women.

Fifty indoor female breast cancer patients treated in this Institute were taken as cases and hundred matched controls were selected from women attending Cancer Screening Department of the Institute. Information was collected from both the groups by direct interview method using a well designed questionnaire about the different parameters along with special emphasis on parameters i.e. working in night shift, not having adequate sleep and not sleeping in total darkness.

Odds eatios (OR) was calculated for assessing the risks associated factors under consideration fitting the logistic regression. For this purpose, Software R was used. When a logistic regression is calculated, the regression coefficients are the estimated increases in the log odds of the outcome per unit increase in the value of the exposure of the factors. In other words, the exponential function of the regression coefficients are the odds ratio associated with a one-unit increase in the exposure of the factor. The odds ratio is used to determine whether a particular exposure is a risk factor for a particular outcome, and to compare the magnitude of various risk factors for that outcome. The 95% confidence interval (CI) is used to estimate the precision of the OR. A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR. The interpretation of OR is given below.

Three factors were considered in this study, namely, having adequate sleep, not sleeping in total darkness and working at night shift. It is defined that adequate sleep means duration of sleep is more than 6 hours

Results

In this case-control study, the objective is to evaluate the effects of multiple explanatory factors on a binary outcome variable, i.e., effects of habitual factors like working in night shift, not having adequate sleep, not sleeping in total darkness on breast cancer of women. Here, 50 cases and 100 control (1:2 matched controls), matched by age, obesity factors and food habits were taken. Table 1, Table 2 and Table 3 give the matching figures.

Three factors were considered in this study, namely, having adequate sleep, not sleeping in total darkness and working at night shift. It is defined that adequate sleep means duration of sleep is more than 6 hours.

Table1 shows that 80% of cases did not get adequate sleep, whereas that percentage in controls is 55%. Also, it is found that not getting adequate sleep is highly associated with causation of the disease (chi-square 6.92, p-value 0.004) and only 48% cases slept in total darkness while it was 82% in controls. 52% of cases were found not to sleep in darkness vis-à-vis 18% controls. It shows that not sleeping in darkness is another significant factor (chi-square 18.589, p-value 0.000. It shows that 18% were night shift workers among cases whereas 8% were night shift workers among controls. It reveals association of breast cancer with night shift working is marginally significant (chi-square 3.17, p-value 0.099).

Odds ratios for different factors are presented in Table 2. It reveals that odds ratio for not sufficient sleep is 2.832 (95%CI: 0.787-10.196). Also, that for not sleeping in darkness is 4.257 (95%CI: 1.275-14.225). Finally, for working at night shift the odds ratio is found to be 1.509 with 95%CI 0.267-8.516.

So from analysis, it can be clearly said that exposures

Table 1. Distribution of Cases and Controls According to Reported Sufficiency of Sleep, Sleeping in Darkness and Working at Night Shift

	Case		Control	
	No	%	No	%
Sufficiency of sleep	(Chi-square=8.91, p-value=0.004)			
Sufficient	10	20	45	45
Insufficient	40	80	55	55
Total	50	100	100	100
Sleeping in darkness	(Chi-square=18.6, p-value=0)			
Yes	24	48	82	82
No	26	52	18	18
total	50	100	100	100
Working at night shift	(Chi-square=3.17, p-value=0.099)			
Yes	41	82	92	92
No	9	18	8	8
total	50	100	100	100

Table 2. Risk Estimates of Different Factors

	Odds ratio	95%CI
Not sufficient sleep	2.832	0.787-10.196
Not sleeping in darkness	4.257	1.275-14.225
Working at night shift	1.509	0.267-8.516

to working in night shift, not having adequate sleep, not sleeping in total darkness are associated with higher odds of outcome of breast cancer of women.

Discussion

Chittaranjan National Cancer Institute (CNCI) in Kolkata is serving as a premier Regional Cancer Centre (RCC) for the Eastern Region of the Country. The hospital was formally inaugurated by Prof. Madam J. Curie in January 2, 1950 and named after Desbandhu Chittaranjan Das in acknowledgement of his enormous support.

The results of the pilot study are consistent with various studies done by different study groups. The results from this study suggest a potential increased risk of breast cancer associated with domestic exposure to light at night.

Brzezinski (1997) showed that melatonin is synthesized and secreted by the pineal gland in the brain and plays a key role in controlling the body's circadian rhythm. Sanchez-Barcelo et al. (2005) showed darkness stimulates the release of melatonin and light suppresses its activity. Normal melatonin cycles are disrupted by exposure to excessive light in the evening. According to the circadian disruption hypothesis, factors in the environment (e.g. light at night) that might disrupt the endogenous circadian rhythm and that suppress nocturnal melatonin production may increase the risk of breast cancer. The favoured hypothesis is that melatonin influences breast cancer risk via its effect on oestrogen signalling.

To date, no study of breast cancer and light at night has used measures based on sleep habits or bedroom lighting environment as estimates of exposure to light at night. Our findings are consistent with results obtained from study done by Hansen. (2001) and Rafnsson et al. (2001) showing a relationship between the risk of breast cancer and shiftwork.

Our study report supports other such studies in this field regarding night shift workers having greater chance of breast cancer. Schernhammer et al. (2001) and Davis et al. (2001) showed that disruption of diurnal sleep–wakefulness rhythms, especially through night-time shift work, was associated with higher subsequent breast cancer incidence. Studies by Parkin (2011) and Slack et al. (2012) showed that an estimated 4-5% of female breast cancers in the UK are linked to shift work. Jia et al. (2013), Kolstad (2008) and Wang et al (2013) underwent studies that explain the link between shift work and breast cancer risk, but confounding by other lifestyle factors such as tobacco use, BMI and physical activity is possible. The findings also support our study result.

Some studies based on Sleeping in darkness or in light are also consistent with our findings. A case-control study by Davis et al. (2001) reported a non-significant 40% greater risk of breast cancer (OR=1.4, 95%CI 0.8, 2.6) for women who reported the highest ambient light level in the bedroom than those who reported total darkness in the bedroom while sleeping Another study by O'Leary et al. (2006) reported a significant 65% increased risk (OR=1.65, 95%CI 1.02, 2.69) of breast cancer among women who frequently turned on lights at night during sleeping hours.

An increased risk of breast cancer associated with exposure to light at night is supported by experimental studies suggesting that electric LAN could suppress the normal nocturnal rise in melatonin, which could in turn increase circulating estrogen levels or inhibit tumor anti-proliferative mechanisms and thus possibly increase breast cancer risk.Studies by Davis et al. (2001), O'Leary et al. (2006), Stevens (2009) and Stevens (2009) are in favour of this fact.

The association of breast cancer with duration of sleep has been found in some studies supporting our findings. McElroy et al. (2006) conducted a multistate population-based case-control study of 4,033 women with invasive breast cancer and 5,314 community women without breast cancer in which we inquired about women's sleep habits in the recent past and during adult lifetime suggesting that decreasing sleep duration is modestly associated with an increased breast cancer risk in a large population-based case-control study. Long duration of sleep is associated with reduced risk of breast cancer.

Anna et al. (2008) observed a prospective, population-based cohort of the Singapore Chinese Health Study and excluded from the study women with <2 years of follow-up related to change in sleep pattern among breast cancer cases close to the time of diagnosis. Five hundred and twenty-five incident cases of breast cancer were identified among the remaining 33528 women after 11 years of follow-up. Result showed that among women postmenopausal at baseline, breast cancer risk decreased with increasing sleep duration (P trend=0.047.The study conclusion shows that sleep duration may influence breast cancer risk, possibly via its effect on melatonin levels.

The light-at-night (LAN) theory states that the introduction and increasing use of electricity to light the night accounts for some of the international differences in risk of breast cancer, and for a portion of the rising risk

worldwide. The postulated biological mechanism was that electric LAN would lower melatonin production by the pineal gland, and that this suppression of melatonin might then lead to increased breast cancer risk by leading to increased oestrogen production. Studies by Stevens RG (1987), Stevens RG(2007) and Schernhammer ES(2009) support this view. Exposure to light at night is associated with higher levels of sex hormones, because it disturbs the circadian system, which suppresses melatonin production, and melatonin is thought to reduce circulating oestrogen.

Cohen et al. (1978) proposed that reduced production of the hormone melatonin might increase the risk of breast cancer and citing "environmental lighting" as a possible causal factor. Blask et al. (2005) at the National Cancer Institute (NCI) and National Institute of Environmental Health Sciences conducted a study in 2005 that suggests that artificial light during the night can be a factor for breast cancer by disrupting melatonin levels.

In conclusion, the present study analysis reveals that exposures to working in night shift, not having adequate sleep, not sleeping in total darkness are associated with higher odds of outcome of breast cancer of women. This also points out the importance of life style modification to prevent breast cancer. Breast Cancer occurs a decade earlier in Indian Women as compared with the women of developed countries and is a leading cause of mortality in developing countries like India so raising awareness about the screening procedure and treatment of Breast cancer can help to reduce mortality. This also points out the importance of life style modification to prevent breast cancer. A future study with a large study group can throw more light in this aspect.

Acknowledgements

Chittaranjan National Cancer Institute (CNCI) in Kolkata is serving as a premier Regional Cancer Centre (RCC) for the Eastern Region of the Country. The authors declare that they have no competing interests.

References

Ai-Ren Jiang, Chang-Ming Gao, Jian-Hua Ding, et al (2013). Abortions and breast cancer risk in premenopausal and postmenopausal women in Jiangsu province of China cancer registries. *Asian Pac J Cancer Prev*, **13**, 33-35.

Anna H Wu, Renwei Wang, Woon-Puay Koh, et al (2008). Sleep duration, melatonin and breast cancer among Chinese women in Singapore. *Carcinogenesis*, **29**, 1244-8.

A Nandakumar, T Ramnath, Meesha Chaturvedi (2010).The magnitude of cancer breast in India: a summary. *Indian J Surg Oncol*, **1**,8-9.

Blask DE, Brainard GC, Dauchy RT, et al (2005). "Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats". *Cancer Res*, **65**, 11174-84.

Brzezinski A(1997). Melatonin in humans. *N Engl J Med*, **336**, 186-95.

Cohen M, Lippman M, Chabner B (1978). Role of pineal gland in aetiology and treatment of breast cancer. *Lancet*, **2**, 814-6.

Datta K, Biswas J (2009). Influence of dietary habits, physical activity and affluence factors on breast cancer in east india - a case-control study. *Asian Pac J Cancer Prev*, **10**, 217-20.

Davis S, Mirick DK, Stevens RG (2001). Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst*, **93**, 1557-62.

Dikshit J, Gupta PC, Ramasundarahettige C, et al (2012). Cancer mortality in India: a nationally representative survey. *Lancet*, **79**, 1807-16.

Ferlay J, Bray F, Pisani P, Parkin DM (2001). GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide. IARC cancer base No. 5. [1.0]. Lyon, France: IARC.

Ferlay J, Parkin DM, Steliarova-Foucher E (2010). Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*, **46**, 765-81.

Hansen J (2001). Increased breast cancer risk among women who work predominantly at night. *Epidemiol*, **12**, 74-7.

Jia YJ, Lu YS, Wu KJ, et al (2013). Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol*, **37**, 197-206.

Kruk J, Marchlewicz M (2013). Dietary fat and physical activity in relation to breast cancer among Polish women. *Asian Pac J Cancer Prev*, **14**, 2495-502.

Kolstad HA (2008). Nightshift work and risk of breast cancer and other cancers-a critical review of the epidemiologic evidence. Scand. *J Work Environ Health*, **34**, 5-22.

McElroy JA, Newcomb PA, Titus-Ernstoff L, et al (2006). Duration of sleep and breast cancer risk in a large population-based case-control study, **15**, 241-9.

O'Leary ES, Schoenfeld ER, Stevens RG, et al (2006). Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol*. **164**, 358-66.

Parkin DM (2011). Cancers attributable to occupationet exposures in the UK in 2010. *Br J Cancer*, **105**, 70-2.

Qian Li, Tongzhang Zheng, Theodore R, et al (2010). Light at night and breast cancer risk: results from a population-based case–control study in Connecticut, *USA Cancer Causes Control*, **21**, 2281-5.

Rafnsson V, Tulinius H, Jonasson J, Hrafnkelsson J (2001). Risk of breast cancer in female flight attendants: a population-based study (Iceland). *Cancer Causes Control*, **12**, 95-101.

Kamath R, Mahajan KS, Ashok L, Sanal TS (2013). A study on risk factors of breast cancer among patients attending the tertiary care hospital, in udupi district. *Indian J Commun Med*, **38**, 95-99.

Sanchez-Barcelo EJ (2005). Melatonin-estrogen interactions in breast cancer. *J Pineal Res*, **38**, 217-22.

Schernhammer ES, Laden F, Speizer FE, et al (2001). Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst*, 93, 1563-8

Schernhammer ES, Hankinson SE (2009). Urinary melatonin levels and postmenopausal breast cancer risk in the nurses' health study cohort. *Cancer Epidem Biomar Prev*, **18**, 74-9.

Shamsi U, Khan S, Usman S, Soomro S, Azam I (2013). A multicenter matched case control study of breast cancer risk factors among women in Karachi, Pakistan. *Asian Pac J Cancer Prev*, **14**, 183-8

Slack R, Young C, Rushton L (2012). Occupational cancer in Britain. *Br J Cancer*, **107**, 27-32.

Stevens RG (1987). Electric power use and breast cancer: ahypothesis. *Am J Epidemiol*, **125**, 556-61.

Stevens RG, Blask DE, Brainard GC, et al (2007). Meeting report: the role of environmental lighting and circadian disruption in cancer and other diseases. *Environ Health Perspect*, **115**, 1357-62.

Stevens RG (2009). Working against our endogenous circadian clock: breast cancer and electric lighting in the modern world. *Mutat Res*, **680**, 106-8.

Stevens RG (2009). Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J*

Epidemiol, **38**, 963-70.
Stevens RG (2009). Electric light causes cancer? surely you're joking, Mr. Stevens. *Mutat Res*, 682, 1-6.
Three-year Report of Population Based Cancer Registries, 2009-2011. Report of 25 PBCRs in India. National cancer registry programme. national centre for disease informatics and research.
U.S. Cancer Statistics Working Group (2013). United states cancer statistics: 1999-2010 Incidence and mortality web-based report. atlanta (GA): Department of health and human services, centers for disease control and prevention, and national cancer institute; 2013.
Wang F, Yeung KL, Chan WC, et al (2013). A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. *Ann Oncol*, **24**, 2724-32.