RESEARCH ARTICLE

Editorial Process: Submission:03/17/2022 Acceptance:07/24/2022

Modifiable (Sleeping Pattern and Stress) and Non-Modifiable Risk Factors Associated with Breast Cancer: A Matched Case-Control Study in Delhi, India

Gayatri Vishwakarma[1]*, Anurag Mehta[2], Mumtaz Saifi[3], Disha Garg[1], Deepika Paliwal[2]

Abstract

Background: An utmost increase of breast cancer burden during the last several decades was reported in Asian countries. Findings from literature confirm that risk factors of breast cancers can be modifiable and non-modifiable in nature. **Objective:** The present study is designed to identify specific modifiable and non-modifiable risk factors associated with breast cancer. **Methods:** A matched case-control study was conducted considering 187 cases as women diagnosed with breast cancer and 187 hospital-controls as women without having breast cancer visiting the hospital. Other than standard risk factors, stress is measured using Perceived Stress Scale (PSS) and stress is measured using Pittsburgh Sleep Quality Index (PSQI). Several modifiable and non-modifiable risk factors were assessed using conditional logistic regression to find out significant association with breast cancer. Results: Regular multi-vitamin uptake (OR = 3.38; 95%CI = 1.69 – 6.77; p-value = 0.001), poor sleep (OR = 11.29; 95%CI = 4.36 – 29.25; p-value < 0.001), irregular sleep (OR = 34.11; 95%CI = 10.03 – 115.92; p-value < 0.001) and severe stress (OR = 6.74; 95%CI = 3.06 – 14.81; p-value < 0.001) were found to be the highest odds ratio among all modifiable risk factor of breast cancer. Also, age at first childbirth less than 30 years (OR = 0.44; 95%CI = 0.25 – 0.78; p-value = 0.005) was found protective against breast cancer. **Conclusion:** In our study, stress, sleeping pattern, and regular multi-vitamin uptake were found to be significant modifiable risk factors of breast cancer. None of the non-modifiable risk factors were found to be significantly associated with the risk of breast cancer.

Keywords: Risk factor- breast cancer- stress- sleeping pattern- case-control study

Asian Pac J Cancer Prev, **23 (7)**, 2469-2476

Introduction

India has the world's most bio-diverse regions. Much of Indian biodiversity is intricately related to the socio-cultural practices of the land. Unfortunately, due to population explosion, climate change and lax implementation of environmental policies, the incidence of cancer is increasing in India. Cancer is the second foremost cause of mortality in Indians followed by cardiovascular disease(The Times of India, Feb 2020). The current scenario and data from the various cancer registries show various patterns in different sites of cancer. Urban Indian women are having the most commonest cancer like breast cancer however it is the second commonest cancer among the rural women Agarwal and Ramakant (2008).

There is no central cancer registry to provide comprehensive nationwide data. However ICMR-PBCR data says breast cancer is the commonest cancer among women in urban registries where it constitutes > 30% of all cancers in females. NCRP's latest report (2012 – 2014) revealed that Nagpur (31.9), Ahmedabad (31.5), Pune (31.4), and Bhopal (31.2) are the cities with highest relative proportion of leading breast cancer are being reported followed by Chennai (30.7) and Aurangabad (30.6) (National Cancer Registry Programme (NCRP) 2014: Annual report).

India is undergoing a period of dramatic social and economic changes. A Systematic review and meta-analysis of breast cancer showed a protective effect of ever breastfeeding against hormone receptor-negative breast cancers, and this effect seems to be several times stronger than what had been suggested by studies of all breast cancers without stratification by receptor status. Women with the highest risk of receptor-negative breast cancers, such as African-American women and BRCA1 carriers, can potentially benefit more from breastfeeding. Similarly, other case-control studies on breast cancer reported several risk factors such as overall poor health

*[1]Indian Spinal Injuries Centre, New Delhi, India. [2]Department of Laboratory Services, Director Laboratory Services and Director Research, Rajiv Gandhi Cancer Institute, Research Centre, Delhi, India. [3]Molecular Diagnostics, Rajiv Gandhi Cancer Institute Research Centre, India. *For Correspondence: gayatri.singh.v@gmail.com*

awareness, socio-economic status, environmental factors etc. A meta-analysis on Indian case-control studies revealed that family history of breast cancer, never breastfeeding, nulli-parity, age at menarche (<13 years), age at menopause >50 years, first pregnancy age >25 years, BMI more than 25 years, post-menopausal status and never married are risk factors of breast cancer for women in India Vishwakarma et al.,(2019).

Findings from literature confirm that risk factors of breast cancers can be modifiable (BMI, age at first pregnancy, breastfeeding, OCP, parity, dietary pattern, residence, sleeping patter, and marital status) Gajalakshmi and Shanta (1991); Mathew et al., (2008); Datta et al., (2009); Gajalakshami et al., (2009); Jayalekshmi et al., (2009); Saxena et al., (2009); Singh et al., (2011); Singh and Jangra (2013); Datta et al., (2014); Devi et al., (2015); Mohite et al., (2015); Gathani et al., (2017); Sambyal et al., (2015); Yilmaz (2020) and non-modifiable (FH of breast cancer, menopausal status, age at menarche, and age of menopause) (Parameshwari et al., 2013; Kapahi et al., (2014); Wirth et al., 2014; Mohite et al., 2015; Sambyal et al., 2015; Gathani et al., 2017). Keeping above various risk factors in the mind a matched case-control study is conducted to find risk factors of breast cancer in the Indian scenario. Sleeping pattern and use of multi-vitamins are also significant risk factors for developing breast cancer (Larsson et al., 2010; Chan et al., 2011; Dutta et al., 2014; Erren et al., 2016; Lu et al., 2017; Trudel-Fitzgerald et al., 2017). Studies show that women who work in night-shifts continuously for more than 3-year period found a 60% higher risk for developing breast cancer (Sleep Charity, 2019). Studies reported in the literature that there is an increased risk of breast cancer in women who had experienced stressful life events and have more than 2-times more risk who experienced severe stress events Dey et al., (2009); Moreno-Smith et al., (2010), Antonova et al. (2011). The objective of the study was to identify various risk factors associated with breast cancer including demographic and clinical characteristics of women registered in a tertiary care center in Delhi.

Materials and Methods

This study is conducted in a tertiary care center of Delhi, includes women diagnosed with breast cancer at the hospital from Dec 2017 to Jan 2020. A matched case-control study was conducted considering cases as women diagnosed with breast cancer and women without breast cancer visiting the hospital i.e. hospital control. We excluded patients who were diagnosed outside the hospital, were male and were non-resident Indian. Cases and controls are defined as

CASES: All type of histo-pathologically confirmed cases of breast cancer irrespective of their stage will be included in the study diagnosed after 15 December 2017.

CONTROLS: ± 2 years age matched individuals; patients other than breast cancer in the hospital or visitors or individual outside the hospital setup.

A retrospective review of patient records was done to determine the demographic profile, clinical characteristics and treatment details. A 20-minutes questionnaire was got filled by a trained assistant in-person. Consent was taken from patients as well as controls before filling this questionnaire. The study duration was of 2.5 years to reach the proposed sample size. The expected outcomes of the study was to identify various risk factors (modifiable and non-modifiable) of breast cancer in the Indian scenario.

Composite variable for physical activity (Yoga/Sports/Swimming/Housework/walking) was created for analysis based on four dimensions i.e. Mode (Specific activity performed e.g. walking, gardening, cycling), frequency (Number of sessions per day or week), intensity (Rate of energy expenditure) and duration (Time (minutes or hours) of the activity) Strath et al., (2013). Further, it is classified into three categories i.e. very light, moderate and very hard. Another composite variable was created for sleeping patterns based on a scale developed by Fukuda 1999 and three categories are formed i.e. good sleeper, poor sleeper and irregular sleeper Fukuda et al., (1999). Duration (months and years) of use of multi-vitamins were recorded into three categories based on ingredients: (1) multi-vitamins (alone) (2) multi-vitamins with minerals and (3) stress multi-supplements (higher doses of several B vitamins and of vitamin C or selected minerals, such as selenium or zinc. Category 1 and 2 were considered as a multi-vitamin supplements as risk factors. Collected data were compiled into three categories i.e. never use, regular use and occasional (used at least a month) (Neuhouser et al., 2009). The Perceived Stress Scale (PSS) is used to assess stress. The questions were asked about your feelings and thoughts during the last month on a five-point scale (0 – never, 1– almost never, 2 – sometimes, 3 – fairly often, 4 – very often) Cohen et al. (1983). Individual scores are ranging from 0 to 40 with higher scores indicating higher perceived stress. For data analysis, we considered three categories of stress i.e. scores ranging from 0-13 would be considered low stress, scores ranging from 14-26 would be considered moderate stress and scores ranging from 27-40 is considered high perceived stress.

The Pittsburgh Sleep Quality Index (PSQI) is a systematized measure of sleep quality that consists of 19 items reflecting sleep quality, sleep latency, sleep duration, habitual sleep efficiency, use of sleeping medications, sleep disturbance, and daytime dysfunction. The scores range from 0 to 21 and for data analysis we categorized it into three categories to better understand the pattern that a score >5 is considered as a poor sleeper, 1-3 irregular sleeper and 0 is for good sleeper.

The total sample size needed for this matched case-control study was 374 (187 cases and 187 controls). It was calculated using nMaster v2.0 software with an exposure of 30% in the control group, anticipated odds ratio (OR) of 2 for 90% power and 5% level of significance. In matched case/control study designs, useful data come from only the discordant pairs of subjects. Matching of cases and controls on a confounding factor of age increases the efficiency of a case-control study.

Statistical Analyses

Descriptive statistics summary were presented using mean ± standard deviation (SD) or median with inter-quartile range (IQR) for quantitative variables.

Summary of categorical variables were represented with frequencies with corresponding percentages. Association between two categorical factors was analyzed using Fisher's exact test or the chi-square test while Pearson's/ Spearman correlation analysis was performed to find association between two quantitative variables depends upon normality of data. A univariate logistic regression analysis was performed to evaluate significant factors associated with breast cancer followed by multivariable logistic regression analysis to calculate adjusted OR with 95% CI. The backward stepwise elimination (Conditional) method was used as removal testing which is based on the probability of the likelihood-ratio statistic. The p-value threshold was set at 0.05 and SPSS v23.0 was used for statistical analysis.

Missing data management: Complete-case analysis may be biased and insufficient where exclusion of a case or control leaves a matched set. Multiple imputation (MI) method is used to deal with missing observations which use matching variables that imputes missing values assuming age and time of questionnaire completion Seaman et al., (2015).

Results

The study population comprised of 187 cases (recruitment rate of 78%) and 187 controls (recruitment rate of 75%). Most women had more than a high school education (75.4%), were home maker/unemployed (71.9%), were married (97.9%), and refrained from tobacco use (99%). Average age of cases was recorded 50.8±11.6 years and of controls 49.3±10.9 while average BMI for cases and controls was 26.7±4.8 and 25.6±3.6 respectively (Table 1).

Table 2 shows the results of univariate conditional logistic regression analysis for socio-demographic factors and modifiable risk factors of breast cancer. In univariate analysis, among socio-demographic variable, BMI for obese (OR = 1.58; 95%CI = 1.02 – 2.46; p-value = 0.041), marriage age between 18 – 24 year (OR = 0.54; 95%CI = 0.33 – 0.90; p-value = 0.019), breastfeeding (OR = 2.05; 95%CI = 1.04 – 4.04; p-value = 0.039), semi-vegetarian diet (OR = 0.30; 95%CI = 0.09 – 0.96; p-value = 0.043), regular multi-vitamin uptake (OR = 3.39; 95%CI = 1.87 – 6.13; p-value <0.001), very light physical activity (OR = 16.30; 95%CI = 2.07 – 128.66; p-value = 0.008), poor sleep (OR = 11.34; 95%CI = 4.72 – 27.22; p-value < 0.001), irregular sleep (OR = 24.41; 95%CI = 8.48 – 70.25; p-value < 0.001), mild-to-moderate stress (OR = 2.62; 95%CI = 1.31 – 5.22; p-value = 0.007) and severe stress (OR = 7.73; 95%CI = 3.83 – 15.50; p-value < 0.001) were found to be significant risk factor of breast cancer.

In multivariable conditional logistic regression analysis (Table 2), age at first childbirth less than 30 years (OR = 0.44; 95%CI = 0.25 – 0.78; p-value = 0.005) were found protective factor against risk of having breast cancer. There is 75% less risk of getting breast cancer if a woman has her first child before the age of 30 years. Regular multi-vitamin uptake (OR = 3.38; 95%CI = 1.69 – 6.77; p-value = 0.001) and occasional use of multi-vitamins (OR = 3.31; 95%CI = 1.80 – 6.06; p-value < 0.001), both found to be significant risk factor of breast cancer. There is 3-times more risk of having breast cancer if a woman

Table 1. Study Population Characteristics

Characteristics	Cases (N=190)	Control (N=187)	Total (N=377)
Age in years, Mean (SD)	50.8 (11.6)	52.3 (11.9)	51.6 (11.8)
Age in years, n (%)			
<40 years	36 (18.9)	34 (18.2)	70 (18.6)
40 – 60 years	112 (58.9)	98 (52.4)	210 (55.7)
> 60 years	42 (22.1)	55 (29.4)	97 (25.7)
BMI, Mean (SD)	26.7 (4.8)	25.6 (3.6)	26.1 (4.2)
Education, n(%)			
Illiterate/<5yrs of school	34 (17.9)	19 (10.2)	53 (14.1)
Middle school	11 (5.8)	29 (15.5)	40 (10.6)
High school/Inter/Diploma	40 (21.1)	40 (21.4)	80 (21.2)
Graduate/Post-graduate	82 (43.2)	79 (42.2)	161 (42.7)
Professional degree	23 (12.1)	20 (10.7)	43 (11.4)
Marital Status, n(%)			
Married/separated/ divorced	171(90.0)	169(90.4)	340 (90.2)
Widowed	12(6.3)	17(9.1)	29 (7.7)
Unmarried	7(3.7)	1(0.5)	8 (2.1)
Occupation, n(%)			
Unemployed	135 (71.1)	129 (69.0)	264 (70.1)
Professional	52 (27.4)	50 (26.7)	102 (27.1)
Skilled worker	3 (1.6)	6 (3.2)	9 (2.4)
Unskilled worker	0 (0.0)	2 (1.1)	2 (0.5)

Table 2. Risk of Breast Cancer associated with Socio-Demographic Characteristics and Modifiable Risk Factors

Characteristics	Cases (N=190)	Control (N=187)	Univariate Regression OR (95%CI)	P-value	Multivariable Regression# OR (95%CI)	P-value
BMI, n(%)						
Underweight	9 (5.0)	6 (3.2)	Ref	-		
Normal	52 (29.1)	74 (39.8)	0.74 (0.26 – 2.15)	0.583		
Obese	118 (65.9)	106 (57.0)	1.58 (1.02 – 2.46)	0.041		
Age in years, n(%)						
<40 years	36 (18.9)	34 (18.2)	Ref	-		
40 – 60 years	112 (58.9)	98 (52.4)	0.93 (0.54 – 1.59)	0.782		
> 60 years	42 (22.1)	55 (29.4)	1.39 (0.75 – 2.57)	0.299		
Education, n(%)						
Illiterate/<5yrs of school	19 (10.9)	19 (10.2)	Ref	-		
Middle school	11 (6.3)	29 (15.5)	2.64 (0.89 – 7.81)	0.044		
High school/Inter/Diploma	40 (22.9)	40 (21.4)	1.00 (0.46 – 2.17)	0.998		
Graduate/Post-graduate	82 (46.9)	79 (42.2)	0.96 (0.47 – 1.95)	0.918		
Professional degree	23 (13.1)	20 (10.7)	0.87 (0.36 – 2.08)	0.754		
Marital Status, n(%)						
Unmarried	7 (3.7)	1 (0.5)	7.12 (0.87 – 58.40)	0.068		
Married/separated/ divorced/Widowed	183 (96.3)	186 (99.5)	Ref	-		
Age at Marriage, n(%)						
< 18 yrs	35 (18.4)	55 (29.4)	Ref	-		
18 – 24 yrs	101 (53.2)	86 (46.0)	0.54 (0.33 – 0.90)	0.019		
≥ 25 yrs	47 (24.7)	43 (23.0)	0.58 (0.32 – 1.05)	0.073		
Single	7 (3.7)	3 (1.6)	0.27 (0.07 – 1.12)	0.072		
Age at 1st Childbirth, n(%)						
< 25 yrs	93 (56.0)	108 (62.1)	Ref	-	Ref	-
25 – 30 yrs	67 (40.4)	57 (31.8)	0.73 (0.47 – 1.15)	0.174	0.44 (0.25 – 0.78)	0.005
30 – 35 yrs	6 (3.6)	9 (5.2)	0.64 (0.44 – 3.76)	0.639	0.83 (0.25 – 2.73)	0.754
Type of Delivery, n(%)						
No delivery	19 (10.0)	13 (7.0)	Ref	-		
Normal	126 (66.3)	135 (72.2)	1.57 (0.74 – 3.30)	0.239		
Cesarean	36 (18.9)	24 (12.8)	0.97 (0.41 – 2.34)	0.954		
Both	9 (4.7)	15 (8.0)	2.44 (0.82 – 7.22)	0.108		
Late Pregnancy, n(%)						
No delivery	14 (7.4)	13 (7.0)	Ref	-		
No	150 (78.9)	162 (86.6)	1.16 (0.53 – 2.56)	0.707		
Yes	26 (13.7)	12 (6.4)	0.50 (0.18 – 1.38)	0.179		
Breastfeeding, n(%)						
Yes	163 (85.8)	173 (92.5)	Ref	-		
No	27 (14.3)	14 (7.5)	2.05 (1.04 – 4.04)	0.039		
Breastfeeding duration in months (Median, IQR)	12 (18)	18 (12)	1.01 (0.99 – 1.02)	0.116		
Oral Contraceptive Pill, n(%)						
Yes	11 (5.8)	5 (7.2)	Ref	-		
No/Never	179 (94.2)	182 (97.3)	0.45 (0.15 – 1.31)	0.143		
Hormone replacement therapy, n(%)						
Yes	12 (6.3)	9 (4.8)	Ref	-		
No	178 (93.7)	178 (95.2)	0.75 (0.31 – 1.82)	0.526		
Diet, n(%)						
Non-Veg	52 (27.4)	50 (26.7)	Ref	-		
Semi-Veg	14 (7.4)	4 (2.1)	0.30 (0.09 – 0.96)	0.043		
Vegan/ Lacto-Veg	124 (65.2)	133 (71.1)	1.12 (0.71 – 1.77)	0.641		

Table 2. Continued

Characteristics	Cases (N=190)	Control (N=187)	Univariate Regression OR (95%CI)	P-value	Multivariable Regression# OR (95%CI)	P-value
Dysmenorrhea, n(%)						
Yes	23 (12.1)	22 (11.8)	Ref	-		
No	167 (87.9)	165 (88.2)	1.03 (0.55 – 1.93)	0.919		
Multi-vitamin uptake, n(%)						
Never	131 (68.9)	87 (46.5)	Ref	-	Ref	-
Regular	20 (10.5)	45 (24.1)	3.39 (1.87 – 6.13)	<0.001	3.38 (1.69 – 6.77)	0.001
Occasional (Iron/Calcium)	39 (20.5)	55 (29.4)	2.12 (1.30 – 3.47)	0.003	3.31 (1.80 – 6.06)	<0.001
Physical activity, n(%)						
Very hard	11 (5.8)	1 (0.5)	Ref	-		
Moderate	83 (43.7)	123 (65.8)	7.22 (0.91 – 57.31)	0.061		
Very light	96 (50.5)	63 (33.7)	16.30 (2.07 – 128.66)	0.008		
Sleeping pattern, n(%)						
Good sleeper	121 (63.7)	147 (78.6)	Ref	-	Ref	-
Poor sleeper	13 (6.8)	34 (18.2)	11.34 (4.72 – 27.22)	<0.001	11.29 (4.36 – 29.25)	<0.001
Irregular sleeper	56 (29.5)	6 (3.2)	24.41 (8.48 – 70.25)	<0.001	34.11 (10.03 – 115.92)	<0.001
Stress, n(%)						
No stress	53 (27.9)	111 (59.4)	Ref	-	Ref	-
Mild to Moderate stress	89 (46.8)	63 (33.7)	2.61 (1.31 – 5.22)	0.007	1.64 (0.74 – 3.60)	0.221
Severe stress	48 (25.3)	13 (7.0)	7.73 (3.83 – 15.50)	<0.001	6.74 (3.06 – 14.81)	<0.001

#Variable(s) entered: Multi-vitamins-uptake, Sleep type, Stress, Age at 1st childbirth.

is regularly taking multi-vitamins vs those who are not taking it. Poor sleep (OR = 11.29; 95%CI = 4.36 – 29.25; p-value < 0.001) and irregular sleep (OR = 34.11; 95%CI = 10.03 – 115.92; p-value < 0.001) has the highest odds ratio among all modifiable risk factor of breast cancer. Severe stress (OR = 6.74; 95%CI = 3.06 – 14.81; p-value < 0.001) was found to be significant risk factor of breast cancer. Women suffering from severe stress are at around 7-times more risk of having breast cancer as compared to those who are not having it.

Table 3 depicts association between non-modifiable risk factors with breast cancer. In univariate conditional logistic regression, none of the risk factors studied found significantly associated with breast cancer.

Discussion

Our study investigated the association between breast cancer (BC) and several risk factors i.e. modifiable and non-modifiable. In the present hospital-based case-control study in patients with BC, obesity, age at first childbirth, breastfeeding, multi-vitamin uptake, sedentary lifestyle, sleeping patter and stress were significant risk factors. We did observe a significant association with increased risk of developing BC and BMI and literature support this association (Singh et al., 2011; Amadou et al., 2013; Singh and Jangra, 2013; Engin, 2017; Picon-Ruiz, 2017; Vishwakarma et al., 2019). The risk of BC was 56% less in female whose age at first child birth was less than 30 years. (Gajalakshmi et al., 1991; Rao et al., 1994; Samson et al., 2007; Meshram et al., 2009; Saxena et al., 2009; Dey et al., 2009; Jayalekshmi et al., 2009; Lodha et al., 2011; Babita et al., 2014; Rajbongshi et al., 2015; Vishwakarma et al., 2019) confirms our result finding Gajalakshmi and Shanta,1991; Samson et al., (2007); Meshram et al., 2008; Jayalekshmi et al., 2009; Saxena et al., 2009; Gajalakshmi et al., 2009; Dey et al., 2009; Lodha et al., 2011; Babita et al., 2014; Rajbongshi et al., 201; Vishwakarma et al., 2019).

Studies published early Gajalakshami et al., (2009); Parameshwari et al., (2013); Dey et al., (2009); Singh and Jangra (2013); Mohire et al., (2015) reported that late menopausal age (>50 years) was at a high risk of BC, however, we did not observe this association from our data. Many studies reported that age at marriage before 25 years may have a 45% of lower chance of developing BC. Our study did confirm such associations Gajalakshmi and Shanta (1991); Jayalekshmi et al., (2009); Kinlen (2014). Multi-vitamin use was associated with a statistically significant 3-times increased risk of breast cancer. It was also reported in the literature that there is an increased risk of BC with the regular use of multi-vitamin Chan et al, (2010); Larsson et al., (2010); Neuhouser et al., (2010); Mann (2010).

Self-reported stress is a forthcoming risk factor in our daily life. Continuing exposure to stress has been associated with negative changes in body homeostasis. In literature, psychological stress is claimed to contributing to the inception of cancer and increase mortality from a number of non-malignant ailments. Breastfeeding can not only give your baby a healthy start. But it also lowers the risk of developing breast cancer. Our study depicts that women who do not breastfeed their child could have two times more risk of BC than the women who breastfeed which is a similar finding from the literature Rao et al., 1994; Meshram et al., 2008; Gajalakshami et al., 2009;

Table 3. Non-Modifiable Risk Factors Associated with Breast Cancer

Characteristics	Cases (N=190)	Control (N=187)	OR (95%CI)	P-value
Age in years, n(%)				
< 40	7 (3.7)	3 (1.6)	Ref	-
40 – 60	89 (46.8)	74 (39.6)	1.94 (0.49 – 7.77)	0.349
> 60	94 (49.5)	110 (58.8)	2.73 (0.69 – 10.86)	0.154
Dysmenorrhea, n(%)				
Yes	23 (12.1)	22 (11.8)	Ref	-
No	167 (87.9)	165 (88.2)	1.03 (0.55 – 1.93)	0.919
Menarche Age, n(%)				
≤ 13 year	77 (40.5)	64 (34.2)	Ref	-
> 13 years	113 (59.5)	123 (65.8)	1.31 (0.86 – 1.99)	0.207
Menopausal Age, n(%)				
≤ 45 year	29 (15.3)	30 (16.0)	Ref	-
> 45 years	95 (50.0)	108 (58.8)	1.10 (0.62 – 1.96)	0.750
Not reached to menopause yet	66 (34.7)	49 (26.2)	0.72 (0.38 – 1.35)	0.302
Miscarriage/still birth, n(%)				
No	130 (68.4)	137 (73.3)	Ref	-
Yes	60 (31.6)	50 (26.7)	1.27 (0.81 – 1.97)	0.302
Breast Cancer Family History, n(%)				
Yes	23 (12.1)	16 (8.6)	Ref	-
No	167 (87.9)	171 (91.4)	0.68 (0.35 – 1.33)	0.260
Family History of any type of cancer, n(%)				
Yes	57 (30.0)	72 (38.5)	Ref	-
No	133 (70.0)	115 (61.5)	0.69 (0.45 – 1.05)	0.082
Comorbidity – Diabetes, n(%)				
Yes	30 (15.8)	42 (22.5)	Ref	-
No	160 (84.2)	145 (77.5)	1.55 (0.92 – 2.59)	0.101
Comorbidity – Hypertension, n(%)				
Yes	45 (23.7)	57 (30.5)	Ref	-
No	145 (76.3)	130 (69.5)	1.41 (0.90 – 1.41)	0.138
Comorbidity – Thyroid, n(%)				
Yes	37 (19.5)	39 (20.9)	Ref	-
No	153 (80.5)	148 (79.1)	1.09 (0.66 – 1.80)	0.738

Lodha et al., 2011; Mohite et al., 2015; Vishwakarma et al., 2019). Furthermore, it was important to look at the duration of breastfeeding effect on BC. Our data did not show any significant association between the duration of breastfeeding and breast cancer. However, literature has evidence that a longer duration of breastfeeding can be more protected against breast cancer Collaborative Group on Hormonal Factors in Breast Cancer (2002).

The present study found that there is a 7-times more risk of having BC as compared to no stress and the literature confirms our results Cohen et al., (1983); Moreno-Smith et al., (2010); Antonova et al., (2011); Wang et al., (2020). Ng el al., (2017) studied stress in detail and concluded that perceived distress among BC patients is significantly associated with anxiety but not with depression. In contrast, few studies showed no association between stress and BC Robert et al., (1996); Santos et al., (2009); Schoemaker et al., (2016). Therefore this association should be viewed with caution as stress affects the risk of breast cancer is still not known, and greater studies are needed to address this issue Nielsen et al., (2006).

We found that women who has poor sleep and irregular sleep have 11-times and 24-times more risk of developing breast cancer, respectively, than those who sleep for 8 hours and has good sleeping patter. Epidemiological studies also reported the possible association of sleeping patter with BC Datta et al., (2014); Trudel-Fitzgerald et al., (2017). Conversely, evidence-based studies reported that women with a longer sleep duration may have a significantly increased risk of BC, especially ER-positive breast cancer Erren et al., (2016); Lu et al., (2017). None of the non-modifiable risk factors were found to be significantly associated with BC in this case-control study Gajalakshmi and Shanta (1991); Meshram et al., (2008); Saxena et al., (2009); Gajalakshmi et al., (2009); Parameshwari et al., (2013); Babita et al., (2014); Kapahi et al., (2014); Wirth et al., (2014).

A major strength of the present study was the optimum number of cases and controls. The questionnaire was designed to obtain a piece of complete information on modifiable and non-modifiable risk factors.

In the literature, many modifiable and non-modifiable risk factors quoted as risk factors of developing breast cancer. In our study, none of the non-modifiable risk factors were found to be significantly associated with the risk of breast cancer however among modifiable risk factors, age more than 30 years at first childbirth, regular use of multi-vitamin, irregular/poor sleep and severe stress were found to be significant risk factors of developing breast cancer.

Limitation of the study

There are few limitations in this study. One of the limitations is the recall bias and misclassification of non-modifiable risk factors. Also, dysmenorrhea, menarche age and breast cancer history in this study were self-reported and this might also bias results. In India, most of the women over age 50 years are still not able to recall their age, age at marriage and menarche age. Due to budget constraints, the study was restricted to one center for data collection. The most common reasons for not participating were death, change of address, and refusal for both cases and controls.

Abbreviations

Breast Cancer (BC), Body Mass Index (BMI), Standard Deviation (SD), Standard Error (SE), Odds Ratio (OR), 95% Confidence Interval (95% CI), Multiple imputation (MI), Inter-Quartile Range (IQR), FH (Family History), Perceived Stress Scale (PSS), Oral Contraceptive Pill (OCP), Indian Council for Medical Research - Population Based Cancer Registries (ICMR-PBCR), National Cancer Registry Program (NCRP).

Author Contribution Statement

The authors confirm contribution to the paper as follows: study conception and design: Gayatri Vishwakarma, Anurag Mehta; data collection: Mumtaz Saifi, Deepika Paliwal; analysis and interpretation of results: Gayatri Vishwakarma, Disha Garg; draft manuscript preparation: Gayatri Vishwakarma, Anurag Mehta. All authors reviewed.

Acknowledgments

None.

Conflict of interest

None

References

Agarwal G, Ramakant P (2008). Breast Cancer Care in India: The Current Scenario and the Challenges for the Future. *Breast Care*, **3**, 21-7.

Amadou A, Hainaut P, Romieu I (2013). Role of Obesity in the Risk of Breast Cancer: Lessons from Anthropometry. *J Oncol*, **2013**, e906495.

Antonova L, Aronson K, Mueller CR (2011). Stress and breast cancer: from epidemiology to molecular biology. *Breast Cancer Res BCR*, **13**, 208.

Babita R, Kumar N, Karwasra RK, et al (2014). Reproductive risk factors associated with breast carcinoma in a tertiary care hospital of north India: A case-control study. *Indian J Cancer*, **51**, 251-5.

Chan ALF, Leung HWC, Wang S-F (2011). Multivitamin supplement use and risk of breast cancer: a meta-analysis. *Ann Pharmacother*, **45**, 476-84.

Chiriac V-F, Baban A, Dumitrascu Dl (2018). Psychological stress and breast cancer incidence: a systematic review. *Clujul Med*, **91**,18-26.

Cohen S, Kamarck T, Mermelstein R (1983). A global measure of perceived stress. *J Health Soc Behav*, **24**, 385-96.

Collaborative Group on Hormonal Factors in Breast Cancer (2002). Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet Lond Engl*, **360**, 187-95.

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**, 219-22.

Datta K, Roy A, Nanda D, et al (2014). Association of breast cancer with sleep pattern--a pilot case control study in a regional cancer centre in South Asia. *Asian Pac J Cancer Prev*, **15**, 8641-5.

Devi KR, Chenkual S, Majumdar G, et al (2015). TLR2Δ22 (-196-174) significantly increases the risk of breast cancer in females carrying proline allele at codon 72 of TP53 gene: a case-control study from four ethnic groups of North Eastern region of India. *Tumour Biol J Int Soc Oncodevelopmental Biol Med*, **36**, 9995-10002.

Dey S, Boffetta P, Mathews A, et al (2009). Risk factors according to estrogen receptor status of breast cancer patients in Trivandrum, South India. *Int J Cancer*, **125**, 1663-1670.

Engin A (2017). Obesity-associated Breast Cancer: Analysis of risk factors. Adv Exp Med Biol;960:571-606. doi:10.1007/978-3-319-48382-5_25

Erren TC, Morfeld P, Foster RG, et al (2016). Sleep and cancer: Synthesis of experimental data and meta-analyses of cancer incidence among some 1,500,000 study individuals in 13 countries. *Chronobiol Int*, **33**, 325-50.

Fukuda K, Ishihara K, Takeuchi T, Yamamoto Y, Inugami M (1999). Classification of the sleeping pattern of normal adults. *Psychiatry Clin Neurosci*, **53**, 141-3.

Gajalakshmi CK, Shanta V (1991). Risk factors for female breast cancer. A hospital-based case-control study in Madras, India. *Acta Oncol Stockh Swed*, **30**, 569-74.

Gajalakshmi CK, Shanta V (1991).Risk factors for female breast cancer. A hospital-based case-control study in Madras, India. *Acta Oncol Stockh Swed*, **30**, 569-74.

Gajalakshmi V, Mathew A, Brennan P, et al (2009). Breastfeeding and breast cancer risk in India: a multicenter case-control study. *Int J Cancer*, **125**, 662-5.

Gathani T, Barnes I, Ali R, et al (2017). Lifelong vegetarianism and breast cancer risk: a large multicentre case control study in India. *BMC Womens Health*, **17**. doi:10.1186/s12905-016-0357-8.

Jayalekshmi P, Varughese SC, Kalavathi N, et al (2009) A nested case-control study of female breast cancer in Karunagappally cohort in Kerala, India. *Asian Pac J Cancer Prev*, **10**, 241-6.

Kapahi R, Guleria K, Sambyal V, et al (2014). Vascular endothelial growth factor (VEGF) gene polymorphisms and breast cancer risk in Punjabi population from North

West India. *Tumour Biol J Int Soc Oncodevelopmental Biol Med*, **35**, 11171-81.
Kinlen LJ (2014). Breast cancer and ages at first marriage and first birth: a new hypothesis. *Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP*, **23**, 53-7.
Larsson SC, Akesson A, Bergkvist L, Wolk A (2010). Multivitamin use and breast cancer incidence in a prospective cohort of Swedish women. *Am J Clin Nutr*, **91**, 1268-72.
Li M, Han M, Chen Z, et al (2020). Does marital status correlate with the female breast cancer risk? A systematic review and meta-analysis of observational studies. *PLoS One*, **15**, e0229899.
Lodha R, Joshi A, Paul D, et al (2011). Association between reproductive factors and breast cancer in an urban set up at central India: A case-control study. *Indian J Cancer*, **48**, 303.
Lu C, Sun H, Huang J, et al (2017). Long-Term Sleep Duration as a Risk Factor for Breast Cancer: Evidence from a Systematic Review and Dose-Response Meta-Analysis. *BioMed Res Int*, 4845059. doi:10.1155/2017/4845059.
Mann D (2010). Multivitamins Linked to Breast Cancer Risk. WebMD. Accessed August 5, 2021. https://www.webmd.com/breast-cancer/news/20100401/multivitamins-linked-to-breast-cancer-risk.
Mathew A, Gajalakshmi V, Rajan B, et al (2008). Anthropometric factors and breast cancer risk among urban and rural women in South India: a multicentric case–control study. *Br J Cancer*, **99**, 207-13.
Meshram I, Hiwarkar PA, Kulkarni PN (2008). Reproductive Risk Factors for Breast Cancer: A Case Control Study. *Online J Health Allied Sci*, **8**, 1-4.
Mohite VR, Pratinidhi AK, Mohite RV (2015). Reproductive risk factors and breast cancer: a case control study from rural India. *Bangladesh J Med Sci*, **14**, 258-64.
Moreno-Smith M, Lutgendorf SK, Sood AK (2010). Impact of stress on cancer metastasis. *Future Oncol Lond Engl*, **6**, 1863-81.
National Cancer Registry Programme (NCRP) (2014). Annual Reports... Accessed April 14, 2021. https://ncdirindia.org/ncrp/Annual_Reports.aspx.
Neuhouser ML, Wassertheil-Smoller S, Thomson C, et al. (2009). Multivitamin Use and Risk of Cancer and Cardiovascular Disease in the Women's Health Initiative Cohorts. *Arch Intern Med*, **169**, 294-304.
Ng CG, Mohamed S, Kaur K, et al (2017). Perceived distress and its association with depression and anxiety in breast cancer patients. *PLoS One*, **12**, e0172975.
Nielsen NR, Grønbæk M (2006). Stress and breast cancer: a systematic update on the current knowledge. *Nat Clin Pract Oncol*, **3**, 612-20.
Parameshwari P, Muthukumar K, Jennifer HG (2013). A Population Based Case Control Study on Breast Cancer and the Associated Risk Factors in a Rural Setting in Kerala, Southern India. *J Clin Diagn Res JCDR*, **7**, 1913-6.
Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM (2017). Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. *Ca*, **67**, 378-97.
Rajbongshi N, Mahanta LB, Nath DC, Sarma JD (2015). A matched case control study of risk indicators of breast cancer in assam, India. *Mymensingh Med J MMJ*, **24**, 385-91.
Rao DN, Ganesh B, Desai PB (1994). Role of reproductive factors in breast cancer in a low-risk area: a case-control study. *Br J Cancer*, **70**, 129-32.
Roberts FD, Newcomb PA, Trentham-Dietz A, Storer BE (1996). Self-reported stress and risk of breast cancer. *Cancer*, **77**, 1089-93.
Sambyal V, Guleria K, Kapahi R, et al. (2015). Association of the -2518 A/G Polymorphism of MCP-1 with Breast Cancer in Punjab, North-West India. *Asian Pac J Cancer Prev,* **16**, 7243-8.
Samson M, Swaminathan R, Rama R, et aln(2007). Role of GSTM1 (Null/Present), GSTP1 (Ile105Val) and P53 (Arg72Pro) genetic polymorphisms and the risk of breast cancer: a case control study from South India. *Asian Pac J Cancer Prev*, **8**, 253-7.
Santos MCL, Horta BL, Amaral JJF do, et al (2009). Association between stress and breast cancer in women: a meta-analysis. *Cad Saúde Pública*, **25**, 453-63.
Saxena A, Dhillon VS, Raish M, et al (2009). Detection and relevance of germline genetic polymorphisms in glutathione S-transferases (GSTs) in breast cancer patients from northern Indian population. *Breast Cancer Res Treat*, **115**, 537-43.
Schoemaker MJ, Jones ME, Wright LB, et al (2016). Psychological stress, adverse life events and breast cancer incidence: a cohort investigation in 106,000 women in the United Kingdom. *Breast Cancer Res*, **18**, 72.
Seaman SR, Keogh RH (2015). Handling Missing Data in Matched Case-Control Studies Using Multiple Imputation. *Biometrics*, **71**, 1150-9.
Singh M and Jangra B (2013). Association between body mass index and risk of breast cancer among females of north India. S*outh Asian J Cancer*, **2**, 121-5.
Singh P, Kapil U, Shukla N, Deo S, Dwivedi S (2011). Association of Overweight and Obesity with Breast Cancer in India. *Indian J Community Med Off Publ Indian Assoc Prev Soc Med*, **36**, 259-62.
Strath SJ, Kaminsky LA, Ainsworth BE, et al (2013). Guide to the Assessment of Physical Activity: Clinical and Research Applications. *Circulation*, **128**, 2259-79.
The Sleep Charity (2019). Is There A Connection Between Sleeping Patterns And Breast Cancer? The Sleep Charity. Published October 22, 2019. https://thesleepcharity.org.uk/is-there-a-connection-between-sleeping-patterns-and-breast-cancer.
The Times of India Feb 2020. Cancer is killing not just Indians but India's economy too. The Times of India. Accessed April 14, 2021. https://timesofindia.indiatimes.com/india/cancer-is-killing-not-just-indians-but-indias-economy-too/articleshow/73929706.cms.
Trudel-Fitzgerald C, Zhou ES, Poole EM, et al (2017). Sleep and survival among women with breast cancer: 30 years of follow-up within the Nurses' Health Study. *Br J Cancer*, **116**, 1239-46.
Vishwakarma G, Ndetan H, Das DN, et al (2019). Reproductive factors and breast cancer risk: A meta-analysis of case-control studies in Indian women. *South Asian J Cancer*, **8**, 80-4.
Wang X, Wang N, Zhong L, et al (2020). Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. *Mol Psychiatry*, **25**, 3186-97.
Wirth MD, Burch JB, Hébert JR, et al (2014). Case-control study of breast cancer in India: Role of PERIOD3 clock gene length polymorphism and chronotype. *Cancer Invest*, **32**, 321-9.
Yilmaz M (2020). Evaluation of sleep disorders in nonmetastatic breast cancer patients based on pittsburgh sleep quality index. *J Cancer Res Ther*, **16**, 1274-8.