

Case Report

A Case-Control Study on Risk Factors of Breast Cancer among Women Attending a Tertiary Care Hospital in Kolkata, India

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Abstract

Backgrounds: Breast cancer is the leading cancer in female globally. Incidence of breast cancer is also found increasing in developing countries like India owing to the rapid urbanization and life style changes. Presence of multiple risk factors with their varied risk estimates in different studies has made it difficult to design a specific primary prevention program. This study aimed at identifying various factors associated with breast cancer along with estimating their risk among women from an eastern state of India.

Methods: This is a Hospital based age group matched case-control study in which 66 confirmed female breast cancer cases and 264

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female controls (1:4 ratios) were interviewed on various exposure status by a predesigned, pretested questionnaire. Univariate and multivariate techniques were used for the analysis of data and the risk was estimated in terms of Odds Ratio (OR) with 95% Confidence Interval (CI).

Results: Nine factors (positive family history, place of residence, occupation, Body Mass Index, age of menarche, age of first delivery, duration of breastfeeding, exposure to chest X-ray and tobacco chewing) were found to be associated with breast cancer on univariate analysis. Out of them only four factors namely family history of breast cancer, exposure to chest X-Ray, exposure to chewing tobacco, and Body Mass Index ≥ 25 , showed significant risk on multivariate analysis.

Conclusion: This study identified significant risk with the factors relatively less reported like, exposure to chest X-ray, smokeless tobacco.

Keywords: Breast cancer; Case control; Odds ratio; Risk factors

Introduction

Breast Cancer in females is on the rise both globally as well as in developing country like in India. Globally it is the second most common cancer in both sex together and the most frequent one in females with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). According to the recent estimates cases in less developed (883,000 cases) countries are little more than the developed (794,000) regions. According to the latest report of National Cancer Registry Program (NCRP; National Centre for Disease Informatics and Research, Indian Council of Medical Research. Three years Report of Population Based Cancer Registries: 2016; 2012-2014), India it is the leading cancer in female in most (19 out of 27) of the individual Population Based Cancer Registries (PBCRs). Trend of Age Adjusted Incidence Rate (AAR) of breast cancer in also significantly rising in all six older PBCRs (Bangalore, Barshi, Bhopal, Chennai, Delhi and Mumbai). All of these registries except Barshi (three yearly only) showed a significant increase for both three yearly and five yearly annual averages of AARs (NCRP, India, 2016). Different studies identified risk factors such as early menarche, late menopause, nulliparity, delayed age of childbirth etc. and increased duration of breast feeding was found to be protective for breast cancer [1,2]. Studies from India particularly from the eastern part are still limited considering its increasing incidence and overall burden. The present study attempted at analyzing the association of various demographic, reproductive and clinical factors and estimating their risk in relation to breast cancer.

Materials and Methods

The present study is a hospital based case control study conducted in a tertiary care cancer hospital (Chittaranjan National Cancer Institute, CNCI) in Kolkata. Study population, for both cases and controls were the attendees of Surgery Outpatient Departments, In Patient Departments, Cancer Detection Centre and cancer screening camps of the Hospital. A patient with a histopathology or cytology confirmed

breast cancer diagnosed within last 6 months of the date of interview, irrespective of the stage of disease was considered as a case. Women attending cancer detection center of CNCI, Health check-up & cancer screening camp and not having any cancer (at present or past) were chosen as control. Patients with any benign breast disease were also excluded from controls. Controls were selected by matching with the cases for age group. For both the groups those who were mentally sound without any hearing and language problem and gave written consent were included in the study sample. Sample size was calculated using Epi Info Version 3.5.1 considering delayed age at first delivery (>30yrs) as risk factor with an Odds Ratio (OR) of 2.25 and 40% exposure among controls [3]. Thus accepting a case control ratio of 1:4 keeping in mind the feasibility and duration of the study along with 95% level of confidence and 80% power, a sample size of 330 (66 cases and 264 controls) was reached at. All those attendees fulfilling the inclusion criteria were selected in a consecutive manner during the study period i.e. July 2012 - Feb 2013 and interviewed with a by a predesigned, pretested questionnaire. It acquired data on socio-demographic parameter including addiction habits, reproductive factors and other health variables such as BMI, radiation exposure etc. Univariate unadjusted Odds Ratio (OR) with 95% Confidence Interval was estimated for different factors. Finally multivariate analysis using Binary Logistic Regression was performed taking those variables which showed significant ($p < 0.05$) OR in univariate method. SPSS 16 was used for all statistical calculations. Written informed consent was obtained from all the study participants and confidentiality was maintained throughout. The approval of Institutional Ethics Committee of All India Institute of Hygiene and Public Health, Kolkata was also obtained.

Results

A total of 66 cases and 264 age group matched controls were considered for the study. Majority (41%) of them belonged to 40 to 50

years age group followed by 50-60 years (26%). Mean age of the cases and controls were respectively 47.1 (8.88) and 44.4 (12.65). Majority of cases (92%) and controls (97%) are married. Cases were more than 2 times employed compared to the controls ($p = 0.009$). More than 80% of the cases and controls had ≤ 10 years of education i.e. up to secondary level. More than 85% cases and controls were Hindu. No significant difference was observed between cases and controls with respect to education and religion. However risk of developing breast cancer was found to be 2.5 times ($p = 0.001$) for urban women compared to rural (Table 1).

The unadjusted odds ratios for different risk factors particularly clinical and biological were presented in table 2. Body Mass Index (BMI) of ≥ 25 was found to have 2.35 (95% CI: 1.28, 4.32) times risk for breast cancer. A positive family history was associated with 4.41 times (95% CI: 1.43, 13.60) risk. Women with early age (≤ 13 years) of menarche was found to have 1.92 times (95% CI: 1.04, 3.56) risk of breast cancer. Mean (SD) age at menarche was found significantly ($t = -2.77$, $df = 328$, $p = 0.006$) lower in cases (12.77 ± 1.39 years) than controls (13.34 ± 1.52 years). Women who breastfed their children for ≤ 4 years were observed to have a 2.93 times (95% CI: 1.54, 5.59) risk compared to > 4 years. Mean (SD) duration of breastfeeding was also significantly ($t = -2.51$, $df = 328$, $p = 0.012$) lower in cases (3.63 ± 2.49 years) compared to controls (4.79 ± 3.54 years). First childbirth at > 19 years was found to be significantly associated with breast cancer with an odds ratio of 2.39 (95% CI: 1.11, 5.28). Women with history of chest X-Ray (before the present episode) were found to be at 3.08 times (95% CI: 1.42, 6.68) risk of breast cancer compared to those having no history of chest X-Ray. History of tobacco chewing was also found to have a significant positive association with an OR of 2.15 (95% CI: 1.04, 4.45). No significant association was observed with regards to age of menopause, use of oral contraceptives, parity and history of abortion in univariate analysis (Table 2).

	Cases		Controls		Unadjusted OR (95% CI) #	P value
	No.	%	No.	%		
Age (years)						
< 40	15	22.7	60	22.7		
40 - < 50	27	40.9	108	40.9		
50 - < 60	17	25.8	68	25.8		
≥ 60	7	10.6	28	10.6		
Marital status						
Living with their spouse (married)	61	92.4	256	97.0	1.00	0.651
Not living with their spouse (unmarried, widow)	5	7.6	8	3.0	0.79 (0.21 - 2.57)	
Occupational Status						
Not employed	50	75.8	233	88.3	1.00	0.009
Employed	16	24.2	31	11.7	2.41(1.16 - 4.97)	
Education						
≤ 10 years (upto secondary level)	56	84.8	216	81.8	1.00	0.562
> 10 years (Higher secondary & above)	10	15.2	48	18.2	0.80 (0.36 - 1.77)	
Religion						
Muslim	9	13.6	25	9.5	1.00	0.32
Hindu	57	86.4	239	90.5	0.66(0.28 - 1.62)	
Habitat						
Rural	21	31.8	142	53.8	1.00	0.001
Urban	45	68.2	122	46.2	2.49 (1.36 - 4.6)	

Table 1: Distribution of breast cancer cases and controls according to demographic and socioeconomic attributes.

OR = Odds Ratio, CI = Confidence Interval

Multivariate analysis using binary logistic regression (stepwise forward) included all nine variables which were found to have a significant risk on univariate analysis. The regression model revealed that significant risk for breast cancer was associated with four covariates namely exposure to chest X-Ray, family history of breast cancer, BMI ≥ 25 and habit of tobacco chewing (Table 3).

Discussion

Breast cancer is a worldwide public health problem that causes substantial personal and social burdens. Although a recent increase in breast cancer incidence and mortality is observed globally as well as in India, no specific primary prevention is included in the nation

at level public health programs in India so far. This may be due to multiplicity of risk factors involving life style, reproductive and other biological variables. Moreover different studies identified significant association with different factors.

The present study observed nine factors to have significant risk of breast cancer on unadjusted univariate analysis. The risk as estimated by odds ratio was highest for family history of breast cancer (OR = 4.41; 95% CI: 1.43-13.60) followed by chest x- ray exposures (OR = 3.08; 95% CI: 1.42-6.68). Study by Balasubraminum et al., and his group found 3.14 times risk with family history of any cancer [4]. Paul Augustine et al., mentioned around 2 times risk with family history of breast cancer itself [5].

		Cases		Controls		Unadjusted OR (95% CI) #	P value
		No.	%	No.	%		
BMI	< 25	39	59.1	204	77.3	1.00	0.002
	≥ 25	27	40.9	60	22.7	2.35 (1.28 - 4.32)	
Family history of breast cancer	No	58	87.9	256	97.0	1.00	0.002
	Yes	8	12.1	8	3.0	4.41 (1.43 - 13.60)	
Age at Menarche	> 13 years	20	30.3	120	45.5	1.00	0.025
	≤ 13 years	46	69.7	144	54.5	1.92(1.04 - 3.56)	
Age of Menopause	<45 years	21	45.7	69	47.0	1.00	0.879
	≥ 45 years	25	54.3	78	53.0	1.95 (0.51 - 2.96)	
Use of Oral Contraceptives	No	54	81.8	229	86.7	1.00	0.3
	Yes	12	18.2	35	13.3	1.45 (0.66 - 3.14)	
Duration of breastfeeding	> 4 years	17	25.8	133	49.6	1.00	0.000
	≤ 4 years	49	74.2	131	50.4	2.93 (1.54 - 5.59)	
Age of first childbirth	≤ 19 years	10	15.2	79	29.9	1.00	0.015
	> 19 years	56	84.8	185	70.1	2.39 (1.11 - 5.28)	
Parity	>2	22	33.3	92	65.1	1.00	0.81
	≤ 2	44	66.7	172	34.9	1.07 (0.58 - 1.97)	
Past history of chest X- Ray	No	51	77.3	241	91.4	1.00	0.001
	Yes	15	22.7	23	8.6	3.08 (1.42 - 6.68)	
Habits of chewing tobacco	No	53	80.3	237	89.8	1.00	0.03
	Yes	13	19.7	27	10.2	2.15 (1.04 - 4.45)	
History of Abortion	No	48	72.7	212	80.3	1.00	0.178
	Yes	18	27.3	52	19.7	1.53 (0.78 - 2.96)	

Table 2: Distribution of breast cancer cases and controls according to demographic and socioeconomic attributes.

OR = Odds Ratio, CI = Confidence Interval

	B	Sig	Exp (B)	95% Confidence Interval for Exp(B)	
				Lower	Upper
1. Exposure to chest X-ray (reference -No)	1.19	0.00	3.29	1.46	7.43
2. Family history of Br. Ca (reference -No)	1.28	0.03	3.58	1.15	11.14
3. Occupation (reference : not employed)	0.63	0.10	1.87	0.88	3.96
4. Age of menarche (reference: > 13 years)	0.36	0.27	1.44	0.76	2.73
5. Duration of Breast Feeding (reference: > 4 years)	0.69	0.06	2.00	0.98	4.09
6. Age Of First delivery (reference: ≤ 19 years)	0.57	0.13	1.18	0.84	3.70
7. BMI (reference: < 25)	0.80	0.01	2.22	1.18	4.17
8. Addiction to Chewing tobacco (reference -No)	1.15	0.01	3.16	1.34	7.44
9. Place of residence (reference : rural)	0.58	0.07	1.79	0.95	3.38
Constant	-3.54	0.00	0.03		

Table 3: Multivariate analysis showing adjusted risk (odds) of variables found associated with breast cancer on univariate analysis.

Many other studies from different parts of the world reported significant risk in women with a positive family history [6-10]. These observations remained relatively consistent across different countries and over different time periods. However, three other studies did not observe any significant risk with family history of breast cancer [11-13] but one of these reported family histories of ovarian cancer as a significant risk factor [13].

The present study found 2.41 (95% CI: 1.16-4.97) times risk in employed women compared to unemployed. Strangely two studies observed the higher risk among unemployed women [4,10,11].

This study revealed early age of menarche (≤ 13 years) as a significant risk factor (OR = 1.92; 95% CI: 1.04-3.56) compared to > 13 years. Many studies found significant risk with early menarche out of which two were conducted in the eastern India [2,12-15]. Some studies did not observe any significant risk with early menarche [5,11]. Surprisingly one study observed protective effect with early (< 11 years) menarche (OR = 0.321; 95% CI: 0.106-0.971) [3].

Among the other reproductive factors the present study observed late age of first childbirth and lesser duration of breastfeeding having significant risk. Balasubramaniam et al., reported around 2 times higher risk with > 25 years age at first childbirth [4]. Study by Paul Augustine et al., also reported 1.85 times risk at 26 -30 years and 2.96 times at ≥ 30 years compared to < 25 years of age [5]. Two others studies also reported odds of 2 for first childbirth at > 21 years and > 30 years of age [3,15]. In our study women with a lesser duration of breastfeeding (≤ 4 years) were found to have 2.93 times (95% CI: 1.54-5.59) risk of breast cancer. Different studies found significant risk with different duration of breast feeding mostly around 2 times risk ≤ 6 month duration [2,4,11]. However, one study observed around 15 times risk (OR = 14.9; 95% CI: 8.69-25.7) of breast cancer with ≤ 1 year of breastfeeding practice [15]. In this study we did not observe any significant risk when compared the duration of lactation < 6 months or < 1 year or < 2 year with the rest. Two other studies reported significantly lower mean duration of breastfeeding among cases than in controls [6,16].

The study found Body Mass Index (BMI) >25 i.e. overweight and obese to be associated with significant risk (OR = 2.35; 95% CI: 1.28-4.32) compared to ≤ 25 . Several earlier studies also reported increased risk with higher BMI [11-13,16]. A population based case control study from Canada reported significantly higher mean BMI in postmenopausal breast cancer cases than postmenopausal controls, but the same association did not stand in case of Premenopausal women [14]. Increased adipose tissue is believed to produce higher level of estrogen which results in proliferation of mammary cells. Study by PA Harrison observed significant protective effect with BMI > 25 , however most of the cases included in their study belonged to stage III & IV, hence the disease process, treatment and related life style changes might have reduced the body weight in cases when they were actually measured in the study [3].

This study revealed increased risk (OR = 2.49; 95% CI: 1.36-4.6) among urban women compared to rural. Although the known risk factors such as high BMI, sedentary behavior, late childbirth etc. are more common among urban women, two studies reported higher risk in rural women [11,2]. Women with habit of tobacco chewing were found to have 2.15 (95% CI: 1.04 - 4.45) times risk for breast cancer in this study. This is a factor which was not studied frequently.

Study by Kamath et al did not observe any significant risk with tobacco chewing [12].

On multivariate analysis with these nine factors (found significant on univariate analysis), four variables namely positive family history of breast cancer, prior exposure to chest x-ray, BMI > 25 and exposure to tobacco chewing stand as factors associated with significant risk. Out of them, positive family history and increased BMI (overweight and obesity) were reported frequently by earlier studies supported by biologically plausible reasons. However the exposure to diagnostic chest radiation and tobacco chewing were relatively less reported previously.

A retrospective cohort study conducted in three European countries reported an increased risk of breast cancer (Hazard Ratio: -1.90, 95% CI: 1.20-3.00) with any exposure to diagnostic radiation prior to 30 years age in carriers of BRCA1/2 mutations with a dose-response pattern [17].

A case control study in Delaware showed that ever-active smoking had significant risk for breast cancer (OR = 1.43, 95% CI: 1.03-1.99) although no dose-response trend was evident [18]. Another prospective cohort study as a part of Canadian National Breast Screening Study also revealed breast cancer risk was associated with various aspects of cigarette smoking particularly early initiation and longer duration [19]. Two other case control studies also identified significant risk associated with smoking [8,14]. Studies with smokeless tobacco are further less although in rural and semi urban India, women use smokeless forms more commonly.

However, the present study has the following limitations:

1. Recall bias - Since the cases and controls were interviewed for their exposures in the past, some recall bias could not be eliminated from the study. Recall bias is always intrinsic to a case control study.
2. Although Body Mass Index was measured at the initial visit of the patient at the hospital, it was actually the measure after development of the disease. However the study considered only the incident cases and breast cancer commonly presents at early stages, hence we assume that the BMI did not change significantly due to disease process at the time of initial presentation.
3. BRCA1/2 mutation carrier status is an important risk factor for Breast cancer which the study did not able to assess. However the study considered family history as an indirect indicator.

In Brief, the present study identified several factors to be associated with significant risk of breast cancer. Most of them were similar to the findings of previous researches. Factors like previous exposure to chest X-ray and smokeless tobacco consumption were found to have significant risk in this study even after adjustment. These factors were very less reported particularly in studies from India where these exposures are not uncommon. Hence further research is required to establish the association of these factors with breast cancer both at epidemiological and biological levels.

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