Original Article

Reproductive factors and breast cancer: A case–control study in tertiary care hospital of North India

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Abstract

BACKGROUND: Clinical, animal, and epidemiological studies have clearly demonstrated that cancer is a hormonally mediated disease and several factors that influence hormonal status or are markers of change in hormonal status have been shown to be associated with the risk of breast cancer. **AIMS:** To identify the association of various reproductive factors with breast cancer. **SETTINGS AND DESIGN:** A hospital-based, matched, case–control study. **MATERIALS AND METHODS:** Three hundred and twenty newly diagnosed breast cancer cases and three hundred and twenty normal healthy individuals constituted the study population. The subjects in the control group were matched individually with the cases for their age ± 2 years and socioeconomic status. A pre-tested, semi-structured questionnaire was administered to each individual to collect information on identification data, socio-demographic profile, and reproductive factors. **STATISTICAL ANALYSIS USED:** The Chi-square test and unpaired *t*-test were used. The conditional univariate logistic regression analysis (unadjusted odds ratio and confidence intervals) was used to calculate the significance level of each variable followed by multivariate regression analysis. **RESULTS AND CONCLUSIONS:** The cases had a lower mean age at menarche, higher age at marriage, higher mean age at last child birth, lower mean duration of breastfeeding, higher number of abortions, late age at menopause, history of oral contraceptive pills, and a family history of breast cancer as compared to the controls. The results of the present study revealed a strong association of reproductive factors with breast cancer in the Indian population.

Key Words: Breast cancer, case–control study, India, reproductive factors, risk factors

Introduction

Breast cancer is caused by repeated exposure of breast cells to circulating ovarian hormones.[1] Clinical, animal and epidemiological studies have clearly demonstrated that breast cancer is a hormonally mediated disease and several factors that influence hormonal status or are markers of change in hormonal status have been shown to be associated with the risk of breast cancer.[2-4] A variety of constitutional risk factors have been reported, such as nulliparity, early onset of menarche, delayed first birth, late menopause, and decreased parity. These risk factors point toward endogenous estrogens as likely players in the initiation, progression, and promotion of breast cancer.[5,6] Nutrition, in its broadest sense, plays a role in breast cancer, identified through its relationship to known risk factors that probably act early in life.[1] Though a large number of women are affected with breast cancer, very few studies have been undertaken in India on the association of reproductive factors with breast cancer. We conducted a hospital-based case–control study to identify the association of various reproductive factors with breast cancer.

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Materials and Methods

The present study was a hospital-based, matched, case–control study conducted in the tertiary care hospital in New Delhi. Three hundred and twenty newly diagnosed breast cancer cases (all consecutive cases) from the outpatient and hospital admissions of the Departments of Surgery/Surgical Oncology constituted the study population. The criteria for the selection of cases were as follows: (i) They should be proven cases of breast cancer by histopathology/cytopathology; (ii) they should have not undergone any treatment specific to breast cancer; (iii) they should not have suffered from any major chronic illness in the past, before the diagnosis of breast cancer so as to change their dietary pattern; (iv) they should not have taken long course of any vitamin or mineral supplements during the last 1 year; and (v) they should not be on corticosteroid therapy or suffering from hepatic disorders/severe malnutrition.

Three hundred and twenty normal healthy individuals accompanying the cases in the Department of

Gastroenterology, Medicine and Surgery at the hospital constituted the control group. The subjects in the control group were matched individually with the cases for their age ± 2 years and socioeconomic status. The criteria for the selection of controls were as follows: (i) The attendants of cases who did not suffer from any major illness in the past; (ii) they should not have taken long course of any vitamin or mineral supplements during the last 1 year; and (iii) they should not be on corticosteroid therapy or suffering from hepatic disorders or severe malnutrition. The study was ethically approved by the Ethics Committee of the institute. All the investigations to be performed were explained to the subjects, and those who consented for participation were included in the study, and informed consent was obtained.

The patient and control groups were subjected to similar investigations. A pre-tested, semi-structured questionnaire was administered to each individual to collect information on identification data, socio-demographic profile and reproductive factors. The Chi-square test was used for categorical variables, and unpaired *t*-test was used for the continuous variables. The conditional Univariate logistic regression analysis (unadjusted odds ratio [OR] and confidence intervals) was used to calculate the significance level of each variable in the study. Multivariate forward stepwise logistic regression analysis taking inclusion and exclusion criteria of 0.05 and 0.21, respectively, was performed.

Results

A total of 320 breast cancer cases and an equal number of matched controls were included in the present study. The mean age of the cases was 45.5 years. It was found that 62.5% and 61.5% of the cases and controls were in the age-group of 30-50 years, respectively. Majority of the cases (61.9%) belonged to urban area of residence. All the cases were married, and about 95.9% of the cases and 95.6% of the controls were housewives. Nearly 37.2% and 35.9% of the cases and controls were illiterate, respectively. There was no difference in the occupational and educational status of the cases and controls. About 46% of the cases and 36.3% of the controls belonged to lower-middle socioeconomic status.

The distribution of cases and controls according to the presence of risk factors is depicted in Table 1. The mean age at menarche in cases was 13.20 ± 1.33 years as compared to 14.58 ± 0.85 years in controls, and the difference was statistically significant. The cases had a higher age at marriage as compared to the controls; however, the difference was not statistically significant. Similarly, there was no difference in the mean age at first childbirth of cases and controls. The cases had statistically higher mean age at last childbirth (26.09 ± 5.32 years) as compared to the controls (25.05 ± 4.08 years). The mean duration of breastfeeding in cases and controls was 11.16 and 21.00 months, respectively ($P < 0.001$). The cases and controls were comparable with regard to the mean parity. However, the cases had a significantly higher number of abortions (61.3%) as compared to the controls (16.3%). Nearly 33.8% and 29.1% of the cases and controls, respectively, had post-menopausal status. There was a statistically significant difference in the mean age of menopause of cases and controls with cases attaining menopause at a late age (49.38 ± 5.21 years) as compared to the controls (47.89 ± 3.96 years). Nearly 1.9% of the cases were nulliparous. Similarly, 11.9% of the cases reported use of oral contraceptive pills as compared to 1.3% in controls ($P < 0.001$).

The unadjusted odds ratio for breast cancer according to the presence of risk factors is depicted in Table 2. It was found that the risk of breast cancer was 2.76 (95% confidence interval: 1.54, 4.96) times higher in those whose age of menarche was less than 16 years. Similarly, women who had an age of marriage more than 20 years had a 2.69 (95% confidence interval: 1.77, 4.07) times higher risk of breast cancer. No significant association was found between cases and controls with respect to parity. The age at first childbirth was also found to be associated with the risk of breast cancer with a twofold higher risk in women having their first child at more than 21 years of age.

History of abortion was also found to be positively associated with the risk of breast cancer with 6.26 times higher risk in women having a history of abortion. The risk of breast cancer increased 14.9 (95%

Table 1: Distribution of breast cancer cases and controls according to the presence of risk factors

Risk factors	Mean±SD (*n*=320)		*P* value
	Breast cancer cases	Controls	
Age (years)	45±10.29	45±10.5	0.673
Age at menarche (years)	13.20±1.33	14.58±0.85	0.000
Age at marriage (years)	18.42±3.97	17.95±2.39	0.057
Mean age at first child birth (years)	20.12±4.75	19.72±2.45	0.181
Mean age at last child birth (years)	26.09±5.32	25.05±4.08	0.005
Mean duration of breast feeding (months)	11.16±6.28	21.00±8.20	0.000
Mean parity	2.93±1.46	2.78±1.09	0.097
Number of abortions	1.75±0.88	1.23±0.63	0.000
Age at menopause	49.38±5.21	47.89±3.96	0.002

confidence interval: 8.69, 25.7) and 3.29 (95% confidence interval: 2.15, 5.02) times in women having mean duration of breastfeeding less than 13 months and age at last childbirth more than 27 years, respectively [Table 2].

It was found that the risk of breast cancer was 9.50 times higher in women having a history of consumption of oral contraceptive pills. Menopausal status was also found to be associated with the risk of breast cancer with post-menopausal women having a 2.50 (95% confidence interval: 1.20, 5.22) times higher risk. The risk also increased 2.68 times in women having a late age of menopause, more than 49 years [Table 2]. The family history of breast cancer was reported in 21.3% of the cases and none of the controls.

All the covariates at Univariate analysis were included in the multivariate forward stepwise unconditional logistic regression analysis, taking inclusion and exclusion criteria of 0.05 and 0.21, respectively. In the model ≥28 years of age at last childbirth, ≤12 months duration of breastfeeding, positive history of abortions, and ≥22 years of age at first childbirth were found to be positively related to the risk of breast cancer [Table 3].

Discussion

The results of the present study revealed that the breast cancer cases had a lower mean age at menarche as compared to controls. The risk of breast cancer was 2.76 (95% confidence interval: 1.54, 4.96) times higher in those whose age of menarche was less than 16 years. Almost similar findings were observed by other studies.[7,8]

A meta-analysis of three large case–control studies revealed that the RR of breast cancer increased by 20-30% in women who had early menarche, relative to women with menarche at age 15 or over.[9] Age at menarche and breast cancer risk is probably indirectly

Table 2: Unadjusted odds ratio for breast cancer according to the presence of risk factors

Risk factor	Breast cancer (*n*=320)	Controls (*n*=320)	Odds ratio	95% CI
Age at menarche (years)				
≥16	17 (5.3)	43 (13.4)	1.00	1.54, 4.96
≤15	303 (94.7)	277 (86.6)	2.76	
Age at marriage (years)				
≤20	232 (72.5)	282 (88.1)	1.00	1.77, 4.07
≥21	88 (27.5)	38 (11.9)	2.69	
Parity				
>3	71 (22.2)	55 (17.2)	1.00	0.49, 1.08
≤3	249 (77.8)	265 (82.8)	0.73	
Age at first child birth (years)				
≤21	204 (63.7)	255 (79.7)	1.00	1.52, 3.08
≥22	116 (36.3)	65 (20.3)	2.15	
History of abortions				
No	124 (38.8)	268 (83.8)	1.00	4.16, 9.41
Yes	196 (61.2)	52 (16.2)	6.26	
Duration of breastfeeding (months)				
>12	49 (15.3)	246 (76.9)	1.00	8.69, 25.7
≤12	271 (84.7)	74 (23.1)	14.9	
Age at last child birth (years)				
<28	214 (66.9)	280 (87.5)	1.00	2.15, 5.02
≥28	106 (33.1)	40 (12.5)	3.29	
History of oral contraceptive pills				
No	282 (88.1)	316 (98.8)	1.00	3.38, 26.7
Yes	38 (11.9)	4 (1.2)	9.50	
Menopausal status				
Pre	212 (66.3)	227 (70.9)	1.00	1.20, 5.22
Post	108 (33.7)	93 (29.1)	2.50	
Age at menopause (years)				
<50	52 (48.1)	50 (53.8)	1.00	1.42, 5.03
≥50	56 (51.9)	43 (46.2)	2.68	

Figures in parenthesis denote percentages; CI=Confidence interval

associated, with nutrition being the possible common factor.[10] Early menarche leads to an early opening of the first window and results in a substantial cumulative exposure to estrogens and the simultaneous presence of progesterone, an exposure theorized to increase the risk of breast cancer.[11] It was observed that breast cancer cases married at a later age as compared to the controls and hence had their first child at a later age. Women who had an age of marriage more than 20 years had a 2.69 (95% confidence interval: 1.77, 4.07) times higher risk of breast cancer. Similarly, the risk of breast cancer was twofold higher in women having their first child at more than 21 years of age. Similar results were obtained in a study from India in which the OR was 2.4 (95% confidence interval: 1.3, 4.4) when the age at marriage was more than 20 years. Other studies have also revealed similar findings.[12-15]

It has been speculated that a full-term pregnancy at an early age may reduce the likelihood of tumor initiation, while a full-term pregnancy at a later age may promote the growth of existing tumor cells.[16] Pregnancy induces terminal differentiation of human breast glands, which may have a smaller proliferative component. The first pregnancy induces irreversible changes that either render the breast tissue itself less susceptible to induction of cancer or reduced the carcinogenic stimulus to the breast.[15]

The present study revealed that the breast cancer cases had statistically higher mean age at last childbirth as compared to the controls. The risk of breast cancer increased 3.29 (95% confidence interval: 2.15, 5.02) times in women having age at last childbirth more than 27 years. An association between lactation and protection from breast cancer has been postulated for a long time.[17] The results of the present study also revealed similar association, with breast cancer cases reporting a lower mean duration of breastfeeding (11.16 months) as compared to controls (21.00 months). Studies conducted in different countries have also reported similar findings.[18-21] The RR of breast cancer was found to increase 14.9 (95% confidence interval: 8.69, 25.7) times in women having mean duration of breastfeeding less than 13 months. It has been suggested that lactation might reduce breast cancer risk by temporarily draining the breasts of potential chemical carcinogens and finally, the hormone oxytocin, which causes contraction of myoepithelial cells as a response to suction, has been reported to inhibit cell proliferation and tumor growth in animal models. Lactation also has a direct physical effect on the breast, such as changes in breast ductal epithelial cells leading to mechanical "flushing-out" of carcinogens.[17,22-27]

Table 3: Multiple logistic regression derived odds ratios and 95% confidence interval for the association between reproductive risk factors and breast cancer

Risk factor	Odds ratio (95% CI)	*P* value
Age at last child birth (years)		
<28	Reference	
≥28	8.87 (2.79-28.24)	0.000
Duration of breastfeeding (months)		
>12	Reference	
≤12	5.91 (2.02-17.34)	0.001
History of abortions		
No	Reference	
Yes	5.03 (1.58-15.99)	0.006
Age at first child birth (years)		
≤21	Reference	
≥22	5.26 (1.30-21.32)	0.020
Age at menopause (years)		
<50	Reference	
≥50	0.406 (0.14-1.18)	0.098

CI=Confidence interval

Parity was not found to be significantly related to the risk of breast cancer in the present study. However, results of earlier studies have reported a decrease in risk with higher parity.[19,28-30] Nearly 1.9% of the cases were nulliparous. Earlier studies have reported that nulliparity is a risk factor for breast cancer.[14,31]

The history of abortions was found to be significantly higher in breast cancer cases as compared to controls, with the Relative Risk (RR) = 6.26 in women having a history of abortion. Results of other studies are not conclusive, while some reporting an increase in risk with induced abortion,[32] others reporting a decrease in risk of breast cancer,[33] and few studies reporting no association.[34-36] However, it is difficult to compare the results of the present study with any of these studies because we have not collected information on the type of abortion, that is, spontaneous or induced. It has been suggested that abortions leave the breast epithelium in a proliferative state with an increased susceptibility to carcinogenesis.[33]

The breast cancer cases attained a late age of menopause as compared to the controls. The risk increased 2.68 (95% confidence interval: 1.42, 5.03) times in women having a menopause after 49 years. A case–control study conducted in Italy revealed an OR of 1.2 for women having menopause at ≥50 years of age as compared to women <50 years of age (95% confidence interval: 0.7, 2.1).[37] Other studies have also reported increase in risk with late age at menopause.[7,38]

In the present study, the risk of breast cancer was 9.50 times higher in women having a history of

consumption of oral contraceptive pills. Previous studies have also shown similar results.[39,40]

One of the strongest predictors of a woman's risk of breast cancer is the presence of the carcinoma breast disease in her family.[41] The family history of breast cancer was reported in 21.3% of the cases and none of the controls. There might be an underreporting of the family history of breast cancer by controls. However, it is difficult to distinguish between family aggregation and genetic predetermination. There are certain environmental and constitutional factors that may be more prevalent in certain families with no underlying genetic susceptibility.[42,43] The strong relation of family history is supported by other previous studies.[2,44-48] The results of the present study revealed a possible association of reproductive factors with breast cancer in the Indian population.

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