



## STUDIES ON IDENTIFICATION OF POSSIBLE REASONS FOR PREVALENCE OF BREAST CANCER IN GUNTUR, KRISHNA AND PRAKASAM DISTRICTS OF ANDHRA PRADESH

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### Abstract

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*Background: Breast cancer is the second most common female cancer in India. Association of reproductive factors with breast cancer is unclear in our population. Objectives: To find out the association of reproductive factors like parity, age at first live birth and lactation with breast cancer. Design, Setting and Participants: It was a case-control study comprising 200 breast cancer patients and 300 control subjects. The study was done in Gov. Guntur General Hospital, 2008 and April, 2010. Methods: Both cases and controls were interviewed in wards after taking verbal consent. A short structured questionnaire was used to obtain information regarding basic demographic, menstrual and reproductive characteristics. Results: Breast cancer patients and control subjects did not differ regarding age ( $p = 0.9$ ), early menarche (OR for menarche at  $< 12$  years vs.  $\geq 12 = 1.6$ , 95% CI = 0.6 — 4.3), and late menopause (OR for menopause at  $\geq 50$  vs.  $< 50 = 1.0$ , 95% CI = 0.5 — 2.0). History of breast cancer in 1st degree relatives did not increase breast cancer risk (OR = 1.0, 95% CI = 0.5 — 2.1). Nulliparous women had significantly higher risk than parous women (OR = 4.7, 95% CI = 1.9 — 11.0). Women with younger age at first live birth ( $< 30$  years) had less breast cancer risk as compared to women with  $\geq 30$  years of age at first live birth (OR = 0.2, 95% CI = 0.1 — 0.5). Breastfeeding had no effect on the risk of breast cancer in parous women. Conclusion: Nulliparity and more age at first live birth were associated with increased breast cancer risk. Breastfeeding was not protective against breast cancer.*

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**Keywords:** breast cancer, reproductive factors, risk factors.

**INTRODUCTION:** Breast cancer is the 2<sup>nd</sup> most common malignancy in Indian females.<sup>1</sup> Every year approximately 1 million new cases of female breast cancer are diagnosed worldwide, most of which occurs in developed countries<sup>5</sup>. Breast cancer is the most common cancer in females accounting for 20% of all female cancers. Breast cancer is the leading cause of female cancer death. When combined for both genders, lung cancer contributes most to cancer-related mortality worldwide<sup>6</sup>.

There is a wide variation in breast cancer incidence rates in different regions of the world. According to World Health Organization (WHO) estimates, breast cancer incidence is far more in America and Europe than in Asia<sup>6</sup>. South Asia has five times less ASR for female breast cancer than America and Canada. Breast cancer incidence is increasing in all regions of the world with majority of rise seen in developing countries due to progressive westernization of social, cultural and reproductive trends<sup>7</sup>.

Reproductive and hormonal factors contribute most to development of breast cancer. Nulliparity, more age at first live birth and no breastfeeding are major reproductive risk factors for breast cancer in developed countries<sup>8</sup>. These factors are mainly responsible for the variation in breast cancer incidence seen in different regions of the world by virtue of their different prevalence in these regions. Risk of breast cancer increases in successive generations of people moving from low-risk areas to high-risk regions proving that there are changes in reproductive behaviour and lifestyle are more important than hereditary factors in the development of breast cancer<sup>9,30</sup>.

The role of reproductive factors in the development of breast cancer in our population is different as compared to that seen in western population<sup>10</sup>. This is because parity, younger age at first live birth and lactation practices are part of our culture whereas these factors are far less prevalent in western women. We could identify only four case-control studies on risk factors for breast cancer in Guntur region women.<sup>11-14</sup> Not only their results are conflicting but they are also characterized by small sample sizes and errors in design of study and reporting of findings. Three of them had sample sizes of  $\leq 300$  and reported results simply in terms of p values instead of reporting odds ratios and their confidence intervals.<sup>11-13,29</sup> The largest of these studies, in terms of sample size, found that parity had no association with breast cancer and later age at menarche was a risk factor for breast cancer.<sup>14</sup> This is entirely opposite to well-established protective effect of parity and later age at menarche.

The objective of our study is to clarify the current controversies regarding association of reproductive factors with breast cancer in our population.

## **MATERIAL AND METHODS**

**2.1- Design, Settings and Participants:** This case-control study was conducted in Mayo Hospital, Lahore from April 2008 to December 2010. Cases comprised 200 confirmed female breast cancer patients who presented in the departments of Oncology and Surgery during the study period. Breast cancer patients were not eligible for participation in the study if their age was below 25 years or if time duration since diagnosis was more than 2 years.

The control population comprised 300 female patients, aged  $\geq 25$  years, having diagnoses other than breast cancer. Controls were sampled from different wards of the hospital through quota sampling. Patients with any cancer and gynecologic and obstetrical complications were not eligible as controls. We could not use random sampling for controls because there was no central electronic record of all the patients admitted in the hospital. Most of the patients in the hospital belonged to distant areas and taking interviews either at home or at telephone was not feasible. However, proportion of controls in each age-specific stratum was fixed in advance based on the expected age distribution of cases. The pre-determined age-specific quotas for sampling of controls were: 15%, 30%, 30%, and 25% for age groups 25-34 year, 35-44 year, 45-54 year, and  $\geq 55$  year respectively.

**Data Collection:** A structured questionnaire was prepared in English and in-person interviews were conducted in the wards, for both cases and controls. Verbal consent was taken from every patient. In addition to basic demographic details, participants were asked about their marital status, number of live births, age at first live birth and breastfeeding history. Information was also obtained regarding age at menarche, menopausal status, age at menopause and use of oral contraceptives. Information was collected up to the date of interview for controls and date of diagnosis of breast cancer for cases.

**Data Analysis:** For predictor variables other than reproductive ones, both unadjusted odds ratios (OR) and 95% confidence intervals (CI), and age-adjusted OR's and 95% CI's were calculated, using unconditional logistic regression, to assess their association with breast cancer. Early menarche was defined as menarche occurring at age  $< 12$  years. Age at menopause was categorized as  $< 50$  years and  $\geq 50$  years. We included following reproductive variables in our analysis: parity (nulliparous vs. parous), number of live births (1 – 2 live births vs. nulliparous,  $\geq 3$  live births vs. nulliparous), age at first live birth ( $< 30$  years vs.  $\geq 30$  years, nulliparous vs. first live birth at  $\geq 30$  years), lactation for parous women only (never vs. ever), and duration of lactation (never breastfed vs. breastfed for  $< 3$  months, never breastfed vs. breastfed for  $\geq 3$  months, never breastfed vs. nulliparous women).

First un-adjusted OR's and 95% CI's were calculated, using unconditional logistic regression, to assess association of reproductive factors with breast cancer. In the next stage adjustment was done for age, marital status, menopausal status and for variables, other than reproductive ones, who had  $p < 0.25$ . Age was entered as a continuous variable in the logistic regression model. All analyses were done using Statistical Package for Social Sciences (SPSS) version 16.

**Results:** Cases and controls did not differ regarding age, with mean ages 48.32 and 48.35 years respectively ( $p = 0.982$ ). Table 1 shows the results of univariate logistic regression analysis for association of breast cancer and predictor variables other than reproductive ones. More cases than controls were un-married but it was not statistically significant. Case and controls did not differ in age at menarche, menopausal status, and age at menopause. Family history of breast cancer in 1st degree relatives did not increase breast cancer risk. More controls had ever used oral contraceptives, with breast cancer odds ratio of 0.186 (95%CI= 0.066-0.540) for controls as compared with cases. Age-adjusted estimates for these variables were not different from the unadjusted ones (Table 1).

*Table: 1: Reproductive factors, general medical and family history variables of women with respect to the breast disease continuum*

Variable	Normal	Non-Prolif. Benign	Proliferative Benign	Atypical Hyperplasia	In situ Cancer	1 Grade Cancer	2 Grade Cancer	3 Grade Cancer	p value
<b>Age</b> (mean) (SD)	43.85 7.23	44.11 9.30	43.26 7.74	45.38 6.33	46.82 5.80	45.25 8.39	51.09 6.97	56.61 5.72	0.000†
<b>Age at Menarche</b> (mean) (SD)	11.57 0.92	11.38 0.49	11.86 1.04	11.30 0.47	11.82 0.99	11.75 1.11	11.53 0.82	11.66 0.95	0.118†
<b>Regular Menopausal's (%)</b> Yes No	64.3 35.7	61.1 38.9	66.7 33.3	30.8 69.2	70.6 29.4	66.7 33.3	76.7 23.3	83.3 16.7	0.001‡
<b>Menopausal status (%)</b> Premenopausal Postmenopausal	94.4 5.6	60.5 39.5	53.8 46.2	33.3 66.7	35.3 64.7	25.0 75.0	38.9 61.1	7.1 92.9	0.000‡
<b>No. Full Term Birth (%)</b> Nulliparous 1 or more	28.6 71.4	11.1 88.9	0 100	23.1 76.9	5.9 94.1	16.7 83.3	4.7 95.3	5.6 94.4	0.001‡
<b>Breast fed (%)</b> Yes No Not applicable	57.1 14.3 28.6	83.3 5.6 11.1	86.7 13.3 0.0	61.5 15.4 23.1	94.1 0.0 5.9	75.0 8.3 16.7	93.0 2.3 4.7	88.9 5.6 5.6	0.000‡
<b>Oophorectomy &amp; Hysterectomy (%)</b> Yes No	28.6 71.4	22.2 77.8	46.7 53.3	38.5 61.5	17.6 82.4	33.3 66.7	18.6 81.4	27.8 72.2	0.066‡

<b>Previous liver disease (%)</b>	21.4	22.2	26.7	30.8	17.6	25.0	27.9	44.4	
<b>Yes No</b>	78.6	77.8	73.3	69.2	82.4	75.0	72.1	55.6	0.322‡
<b>Oral Contraceptive Use</b>	5.6	5.9	9.3	21.4	23.1	33.3	27.8	33.3	0.001‡
<b>(Past or present) (%)</b>	94.4	94.1	90.7	78.6	76.9	66.7	72.2	66.7	
<b>Yes No</b>									
<b>Previous breast disease (%)</b>									
<b>Yes</b>	25.6	38.5	38.5	42.9	46.7	44.4	58.3	47.1	0.003‡
<b>No</b>	74.4	61.5	61.5	57.1	53.3	55.6	41.7	52.9	
<b>Family history (%)</b>									
<b>No History</b>	64.7	61.5	50.0	50.0	57.3	76.7	53.3	55.6	0.452‡
<b>Some degree</b>	35.3	38.5	50.0	50.0	34.4	41.2	46.7	48.8	

**Key:** † The analysis of variance test was used

‡ The chi-square test was used

SD Standard Deviation

Presents comparison of cases and controls regarding reproductive risk factors. Nulliparous women had higher risk for breast cancer compared to parous women. OR for nulliparous women was 5.1 as compared to women with  $\geq 3$  children (95% CI = 2.149 – 12.212). Although nulliparous women had breast cancer OR of 2.23 compared to women with 1-2 children but it was not significant (95% CI = 0.70-7.13). Younger age at first live birth was associated with decreased breast cancer risk. Women with first live birth at  $< 30$  years of age had breast cancer OR of 0.19 as compared to women with first live birth at  $\geq 30$  years. Among the parous women never breastfeeding, compared to ever breastfeeding, did not increase breast cancer risk. Longer duration of lactation ( $\geq 3$  months) also were not protective (OR = 0.56, 95% CI = 0.203 – 1.530).

**DISCUSSION:** We found that breast cancer patients and controls did not differ in age at menarche, menopausal status, and age at menopause. Many studies have shown that breast cancer risk is more for women whose menarche occur at an early age.<sup>15, 16</sup> In one study early menarche ( $< 13$  years) contributed to 44% of breast cancer cases in young and 26% of cases in older women.<sup>17</sup> However, there are contradictory findings in local and regional literature regarding ages at menarche and menopause and breast cancer risk. In a recent Iranian study, Mohouri et al<sup>18</sup> found that early menarche was a risk factor for breast cancer while age at menopause was similar in cases and controls. Two case-control studies, Gajalakshmi et al<sup>19</sup> and Pakseresht S et al,<sup>20,29</sup> found no association between age at menarche and breast cancer risk. In

the first and still the largest case-control study on female breast cancer done in Guntur and Krishna Districts, which showed that both early menarche and late menopause were protective. Various explanations have been put forward for this discrepancy. The estimates of the association of menstrual characteristics with breast cancer in our women are highly subjected to recall bias. This is because here most women are poor and illiterate and they do not remember exactly their ages at menarche and menopause.

We found that history of breast cancer in 1st degree relatives did not increase breast cancer risk. This is in contrast to most western literature and local literature that have shown increased risk for breast cancer if one had affected 1st degree relative.<sup>21,30</sup> In our study nulliparous women had more risk of breast cancer as compared to parous women. Nulliparous women were at increased risk of breast cancer compared to parous women in many previous studies.<sup>17,22,30</sup> In parous women as the number of live births increased, the breast cancer risk further decreased. A study found that each live birth reduced life-time risk of breast cancer by 7%.<sup>23</sup> Previous local studies have produced inconsistent results regarding breast cancer and parity. On the other hand Mahmood S et al<sup>11</sup> found increased breast cancer risk for parous women. This is entirely opposite to well-established protective effect of parity. Our women have more children than do western women, and this is one of the major causes of low incidence of breast cancer in our population as compared to western population.

Later age at first live birth was associated with increased risk for breast cancer. This has been found in most of western and local studies.<sup>17, 14, 29</sup> A review article concluded that compared to women with first live birth below 20 years of age, women with first live birth after age 30 years have two times more breast cancer risk.<sup>5</sup> Reduction of breast cancer risk with ever breastfeeding was seen in many case-control and cohort studies.<sup>25-27</sup> Prolonged duration of lactation further reduced breast cancer risk. In a collaborative reanalysis of 53 studies, authors concluded that every 12 months of lactation reduces relative risk of breast cancer by 4.3%.<sup>28</sup> Breastfeeding practices are high in our country and most women breastfeed for longer durations. Their results can be explained by the fact that their analysis for lactation and breast cancer risk was not restricted to parous women, instead they included all women. In Faheem et al<sup>13</sup> 12% of cases were unmarried compared to 3.3% of controls ( $p = 0.008$ ). The proportion of married women who were nulliparous was not reported in their study. Since it is rare in our society that an unmarried woman has children, so more cases than controls in their study were nulliparous. And if the analysis for association of lactation and breast cancer is restricted to parous women only, it would have resulted in no association between lactation and breast cancer. Our study had

some limitations. First we could not explain our results regarding family history of breast cancer and breast cancer risk. Second, we think that our findings about age at menarche and menopause are subjected to recall bias.

**Conclusion:** Nulliparity and more age at first live birth are major repro-ductive risk factors for breast cancer in our population. The role of breastfeeding, ages at menarche and menopause needs clarification and further work.

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