Reproductive Risk Factors for Female Breast Cancer: A Case – Control Study


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Background: Breast cancer is the most common female cancer in Pakistan. Its incidence in Pakistan is 2.5 times higher than that in neighboring countries like Iran and 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 150 breast cancer patients and 300 control subjects. The study was done in Mayo Hospital Lahore between October, 2008 and April, 2009.

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. ≥ 12 = 1.6, 95% CI = 0.6 — 4.3), and late menopause (OR for menopause at ≥ 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 ≥ 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 was associated with increased breast cancer risk. Breastfeeding was not protective against breast cancer.

Keywords: breast cancer, nulliparity, lactation, risk factors.

Introduction
Breast cancer is the most common malignancy in Pakistani females, where as in neighboring countries like India and Iran, breast cancer is the 2nd commonest female cancer. Breast cancer incidence in Pakistan is about 2.5 times that in India and Iran. Pakistan has the highest breast cancer incidence rate in Asia except that in Israel. According to Karachi Cancer Registry, the first population-based cancer registry in Pakistan, the age-standardized incidence rate (ASR) for breast cancer in Karachi South (KS) for period 1995-1997 was 51.7/100,000 which accounted for one third of all female cancers. This breast cancer incidence rate can be taken as an estimate of that in whole of Pakistan as the age, gender and religion distribution of population of Karachi South is similar to whole population of Pakistan.

Every year approximately 1 million new cases of female breast cancer are diagnosed worldwide, most of which occurs in developed countries. 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. 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. 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.

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. 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 changes in reproductive behaviour and lifestyle are more important than hereditary factors in the development of breast cancer.

The role of reproductive factors in the development of breast cancer in our population is different as compared to that seen in western population. 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 Pakistani
women.\textsuperscript{11-14} 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.\textsuperscript{11-13} 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.\textsuperscript{14} 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.

Materials and Methods

Design, Settings and Participants

This case-control study was conducted in Mayo Hospital, Lahore from November 2008 to April 2009. Cases comprised 150 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 unadjusted 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 unmarried 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 1\textsuperscript{st} 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 2 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. In one study early menarche (< 13 years) contrib-
ted to 44% of breast cancer cases in young and 26% of cases in older women. 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 found that early menarche was a risk
factor for breast cancer while age at menopause was similar in cases and controls. Two Indian case-
control studies, Gajalakshmi et al and Pakseresht S et al, found no association between age at men-
arche and breast cancer risk. In the first and still the largest case-control study on female breast
cancer done in Pakistan, Gilani GM showed that both early menarche and late menopause were
protective. Various explanations have been put forward for this discrepancy. As suggested by Gilani GM, 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 con-
trast to most western literature and local literature that have shown increased risk for breast cancer if one had affected 1st
degree relative.

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. 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%. Previous local studies have produced inconsistent results regarding breast can-
cer and parity. Gilani GM found that nulliparous women were not at increased risk for breast cancer compared to
parous women. On the other hand Mahmood S et al 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. 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.

Reduction of breast cancer risk with ever breastfeeding was seen in many case-control and cohort studies. 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%. Breastfeeding practices are high in our country and most women breastfeed for longer

### Table 1: Characteristics of cases and controls regarding risk factors other than reproductive ones.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 150</th>
<th>N = 300</th>
<th>OR&lt;sup&gt;1&lt;/sup&gt;</th>
<th>95% CI</th>
<th>OR&lt;sup&gt;2&lt;/sup&gt;</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5</td>
<td>3</td>
<td>3.4</td>
<td>0.8—14.5</td>
<td>3.5</td>
<td>0.8—15.4</td>
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<tr>
<td>Married</td>
<td>145</td>
<td>297</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age at menarche</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt; 12 years</td>
<td>7</td>
<td>9</td>
<td>1.6</td>
<td>0.6—4.3</td>
<td>1.6</td>
<td>0.6—4.3</td>
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<tr>
<td>≥ 12 years</td>
<td>143</td>
<td>291</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Premenopausal</td>
<td>64</td>
<td>111</td>
<td>1.3</td>
<td>0.8—1.9</td>
<td>1.6</td>
<td>0.9—2.8</td>
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<tr>
<td>Postmenopausal</td>
<td>86</td>
<td>189</td>
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<td></td>
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</tr>
<tr>
<td>Age at menopause&lt;sup&gt;3&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>≥ 50 years</td>
<td>17</td>
<td>36</td>
<td>1.0</td>
<td>0.5—2.0</td>
<td>1.0</td>
<td>0.5—2.0</td>
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<tr>
<td>&lt; 50 years</td>
<td>69</td>
<td>153</td>
<td></td>
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<td>Family history</td>
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<td></td>
<td></td>
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<tr>
<td>Present</td>
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<td>24</td>
<td>1.0</td>
<td>0.5—2.1</td>
<td>1.0</td>
<td>0.5—2.0</td>
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<tr>
<td>Absent</td>
<td>138</td>
<td>276</td>
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<td>Ever</td>
<td>4</td>
<td>38</td>
<td>0.2</td>
<td>0.1—0.5</td>
<td>0.2</td>
<td>0.1—0.5</td>
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<tr>
<td>Never</td>
<td>146</td>
<td>262</td>
<td></td>
<td></td>
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</tbody>
</table>

<sup>1</sup>Unadjusted Odds Ratio  
<sup>2</sup>Odds Ratio adjusted for age  
<sup>3</sup>For postmenopausal women only
durations. This has led some experts to say that breastfeeding has no relation with breast cancer in Pakistan. We found that ever breastfeeding did not decrease breast cancer risk. Many local studies support our results. Parvez T et al. and Gilani GM have reported that breastfeeding did not affect breast cancer risk. However, Faheem et al. and Mahmood S et al. showed that breast cancer risk was more for women with no history of breast cancer. Their results can be explained by the fact that their analysis for lactation and breast cancer was restricted to parous women only, instead they included all women. In Faheem et al. 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. Similar is the case with Mahmood S et al. 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 reproductive risk factors for breast cancer in our population. The role of breastfeeding, ages at menarche and menopause needs clarification and further work.

**References**


### Table 2: Characteristics of cases and controls regarding reproductive risk factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case</th>
<th>Control</th>
<th>OR¹</th>
<th>95% CI</th>
<th>OR²</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td></td>
<td></td>
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<tr>
<td>Nulliparous</td>
<td>17</td>
<td>8</td>
<td>4.7</td>
<td>1.9—11.0</td>
<td>4.6</td>
<td>1.6—13.5</td>
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<tr>
<td>Parous</td>
<td>133</td>
<td>292</td>
<td></td>
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<td></td>
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<tr>
<td>No. of live births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>17</td>
<td>8</td>
<td>5.1</td>
<td>2.1—12.2</td>
<td>5.2</td>
<td>1.8—15.2</td>
</tr>
<tr>
<td>≥ 3</td>
<td>112</td>
<td>270</td>
<td>1.0</td>
<td>Reference</td>
<td>1.0</td>
<td>Reference</td>
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<tr>
<td>Age at 1st live birth</td>
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<td>Nulliparous</td>
<td>17</td>
<td>8</td>
<td>0.9</td>
<td>0.3—3.4</td>
<td>1.1</td>
<td>0.3—4.4</td>
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<tr>
<td>&lt; 30 years</td>
<td>118</td>
<td>285</td>
<td>0.2</td>
<td>0.1—0.5</td>
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<td>0.1—0.5</td>
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<tr>
<td>≥ 30 years</td>
<td>15</td>
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<td>1.0</td>
<td>Reference</td>
<td>1.0</td>
<td>Reference</td>
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<td>Lactation³</td>
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<tr>
<td>Never</td>
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<td>9</td>
<td>1.7</td>
<td>0.6—4.8</td>
<td>1.8</td>
<td>0.6—5.0</td>
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<tr>
<td>Ever</td>
<td>126</td>
<td>283</td>
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<tr>
<td>Duration of lactation</td>
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<tr>
<td>No lactation</td>
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<td>1.0</td>
<td>Reference</td>
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<td>Reference</td>
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<tr>
<td>&lt; 3 months</td>
<td>6</td>
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<td>0.3—5.8</td>
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<td>0.3—6.4</td>
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<tr>
<td>≥ 3 months</td>
<td>120</td>
<td>277</td>
<td>0.5</td>
<td>0.2—1.5</td>
<td>0.5</td>
<td>0.2—1.5</td>
</tr>
<tr>
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<td>8</td>
<td>2.7</td>
<td>0.7—10.0</td>
<td>2.6</td>
<td>0.6—11.4</td>
</tr>
</tbody>
</table>

¹Unadjusted Odds Ratio
²Odds Ratio adjusted for age, marital status, menopausal status, and use of oral contraceptives
³For parous women only


