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Original Article

# The Role of Family History on the Risk of Developing Breast Cancer

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## Abstract

**Objective:** To determine the frequency of family history of breast cancer among women with breast cancer.
**Study type settings & duration:** This cross sectional study was carried out at the Department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi from January 2019 to July 2019.
**Methodology:** Total 176 females of age 26-74 years suffering from histopathological proven breast carcinoma were included in the study. The socio-demographics data and clinicopathological characteristics were recorded on the predesigned proforma. Family history regarding number and age of family members suffering from breast cancer at the time of diagnosis and degree of relationship with the patient was also obtained. The data was analysed via SPSS version 23.
**Results:** Out of 176 enrolled patients, 42 females had family history of breast cancer (23.8%). Among them almost all (95.2%) had one family member affected and only 2 patient had 2 family members affected by breast cancer. Out of 42, 30 patients had history in their 1st degree of relationship, followed by 2nd (n = 9) and 3rd (n = 3) degree. The most common relation affected by breast cancer was mother (47.6%), followed by sister (26.2%).
**Conclusion:** Family history plays a significant role in breast cancer. Positive relationship between age of the patients and age at diagnosis of breast cancer with family history showed statistical significant difference.
**Key words:** Breast cancer, family history, histological type, age at menopause, degree of relationship.

## Introduction

Globally, each year 2.1 million women get diagnosed with breast cancer. It is the most frequent malignancy after lung cancer and one of the main causes of cancer-related deaths in females.[1] In 2018, breast cancer accounted for 25% of all malignancies in US.[2]

Approximately 15-20% of the females diagnosed with breast cancer have positive family history of breast cancer.[2,3] Therefore the risk of having breast cancer is more in females with positive family history of breast or ovarian cancer, especially before the age of 50. Further studies concluded that if a female has two first-degree breast cancer relatives (mother and sibling), then the possibility of having the disease is five times higher as compared to the average risk.[4] The "standardized incidence ratios" (SIRs) of breast cancer is 3.52 with no family history, 4.29 with one 1st degree relative and 3.90 with 2 or more 1st degree relatives while the SIRs for one or two 1st degree relative is 4.79, three 1st degree relative is 4.13 and four or more 1st degree relative is 3.55 at any age.[5] In United Kingdome, 25% of the breast cancer patients had one or more relatives affected by breast cancer.[6] The women who had 2 or more 1st degree affected family members had 2.5 times more odds of developing breast cancer than women with no history of breast cancer in family.[7].

Breast carcinoma is more frequent among young women in Pakistan, whereas it is more common among older women in the west.[8] Approximately 46% of the breast cancer effected women in Pakistan were of age less than 50 years[9], 35.2% of them had positive history of cancer other than breast in relatives and 30% of the females had positive history of breast cancer in relatives.[8] Recent studies conducted in Pakistan also showed 17-34%

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**Authors Contribution**

NB conceptualized the project. NB & MAH did the data collection and literature search. Statistical analysis was done by AY. NB, GH & SK did the drafting, revision & writing of manuscript.

of the females with carcinoma of breast had strong family history.[8,10-12]

Although the presence of history of breast cancer in family is an intrinsic and unmodifiable element, there is a serious need to assess the risk among females with breast cancer in family. Hence, the purpose of this research was to determine the frequency of family history of breast cancer among women diagnosed with breast cancer.

## Methodology

It was an observational study conducted at the Medical Oncology Department, Jinnah Postgraduate Medical Center (JPMC), Karachi, Pakistan from January 2019 to July 2019. The sample size of 176 breast cancer patients was estimated using Open EPI sample size calculator by taking the percentage of positive history of breast cancer in family as 34, absolute precision as 7% and 95% confidence level.[10] Non-probability consecutive sampling technique was used for sampling. Females aged 26-74 years with histopathological confirmed diagnosis of breast carcinoma were included in this study. Females with benign breast lump, terminal stage of breast cancer, pregnancy or psychiatric problems were excluded from the study.

Before gathering data, informed consent was taken from all females fulfilling inclusion criteria. Data on socio-demographic variables along with clinical and pathological characteristics and family history was recorded on the predesigned proforma.

Data on number of family members affected with breast cancer along with their age at diagnosis and the degree of relationship with study participant was also gathered. The degree of relationship was divided into three categories i.e. mother and sisters were categorized as first degree, aunts and grandmothers as second degree and great grandmothers and cousins as third degree relationship. Further family history of cancer other than the breast was also taken. The confidentially and privacy of the data were maintained during the collection and analysis by coding of the data

Data was analysed using SPSS version 23. Numeric variables were reported as mean and standard deviation whereas qualitative variables were reported as frequency and percentage. Bivariate logistic regression model was applied to assess the association among the family history and potential confounders and odd ratios were calculated. The significant confounders ($p$ <0.15) were incorporated in the final multivariate analysis. The adjusted odd ratios were computed. $p$-value <0.05 was taken as statistically significant for multivariate model.

The prior ethical approval was taken from ethical review board of the Jinnah Postgraduate Medical Center, Karachi, Pakistan.

## Results

The mean age of the study participants was 49.85 years and almost half of them i.e. 54% were of more than 50 years of age, whereas the average age at menarche and the diagnosis time of disease were as 13years and 46.85 years respectively. Majority of the females were married (89.2%), Urdu speaking (60.2%), 45.5% had parity more than 3 and average age at first child birth was estimated as 21.39 years. The majority of the females having breast cancer had menopause started less than and equal to 40 years of age (77.8%). According to pathological type, majority of the females had invasive ductal (73.3%) followed by invasive lobular (16%). Almost half of the females had grade 2 (moderately differentiated) tumor histology (54%) and stage III disease (49.4%). About 80.7% of the females had history of breast feeding and average duration of breast feed was estimated as 2.4 years. According to hormonal status, 71% had ER positive, 67.6% had PR positive and 31.3% had HER 2 NEU positive. Thirty one females had family history of cancer as listed in Table-1.

Out of 176 breast cancer patients, 42 females had family history of breast cancer (23.8%). Among them almost all (95.2%) had one affected family member and only 2 patient had 2 family members with breast cancer. Out of 42, 30 patients had history of breast carcinoma in their 1st degree family member, followed by 2nd (n=9) and 3rd (n=3) degree. The most common relation was mother affected by breast cancer (47.6%), followed by sister (26.2%). The mean age of family member at the time breast cancer diagnosis was estimated as 49.2 years and majority of them were aged more than 50 years (61.9%) as listed in Table-2.

A univariate logistic regression was carried out to determine the effect of potential confounders on the probability of breast cancer with positive history in family. With increase in age, age at the time of diagnosis and age at menopause, the likelihood of having breast cancer increased by one unit in women with family history. The Punjabis were 5.62 times more probable to exhibit positive family history as compared to other ethnicities. Whereas, married females were 0.15 times less probable to exhibit family history as compared to unmarried. The females with parity more than 3 has 1.38 times

**Table 1: Socio-Demographic and clinicopathological characteristics of study participants effected with breast cancer.**

| *Variables* | *n* | *%* | *Variables* | *n* | *%* |
|---|---|---|---|---|---|
| *Age (years)* | | | *Pathological type* | | |
| <= 50 y | 81 | 46.0 | Invasive ductal | 137 | 77.3 |
| > 50 y s | 95 | 54.0 | Invasive lobular | 29 | 16 |
| Mean ± SD | 49.12±11.45 | | Mucinous | 2 | 1.1 |
| *Age at diagnosis (years)* | | | *Medullary* | *8* | *4.5* |
| <= 50 y | 66 | 37.5 | Grade of tumor | | |
| > 50 y | 110 | 62.5 | Well differentiated | 33 | 18.8 |
| Mean ± SD | 46.85±10.98 | | Moderately differentiated | 95 | 54.0 |
| *Age at menarche (years)* | | | *Poorly differentiated* | *48* | *27.3* |
| <= 13 y | 142 | 80.7 | Stage of tumor | | |
| > 13 y | 34 | 19.3 | 1 | 5 | 2.8 |
| Mean ± SD | 13.19±0.94 | | 2 | 78 | 44.3 |
| *Marital status* | | | *3* | *87* | *49.4* |
| Unmarried | 19 | 10.8 | 4 | 6 | 3.4 |
| Married | 157 | 89.2 | *Duration of breast feed* | | |
| *Parity* | | | <= 1 y | 163 | 92.6 |
| Null | 22 | 12.5 | > 1 y | 13 | 7.4 |
| 1 | 22 | 12.5 | Mean ± SD | 2.40±0.95 | |
| 2 | 12 | 6.8 | *Hormonal status* | | |
| 3 | 40 | 22.7 | ER positive | 125 | 71 |
| > 3 | 80 | 45.5 | PR positive | 119 | 67.6 |
| *Age at first child birth* | | | HER 2 NEU positive | 55 | 31.3 |
| <= 25 y | 56 | 31.8 | *Family history of cancer* | | |
| > 25 y | 120 | 68.2 | Yes | 31 | 17.6 |
| Mean ± SD | 21.39±4.76 | | No | 145 | 82.4 |
| *Age at menopause* | | | *Ethnicity* | | |
| <= 40 y | 137 | 77.8 | Urdu | 106 | 60.2 |
| > 40 y | 39 | 22.2 | Sindhi | 42 | 23.9 |
| Mean ± SD | 45.01±5.83 | | Punjabi | 14 | 8.0 |
| *History of breast feeding* | | | Balochi | 6 | 3.4 |
| Yes | 142 | 80.7 | Pashto | 8 | 4.5 |
| No | 34 | 19.3 | | | |

**Table 2: Details of History of Breast Cancer in Family.**

| *Variables* | *Positive Family history of breast cancer (n=42)* |
|---|---|
| *No. of family members having history of breast cancer* | |
| 0 | 0 |
| 1 | 40 |
| 2 | 2 |
| *Degree of Relationship* | |
| 1st | 30 |
| 2nd | 9 |
| 3rd | 3 |
| *Relation* | |
| Mother | 20 |
| Sister | 11 |
| Cousin | 4 |
| Aunt | 4 |
| Grandmother | 4 |
| *Age of family member at diagnosis* | |
| ≤50 years | 16 |
| >50 years | 26 |
| Mean±SD | 49.20±11.64 |

more probable to have positive history of breast cancer in family as compared to females with parity less than and equal to 3. The females with invasive lobular type has 2.57 times more probable to exhibit history of breast cancer in family than other types. The females with poorly differentiated & stage 2 tumor and family history of any other cancer revealed positive linkage with family history of breast cancer. Furthermore, the history of breast feeding and hormonal status were insignificantly related to history of breast cancer in family. After adjusting the odds in multivariate analysis, only age of the patient & age at diagnosis of breast cancer showed significant association with positive family history ($p$ <0.05) as listed in Table-3.

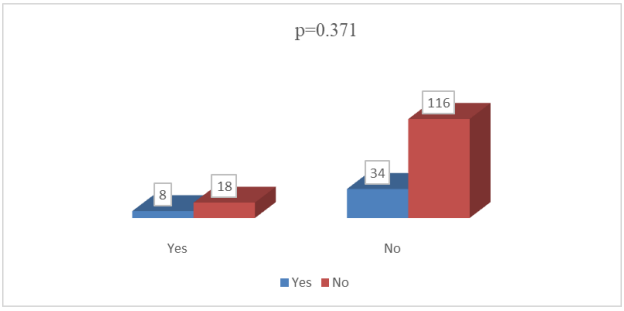


**Figure: Correlation between family history of breast cancer and triple negative breast cancer.**

**Table 3: Univariate and Multivariate Analysis for Family History of Breast Cancer among enrolled patients of breast cancer.**

| *Variables* | *p-value* | *O.R (95% CI)* | *p-value* | *Adjusted OR (95% CI)* |
|---|---|---|---|---|
| Age (yrs) | 0.043 | 1.03(1.00-1.06) | 0.043 | 0.85(0.72-0.99) |
| Age at diagnosis (yrs) | 0.008 | 1.04(1.01-1.08) | 0.008 | 1.23(1.05-1.44) |
| Age at menarche (yrs) | 0.833 | 0.96(0.67-1.38) | | |
| Age at first child (yrs) | 0.233 | 0.95(0.88-1.03) | | |
| Age at menopause (yrs) | 0.047 | 1.07(1.00-1.15) | 0.536 | 1.03(0.93-1.14) |
| *Ethnicity* | | | | |
| Urdu | 0.209 | Reference | | |
| Sindhi | 0.097 | 2.16(0.86-5.37) | | |
| Punjabi | 0.103 | 5.62(0.70-44.80) | | |
| Balochi | 0.489 | 2.16(0.24-19.25) | | |
| Pashto | 0.309 | 3.02(0.35-25.62) | | |
| *Marital status* | | | | |
| Unmarried | 1 | Reference | 0.167 | 0.171(0.01-2.09) |
| Married | 0.005 | 0.15(0.02-1.21) | | |
| *Parity* | | | | |
| Null | 1 | Reference | | |
| 1 | 1.000 | 1(0.24-4.09) | | |
| 2 | 0.253 | 0.41(0.09-1.88) | | |
| 3 | 0.420 | 0.61(0.18-2.02) | | |
| >3 | 0.578 | 1.38(0.43-4.38) | | |
| *Pathological type* | | | | |
| Invasive ductal | 1 | Reference | | |
| Invasive Lobular | 0.499 | 1.71(0.35-8.25) | | |
| Infiltrative ductal | 0.462 | 0.57(0.13-2.52) | | |
| Infiltrative lobular | 0.224 | 2.57(0.56-11.87) | | |
| Mucinous | 0.455 | 0.34(0.02-5.65) | | |
| Medullary | 0.420 | 0.24(0.28-20.29) | | |
| Grade | | | | |
| Well differentiated | 1 | Reference | | |
| Moderately differentiated | 0.252 | 1.65(0.69-3.94) | | |
| Poorly differentiated | 0.139 | 2.16(0.77-6.03) | | |
| *Stage* | | | | |
| 1 | 1 | Reference | | |
| 2 | 0.966 | 1.05(0.10-10.08) | | |
| 3 | 0.751 | 0.69(0.07-6.55) | | |
| 4 | 0.317 | 0.25(0.01-3.77) | | |
| *Family history of any other cancer* | | | | |
| No | 1 | Reference | | |
| Yes | 0.854 | 1.09(0.43-2.74) | | |
| *History of breast feeding* | | | | |
| Yes | 1 | Reference | | |
| No | 0.170 | 2.04(0.73-5.67) | | |
| *Hormonal status* | | | | |
| *ER* | | | | |
| Positive | 1 | Reference | | |
| Negative | 0.476 | 0.76(0.36-1.60) | | |
| *PR* | | | | |
| Positive | 1 | Reference | | |
| Negative | 0.598 | 0.82(0.39-1.70) | | |
| *HER 2 NEU* | | | | |
| Positive | 1 | Reference | | |
| Negative | 0.66 | 0.84(0.39-1.81) | | |

Out of 176 females 14.8% had triple negative breast cancer and 19% had positive family history of breast carcinoma, however there was no statistically relevant correlation between triple negative breast cancer and family history ($p$ >0.05) as shown in Figure.

## Discussion

Family history is the potential risk factor in females for the prediction of breast carcinoma. Therefore it is important to determine the correlation between family history of breast carcinoma and occurrence of breast cancer.

The likelihood of breast cancer is more if someone has 1st and 2nd degree relatives with breast cancer.[13] In the present research, 42 females (23.8%) had positive history of breast cancer. Among them most females had a minimum one member of the family affected by breast cancer (95.2%). Thirty patients had positive history in their 1st degree family member, followed by 2nd (n=9) and 3rd (n=3) degree and the most frequent relation affected by breast cancer was mother followed by sister. In the research conducted by Brewer HR et al. revealed that most breast cancer patients had no family history (85%) whereas 15% had one or more family member affected by breast cancer. About 11.5% of the mothers were affected by breast cancer, followed by sisters (2.6%).[7] In the study conducted by Sufian SN et al. observed 27.8% of the females with breast cancer had positive family history, moreover the patients with positive history in family had 1.8 times more probability to have breast cancer than controls.[12] In the study carried out by Lofti MH et al. observed that patients were 4 times more at risk of developing breast cancer when family history of breast carcinoma was positive.[14] In an other study conducted by Elkum N et al. also found positive correlation between family history and breast cancer with 2.31 times higher risk.[15] In a recent study conducted in Pakistan concluded that 34% of the patients had positive history of breast cancer in their 1st degree relation and had statistically significant correlation ($p$ <0.05).[10] In another study conducted at Pakistan, about 10% of the patients had positive history of breast cancer in family.[16]

In this study, univariate and multivariate analysis revealed that age and age at diagnosis time are separate risk factors for breast carcinoma. We observed that the impact of age and age at diagnosis on the risk of breast cancer among females increases if the patients exhibits positive family history in contrast to those with no history in family ($p$ <0.05). In the present research, the mean age and age at diagnosis of breast cancer were estimated as 49 & 46 years approximately and majority of them were of age more than 50 years furthermore the mean age of diagnosis in the affected relative was estimated as 49 years. Brewer HR et al. found in their study that most of the patients were aged more than 45 years and 55% of them having breast cancer were diagnosed at the age of less than 60 years. Furthermore, the mean age at diagnosis of breast cancer in relatives was 57 years and majority of the relatives were diagnosed when they were of age 45 years or more.[7] Alieldin NH et al. in their study concluded that the median age at diagnosis time was 49 years and majority of the females were older than forty years (81%).[17] In another study conducted at Saudi Arab the median age was estimated as 45 years and 67% of them were of age more than 45 years.[18] In the collaborative reanalysis, the high risk ratio has been estimated for younger age females and increased risk has been observed among females with positive history in their 1st degree relatives and most of them were of age more 50 years when diagnosed with breast cancer.[19] In the research conducted by Gilani GM et al. found that females having history of breast cancer in family and older age are at higher risk of developing breast cancer.[20] In another research conducted in Pakistan, the mean age of the women was estimated as 53 years and majority of diagnosed were in the age ranging from 41 to 60 years (76%) and majority of them had negative history of breast cancer in family (97%).[21] In a research conducted by Bano R et al. the mean age of the females having breast cancer was estimated as 51 years.[22] In a study carried out by Rashid MU et al. the patients with triple negative breast cancer diagnosed early in life showed strong family history association ($p$ <0.05).[23] The incidence of breast carcinoma thus increased with increasing age and it shows distinctive age-specific variation.

Family history of cancer is one of the major risk factor for breast cancer. Positive relationship between age of the patients and age at diagnosis of breast cancer with family history showed statistical significant difference. Thus, females with a strong family history in their 1st degree relatives, their screening should be done more frequently especially after the age of 35 years. They should also be educated about the self-examination, clinical examination and screening tests of the breast.

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