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Original Article

Association of Parity with Triple Negative Breast Cancer, A Case Control Study

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ABSTRACT

Objective: To find out association between number of children and triple negative breast cancer among females presenting at a tertiary care hospital of Karachi.

Study Design: Case control study.

Place and Duration of Study: Medical Oncology Department, Jinnah postgraduate Medical Centre, Karachi, Pakistan from Aug 2019 to Mar 2020.

Methodology: Total 465 patients of age 17-80 years were included using non-probability consecutive sampling technique. About 150 cases were patients with triple negative breast cancer and 315 controls were breast cancer patients other than triple negative breast cancer. SPSS version 23 was used to analyse data.

Results: The mean age of study sample was estimated as 46.07±11.32 years. Most of the females had grade II (53.3%), stage III (44.9%) and invasive ductal carcinoma (IDC) (94.2%) histological type of tumor. In univariate logistic regression model, triple negative breast cancer was found to be associated with high parity (OR=4.51,95% CI=2-10.15, p<0.10), age at menarche [Mean 11.8yrs.] (OR=1.38,95%CI=1.08-1.78, p<0.10) and age at first birth [Mean 20.61yrs.] (OR=1.17,95% CI=1.10-1.23, p<0.10. In multivariate logistic regression model, predictors such as high parity (OR=4.26,95% CI=1.84-9.83, p<0.05), age at menarche (OR=1.31,95%CI=1.01-1.69, p<0.05) and age at first birth (OR=1.20,95% CI=1.13-1.27, p<0.05) remained significantly associated with triple negative breast cancer.

Conclusion: Study showed that high parity is significantly associated with triple negative breast cancer.

Keywords: Breast cancer, Estrogen receptor (ER), Human epidermal growth factor receptor 2 (HER 2), Progesterone receptor (PR), Parity, Triple negative breast cancer (TNBC).

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INTRODUCTION

Breast cancer is the commonest cancer among females in world as well as in Pakistan.[1] In United States, breast cancer is the leading cause of death.[2] Globally, it is the second leading cause of mortality.[3] Breast cancer is a diverse disease that can be divided into subtypes depending on the presence or absence of ER, PR and human epidermal growth factor receptor-2 (Her-2). Literature revealed that female hormones play an imperative role in the aetiology of breast carcinoma. Each subtype is associated with different risk factors.[4] Triple negative breast cancer (TNBC) constitutes around 10-20% among all breast cancers and around 80% of all basal like tumors. TNBC is characterized by having negative expression for ER/PR, and lack of over expression of HER2 on IHC and/or absence of gene amplification by FISH for HER2.[5]

The TNBC is found to be most invasive and aggressive among all breast cancer types along with poor prognosis and survival rates.[6] Being an aggressive cancer, it is of utmost importance to investigate risk factors for TNBC. Literature has claimed that younger age, increased parity, decrease duration of breast feeding, white and Hispanic women are risk factors for TNBC.[6] In addition, BMI, family history, ethnicity and consanguinity is also related with TNBC.[7] Nevertheless, studies suggest that TNBC is highly prevalent in African American females and among the carriers of BRCA-1 germline mutations.[8]

The parity and lactation affects progenitor cells that are present in parenchyma of breast. These adult mammary stem cells (MaSC) have increased survival ability under physiological or pathological stress. Epithelium of breast proliferates during pregnancy and breastfeeding due to expansion of progenitor cells in the terminal ducts of breast. It is followed by epithelial cell death after pregnancy and cessation of breastfeeding. This huge pool of MaSCs provide direct target of transformation for TNBC tumors, as their replicative ability might lead to overt tumor formation during pregnancy.[9]

Parity being an important role player in TNBC, it is evident that women with TNBC have increased

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parity.[10] The recurrence of TNBC is quite high. Its treatment options include surgery along with neo adjuvant or adjuvant chemotherapy followed by radiotherapy depending upon stage. The hormonal or biological agents have no role, so overall there are fewer treatment options available. The prognosis varies according to individual and is subjective to risk factors that influence the disease. Therefore, the present study aims to elucidate whether parity is associated with TNBC.

The association between high parity and TNBC is well known in western literature. So far very few studies have been done regarding association of TNBC with reproductive factors in our population. As, TNBC is most aggressive subtype of breast cancer, our study will help in true estimate of population at risk of TNBC in Pakistan. Also Pakistan is a country where average no. of children are higher than west so our study will help in counselling the women regarding importance of family planning.

METHODOLOGY

The case-control study was conducted at the Medical Oncology Department, Jinnah postgraduate medical centre, Karachi, Pakistan from August 2019 to March 2020. Sample size of 462 was estimated using online Open epi calculator, by taking statistics of nulliparous females among triple negative as 4% and 10.7% among triple positive.[11] ratio of cases to controls as 1:2, 95% confidence level and 80% power of test, including 149-150 cases and 313-315 controls.

Inclusion Criteria: All female patients of age 17-80 years with confirmed diagnosis of breast cancer were included in the study by using non-probability consecutive sampling technique. Cases were patients with TNBC. Controls were breast cancer patients other than TNBC.

Exclusion Criteria: Pregnant and lactating women were excluded from the study.

Review Board approval was taken the eligible subjects. All information regarding socio-demographics like age at presentation, age at first birth, age at menarche, residence, occupation, ethnicity, number of children and comorbidity were noted on pre-designed by ethical review committee (Ref no. F.2-81-IRB/2019-GENL/32730/JPMC) before starting the research. Informed consent was obtained from all proforma. Data regarding stage, grade, histological types, laterality, family history of breast cancer and other cancer and menopausal status were also collected from each subject.

SPSS version 23 was used to analyse data. The descriptive analysis was performed for all numeric and categorical variables. Mean (standard deviation)/ Median (interquartile range) was computed for numeric variables. Frequency and percentage were computed for categorical variables. Bivariate analysis was performed to see association between risk factors and TNBC using chi-square/independent t test. Univariate logistic model was applied to see association between significant predictors at 0.10 level of significance. Unadjusted odd ratios (OR) along with 95% confidence interval were calculated. All the significant predictors in univariate analysis were moved to multivariate logistic regression model and adjusted odd ratios (aOR) along with 95% confidence interval were calculated. The p-value<0.05 was considered as statistically significant for bivariate and multivariate analysis.

RESULTS

Total 465 females were included in the study. The mean age of study sample was estimated as 46.07±11.32 years ranging from 22-76 years, whereas the mean age at menarche and first birth was estimated as 11.96±0.83 (Range: 10-16) and 22.21±4.06 (Range 15-35) years respectively. About 429(92.3%) females had parity of 1 or more whereas 36 females (7.7%) had no children. The median of number of children was 4 with interquartile range as 2-6.

Most of the females were living in urban area 360(77.4%) and unemployed 453(97.4%). Majority of the females were Urdu speaking 241(51.8%), followed by Sindhi 91(19.6%) and Punjabi 63(13.5%). About 269(57.8%) females had premenopausal and 196(42.2%) had postmenopausal status. Most of the females had grade II 248(53.3%) and stage III 209(44.9%). The most frequent histological type was invasive ductal carcinoma (IDC) 438(94.2%) followed by invasive lobular carcinoma (ILC) 19(4.1%), papillary breast cancer 2(0.4%) and others 6(1.3%) respectively. Almost half of the females had left-sided breast cancer 237(51%),222(47.7%) had right-sided breast cancer and 6(1.3%) had bilateral breast cancer. About 69(14.8%) females had family history of breast cancer and 31 (6.7%) had family history of other cancers. Hypertension was present in 108(23.2%) females whereas diabetes mellitus was observed in 48(10.3%) and hepatitis C virus in 12(2.6%) respectively.

At presentation, most of the females were of age <41 years 175(37.6%), followed by 41-50 years 149(32%). Almost 54(36%) females had TNBC who

were of age <41 years. However, insignificant association was observed between age at presentation and TNBC (p=0.079). Similarly, no statistically significant difference was between the mean age of cases and controls (p=0.161).

Among TNBC, 79(52.7%) females had premenopausal status and 71(47.3%) females had postmenopausal status. Statistically insignificant difference was found between menstrual status and TNBC (p=0.018).

The females with TNBC, 7(4.7%) had 0 parity, 3(2%) had para 2, 8(5.3%) had para 3 and 132(88%) had para ≥4. Whereas among controls, 29(9.2%) had para 0, 28(8.9%) had para 1, 58(18.4%) had para 2, 91(28.9%) had para 3 and 109(34.6%) had para ≥4. Hence, statistically significant association was found between TNBC and parity (p<0.05).

In most of the cases reported age at menarche was 12-13 years 92(61.3%), followed by <12 years 54,(36%) respectively. On comparing frequency of TNBC and age at menarche, statistically significant association was found (p<0.05). Similarly, the mean age at menarche also showed statistically significant difference between cases and controls (p<0.05).

Among TNBC females, majority of the females reported the age at first birth as <20 years 69(46%) whereas among controls, majority of the females reported the age at first birth as 20-25 years 158(50.2%). The statistically significant association was found between TNBC and age at first birth (p<0.05). Similarly, the mean age at first birth also showed significant difference between cases and controls (p<0.05). The Figure shows the frequency of TNBC and cont-rols with respect to age at presentation of women (parity≥1). The peak of cases has been observed at the age of 40 years followed by 45 and 56 years respectively.

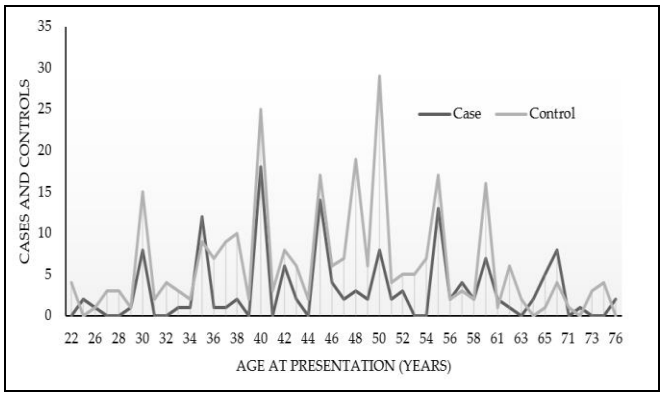

Figure: Relationship Betweem Age at Presentation and Triple Negative Breast Cancer For Parous Women (n=465)

The univariate logistic regression was applied to assess the effect of predictors on likelihood that females have TNBC. TNBC was found to be associated with age at menarche (OR=1.38,95%CI=1.08-1.78, p<0.10), age at first birth (OR=1.17,95% CI=1.10-1.23, p<0.10) and high parity (OR=4.51,95% CI=2-10.15, p<0.10).

All the predictors which were significant in univariate analysis at the significance level of 0.10 were added in single multivariate logistic regression model. In multivariate model, 72.7% of the cases were correctly classified (p<0.05). The predictors such as age at menarche (OR=1.31,95%CI=1.01-1.69, p<0.05), age at first birth (OR=1.20, 95% CI=1.13-1.27, p<0.05) and high parity (OR=4.26,95% CI=1.84-9.83, p<0.05) remained significantly associated with TNBC.

Table-I: Comparison of Menstrual and Reproductive History Between Cases and Controls (n=465)

	Cases (n=151)	Controls (n=315)	*p*-value
Age at presentation (year)			
<41	54(36%)	121(38.4%)	0.07
41-50	42(28%)	107(34%)	
51-60	33(22%)	65(20.6%)	
>60	21(14%)	22(7%)	
Mean±SD	47.13±12.24	45.56±10.85	0.161
Median(IQR)	45(40-55)	46 (37-52)	
Menstrual status			
Premenopausal	79(52.7%)	190(60.3%)	0.118
Postmenopausal	71(47.3%)	125(39.7%)	
Parity			
0	7(4.7%)	29(9.2%)	0.001
1	0	28(8.9%)	
2	3(2%)	58(18.4%)	
3	8(5.3%)	91(28.9%)	
≥4	132(88%)	109(34.6%)	
Age at menarche (year)			
<12	54(36%)	78(24.8%)	0.017
12—13	92(61.3%)	223(70.8%)	
13—14	3(2%)	14(4.4%)	
>14	1(0.7%)	0	
Mean±SD	11.81±0.82	12.03±0.85	0.008
Median(IQR)	12(11-12)	12(12-13)	
Age at first birth (year)			
<20	69(46%)	51(16.2%)	0.001
20-25	62(41.3%)	158(50.2%)	
25-30	15(10%)	92(29.2%)	
>30	4(2.7%)	14(4.4%)	
Mean±SD	20.61±3.74	22.97±4.00	0.001
Median(IQR)	20(18-23)	23(20-26)	

Table-II: Association Between Triple Negative Breast Cancer, Reproductive Status and Tumor Characteristics (n=465)

	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Ageatpresentation	0.98(0.971.0)	0.162		
Age atmenarche	1.38(1.081.7)	0.008	1.31(1.011)	0.039
Age at first birth	1.17(1.101.2)	0.001	1.20(1.131.27)	0.001
Menopausal status				
Premenopausal	1.36(0.922.0)	0.119		
Postmenopausal	1	-		
Stage				
I	1	-		
II	1.01(0.432.3)	0.972		
III	0.95(0.442.0)	0.903		
IV	0.81(0.361.8)	0.612		
Grade				
I	1	-		
II	1.19(0.433.3)	0.727		
III	0.90(0.322.5)	0.842		
Laterality				
Bilateral	1			
Right	2.26(0.4411.)	0.324		
Left	2.00(0.3910)	0.403		
High parity				
<2	4.51(2.0010)	0.001	4.26(1.849)	0.001
≥2	1		1	

DISCUSSION

TNBC comprise of distinctive molecular profile, aggressive behaviour, and worse prognosis.[12,13] Therefore, it is important to look for different risk factors that are responsible for TNBC.[12,14] The present study showed that age is not a significant risk factor for TNBC development. However, literature has mostly revealed that age and ethnicity as a significant factor.[15] The literature reports that TNBC is more likely to occur in younger age in Asian population specifically Pakistani population.[16,17] whereas western population is more likely to be diagnosed at older age.[18] Menopausal status was also assessed as a risk factor but there was insignificant association with TNBC. This study demonstrated TNBC diagnosis among both groups. However, majority of cases were found in females that did not reach their menopause. Fatima *et al*. & Lee *et al*. confirmed similar findings.[11,19]

The present study result reveals the significant factors that are linked with occurrence of TNBC similar to other studies.[20,21] It is found that the higher number of parity is associated with higher risk of developing TNBC. By univariate analysis, it shows that the likelihood of having TNBC increased by 4.26 times in females having high parity. The age at menarche and first birth is likely to be associated 1.31 and 1.2 times more in developing TNBC respectively. The findings are confirmed by Phipps AI *et al*. and Faria *et al*. However, Van Erkelens *et al*. in his study states that breast cancer risk decreases as parity increases.[22] Lara-Medina *et al*. also evaluated different risk factors associated with TNBC among Hispanic women. The study showed that younger age, premenopausal status, increased parity and higher histologic grade were associated independently with TNBC,[6] Faria *et al*. revealed that delay in first child birth and fewer kids are related with the development of TNBC.[11]

Rashid et al. compared TNBC and non TNBC patients and reports that TNBC had high BRCA,[1] mutations and were diagnosed at later age in BRCA mutated patients.[23-25] Abu Bakar *et al*. conducted similar comparative study and found age, family history and grade to be significant factors.[16] Although various studies have been conducted to study the characteristics of TNBC, however the present study will be a beneficial addition to previous literature as it has analysed the comparison between cases and controls and found risk factors of TNBC in Pakistani population. Considering the aggressiveness and high mortality of TNBC, we recommend further studies to be conducted to find out more modifiable risk factors which can be helpful in reducing the incidence of TNBC.

CONCLUSION

There is significant positive association between TNBC and high parity, on analysis of other variables there was also positive association between TNBC and early age at first child birth as well as early age at menarche. Hence, studies with bigger sample size are needed to assess more detail risk factors causing TNBC.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

BAM: & GH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

MA: & KA: Conception, study design, drafting the manuscript, approval of the final version to be published.

AT: & BR: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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