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Original Article

Evaluation of Risk Factors in Patients with Triple Negative Breast Cancer in a Tertiary Hospital

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Abstract

Introduction: Triple Negative Breast Cancer (TNBC) is known to have high recurrence, poor prognosis and has limited treatment options. This study was designed to evaluate the risk factors associated with patients with breast cancer.

Methods: This cross-sectional study was conducted in the Department of General Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU) from January 2023 to December 2023 where 116 patients were analyzed which included 58 diagnosed cases of TNBC and 58 non-TNBC cases. Both non-modifiable and modifiable risk factors were recorded.

Result: Non-modifiable risk factors, such as family history of breast cancer (22.41% vs. 0%) were significantly associated with TNBC patients while there was no history of family history of breast cancer among non-TNBC respondents. Among TNBC respondents who had the family history of breast cancer underwent gene amplification test and results showed that 84.6% had BRCA1/BRCA2 gene mutation. Other non-modifiable risk factors such as early menarche and early menopause were not significantly associated with TNBC. Modifiable risk factor, such as moderate intensity physical activity had shown significant risk for TNBC (96.6% and 82.8%). However, only 6.9% TNBC respondents had obesity while 17.2% were obese in non TNBC respondents and 62.1% had history of OCP in TNBC while 48.3% respondents had history of OCP in non TNBC patients. No respondents had history of smoking and alcohol.

Conclusion: Family history of breast cancer, gene mutation and moderate physical activity are found significant as risk factors for TNBC.

Key words: Triple Negative Breast Cancer (TNBC), Basal-like breast cancer, ER-positive PR-positive HER2-negative breast cancer, HER2 enriched.

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Introduction

Triple negative Breast cancer is those which fail to express ER, PR, HER2 receptors. According to a study 24% newly diagnosed breast cancers are TNBC.[1] Triple negative breast cancer occurs in younger women <50 years[2-8] and it range from (15-25%) in Asian or south Asian women. According to the American Society of Clinical Oncology/ College of American Pathologists (ASCO/CAP) guidelines, TNBCs present with cellular expression of progesterone and estrogen receptors of d"1% and human growth factor receptor 2 expressions between 0 and 1+.[9] TNBCs is relatively aggressive and constitute 12% -17% of all breast cancers and have a

high propensity for recurrence. In West Bengal, India, where race and culture of the population are similar to that of Bangladesh, TNBC was found in about 22% of the cases.[10] In another study in 2018, 2,088,849 cases of TNBC were reported reflecting that TNBC is common cancer in women.[11] The prognosis is gloomy as the average survival rate is <"10.2 months with current treatment regime, 65%, 5 years survival in regional disease and only 11% where the tumor metastasized to distant organs.[12] Modifiable risk factors are; obesity: BMI>30-increased risk of breast cancer in postmenopausal women, parity also has influence, increased risk in nulliparous women or first pregnancy after 35 years of age, while breastfeeding is protective for breast cancer, younger age at first childbirth also reduces risk, HRT use for more than 10 years increased risk. In another study , risk factors for breast cancers can be divided into 'modifiable risk factors' such as drugs, obesity, smoking, alcohol consumption, physical exercise, insufficient vitamin supplementation, intake of processed food, exposure to chemicals and ' non-modifiable risk factors' such as age, sex, family history of breast cancer, genetic mutations ,time of 1st pregnancy and breast feeding, early menarche and late menopause, density of breast tissue, previous history of breast cancer, non-cancerous breast diseases, history of radiation exposure.[13] Treatment option rely on ER and PR and HER2 protein expression or gene amplification. Despite major advances in the role of receptor status, there is no targeted therapy available for TNBC, leaving cytotoxic chemotherapy as the only systemic therapy. In addition, TNBCs are biologically aggressive type of breast cancer with its propensity for recurrence and metastasis and is associated with worse prognosis.[14] Although TNBC is of growing interest in the clinical and research community, its etiology remains an enigma. The study focused to evaluate the risk factors of TNBC in the context of our country.

Materials and Methods

This cross-sectional study was conducted in Department of General Surgery BSMMU, between January 2023 to December 2023. The study population were the patients with diagnosed cases of TNBC and non-TNBC who were treated in this department. Prior commencing, inclusion and exclusion criteria were matched for each group. A total of 116 patients were included in the study, 58 patients had TNBC and 58 patients were non-TNBC based on the Selection criteria. Inclusion criteria were 1) Diagnosed case of TNBC, 2) Diagnosed case of non TNBC which include ER, PR, HER2 positive breast cancer patients. 3) ER, PR, HER2 negative breast cancer patients, 4) HER2 enriched. Patients with 1) Recurrent breast cancer, 2) New primary on the contralateral breast were excluded from the study. The purpose and procedure of the study were discussed with the participant, and a written informed consent was taken from each and every participant this study. Ethical clearance was obtained from the institutional review board (IRB), BSMMU, before commencement of the study. After getting consent, the data were collected, and Separate data collection sheet was used for each subject maintaining confidentiality.

After collecting the data, these were checked, verified for consistency and tabulated by using SPSS version 26 (IBM Corp., Armonk, NY). Socio-demographic characteristics, modifiable and non-modifiable risk factors were recorded. Frequencies and percentages were calculated as summary measures for the qualitative variables. Arithmetic mean and standard deviation were used to describe the quantitative variables. A 'p' value <0.05 is considered as statistically significant. After completion, the data were presented in tables, figures and graphs.

Result

There is significant association between age group with triple negative breast cancer. Among TNBC patients, majority of the respondents were between 31-40 years (44.83%), while mean age of the TNBC respondents was 39.79±8.983 years and non-TNBC respondents was 45.22±11.220 years.

Table I: Comparison of age distribution between TNBC and non-TNBC patients (n=116)

Age	Triple negative breast cancer		p-value
	TNBC n=58 n (%)	Non-TNBC n=58 n (%)	
20-30 years	7(12.07)	2(3.45)	0.046*
31-40 years	26(44.83)	21(36.21)	
41-50 years	18(31.03)	17(29.31)	
51-60 years	7(12.07)	12(20.69)	
61-70 years	0 (0.00)	5 (8.62)	
71-80 years	0 (0.00)	1 (1.72)	
Mean age ± SD	39.79±8.983	45.22±11.220	0.005**

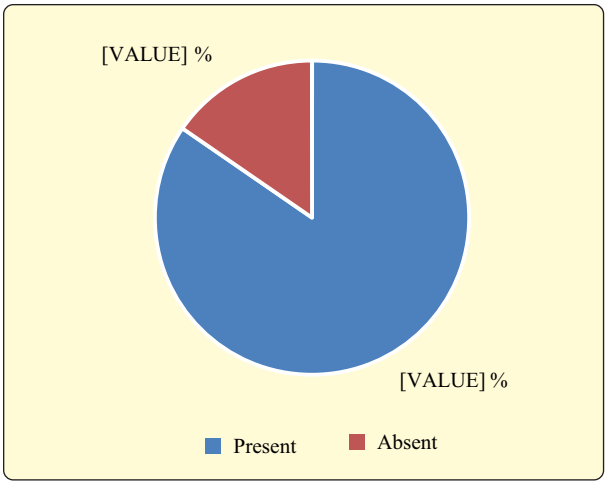
*Chi-square test, **Student t test was done.

Table II: Association of non-modifiable risk factors between TNBC and non-TNBC patients (n=116)

Variables	Triple negative breast cancer		p-value
	TNBC n=58 n (%)	Non-TNBC n=58 n (%)	
Early menarche			
Yes	17 (29.3)	16 (27.59)	0.837
No	41 (70.7)	42 (72.41)	
Late menopause			0.570
Yes	25 (43.1)	22 (37.93)	
No	33 (56.9)	36 (62.07)	
Family history of breast cancer			
Present	13(22.4%)	0(0.0%)	<0.001*
Absent	45(77.6%)	58(100.0%)	

*Fisher's Exact test. Values were expressed as frequency with percentage in parenthesis over column

Among TNBC respondents 13 had family history of breast cancer, while patient with non-TNBC had no family history of breast cancer. Significant association has been found with positive family history with TNBC.



The pie-chart: Frequency of genetic mutation (BRCA1/ BRCA2) among TNBC (n=58)

Table III: Comparison of modifiable risk factors between TNBC and non-TNBC patients (n=116)

Modifiable risk factors	Triple negative breast cancer		p-value
	TNBC (n=58)	Non-TNBC (n=58)	
Oral contraceptive pill			
Yes	36 (62.1)	28 (48.3)	0.135
No	26 (44.83)	26(44.83)	
Mean duration of OCP (year)			
Mean ± SD	7.79±6.679	7.47±4.294	
Late pregnancy			
Yes	28 (48.28)	35 (60.34)	0.192
No	30 (51.72)	23 (39.66)	
Breastfeeding			
Yes	46(79.31)	50(86.21)	0.326
No	12(20.69)	8(13.79)	
Physical activity			
Low intensity	2(3.4%)	10(17.2%)	0.015
Moderate intensity	45(96.6%)	48(82.8%)	
Obesity			
Obese	4(6.9%)	10(17.2%)	0.087
Non obese	54(93.1%)	48(82.8%)	
Process food intake			
Present	10(17.2%)	8(13.8%)	0.608
Absent	48(82.8%)	50(86.2%)	

*Pearson chi-square test was done. Values were expressed as frequency with percentage in parenthesis over column

Table 3 shows that most modifiable risk factors, including OCP use, late pregnancy, breastfeeding, obesity, and processed food intake, were not significantly associated with TNBC (p>0.05). However, physical activity showed a significant association (p=0.015), with moderate-intensity activity being more common among TNBC patients.

Table-IV: *Logistic regression analysis for TNBC respondents (n=116)*

variables	P value	OR	95%CI
Age (<40 years)	0.065	2.006	0.959-4.208
Early pregnancy	0.193	0.613	0.294-1.281
Breastfeeding history	0.328	0.613	0.230-1.634
Early menarche	0.837	1.088	0.486-2.439
Late menopause	0.571	1.240	0.590-2.605
Obesity	0.097	0.356	0.105-1.208
Moderate intensity physical activity	**0.027**	5.833	1.218-27.937

OR= Odds ratio

According to logistic regression analysis, moderate intensity physical activity had 5.833 times significantly risk for triple negative breast cancer. However, early menarche had 1.088 OR and late menopause had 1.240 OR for TNBC respondents though, not statistically significant.

Discussion

The aim of this study was to observe the known modifiable and non-modifiable risk factors of TNBC patients. According to this study majority of the respondents were in their thirties to forties with the mean age of 39.79±8.983years in TNBC respondents and 45.22±11.22 years among non-TNBC respondents. In a study in Bangladesh, patients from 40-49 (39%) and 30-39 (27%) year-age group were found to had highest number breast cancer.[17] Increasing age is a risk factor for breast cancer but TNBC occurs at younger age. Median age at presentation is around 60 years in west (UK, USA), while it is below 50 years in low and middle-income countries. In this study, 22.41% had the family history of breast cancer and 18.97% had genetic mutation among TNBC respondents, while no one had family history of breast cancer in non-TNBC respondents. Also, studies had showed, having a first-degree relative (mother, sister, or daughter) with breast cancer almost doubles a woman's risk. Having two first-degree relatives, increases the woman's risk about 3-fold.[19] This finding showed similarity to this study findings. In this study genetic mutation BRCA1 and BRCA 2 germline sequencing was done only who have positive family history in TNBC, genetic mutation was significant according to this study (p<0.05), which might be useful in evaluating the interaction between germline predisposition and risk factors because as 5-10% of all breast cancer are hereditary; BRCA1 and BRCA2 mutation accounts for up to 70% of hereditary breast cancer. Furthermore, 62.1% respondents in TNBC and 48.3% respondents in non-TNBC group had history of oral contraceptive pill. OCP is not significantly associated with TNBC (ever vs never use, OR 0.80, 95% CI 0.49–1.59, p = 0.7) but as an important risk factor for TNBC according to study by Nag et al[24]. Modifiable risk factors such as obesity were found in 6.9% respondents in TNBC group, though, did not show any significant association with TNBC respondents [OR=0.356, p=0.097]. Though, obesity is found to a crucial risk factor of TNBC especially in African American population (BMI=34.2kg/m2).[25] However, Nag et al.[24] showed BMI >24.9 kg/m2 respondents had 0.89 odds for TNBC, which was quite similar to this study findings. Obesity causes breast cancer due to excess production of estrogen from fat or adipose tissue which stimulate breast tissue. Also, 96.6% respondents had moderate physical activity in TNBC respondents which was significantly higher than Non-TNBC respondents [OR5.833, p=0.027]. Which was similar to Afroz et al.[18] where about 40% female patients with TNBC do not walk as exercise. In many studies, alcohol consumption was found to be associated with development of breast cancer Horakova et al.[26] but in this study no result could be obtained because the whole study population was non -alcoholic. No respondents had other modifiable risk factors such as history of smoking but 17.24% respondents in TNBC group and 13.79% respondents in Non-TNBC group had history of processed food consumption occasionally in this study. However, in the review of Strober and Brady[27] showed increased dietary fructose consumption, development of metabolic disturbances and increased incidence of TNBC. This difference between findings due to social and cultural aspect of alcohol and smoking consumption, as

female of the west seldom take alcohol or cigarette in their daily life[28] . Also, similarly in Kabat et al.[29] smoking and alcohol consumption are not associated with increased risk of TNBC, though, discreetly associated with increased risk of ER+ breast cancer.

Conclusion

Triple Negative Breast Cancer (TNBC) has chances of high recurrence and poorer prognosis. Finding out the risk factors is important to take actions to reduce the incidence. This study shows that family history of breast cancer, genetic mutation and moderate physical activity are significant risk factors for TNBC. However other risk factors like history of breast feeding, late pregnancy, menstrual history, obesity, and processed food intake were not found to significant among triple negative breast cancer patients.

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