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Original Research Article

Clinical pathological and epidemiological study of triple negative breast cancer

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ABSTRACT

Background: Worldwide breast cancer is the most frequently diagnosed life threatening cancer in women and a leading cause of cancer death among women. In Kerala, India around 30% of cancer-affected women have carcinoma breast. Breast carcinomas which do not express estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER-2/neu) receptors are known as triple negative breast carcinomas (TNBC). They are extremely aggressive with poor prognosis. Here the authors described the clinical pathological and epidemiological characters of triple negative breast carcinomas in a tertiary care hospital in Kerala, India and compare with non-TNBC.
Methods: It was a cross sectional comparative study. Clinical, pathological and epidemiological characteristics of 75 cases of TNBC were compared with that of 225 cases of non-TNBC presented in Department of General Surgery, Government medical college, Kozhikode, Kerala, India between a period from March 2014 to October 2015 (20 months). Patients were recruited after obtaining an informed consent. ER, PR, HER-2/neu status were determined by immunohistochemical staining. Data obtained were statistically analyzed using SPSS software.
Results: Triple negative breast carcinoma was significantly associated with a younger age (mean age 43.67 years), early age of menarche. Commonly seen in premenopausal age group (78.7%). Patients with the triple-negative carcinoma had relatively large tumors (mean size 4.45cm compared to 3.14cm) and a high rate of node positivity (86.67%). More advanced stage at diagnosis with high grade tumor characteristics. Most common histopathology was invasive ductal carcinoma (98.7%) but no statistical difference was noted with non-TNBC.
Conclusions: No significant difference was noted between TNBC and non TNBC on comparing family history, parity, age at 1st child birth, OCP use. The outcome of the disease following treatment was unable to study due to short time frame of the study.

Keywords: Triple Negative Breast Cancer; TNBC; non-TNBC; lymph node status in TNBC; epidemiology of TNBC

INTRODUCTION

Worldwide, breast cancer is the most frequently diagnosed life-threatening cancer in women and the leading cause of cancer death among women. There is an ever increasing incidence of breast cancer in developing countries for which no definitive cause is found. In India Ca breast is the second commonest cancer and in Kerala around 30% of cancer-affected women have Ca breast.

Over the past decade, our understanding and treatment of breast cancer has undergone a metamorphosis, shifting from a generally homogeneous approach to a more sophisticated view as guided by gene expression analysis. In the year 2000, Perou et al published a novel classification based on gene-expression analysis that considered four breast cancer subtypes: Luminal, HER2-positive, normal breast, and basal-like.[1] Within these groups, basal-like cancer emerged as a unique subtype

because of its absence of expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, also showing the worst outcome and having no known therapeutic target. Despite triple-negative breast cancer (TNBC) is universally used as a surrogate marker, triple negative and basal-like are not equivalent terms.

Breast carcinomas which do not express oestrogen (ER), progesterone (PR), and Human Epidermal growth factor Receptor 2 (HER-2/neu) receptors are known as triple negative breast carcinomas (TNBC). They have been found to be aggressive with poor prognosis.[2,3] There is paucity of data on TNBC from the state of Kerala, India. The objectives were to study the clinicopathological and epidemiological characteristics of our patients with TNBC and to compare with non-TNBC.

METHODS

The study conducted was a cross sectional comparative study among the patients undergoing surgery for carcinoma breast in the Department of General Surgery, Government Medical college, Kozhikode, Kerala, India. The study was conducted for a period of 20 months, between March 2014 and October 2015. A total of 300 patients were included in the study of which 75 cases of TNBC were compared with 225 cases of non-TNBC.

Inclusion criteria

All female patients with carcinoma breast who underwent primary surgery (modified radical mastectomy or breast conservation surgery) and those who underwent surgery after neoadjuvant chemotherapy.

Exclusion criteria

- Male patients with carcinoma breast
- Patients with inoperable carcinoma breast
- Patients with metastasis to breast

Patients were recruited after obtaining an informed consent in local dialect. All necessary relevant details were collected by direct clinical examination, contacting patients over telephone, inpatient case sheets, operation registers maintained in respective surgery units and histopathology and IHC registers maintained in the Department of Pathology in our institution.

The presence of ER, PR and HER2/neu receptors were determined by immunohistochemical staining from Pathology department in our college. For this study, triple negative breast cancers (TNBC) were defined as those that were ER negative, PR negative, and HER-2 neu negative. "Other"/non-TNBC were defined as those that were positive for any of these IHC markers. Epidemiological, clinical and pathological parameters were compared between these two groups. The obtained data were statistically analyzed using SPSS software and arrived at the results.

RESULTS

75 cases of TNBC were compared with 225 cases of non-TNBC. The mean age at diagnosis of TNBC patients were significantly lower than non-TNBC group (43.67 years vs. 55.74 years, p=0.000). The mean age of menarche in TNBC patients were significantly lower than of non-TNBC patients (13.44 years vs. 14.24 years, p=0.000) (Table 1). 78.7% cases of triple negative group were premenopausal whereas only 16.9% cases of non-TNBC were pre-menopausal (Figure 1). The results were statistically significant (p=0.000).

Table 1: Demographic and clinical characteristics.

Characteristics		TNBC	Non-TNBC	P-value
Mean age		43.67	55.74	0.000
Mean age at menarche		13.44	14.24	0.000
Age at 1st pregnancy		19.71	19.01	0.434
Mean parity		2.43	2.71	0.179
Mean size of lump (cm)		4.45	3.14	0.000
Family history of Ca breast (%)		5.3%	7.6%	0.514
OCP use (%)		9.3%	4.4%	0.113
Breast feeding >6 months (%)		81.3%	86.2%	0.304
Choice of surgery	MRM	96%	92.9%	0.338
	BCS	4%	7.1%	

No significant difference was noted between TNBC and Non-TNBC group for a positive family history of breast cancer (5.3% vs. 7.6%, p=0.514), history of oral contraceptive use (9.3% vs. 4.4%, p=0.113), history of breast feeding for more than 6 months (81.3% vs. 86.2%, p=0.304). Mean age at 1st child birth and mean parity also had no significant difference between the two groups (Table 1).

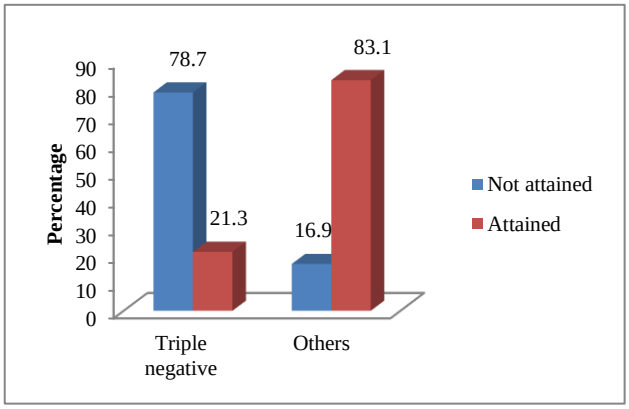

Figure 1: Menstrual distribution- menopause

The mean size of the lump at the time of diagnosis of TNBC cases were significantly larger than non-TNBC (4.45cm vs. 3.14cm, p=0.000) (Table 1). Lymph node involvement was noted in 86.67% of cases of triple

negative carcinoma of which 81.3% had N1 node and 5.3% had N2 node status (Figure 2).

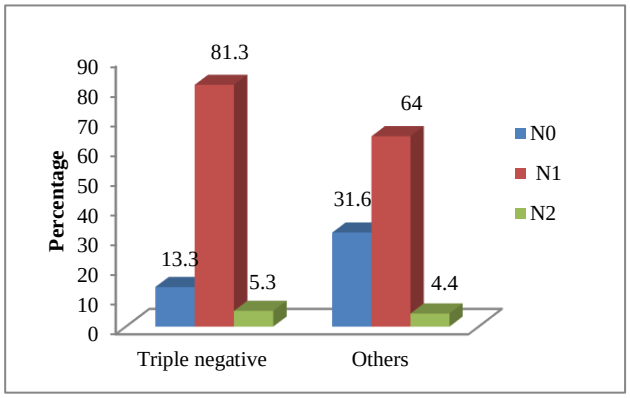

Figure 2: Lymph node status.

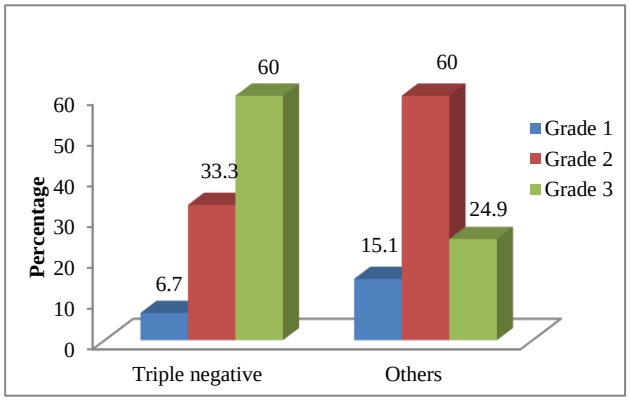

Figure 3: Grade of the tumour.

In other group 68.44% of cases had lymph node involvement of which 64% had N1 node status and 4.4% had N2 node status (p=0.009). Infiltrating duct carcinoma (IDC) was the histopathological report in 98.7% cases of TNBC and 95.6% of non-TNBC. Patients with TNBC had a significantly higher proportion of high-grade tumors as compared to the non-TNBC group (Figure 3) (60% grade 3 vs. 24.9% grade 3, p=0.000). 45.3% cases of TNBC had stage 3a disease where as 49.3% of non-TNBC had stage 2b disease, p=0.001(Figure 4).

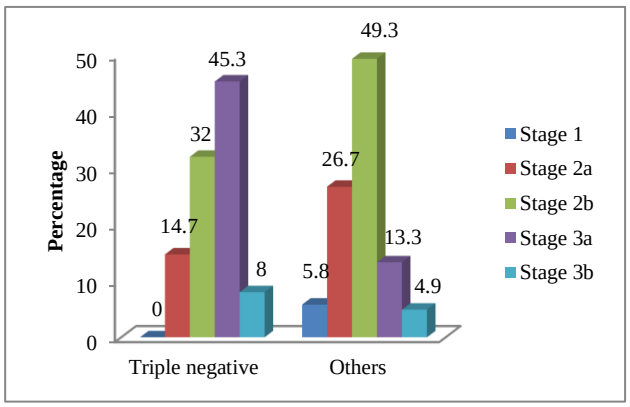

Figure 4: Stage of the disease.

DISCUSSION

The mean age at diagnosis was significantly younger in TNBC patients (43.67 years) as compared to non-TNBC group (55.74 years) (P=0.000). Similar results were seen in a study conducted by Bauer et al with mean age of 54years in TNBC compared to 60 years in non TNBC.[2] Dent et al in her study noted mean age of 53.0 versus 57.7 years respectively in TNBC and non TNBC which was also comparable with this study.[3] Similarly, Krishnamurthy et al, Rao et al also reported that mean age of diagnosis of TNBC was significantly younger compared to non TNBC.[4,5] The mean age at menarche in TNBC group was 13.44 years and in other group was 14.24years and the difference was statistically significant. In a pooled analysis of 34 studies from breast cancer association consortium, Yang et al concluded that there was no statistically significant difference in the age of menarche between TNBC and other breast cancers, which was against the observations in present study.[6]

Majority of cases of TNBC were premenopausal (78.7%) compared to non-TNBC cases in present study. This statistically significant observation was consistent with studies by Carey LA et al (Carolina breast cancer study).[7] A positive family history of breast cancer was noted in 5.3% cases of triple negative and 7.6% cases of other group in the current study which was not statistically significant. In the meta analysis by Yang et al a positive family history increased the risk for all the subtypes of breast cancer, though possibly somewhat more for basal like tumors (identified by gene expression analysis).[6] But this difference was absent when the tumor subtypes were defined only by immunohistochemistry. No statistically significant difference was observed in OCP use between TNBC and non-TNBC in our study. Kwan et al observed that 72% cases of TNBC in his study had history of OCP use.[8] 55% of cases of TNBC had used OCP in Phipps et al study.[9] Population based study by Dolle JM et al observed that OCP use was associated with a 3.1-fold increased risk of triple-negative breast cancer and not related to risk of non-triple-negative breast cancer.[10] No statistically significant difference was noted between TNBC and non TNBC in the mean age of 1st pregnancy (19.71years and 19.01years respectively) and parity (2.43 and 2.71 respectively) in the study. Yang et al suggested that nulliparity and increasing age at first birth do not increase risk for triple-negative tumors.[6] Millikan et al reported that parity and early age at first full-term birth were not protective for TNBC and suggested that these factors may actually increase the risk for TNBC.[11] 18.7% cases of TNBC and 13.8% cases of non TNBC had short duration of breast feeding. But the observations were statistically not significant. Elevated risk of TNBC with short duration of breast feeding was demonstrated in studies of Millikan et al and Ma et al.[11,12] Patients in the triple negative group had relatively large tumors (4.45cm compared to 3.14cm) and the difference was statistically significant. This observation was consistent with the findings in the studies of Dent et al and Bauer et al.[2,3]

Lymph node involvement was more in TNBC group (86.67%) as compared to non TNBC group (68.44%) which was statistically significant. Results of the present study was consistent with Studies by Dent et al, and Li et al which also showed a higher propensity for Lymph node involvement in TNBC in 54.4% and 71.3% patients respectively.[3,13] Tumor grade was found to be significantly higher in TNBC, with majority having grade 3 tumor compared to the non-TNBC, similar observations were noted by Dent et al, Bauer et al, Gogia et al and Carey et al.[2,3,7,16] Stage 3a was the commonest stage at presentation in TNBC comprising 45.3% of cases followed by stage 2b, 32%. Whereas only 13.3% cases of non-TNBC group had stage 3a disease and the observation was statistically significant. This means that triple negative cancer was diagnosed at a higher stage compared to non TNBC revealing the aggressiveness of the TNBC. In a Japanese study by Ishikawa et al 86.5% of cases of TNBC had stage 1 and 2 while only 10.3% had stage 3 disease.[14] Infiltrating duct carcinoma (IDC) was the histopathology of 98.7% cases of TNBC and 95.6% of non-TNBC group. This finding was consistent with studies by Livasy et al, Ishikawa et al, Carey et al.[7,14,15] 86.7% of cases with TNBC underwent primary surgery compared to 89.8% with non-TNBC. 96% cases with TNBC underwent modified radical mastectomy (MRM) and 4% underwent breast conservation surgery (BCS) compared to 92.9% and 7.1% of MRM and BCS respectively in cases with non-TNBC. These observations were not statistically significant. Despite the fact that TNBC tends to be more aggressive, surgical decision making likely rests on more traditional clinicopathological variables and patient preference.[17] Studies also showed that the type of surgery, either breast-conserving or total mastectomy, had no significant impact on the rate of locoregional recurrence.[18] In present study the outcome of the disease following treatment were not assessed due to the short time frame of the study.

CONCLUSION

Triple negative breast carcinoma is significantly associated with younger age, early age of menarche. Commonly seen in premenopausal age group. Patients with the triple negative breast carcinoma will have relatively large tumors and a high rate of node positivity and more advanced stage at diagnosis with high grade tumor characteristics. No significant difference was noted in the influence of a positive family history, oral contraceptive use, parity or age of 1st child birth between TNBC and non-TNBC. There were some limitations in our study. We included only the patients who had all the three receptors available. Triple negative breast cancer represents a unique subgroup, with a specific molecular profile, an aggressive behavior pattern, a relative lack of effective therapies and a poor prognosis. More studies around the world are on the way to tackle this unique and aggressive disease.

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