RESEARCH ARTICLE

# Triple Negative Breast Cancer in People of North East India: Critical Insights Gained at a Regional Cancer Centre

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## Abstract

**Background: Breast cancer is a heterogeneous disease comprising of distinct biological subtypes with many targeted prognostic biomarkers having therapeutic implications. However, no specific targeted therapy for triple negative breast cancer has been discovered to date and hence further research is needed. Aim: The aim and objectives of the present study were to examine the prevalence of triple negative breast cancer (TNBC) in North-East India and to compare the clinicopathological parameters in two study groups defined by immunohistochemistry (IHC) –"TNBC" and "Others". Materials and Methods: We carried out a retrospective study in a cohort of 972 patients diagnosed with invasive breast carcinoma in the Department of Pathology, Dr. B. Borooah Cancer Institute, a Regional Cancer Centre for treatment and research, Guwahati, for a period of 3 years and 10 months from January 2010 to October 2013. Based on IHC findings, patients were divided into two groups - "TNBC" and "Others". All relevant clinicopathological parameters were compared in both. TNBC were defined as those that were estrogen receptor (ER), progesterone receptor (PR), and HER2/neu negative while those positive for any of these markers were defined as "Others". Results: In this study, out of total 972 cases 31.9% (310 cases) were defined as TNBC and 662 cases (68.1%) as "Others" based on IHC markers. Compared to the "Others" category, TNBC presented at an early age (mean 40 years), were associated with high grade large tumours and high rate of node positivity, IDC NOS being the most common histological subtype in TNBC. Conclusions: TNBC accounts for a significant portion of breast cancers in this part of India and commonly present at younger age and tend to be large high grade tumours.**

**Keywords:** Triple negative breast cancer - breast cancer - immunohistochemistry - node positivity

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## Introduction

Breast cancer is by far the most frequent non-skin cancer among women worldwide with an estimated 1.68 million new cases (11.9% of all non-skin cancers in both sexes and 23% of all cancers in women). Since the 2008 estimates, breast cancer incidence has increased by more than 20%, while mortality has increased by 14%. Breast cancer is also the most common cause of cancer death among women (522,000 deaths in 2012) and the most frequently diagnosed cancer among women in 140 of 184 countries worldwide. It now represents one in four of all cancers in women. In India, for decades together, cervical cancer was the most common cancer in women, but now breast cancer is the most common cancer in women accounting for 144,937 newly detected cases (Ferlay et al., 2013). As per population based cancer registry data, Bangalore ranks the topmost position in India (age adjusted incidence rate or AAR per 100,000 population being 36.6%) and in North-East region, Aizawl recorded maximum number of cases (30.3% in India) and Kamrup Urban district recording 22.8% (National Cancer Registry Programme, 2009-2011).

Breast cancer is a heterogeneous disease comprising of distinct biological subtypes with diverse natural history, presenting with varied spectrum of clinical, pathological and molecular features with different prognostic and therapeutic implications. Increasing burden of breast cancer has led to enormous change in the treatment strategies due to discovery of specific prognostic and predictive biomarkers that enable the application of more individualized targeted therapies following hormone receptor testing (Quiet et al., 1995). Therefore hormone receptor analysis has been accepted as a standard established procedure in the routine management of patient with breast cancer.

Estrogen receptor (ER) positivity predicts response to endocrine therapy such as antiestrogen (tamoxifen) and Trastuzumab therapy (Herceptin) for tumor with HER2/neu overexpression (Huang et al., 2005). Based on these three molecular markers (ER, PR and HER2/neu) and cytokeratin subtypes (CK 5&6, EGFR), recent

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gene expression profiling studies have provided newer insight into the classification of breast cancer into two ER positive (Luminal A & Luminal B) subtypes and three ER negative subtypes(HER2/neu expressing, Basal like tumor & Unclassified). Tumour that were negative for all 5 markers were considered unclassified (Sorlie et al., 2003; 2006; Perou et al., 2000).

Basal like phenotype is of major concern nowadays. It accounts for 15% of breast cancer cases. Most of these are ER, PR and HER2/neu negative (approx. 75%), also referred to as Triple negative breast cancer.TNBC has once been used interchangeably with Basal like carcinoma because they share similar characteristics . However they do not belong to the same entity (Ma et al., 2012). They are associated with aggressive histology, poor clinical outcome, associated with BRCA1 mutation, unresponsive to usual endocrine therapies and shorter survival (Perou et al., 2000; Sorlie et al., 2003; Sotriou et al., 2003). It lacks any specific targeted therapy at any at the current time. Combined chemotherapy is the present treatment modality (Hudis and Gianni, 2011).The emergence of novel agents (poly-ADP-ribose – polymerase-1 inhibitor) may improve the prognosis of TNBC but it is still at very preliminary stage of research (Ma et al., 2012). (So search for more predictive biomarkers for TNBC is the primary aim and goal of breast cancer research (Luo et al., 2010).

Many studies from different parts of the country had appeared featuring the receptor in breast with particular emphasis on Basal-like/triple negative phenotype. This encouraged us to carry out this study with the objective of: *i*) To study the prevalence of TNBC in people of North-East India as a surrogate marker for Basal –like phenotype; *ii*) To compare the clinico-pathological variables among the two study group- "TNBC" and "Others".

## Materials and Methods

We carried out a retrospective study of 3 years and 10 months duration from January 2010 to October 2013 at Dr. B. Borooah Cancer Institute, a regional cancer centre for treatment and research, Guwahati Study population: All women attending Dr. B. Borooah Cancer Institute from different parts of North-East India and diagnosed with invasive Breast cancer (on core biopsy or lumpectomy, BCS and mastectomy) comprised the primary study population. All these cases were subjected for immunohistochemistry (ER, PR and HER2/neu). Relevant clinical and pathological information (including date of diagnosis, age, tumour size, histological subtype, grade, nodal status) were recorded.

*Immunohistochemistry*

All the cases were subjected to immunohistochemistry for ER, PR and HER2/ neu expression on formalin fixed, paraffin embedded tissue sections by using ready to use monoclonal antibody and HRP polymer detection system with 3'-3' diaminobenzidine hydrochloride (DAB) as the chromogen. Positive control was included in each case using endometrium or adjoining normal breast tissue.

In all the cases, both H&E and IHC slides were reviewed using light microscopy and the percentage and intensity of nuclear immunostaining was semi-quantitatively assessed.

*Assessment of ER and PR*

ER or PR was considered positive if >1% tumor cell nuclei are immunoreactive and negative if finding of <1% tumour cell nuclei are immunoreactive (Hammond et al., 2010).

*Assessment of HER2/neu*

HER2/neu immunohistochemical staining was scored from 0 to 3+ using FDA approved Hercept test guideline into the following categories (Wolff et al., 2007): 0- No immunostaining; 1- Weak incomplete membranous staining in any proportion of tumour cells; 2- Compete membranous staining , either non-uniform or weak in at least 10% of tumour cells; 3- Uniform intense membranous staining in 30% of tumour cells (0 &1+ is negative, 2+ is equivocal or borderline and 3+ is considered as positive).

Based on the IHC findings, all cases were divided into two categories- "Triple negative breast cancer (TNBC)" and "Others". "TNBC" defined as those were ER, PR and HER2/neu negative. 'Others" was defined as those that were positive for any of these markers. All the clinicopathological prognostic parameters were compared in both groups. In this study, cases which were ER, PR negative and HER2/neu equivocal (borderline) were excluded as data on further confirmation of HER2/neu status by FISH was not available in all the cases. This study is in compliant with requirement of local research ethical committee.

## Results

In the present study, final analysis included 972 cases of invasive breast cancer subjects identified in Dr. B. Borooah Cancer Institute from January 2010 to October 2013. Out of these 972 cases, 310 (31.9%) cases were defined as having "TNBC" and remaining 662 (68.1%) cases as "Others". The clinicopathological parameters in both the categories are compared and displayed in Figure 1.

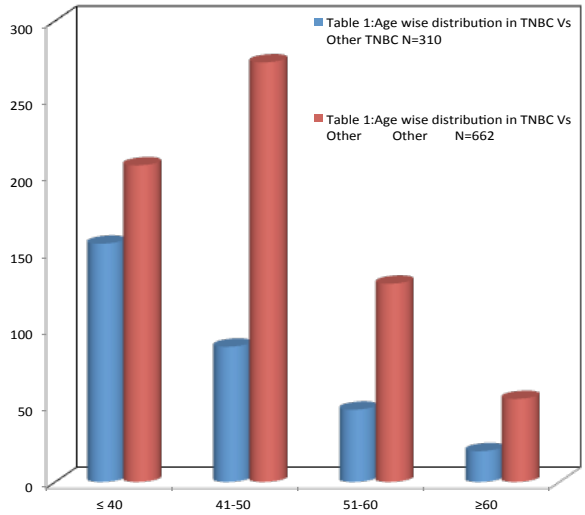


**Figure 1. Age wise Distribution of Patients in TNBC vs "Others" (n=972)**

In our study, age of all patients were in the range from 20 to 78 years and maximum number of patients belonged to ≤40 years of age group in "TNBC" and 41-50 years age group in "Others" group (Table 1). Mean age at diagnosis being significantly younger in TNBC compared to "Others" group (40 vs 49 yrs).

Patients with TNBC presented with larger sized tumor compared to "Others" group (mean tumor size - 5.2 cm vs 3.4 cm), more likely to be associated with positive lymph nodal status compared to "Others" group (55.8% vs 51%). Comparing histological subtypes (Figure 2), most of the patients with TNBC were diagnosed to have Invasive duct carcinoma, NOS subtype (95.8%) followed by Medullary carcinoma (3.2%). In "Others" group, also most of the patients had IDC, NOS subtype (96%) followed by invasive lobular carcinoma (1.5%). All cases of lobular carcinoma were ER, PR positive and HER2/neu negative.

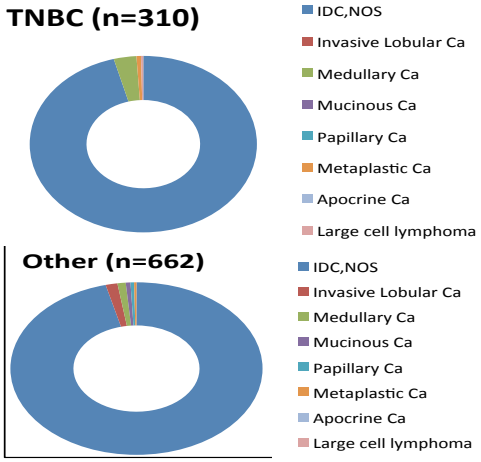


**Figure 2. Graphical Representations Showing Comparison of Histological subtypes in TNBC vs Other**

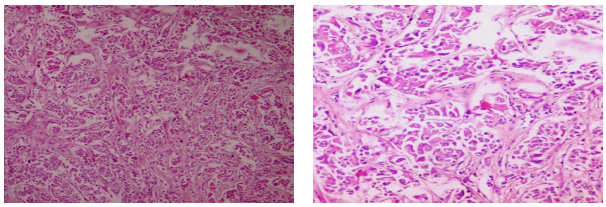

**Figure 3. Infiltrating Duct Carcinoma- NOS (H&E) A) 100x and B) 400x**

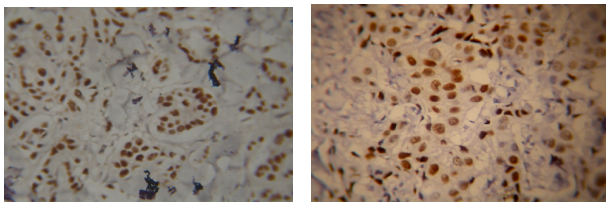

**Figure 4. Immunohistochemical Staining Showing A) ER Positivity and B) PR Positivity in a Case of IDC-NOS, Non TNBC (DAB, 400x)**

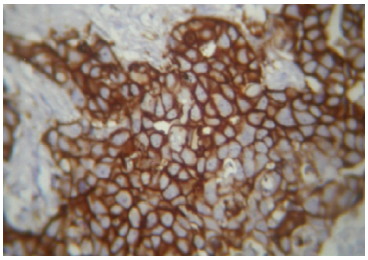

**Figure 5. HER2/neu Expression (3+ score) in a Case of IDC-NOS (400x)**

**Table 1. Comparison of Tumour Size by Nodal Status in "TNBC" vs "Others"**

| Tumor Size | Lymph Nodal Status | | | | | |
|---|---|---|---|---|---|---|
| | TNBC | | | Others | | |
| | Total | Node | | Total | Node | |
| | | ve+ | ve- | | ve+ | ve- |
| <2 cm | 62 (20%) | 21 | 41 | 248 (37.5%) | 50 | 198 |
| 2-5 cm | 134 (43.2%) | 82 | 52 | 260 (39.5%) | 185 | 75 |
| >5 cm | 98 (31.6%) | 70 | 28 | 134 (20.2%) | 103 | 31 |
| Missing | 16 | | 20 | | | |

**Table 2. Comparison of Characteristics in "TNBC" vs "Others"**

| Variables | | TNBC 310 (31.9%) | Others 662 (68.1%) |
|---|---|---|---|
| Mean age at Diagnosis (yrs) | | 40 | 49 |
| Mean Tumor Size (cm) | | 5.2 cm | 3.4 cm |
| | <2 | 62 (20%) | 248 (37.5%) |
| | 2-5 | 134 (43.2%) | 260 (39.3%) |
| | >5 | 98 (31.6%) | 134 (20.2%) |
| Tumor grade (IDC, NOS 297) | I | 12 (04%) | 37 (5.8%) |
| | II | 84 (28.3%) | 218 (34.4%) |
| | III | 201 (67.7%) | 380 (59.8%) |
| Other histological types | | 13 | 28 |
| Lymph nodal status | Positive | 173 (55.8%) | 338 (51%) |
| | Negative | 121 (39%) | 304 (45.9%) |
| | Missing | 16 | 20 |
| ER Level | Positive | 0 384 | (58%) |
| | Negative | 310 278 | (42%) |
| PR Level | Positive | 0 324 | (49%) |
| | Negative | 310 338 | (51%) |
| HER 2/ NEU | Positive | 0 215 | (32.5%) |
| | Negative | 310 184 | (27.7%) |
| Borderline (equivocal) | | 0 263 | (39.7%) |

**Table 3. Comparison of Prevalance of TNBC in Different Studies**

| Study | No. of Cases | Prevalance of TNBC |
|---|---|---|
| Dunwald et al ,2007,USA | 155,175 | 25% |
| Bauer et al , 2007 ,California | 92,358 | 12.50% |
| Rakha et al UK , 2007 | 1,726 | 16.30% |
| Adedayo et al USA,2009 | 1134 | 13.40% |
| Ghosh et al , India 2011 | 2001 | 29.80% |
| KK Ma et al, Hong Kong 2012 | 1800 | 12% |
| Chun-Yan Li et al, China 2013 | 21749 | 12.18% |
| Isil Somali et al, Turkey 2013 | 882 | 15% |
| Syeda Jubeda et al, India 2013 | 619 | 46% |
| Present study | 972 | 31.90% |

Both study groups were found to have high histological grade (grade III), though percentage was higher in TNBC compared to "Others" group (67.7% vs 59.8%). In "Others" group, 58% were ER positive, 48.9% PR positive and 32.5% were HER2/ neu positive.

## Discussion

With the increasing burden of Breast cancer, it has become the leading cause of concern and major field of research worldwide. With advancement in science and

technology, new molecular methods are giving insight into biology of breast cancer and opening avenues for developing therapeutic strategies and predict the outcome (Cummings et al., 2011). Present study was carried out to analyse the prevalence of Triple negative phenotype in people of North-East India as a surrogate marker of Basal like cancer.

Basal like cancer accounts for 15% of all breast carcinoma, 75% being triple negative. Studies have shown that this phenotype is more common in young African women facing worse prognosis compared to other ethnic group (Reynolds and Sharon, 2007; Chutstecka, 2008). In 2009, a case control study showed 2.5 fold increased risk for Oral Contraceptive Pill (OCP) users using for more than one year than women using for less than a year or never (Dolle et al., 2009). This phenotype show significantly higher FDG uptake compared to ER, PR positive and HER2/NEU negative, probably related to aggressive biology of the tumor (Basu et al., 2008).

At the current time, TNBC lack any specific targeted therapy. Combined chemotherapy is the standard treatment like anthracycline, taxanes, ixabepitine and platinum agents. Combination of imiparib and Gemcitabine provides significant clinical benefit. BRCA1 related TNBC appears to be particularly susceptible to chemotherapy involving Platinum based agents and Taxanes (Hudis and Gianni, 2011).

Present study was carried out based on IHC confirmation of all cases of invasive breast carcinoma without the help of microarray.

Our study comprised of 972 cases of invasive breast carcinoma and TNBC constituted 31.9% (310 cases) of total cases which shows a good burden of TN phenotype in this part of India (North-East) compared to other studies published from different parts of world, as presented in Table 3 (Ma et al., 2012; Li et al., 2013; Somali et al., 2013; Routa et al., 2013; Zubeda et al., 2013).

Studies have shown that TNBC vary markedly with ethnicity and have documented higher incidence in young African women compared to White women accounting for approximately 47% vs 22% in Whites (Lund et al., 2009). In the present study, patients with TNBC were significantly younger compared to "Others" group (40 vs 49 years). This observation was concordant with many other studies (Tischkowitz et al., 2007; Cheang et al., 2008; Iwase et al., 2010; Li et al., 2013). However few studies have shown higher incidence of TNBC in postmenopausal women (Bauer et al., 2007; Iwase et al., 2010; Ambroise et al., 2011). In one published study in Turkey,no significant difference in age was found in both two groups (Ma et al., 2012). According to the literature patients with TNBC present with relatively larger size compared to other group (Bauer et al., 2007; Li et al., 2013; Somali et al., 2013). Consistent with these data,in the present study TNBC patients had larger tumor size compared to Other group , mean tumour size being 5.2 vs 3.4 cm .There are conflicting reports in literature regarding lymph node status in TNBC. While some publication report a higher rate of node positivity (Bauer et al., 2008; Li et al., 2013) some reports node negativity more common in TNBC (Foulkes et al., 2003; Cheang et al., 2008; Somali et al., 2013). In our study a high rate of node positivity was found in TNBC compared to Other group (55.8 vs 51%). Comparing the histological subtypes, IDC NOS comprised maximum number of cases in both the study groups (95.8 vs 96%) followed by Medullary ca (3.2%) and rare subtypes like Metaplastic carcinoma(0.7%) and Large cell lymphoma (0.3%) in TNBC but in "Others" group next to IDCNOS , Invasive lobular ca (1.5%) predominated . Similar results were observed in other studies (Beatty et al 2006; Carey et al., 2006; Filho et al., 2006; Livsay et al., 2006; Somali et al., 2013).

In our study, patients with TNBC mostly diagnosed to have grade III tumor with a percentage higher than the "Others" study group (64.8 vs 59%). Other studies also documented similar results (Carey et al., 2006; Bauer et al., 2007; Ma et al., 2012; Li et al., 2013; Somali et al., 2013). Among total 662 cases of Other study group, ER accounted for 58%, PR 48.9% and HER2/neu 32.5%. These findings were nearly similar to previous study carried out by Ambroise et al. (2011) in India. In previous studies, ER expression were found to account for approximately 70 % in IDC, 70-95% in ILC (Gown et al., 2008), PR expression in 60-70% (Zafrani et al., 2000) and HER2/neu in 10-34% (Ross et al., 2003).

In the present study result of our analysis shows that Triple negative phenotype is prevalent in a large proportion of patients in people of North East India accounting for 31.9% of total breast cancer patients and compared to the "Others" category, they present at an early age (mean 40 years) , associated with high grade large tumour with high rate of node positivity.

In conclusion, despite many limitations in the present study, our study is of value because it includes sufficiently adequate number of breast cancer cases and highlights the importance of Triple negative phenotype as a surrogate marker for Basal like breast ca in this part of India. Furthermore, it emphasizes the role of different clinicopathological factors as important risk factors. However, our findings underscore the need for further research in this field which could lead to identification of new molecular biomarkers and help to develop appropriate Targeted therapy for triple negative breast cancer.

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