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REVIEW ARTICLE

Breast cancer of Northeastern India: a critical review on early onset disease and TNBC subtype

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ABSTRACT

Breast cancer is now the most common malignancy in the world, surpassing lung cancer with an estimated 2.3 million new cases every year. It has emerged as a leading cause of cancer incidence and mortality in India, accounting for 13.5% of new cancer cases and 10.6% of all cancer deaths in 2020. Northeast India is the cancer hub of India. Yet paradoxically, breast cancer burden is much lower in this region than the rest of India. Despite this, breast cancer mortality remains high with lower survival rates, mostly due to more aggressive variants, poor health care accessibility and lack of advanced facilities. Breast cancer molecular subtypes defined on the basis of differential expression of cell surface receptors include Luminal A type, Luminal B type, Her2 positive, and triple negative subtype, each having prognostic and therapeutic implications. Studies into molecular subtypes reveal increased proportion of the triple negative subtype and higher mortality rates due to the disease as well as early onset of disease with a median age at diagnosis of 47 years. Breast cancer awareness remains low in this population. Apart from the usually implicated lifestyle factors, betel quid chewing is a risk factor for breast cancer in this region. Intra- regional differences in the study variables amongst the north eastern states reflect the cultural and genetic heterogeneity of the people of the north-eastern states. There is a need for increased awareness of breast cancer, improved screening and better diagnostics and healthcare to decrease breast cancer deaths in this region.

Keyword: breast cancer, Northeast India, triple negative breast cancer, survival.

Introduction

Breast cancer is now the most common malignancy in the world, surpassing lung cancer with an estimated 2.3 million new cases every year (11.7% of all cancer cases)[1]. Breast cancer was the leading cause of cancer incidence and mortality in India, accounting for 13.5% of new cancer cases and 10.6% of all cancer deaths in 2020[2]. India being a country of cultural, demographic and economic heterogeneity, each state has its own population characteristics which reflect on the difference in cancer burden and disease characteristics in different parts of the country. An epidemiological study on breast cancer in the country is complicated by factors like difference in genetic makeup and ethnicity, cultural practices, economic development and health care facilities and health seeking behaviour of the study population. It is of particular importance since the incidence, mortality, and mortality-to-incidence ratio (MIR) of breast cancer are closely related to the geographical indicators of development[3].

The highly aggressive triple-negative type of breast cancer (TNBC) ranges from 6.7% to 27.9% in different countries, with India reporting a high percentage of cases[4,5]. The TNBC subtype in the Indian population is associated with additional risk factors, such as early onset of disease, lifestyle, obesity, substance abuse, family history of breast cancer, a high mitotic index, and BRCA1/2 mutations[6].

North-east India has emerged as a cancer hub of India with probability of developing cancer over a lifetime as high as 1 in every 4 males and 1 in every 6 females in Kamrup Urban of Assam as reported by ICMR-NCDIR[7]. Interestingly however many north-eastern states had a lower burden of breast cancer as compared to other states of India, with Meghalaya having the lowest burden (142.4 DALYs per 100,000 women)[8]. Yet breast cancer remains an important cause of mortality in this population. The northeast region lacks required infrastructure for specialized treatment facilities, human resources, and therefore has a low 5-year survival of cancer breast along with cancer cervix, head and neck cancer as compared to rest of India. This region, particularly Assam, has shown a higher incidence of early onset disease[9]. Triple negative breast cancer was also found in a higher proportion of population in North east India[10]. This article discusses the biological variants of breast cancer with special emphasis on TNBC and also highlights the breast cancer patterns in North east India with a critical review of existing research on breast cancer in this population.

Breast cancer molecular subtypes

Breast cancer molecular subtypes are defined on the basis of differential expression of cell surface receptors. Tumours may be positive for ER, PR or HER-2 or negative for all three markers (the triple negative group). Common intrinsic molecular subtypes of breast cancer include Luminal A type, Luminal B type, Her2 overexpressing, and basal like subtype which are further stratified into special subtypes. Hierarchical cluster analysis of the genes that vary more between tumours than between repeated samples of the same tumour (i.e. intrinsic genes) has revealed the existence of four major breast cancer intrinsic subtypes (luminal A, luminal B, HER2-enriched, and basal-like), as well as a normal breast-like group and rare subtypes, such as the claudin low type. In order to improve the standardization and reproducibility of the intrinsic subtype classification, a quantitative BT-PCFL based test with a curated list of 50 genes (the PAM50 gene signature) was proposed. These genes were selected to classify Invasive breast cancers (IBC) into luminal A, luminal B, HER2-enriched, and basal-like subtype. But since transcriptomic analysis is costly and not feasible for many, a classification based on immunohistochemical biomarkers (ER, PR, HER 2 and Ki-67) was developed categorising breast cancer into 5 categories- Luminal A like, Luminal B like (HER 2 negative), Luminal B like (HER 2 positive), HER 2 positive (non-luminal) and Triple negative[11].

As Triple-negative breast cancer (TNBC) shows lack of expression of ER, PR, and HER 2 by immunohistochemistry, targeted therapeutic options are limited. Triple negative breast cancer tends to present in younger women, and has a higher mortality rate of 40% in advanced stages within the first 5 years after diagnosis[12]. Prevalence of TNBC across different geographical regions is shown in **Table 1**. Approximately 45% of patients with advanced stage TNBC develop distant metastasis to the brain and/or visceral organs, with a median survival time of only 13.3 months[13]. These have led to an increased interest in this subtype with many studies dedicated to this aggressive type of breast cancer.

Table 1: Prevalence of TNBC across different geographical regions.

Region / Population	TNBC Prevalence (% of all breast cancers)	Reference (Study)
Global average (est.)	~ 15 - 25%	Almansour NM (2022) [44]
United States of America and Canada (pooled)	~ 11.2 - 13.4%	Dent et al. (2007) [12], Onitilo et al. (2009) [45]
Europe (pooled)	~ 15%	Thakur et al. (2018) [6]
Africa (pooled)	~ 20.8%	Thakur et al. (2018) [6]
South East Asia (pooled)	~ 6.7 – 27.9%	Thakur et al. (2018) [6]
India (pooled meta-analysis)	~ 27 - 31%	Kulkarni et al. (2020) [5], Sandhu et al. (2016) [4]
North East India (our study population)	~ 14 - 26.09%	Sharma et al. (2021) [36], Gogoi et al. (2016) [30], Hawaibam et al. (2023) [37]

In 2011, Lehmann et al. categorized TNBC into six subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR), by performing gene expression profiling of tumor samples from 587 TNBC patients[14,15]. Using gene expression data, a classification of TNBC into the following four tumour-specific subtypes has been developed: basal-like 1 and basal-like 2 (which differ in immune response), mesenchymal, and luminal AR each of which present distinct survival patterns and sensitivity to neoadjuvant chemotherapy[11].

Triple Negative Breast Cancer also has a greater hereditary predisposition. In the American Cancer Society study on newly diagnosed breast cancer, 10% of patients had breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) mutations, whereas 35% of patients with TNBC carried a BRCA1 mutation, and 8% carried a BRCA2 mutation, that is, a greater than one-third chance of developing TNBC in carriers of BRCA 1 mutation[16]. Therefore improved and rapid diagnosis of this subtype is essential as are proper treatment facilities to improve the mortality rate of this difficult to treat cancer. Regional variations in facilities of surgery and chemotherapy as is seen in many of the north eastern states of India would therefore have an impact on mortality rates from TNBC. Also, genetic variations are observed among the subtypes of TNBC which suggest individualized therapy rather than a generalized approach to the treatment of these cancers[17].

Breast cancer and Northeast India: the demographics of the disease

In northeastern India, breast cancer shows wide variation in incidence due to sociocultural, dietary, and racial factors which show a wide diversity[18,19,20]. This can be highlighted by the fact that while in the Aizawl district of Mizoram state, the AAR is 30.7, comprising 15.4% of all female cancers, neighbouring Tripura shows a low incidence of breast cancer at AAR of 7.9, accounting for 14.4% of female cancers[21]. Biswas et al. (2025) in their study on risk factors and protective factors for breast carcinoma in North east population found that that women in Aizawl reach menarche at the mean age of 14.45 years, whereas women in Agartala (Tripura) reach it at 13.03 years old ($p<0.001$).

The study reported that in Aizawl, a high prevalence of delayed marriages, late pregnancies, postmenopausal obesity and family history are potential risk factors for breast cancer in women, while an elevated mean age at menarche, high parity, and extended breastfeeding are protective factors. Conversely, in Agartala, early marriage, early first childbirth, high parity, prolonged breastfeeding, and healthy BMI are associated with low breast cancer risk in women[22]. A study by Vaiphei and Sisodia found that breast cancer was a major cause of terminal cancer deaths in Northeast and unhealthy lifestyle, alcohol intake and genetics appeared to play a role in this as also the lack of cancer awareness in the region which leads to cancer patients coming for treatment very late in the course of their illness[23].

Kulothungan et al. (2024) in their study on burden of breast cancer in India found that compared to the high occurrence of this malignancy in the northern and southern part of the country, the north-eastern region had the lowest breast cancer burden, with 287.8 DALYs (disability-adjusted life years) per 100,000 women (as compared to 685.5 and 677.6 DALYs per 100,000 women, in northern and southern India respectively). The state of Meghalaya had the lowest burden (142.4 DALYs per 100,000 women[8]. Most developed nations

have a higher burden of breast cancer than the developing world and this is perhaps a factor in the high prevalence of the disease in the more developed regions of the country as compared to the predominantly rural and less developed regions of north east India. This is because known risk factors like delayed first childbirth, lower parity, higher levels of obesity, a shorter duration of breastfeeding, and physical inactivity are linked to the socio-economic development of a region[24]. However a word of caution is required here as some contribution to the lower rates of breast cancer in the northeast could very well be due to the lower rate of diagnosis in these states where healthcare facilities are not as advanced and accessible as the developed cities of India.

Cancer survival also varied widely amongst the northeastern states. In a large population based cancer survival study covering 17331 female breast cancer cases diagnosed between 2012 and 2015 in India, wide heterogeneity in cancer survival was seen across the country, with a 33% disparity ranging from 41.9% in Pasighat (Arunachal Pradesh) to 74.9% in Mizoram. Diagnosis of breast cancer at a late stage is often seen in people living in rural and geographically inaccessible areas, poor people, those with low education, lack of awareness, and inadequate access to healthcare which affects the survival rates. The overall Health Index Score, that measures health outcomes and the performance of health systems, was the second highest in Mizoram state which may be attributed to the higher survival rate of patients with breast cancer in the region while lower survival rates were seen in Manipur, Tripura and Pasighat of Arunachal Pradesh[25]. Overall, the survival of breast cancer is lower in North east India as compared to the rest of India with 5 year survival of stage 2 breast cancer being 63.5% and stage 3 breast cancer being only 20.1%[26].

The median age at diagnosis of breast cancer in females in North east India was found to be less than the rest of India (Breast: 47 years in North east region and 54 years in rest of India). Comparison of age at diagnosis across different geographical regions is shown in **Table 2**. Projected number of incidence cases of breast cancer in Northeast for year 2020 and 2025 were 55 and 68 respectively for males and 3619, 4126 respectively for males. 58.2% of breast cancer cases were diagnosed at the stage of distant metastasis and 28.4% at localised stage. The female population of North east India had the highest probability of developing breast cancer (1 in every 76 females) as breast was the leading cancer site in females (14.5%) followed by cervical cancer[7].

Table 2: Age at diagnosis of TNBC across different geographical regions.

Region / Population	Average age at diagnosis (in years)	Reference (Study)
United States of America and Canada	53.0 – 61.0 years	Dent et al. (2007) [12], Bilani et al. (2020) [43]
Europe	50 – 60 years	Thakur et al. (2018) [6]
Africa	40 – 59 years	Thakur et al. (2018) [6]
South East Asia	53 years	Thakur et al. (2018) [6]
India (pooled meta-analysis)	43 – 55 years	Kulkarni et al. (2020) [5], Sandhu et al. (2016) [4]
North East India (our study population)	47 ± 2 years	Sharma et al. (2021) [36], Gogoi et al. (2016) [30], Hawaibam et al. (2023) [37]

A study on the Mizo Mongoloid population of North east found that ethnic dietary/ life style habits such as smoked food, local smokeless tobacco ('Khaini' and 'Tuibur'), life style diseases such as diabetes and hypertension, 1st and/ or 2nd degree relatives with breast cancer and various cancer types were found to contribute the risk of breast cancer among the Mizo tribal women of Mizoram, India[27].

In a study by Oswal et al. (2020) in the states of Assam, Meghalaya and Nagaland, it was observed that only half of the participants had heard about breast cancer. Of these, knowledge about a lump in the breast (47%) and discharge from the nipple (47%) and change in shape and size of the breast (46%) were identified as common warning signs for breast cancer among the female participants. Subjects stated that first child at a late age (43%) and high-fat diet (32%) were the most common risk factors for breast cancer[28].

A study in Manipur which evaluated the patient and disease profile of breast cancer patients presenting in 2002–2004 and 2015–2017 found that most common age group in 2002–2004 was 46–55 years

while the most common age group in 2015–2017 was 36–45 years. There was significant increase in proportion of patients giving a positive history of tobacco consumption in any form in 2015–2017 against 2002–2004. Proportion of overweight patients increased significantly over the decade ($P < 0.05$) while the proportion of women breast feeding their babies in 2015–2017 decreased as compared to 2002–2004. The mean age at first childbirth also increased in 2015-17[29]. These findings highlight the fact that over and above the ethnic and cultural factors affecting cancer incidence, the demographic characteristics of the population are in a state of continuous flux. Westernisation of the population has introduced many new risk factors for malignancy from which the indigenous populations were previously protected.

Various studies from North east India have shown an earlier age of onset of breast carcinoma in this population[30,31]. A study from Dibrugarh district of Assam showed a strong correlation between age at diagnosis and survival rates with younger patients (Below 45) showing a 95% 1-year and 89% 3-year survival rate, whereas middle or older patients (45 and above) had reduced survival rates (89% at 1 year and 45% at 3 years)[31]. Another study from Assam showed that most of the breast cancer patients (18.6%) belonged to the 38-43 age groups, were married women (94 %) and from rural area (66.2%). Maximum patients (63.8%) had children less than 2[32]. This early onset of cancer and the survival advantage in treated cases highlight the importance of breast cancer screening in this population.

A different study from the state of Assam established that betel quid chewing, with or without tobacco was a significant risk factor for breast cancer. This is important as the females of this state do not commonly smoke but are habituated to chewing betel nut and tobacco[33]. Another previous case control study on the impact of consumption of Betel Quid on environmental and genetic factors of the North east Indian population revealed that there was a significant rise in the risk of occurrence of breast cancer due to the same[34].

Breast cancer subtypes in the study population:

Morphologically, the most common type of breast cancer in north east India appeared to be Invasive breast carcinoma - NOS. A three year study from a tertiary care centre in northeast India showed that predominant histological type was infiltrating ductal carcinoma (95.8% cases) followed by infiltrating lobular carcinoma(3%) .55.38% were hormone receptor (HR) positive, 49% were positive for human epidermal growth factor receptor and 16.4% had triple-negative breast cancer. The most frequent sites of metastasis included bone (28.7%), lung (27%) and liver (17.4%), followed by non-regional lymph nodes (11.8%) and brain (5.6%)[35]. Another study reported infiltrating duct carcinoma to be the most common type and it was noted that in the age group ≤40 years which comprised 26.6% of cases, the most common molecular subtype was luminal B (31%) followed by triple negative (20%), luminal A (14%), and then HER 2 (5.3%), while in the age group above 40 yrs (73.4% cases) most common molecular subtype was luminal B (27.8%) followed by triple negative (14%), HER 2 (12.2%), and then luminal A (12%)[36]. In a study from Upper Assam, 82.11% of the cases were invasive duct carcinoma followed by invasive lobular carcinoma (8.13%) and other types were invasive papillary (3.25%), micropapillary (2.43%), mucinous carcinoma (1.62%), metaplastic type, adenoid cystic type and cribriform carcinoma type. Histologic Grade 3 tumours were 50.4%, Grade 2 were 41%, and Grade 1 was only 8.1%. Tumours showed ER+ in 40.62%, PR+ 35.77%, Her2/Neu+ 18.69%. The molecular subtypes were luminal A (19.51%), luminal B (21.13%), Her2/Neu overexpressed 22 (17.88%), and TNBC (38.21%).TNBC were further classified by CK 5/6, EGFR into basal type (53.19%) and non-basal type (46.80%). Luminal B was expressed in young women (41.1 years), whereas HER2/Neu over-expressed was found in middle age women, that is, 50.4 years. Younger age and TNBC types were showing strong statistical significance. This study too noted a significant percentage of cancer occurring at a younger age group with 63.4% women with breast cancer under 45 years, whereas women over 46 years was 37.6% only. The average age of TNBC type diagnosis was 35.77 years[30].

A study from the state of Manipur studying the changing trends of breast carcinoma also found infiltrating duct carcinoma NOS to be the most common type and grade III to be the most common grade of breast cancer. This study found

that while in 2002-2004, 58.81 % cases were ER, PR positive, 27.94% HER2 positive and 25% triple negative, in 2015-17, 43.32% were ER, PR positive, 38% HER2 positive and 39.33% triple negative[29]. Thus there was an increase in the number of HER2 positive and triple negative cases.

Another study from Manipur showed Invasive Ductal Carcinoma Not Otherwise Specified (IDC, NOS) (83.4%) as the most frequently diagnosed histological type. According to the Tumour, Lymph Node, Metastasis (TNM) staging system, 50.44%patients were diagnosed in stage II, 31.30% in stage III, 11.30% in stage I, 5.22%in stage IV and only 1.74% in stage 0. According to Modified Bloom Richardson histological grading, poorly (Grade III) and moderately differentiated (Grade II) tumours had a higher proportion when compared to well-differentiated (Grade I) tumours (86.95% vs. 13.04%). Luminal A (30.43%) and TNBC subtype (26.09%) were the two common molecular subtypes found followed by HER2 overexpressed and Luminal B types with 16.52% and 10.43%, respectively. TNBC molecular subtype was diagnosed in the majority of the patients of age below 48 years (29.62%), while Luminal A was largely predominant in older patients (37.7%). HER2 enriched subtype was the least common subtype observed in younger age groups (<48 years) (14.8%) while older age groups (≥48 years) showed Luminal B tumours to be the least diagnosed subtype (4.91%)[37].

A study from Mizoram also reported infiltrating duct carcinoma grade II as the most common type.ER, PR and HER 2/neu expression was found in 52%, 46% and 43% cases, respectively. Hormonal receptor positivity and HER2/neu overexpression was observed more in younger age group[38].

A study from Nagaland found Triple Negative Breast Cancer (TNBC) and Luminal A subtypes constituted 32.8% and 39.3% cases respectively. The study demonstrated comparatively good percentage of Luminal A, as compared to rest of North East region, but lower when compared to other states in India and very low compared to international studies[39].

Copy number analyses of 30 breast tumours from Northeast India using the SNP 10K array showed copy number gains on Chromosome 1q31, 1q41-42, 20q13, 20p11-12, 3q26-27, 6p22, 8q22-24 and 8q13 and high level amplifications on Chromosome 1q and 3q. Losses were observed less frequently than gains and the minimal common regions of the most frequent losses were 11q23-q24, 17p12-p13, 18q21, 13q12-q13, 13q21, 8p21- p22 and 9p21-p23[40].

Luminal breast cancers, which are estrogen receptor-positive (ER-positive) tumours, account for approximately 70% of all breast cancer cases in Western populations[41], whereas the HER2-enriched cancers account for 10–15% of breast cancers[42]. In the United States, TNBC represents 15 to 20% of all breast cancers[43]. An analysis of different studies from North east India revealed a higher incidence of triple negative cancers, most of which are seen in the younger age group. Invasive breast cancer (NOS) remains the most common type comparable to Indian and international statistics. While some studies reported luminal B as the most common type, others reported luminal A to be the commonest type. TNBC was a predominant category in most of the studies. These molecular variations may reflect the genetic and cultural heterogeneity of the states of this region and need further genetic and epidemiological studies.

Conclusion:

Northeast India, which is a major cancer hub of the country appears to have a somewhat lower incidence of breast cancer as compared to the rest of India. Whether this is an advantage conferred by the genetic makeup of the people, food and lifestyle habits, or some part of the low incidence is a result of failure to diagnose breast cancer due to lack of advanced health care facilities in many rural and out of reach areas remains a matter that need further evaluation. Despite this, breast cancer remains an important cause of cancer death in northeast India highlighting the need for awareness generating measures and improved healthcare and diagnostic facilities. A higher percentage of early onset cancer and TNBC subtypes underline the need for early detection and treatment of breast cancer cases in this region.

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Conflict of Interest Statement:

The authors have no Conflict of Interest to declare.

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