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Breast Cancer

A Clinicopathological Analysis of Molecular Subtypes of Breast Cancer using Immunohistochemical Surrogates: A 6-Year Institutional Experience from a Tertiary Cancer Center in North India

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Abstract

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Objective Classification of breast cancer into different molecular subtypes has important prognostic and therapeutic implications. The immunohistochemistry surrogate classification has been advocated for this purpose. The primary objective of the present study was to assess the prevalence of the different molecular subtypes of invasive breast carcinoma and study the clinicopathological parameters in a tertiary care cancer center in rural North India.

Materials and Methods All female patients diagnosed with invasive breast cancer and registered between January 1, 2015, and December 31, 2020, were included. Patients with bilateral cancer, missing information on HER2/ER/PR receptor status, absence of reflex FISH testing after an equivocal score on Her 2 IHC were excluded. The tumors were classified into different molecular subtypes based on IHC expression as follows-luminal A-like (ER- and PR-positive, Her2-negative, Ki67 $< 20\%$), luminal B-like Her2-negative (ER-positive, Her2-negative and any one of the following Ki67% $\geq$ 20% or PR-negative/low, luminal B-like Her2-positive (ER- and HER2-positive, any Ki67, any PR), Her2-positive (ER- and PR-negative, Her2-positive) and TNBC (ER, PR, Her2-negative).

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Chi square test was used to compare the clinicopathological parameters between these subtypes.

Results A total of 1,625 cases were included. Luminal B-like subtype was the most common (41.72%). The proportion of each subtype was luminal A (15.69%), luminal B Her2-negative (23.93%), luminal B Her2-positive (17.78%), Her2-positive (15.26%), TNBC (27.32%). Majority of the tumors were Grade 3 (75.81%). Nodal metastases were present in 59%. On subanalysis of the luminal type tumors without Her2 expression (luminal A-like and luminal B-like (Her2-negative), luminal A-like tumors presented significantly with a lower grade ($p < 0.001$) and more frequent node-negative disease in comparison to luminal B-like (Her2-negative) tumors. In comparison to other subtypes, TNBC tumors were more frequently seen in the premenopausal age group ($p < 0.001$) and presented with node-negative disease ($p < 0.001$).

Conclusion This is one of the largest studies that enumerates the prevalence of various molecular subtypes of breast cancer in North India. Luminal B-like tumors were the most common followed by TNBC. TNBC tumors presented more commonly in premenopausal age group and with node negative disease in comparison to other subtypes.

Keywords

- molecular subtypes
- breast cancer
- India
- immunohisto-chemical surrogates
- TNBC

Introduction

Breast cancer is the most common cancer in women worldwide and is also the leading cause of cancer death. It accounts for almost one in four cancer cases in women.[1] In India, the incidence of breast cancer has been increasing in recent years and it has replaced cervical cancer as the most common cancer in urban areas. In comparison to the western population, breast cancer occurs at a younger premenopausal age in India, and most of the patients present with locally advanced or metastatic disease.[2]

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (Her2) are biomarkers that are routinely assessed in breast cancer as they are important prognostic factors and guide treatment strategies. ER is expressed in up to 75% of all breast cancers. PR is an estrogen-regulated gene and is expressed in more than 50% of ER-positive tumors.[3]

Global gene expression profiling (GEP) studies have identified distinct biological subtypes with different clinical and pathological features and therapeutic implications. These subtypes are luminal A, luminal B, Her 2-enriched, basal-like breast cancers, and normal-like tumors.[4] The gene expression profiles of luminal A and B subgroups resemble normal luminal epithelial cells of the breast and genes associated with ER activation.[4,5] Luminal A is the most common subtype accounting for almost 40 to 50% of all breast cancers. In general, luminal A cancers are typically low grade, have a good prognosis, and are more sensitive to hormonal therapy alone, while Luminal B cancers tend to be of a higher grade and have a worse prognosis. They are also resistant to endocrine therapy, and most patients are candidates for additional chemotherapy.[4,5] These subtypes also show distinct patterns of genomic alterations with *PIK3CA* mutations more frequently noted in luminal A tumors and *p53* mutations more common in luminal B.[4,6]

The Her2-enriched subgroup is characterized by the overexpression of *Her2*, and other genes located in the *Her2* amplicon. This subgroup comprises around 15 to 20% of all invasive breast cancers. These tumors are usually of higher grade and have an aggressive course; however, the advent of anti-Her2 targeted therapy has greatly improved the overall outcome.[4] The basal-like subgroup is characterized by the expression of genes in normal breast basal/myoepithelial cells, a high proliferation rate, a lack of expression of ER, PR, HER2, and a poor clinical outcome. *P53* mutations are most frequent in this subtype.[4,6] Additional rare subtypes such as claudin-low, molecular apocrine, luminal C, luminal N, and interferon-rich have also been identified recently.[4,6]

The technical complexities and high cost of gene expression profiling limit its use in routine clinical practice. A more practical immunohistochemical surrogate classification was put forth by Cheang et al.[7] In their study, they further distinguished between the two subgroups of ER-positive tumors defined by GEP (luminal A and B) according to their recurrence-free and disease-specific survival.[7] This classification was endorsed by the 2011 St. Gallen consensus.[8] Other studies have also illustrated that using Ki67 proliferation index and a 20% cut-off for PR best distinguishes between luminal A and luminal B subtypes.[9]

The prevalence of these molecular subtypes has not been studied extensively in the north Indian population. The present study aimed to decipher the prevalence of molecular subtypes of invasive breast carcinoma using the immunohistochemical surrogate classification and the distribution of various clinicopathological parameters in these subtypes.

Materials and Methods

All female patients diagnosed with invasive breast cancer and registered at our center between January 1, 2015, and December 31, 2020, were included in this study. We also

included referral cases in this study. Patients with missing information on HER2/neu or ER/PR receptor status, those who did not undergo reflex fluorescence in-situ hybridization (FISH) testing after an equivocal score of 2+ on Her 2 IHC, patients with synchronous and metachronous bilateral invasive carcinoma were excluded from the study.

Clinicopathological Characteristics

For the selected cases, the data regarding baseline clinical characteristics, and pathological findings were collected from the electronic medical records. The parameters assessed for each patient were age at the time of diagnosis, tumor size, histological subtype, tumor grade, type of surgery undertaken (if any), histologically proven axillary lymph node metastasis, presence of distant metastasis at initial presentation, and type of chemotherapy received. In patients who underwent upfront surgery, the histological tumor size was considered. For patients who did not undergo any surgical procedure, the radiological tumor size was considered. In patients who underwent surgery after neoadjuvant chemotherapy (NACT), the pre-chemotherapy radiological tumor size was considered. Histological tumor grade was assessed according to the Nottingham modification of the Bloom–Richardson system.

Immunohistochemistry Evaluation

Immunohistochemical (IHC) testing was performed using the standard procedures on paraffin-embedded tissue specimens stained with the following monoclonal antibodies-ER (Ventana, Clone SP1), PR (Ventana, Clone 1E2), Her2 (-Biocare/Ventana, Clone EP3/4B5), and Ki67 (Ventana, Clone Mib1).

The ER and PR IHC slides were assessed by the Allred scoring system as per the 2010 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines.[10] To categorize a tumor as ER/PR-positive, a cut-off of 1% tumor cell staining was taken. The assessment of HER2 IHC slides was done using the ASCO/CAP 2013 guidelines.[11] Cases with equivocal HER2 staining on IHC were sent for further examination by FISH and their results were documented. The cases in which FISH testing could not be done were excluded from the study. Assessment of the Ki67 proliferation index was done as per the guidelines of the International Ki67 in Breast Cancer Working Group.[12]

Classification of Different Molecular Subtypes

We classified the cases into the following molecular subtypes based on the current established immunohistochemical surrogate definitions[9,13] (►Table 1).

There is currently no standardized cut-off value established for the Ki67 proliferation index.[9,12] Although a cut-off of 14% was endorsed in the St. Gallen expert consensus Panel recommendation guidelines in 2011, the majority of the panel in the St. Gallen 2013 meeting voted a threshold of $\geq$ 20% as indicative of high Ki67 status.[13] We have taken a cut-off of $\geq$ 20% as indicative of high Ki67 in the present study.

Table 1 Immunohistochemical characterization of different molecular subtypes

Molecular subtype	Receptor expression
Luminal A-like	ER- and PR-positive, Her2-negative, Ki67 < 20%
Luminal B-like	• Luminal B-like (Her2-negative)-ER-positive, Her2-negative and atleast one of the following- Ki67% ≥20% or PR-negative/low (<20%) • Luminal B-like (Her2-positive): ER and HER2-positive, any Ki67, any PR
Her2-positive	ER- and PR-negative, Her2-positive
Triple-negative	ER- and PR-negative, Her2-negative

Data Analysis

Statistical analysis was performed using Statistical Product and Service solution, SPSS version 20.0 (IBM, Armonk, NY). Pearson's chi-square was used for comparison of categorical data. A p-value < 0.05 was considered significant. The present study was approved by the Institutional Ethics Committee.

Results

A total of 1,625 cases were included in the present study. Most patients were older than 50 years (55.2%) and presented with grade 3 tumors (75.8%). Ductal carcinoma was the most common subtype followed by lobular carcinoma and metaplastic carcinoma. Tumor size was available in 1,431 cases. Most tumors were T2 (>2.0 cm but $\leq$ 5.0 cm). Data regarding histologically proven axillary nodal metastases was available in 1,144 cases, out of which 59% of cases had axillary lymph node metastases. Data regarding distant metastases were available in 1,405 cases, out of which 21% of cases had distant metastases at presentation. These clinicopathological parameters are outlined in ►Table 2.

ER positivity was found in 56% of the cases while PR positivity was found in 45.5% of the cases. Her2 positivity was noted in 33.04% of cases (►Table 3).

Categorization into Molecular Subtypes

Luminal B-like subtype was the most common constituting 41.72% of the total study population and triple-negative (TNBC) subtype was the second most common constituting 27.32%. On further stratification of the luminal B-like category, most cases were of luminal B-like Her2 negative subtype (389/678, 57.37%) (►Table 4 and ►Fig. 1).

Age at Presentation

The mean age at presentation was 53 years with a range of 22 of 98 years. Amongst the different molecular subtypes, TNBC subtype presented with the lowest mean age of 50.4 years, while luminal A-like presented with the highest mean age of

Table 2 Clinicopathological parameters of entire study population

Patient characteristics	No. of cases (%) (total no. = 1,625)
Mean age at presentation (y)	53
Age (y)	
≤ 30	30 (1.84)
31–50	698 (42.95)
> 50	897 (55.2)
Grade	
I	09 (0.55)
II	384 (23.63)
III	1,232 (75.81)
Tumor size	
≤ 2.0 cm	147 (10.27)
> 2.0 cm but ≤ 5.0 cm	905 (63.24)
> 5.0 cm	379 (26.48)
Size not available	194
Tumor subtype	
Invasive ductal	1,530 (94.15)
Invasive lobular	22 (1.35)
Metaplastic	23 (1.41)
Mucinous	22 (1.35)
Papillary	08 (0.5)
Micropapillary	05 (0.3)
Mixed ductal and lobular	08 (0.5)
Cribriform	02 (0.12)
Apocrine	03 (0.18)
Adenoid cystic	01 (0.06)
Tubular	01 (0.06)
Axillary lymph node metastasis	
Present	675 (59)
Absent	469 (41)
Data not available	481
Metastatic disease at presentation	
Present	301 (21.42)
Absent	1,104 (78.57)
Data not available	220
Types of surgery	
Mastectomy	779 (47.93)
Breast conservation therapy/lumpectomy	434 (26.70)
Patients who received NACT	462 (28.43)

56 years. Most subtypes had a higher proportion of cases in the postmenopausal age group (>50 years), while TNBC had most cases in the younger age group of 31 to 50 years.

Table 3 Prevalence of ER, PR, and Her2 expression

Receptor	Positive (*n* [%])	Negative (*n* [%])	Total (*n*)
ER	913 (56.18)	712 (43.8)	1,625
PR	740 (45.53)	885 (54.46)	1,625
Her2	537 (33.04)	1,088 (66.95)	1,625

Table 4 Prevalence of different molecular subtypes

Molecular subtypes	No. of cases (%)
Luminal A	255 (15.69)
Luminal B	678 (41.72) • Luminal B-like (Her2-negative) = 389 • Luminal B-like (Her2-positive) = 289
Her2-positive	248 (15.26)
Triple-negative	444 (27.32)
Total number of cases	1,625 (100)

Tumor Size

Tumor size was available in 1,431 cases. The mean tumor size was 4.39 cm. Luminal A-like subtype had the smallest mean tumor size (3.83 cm). The majority of the tumors in all subtypes were in the T2 category (>2.0 but ≤ 5.0 cm). Luminal B-like (Her2-negative) tumors accounted for most of the small tumors (< 2.0 cm) ($n = 38/147$, 25.9%), while TNBC accounted for most of the larger tumors (>5.0 cm) ($n = 109/379$, 28.8%). There was no statistically significant difference in distribution of tumor size among various molecular subtypes ($p = 0.157$).

Tumor Grade

Most tumors in the present analysis were grade 3 tumors. Luminal A-like tumors accounted for all grade 1 tumors. Luminal A-like tumors also had a higher proportion of grade 2 tumors ($n = 177/255$, 69.17%), while all other subtypes had a higher proportion of grade 3 tumors.

Axillary Lymph Node Metastasis

Data regarding axillary lymph node metastases were available in 1,144 cases. Out of these 1,144 cases, 675 (59%) presented with nodal metastases. Luminal B-like (Her2-negative) tumors had the highest proportion of nodal metastases (70.3%), followed by luminal B-like (Her2-positive) (67.95%), Her2-positive (63.97%) and Luminal A-like (59.07%). In contrast, only 42.56% of cases of the TNBC tumor subtype presented with nodal metastases.

On statistical analysis, a statistically significant difference was found in the presence of axillary nodal metastases among the various molecular subtypes ($p < 0.001$).

Distant Metastasis at Presentation

Data regarding distant metastases were available in 1,405 cases. Out of these 1,405 cases, distant metastases were present in 301 cases (21.42%). It was found to be least

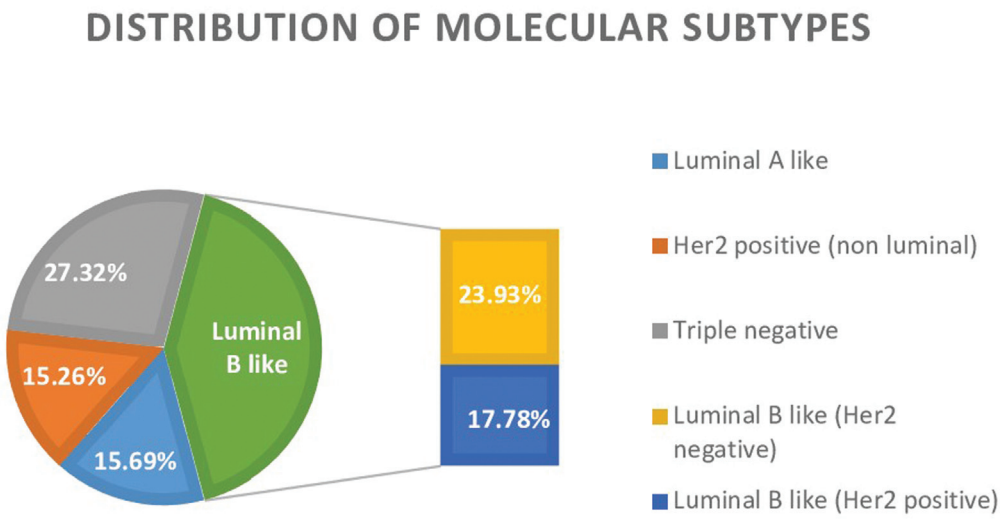

Fig. 1 Distribution of various molecular subtypes.

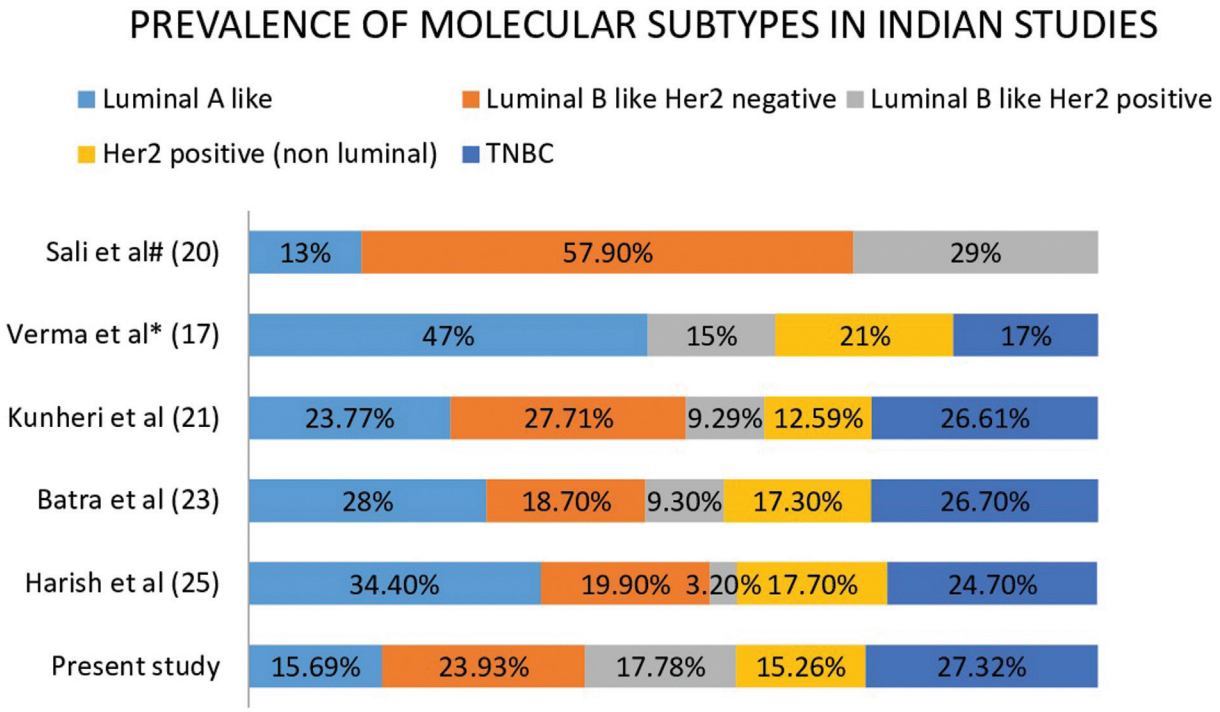

Fig. 2 Comparison of various Indian studies with regard to molecular subtypes. Footnote: # Study only included luminal tumors. *Study categorized Luminal A- and Luminal B-like (Her2-negative) tumors as Luminal A.

common in the luminal A-like subtype ($n = 38/301$, 12.6%), while the proportion was found to be similar in the luminal B-like (Her2-negative) (21.69%), luminal B-like (Her2 positive) (26.89%), and Her2-positive subtypes (23.08%). In the TNBC subtype, 19.51% of all cases presented with distant metastases. On statistical analysis, there was no statistically significant difference in the presence of distant metastases among various molecular subtypes ($p = 0.053$). The comparison of clinicopathological features of the molecular subtypes is outlined in ►Table 5.

Sub-analyses of Luminal Type (Her2-Negative) Tumors

On further subanalyzing the luminal type tumors without Her2 expression (i.e., luminal A-like and luminal B-like

Table 5 Comparison of clinicopathological features of the molecular subtypes

Clinicopathological characteristics	Luminal A-like ($n = 255$)	Luminal B-like (Her2-negative) ($n = 389$)	Luminal B-like (Her2-positive) ($n = 289$)	Her2-positive ($n = 248$)	TNBC ($n = 444$)
Age at presentation (y)					
≤ 30	0	5 (1.3)	6 (2.1)	5 (2.0)	14 (3.2)
31–50	90 (35.3)	157 (40.4)	132 (45.7)	102 (41.1)	217 (48.9)
> 50	165 (64.7)	227 (58.4)	151 (52.2)	141 (56.9)	213 (48.0)
Mean age	56	54.18	52.53	52.92	50.4
Tumor size (cm)					
≤ 2.0 cm	**29 (12.08)**	38 (11.01)	24 (9.06)	21 (10.10)	35 (9.38)
> 2.0 but ≤ 5.0 cm	166 (69.17)	221 (64.06)	162 (61.13)	127 (61.06)	229 (61.39)
> 5.0 cm	45 (18.75)	86 (24.93)	79 (29.81)	60 (28.85)	109 (29.22)
Size not available	15	44	24	40	71
Mean tumor size	3.83	4.24	4.67	4.59	4.6
Tumor grade					
I	9 (3.5)	0	0	0	0
II	177 (69.4)	108 (27.8)	41 (14.2)	14 (5.6)	44 (9.9)
III	69 (27.1)	281 (72.2)	248 (85.8)	234 (94.4)	400 (90.1)
Lymph node metastasis					
Present	114 (59.07)	**192 (70.33)**	**123 (67.95)**	**103 (63.97)**	**143 (42.56)**
Absent	79 (40.93)	81 (29.67)	58 (32.04)	58 (36.02)	193 (57.44)
Data not available	62	116	108	87	108
Metastatic disease at presentation					
Present	38 (16.38)	72 (21.69)	**71 (26.89)**	48 (23.08)	72 (19.51)
Absent	194 (83.62)	260 (78.31)	193 (73.11)	160 (76.92)	297 (80.49)
Data not available	23	57	25	40	75

(Her2-negative), the luminal A-like tumors presented significantly with a lower grade (Grade 2 = 69.4% vs. 27.8%, $p < 0.001$) and more frequent node-negative disease (N0 = 40.93% vs. 29.67%, $p = 0.012$) in comparison to Luminal B-like (Her2-negative) tumors.

Sub-analyses of TNBC Tumors

Sub-analyses of the TNBC tumors versus all other subtypes (non-triple negative group) showed TNBC tumors to be more common in the premenopausal age group (48.87% vs. 40–72%, $p < 0.001$), presented more commonly with node-negative disease (57.44% vs. 34.115%, $p < 0.001$) and were more frequently grade 3 (90.09% vs. 70.4%, $p < 0.001$). Larger tumors (>5.0 cm) were also more common in TNBC (29.22% vs. 25.52%); however, the difference was not statistically significant ($p = 0.35$).

Discussion

The pioneering work done by Perou and Sorlie et al using global gene expression profiling led to a paradigm shift in the understanding of the biology of breast cancer. The authors demonstrated that breast cancer was a heterogeneous disease at the transcriptome level and classified breast cancer into different subtypes by hierarchical clustering.[14] Further studies have revealed that the various molecular subtypes differ in their clinical presentation and response to systemic therapy. Luminal A cancers have the best prognosis amongst all subtypes.[4] In comparison to the more expensive traditional gene expression profiling, an IHC-based surrogate classification has been advocated as a more practical alternative for routine practice.

The present study assessed the prevalence of molecular subtypes of invasive breast carcinoma in rural population of Punjab. The mean age at presentation was 53 years, which is like other Indian studies but is about a decade lower than that reported in the Western population.[15] We also found a low proportion of patients presenting at a younger age (≤30 years) ($n = 30$, 1.84%). Another study, however, observed that 10% of their study population comprised of young breast cancer patients (< 35 years).[16] The majority of our patients were older than 50 years ($n = 897$, 55.2%) which is similar to the data published in the Indian literature.[16–18]

At presentation, the patients in our study population had a larger tumor size and more frequent nodal involvement in comparison to data presented in western population.[15] This

discrepancy can be attributed to the lack of a robust screening program in our country, the poor socioeconomic status of most of the population, and lack of cancer awareness in the general population.

In the present study, ER and PR positivity was noted in 56% and 45% of the study population respectively. Most Indian studies report the prevalence of ER/PR positive tumors to be in the range of 50 to 60%.[16–19] This is, however, lower than the ER/PR positivity reported in some western studies.[15] This variation can be attributed to the different epidemiological factors associated with the Indian population, wherein most patients present at a younger age and with a higher tumor grade.[2,19] Her2 positivity was noted in 33% of the study population. This result is in accordance with the published Indian literature with Her2 positivity being reported in around 20 to 30% of breast cancers.[16–18]

Luminal B-like was the most common molecular subtype (41.72%), followed by TNBC (27.32%), luminal A-like (15.69%), and Her2-positive (15.26%). A few other studies have also reported a predominance of luminal B subtype in comparison to luminal A.[20–22] However, our results contrasted those of Batra et al, Vasconcelos et al, Harish et al, and Park et al, who reported luminal A as the most common subtype.[23–26] (►**Fig. 2**) A predominance of grade 3 tumors in our study population in comparison to other studies may explain this prevalence of Luminal B-like subtype.

On subanalyses of the luminal A-like subtype and the luminal B-like (Her2-negative) subtype, luminal A-like tumors presented significantly with a lower tumor grade and more frequent node-negative disease in comparison to luminal B-like (Her2-negative) tumors. These findings are in accordance with other studies.[20,21,24] Luminal A tumors are differentiated from luminal B tumors with the help of proliferation markers and PR positivity. This distinction is necessary due to the differing therapeutic implications.[13] In the study by Prat et al, the authors first proposed a cut-off of more than 20% PR positivity to further refine the definition of IHC-defined luminal A tumors. This was based on the finding that low or negative PR expression is associated with a worse prognosis in luminal cancers.[27]

Her2-positive subtype (non-luminal) was the least common molecular subtype in the present analysis. Kunheri et al have also reported similar findings in their study.[21] TNBC subtype constituted 27.32% of our study population. In a comprehensive meta-analysis, the prevalence of TNBC ranged from 27 to 35% across various Indian studies.[28] The prevalence of TNBC is comparable to data reported in African American women; however, it is almost twice than that reported in White women.[15,28,29] This higher prevalence of TNBC in the Indian population could be a contributing factor to the higher fatality rate of breast cancer patients in India as TNBC tumors are known to be more aggressive in behavior.[30]

TNBC tumors were more frequent in the premenopausal age group. Similar findings have been reported in other studies.[18,24,26,30] We observed that TNBC more frequently presented with node-negative disease in comparison to other subtypes. While many studies have reported similar observations,[18,24,26,29] a few others have reported more node positivity in TNBC.[30,31]

One of the strengths of the present study is that all cases with an equivocal score of Her2 on IHC were subjected to FISH and the categorization of HER2-positive tumors was done accordingly. One of the main limitations of the present study was that certain clinicopathological factors were not available for all cases. Because our hospital serves as a referral center, this may have also contributed to an inherent referral bias. This could explain the high prevalence of grade 3 tumors in our study population.

Conclusion

This is one of the largest studies to describe the prevalence of various molecular subtypes of breast cancer in rural North Indian population. At presentation, the patients in our study population had a larger tumor size and more frequent nodal involvement in comparison to western population. The majority of the tumors were grade 3. Luminal B-like tumors were most common followed by TNBC. TNBC tumors presented more commonly in premenopausal age group and with node-negative disease compared with other subtypes.

Conflict of Interest

None declared.

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