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Immunohistochemical Characterization of Breast Carcinoma: Clinical Correlations, Molecular Subtypes, and Therapeutic Implications

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ABSTRACT

Background: Breast carcinoma exhibits heterogeneity in terms of morphology, molecular, treatment response, and clinical outcomes. The objective of the study was to classify the various malignant breast cancer cases based on their immunohistochemical characteristics and understand their association and behavior, which may be useful for predicting treatment and prognosis.

Methods: In this study, 12808 malignant breast cancer cases were studied based on hormone receptor IHC biomarkers, age, gender, histological type, grade and molecular classifiers.

Results: The mean age of patients was 53.63+13.08 years, around 45.43% were grade 3 tumors, and the invasive duct carcinoma of non-specified type was the most common type seen. ER positivity was 83.89% in grade 1, 69.9% in grade 2, and 36.86% in grade 3 tumors, and the overall PR and Her-2 positivity was 47.06% and 18.67%, respectively. A relatively higher percentage of Triple Negative cases was seen, followed by 25.43% Luminal A cases. There was a significant association between molecular subtypes with respect to age, gender, Scarff Bloom Richardson grade, and histological type. Overall, grade 3 tumor cases were most common, the majority of which were Triple Negative. Maximum cases of triple negative tumors were seen among women, being mostly concentrated in younger age group i.e. <40 years.

Conclusion: Immunohistochemistry for hormone receptor positivity remains the mainstay of diagnosis and molecular sub-classification. The hormone response of tumors is important prognostically, and in predicting the treatment outcomes. Going further, molecular analysis and gene expression studies can further augment the histopathological diagnosis to assist strategies of targeted therapy and precision medicine, resulting in better patient outcomes.

INTRODUCTION

Breast cancer and the related deaths, as seen by the global and national figures have increased rapidly over the past decade. The GLOBOCAN 2020 statistics have shown that, worldwide, breast cancer accounted for 24.6% of all cancers and around 16% of all deaths among females. In India, from the year 1965 to 1985 there was an almost 50% rise in breast cancer cases. Recent statistics show that breast cancer accounted for 13.5% of all cancers and 10.6% of all deaths with a cumulative risk of 2.81 in India[1]. Studies have also shown that the incidence of breast cancer is rising among younger women. Although the breast cancer figures among Indian women is lower as compared to the West, epidemiological studies have estimated that breast cancer cases will reach almost 2 million by 2030.[2,3]

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As breast cancer cases continue to rise, there has also been significant progress in the diagnosis of breast cancer malignancies, with significant advances in molecular genomics and onco-pathological studies for earlier detection of disease and subsequent development of more effective targeted therapy for patient management. This may contribute to the reduction in the mortality and morbidity rates of breast cancer in the developed countries.

Breast cancer exhibits significant heterogeneity in terms of histopathological features, metastatic patterns, molecular features, outcome and response to therapy. This has an impact on the clinical outcome of the breast cancer patients as well. Prognostic variations occur with respect to tumor size, histologic grade, histologic type, and biological markers such as estrogen receptor (ER), progesterone receptor (PR), and Her-2-2/neu expression profile[4].

Presently IHC is accepted as an adequate surrogate marker for molecular subtypes. This surrogate IHC method aids the determination of molecular subtypes[5]. Immunohistochemistry markers like estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2(Her-2) proteins give valuable information and help in patient management.[6] Knowing the hormone receptor status of these tumors helps in predicting the patient response to the treatment. If the tumor is hormone receptor positive, i.e. ER PR positive, it is more likely that the patient will respond to endocrine therapy. The hormone therapy is unlikely to be effective if the tumor is hormone receptor negative. Hormone receptor expression is thus a weak prognostic but a strong predictive biomarker in breast cancer cases. All invasive breast cancers should be tested for the hormone receptor status as well as Her-2/neu.[7] Combined expression of these three hormone receptors is important in the further molecular classification of breast cancer cases for the clinical assessment and deciding on further treatment. Molecular classification of breast tumors is the grouping of cases that share characteristics and hormone receptor status, which can guide the response of tumors to various lines of hormonal therapies.[8] Triple- negative cases of breast cancer are known to grow and spread faster and are less responsive to hormonal or targeted therapy. Apart from this, with latest advances in the field of molecular diagnostics and therapeutics, newer non-invasive prognostic biomarker tests aid the detection of breast cancer cases in the early stages itself. Molecular subtyping using immunohistochemistry can provide additional prognostic and predictive information.

In India, the last decade has seen an exponential rise in the incidence of breast cancer cases, with the age of onset also markedly reducing. Utilizing genomics to understand India-specific differences with respect to breast cancer cases may enable the identification of women at high risk of developing cancer, where targeted screening may be cost-effective. There is an urgent need to identify Indian-specific genetic/epigenetic biomarkers. These may have the potential to be used as biomarkers for early detection at the screening stage.[9] The current study aims to analyze the hormone receptor positivity status and the subsequent morphological classification in the Indian population.

Aims of the study

- To study the immunohistochemical markers across breast cancer patients in the Indian population over the period of seven years from January 2015 to June 2022.
- To understand the association of molecular subtypes of breast cancers with respect to demographics and tumor grade.

METHODS

A retrospective study was conducted at Global Reference Laboratory, Mumbai, Metropolis Healthcare Ltd. In this study, 12808 malignant breast tumor samples received in seven years [2015 to 2022] were studied. The type and grade of the tumor were assessed as per WHO 5th edition classification of breast tumors.[10]

IHC for ER, PR and Ki-67

IHC was considered positive if >1% of tumor cell nuclei were immunoreactive to respective hormone receptor. College of American Pathologists (CAP) guidelines were used for ER, PR, Her-2/ Neu and Ki-67 assessment.[11] As per CAP guidelines, the wet tissue was fixed in 10% neutral buffered formalin for 6 to 72 hours and processed overnight in an automated tissue processor. In many cases, paraffin blocks were received. Four-micron thick sections were cut and stained with hematoxylin and eosin. ER/PR scoring was done as per the Allred scoring system.[12]

Her-2 by IHC

The results were scored from 0 to 3+ according to the criteria of the HercepTest™. HercepTest™ mAb pharmDx (Dako Omnis) is a semi-quantitative immunohistochemical assay based on a primary monoclonal rabbit antibody (clone DG44) and an assay-specific visualization reagent. The assay determines HER2 protein overexpression in formalin-fixed, paraffin-embedded (FFPE) breast cancer tissues processed for histological evaluation. HercepTest™ mAb pharmDx (Dako Omnis) is

indicated as an aid in the assessment of breast cancer patients for whom Herceptin® (trastuzumab) treatment is being considered.[13]

Her-2 by FISH

For 509 cases where IHC was done, Fluorescence in situ hybridization (FISH) was also performed using HER-29 PathVysion® HER-2 DNA Probe Kit II, a dual probe assay. The PathVysion HER-2 DNA Probe Kit II (PathVysion Kit II) has been designed to detect amplification of the HER-2/neu gene via fluorescence in situ hybridization (FISH) in formalin-fixed, paraffin-embedded human breast and gastric cancer tissue specimens.[14] FDA approved automated result scanning is available for PathVysion.[15,16] HER-2 scoring was done as per ASCO/CAP guidelines.

Molecular classification of breast tumors

Details of tumor type, grade, ER, PR, Her-2 and Ki-67 were used for further molecular classification.[17] Further comparisons between age, gender, histological type, and grade were made.

Statistical Analysis

The data were analyzed using "R Studio version 1.4.1103". Descriptive analyses were done to obtain the frequency and percentage of Morphological classification, Hormone Receptor status, Her-2 expression, Molecular Subtype in this given population, in addition to the characteristics of the sample Age, Gender and Scarff Bloom Richardson (SBR) grading. Comparison of Molecular Subtype with Age, Gender, Scarff Bloom Richardson (SBR) grading and Morphological classification was done by the Chi-square test. Concordance between the results of Her-2 by IHC & Her-2 by FISH was calculated in cases in which both tests had been performed. A P-value of less than 0.05 was considered to be statistically significant.

The formula below was used to calculate the concordance rate:

CONR=C/SA*100, where CONR was the concordance rate, "C" was the number of subjects with concordant results, and "SA" was the total number of subjects assessed for concordance.

RESULTS

In this study, 12808 malignant breast cancer cases were analyzed over a period of seven years; the mean age of patients seen was 53.63+13.08 years, with the minimum age of 18 years and the maximum age of 92 years (Table 1).

Table 1. Demographic distribution of breast cancers

	Frequency	Percentage
Age Group		
18-30	344	2.69
31-40	1846	14.41
41-50	3369	26.30
51-60	3249	25.37
61-70	2384	18.61
71-80	1006	7.85
>80	303	2.37
NA	307	2.40
Sex		
Female	12598	98.36
Male	210	1.64

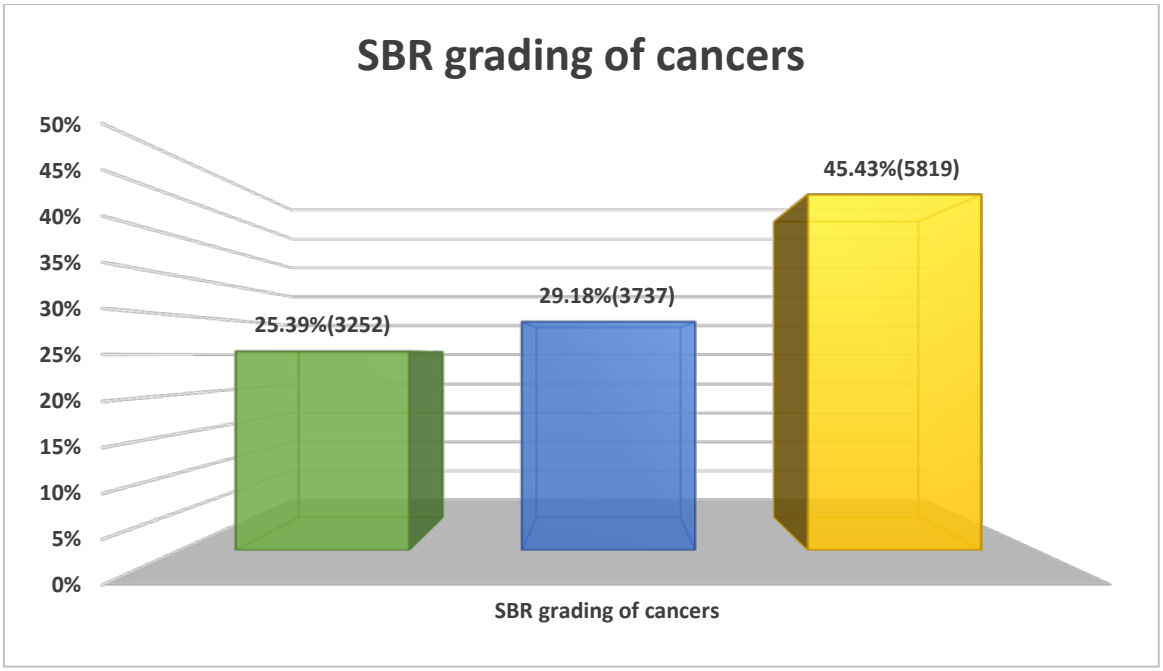

Figure 1. Scarff Bloom Richardson (SBR) grading of cancers.

Morphologically, invasive duct carcinoma of NST, (12018, 93.83%) was the most prevalent subtype followed by Invasive lobular carcinoma (380, 2.97%). There were also some extremely rare subtypes observed, such as apocrine carcinoma (5, 0.04%), adenoid cystic carcinoma (2, 0.02%) and neuroendocrine carcinoma (1, 0.01%) (Table 2).

Table 2. Morphological classification of breast cancer cases

Morphological classification	Frequency	Percentage
Invasive duct carcinoma of NST/ Invasive Breast carcinoma of NST	12018	93.83
Invasive lobular carcinoma	380	2.97
Invasive mucinous carcinoma	264	2.06
Invasive papillary carcinoma	57	0.45
Invasive Metaplastic carcinoma	29	0.23
Invasive Micro Papillary Carcinoma	17	0.13
Invasive Cribriform Carcinoma	13	0.10
Mixed Invasive duct and lobular carcinoma	13	0.10
Invasive Tubular carcinoma	8	0.06
Invasive apocrine carcinoma/ Carcinoma with apocrine differentiation	5	0.04
Adenoid Cystic Carcinoma breast	2	0.02
Neuroendocrine tumor	1	0.01
Neuroendocrine carcinoma breast	1	0.01
Grand Total	12808	100.00

Overall, ER expression was seen in 58.44% (7485) cases while 47.06 % of the cases (6028) were PR-positive. Her-2 by IHC showed a positivity of 18.67 % (2269). The Ki67 proliferation index was known for 6447 cases, and 44.44% (2865) cases showed Ki-67 proliferation index <20%, while the rest showed Ki-67 >20% (Table 3).

Table 3. Hormone Receptor status, Her-2 expression and Ki67 Proliferation Index

	Frequency	Percentage
ER		
Negative	5323	41.56
Positive	7485	58.44
PR		
Negative	6780	52.94
Positive	6028	47.06
C-erbB-2/ Her-2 neu by IHC		
Equivocal	1410	11.60
Negative	8474	69.73
Positive	2269	18.67
Ki67% (n=6447)		
<10%	570	8.84
11-20%	2295	35.60
21-30%	2105	32.65
31-40%	903	14.01
41-50%	320	4.96
51-60%	146	2.26
>60%	108	1.68

The relationship of ER PR positivity with respect to grade showed that ER PR positivity was higher in grade 1 and 2 as compared to grade 3 cases (Table 4).

Her-2 by FISH was performed in 4617 cases. Out of this, Her-2 by FISH was positive in 1631 cases (35.33%) while 39 cases (0.84%) showed equivocal results.

In addition, 509 cases were tested for both Her-2 by IHC and Her-2 by FISH and the concordance was established. Her-2 by IHC and Her-2 by FISH showed a concordance rate of 97.53% (Table 5).

Table 4. Relationship of ER, PR and Her-2 with tumor grade

	Grade						
	1		2		3		
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	P value
ER							
Negative	524	16.11	1125	30.10	3674	63.14	<0.0001
Positive	2728	83.89	2612	69.90	2145	36.86	
PR							
Negative	1110	34.13	1677	44.88	3993	68.62	<0.0001
Positive	2142	65.87	2060	55.12	1826	31.38	
Her-2							
Negative	2155	71.24	1909	54.43	4410	78.46	<0.0001
Equivocal	504	16.66	567	16.17	339	6.03	
Positive	366	12.10	1031	29.40	872	15.51	

Chi square test was used.

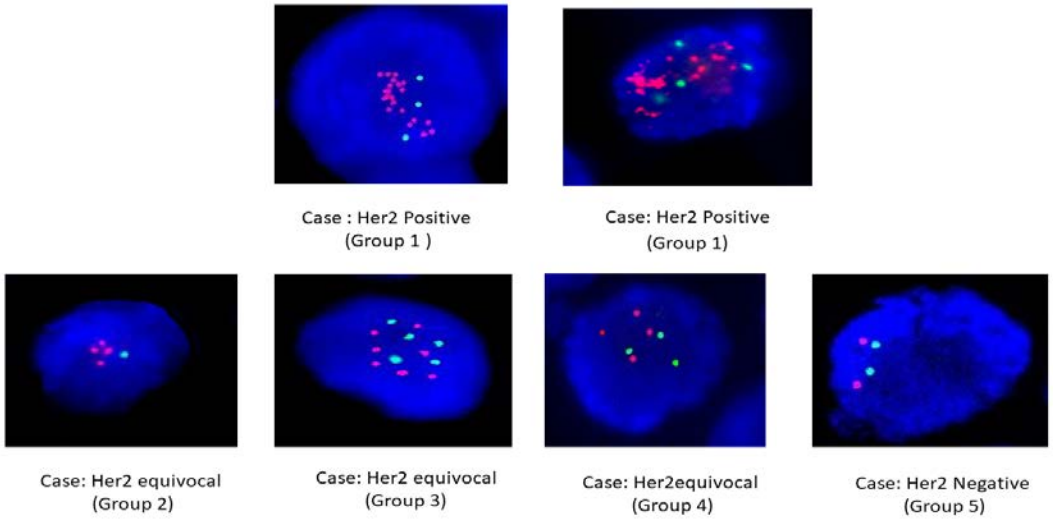

Figure 2. Her-2 FISH Images

Table 5. Her-2 by IHC vs Her-2 by FISH

IHC Result	Fish Result			
	Negative	Positive	Equivocal	Total
Negative	186	4	0	190
Positive	2	51	0	53
Equivocal	139	122	5	266
Total	327	177	5	509

On comparison of Ki-67proliferation index with respect to grade, Ki-67 proliferation index was seen to be lower in grade 1 breast cancer cases as compared to the grade 2 and 3 cases (Table 7).

Table 6. Ki67 proliferation index with respect to age

Age Group	Ki67%			
	Less than 20%		More than 20%	
	Frequency	Percentage	Frequency	Percentage
18-30	47	27.01	127	72.99
31-40	334	37.36	560	62.64
41-50	669	40.01	1003	59.99
51-60	715	43.89	914	56.11
61-70	656	51.25	624	48.75
71-80	307	57.28	229	42.72
>80	91	53.53	79	46.47

The further classification of molecular subtypes is as follows:

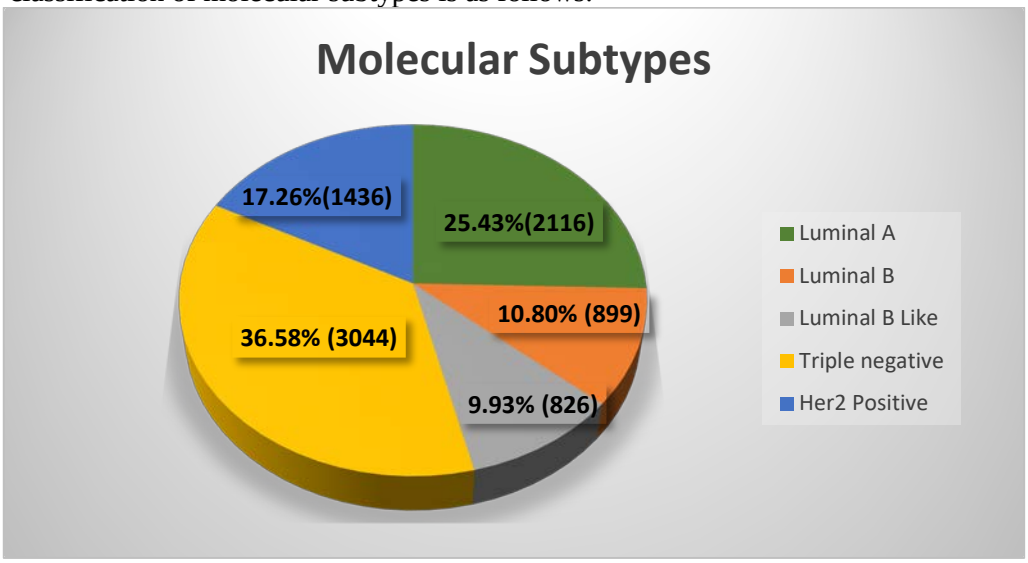

Figure 3. Surrogate molecular classification

Table 7. Relationship of Ki67% with tumor grade

	Grade						
	1		2		3		
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	P value
Ki67%							
<10%	503	88.25	43	7.54	24	4.21	
11-20%	1515	66.01	519	22.61	261	11.37	
21-30%	237	11.26	956	45.42	912	43.33	
31-40%	48	5.32	130	14.40	725	80.29	<0.0001
41-50%	17	5.31	37	11.56	266	83.13	
51-60%	7	4.79	12	8.22	127	86.99	
>60%	3	2.78	8	7.41	97	89.81	

Chi square test was used.

There was a significant association seen between molecular subtype with respect to age, gender, SBR grade, and histological type (P<0.0001) (Table 8).

DISCUSSION

Breast cancer burden is rapidly increasing worldwide as well as in India.

Table 8. Correlation of molecular subtypes with age, histological type and SBR grade

	Molecular Subtypes										
	Luminal A		Luminal B		Luminal B Like		Triple negative		Her-2 Positive		P value
	N	%	N	%	N	%	N	%	N	%	
Age group											
18-30	26	10.36	40	15.94	29	11.55	119	47.41	37	14.74	
31-40	234	18.48	141	11.14	156	12.32	556	43.92	179	14.14	
41-50	471	20.77	221	9.74	258	11.38	899	39.64	419	18.47	
51-60	512	24.62	205	9.86	200	9.62	712	34.23	451	21.68	<0.0001
61-70	505	33.76	183	12.23	120	8.02	437	29.21	251	16.78	
71-80	261	42.58	73	11.91	45	7.34	185	30.18	49	7.99	
>80	81	43.32	28	14.97	10	5.35	52	27.81	16	8.56	
SEX											
Female	2081	25.32	875	10.65	822	10.00	3016	36.70	1424	17.33	<0.0001
Male	35	33.98	24	23.30	4	3.88	28	27.18	12	11.65	
Final Grade											
1	1854	80.40	85	3.69	138	5.98	4	0.17	225	9.76	
2	213	11.87	479	26.70	288	16.05	75	4.18	739	41.19	<0.0001
3	49	1.16	335	7.94	400	9.48	2965	70.24	472	11.18	
Final											
Invasive duct carcinoma	1792	22.68	876	11.09	819	10.37	2993	37.88	1421	17.99	
Invasive lobular carcinoma	158	79.80	13	6.57	2	1.01	17	8.59	8	4.04	
Invasive mucinous carcinoma	124	93.94	6	4.55	0	0.00	0	0.00	2	1.52	
Invasive Metaplastic carcinoma	0	0.00	0	0.00	1	3.85	22	84.62	3	11.54	
Invasive papillary carcinoma	16	66.67	1	4.17	0	0.00	7	29.17	0	0.00	<0.0001
Invasive Micro papillary Carcinoma	4	36.36	2	18.18	3	27.27	1	9.09	1	9.09	
Invasive Cribriform Carcinoma	9	81.82	0	0.00	0	0.00	2	18.18	0	0.00	
Mixed Invasive duct and lobular carcinoma	8	80.00	0	0.00	1	10.00	0	0.00	1	10.00	
Other	5	62.50	1	12.50	0	0.00	2	25.00	0	0.00	

Chi-square test was used.

Studies on breast cancer have shown that the pathophysiology of breast cancer involves multiple modifiable as well as non-modifiable risk factors that may affect the further course of the treatment. Age and gender are known risk factors for breast cancers, as seen by various studies. In the current study, more than half of the malignant breast cancer cases were seen in those >50 years of age, with a mean age of patients being 53.63+13.08 (SD) years (Table 1). This was very similar to that seen in a study by Ambroise *et al.* where the mean age of breast cancer cases seen was 53.8 years.[18] As observed in a study by Upadhyay *et al.* and in some previous studies as well, the mean age of breast cancer patients in the Indian population is seen to be almost a decade younger as compared to the western counterparts.[19] However, carcinomas related to the BRCA1 and BRCA2 gene mutation may occur at younger ages as well.[20] Majority of the patients in this study had grade 3 carcinomas (45.43%), followed by grade 2 and grade 1 cases (Figure 1).

Maximum cases seen in our study were invasive duct carcinoma, comprising around 93.83% cases (Table 2). As breast carcinoma is a heterogeneous tumor with multifaceted features, its classification into subtypes is important. As stated in the study by Britta *et al.*, clinicopathological classification of breast carcinoma is crucial from the diagnostic, theranostic and prognostic perspective.[21] The statistical significance seen in the present study further reinforces this. Tumor differentiation is highly important in the management of breast carcinomas. Hormonal estrogen receptors are major markers of tumor differentiations.[22] The treatment of breast cancer includes a multi-disciplinary approach with surgery as the mainstay. The other important adjuvant types of treatment are hormone receptor status based endocrine therapy and anti-Her-2 drugs based on the Her-2 expression.[23] In the present study, overall we saw an ER and PR receptor positivity of 58.44% and 47.06%, respectively, with maximum hormone receptor positivity seen in the grade 1 and 2 cases as compared to grade 3 cases. The overall Her-2 positivity seen was 18.67% (Table 3 and 4). In a study done in the African population by Dimitri *et al.* in the Republic of Congo among 150 patients, maximum cases belonged to grade 2 tumors, with an overall hormone positivity seen of 68%.[24] However, an Indian study done in Kerala showed an ER positivity of 52%.[7] Ambroise *et al.* reported that the hormone expression seen in the Indian studies is much lower than that in the western counterparts, which again could be due to the late stage diagnosis or the grade 3 cases seen among Indians.[18]

Among those patients tested for Ki67 proliferation index, 44.44% showed a Ki67 percentage <20% (Table 3). This is of value prognostically as breast cancers with high Ki67 index are known to have poor prognosis and survival rates as well. Even in the current study, most of the grade 3 tumor cases showed a high Ki67 proliferation index >20% (Figure 4). Some studies have also been done to analyze the importance of Ki67 index as an independent prognostic marker in routine clinical decision-making.[25,26] Molecular techniques have improved our understanding of breast cancer biology, refining molecular classification, and have led to the development of novel prognostic and predictive molecular assays. In this study, the molecular classification of the tumors was done based on hormone receptor and Her-2 gene expressions and the Ki-67 proliferation index.[7] Based on this, the cases were divided into Luminal A, Luminal B, Luminal B Like, HER-2 positive and Triple negative (basal-like). Triple negative group includes cases that are non-responsive to all three biomarkers. Thus, in the current study, we observed 25.43% Luminal A group, 10.80% Luminal B, 9.93 % Luminal B Like 17.26% Her-2 positive and 36.58% Triple negative group (Figure 5). These results were somewhat similar to those seen in the study by Dimitri *et al*.[24] In our study, maximum cases of luminal A were seen. In 2021, Jonnada *et al.* performed a meta-analysis on breast cancer studies among the Indian population which also showed similar results.[27] A 2015 study by Kumar *et al.* showed Luminal A subtype as the most prevalent (34%), followed by Basal like/Triple negative subtype (25%). Luminal B and Her-2/neu subtypes had a lower prevalence, i.e. 18% each. This study was, however, done on a small data set of 50 patients with maximum (54%) belonging to grade 2.[28] Luminal A is known to have a good response to hormonal therapy, whereas non-Luminal A cancers are at greater risk of recurrence. Luminal B cases have a variable response to hormonal therapy but a good response to chemotherapy.[29,30] Majority of the invasive duct carcinoma cases in our study were triple negative cases (37.88%) (Table 8). Triple negative tumors show aggressive clinical behavior, indicate a high histological grade, often present with advanced disease, and may show early metastases. These have been found to be less responsive to treatment and are known to have the worst prognosis.[27] The probable factors for high rate of triple negative cases in the Indian population could be the mean age of cancer origin, family history, lifestyle factors like obesity, reproductive status, multiparity, socio-economic status and cancer screening.[31] The correlation of molecular subtypes with age, histological type and SBR grade performed in our study showed that there was a significant association between molecular subtype and each of these parameters. The percentage

of Luminal A cases was seen to increase with age, whereas a contradictory finding was seen in the triple negative cases (Table 8). Thus, based on the results of our study, the triple negative cases were more predominant in the younger age group <40 years, while the luminal A cases were more frequent in the older age group. This finding was in contradiction to the finding by Ambroise *et al.* where maximum triple negative cases were grade 3 and were seen in the older age group (>50 years). However, some other worldwide studies have also shown that triple negative cases are more common in younger women< 40 years.[18,32-34] Some factors that may contribute to this observation could be racial predisposition, family history, drug history like oral contraceptive pills and the presence of BRCA genes. Further research may be required to understand the increased prevalence of triple negative cases in the Indian scenario as well. In our study, maximum percentage of triple negative cases were grade 3. This further reinstates that triple negative tumors are more aggressive clinically and poor prognostically. There is continuous ongoing research in the field of targeted therapy and precision medicine to overcome this hurdle. Newer technologies and platforms like next generation sequencing and microarrays have shown that the tumor response to treatment is hugely dependent on the intrinsic molecular makeup of these tumors and less on the anatomic structure. Hence, newer assays and comprehensive panels may help identify these otherwise overlooked and biologically aggressive tumors with the long term aim of guiding therapeutic strategies to deliver optimum patient outcome.[35]

CONCLUSION

It was observed that grade 3 tumor cases were most common and most of the cases of triple negative tumors were seen among women, mostly concentrated in those <40 years. Her-2 gene status and Ki-67 proliferation index are major biomarkers that predict the tumor behavior and, thus, are important clinically for tumor responsiveness to various lines of therapies. We can conclude that molecular sub-classification of tumors is primarily guided by immunohistochemistry, and it can be recommended that the use of molecular analysis and gene expression studies can further augment the histopathological diagnosis to assist strategies of targeted therapy and precision medicine resulting in better patient outcomes.

ETHICAL CONSIDERATIONS

All patients signed an informed consent for the unanimous presentation of their data in a medical journal. The local ethical committee has approved the protocol of this retrospective study.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. International Agency for Research on Cancer. India Source: *Globocan* 2020. Available from: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
2. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. *CA Cancer J Clin* 2011; 61: 409-418. doi: 10.3322/caac.20134
3. Mehrotra R, Yadav K. Breast cancer in India: Present scenario and the challenges ahead. World J Clin Oncol 2022; 13(3): 209-218
4. Arpita J, Priyanka G, Ranjana S. A Study of Molecular Subtypes of Carcinoma Breast by Immunohistochemistry at Tertiary Care Center, Jaipur. *Asian Pacific Journal of Cancer Biology*, 2022*:7*(3), 219-223. doi:10.31557/apjcb.2022.7.3.219-223.
5. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, Hernandez-Boussard T, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clinical Cancer Research: *An Official Journal of the American Association for Cancer Research*. 2004 08 15;10(16):5367- 5374. doi:10.1158/1078-0432.CCR-04-0220
6. Yeh IT, Mies C. Application of Immunohistochemistry to Breast Lesions. *Arch Pathol Lab Med*. 2008;132:349– 358
7. Achalkar GV. Immunohistochemistry in breast carcinoma. *Ind J Pathol Oncol*, 2018;5(3):415-417
8. Mittal, A., & Mani, N. (2021). Molecular classification of breast cancer. *Indian Journal of Pathology and Oncology*, *8*(2), 241–247. doi:10.18231/j.ijpo.2021.047
9. Sundar S, Khetrapal-Singh P, Frampton J, Trimble E, Rajaraman P, Mehrotra R, et al. Harnessing genomics to improve outcomes for women with cancer in India: key priorities for research. *Lancet Oncol* 2018; 19: e102-e112. doi: 10.1016/S1470-2045(17)30726-X

10. Board, W. C. O. T. E. (2019). *WHO classification of breast tumours: WHO Classification of Tumours, Volume 2*. International Agency for Research on Cancer.
11. (College of American Pathologists, 2023) https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/guideline-recommendations-for-immunohistochemical-testing-of-estrogen-and-progesterone-receptors-in-breast-cancer
12. Ahmad Fauzi MF, Wan Ahmad WSHM, Jamaluddin MF, Lee JTH, Khor SY, Looi LM, et al. Allred Scoring of ER-IHC Stained Whole-Slide Images for Hormone Receptor Status in Breast Carcinoma. *Diagnostics (Basel)*. 2022 Dec 8;12 (12):3093. doi: 10.3390/diagnostics12123093.
13. https://www.agilent.com/en/product/pharmdx/herceptest-kits/herceptest-mab-pharmdx-dako-omnis-1324550
14. https://www.molecular.abbott/int/en/products/oncology/pathvysion-her-2-dna-probe-kit-II
15. http://www.accessdata.fda.gov/cdrh_docs/pdf6/k061602.pdf BioView Duet approval for PathVysion
16. http://www.accessdata.fda.gov/cdrh_docs/pdf8/k080909.pdf Ikonisys approval for PathVysion
17. *The molecular subtypes of breast cancer*. (n.d.) https://www.breastcancer.org/types/molecular-subtypes
18. Ambroise M, Ghosh M, Mallikarjuna VS, Kurian A. Immunohistochemical profile of breast cancer patients at a tertiary care hospital in South India. *Asian Pac J Cancer Prev*. 2011;12(3):625-9.
19. Upadhyay AK, Prakash A. Clinicopathological Profile of Breast Cancer at a Tertiary Cancer Center in Jharkhand, India: A Descriptive Cohort Study. *Cureus*. 2023 Jun 5;15(6):e39990. doi: 10.7759/cureus.39990.
20. Kim EK, Park SY, Kim SW. Clinicopathological characteristics of BRCA-associated breast cancer in Asian patients. *J Pathol Transl Med*. 2020 Jul;54(4):265-275. doi: 10.4132/jptm.2020.04.07.
21. Britta Weigelt, Felipe C. Geyer, Jorge S. Reis-Filho. Histological types of breast cancer: How special are they? Molecular Oncology,Volume 4, Issue 3,2010, Pages 192-208,ISSN 1574-
22. Clusan L, Ferrière F, Flouriot G, Pakdel F. A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer. *Int J Mol Sci*. 2023 Apr 6;24(7):6834. doi: 10.3390/ijms24076834.
23. Ditsch N, Kolberg-Liedtke C, Friedrich M, Jackisch C, Albert US, Banys-Paluchowski M, et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2021. *Breast Care (Basel)*. 2021 Jun;16(3):214-227. doi: 10.1159/000516419.
24. Mboungou Malanda DM, Magloire Boumba AL, Malonga GA, Mouamb FG, Mambouene FD, Moukassa D, et al. Breast cancer in women: epidemiological, histological, immunohistochemical and molecular sub-types in the Republic of Congo. *Int J Health Sci Res*. 2021; 11(5): 103-116. doi:10.52403/ijhsr.20210515
25. Inwald EC, Klinkhammer-Schalke M, Hofstädter F, Zeman F, Koller M, Gerstenhauer M, et al. Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. *Breast Cancer Res Treat*. 2013 Jun;139(2):539-52. doi: 10.1007/s10549-013-2560-8.
26. de Azambuja E, Cardoso F, de Castro G, Colozza M, Jr, Mano MS, Durbecq V, et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. *Br J Cancer*. 2007;96(10):1504–1513. doi: 10.1038/sj.bjc.6603756.
27. Jonnada PK, Sushma C, Karyampudi M, Dharanikota A. Prevalence of Molecular Subtypes of Breast Cancer in India: a Systematic Review and Meta-analysis. *Indian J Surg Oncol*. 2021 Apr;12(Suppl 1):152-163. doi: 10.1007/s13193-020-01253-w.
28. Kumar N, Patni P, Agarwal A, Khan MA, Parashar N. Prevalence of molecular subtypes of invasive breast cancer: A retrospective study. *Med J Armed Forces India*. 2015 Jul;71(3):254-8. doi: 10.1016/j.mjafi.2015.04.006.
29. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. *N Engl J Med*. 2009; 360(8): 790-800.
30. Hu Z, Fan C, Oh DS, Marron JS, He X, et al. The molecular portraits of breast tumors are conserved across microarray platforms. *BMC Genomics*. 2006; 7: 96.
31. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *The New England Journal of Medicine*. 2010 Nov 11;363(20):1938-1948. doi:10.1056/ NEJMra1001389
32. Almansour NM. Triple-Negative Breast Cancer: A Brief Review About Epidemiology, Risk Factors, Signaling Pathways, Treatment and Role of Artificial Intelligence. *Front Mol Biosci.* 2022 Jan 25;9:836417. doi: 10.3389/fmolb.2022.836417.
33. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative Breast Cancer: Clinical Features and Patterns of Recurrence. *Clin Cancer Res.* 2007:13, 4429–4434. doi:10.1158/1078-0432.ccr-06- 3045.
34. Akhtar M, Dasgupta S, Rangwala M. Triple negative breast cancer: an Indian perspective. *Breast Cancer (Dove Med Press).* 2015 Aug 14;7:239-43. doi: 10.2147/BCTT.S85442.

35. Weigelt B, Baehner FL, Reis-Filho JS. The contribution of gene expression profiling to breast cancer classification, prognostication and prediction: a retrospective of the last decade. *J Pathol*. 2010:220:263–280.

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