

Breast Cancer in 2020: Does Receptor Status Still Drive the Cancer as Before – An Indian Study

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Abstract

Background: Incidence of breast cancer has increased globally over the past several decades with the greatest increase in the Asian countries. The hormone status perhaps plays the most vital part in disease discordance and impacts the clinical behavior of the disease. This study attempts to study the receptor status in carcinoma breast in the Indian Population and study any change in its correlation with the clinical profile, tumor characteristics, and metastatic profile. **Methods:** This was a prospective observational study done on all patients with breast cancer treated at Command Hospital Airforce, Bangalore, between January 2017 and December 2019. Two hundred and eight female patients with breast carcinoma were included in the study. **Results:** Estrogen (ER) and progesterone receptors (PR) are found positive in only 20%–45% of Indian patients. ER-positive rates are lower in Indian patients than those in Western countries. Triple-negative breast cancer (TNBC) metastasizes especially to the liver and lung; however, Her 2nu-positive tumors present as Stage III rarely metastasize. Hormone-positive tumor showed a bimodal peak pattern, while TNBC is seen uniformly in all age groups now. BIRADS 5 was seen exclusively in triple-positive disease. Grade I tumors are exclusively seen in hormone-positive tumors, but 25% of these tumors present with distant metastasis and 90% with node-positive disease. **Conclusion:** Breast cancer patients of Indian origin tend to be younger; tumors are often large when first diagnosed, and of a high grade as compared to Western countries. The hormone receptor status still determines and drives the disease; however, there is a major paradigm shift in the disease behavior now as compared to the earlier data. The biology of the disease and the clinicoepidemiological profile of breast cancer in relation to the receptor status is an ever-evolving event and periodic evaluation of their correlation is the need of the hour. This will improve the further understanding of the disease, help in therapeutics, and improve outcomes in such patients

Keywords: Breast carcinoma, epidemiology, receptor status

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in females in the United States, affecting one in eight women. Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths, although there is a five-fold variation in incidence between high-incidence areas such as the United States and Western Europe and low incidence areas such as Africa and Asia.^[1]

Breast cancer is extremely rare among women younger than 20 years and is uncommon among women younger than 30 years. The incidence of estrogen/progesterone receptor (ER/PR positive) tumors increases at 11.0% per year during premenopausal years and at 4.6% per year after natural menopause. In contrast, the incidence of ER/PR-negative

tumors increases at 5.0% per year during premenopausal years and 1.3% after natural menopause.^[2]

The lifetime risk of breast cancer is positively associated with higher socioeconomic status due to the known reproductive risk factors; women in lower socioeconomic strata are more likely to have more children and at younger ages than women in higher socioeconomic strata.^[2] In India, the issue seems to be due to its economic development and rapid urbanization, leading to the westernization of Indian women who start their

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family late, have fewer children, and breastfeed them less than their rural counterparts.

The incidence of the biologically aggressive ER-negative and PR-negative breast cancer in women younger than 40 years has been increasing in African Americans in the US, Nigerian, Chinese, Vietnamese, and Taiwanese populations.^[3]

In Asian population, there is an increase in the incidence of breast cancer and studies show that seen in younger women, have larger tumor sizes, more lymph node metastasis, and are more invasive cancers than those in older women.^[3]

ER status is a predictive factor for breast cancer treatment. It is also a prognostic factor for survival, and it is possible that ER+ and ER-tumors have distinctively different disease profile. Moreover, the significance of PR status has been not been studied extensively and though its role in the disease as a prognostic and predictive marker is established.^[4] Majority of the studies related to the estrogen and progesterone status

The primary aim of the study was to study the clinicopathological and demographic profile of carcinoma breast and correlation with the receptor status in a tertiary care center and to study the metastatic profile of breast cancer.

MATERIALS AND METHODS

This is a prospective observational study done on all patients with breast cancer treated at Command Hospital Air Force, Bangalore, between January 2017 and December 2019, which is the largest tertiary defense hospital of the armed forces in Southern India. All patients of Carcinoma breast presenting to our hospital were included in the study.

All data including age, menopausal status, and pathological characteristics including grade (modified Bloom-Richardson grade), stage of the disease (AJCC), tumor size, and axillary nodal status were recorded. The hormone receptor (HR) (ER, PR, Her2Neu, and AR) status of all patients was recorded, and those without these were excluded from the study. In cases where Her2Neu status was equivocal (2+) by immunohistochemistry (IHC), analysis of HER2Neu by fluorescence *in situ* hybridization was undertaken at an outsourced laboratory.

Patient consent

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' written approval (consent attached).

RESULTS

Two hundred and eight female patients and one male patient with breast carcinoma were included in the study at Command Hospital Airforce, Bangalore. Out of the 208 patients, 118 (56.7%) were menopausal and 90 were premenopausal. One hundred and forty-three (68.75%) patients were below the age of 55 [Table 1].

Table 1: General characteristics of the studied population

Variable	n=208, n (%)
Menstruation	
Premenopausal	90 (43.30)
Postmenopausal	118 (56.70)
Stage	
I	4 (1.9)
II	58 (25.9)
III	119 (57.2)
IV	31 (14.9)
Tumor size	
T1	5 (2.4)
T2	98 (47.5)
T3	79 (37.9)
T4	25 (12)
Nodal status	
N0	21 (10)
N1	108 (51.9)
N2	53 (25.4)
N3	27 (12.9)
ER status	
ER+	123 (59.1)
ER-	85 (40.9)
PR status	
PR+	111 (53.4)
PR-	97 (46.6)
Her2 neu status	
Her2+	84 (40.3)
Her2-	124 (59.7)
Receptor status	
Luminal A (ER/PR+HER-)	92 (44.2)
Luminal B (ER/PR+HER+)	44 (21.1)
Her 2 enriched	37 (17.7)
TNBC	35 (16.8)

ER: Estrogen receptor, PR: Progesterone receptor, TNBC: Triple-negative breast cancer

The upper outer quadrant of the breast was the primary site for 97 (46.6%) of the tumors. The lower outer quadrant was involved in 28.8% of tumors. The average size of the tumors was 5.1 cm (radiological measurement) [Figure 1]. T2 tumors accounted for 98 (47.5%) of the cases. 107 (51.4%) of patients had N1 disease, and this was statistically significant ($P < 0.001$). Staging was done as per AJCC/IUCC staging system and 119 (57.2%) were Stage III, and this was statistically significant ($P < 0.003$). Thirty (14.4%) patients had presented with metastatic disease and 15 (7.2%) patients developed metastases during the study period. Histopathological subtypes are shown in Figure 2.

On correlating the histopathological grade with receptor subtype, IDC Grade III tumors were seen to have lesser Luminal B/A (ER/PR +ve/Her 2nu-ve) and more percentage of triple-negative breast cancer (TNBC), and HER2 enriched subtypes compared to Grade II tumors. In Grade I tumors, all tumors were ER/PR positive as shown in Figure 3.

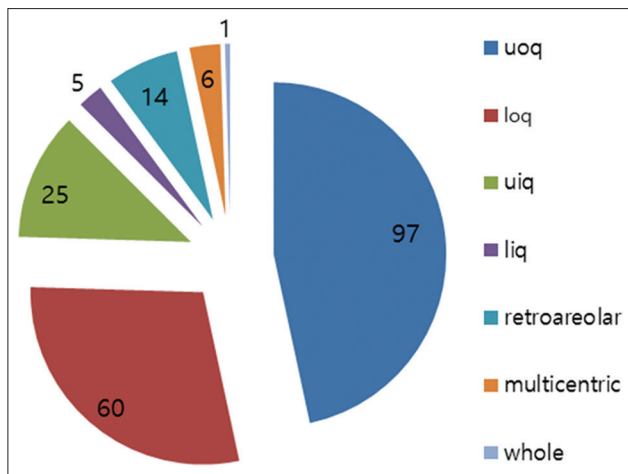


Figure 1: Distribution of side and quadrant

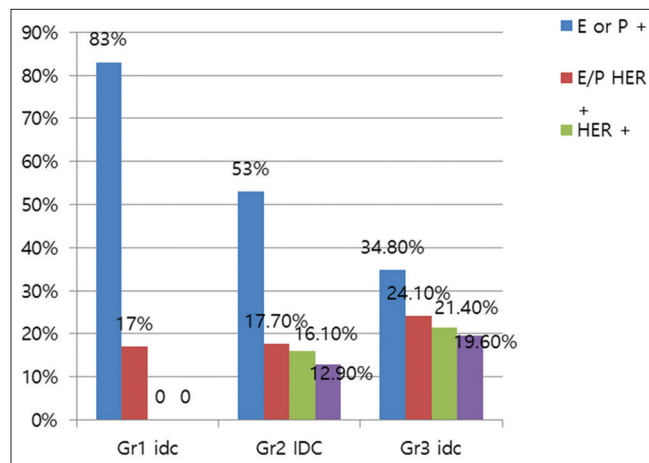


Figure 3: Correlation of histopathology grade with receptor subtype

The HR status was correlated with the TNM stage. Luminal Type A accounted for 90 (43%) of all tumors [Figure 2]. Forty-six (50%) of luminal A type was T2 disease. Fifty-five (59.7%) of luminal type A was N1 disease and 23 (25%) had metastatic disease. Among HER 2 enriched population, Stage III accounted for 78% of the cases, which was statistically significant ($P < 0.005$). Twelve (36.3%) patients in the TNBC group developed distant metastases, which was also statistically significant ($P < 0.003$). In patients who were HER2 enriched (Her2+, ER/PR negative), 78.4% presented with Stage III disease. Among all receptor subtypes, Stage III was the most common presentation [Table 2].

Patients underwent either modified radical mastectomy (MRM) or breast conservation surgery (BCS) depending on stage at presentation and patient profile. One hundred and sixty-six (79%) patients underwent MRM and 24 (11%) received BCS. All of the TNBC underwent MRM as per Armed Forces oncology group guidelines.

Luminal A was seen in 50% young age below 45 years and then again after 60 years, while the luminal B and Her 2 enriched were seen maximum between the age of 45–60 years. TNBC

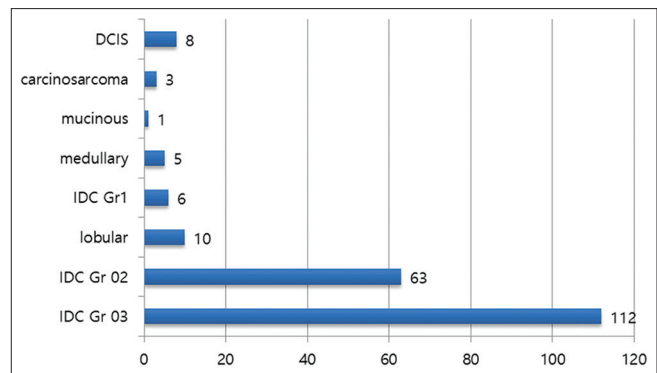


Figure 2: Histopathological subtypes

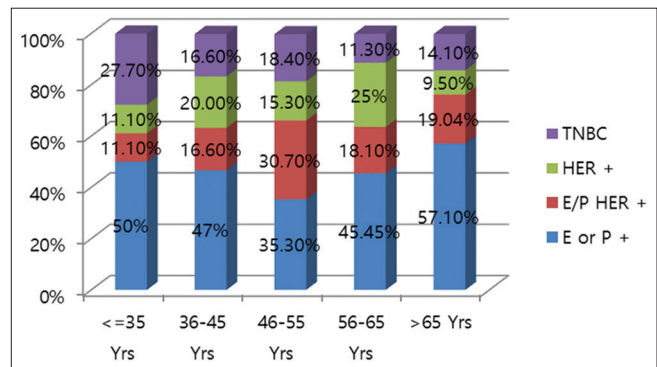


Figure 4: Receptor group correlation with age groups

was maximum in the age below 35 years but consistently remained high above 10% in all other age groups [Figure 4].

On correlating the receptor subtype and the BIRADS score, it is seen that BIRADS 4 is the most common score in all receptor subtypes except in the luminal B subtype, where BIRADS 5 was the most common score [Figure 5].

On correlating the metastatic sites in different receptor subtypes, brain metastases were seen in 22.8% of HER 2-enriched cases and 18% of luminal B cases with a definite trend in patients in HER + is positive though not statistically significant ($P > 0.05$). In metastatic patients who were either ER and/or PR positive, 56.7% of metastases were skeletal ($P < 0.004$). In patients with TNBC, 37.1% and 31.4% had lung and liver metastases, respectively, while in patients with luminal B metastases occurred in all sites with no particular predilection. Other sites of metastases were adrenals, endometrium, ovaries, skin, and soft tissue which occurred in all subgroups [Table 3].

DISCUSSION

The incidence of breast cancer in India is around three-fifth of the incidence of the United States, but the mortality is around one and a half times that of the US. Clearly, the biology and epidemiology of breast cancer in India are different from that of the West.

In our study, the age group affected most was between 46 and 55 years (31.2%), followed by the 36 and 45 age

Table 2: Hormone receptor status and stage

	ER or PR + (luminal A)	ER/PR and HER + (luminal B)	HER +	TNBC	Total	P
Tumor grade						
2	46	19	20	14	99	0.56
3	35	16	12	16	79	
4	9	9	3	4	25	
Lymph node						
0	10	5	1	5	21	<0.001
1	55	22	13	17	107	
2	24	6	11	12	53	
3	3	11	12	1	27	
Mets						
0	69	38	35	21	163	<0.005
1	23	6	2	12	45	
Stage						
2	28	14	6	10	58	<0.003
3	51	26	29	13	119	
4	13	4	2	12	31	

ER: Estrogen receptor, PR: Progesterone receptor, TNBC: Triple-negative breast cancer

Table 3: Correlation of metastatic sites with receptor subtype

Site of metastasis	Metastasis with receptor status				Total (129)
	(Luminal A) (37)	(Luminal B) (22)	HER+enriched (35)	TNBC (35)	
Brain					
Number of patients	0	4	8	3	15
Percentage within status	0	18	22.8	8.5	
Skeletal					
Number of patients	21	7	4	8	40
Percentage within status	56.7	31.8	11.4	22.8	
Lung					
Number of patients	8	8	7	13	36
Percentage within status	21.6	36.3	20	37.1	
Live					
Count	8	3	6	11	28
Percentage within status	21.6	13.6	17.1	31.4	

TNBC: Triple-negative breast cancer

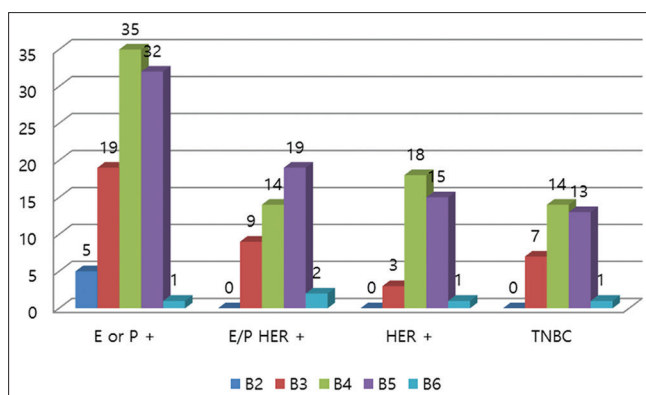


Figure 5: BIRADS score and receptor subtype

group (28.8%). The incidence in India begins to rise in the early thirties and peak at ages 50–64 years a decade earlier than in the US where peak is beyond 75 years. The incidence rate in

US dramatically rises beyond 65 years, whereas in India, the rates remain relatively stable.^[5]

Nearly 61.2% of cases belonged to Stage II in the study by Raina *et al.*^[5] In the study by Vettuparambil from Kerala,^[6] T2 tumors were 63.2%. In the present study, T2 tumors were 49% of the population, whereas T3 tumors were 37.9%, suggesting that women in our study group presented with higher sized tumors. Premenopausal population in this study amounted to 43.3% and postmenopausal was 56.7%, whereas in the US, 73% of the white females are postmenopausal at diagnosis barring the African American population where the postmenopausal population is around 49%.^[7]

In other Indian studies, majority of patients presented with Stage III (47%^[8] and 52%^[9]). In the present study, Stage III was the most common presentation (57.2%), suggesting that our women present with advanced disease at onset due to lesser awareness regarding breast cancer. Nearly 89% of the

studied population was literate, with 14% having completed graduation and five patients had completed postgraduation. Education status did not seem to make a difference in the duration of disease before diagnosis, although it was expected that the higher educated patients would have presented earlier.

Ali Pourzand *et al.* reports that 77.7% of the younger women had positive lymph nodes, as compared to 56.3% of the older women. Saxena *et al.* in a Delhi hospital-based study reports nodal positivity to the tune of 80.2%.^[8] In our study, 188 out of 208 patients (90.4%) had positive node which implies that breast cancer now is more aggressive.

The HR status of breast cancer is an important prognostic factor and predictive parameter of the response to hormone therapy. At TMH Mumbai, the ER+ status was found in 33% and PR + in 46% of patients.^[10] Anderson *et al.* documented an 80% incidence of ER positivity in a SEER analysis. Yang *et al.* from Taiwan reported ER positivity to be 65% in his study.^[11] ER and PR are found positive in only 20%–45% of Indian patients. ER-positive rates were reported to be lower in Indian patients than those in Western countries were. A study from Mumbai reported that the ER-/PR + reported on IHC was actually due to suboptimal manual assays, and when the same tumors were evaluated using well-standardized international kits, they were found ER+/PR+.^[11,12] In the present study, ER expression was seen in 123 (59%) patients, PR expression was seen in 111 (53.4%) participants, and Her2Neu expression was seen in 84 (40.3%) patients. SEER data show ER positivity to be around 77% from various studies.^[13] It can safely claimed that, in the present study, the receptor positivity is comparable to the available national data. Our higher rate of ER and PR positivity may be due (a) cutoff for ER/PR positivity has been reduced from >10% to “any positivity” seen on the slide and (b) better immunohistochemical staining methods available presently.

Histopathology subtypes

In a study from New Delhi,^[8] invasive ductal carcinoma was found to be the most common type (88%). At a premier institute in Lucknow, again IDC was the most common variety, with very few noninvasive (DCIS).^[14] At a major cancer center in the city of Mumbai, 70% of patients were reported as having Grade III disease.^[15] In our study, invasive ductal carcinomas accounted for 181 (87%) cases. IDC Grade 3 accounted for 112 (53%) of all the cases.

On correlating the histopathological grade with receptor subtype, IDC Grade III tumors were seen to have lesser ER/PR positivity and more percentage of TNBC and HER2+ subtypes compared to Grade II tumors. In Grade I tumors, all tumors were ER/PR positive which implies that higher the grade, lesser the ER/PR positivity and more the HER2+/TNBC status, i.e., increasing grade is a marker for poorer disease biology.

Estrogen receptor and progesterone receptor and HER2 Neu with age groups

Average age at diagnosis of luminal A tumors in one as per Western data was around 62 years and 84% of these tumors

were Stage I or II.^[16] In Kerala,^[6] 63.8% of patients between 30 and 40 years were luminal A and TNBC tumors were only 2.5% in that age group. Advancing to the 40 and 50 age group, the luminal A group reduced to 58% and the TNBC group increased to 40%. In the present study, luminal A accounted for 47% of cases in the 35–45 years and 35.30% in the 45–55 year age group. In the Caucasian study, the luminal A type was 50% in both young and older women.^[3] Raina *et al.* in his study states an overall ER positivity of 53% in the 193 patients studied. ER positivity status on adding the luminal B group is 59% and hence consistent with existing Indian data.

Metastatic profile of breast cancer

Despite advances in therapeutic modalities, 20% to 30% of patients with early breast cancer experience relapse with distant metastatic disease.^[15] HER2 and ER expression status has been associated with increased risk of spread to specific sites. However, few studies have described patterns of metastasis according to the major breast cancer intrinsic biologic subtypes (those expressed by IHC and/or gene expression profiling).

Very few Indian studies describe the metastatic profile of breast cancers in our subcontinent. The present study is one of the few studies describing the same.

Kennecke *et al.* showed low risks of brain metastases in 2.2% of luminal A, whereas both HER2 enriched (28.7%), TNBC (47.5%), and luminal B (15.4%) subtypes had a relatively high rate of metastasis to brain, liver, bone, and lung sites. In the present study, 22.8% of those with HER-enriched subtype developed brain metastases. The same study described that, in TNBCs, high rates of lung, bone, and distant nodal metastases of 18.5%, 16.6%, and 17.2%, respectively, but a comparatively lower rate of liver metastases (9.3%). In the present study, rates of lung and bone metastasis were 37.1% and 22.8%, respectively. Liver metastasis in the TNBC subtype was higher (31.4%) than Kennecke *et al.* study.

Bone was the predominant site of metastasis for the luminal A (69%) and luminal B (65%) groups and the least common site in the TNBC group (39%). In the present study, bony metastases were predominantly seen in the luminal A accounting for 56.7% of the patients with bone metastases. Nearly 31.3% of the luminal B subtype had bone metastases. Both HER2-positive subtypes were associated with a significantly higher rate of brain, liver, and lung metastases compared with luminal tumors.

CONCLUSION

Breast cancers in Indian women occur early involving more premenopausal females; tumors are larger in size, node positive, higher stage, and more aggressive as compared to that in the west where the population is postmenopausal elderly with a lower stage of cancer. Receptor status in breast cancers is a still an important driver for as per our study, but there are some significant changes over the past few years. Grade I

tumors are exclusively seen in hormone-positive tumors, but one-fourth of these tumors may present with distant metastasis and almost all with node-positive disease. TNBC is the most notorious to metastasize, especially to the liver and the lung; however, Her 2nu-positive tumors present, which present as Stage III rarely metastasize. Hormone-positive tumor shows a bimodal peak pattern, while TNBC is seen uniformly in all age groups. BIRADS 5 in our study was seen exclusively in triple-positive disease. As the diseases evolve, the need for further such correlation with receptor status will open new doors into the biology of breast cancer enabling improvement in diagnosis and management, thereby achieving better prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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