Original Article

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Breast Carcinoma, Receptor Status, and Her2 neu Overexpression Revisited

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Abstract

Background: A study conducted by the WHO revealed that Chennai has the highest incidence of breast carcinoma among all leading centers in India. For every two newly diagnosed case, one is dying. Early detection and treatment are the only way to prevent such deaths. Estrogen receptor (ER) progesterone receptor (PR) status, and Her2 neu (human epidermal growth factor receptor 2) overexpression study aid in deciding the treatment strategies. Study design: Cross-sectional descriptive study.

Aim: To statistically evaluate the occurrence of breast lesions in patients attending Coimbatore Medical College hospital and compare it with the global census. In addition to compare ER, PRs, and Her2 neu status with the possible variables we encounter.

Materials and Methods: The 368 breast specimens that were sent to the pathology department for the period of 3-year were analyzed. Both H&E stained sections and ER, PR, and Her2 neu status were reviewed by a team of experienced pathologists in our post-graduate teaching institute.

Results: Totally 368 breast tumor cases were analyzed in our study. Out of that, 63.35% were malignant breast cases. Invasive ductal carcinoma (not otherwise specified [NOS]) [79%] was most commonly encountered, and most of them were grade two tumors (88.5%). The ER/PR expression was more in carcinoma in stage 1 and II and in tumors without nodal metastasis (P = 0.001). Her2 neu expression was seen more in high-grade tumors and in those with nodal metastasis (P = 0.001). There was an inverse relationship between ER/PR status and Her2 neu expression (P = 0.001).

Conclusion: When compared with the western studies the ER, PR expression was low in our study group. Moreover, there was an inverse relationship between the ER, PR expression, and Her2 neu status.

Key words: Ductal carcinoma, Estrogen receptor, Progesterone receptor, Node

INTRODUCTION

For the past 4 years, breast cancer (BRCA) in overtaking all other cancers that affect women with an alarming number (1, 55,000 new cases/year) causing more than 6 million deaths per year.[1,2] The mean age of occurrence is 42 years.[2,3] Racial difference was also noted, black women were affected at a relatively younger age (45 years).[4] Prognosis and management of breast carcinoma are influenced by variables such as histological type and grade, tumor size, lymph node status, lymphovascular invasion, proliferating rate, DNA content, estrogen receptor (ER), progesterone receptor (PR) status, and Her2 neu overexpression and fluorescence *in situ* hybridization studies using centromere enumeration probe 17.[5] Of all these factors, the receptor and molecular studies had made a sea of change in the diagnosis and the treatment of breast carcinoma. While molecular tests are expensive and are not easily available, immunohistochemical (IHC) analysis is comparatively cheaper, useful for targeted therapy and a good prognostic factor.

The interrelationship of ER, PR status, and Her2 neu overexpression has an important role in the management of breast carcinoma. ER/PR status is inversely related to Her2 neu status. Survival and response to hormone therapy (tamoxifen) are more favorable among women who are receptor positive, intermediate for tumors discordant

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on receptor status and less favorable for receptor negative patients. However, if there is an amplification of both ER and Her2 neu, then the patient would not respond to tamoxifen.[6] Tamoxifen acts as an agonist if there are both ER expression and Her2 expression and cause proliferation of the tumor tissue, leading on to the resistance of tamoxifen.[7] In such cases, it has been shown that trastuzumab therapy is more effective. Patients with lone Her2 neu overexpression are also candidates for trastuzumab.[5,8,9] Thus, IHC studies have a role as a decision maker in the targeted therapy. This study is done to evaluate the ER, PR, and Her2 neu status and to compare it with the various variables we encounter as we analyze the cases.

MATERIALS AND METHODS

This is a cross-sectional study spanning over a three year period. 368 breast specimens were received during the study period. A detailed history regarding age, parity, socioeconomic status, family history, menstrual history, lactation history, and previous biopsy reports was reviewed in all the cases.

Inclusion Criteria

Newly diagnosed cases were included in our study.

Exclusion Criteria

Patients who had the neoadjuvant therapy were excluded from our study.

Patients with other associated malignancies were excluded from our study.

Macroscopy

Detailed gross examination pertaining to the overall size of the specimen, appearance of skin with measurements of scars or incisions, the appearance of the nipple and areola, tumor size, consistency, margins, and nodal status was noted from the records.

Microscopy

Slides from all the cases stained with hematoxylin and eosin were assessed. The histological assessment of tumor grade was done by modified Bloom–Richardson scoring system. Nodal status and margin involvement were recorded in each case. The WHO classification was used to classify the tumors.

Immunohistochemistry

Both ER/PR assay and Her2 neu assay were done in our study because of the following reasons: Hormone receptors are well-established biomarkers in breast carcinoma and their assessment helps in predicting the response to endocrine therapy.[10-12] Her2 neu is a prognostic marker as overexpression of Her2 neu in breast carcinoma leads to recurrence and worst prognosis.[13,14] IHC analysis of hormone receptor assay and Her2 neu status was done on the paraffin-embedded tissue blocks by the supersensitive polymer HRP system based on non-biotin polymeric technology.

Scoring System

IHC stained slides were evaluated for the presence of reaction, cellular localization (nuclear or cytoplasm), pattern of staining (focal or diffuse), and intensity of reaction in the individual tumor cells (strong or weak). Scoring for ERs and PRs was done using Quick score system and for Her2 neu, the scoring was done according to the guideline published by Ellis *et al.*[15,16] Quick score system uses two principles, intensity and proportion.[15] The quick score system based on intensity is as follows: When there are no staining - score 0. Weak stain- score 1, moderate stain - score 2, and strong stain - score 3. The staining system based on the proportion of stain is as follows: 1% nuclear stain - score 0, 1-10% stain-score 2, 11-33% - score 3, 34-66% - score 4, and 67-100% - score 5. This comes with a maximum score of eight. Score of more than two is considered as positive.[17] The advantage of this score is that it correlates with the probability of response to endocrine therapy.[18]

For Her2 neu scoring the following rule was followed: No staining or incomplete membrane staining and faint/barely perceptible in ≤10% of the tumor cells - Her2 neu negative. Incomplete and faint membrane staining in >10% of the invasive tumor cells are taken as Her2 neu 1+. A weak to moderate complete membrane staining in >10% tumor cells are graded as Her2 neu 2+. A strong complete membrane staining in> 10% tumor cells are graded as Her2 neu 3+.

Statistics

The statistical analysis was performed with Statistical Package for Social Science (SPSS) software version 11. The Pearson Chi-square test was used to compare the possible correlation between ERs, PRs, and Her2 neu with tumor size, nodal status, histological variants, and grades.

RESULTS

A total of 27,638 specimens were received. The distribution of benign breast disease (36.65%) and malignant breast tumors (63.35%) are depicted in (Table 1). Benign tumors had a peak incidence in the age group 21-30 years, whereas the malignant tumors had a peak incidence in the age group 41-50 years (Table 2).

Table 3 shows the distribution of histological variants in breast carcinoma. 79% were invasive ductal carcinoma (IDC), NOS type (Table 3), 88% of cases were Grade II tumors, and 46% of the cases had metastatic deposits in the lymph nodes. Dixon *et al.* and Omar Hameed in their studies had mentioned that IDC was the predominant histological variant.[19,20] In our study, the incidence of invasive lobular carcinoma was 3%, and it correlated with Foote and Stewart *et al.*'s study.[21]

When ER/PR status was analysed, both were positive in 24.24% of the cases and both were negative in 48.48% (Table 4). In Wilbur and Barrows study, ER positivity was observed in 73% of the cases and PR positivity was observed in 63% of the cases.[22] 70% of the BRCA were ER positive, and 60-65% were PR positive, according to Mohsin.[12] ER/PR expression increases as the age of the patient advances (Table 5). Her2 neu expression and inverse relationship between ER/PR and Her2 neu is depicted in (Tables 6 and 7). When ER/PR status was correlated with tumor grade, it was strongly expressed in low-grade tumors (Table 8). Most of the ER/PR positive cases were 2-3 cm in size (Table 9). When it was statistically analyzed, the $P = 0.003$ which highlight the significance of this correlation. When the nodal status was correlated with ER/PR expression, high ER/PR expression was seen in those without nodal metastasis (Table 10). Statistical analysis was done between these variables and was found to be significant ($P = 0.001$). In Huang *et al.*'s study, ER positivity was less in nodal positive tumors.[23]

Table 1: Distribution of cases

Total number of specimens	Total number of breast specimens	
	Benign	Malignant
27,638	135	233

Table 2: Age distribution

Age group (in years)	Benign tumors	Malignant tumors
<20	24	-
21-30	58 (57%)	12
31-40	30	32
41-50	14	105 (63.33%)
51-60	7	46
60 and above	2	38

Table 3: Distribution of the histopathological variants

Histological variants	Number of cases	Percentage
IDC-NOS type	184	79
Invasive lobular carcinoma	7	3
Mucinous carcinoma	14	6
Papillary carcinoma	7	3
Metaplastic carcinoma	7	3
Neuroendocrine carcinoma	7	3
Medullary carcinoma	7	3

NOS: Not otherwise specified, IDC: Invasive ductal carcinoma

Table 4: Distribution and correlation of ER/PR status

Group	Percentage
ER+/PR+	24.24
ER−/PR+	18.18
ER+/PR−	9.10
ER−/PR−	48.48

ER: Estrogen receptor, PR: Progesterone receptor

Table 5: Correlation of age and receptor status

Age group (years)	ER/PR positive (%)
21-30	-
31-40	50
41-50	27.3
51-60	77.77
61-70	80
>70	-

ER: Estrogen receptor, PR: Progesterone receptor

Table 6: Expression of Her2 neu in breast carcinoma

Her2 neu positive	Her2 neu negative (%)
42.42	57.58

Table 7: Correlation of receptors with protein expression

ER/PR status	Her2 neu (%)	
	Positive	Negative
Positive	6	45
Negative	36	12

ER: Estrogen receptor, PR: Progesterone receptor

Table 8: Correlation of grade, receptor status and Her2/neu expression

Histological grade	Number of cases (%)	ER/PR positive (%)	Her2 neu positive (%)
Grade I	4	4	-
Grade II	88	54	50
Grade III	8	-	8

ER: Estrogen receptor, PR: Progesterone receptor

Table 9: Correlation of tumor size with hormone receptors and Her2 neu expression

Tumor size (cm)	ER/PR positive (%)	Her2 neu positivity (%)
T1 - <2	66	14
T2-2-5	75	29
T3 - >5	33	57

ER: Estrogen receptor, PR: Progesterone receptor

42% of the cases were Her2 neu positive in our study (Table 6). Kumar *et al.* in their study had mentioned that Her2 neu oncogene overexpression was much higher among Indian BRCA patients 46.3% compared to 25-30% in the western literature.[24] Her2 neu positivity was seen more when the tumor size was >5 cm (Table 9). When the tumor grade was correlated with Her2 neu expression, all higher grade tumors expressed Her2 neu. When it was statistically analyzed, the significant *P* value was obtained (0.001). Her2 neu expression was seen more in those who had metastasis in the node and was analyzed statistically (Table 10). Significant *P* value was obtained ($P = 0.001$).

Table 7 shows an inverse relationship of ER, PR expression, and Her2 neu status. Statistical analysis was performed with the SPSS version 11 and found to be significant ($P = 0.001$). In Huang *et al.*'s study, an inverse relationship with receptor and oncoprotein expression was observed, which correlated with our study.[23]

Table 10: Correlation of receptor status and Her2 neu expression with nodal status

Nodal status	Number of cases (%)	ER/PR positive (%)	Her2 neu positivity
Positive	46	33	67
Negative	54	56	11

ER: Estrogen receptor, PR: Progesterone receptor

Table 11: Comparative analysis of distribution of histological variants of our study with others

Histological types	Dixon *et al.*[19] (%)	Hameed[20] (%)	Current study (%)
IDC-NOS type (Figure 1)	79	>70	79
Lobular carcinoma	10	5-15	3
Mucinous carcinoma (Figure 2)	2	1-5	6
Medullary carcinoma	2	1-7	3
Papillary carcinoma (Figure 3)	1	2	3
Solid neuroendocrine carcinoma	<1	Rare	3
Metaplastic carcinoma	-	2-5	3

NOS: Not otherwise specified, IDC: Invasive ductal carcinoma

DISCUSSION

In the Indian scenario, breast carcinoma and cervical carcinoma account for about 60% of malignancies in women, the incidence of BRCA alone being 10.4%.[2] It has been proposed that the common denominator of risk factors such as menarche, nulliparity, age at first birth and late menopause that lead on to the breast carcinoma is a strong and prolonged estrogen stimulation operating in a genetically susceptible background.[3,25,26] Breast carcinoma can occur sporadically or in a hereditary background. About 25% familial cancers can be attributed to two highly penetrant autosomal dominant genes BRCA 1, early onset and BRCA 2, early onset located in 17q21 and 13q12.3, respectively. BRCA 1 associated BRCA are medullary carcinoma (67%) and mucinous carcinoma (55%). BRCA 2 mutation does not have a distinct morphologic appearance.[8]

The peak age incidence of malignant breast tumors in our study was 41-50 years. Ejam and Farhood in his study had observed the peak age incidence as 30-50 years, which correlated with our study.[27] Onitilo *et al.* in their study had mentioned the peak incidence as 62.7 years.[28] The mean age incidence in Ghosh *et al.*'s study was 49 years, which correlated with our study.[29]

The incidence of various histological variants encountered by Dixon *et al.* and Hameed were comparable to our study (Table 11).[19,20] In Nikhra *et al.*'s study, 95.34% of the tumor was infiltrating ductal carcinoma.[30] Foote and Stewart had recorded that the incidence of lobular carcinoma was 4.9-12% in a post-menopausal age group in their study.[21] In our study, the incidence of lobular carcinoma was 3%, which correlated with their study, but the age incidence in our study was 35 years in contrast to theirs.

Both ER/PR and Her2 neu were employed in our study. A brief introduction of both: ERs and PRs are nuclear transcription factors that are involved in breast development, growth, differentiation, and tumorigenesis.[18,31] ER regulates the expression of other genes such as progesterone and bcl2.[31] There are two forms of ER referred to as ER alpha and ER beta encoded by 6p25.1 and 14q, respectively.[32] ER alpha is found in endometrium, BRCA cells, ovarian stroma, and hypothalamus. ER beta distribution is seen in kidney, brain, bone, heart, and lungs.[33] ER and PR positive tumors tend to have a significantly longer disease-free survival than with receptor negative tumors.[10-12]

Her2 neu [c-erb B -2] belongs to epidermal growth factor receptor family. It is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity located in 17q 11.2 –q12.[13] Her-2 neu overexpression in breast carcinoma leads to recurrence and worst prognosis.[13,14]

In our study, ER and PR were positive in 51.6% cases, and both the receptors were negative in 48.4% cases (Table 7). Her2 neu overexpression was observed in 42.7% cases. This is in correlation with Kumar *et al.*'s study [Her2 neu-46.3%], Shet *et al.*'s study (receptor expression range from 52 to 57%), and Mudduwa study (ER - 45.7%, PR -48.3%).[17,24,34] In our study, ER/PR positivity and Her2 neu negativity were observed in mucinous carcinomas, papillary carcinoma, and neuroendocrine carcinoma. Lee *et al.* in their study had observed ER and PR positivity and Her2 neu negativity in the neuroendocrine tumor of the breast.[35]

Reiner *et al.* and Rosen *et al.* had observed that papillary carcinoma of the breast was ER/PR positive and Her2 neu negative.[9,36] Diab *et al.* and Shousha *et al.* had observed ER/PR positivity and Her2 neu negativity in mucinous carcinoma of the breast.[37,38] All these studies correlated with our study. In our study, medullary carcinoma and metaplastic carcinoma were triple-negative (ER, PR, and Her2 neu). Oberman *et al.*, Rosen *et al.*, and Soomro *et al.* in their studies had encountered similar results.[9,39,40]

Young patients tend to have a high level of circulating estrogen and correspondingly low expression of receptors. Accordingly, in our study, there was increased immune reactivity to ER/PR as the age advances. Dutta *et al.* and Almasri and Al Hamad studies showed similar results.[41,42]

In our study, there was an inverse relationship between hormone receptors and oncoprotein expression (Table 7). Huang, *et al.*'s study showed similar results.[23]

In our study, ERs/PRs were 100% positive in Grade I tumors, and Her2 neu overexpression was 100% positive in Grade III tumors (Table 8). Rosen *et al.* and Jovicic-Milentijevic *et al.*'s studies correlated with ours in this aspect.[9,43]

For the practical purpose, we had categorized the tumor size based on TNM stage as follows: T1- <2 cm, T2 = 2-5 cm, and T3 - >5 cm. As depicted in Table 9, 75% of T2 showed receptor positivity and Her2 neu overexpression was seen in T2 and T3 tumors. Rosen *et al.* and Dutta *et al.*'s study also showed an inverse relationship between tumor size and Her2 neu overexpression and ER/PR status respectively.[9,41]

In our study, receptor positivity was found to be higher among the nodal metastasis negative patients 55.55% and Her2 neu overexpression was seen more in node positive cases than the node-negative patients (Table 10). Dutta *et al.* in their study had observed Her2 neu overexpression in node-positive patients.[41] Huang *et al.* in their study had mentioned that ER/PR expression was less in node-positive patients.[23] The results of these two studies were similar to our study.

Two cases in our study showed positivity for ER/PR and Her2 neu (Table 7). Francis *et al.* and Bhargava *et al.* in their studies had observed hybrid ER/PR and Her2 neu expressions.[44,45]

CONCLUSION

ERs and PRs positive tumors were common in post-menopausal women, tumors of more than 2 cm size, histological Grade-I, and in nodal negative patients.

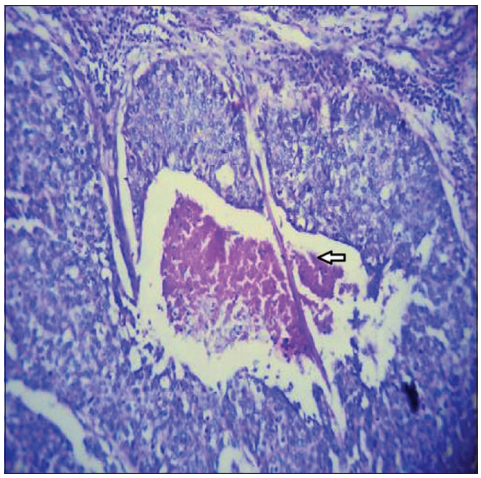

Figure 1: Tumor cells arranged in ductular pattern with central comedo necrosis (arrow) - Invasive ductal carcinoma (H and E, ×40)

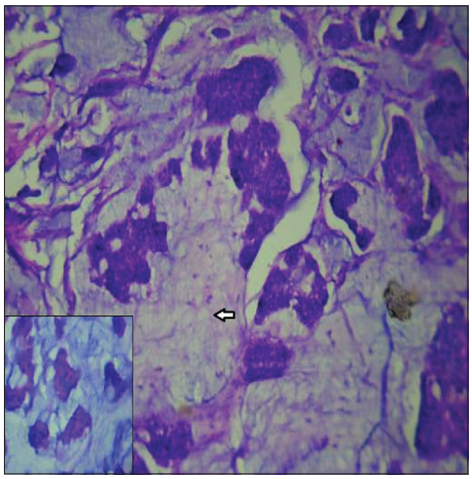

Figure 2: Tumor cells floating in a mucinous pool (arrow). Inset shows the tumor cells (H and E, ×10)

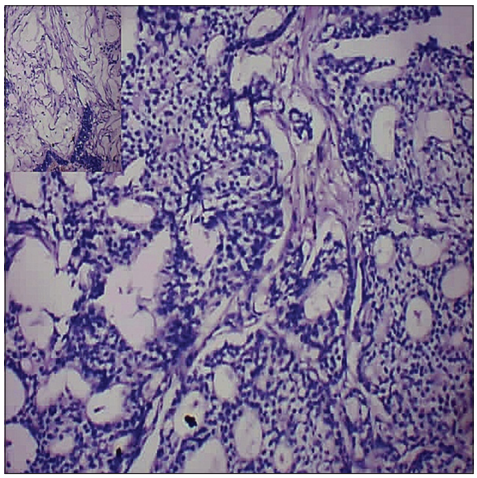

Figure 3: Solid papillary carcinoma showing a cribriform pattern. Inset show focal mucinous areas (H and E, ×10)

Oncoprotein overexpression was common among the tumors of more than 2 cm size, Grade III tumors and in

nodal positive patients. Hormone receptor and oncoprotein expression showed inverse relationship. Compared to the studies from the western world, ER/PR positive tumors were found to be low, while Her2 neu overexpression was higher in our study group.

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