



Histopathological Evaluation of Estrogen Receptors, Progesterone Receptors, and Human Epidermal Growth Factor Receptor-2/Neu Expressions in Breast Carcinoma and their Correlations with Other Prognostic Factors: A Hospital-based Study

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Background: Breast carcinoma is a leading cause of death among women. Factors such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER-2/neu) have important prognostic and predictive value. **Aim:** The aim of the study is to demonstrate ER, PR, and HER-2/neu expression in breast cancer specimens and to correlate these expressions with other prognostic factors such as tumor size, type, grade, and lymph node status. **Methods:** This prospective study included 70 cases of female breast carcinoma. Histopathological evaluation of all cases done and tumor size, site, presence, or absence of lymph node was recorded. Typing of tumor, grade, and lymph node status were determined. Immunohistochemical staining for ER, PR, and HER-2/neu of breast lesions was done, and the data were analyzed to find out any correlation of expression of ER, PR, HER-2/neu with the above prognostic factors. **Results:** The majority of patients were in 41–50 years (44.29%). Most of tumors were 2–5 cm in size and the infiltrating duct carcinoma-not otherwise specified was the commonest type. ER and PR expression decreases ($P = 0.02340$ and $P = 0.02413$ respectively), while HER-2/neu expression increases with increase tumor size ($P = 0.02289$). ER and PR expression were low while Her-2/neu expression was more in higher tumor grade ($P = 0.022472$, $P = 0.04149$ and $P = 0.03339$ respectively). No significant association was identified between ER, PR, HER-2/neu and number of metastatic lymph node. **Conclusion:** ER, PR, and HER-2/neu status correlates well with histopathological grading and tumor size. However, no significant association is seen with cancer type and lymph node status.

Key words: Breast carcinoma, estrogen receptor, progesterone receptor, human epidermal growth factor receptor

INTRODUCTION

Breast carcinoma is the most common site-specific malignant tumor and a leading cause of death from carcinoma among females worldwide.¹ In India, breast cancer is the second most common cancer among women, second only to carcinoma cervix. However, in urban India, breast cancer is the most common cancer among women.²

History, clinical examination, mammography, ultrasonography, and fine-needle aspiration cytology have been the mainstay for diagnosing cancer breast, but the

diagnostic confirmation is best done by histopathological examination. Early diagnosis and proper treatment in breast cancer can prolong survival of patients. Various predictive and prognostic factors have been identified to be associated with breast cancer that affects tumor progression.³⁻⁵ Prognostic markers help to measure the prognosis without treatment. On contrary, predictive markers help to predict whether a patient will respond to a certain therapy or not.⁶

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Received: July 12, 2021; Revised: September 25, 2021;
Accepted: October 01, 2021; Published: December 27, 2021;
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How to cite this article: Kawsar H, Sinha A, Ali MS, Phukan JP, Pathak S. Histopathological evaluation of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor-2/ Neu expressions in breast carcinoma and their correlations with other prognostic factors: A hospital-based study. J Med Sci 2022;42:221-7.

Breast cancer, the most common malignant tumor of the female, is a heterogeneous group of tumors with a wide range of clinical manifestations and histological types. Breast carcinoma also showed a wide range of heterogeneity in its clinical behavior.⁷ Prognostic factors in breast carcinoma are indicators that reflect individual characteristics of the tumor and the patient. Analysis and evaluation of these factors play a fundamental role in selection of the most effective cancer-specific therapy with the least unnecessary toxic effects produced by inadequate treatment regimens. By enabling prediction of the prognosis, these factors also contribute directly to prolonging survival of women diagnosed with breast cancer, and they have an impact, especially in the short term, on the breast cancer mortality.^{8,9}

Estrogen receptor (ER) is the most important predictive marker in breast carcinoma, which determines prognosis as well as predicts response to hormone therapies.¹⁰ Progesterone receptor (PR) is also widely used with ER, although its value is less well established than ER. Breast carcinomas that express ER and/or PR, likely to response well from endocrine therapy like tamoxifen. Human epidermal growth factor receptor-2/neu (HER) is a transmembrane protein which regulates normal breast cell growth, division, and repair.⁶ HER-2/neu is both a prognostic as well as predictive marker. Overexpression of HER-2/neu in breast cancer is associated with poor prognosis, however it also predicts that these patients may get benefitted from target therapy against HER-2/neu like trastuzumab and taxane-based chemotherapies and anthracycline.¹¹ Other prognostic factors of breast carcinoma includes type of tumor, tumor size, tumor grade, total number of lymph node involved at the time of diagnosis, patient's age etc.^{4,12} Many studies have been done on these prognostic factors but concluded with disparate results.^{3-5,12,13}

Hence, we have undertaken the present study with the following aims and objectives:

- i. Histopathological evaluation of various prognostic factors of breast carcinoma like tumor size, type, grade, and lymph node status
- ii. To demonstrate ER, PR, and HER-2/neu expression in breast carcinoma specimen and their correlation with above mentioned prognostic factors.

MATERIALS AND METHODS

Study subjects and study area

This study was conducted in the Department of Pathology of a Tertiary Care Hospital of Eastern India from January 2012

to June 2013. A total of 70 cases of female breast carcinoma were included in the study.

Inclusion and exclusion criteria

Inclusion criteria

All female patients undergoing surgery for breast carcinoma regardless of age and given informed consent.

Exclusion criteria

- i. Patients already in neo-adjuvant chemotherapy
- ii. Previously diagnosed, recurrent breast carcinoma
- iii. Male patients with breast carcinoma
- iv. Patients not willing to give written consent.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee before commencing the study vide memo No: 157/01/31, dated January 13, 2012. Informed written consent was obtained from all patients prior to their enrolment in this study.

Procedure

Detailed clinical and family history of all patients taken. Histopathological examination of mastectomy specimens carried out. During grossing, tumor site, size, and whether any lymph node was present or not; and if present, then the number of lymph nodes recorded. Classification of breast carcinoma according to the World Health Organization (WHO) criteria and microscopic examination of resected lymph nodes done to see whether metastasis present or not and were recorded. Histopathological grading of breast carcinomas was done according to Nottingham modification of Bloom-Richardson system in hematoxylin and eosin-stained slides.¹⁴

Immunohistochemical staining done for ER and PR nuclear receptors and Allred scoring system was used for scoring of ER and PR expression.⁶ HER-2/neu membrane staining was done and depending on the intensity of staining a score of 0–3 was given to the cells; with no staining or membrane staining in <10% of tumor cells scored as 0 and strong complete membrane staining in more than 30% of tumor cells scored as 3+. Score 0–1 considered as negative, while 2+, 3+ was considered as positive according to the American Society of Clinical Oncology and the College of American Pathologist.¹⁵

Statistical analysis

Data were compiled and analyzed to find out any correlation of expression pattern of ER, PR, HER-2/neu with different prognostic factors of breast carcinoma such as tumor size, tumor grade, and number of metastatic lymph nodes. Data

analysis was done by Epi-info software version 3.4.3 (Centre for Disease Control and Prevention, Atlanta, Georgia, US) by applying Pearson Chi-square, Chi-square for linear trend, and P value calculation. $P < 0.05$ is applied to be significant.

RESULTS

In the present study, total of 70 cases of breast carcinomas included. The clinicopathological parameters were included in Table 1. Most of the patients were 41–50 years age group (31 case, 44.29%) with mean age was 47.46 years. 44 numbers of tumors were 2–5 cm in size which is the commonest size of the tumor. Histologically, 65 numbers of cases (92.86%) were diagnosed as infiltrating duct carcinoma not otherwise specified, followed by 2 cases of mucinous and medullary carcinoma of breast [Table 1]. Histological Grade II was the commonest grade of tumor comprising 34 cases (48.57%), followed by Grade III (22 cases). Majority of patients presented with

more than 3 metastatic lymph nodes (34 cases, 48.57%), with 1–3 lymph node involvement was second-most common [Table 1].

Immunohistochemical study for ER, PR, and HER-2/neu revealed that overall ER [Figure 1], PR [Figure 2], and HER-2/neu [Figure 3] positivity was 45.71%, 30.0%, and 25.71%, respectively [Table 2]. With comparison to size of the tumor, we found that percentage of ER and PR positive cases were decreasing as the tumor size increases which is statistically significant ($P = 0.02340$ and $P = 0.02413$ respectively); while HER-2/neu expression decreases significantly as tumor size increases [$P = 0.02289$; Table 3]. Among the Infiltrating duct carcinoma (IDC), 29 cases were ER, 18 Cases were PR, and 18 cases were HER-2/neu positive; while mucinous carcinoma and infiltrating lobular carcinoma were both ER, PR positive but HER-2/neu negative [Table 4]. Both cases of medullary carcinoma were triple negative.

While comparing hormone expression in different grades of tumor, ER, and PR positivity were significantly decreasing as tumor grade increases; while HER-2/neu positivity increases with tumor grade increases which was also statistically significant [$P = 0.022472$, $P = 0.04149$ and $P = 0.03339$ respectively; Table 5]. However, we have not found any significant correlation between ER, PR and HER-2/neu positivity and number of metastatic lymph node in breast carcinoma [Table 6].

DISCUSSION

Various clinicopathological variables such as tumor type, tumor size, histologic grade, lymph node status, vascular space invasion, tumor necrosis, age, extent of ductal carcinoma *in situ* are predictors of prognosis.¹⁶ ER, PR, and HER-2/neu receptor status has been used to determine prognosis as well as helps in

Table 1: Clinicopathological parameters of malignant breast lesions

Clinicopathological parameters	Number of cases, n (%)
Age (years)	
≤40	17 (24.29)
40-50	31 (44.29)
51-60	15 (21.43)
>60	7 (10.00)
Tumor size (cm)	
<2	5 (7.14)
2-5	44 (62.86)
>5	21 (30.00)
Histological type	
Infiltrating ductal carcinoma	65 (92.86)
Mucinous carcinoma	2 (2.86)
Medullary	2 (2.86)
Lobular	1 (1.43)
Histological Grade	
Grade I	14 (20.00)
Grade II	34 (48.57)
Grade III	22 (31.43)
LN status	
0	21 (30.00)
1-3	15 (21.43)
>3	34 (48.57)
Total	70 (100.00)

LN=Lymph node

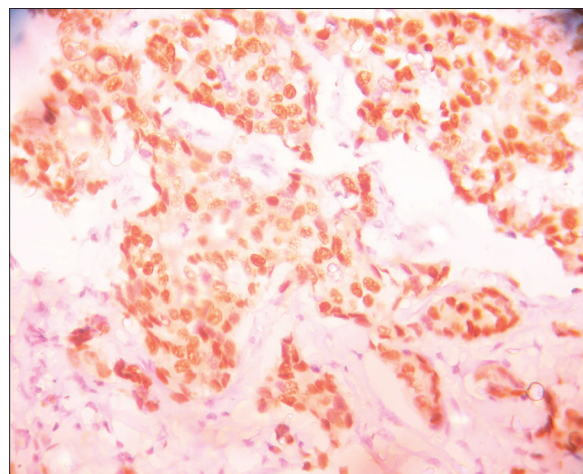


Figure 1: Estrogen receptor positivity-infiltrating duct carcinoma (IHC, ×400)

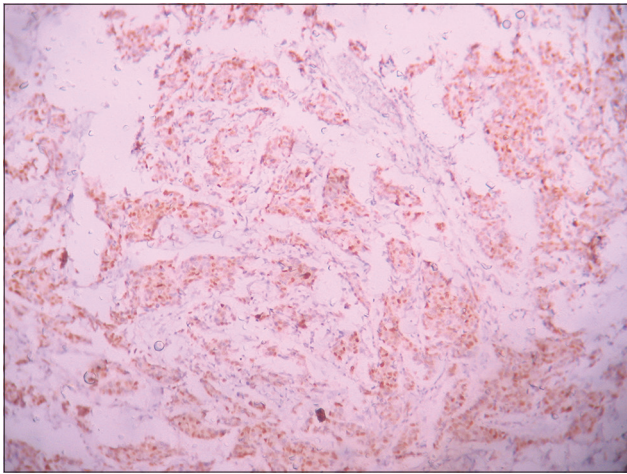


Figure 2: Progesterone recepto positivity-infiltrating duct carcinoma (IHC, ×100)

Table 2: Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2/neu status of the tumors (number of cases/percentage)

Status	ER, n (%)	PR, n (%)	HER-2/neu, n (%)
Positive	32 (45.71)	21 (30.0)	18 (25.71)
Negative	38 (38.0)	49 (70.0)	52 (74.29)
Total	70 (100.0)	70 (100.0)	70 (100.0)

ER=Estrogen receptor; PR=Progesterone receptor; HER=Human epidermal growth factor receptor

deciding treatment for breast cancer.⁶ ER and PR are hormone receptor found on breast cells and pick up hormone signals which causes cell growth.⁶ Breast carcinoma cells when have receptors for hormone estrogen and progesterone, they are called ER and PR positive and this determines that patients are suitable for endocrine therapy.^{6,7} Hormone receptor status is one of the most important prognostic factors which have effect on 5-years survival rates and disease-free survival rates.¹⁷ HER-2/neu protein normally control healthy cell growth, division, and repair in breast. In HER-2/neu positive breast cancer, HER-2/neu gene is overexpressed that causes breast cells to grow and divide in an uncontrolled way.⁶ HER-2/neu positivity is associated with high grade tumors, lymph node metastasis, increase disease recurrence and mortality and thus with a poorer prognosis.¹⁸ Again, HER-2/neu status is also predictive marker of response to various targeted therapies like trastuzumab (Herceptin) and taxane-based chemotherapies.

Our study comprised 70 cases of breast carcinoma. Most of the patients were in the group 41–50 years with mean age of 47.46 years. Various studies found similar age distribution for breast cancer^{1,13,19} However, few studies found that Indian women presented with breast cancer early than Western countries.²⁰ Tumor size, lymph node involvement

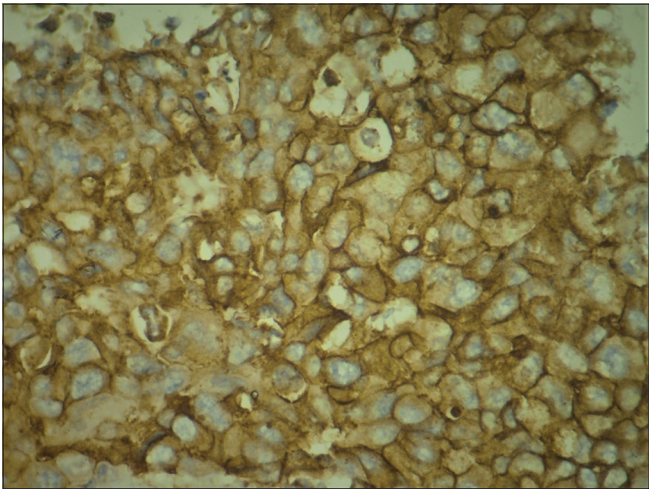


Figure 3: Human epidermal growth factor receptor 2/neu positivity-infiltrating duct carcinoma (IHC, ×400)

and histological grade are other most important prognostic factors in breast carcinoma. 30%–50% of patients with breast cancer showed presence of metastasis and they have a higher tumor size.¹³ Majority of our tumors were >2 cm in size and this finding corroborates well with previous studies.^{1,21} Tumor size alone is an important predictor of tumor behavior. Most common histological type is invasive ductal carcinoma (IDC) comprised of 92.86% of cases and 48.57% of tumors were in histological Grade II; which is comparable to other studies.^{1,22,23}

In our study, ER, PR, and HER-2/neu positivity was found to be 45.71%, 30%, and 25.71%, respectively. The same type of value was found by various other studies.^{1,21,24} However, few studies showed higher percentages of hormone receptor status.^{13,25} This difference may occur due to demographic differences of patients and some biological and socioeconomic factors, such as lifestyle, nutritional status, and environmental exposure may influence hormone receptor expression in breast cancer. Other causes of low positivity in our study may be due to higher tumor grade, and majority of the patients were postmenopausal.

The tumor size of breast carcinoma is also an important prognostic factor because it has been shown to be associated with decreasing expression of ER and PR and increase expression of HER-2/neu, in relation to increasing size. We have found that as the tumor size increases, ER, PR status decreases with $P < 0.005$ (0.02340 and 0.02413 respectively) whereas overexpression of HER-2/neu increases with $P < 0.005$ ($P = 0.02289$). Similar type of correlation was also detected by Azizun-Nisa *et al.*,²⁶ Carlomagno *et al.*²⁷

Histological grade of tumor is another important prognostic factor in the breast cancer, tumor expressing higher grade tend to carry poor prognosis. In our study, Grade II tumor

Table 3: Expression of of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2/neu with tumor size

Tumor size (cm)	ER positive, n (%)	ER negative, n (%)	PR positive, n (%)	PR negative, n (%)	HER-2/neu positive, n (%)	HER-2/neu negative, n (%)
<2 (n=5)	4 (80)	1 (20)	3 (60)	2 (40)	1 (20)	4 (80)
2-5 (n=44)	23 (52.27)	21 (47.73)	15 (34.09)	29 (65.91)	7 (15.91)	37 (84.09)
>5 (n=21)	5 (23.8)	16 (76.19)	3 (14.29)	18 (85.71)	10 (47.62)	11 (52.38)

For ER $\chi^2=7.088$; $P=0.0234$; For PR $\chi^2=4.840$; $P=0.02413$; For HER-2/neu $\chi^2=5.513$; $P=0.2289$. n=Total number of cases; ER=Estrogen receptor; PR=Progesterone receptor; HER=Human epidermal growth factor receptor

Table 4: Expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2/neu in different histological types

Type	Number of cases	ER positive, n (%)	ER negative, n (%)	PR positive, n (%)	PR negative, n (%)	HER-2/neu positive, n (%)	HER-2/neu negative, n (%)
IDC	65	29 (44.62)	36 (55.38)	18 (27.7)	47 (72.3)	18 (27.7)	47 (72.3)
Mucinous	2	2 (100)	0	2 (100)	0	0	2 (100)
Medullary	2	0	2 (100)	0	2 (100)	0	2 (100)
ILC	1	1 (100)	0	1 (100)	0	0	1 (100)
Total	70	32 (45.71)	38 (54.29)	21 (30)	49 (70)	18 (25.71)	52 (74.29)

ER=Estrogen receptor; PR=Progesterone receptor; HER=Human epidermal growth factor receptor; IDC=Infiltrating duct carcinoma; ILC=Infiltrating lobular carcinoma

Table 5: Expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2/neu with tumor grade

Tumor grade	n	ER positive, n (%)	ER negative, n (%)	PR positive, n (%)	PR negative, n (%)	HER-2/neu positive, n (%)	HER-2/neu negative, n (%)
Grade I	14	9 (64.29)	5 (35.71)	7 (50%)	7 (50%)	1 (7.14)	13 (92.86)
Grade II	34	18 (52.94)	16 (47.06)	13 (38.24)	21 (61.76)	7 (20.59%)	27 (79.41)
Grade III	22	5 (22.57)	17 (77.27)	3 (13.64)	19 (86.36)	10 (45.45)	12 (54.54)

For ER, $\chi^2=6.638$, $P=0.02472$; For PR, $\chi^2=5.480$, $P=0.04149$; For HER-2/neu, $\chi^2=7.09$, $P=0.03339$. n=Total number of cases; ER=Estrogen receptor; PR=Progesterone receptor; HER=Human epidermal growth factor receptor

Table 6: Expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2/neu with lymph node status

LN	n	ER positive, n (%)	ER negative, n (%)	PR positive, n (%)	PR negative, n (%)	HER-2/neu positive, n (%)	HER-2/neu negative, n (%)
0	21	9 (42.86)	12 (57.14)	5 (23.81)	16 (76.19)	4 (19.05)	17 (80.95)
1-3	15	6 (40)	9 (60)	6 (40)	9 (60)	4 (26.67)	11 (73.33)
>3	34	17 (50)	17 (50)	10 (29.41)	24 (70.59)	10 (29.41)	24 (70.59)

For ER, $\chi^2=0.320$, $P=0.81867$; For PR, $\chi^2=0.108$, $P=0.55404$; For HER-2/neu, $\chi^2=0.693$, $P=0.72321$. LN=Lymph node; n=Number of cases; ER=Estrogen receptor; PR=Progesterone receptor; HER=Human epidermal growth factor receptor

constitute the highest number of cases (48%), followed by Grade III and Grade I. Similar findings were recorded by various studies.^{1,13,28} Tumor grade is inversely proportional to the expression of ER and PR. In this study, expression of ER and PR was inversely associated with histological grade with $P < 0.05$ (0.022472 and 0.041494 respectively). This finding is similar to various other studies done in India and abroad.^{13,23,28,29} We have also found that HER-2/neu overexpression was increased with the tumor grade, as observed in 7.14%, 38.89% and 45.45% in Grade I, II and III

tumors respectively with $P = 0.03339$ which was statistically significant. Similar observation was made by Santosh *et al.*, Thiagarajan *et al.*, Siadati *et al.*, Reddy *et al.*^{13,24,28,29} Hence, large tumors less likely to respond to hormone therapy but likely to be benefitted from targeted therapy like Herceptin.

However, in this study, no significant correlation was seen between lymph node metastasis and ER, PR, and HER-2/neu expression status as P value was not significant. This type of result was also found in study done by Thiagarajan *et al.*, Azizun-Nisa *et al.*, Reddy *et al.*^{24,26,28}

Limitations of our study

Our study has some limitations. We have conducted the study in a small number of samples and only for 1½ years duration. The fluorescent *in situ* hybridization technique was also not used to determine HER-2/neu positivity in equivocal cases. It has been known that abnormal body weight, shorter or no periods of breastfeeding, age of menarche, age of first pregnancy, fewer pregnancies, menopausal status, alcohol intake, regular exercise and comorbidity were the risk factors to the burden of breast cancer. Women who are overweight or obese after menopause have increased risk of breast cancer as more fat tissue increases estrogen level which is a risk factor for breast cancer. Various reproductive factors such as early age of menarche, delayed age of first pregnancy and low parity increases the risk of breast cancer.³⁰ Other factors such as excessive alcohol intake and heavy fat consumption can also increase the risk of breast cancer by increasing the blood level of estrogen-related hormones and triggering the ER pathways.³⁰ Various epidemiological studies revealed that there is about 25% reduction of risk of breast cancer among physically active women as compared to the least active women.³¹ However, these factors have not been considered in our study which is also a shortcoming of our study.

CONCLUSION

ER, PR, and HER-2/neu correlate well with histopathological grade and tumor size. Higher grade and larger tumor size are associated with ER, PR negativity, and HER-2/neu positivity. But, there was no significant association with cancer type and lymph node metastasis. Hence, immunohistochemical assessment of ER, PR, and HER-2/neu should be incorporated as a routine investigation in every breast cancer patient. This status along with other parameters will guide the clinicians to make correct choice of treatment protocols and helps in improving quality of life.

Acknowledgement

We would like to thank Dr. Mohua Mazumdar, Rampurhat Government Medical College for English proofreading of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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