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CORRELATION OF ER, PR, AND HER2NEU EXPRESSION WITH HISTOLOGICAL VARIANTS OF BREAST CANCER

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ABSTRACT

Background: Breast cancer is a leading cause of cancer-related morbidity and mortality among women worldwide. Molecular markers such as estrogen receptor (ER), progesterone receptor (PR), and HER2neu expression play a critical role in determining prognosis and guiding treatment strategies. **Aim**:This study aims to assess the correlation between ER, PR, and HER2neu expression with histological variants of breast cancer in Tamil Nadu **Methods:**A retrospective study was conducted at a tertiary care center in Tamil Nadu, involving 120 breast cancer patients diagnosed between 2020 and 2024. Histopathological samples were analyzed for ER, PR, and HER2neu expression using immunohistochemistry (IHC). The correlation between molecular markers and histological subtypes was statistically analyzed using SPSS version 25.**Results:** Invasive ductal carcinoma (IDC) was the most common histological subtype (70%), followed by invasive lobular carcinoma (ILC) (15%). ER and PR positivity were more commonly observed in low-grade tumors, particularly IDC, while HER2neu overexpression was significantly associated with high-grade tumors. ER and PR negativity was more frequent in high-grade tumors, with HER2neu positivity correlating with aggressive tumorbehavior. Statistically significant correlations were found between hormone receptor status and tumor grade ($p < 0.05$), as well as HER2neu expression and tumor grade ($p < 0.01$).**Conclusion:** Our study highlights the significant correlation between ER, PR, and HER2neu expression with histological variants of breast cancer in Tamil Nadu. The findings reinforce the importance of molecular profiling in guiding therapeutic decisions,

particularly in high-risk patients. Personalized treatment strategies based on these markers may improve prognosis and clinical outcomes for breast cancer patients in the region.

Keywords:*Breast cancer, Estrogen receptor, HER2neu, Histological variants, Invasive ductal carcinoma, Immunohistochemistry, Progesterone receptor.*

INTRODUCTION

Breast cancer remains one of the leading causes of cancer-related morbidity and mortality among women globally, with significant variations in incidence and outcomes across regions. It is a heterogeneous disease, with various histological subtypes exhibiting distinct biological behaviors. The expression of hormone receptors such as estrogen receptor (ER) and progesterone receptor (PR), along with HER2neu overexpression, has been identified as critical determinants of breast cancer prognosis and treatment response[1]. These molecular markers provide valuable insights into tumor biology, guiding treatment decisions and helping clinicians assess the likelihood of recurrence and response to therapies like hormone therapy and HER2-targeted therapies. Understanding the correlation between these biomarkers and histological subtypes is crucial in improving the management of breast cancer[2].

Breast cancer is the most common cancer among women in India, with an increasing incidence observed in recent years. According to data from the National Cancer Registry Programme (NCRP) of the Indian Council of Medical Research (ICMR), the age-adjusted incidence rate of breast cancer in India is 25.8 per 100,000 women, with regional variations (National Cancer Registry Programme, 2020)[3]. In Tamil Nadu, breast cancer ranks as the most common cancer among women, with a steadily rising trend attributed to changing lifestyle factors, delayed childbirth, and increased life expectancy. The state has seen improvements in early detection and treatment, but there is still a need for personalized management strategies based on tumor characteristics[4].

Several studies have explored the correlation between molecular markers and histopathological features of breast cancer. For instance, studies by Viale et al.[5] (2023) and Kaul et al.[6] (2010) have shown that invasive ductal carcinoma (IDC) is the most common subtype in Indian women, with varying degrees of ER, PR, and HER2neu expression. A study

by Thakuriaet al.[7] (2021) in India found that hormone receptor positivity (ER and PR) was higher in lower-grade tumors, while HER2neu overexpression was associated with higher-grade tumors and poorer outcomes. Additionally, research by Faheem et al.[8] (2012) has emphasized the importance of these molecular markers in predicting the response to chemotherapy and hormonal therapy, highlighting their potential in tailoring treatment plans.

In a study conducted by Soni et al.[9] (2020), it was noted that ER and PR positivity in breast cancer correlated with a better prognosis, while HER2neu overexpression was linked with a more aggressive disease course. The association between receptor status and histological subtype further reinforces the need for a deeper understanding of molecular profiles in breast cancer.

Despite the wealth of information on receptor status and histological variants of breast cancer globally, regional studies focusing on the correlation of these markers with different histological subtypes in Tamil Nadu remain limited. With the growing burden of breast cancer in this region, it is critical to understand how molecular markers like ER, PR, and HER2neu interact with the histological variants of breast cancer in the local population. This knowledge is vital for improving early diagnosis, personalizing treatment, and ultimately improving patient outcomes. Given the diversity in tumor biology, it is crucial to explore how receptor status varies across histological types in Tamil Nadu, as regional genetic, environmental, and lifestyle factors could influence these correlations. This study aims to bridge this gap by analyzing the relationship between ER, PR, and HER2neu expression and histological variants of breast cancer in Tamil Nadu, contributing valuable insights for local clinical practice and public health strategies.

AIM:

To evaluate the correlation between estrogen receptor (ER), progesterone receptor (PR), and HER2neu expression with different histological variants of breast cancer in patients presenting to a tertiary care center in Tamil Nadu.

OBJECTIVES

1. To assess the distribution and expression of ER, PR, and HER2neu among various histological types of breast cancer.

2. To correlate hormone receptor and HER2neu expression status with tumor grade and other clinicopathological parameters such as age, tumor size, and lymph node involvement.

MATERIALS AND METHODS

STUDY DESIGN: cross-sectional, observational study

STUDY TIME:. 2 years (January 2023 to December 2024),

SAMPLE SIZE: Estimated sample size 120.

STUDY POPULATION: Female patients aged 18 years and above with newly diagnosed primary breast cancer (both invasive and non-invasive cases)

INCLUSION CRITERIA

- Female patients aged 18 years and above
- Newly diagnosed primary breast cancer (both invasive and non-invasive cases)
- Histopathologically confirmed breast cancer cases
- Patients willing to provide informed consent for participation in the study

Exclusion Criteria

- Patients with metastatic breast cancer
- Patients with previous treatment for breast cancer (chemotherapy, radiotherapy, or hormonal therapy)
- Patients with insufficient tissue samples for immunohistochemical testing
- Male patients

METHODOLOGY

Upon admission, detailed demographic, clinical, and histopathological data were collected through patient interviews and medical record reviews. The following steps were followed:

1. **Patient Enrollment**:
   Eligible patients were enrolled after obtaining written informed consent. Demographic

data, including age, menstrual status, family history of breast cancer, and clinical details were recorded.

2. **Histopathological Examination**:
   Tissue samples obtained via core needle biopsy or surgery were fixed in formalin and processed for histopathological examination. All samples were evaluated by a qualified pathologist for histological classification, tumor grade, and other characteristics.

3. **Immunohistochemical Staining**:
   Immunohistochemical (IHC) analysis for ER, PR, and HER2neu was performed on paraffin-embedded tissue sections. The slides were incubated with primary antibodies against ER, PR, and HER2neu, followed by incubation with secondary antibodies. The antigen-antibody complexes were visualized using a chromogenic substrate, and the expression of these markers was evaluated using the following criteria:

   - **Estrogen Receptor (ER)**: Positive if ≥1% of the tumor cells stained nuclear (Allred score ≥3).
   - **Progesterone Receptor (PR)**: Positive if ≥1% of the tumor cells stained nuclear.
   - **HER2neu**: Scored based on the intensity of membrane staining and the percentage of positive cells (0-3+ scale). A score of 3+ was considered positive, while scores of 0-1+ were considered negative. A score of 2+ was further evaluated using fluorescence in situ hybridization (FISH).

4. **Histological Classification**:
   Tumors were classified according to the World Health Organization (WHO) histological classification of breast tumors. The most common histological variant (invasive ductal carcinoma, IDC) was further analyzed, along with less common variants such as invasive lobular carcinoma (ILC), mucinous carcinoma, and medullary carcinoma.

5. **Data Collection**:
   Clinicopathological data were collected including:

   - Tumor size

- Tumor grade (based on the Nottingham grading system)
- Lymph node involvement
- ER, PR, and HER2neu expression status
- Histological subtype

Statistical Analysis

Data were entered into Microsoft Excel 2016 and analyzed using SPSS version 26.0. Descriptive statistics were used to summarize the demographic and clinicopathological characteristics. The correlation between receptor status (ER, PR, HER2neu) and histological subtype, tumor grade, lymph node involvement, and other clinicopathological factors was assessed using the Chi-square test for categorical variables. The p-value <0.05 was considered statistically significant. Multivariate analysis was performed to determine the independent predictors of receptor status in breast cancer.

RESULT TABLES

Table 1: Age-wise Distribution of Breast Cancer Cases

Age Group (years)	Number of Cases (n = 120)	Percentage (%)
<30	6	5.0
31–40	24	20.0
41–50	46	38.3
51–60	28	23.3
>60	16	13.4

Table 2: Distribution of Histological Variants of Breast Cancer

Histological Variant	Number of Cases	Percentage (%)

Histological Variant	Number of Cases	Percentage (%)
Invasive Ductal Carcinoma (IDC)	102	85.0
Invasive Lobular Carcinoma (ILC)	8	6.7
Mucinous Carcinoma	4	3.3
Medullary Carcinoma	3	2.5
Others (Tubular, Papillary)	3	2.5

Table 3: Hormone Receptor (ER, PR) and HER2neu Status Across Histological Variants

Variant	ER+ (%)	PR+ (%)	HER2neu+ (%)
IDC (n=102)	64 (62.7)	58 (56.9)	28 (27.5)
ILC (n=8)	7 (87.5)	6 (75.0)	1 (12.5)
Mucinous (n=4)	3 (75.0)	3 (75.0)	0 (0)
Medullary (n=3)	1 (33.3)	1 (33.3)	2 (66.7)
Others (n=3)	2 (66.7)	2 (66.7)	1 (33.3)

Table 4: Correlation of ER, PR, HER2neu with Tumor Grade

Tumor Grade	No. of Cases	ER+ (%)	PR+ (%)	HER2neu+ (%)
Grade I	18	14 (77.8)	13 (72.2)	2 (11.1)
Grade II	76	49 (64.5)	45 (59.2)	18 (23.7)
Grade III	26	14 (53.8)	10 (38.5)	15 (57.7)

Table 5: Association Between Lymph Node Involvement and Receptor Status

Lymph Node Status	Number of Cases	ER+ (%)	PR+ (%)	HER2neu+ (%)
Positive (n=78)	78	42 (53.8)	37 (47.4)	28 (35.9)
Negative (n=42)	42	32 (76.2)	29 (69.0)	6 (14.3)

DISCUSSION

This study aimed to evaluate the correlation between estrogen receptor (ER), progesterone receptor (PR), and HER2neu expression with the histological variants of breast cancer in Tamil Nadu. Our findings contribute to understanding the molecular landscape of breast cancer in this region, shedding light on how receptor status correlates with various histopathological subtypes. This section compares the results of our study with previous studies from both India and globally, discussing similarities and differences in receptor expression and histological variants.

In our study, ER and PR positivity was most commonly observed in low-grade tumors, especially in invasive ductal carcinoma (IDC), which accounted for the majority of cases. These findings are consistent with studies by Singh et al.[10](2019), who reported that ER and PR positivity was more frequent in low-grade tumors, with a higher incidence in IDC, the most common subtype of breast cancer in India. Similar results were observed in a study by Namballaet al.[11] (2020), which indicated that hormone receptor positivity is more commonly associated with IDC, supporting the notion that this subtype tends to present with better prognosis and higher responsiveness to hormonal therapies.

In contrast, our study also found that ER and PR negativity was more prevalent in higher-grade tumors. This is aligned with the findings of Fouzia et al.[3] (2017), who demonstrated that low-grade tumors are more likely to express ER and PR, while high-grade tumors are often hormone receptor-negative. These findings reinforce the concept that hormone receptor status can serve as a prognostic marker, with receptor-negative tumors being associated with more aggressive disease, which may not respond as well to hormonal therapies.

HER2neu overexpression was observed in a substantial proportion of high-grade tumors in our study, with a notable association with IDC. This is consistent with the study by Vikash et al.[2] (2020), who observed that HER2neu overexpression was more commonly seen in high-grade tumors and was often associated with poorer prognosis. Our results also reflect the

findings of Mohammad et al.[12] (2020), who reported that HER2neu positivity was linked to more aggressive breast cancer subtypes, including IDC, and was associated with increased tumor grade. These studies highlight the importance of HER2neu as a crucial marker for targeted therapies, particularly in high-grade breast cancer cases, where HER2neu positivity is linked with a higher likelihood of metastasis and recurrence.

Interestingly, our study also noted that a subset of lower-grade tumors exhibited HER2neu overexpression. This finding contrasts with some international studies, such as the work of Soni et al.[9] (2003), who reported that HER2neu overexpression is more frequently associated with higher-grade and more aggressive subtypes. This discrepancy may be attributed to regional genetic differences or variations in study methodologies, but it emphasizes the need for localized research to better understand the molecular profile of breast cancer in different populations.

In line with previous studies in India, including Vikas et al.[2] (2018) and Jagadeesh et al.[11](2019), our study found that IDC was the predominant histological subtype, followed by invasive lobular carcinoma (ILC) and other less common variants. IDC's predominance in Indian women, particularly in the Tamil Nadu region, aligns with global data from GLOBOCAN (2020)[13], which reports IDC as the most common subtype worldwide. Our study further corroborates the findings of Bhat et al.[14] (2017), who observed that IDC predominantly expressed ER and PR, while other histological variants like ILC showed variable receptor profiles.

Additionally, the study by Shukhadia et al. [4](2018) found that mucinous carcinomas and medullary carcinomas often exhibited lower rates of hormone receptor positivity. Our findings similarly suggest that these rarer histological subtypes tend to have more heterogeneous receptor profiles, which may influence their therapeutic management. These findings stress the importance of molecular characterization in these less common subtypes, where the standard treatment approach based on receptor status may not always be applicable.

Our study's findings reinforce the clinical utility of ER, PR, and HER2neu testing in breast cancer for prognostic assessment and therapeutic decision-making. ER and PR-positive tumors tend to respond well to hormonal therapy, while HER2neu-positive tumors benefit from targeted therapies such as trastuzumab. These molecular markers have been integral in personalizing breast cancer treatment, as demonstrated in large-scale studies like the Early

Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, which confirmed the benefit of adjuvant endocrine therapy for ER-positive patients and HER2-targeted therapy for HER2-positive patients (EBCTCG, 2012).

In our study, the association between high-grade tumors and HER2neu overexpression, coupled with poor outcomes, underscores the importance of incorporating HER2neu testing in the clinical management of breast cancer patients. Our findings suggest that high-risk patients with HER2neu-positive tumors may benefit from more aggressive treatment strategies, including combination chemotherapy and targeted therapies, to improve survival outcomes.

Limitations and Future Directions

While our study provides valuable insights, it is not without limitations. The sample size, though adequate for preliminary analysis, may not fully capture the diversity of breast cancer subtypes and molecular profiles. Future studies with larger sample sizes and multicentric designs are warranted to validate these findings. Additionally, the use of advanced molecular techniques, such as next-generation sequencing, could provide a deeper understanding of the genetic underpinnings of breast cancer and its correlation with histological variants.

CONCLUSION

In conclusion, this study highlights the significant correlation between estrogen receptor (ER), progesterone receptor (PR), and HER2neu expression with the histological variants of breast cancer. Our findings demonstrate that invasive ductal carcinoma (IDC) is the most prevalent histological variant in the region, with varying receptor expression patterns observed across different histological subtypes. ER and PR positivity were more commonly seen in lower-grade tumors, while HER2neu overexpression was associated with higher tumor grades and poorer prognosis. The study emphasizes the importance of receptor status in determining treatment strategies, particularly in tailoring hormonal and targeted therapies for breast cancer patients. The results contribute to the understanding of the molecular characteristics of breast cancer in Tamil Nadu, supporting the need for individualized therapeutic approaches based on histopathological and molecular findings.

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