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Original Research Article

BREAST CANCER SUBTYPES IN PAKISTANI POPULATION: DATA FROM A SINGLE CENTER

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Abstract: *Breast cancer is a complex disease that includes different types of tumors. These tumors can vary in their characteristics, such as the levels of estrogen, progesterone, and HER2/neu receptors. These differences can impact how the tumors respond to treatment, progress, and change over time. The study conducted at the Department of Oncology, Jinnah Hospital, Lahore, from May to November 2019, was a cross-sectional study that involved 90 female patients with breast cancer aged 25 to 75. The researchers analyzed the tumor samples using immunohistochemistry to evaluate ER, PR, and HER2neu levels. FISH was used to evaluate models that had equivocal HER2 by IHC. The participants in this study were 25 to 75 years old, with an average age of 47.10 ± 11.55 years. The average duration of the disease before presenting to the hospital was 6.71 ± 2.63 months. The study found that 74.44% of the female patients had tumors that were ER-positive, 56.67% had tumors that were PR-positive, and 20.0% had tumors that were HER2neu-positive. In conclusion, this study showed that the frequency of positive expression of estrogen, progesterone, and HER2neu in breast cancer patients in this population was consistent with international rates. However, more extensive studies are necessary to determine the exact prevalence of these tumors.*

Keywords: Breast Cancer, Estrogen, Progesterone, HER2neu Expression

Introduction

Approximately 22% of all female malignancies are breast cancers, making it the most prevalent type in women. This is more than twice as common as cancer in any other place in women. 1,2 Globally, breast cancer has surpassed all other malignancies affecting women in the last several years; one estimate places the annual number of new cases at 1,55,000, and it is responsible for nearly 6 million deaths. Although the mean age of occurrence varies, a study found that it is 42 years old (Puvitha and Shifa, 2016). While some reports place the median age of breast cancer occurrence at 50–60 years old, this number can vary. Breast cancer is recognized as a multifaceted and diverse neoplasia that includes many illnesses, histological features, and clinical consequences (Okuyama Kishima et al., 2015).

The traditional factors that affect the prognosis and treatment of breast cancer include the histologic type and grade, tumor size, lymph node status, and the tumor's ER and PR hormone receptor status. More recently, HER-2/neu status has also been found to have an impact (Safarpour et al., 2014). The morphological characteristics of breast cancer are the basis for the histopathological examination. However, the immunohistochemical (IHC) testing of the human epidermal growth factor receptor Her2/neu, estrogen receptors (ER), and progesterone receptors provide more precise prognostic information about its biology (PR).

Estrogen, progesterone, and HER2/neu receptor expression levels can predict different responses to systemic treatment, variations in the pattern of progression, and occasionally change as the disease progresses (Marcuzzo et al., 2016). Together with stage and other variables, the status of the human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and estrogen receptor (ER) influence a patient's course of treatment for breast cancer. Immunohistochemical (IHC) tests5 and fluorescence in situ hybridization (FISH) determine the patient's HER2 status if there is equivocal HER2 IHC (Tarulli et al., 2014). According to one study, among females with breast cancer, 50.8 percent had positive ER, 57.5 percent had positive PR, and 17.5% had positive HER2neu. 8 According to another study, among females with breast cancer, 77.9 percent had positive ER, 59.1 percent had positive PR, and 17.7 percent had positive HER2neu. 9 In contrast, a different study found that among females with breast cancer, 32% of cases had positive ER, and 29% had positive PR. 10 Consequently, these traits vary within age groups and among various demographic diasporas.

The purpose of this study was to ascertain the frequency of HER2neu, progesterone, and estrogen receptor expression in Pakistani breast cancer patients. Even in nations with limited resources, like Pakistan, this testing has become standard practice and requirement; nonetheless, not much research has been done in this area, and scant data is available. This can facilitate better planning and monitoring options for the Pakistani populace.

Methodology

This descriptive, cross-sectional study was conducted in the Department of Oncology, Jinnah Hospital, Lahore.

The study was from May 22, 2019, to November 21, 2019. The sample size of 90 cases was calculated with a 95% confidence level 8% margin of error. Non-probability, consecutive sampling was done for this study. Ninety patients fulfilling the selection criteria were enrolled through OPD. Biopsy of samples was received in the Department of Oncology, Jinnah Hospital, Lahore. Demographic information (name, age, duration, and stage of breast cancer) was also obtained. Then, surgical specimens were processed for routine hematoxylin and eosin staining. Slides were made and immunohistochemically analyzed to assess estrogen (ER), progesterone (PR), and HER2neu. FISH evaluated equivocal HER2 neu by IHC.

Data was analyzed by SPSS version 20. Quantitative variables like age and duration of breast cancer were calculated as mean and standard deviation. Qualitative variables like stage of cancer and positive ER, PR, and HER2neu were presented as frequency and percentage.

Data was stratified for age, stage (depending on histopathology and radiology working), and duration of breast cancer. Post-stratification, chi-square was applied to compare stratified groups. P-value≤0.05 was considered as significant.

Results

The study involved ninety participants between the ages of 25 and 75, with a mean age of 47.10 ± 11.55 years. The average duration of the disease was found to be 6.71 ± 2.63 months.

Table 1: Patient Demographics, Disease Duration, and Cancer Stage Distribution

Category	No. of Patients	Percentage	
Age (in years)			
25-50	64	71.11	
51-75	26	28.88	
Duration of Disease (months)			
<6	43	47.78	
≥6	57	52.22	
Stage of Cancer			
I	6	6.67	
II	40	44.44	
III	24	26.67	
IV	17	18.89	
Total		90	100.0

Stratification of the expression of estrogen, progesterone, and HER2neu receptors concerning age groups is shown in Table 2.

This study showed that in breast cancer females, ER was positive in 67 (74.44%), PR was positive in 51 (56.67%), and HER2neu was positive in 18 (20.0%) females, as shown in Figure 1. Table 2 displays the distribution of patients according to age groups (25-50 and 51-75) and their respective statuses for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). In the 25-50 age group, most patients showed positive statuses for ER (50 patients), PR (38 patients), and HER2 (15 patients). On the other hand, in the 51-75 age group, fewer patients had positive statuses for these biomarkers (17 for ER, 13 for PR, and 3 for HER2).

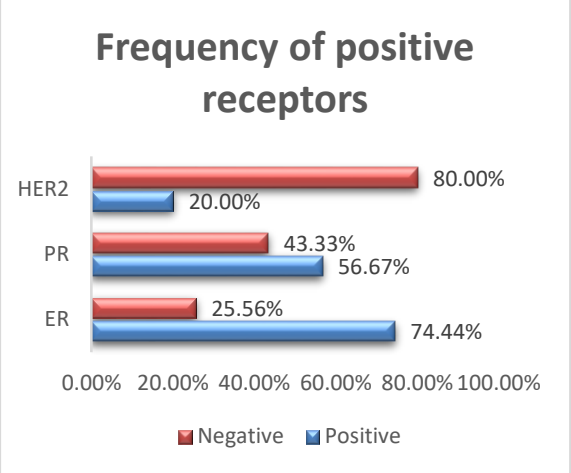

Figure 1 Frequency of positive expression of estrogen, progesterone, and HER2neu receptors in breast cancer patients

Table 2: Stratification of estrogen, progesterone, and HER2neu receptor expression concerning age groups.

		25-50 (n=64)	51-75 (n=26)	P-value
ER	Positive	50	17	**0.209**
	Negative	14	09	
PR	Positive	38	13	**0.416**
	Negative	26	13	
HER2	Positive	15	03	**0.201**
	Negative	49	23	

The table also lists the number of patients with negative biomarker statuses in both age groups. The p-values associated with these observations are 0.209 for ER, 0.416 for PR, and 0.201 for HER2, indicating the statistical significance of the observed associations. These findings suggest that there may be age-related differences in the expression of these biomarkers, which can be valuable for further research and clinical considerations in cancer management.

Stratification of the expression of estrogen, progesterone, and HER2neu receptors with respect to the duration of breast cancer is shown in Table 3.

Table 3: Stratification of the expression of estrogen, progesterone, and HER2neu receptors with respect to duration of disease.

		≤6 (n=43)	>6 (n=57)	P-value
ER	Positive	30	47	**0.136**
	Negative	13	10	
PR	Positive	23	38	**0.181**
	Negative	20	19	
HER2	Positive	05	13	**0.150**
	Negative	38	44	

Table 3 illustrates the distribution of patients based on the duration of disease (≤6 months and > six months) and their respective statuses for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Among patients with a disease duration of ≤6 months (43 patients), a substantial number exhibit positive statuses for ER (30 patients), PR (23 patients), and HER2 (5 patients). In contrast, for patients with a disease duration of >6 months (57 patients), higher counts are observed for positive statuses in ER (47 patients), PR (38 patients), and HER2 (13 patients). The table also provides the counts for patients with negative statuses for each biomarker in both duration groups. The associated p-values (0.136 for ER, 0.181 for PR, and 0.150 for HER2) suggest the degree of statistical significance in the relationship between disease duration and the expression of these biomarkers. These findings imply potential associations between the disease's time and the cancer's molecular characteristics, warranting further investigation for clinical implications in treatment planning and prognosis.

Stratification of the expression of estrogen, progesterone, and HER2neu receptors with respect to the stage of cancer is shown in Table 4.

Table 4 depicts the distribution of patients across different cancer stages (I-V) and their respective statuses for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Notably, as the cancer stage progresses from I to V, there is an increase in the number of patients with ER-negative, PR-negative, and HER2-negative statuses. However, the p-values (0.353 for ER, 0.642 for PR, and 0.150 for HER2) indicate that these associations are not statistically significant. These findings suggest that while there is a trend of changes in biomarker expression with advancing cancer stages, additional factors may contribute to the overall molecular characteristics, emphasizing the complexity of cancer progression

Table 4: Stratification of the expression of estrogen, progesterone, and HER2neu receptors with respect to stage of cancer.

		I (n=06)	II (n=40)	III (n=24)	IV (n=17)	V (n=03)	P-value
ER	Positive	06	28	20	11	02	**0.353**
	Negative	00	12	04	06	01	
PR	Positive	02	24	12	11	02	**0.642**
	Negative	04	16	12	06	01	
HER2	Positive	02	10	01	05	00	**0.150**
	Negative	04	30	23	12	03	

Discussion

To identify the suitability of using targeted treatments like tamoxifen and trastuzumab, as well as two other neu-targeted medicines, receptor status is an essential evaluation for all types of breast cancer. Because estrogen is necessary for the growth of estrogen receptor-positive (ER+) cancer cells, these cells can be treated with medications that either lower the amount of estrogen in the body (such as tamoxifen) or its effect (such as aromatase inhibitors). These patients also typically have a better prognosis. HER+ cancer cells generally had a poorer prognosis before the advent of current treatments (Mouttet et al., 2016). However, HER2+ cancer cells respond to medications like trastuzumab, a monoclonal antibody, when combined with traditional chemotherapy, dramatically improving the prognosis. On the other hand, the prognosis for triple negative cancer, which lacks focused therapy and has no positive receptors, is now rather dismal (Kroese et al., 2007; Marcuzzo et al., 2016).

According to newly published guidelines (Sughayer et al., 2006), the estrogen receptor (ER) content of breast carcinomas is significant as a prognostic and predictive biomarker, and screening of ER status is part of the usual assessment of these neoplasms. The evaluation of ER status has been validated multiple times since the initial publication of its independent prognostic importance about two decades ago (Onitilo et al., 2009). It is widely accepted as the gold standard by which other techniques are evaluated. Most detection challenges may be solved with highly specific monoclonal antibodies22 and immunohistochemistry (IHC) methods for ER localization. Most studies that assessed the clinical utility of using IHC to measure ER state found statistically significant associations with clinical outcomes24. Today, most labs have already transitioned to using IHC almost solely on routine archival tissue samples (i.e., formalin-fixed paraffin-embedded).

Nuclear receptor subfamily 3, group C, member 3—also referred to as the progesterone receptor (PR)—is an intracellular steroid receptor that binds progesterone exclusively. The human PGR gene, found on chromosome 11q22,215,216, encodes two primary types of PR, A and B, which have different molecular weights (Kamil et al., 2010; Pervaiz et al., 2015).

The receptor tyrosine kinase HER2 is surface-bound on the cell membrane and is typically engaged in signal transduction pathways that lead to cell proliferation and differentiation. It is encoded by the well-known proto-oncogene HER2/neu inside the genome. Due to its inability to be activated by any ligand from the EGF family, HER2 is believed to be an orphan receptor. On the other hand, HER2 is the preferred dimerization partner of other ErbB family members. ErbB receptors dimerize upon ligand interaction. 28 A proto-oncogene, the HER2 gene, is at the long arm of human chromosome (17q21-q22) (Sariego, 2010).

The HER2/neu gene is amplified in 20–30% of breast cancer cases, and its protein product is overexpressed in these cases as well (Saini et al., 2012).

A poorer prognosis and a higher risk of disease recurrence are linked to this receptor's overexpression in breast cancer. Breast cancers are commonly examined for HER2/neu overexpression due to their prognostic importance and capacity to predict response to trastuzumab and other

targeted medicines. In addition, overexpression is seen in biologically aggressive forms of uterine cancer, including uterine serous endometrial carcinoma, as well as ovarian and stomach cancers (Sotiriou and Pusztai, 2009).

An investigation was carried out at the Armed Forces Institute of Pathology, Rawalpindi, in the Department of Histopathology. 481 (89.9%) of the 535 cases had to infiltrate ductal carcinoma, with a mean tumor size of 4.4 cm and an age of 48 years. Sixty-eight percent of subjects had a tumor grade II, and sixty-five percent had lymph node metastases. Thirty-one percent of the patients showed HER-2/neu expression, compared to seventy-three percent with ER and sixty-six percent with PR expression. While there was a positive correlation with lymph node metastases ($p < 0.05$), there was an inverse correlation between HER-2/neu and ER and PR. There was no correlation observed between the size and grade of the tumor. Additionally, a more significant percentage of HER-2/neu negative patients (73.5%) were demonstrated by joint ER and PR expression (Fritz and Speroff, 2011; Romond et al., 2005).

The mean age of the patients in another study carried out at Aga Khan University Hospital's Department of Pathology and Microbiology was 48.3 years (95 percent CI 46.5, 50.2). More often, the left breast was affected (57 percent). The tumor size varied from 0.3 to 15.0 cm; its diameter varied between 2.0 and 5.0 cm in 12.6 and 35.3 percent of cases. The most common form of the cancer was infiltrating ductal carcinoma (85.3 percent). Most patients had grade II (55.3%) lesions, 70% with tumour necrosis and lymph node involvement (71.3 percent). In 32.7 percent of cases, the ER and 25.3 percent of cases, the PR, were positive. Of those, 24.7% had positive (3+) HER-2/neu results. As one grew older, ER-positive rose, and HER-2/neu positivity fell. When HER-2/neu positive tumours were compared to HER-2/neu negative tumours, ER and PR expression was considerably lower in the former (ER 83.8 percent vs. 69.8 percent; PR 91.9 percent vs. 77.8 percent). When comparing high-grade tumours to intermediate-grade tumours in HER-2/neu positive tumours, there was a significant decrease in ER and PR expression (ER 5.6 percent vs. 10.5; PR 0 percent vs. 5.3 percent). When compared to smaller tumours, the ER expression in HER-2/neu positive, large-sized tumours was likewise much lower (ER 6.3 percent vs. 11.8) 33

In 15 to 25 percent of invasive breast carcinomas, the proto-oncogene HER-2/neu, often called c-erbB-2 (HER-2), is amplified, and the protein (HER-2) is overexpressed. This is linked to a worse clinical prognosis (Dawson et al., 2010; Dent et al., 2007).

On the other hand, 60 percent to 70 percent of invasive breast carcinomas express PR, and 70 percent to 80 percent of invasive ductal carcinomas and invasive lobular carcinomas also express ER (McGuire, 1991; Peters, 1997). In general, better results are linked to ER and/or PR expression. Women whose tumours are positive for both ER and PR have the best survival and response to hormone therapy; those whose tumours are inconsistent with receptor status have intermediate outcomes, and those whose tumours are negative for both have the worst outcomes (Greene et al., 1980; Knight III et al., 1977; Oncology, 1996). How ER, PR, and HER-2 interact has become crucial in treating breast cancer. It has been demonstrated that tamoxifen therapy is ineffective for people whose breast cancer overexpresses HER-2/neu. While ER and PR expression are commonly connected with HER-2/neu expression in varying degrees, (Allred et al., 1998; King and Greene, 1984) the degree of this inverse relationship and its correlation with traditional histologic prognostic markers have not been thoroughly examined in many cases.

Twenty to thirty percent of patients with breast cancer have overexpressed HER-2/neu, which is linked to a more aggressive disease, a worse clinical prognosis, and targeted treatment agents (Misrahi et al., 1987).

The most accurate indicator of responsiveness to hormone therapy is ER/PR expression. While the hormone receptor expression evaluated by immunohistochemistry (IHC) is widely acknowledged as a standard evaluation method, there is still some debate regarding the optimal cut-off point when using IHC (Law et al., 1987). Clinically significant subgroups are primarily based on ER/PR/HER2/neu status. The expression of particular genes, such as the oestrogen receptors (ERs), progesterone receptors (PRs), and HER2/neu, suggests outcomes in breast cancer patients. Though little is currently known about the precise regulation of these genes and receptors, multigene prognostic and predictive tests have been developed, commercialized, and established as tools in breast cancer diagnostics. The ability to classify breast cancers in this way has obvious beneficial implications for developing targeted therapies (Fritz and Speroff, 2011; Gadkar-Sable et al., 2005).

Conclusion

This study concluded that the frequency of positive expression of estrogen, progesterone, and HER2neu receptors in breast cancer patients is 74.44%, 56.67%, and 20.0%, respectively. So, immunostaining for expression of estrogen, progesterone, and HER2-neu is recommended and should be used routinely for diagnosis and precise management of patients to reduce the mortality and morbidity caused by this disease in our community. However, further large-scale studies are needed to find this disease's true incidence and prevalence in the Pakistani population.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department Concerned.

Consent for publication
Approved

Funding
Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

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