Physical Education, Health and Social Sciences

https://journal-of-social-education.org

E-ISSN: 2958-5996

P-ISSN: 2958-5988

Association of ER, PR, and HER2 Biomarker Profiles with Histological Grade of Breast Carcinoma in Pre- and Postmenopausal Patients

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Abstract:

Background: Breast malignancy exhibits distinct molecular and histopathological characteristics depending on menopausal status. Hormone receptors (ER, PR) and HER2 expression play an important role in prognosis and treatment. This study investigates the association of ER, PR, HER2 expression, and histological tumor grading among premenopausal and postmenopausal women with invasive ductal carcinoma. **Objective:** To evaluate and compare the expressions trends of ER, PR, HER2, and histological grades of breast carcinoma between premenopausal and postmenopausal women. **Methodology:** This observational, analytical cross-sectional research was carried out at Jinnah Postgraduate Medical Center, Karachi, from December 2023 to December 2024. A total of 200 histologically confirmed breast carcinoma patients aged 25–75 years were enrolled through nonprobability consecutive sampling. ER, PR, and HER2 values were assessed by immunohistochemistry, and histological grading was done using the modified Bloom-Richardson system. Patients were stratified by menopausal status. Data were analyzed using SPSS version 26; associations were tested using chi-square with a significance level of $p < 0.05$. **Results:** ER and PR positivity were significantly higher in postmenopausal women (73.2% and 66.1%) compared to premenopausal women (47.7% and 43.2%) ($p < 0.001$, $p = 0.001$). HER2 overexpression (3+) was more frequent in premenopausal women (34.1% vs. 19.6%, $p = 0.007$). Grade III tumors predominated in postmenopausal women (48.2%, $p =$ 0.002). HER2 positivity correlated significantly with higher tumor grades, particularly in premenopausal patients ($p = 0.004$). **Conclusion:** Premenopausal women demonstrated a higher prevalence of aggressive HER2-positive subtypes and poorly differentiated tumors, whereas postmenopausal women showed higher ER/PR positivity, suggesting divergent tumor biology and therapeutic implications based on menopausal status.

Keywords: Breast cancer, Estrogen receptor, HER2, Histological grade, Menopausal status.

Introduction

Over the previous few decades, the incidence of breast tumors has markedly increased across many regions of the world [1, 2]. It remains one of the most often diagnosed malignancy worldwide and is the primary etiology of cancer-related mortality, followed by colorectal and lung cancers [3]. In Asia, Pakistan reports the highest incidence of breast carcinoma, with a rate of 34.6% [4]. Among the different histological types, invasive ductal carcinoma is the most prevalent, accounting for approximately 75% of all breast carcinomas [5]. According to India's Population-Based Cancer Registry, the age-specific occurrence of breast cancer rises with advancing age. Although the rates are initially low, they begin to increase between the ages of

25 and 29, peaking around 45–49 years, with another increase noted in women aged 70–75 years [6]. Menopause, marking the end of ovarian reproductive activity, has a significant influence on the risk of developing the breast carcinoma. During the years of reproductively active ages—from menarche to menopause—the ovaries continue to produce the steroidal hormones including estrogen, which plays a very important role in the growth and function of breast tissue. Menopause, typically occurring between the ages of 45 and 54, leads to a substantial decline in ovarian hormone production. Extended exposure to estrogen, due to early menarche or late menopause, rises the risk of developing breast carcinoma and other hormonedependent malignancies like ovarian malignancy [7]. Premenopausal women are approximately 40% more likely to develop breast cancer than their postmenopausal counterparts of the same age [8]. Estrogen has a stronger influence on estrogen receptor-positive (ER+) tumors, and menopause tends to impact ER+ more significantly than ER-negative (ER−) cancers. Additionally, postmenopausal women using hormone replacement therapy are more likely to develop ER+ breast cancers [9, 10].

The expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) serves as important clinical markers for molecular subtyping and prognosis of breast cancer [11]. Approximately 70% of breast cancers are ER+, and 15% are HER2 positive [27,40,48]. Based on these markers, breast cancers can be classified as ER+/HER2− (around 75%), triple-negative (ER−/PR−/HER2−, ~10%), or HER2-enriched. Triple-negative breast cancer (TNBC), characterized by a lack of ER, PR, and HER2 expression, is associated with poor prognosis, higher rates of recurrence, and increased metastatic potential [12]. Survival outcomes also vary among subtypes: while patients with ER/PR+/HER2− tumors have a 5-year survival rate close to 95%, those with TNBC show a significantly lower rate, at just over 75% [12]. In general, ER+ breast cancers have better prognoses than ER− tumors [13], and dual hormone receptor-positive tumors (ER+/PR+) are more favorable than single receptorpositive or ER+/PR− subtypes [14] [15] [16].

Moreover, single hormone receptor-positive subtypes (ER+/PR− or ER−/PR+) are linked to more aggressive behavior and worse outcomes. In fact, ER−/PR+ tumors have prognoses comparable to ER−/PR− breast cancers [16]. HER2 overexpression is seen in 13–22% of cases and is correlated with a more aggressive disease course, higher recurrence, and mortality [11]. Among HER2+ breast cancers, around 60–70% co-express hormone receptors. However, patients with HR+/HER2+ tumors tend to have poorer outcomes than those with HR+/HER2− disease [17]. Given the hormonal and molecular heterogeneity of breast cancer and the physiological shifts that occur with menopause, it is important to investigate how receptor status and histological grading differ between pre- and postmenopausal women. The objective of this study is to assess the association between ER, PR, HER2 expression, and histological grading of breast carcinoma in pre- and postmenopausal women.

Methodology

This observational, analytical cross-sectional study was conducted at the Department of General Surgery, Jinnah Postgraduate Medical Center (JPMC), Karachi, from December 2023 to December 2024. The primary objective was to evaluate the association of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and histological grading of breast carcinoma in premenopausal and postmenopausal women. Ethical approval for the study was obtained from the College of Physicians and Surgeons Pakistan (CPSP) Research and Ethics Committee under approval number CPSP/REU/SGR-2022-186-13857, dated 24th November 2023. The sample size was calculated using OpenEpi version 3.01, considering a 95% confidence level, 80% power of the study, and a minimum expected frequency of hormone receptor positivity of 70% based on previously published literature. The minimum sample size determined was 196, which was rounded to 200 to account for potential

data loss or exclusions. were eligible for inclusion. Patients were categorized into premenopausal and postmenopausal groups based on their menstrual history. Premenopausal women were defined as those having regular or irregular menstrual cycles within the past 12 months, while postmenopausal women were defined as those with amenorrhea Patients were enrolled through non-probability consecutive sampling. All female patients aged between 25 and 75 years, presenting with histologically confirmed invasive ductal carcinoma of the breast, and undergoing surgical intervention or biopsy during the study period, for 12 consecutive months without any other pathological or physiological cause Exclusion criteria included patients with recurrent breast cancer, those who had received neoadjuvant chemotherapy or hormone therapy prior to tissue sampling, individuals with metastatic disease at presentation, male breast cancer patients, and patients with incomplete histopathological or immunohistochemical records.

After obtaining informed consent, demographic data including age, menopausal status, and clinical presentation were recorded. Histopathological examination of the breast tissue was carried out at the institutional pathology department. Tissue samples were processed for hematoxylin and eosin (H&E) staining to confirm the diagnosis and determine histological grade using the modified BloomRichardson grading system, which evaluates tubule formation, nuclear pleomorphism, and mitotic count. Each parameter was scored from 1 to 3, with the total score determining the grade as follows: Grade I (welldifferentiated, score 3–5), Grade II (moderately differentiated, score 6–7), and Grade III (poorly differentiated, score 8–9).

Immunohistochemistry (IHC) was performed on formalin-fixed, paraffin-embedded tissue sections to determine ER, PR, and HER2 status. For ER and PR, a nuclear staining of ≥1% of tumor cells were considered positive. HER2 status was scored from 0 to 3+ following ASCO/CAP guidelines. Scores of 0 and 1+ were considered negative, 2+ as equivocal (and subsequently confirmed with fluorescence in situ hybridization [FISH]), and 3+ as positive.

All data were entered and analyzed using IBM SPSS Statistics version 26. Continuous variables such as age were expressed as mean ± standard deviation. Categorical variables including menopausal status, receptor status (ER, PR, HER2), and histological grade were expressed as frequencies and percentages.

The chi-square test was used to assess associations between categorical variables. A p-value of less than 0.05 was considered statistically significant. Subgroup analysis was also conducted to compare the distribution of hormone receptor expression and tumor grade between premenopausal and postmenopausal groups.

Results

A total of 200 female patients with histologically confirmed invasive ductal carcinoma of the breast were included in the study. The mean age of the participants was 52.4 ± 10.7 years. Of the total, 88 patients (44%) were premenopausal and 112 patients (56%) were postmenopausal.

Demographic and Clinical Characteristics

Table 1 shows the age and tumor grade differences by menopausal status. Postmenopausal women were significantly older (mean age 59.1 vs. 44.2 years, $p < 0.001$). Grade III tumors were more common in postmenopausal women (48.2%) compared to premenopausal women (22.7%), which was statistically significant ($p = 0.002$).

Table 1: Demographic and Histological Characteristics by Menopausal Status

Characteristic	Premenopausal (n=88)	Postmenopausal (n=112)	Total (n=200)	p-value
Mean Age (years)	44.2 ± 6.5	59.1 ± 7.2	52.4 ± 10.7	<0.001*

Histological Grade				
Grade I (Well differentiated)	28 (31.8%)	14 (12.5%)	42 (21.0%)	
Grade II (Moderately diff.)	40 (45.5%)	44 (39.3%)	84 (42.0%)	
Grade III (Poorly diff.)	20 (22.7%)	54 (48.2%)	74 (37.0%)	0.002*

*p-value calculated using chi-square test for categorical variables and independent t-test for age.

Immunohistochemical Receptor Expression (ER, PR, HER2)

ER and PR positivity was seen more in postmenopausal women (ER: 73.2%, PR: 66.1%) than premenopausal women (ER: 47.7%, PR: 43.2%), with both differences being significant ($p < 0.001$ and $p = 0.001$). HER2 overexpression (3+) was found more in premenopausal women (34.1% vs. 19.6%, $p = 0.007$). HER2 equivocal cases (2+) were also higher in the premenopausal group (20.5% vs. 5.4%, $p =$ 0.0016) (Table 2).

Table 2: Hormonal Receptor Status by Menopausal Status

Receptor Status	**Premenopausal (n=88)**	**Postmenopausal (n=112)**	**Total (n=200)**	**p-value**
Estrogen Receptor (ER)				
Positive	42 (47.7%)	82 (73.2%)	124 (62.0%)	<0.001*
Negative	46 (52.3%)	30 (26.8%)	76 (38.0%)	
Progesterone Receptor (PR)				
Positive	38 (43.2%)	74 (66.1%)	112 (56.0%)	0.001*
Negative	50 (56.8%)	38 (33.9%)	88 (44.0%)	
HER2/neu Expression (IHC Score)				
Positive (3+)	30 (34.1%)	22 (19.6%)	52 (26.0%)	0.007*
Negative (0 or 1+)	40 (45.4%)	84 (75.0%)	124 (62.0%)	<0.001*

Equivocal (2+)	**18 (20.5%)**	**6 (5.4%)**	**24 (12.0%)**	**0.0016***
Equivocal (2+) *FISH Positive (HER2 Amplified)*	*6 (6.8%)*	*2 (1.8%)*	*8 (4%)*	
Equivocal (2+) *FISH Negative*	*12 (13.7%)*	*4 (3.6%)*	*16 (8%)*	

*Statistically significant at $p < 0.05$. Calculated using Chi-square test.

Association of Hormonal Receptor Status with Histological Grade

HER2 positivity was significantly linked with higher tumor grade, especially in premenopausal women. Among Grade III tumors, 39% of premenopausal and 22.2% of postmenopausal women had HER2 overexpression. The association between HER2 status and Grade III tumors was significant ($p = 0.004$) (Table 3).

Table 3: Distribution of HER2 Expression Across Tumor Grades in Premenopausal and Postmenopausal Women

Tumor Grade	**HER2 Status**	**Premenopausal (n=88)**	**Postmenopausal (n=112)**	**Total (n=200)**	**pvalue**
Grade I (Well diff.)	Positive (3+)	2 (6.7%)	4 (18.2%)	6 (12.5%)	
	Equivocal (2+)	2 (6.7%)	1 (4.5%)	3 (6.3%)	
	Negative (0/1+)	26 (86.6%)	17 (77.3%)	43 (81.1%)	
	Subtotal	30	22	52	0.317
Grade II	Positive (3+)	12 (33.3%)	8 (21.6%)	20	
(Mod. diff.)				(27.8%)	
	Equivocal (2+)	6 (16.7%)	3 (8.1%)	9 (12.5%)	

	Negative (0/1+)	18 (50.0%)	26 (70.3%)	44 (61.1%)	
	Subtotal	36	37	73	0.205
Grade III (Poorly diff.)	Positive (3+)	16 (39.0%)	10 (22.2%)	26 (30.6%)	
	Equivocal (2+)	10 (24.4%)	2 (4.4%)	12 (14.1%)	
	Negative (0/1+)	15 (36.6%)	33 (73.4%)	48 (55.3%)	
	Subtotal	41	45	86	0.004*
Total		107	104	200	

*p-value calculated using Chi-square test for association between HER2 status and tumor grade within menopausal groups. Significant difference observed for Grade III distribution (p = 0.004).

Subgroup Analysis: Hormone Receptor and HER2 Co-expression

The ER+/PR+/HER2– molecular subtype was among the most frequent in postmenopausal women (50.0%) and significantly higher than in premenopausal women (29.5%, $p = 0.001$). The more aggressive ER–/PR– /HER2+ subtype appeared more frequently in premenopausal patients (20.5% vs.
5.4%) (Table 4).

Table 4: Molecular Subtype Distribution Based on ER/PR/HER2 Co-expression

Molecular Subtype	**Premenopausal (n=88)**	**Postmenopausal (n=112)**	**Total (n=200)**	**pvalue**
ER+/PR+/HER2–	26 (29.5%)	56 (50.0%)	82 (41.0%)	0.001*
ER+/PR+/HER2+	10 (11.4%)	14 (12.5%)	24 (12.0%)	
ER–/PR–/HER2+	18 (20.5%)	6 (5.4%)	24 (12.0%)	
Triple Negative (ER–/PR–/HER2–)	22 (25.0%)	20 (17.9%)	42 (21.0%)	
Others (Mixed expression)	12 (13.6%)	16 (14.2%)	28 (14.0%)	

*Statistically significant difference observed in ER+/PR+/HER2– subtype prevalence

Discussion

The mean age of premenopausal women was 44.2 ± 6.5 years, while postmenopausal women averaged 59.1 ± 7.2 years. This is in agreement with studies conducted in South Asian populations, where breast cancer occurs at a younger age compared to Western countries [18] [19]. The earlier onset in premenopausal women is often attributed to genetic factors, environmental exposure, and reproductive health differences in these regions [20].

A significantly higher proportion of Grade III tumors was observed among postmenopausal women (48.2%) compared to premenopausal women (22.7%) ($p = 0.002$). Similar findings were reported by Ibrahim et al., who noted an increased frequency of poorly differentiated tumors in older women [21]. In contrast, a study by Alnahas et al. in Saudi Arabia found Grade II to be the most common across all age groups, consistent with our overall trend [22].

ER positivity was significantly higher in postmenopausal women (73.2%) than in premenopausal women (47.7%) ($p < 0.001$). Several studies support this pattern; Qing et al. and Wang et al. both demonstrated a higher frequency of ER-positive tumors in older women [23] [24]. This trend is attributed to hormonal shifts after menopause, where tumors are more likely to rely on estrogen signaling, making them more amenable to hormone therapy.

PR expression followed a similar pattern, being significantly higher in postmenopausal women (66.1%) compared to premenopausal women (43.2%) ($p = 0.001$). This is in accordance with findings by SchülerToprak et al., who noted that ER and PR positivity increased with age and was associated with betterdifferentiated tumors [25]. High PR expression also predicts a favorable prognosis and responsiveness to hormonal therapies such as tamoxifen [26].

HER2 overexpression (IHC 3+) was more frequent among premenopausal women (34.1%) compared to postmenopausal women (19.6%) ($p = 0.007$). These findings are consistent with data from Venetis et al., who reported higher HER2 amplification in younger patients with aggressive tumor biology [27]. Similarly, a study by Ghosh et al. observed an inverse relationship between HER2 positivity and age, suggesting that HER2-driven tumorigenesis may be more prominent in premenopausal women [28].

HER2 overexpression correlated significantly with poorly differentiated (Grade III) tumors, especially among premenopausal women ($p = 0.004$). This association aligns with previous work by Bergeron et al. and Morales et al., which demonstrated that HER2 positivity is commonly associated with higher tumor grade and worse clinical outcomes [29] [30].

The most common molecular subtype among postmenopausal women was luminal A (ER+/PR+/HER2–) at 50%, whereas premenopausal women had higher proportions of HER2-enriched (20.5%) and triplenegative subtypes (25%). This difference was statistically significant ($p = 0.001$) and mirrors the findings of Carey et al., who reported that luminal A tumors are more common in older women, while triple-negative and HER2-enriched types are more frequent in younger women and associated with poorer prognosis [31]. The higher prevalence of triple-negative tumors among premenopausal women emphasizes the need for aggressive treatment and follow-up, as these tumors lack effective targeted therapies [32].

Conclusion

This study highlights a significant association between menopausal status and breast cancer characteristics. Postmenopausal women were more likely to have hormone receptor–positive tumors, particularly luminal A subtype, which are typically less aggressive and more responsive to hormone therapy. In contrast, premenopausal women had a higher frequency of HER2-enriched and triplenegative tumors, often associated with high-grade histology and poorer prognosis.

Limitations

The study was taken place at a single tertiary care hospital with a small number of samples, which may affect generalizability. Molecular classification was based on

immunohistochemistry without gene expression profiling, which could lead to subtype misclassification.

Clinical Implications

Understanding the variation in tumor biology with menopausal status can guide personalized treatment strategies. Routine receptor testing is essential for optimal therapeutic decision-making, especially in resource-limited settings. Younger women may benefit from early screening and aggressive management due to the higher prevalence of aggressive subtypes.

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