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Hormone Receptor Status in Breast Cancer Patients and Its Association with Age and Histopathological Grade in a Tertiary Care Setting

Manal Afzal, Rashid Ali, Tashaba Qaiser Faizi, Madiha Masood Khan, Mansab Ali, Surrendar Dawani

Abstract

Objective: Hormone receptor testing plays a central role in the classification and treatment planning of breast cancer. This study aims to assess the frequency of estrogen receptor (ER) and progesterone receptor (PR) expression in breast carcinoma and examine their association with age and histopathological grade in a tertiary care setting.

Study design and setting: This study design is cross-sectional, and it took place at Jinnah Postgraduate Medical Centre, Karachi.

Methodology:. A total of 175 breast carcinoma cases diagnosed at a tertiary care center were reviewed. Information regarding patient age, tumor characteristics (type, size, lymph node status, metastasis, histological grade), and ER/PR expression was recorded. Associations between receptor status and clinicopathological parameters were examined using the chi-square test.

Results: The majority of patients (59.4%) were aged 51–80 years. Most tumors were of ductal type (55.4%) and hormone receptor–negative, with 64.6% ER-negative and 70.3% PR-negative. ER and PR positivity were significantly higher in older patients ($p = 0.02$ and $p = 0.04$, respectively). However, no significant association was found between histopathological grade and either ER or PR status.

Conclusion: Hormone receptor negativity was prevalent, especially in younger women: ER and PR expression increased with age and showed no association with tumor grade. These findings support the routine use of hormone receptor testing for informed treatment decisions.

Keywords: Breast Neoplasms, Receptors, Progesterone, Immunohistochemistry, Receptors, Estrogen, Prognosis

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INTRODUCTION

Breast carcinoma is the most frequently diagnosed cancer affecting women globally and stands as the second leading cause of cancer-related deaths among females.[1] In Pakistan, breast cancer represents approximately 24.4% of all cancers diagnosed in women, compared to 23% in western countries. Research indicates that one in every nine women in Pakistan is affected by this disease.[2] Breast carcinoma is a complex and varied disease, characterized by a wide range of histopathological subtypes as well as distinct molecular and clinical profiles. The outcome and effectiveness of treatment in affected individuals are influenced by multiple contributing factors.[3] The prognosis of breast cancer is primarily determined by several critical factors, including the histological subtype, tumor size, presence of necrosis, involvement of the skin, nipple, or chest wall, lymphovascular invasion, tumor grade and stage, and the expression status of biomarkers such as estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2), and the cell proliferation marker Ki-67, along with the type of treatment administered.[4-6]

Prognostic indicators in breast cancer are generally classified into two main groups: those based on pathophysiological

characteristics and those identified as biological markers. [7] Key pathophysiological factors influencing prognosis include the patient's age, tumor size (T), the specific type of tumor tissue, the tumor's histological grade, the extent of lymph node involvement (N), and the presence of distant metastasis (M). Estrogen and progesterone receptors function as ligand-activated transcription factors within target cells, playing a crucial role in regulating gene expression. [8] Research has demonstrated that patients with tumors positive for both estrogen and progesterone receptors tend to have lower mortality rates and show a better response to hormonal treatments. Anti-hormonal therapies are effective in over half of the cases where both receptors are present. In contrast, tumors expressing only one of the receptors are associated with a mortality rate of approximately 33%, while those lacking both receptors have a mortality rate of less than 10%. [8-9]

Research findings have consistently shown that breast tumors expressing both estrogen and progesterone receptors are generally associated with a lower histological grade and a more favorable prognosis. Patients with hormone receptor–positive tumors tend to demonstrate improved survival outcomes across all individual stages of the disease, highlighting the prognostic significance of receptor status in breast carcinoma.[10] This favorable biological behavior is often attributed to the less aggressive nature and better treatment responsiveness of hormone receptor–positive tumors. To date, only a limited amount of research has explored the correlation between tumor histological grade and the expression of estrogen and progesterone receptors. Ayadi et al. found an inverse relationship, indicating that higher-grade tumors tend to show lower levels of ER and PR expression. [6] In a study conducted by Sohail et al, estrogen receptor (ER) and progesterone receptor (PR) positivity were reported in 45.4% and 36.9% of breast carcinoma cases, respectively.[11] Similarly, another study evaluating receptor expression across tumor grades found ER positivity in 19% of grade I, 38% of grade II, and 33% of grade III tumors, while PR positivity was observed in 17.9%, 36%, and 28.3% of the respective grades.[12] These findings further support the association between hormone receptor expression and tumor differentiation, underscoring the importance of ER and PR evaluation in prognostication and therapeutic decision-making.

Given the biologically heterogeneous nature of breast carcinoma disease, in which therapeutic decisions and prognostic expectations increasingly depend on a tumour's molecular profile, the routinely assayed biomarkers, estrogen receptor (ER) and progesterone receptor (PR) statuses are pivotal because they identify tumours likely to respond to endocrine therapy and carry distinct prognostic implications. However, reported receptor-positive frequencies vary widely across regions and populations, and it remains unclear to what extent ER and PR expression patterns correlate with histopathological grade. Establishing the local distribution of ER and PR positivity across the full spectrum of histological grades will therefore not only benchmark our population against global data but also clarify whether receptor testing can refine risk stratification beyond conventional grading. Such evidence is essential for optimising adjuvant treatment algorithms, allocating limited healthcare resources more rationally, and ultimately improving patient outcomes.

METHODOLOGY

This cross-sectional study was conducted to determine the frequency and expression pattern of estrogen and progesterone receptors in patients presenting with breast carcinoma. Further, they were evaluated to find an association between receptor statuses and age and histopathological grade. This study was carried out in the Department of Surgery, Jinnah Postgraduate Medical Centre (JPMC), Karachi. The study started from February 2025 and ended in July 2025, spanning over a six-month period. A total of 175 patients were included in the study following a formal sample size calculation. The sample size was calculated using WHO sample size software, based on a previously reported prevalence of estrogen receptor positivity of 32%, a margin of error of 8%, and a confidence level of 95%.[12] The calculated sample size was considered adequate to detect meaningful associations between hormone receptor expression and histopathological variables. Patients were recruited using a non-probability consecutive sampling method. All eligible patients presenting during the study period and meeting the inclusion criteria were enrolled until the required sample size was achieved. The ethical approval for this study was obtained from the institutional review board of Jinnah Postgraduate Medical Centre (No. E.2-81/2024-GENL/184/JPMC) before the commencement of data collection. All procedures were conducted in accordance with institutional ethical standards. Written informed consent was obtained from all the participants after explaining the purpose of the study. The confidentiality of patient information was strictly maintained throughout the research process.

Patients aged between 20 and 80 years with histopathologically confirmed breast carcinoma were included in the study. Both newly diagnosed and surgically managed cases fulfilling the eligibility criteria were considered. Patients were excluded if their records lacked complete histopathological details, operative findings, or hormonal receptor status data, as incomplete data could affect the validity of receptor correlation analysis. Data were collected from patients admitted and managed surgically at JPMC who fulfilled the study criteria. Demographic and clinicopathological information was recorded using a structured proforma specifically designed for this study. Information collected included patient age, tumor type, tumor size, lymph node status, distant metastasis, histopathological grade, and hormone receptor status.

All surgical breast specimens were subjected to histopathological examination and immunohistochemical analysis for estrogen receptor (ER) and progesterone receptor (PR) expression. Immunohistochemistry was performed using the streptavidin immunoperoxidase technique with monoclonal antibodies, following standard laboratory protocols. Hormone receptor expression was assessed using the H-score method, a semi-quantitative scoring system that combines the proportion of positively stained tumor nuclei and staining intensity. The H-score was calculated by multiplying the percentage of positively stained tumor cells by staining intensity scores ranging from 0 to 3, producing a total score from 0 to 300. Tumors with an H-score greater than 50 were categorized as positive for hormone receptor expression in accordance with previously published criteria.

Histological grading of tumors was performed using the Bloom-Richardson grading system on hematoxylin and eosin–stained sections. Tumors were classified into grade I, grade II, or grade III based on tubule formation, nuclear pleomorphism, and mitotic activity. As they reflect increased degrees of aggressiveness and differentiation. This grading system was used to evaluate any potential relationship between receptor status and tumor grade. Additional tumor-related variables were also documented. Tumor type was classified into ductal, lobular, ductal-lobular, medullary, and mucinous carcinoma based on pathological diagnosis. Tumor size was categorized according to TNM criteria as T1 (=2 cm), T2 (2–5 cm), T3 (>5 cm), and T4 (with skin or chest wall involvement). Lymph node involvement was recorded as N0 to N3 according to the number and extent of involved regional lymph nodes. The metastatic status was categorized as M0 for absence and M1 for presence of distant metastasis. Tumor staging was cross-verified using imaging findings, including ultrasound and mammography where applicable, along with pathology reports to ensure diagnostic consistency.

All collected data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 22. Quantitative variables such as age were assessed for normality using the Kolmogorov–Smirnov test. For normally distributed variables, mean and standard deviation were calculated, whereas median and interquartile range were reported for non-normally distributed data. Categorical variables, including tumor characteristics, receptor status, and histopathological grades, were summarized as frequencies and percentages. To minimize the effect of potential confounding factors, stratification by age was performed during analysis. Associations between estrogen and progesterone receptor expression and clinicopathological variables, particularly histopathological grade and age groups, were evaluated using the chi-square test or Fisher's exact test where appropriate. A p-value of =0.05 was considered statistically significant for all the analyses.

RESULTS

The study analyzed data from 175 patients diagnosed with breast carcinoma. Most participants (59.4%) were between 51 and 80 years of age, while the remaining 40.6% fell within the 20 to 50 age group. Among the histological subtypes, ductal carcinoma appeared most frequently, accounting for 55.4% of cases. Ductal-lobular carcinoma represented 20%, followed by lobular (14.9%), medullary (5.1%), and mucinous types (4.6%). Tumor size varied across the cohort: 45.1% of patients presented with T1 tumors, 20% with T2, 15.4% with T3, and 19.4% with T4. With respect to lymph node involvement, 45.1% of patients were classified as N1, and 39.4% as N2. A smaller proportion fell into N3 (10.3%) and N0 (5.1%) categories. Most patients (90.3%) had no distant metastases at diagnosis (M0), whereas 9.7% had metastases (M1).

Analysis of histological grading showed that Grade II tumors were the most common (38.9%), closely followed by Grade III (38.3%), while Grade I tumors comprised 22.9% of cases. Regarding hormone receptor expression, 35.4% of tumors tested positive for estrogen receptors (ER), while 64.6% were ER-negative. Progesterone receptor (PR) positivity was noted in 29.7% of tumors, with the majority (70.3%) lacking PR expression. Further analysis explored associations between age and receptor status. ER positivity was significantly more frequent among patients aged 51–80 years ($p = 0.02$). Similarly, PR positivity showed a statistically significant association with older age ($p = 0.04$). However, no significant relationship emerged between histological grade and either ER ($p = 0.79$) or PR status ($p = 0.79$).

DISCUSSION

Hormone receptor status remains one of the most important biological markers in breast carcinoma because it provides valuable information regarding tumor behavior, prognosis, and response to therapy. Estrogen receptor (ER) and progesterone receptor (PR) expression are routinely assessed because of their established role in guiding endocrine treatment and predicting clinical outcomes. Given the variability in receptor expression across different populations and age groups, evaluating their distribution and association with clinicopathological parameters remains essential. In the present study, we examined the pattern of ER and PR expression in relation to patient age and histopathological grade.

A considerable proportion of tumors in our cohort lacked hormone receptor expression, with 64.6% testing negative for estrogen receptor (ER) and 70.3% negative for progesterone receptor (PR). This predominance of hormone receptor–negative tumors is noteworthy, as it may reflect a tendency toward more aggressive tumor biology. It also has important implications for prognosis and treatment planning, particularly in settings where endocrine therapy options are guided by receptor status. Our findings are in agreement

Table 1: Distribution of baseline characteristics among the study participants

Variables	n (%)
Age	
20 to 50 years	71 (40.6)
51 to 80 years	104 (59.4)
Tumor type	
Ductal	26 (14.9)
Lobular	97 (55.4)
Ductal-lobular	35 (20)
Medullary	09 (5.1)
Mucinous	08 (4.6)
Tumor size	
T1	79 (45.1)
T2	35 (20)
T3	27 (15.4)
T4	34 (19.4)
Lymph node	
N0	09 (5.1)
N1	79 (45.1)
N2	69 (39.4)
N3	18 (10.3)
Metastasis	
M0	17 (9.7)
M1	158 (90.3)
Histopathological grade	
Grade I	40 (22.9)
Grade II	68 (38.9)
Grade III	67 (38.3)
ER status	
Yes	62 (35.4)
No	113 (64.6)
PR status	
Yes	52 (29.7)
No	123 (70.3)
Total	175 (100)

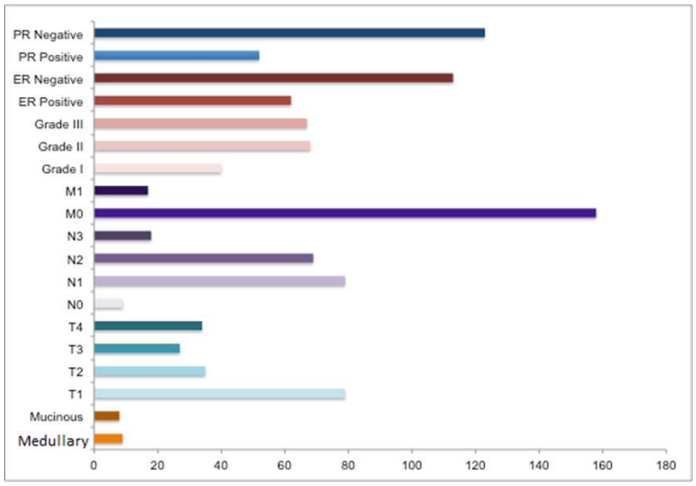
Table 2: Distribution of patient characteristics according to the ER status

Variables	ER status Yes n (%)	ER status No n (%)	P value
Age			
20 to 50 years	18 (25.4)	53 (74.6)	0.02
51 to 80 years	44 (42.3)	60 (57.7)	
Histopathological grade			
Grade I	15 (37.5)	25 (62.5)	0.79
Grade II	22 (32.4)	46 (67.6)	
Grade III	25 (37.3)	42 (62.7)	

Table 3: Distribution of patient characteristics according to the PR status

Variables	PR status Yes n (%)	PR status No n (%)	P value
Age			
20 to 50 years	27 (38)	44 (62)	0.04
51 to 80 years	25 (24)	79 (76)	
Histopathological grade			
Grade I	13 (32.5)	27 (67.5)	0.79
Grade II	21 (30.9)	47 (69.1)	
Grade III	18 (26.9)	49 (70.3)	

Figure 1: Distribution of baseline clinic-pathological characteristics among patients diagnosed with breast cancer



with earlier reports from South Asian populations, where hormone receptor–negative breast cancers have been observed more frequently than in Western cohorts.[13–14] This regional variation may be influenced by differences in tumor biology, genetic predisposition, environmental exposures, delayed presentation, or disparities in screening and diagnostic practices.

In the present study, ER and PR positivity were found to be significantly more common among older patients, particularly those between 51 and 80 years of age. This age-related pattern is consistent with previous literature and may reflect the influence of hormonal and biological changes associated with advancing age, especially in postmenopausal women.[15–16] Several studies have suggested that tumors arising in older women are more likely to exhibit hormone receptor positivity and may therefore show a more favorable response to endocrine-based therapies. The higher prevalence of receptor-positive tumors in this age group further emphasizes the possible role of hormonal milieu in influencing receptor expression and tumor characteristics.

Despite this clear association with age, neither ER nor PR status demonstrated a statistically significant relationship with histopathological grade in our analysis. Although receptor positivity appeared across different tumor grades,

no consistent trend was observed to support a significant correlation. This finding differs somewhat from earlier studies that reported a stronger inverse relationship between hormone receptor positivity and increasing tumor grade, suggesting that well-differentiated tumors are more likely to express ER and PR, whereas poorly differentiated tumors tend to be receptor negative.[14] This discrepancy may be attributable to differences in sample size, tumor distribution, population characteristics, or methodological variations between studies. Nevertheless, our findings suggest that in this cohort, age appeared to have a more prominent association with hormone receptor expression than histological grade.

Our results also contribute to the growing discussion around the clinical relevance of the ER-negative/PR-positive (ER-/PR+) phenotype. This receptor profile was once considered an artifact of testing variability. However, accumulating evidence supports its recognition as a biologically distinct entity with unique clinical behavior. [17-18] Other studies have shown that ER-/PR+ tumors, while rare, often present with aggressive features and worse outcomes than their ER+/PR+ counterparts. [18-19] Importantly, the presence or absence of progesterone receptor (PR) expression appears to carry significant biological and clinical implications, even among tumors that are estrogen receptor (ER) positive. While ER positivity has traditionally been regarded as a favorable prognostic marker and an indicator of responsiveness to endocrine therapy, recent evidence suggests that PR expression provides additional insight into the functional integrity of estrogen signaling pathways. PR negativity in ER-positive tumors has often been interpreted as a marker of impaired or dysregulated ER signaling and has been associated with more aggressive tumor nature, increased cellular proliferation, and relative resistance to endocrine-based treatment.[17,20] This has led to growing recognition that PR status should not be viewed merely as a secondary marker, but rather as an important prognostic and predictive factor. In our dataset, PR-negative tumors constituted the majority of cases, a finding that is noteworthy and consistent with reports linking PR negativity to less favorable prognostic profiles.[15–17] The predominance of PR-negative tumors in our population may partly explain the more aggressive clinicopathological features often reported in similar regional cohorts. Several larger studies have demonstrated that loss of PR expression may be associated with poorer outcomes, including higher recurrence rates and reduced responsiveness to hormonal therapies, particularly when compared with tumors retaining both ER and PR positivity[8,11]. Our findings, while observational, lend support to these previously reported associations.

Further emphasizing the importance of PR expression, researchers have proposed a PR positivity threshold of 10% as a clinically meaningful cutoff for prognostic stratification, particularly in luminal breast cancer subtypes. According to these studies, patients whose tumors exhibit PR expression below this threshold may derive comparatively less benefit from endocrine therapy and may have outcomes more closely resembling those of biologically aggressive disease.[17] Although our study was not powered to validate or challenge this specific cutoff value, our results support the broader concept that PR assessment contributes meaningful prognostic information beyond ER status alone. This reinforces the view that evaluating ER positivity in isolation may not fully capture the biological heterogeneity of hormone receptor–positive breast cancers.

Additionally, our findings are comparable to those of other studies demonstrating that hormone receptor negativity, particularly absence of PR expression, may correlate with adverse pathological features such as lymph node involvement and increased tumor burden.[14] These relationships further underscore the clinical value of assessing both ER and PR routinely, not only for subtype characterization but also for risk stratification and therapeutic planning. Incorporating both receptors into diagnostic evaluation allows for a more nuanced understanding of tumor biology and may assist clinicians in identifying patients who could require closer surveillance or alternative treatment strategies. The importance of PR assessment is also reflected in current international recommendations. The American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) continue to endorse routine evaluation of PR alongside ER because of its recognized predictive role in therapeutic decision-making and prognostic assessment.[21–22] In this context, our findings add to the growing body of evidence supporting the continued relevance of PR testing, particularly in populations where hormone receptor–negative disease appears relatively common.

Our findings further reinforce the inherent biological heterogeneity of breast cancer, highlighting that it cannot be viewed as a single uniform disease entity. The variability observed in hormone receptor expression within our cohort reflects the complex interplay of tumor biology, patient demographics, and possibly regional or environmental influences. In this context, our results strongly underline the importance of comprehensive hormone receptor profiling in all cases of breast carcinoma. While estrogen receptor (ER) status remains a central determinant in guiding endocrine therapy decisions, progesterone receptor (PR) expression provides additional and clinically meaningful information that contributes to a more refined understanding of tumor behavior.

The significance of PR becomes even more apparent when considered alongside ER expression, as it may help identify biologically distinct subgroups within hormone receptor–positive breast cancers. Our findings suggest that reliance on ER status alone may overlook important prognostic nuances that are captured through PR evaluation. This is particularly relevant in resource-limited healthcare

settings, where advanced genomic assays and molecular profiling techniques may not be readily available. In such contexts, routine immunohistochemically assessment of ER and PR remains a practical, cost-effective, and valuable tool for guiding clinical decision-making and treatment planning. Limitations: This study has certain limitations that should be acknowledged when interpreting the findings. First, the study was conducted with a relatively modest sample size, which may limit the statistical power and restrict the generalizability of the results to a broader population. A larger multi-center study would be better suited to confirm and expand upon these observations. Second, the cross-sectional nature of the study and the lack of follow-up data represent an important limitation. As a result, we were unable to assess the impact of hormone receptor status on long-term outcomes such as disease-free survival, recurrence rates, or overall survival. Consequently, the prognostic implications suggested by receptor patterns in this study remain indirect and cannot be fully established without longitudinal evaluation.

CONCLUSION

In conclusion, this study demonstrated that hormone receptor–negative breast cancer was relatively common in our population, particularly among younger patients. Although both ER and PR expression tended to increase with age, neither showed a statistically significant association with histopathological grade. These findings highlight the biological heterogeneity of breast carcinoma and reinforce the importance of routine ER and PR testing in all cases to support accurate prognostication and guide endocrine therapy decisions, especially in resource-limited settings where advanced molecular profiling is not widely available.

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Rashid Ali Assisted in study design, methodology supervision, data interpretation, critical manuscript review.
Tashaba Qaiser Faizi Data collection, data entry, statistical support, contributed to manuscript writing.
Madiha Masood khan Patient management/data acquisition, literature review, drafting sections of the results
Surrendar dawani Critical revision of the manuscript, contribution to discussion writing, approval of final draft.
Mansab Ali Overall supervision, guidance throughout study, final approval of the version to be published, guarantor of the work

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