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Original article

The Role of Progesterone (PR), Estrogen Receptors (ER), and Human Growth Factor 2 (HER2) As Early Diagnostic Markers in Women with Breast Cancer

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Abstract
Breast cancer is one of the leading causes of death among women worldwide. Expression of three receptors, including estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2), plays an important role in the prognosis and treatment of breast cancer. This study aims to analyze the demographic profile of BC patients and evaluate the steroid receptor status and its association with the grading of breast cancer. A total of 124 women diagnosed with breast cancer attended the Department of the National Cancer Institute, Sabratha (NCI) from November 2024 to March 2025. Demographic and clinical data were obtained from these patients. A significant association was found in age group, marital status, family history, and body mass index. Positive expression of ER and PR was significantly higher among patients. Furthermore, an inverse relationship was revealed between positive expression of ER and PR status and HER2. Furthermore, tumor grade II was more common among the patients in our study, followed by grades III and I, and there was a significant association between grade II and positive expression of PR (P = 0.002); however, HER2 expression did not show a significant association with tumor grade. Analysis of ER, PR, and HER2 receptors has clinical importance in breast cancer prognosis and treatment response
Keywords. Breast Cancer, Estrogen Receptors, Progesterone Receptors, Grade.

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Introduction

Breast cancer (BC) is the second leading cause of death in the world, and it is the most common cancer among women (1). BC is a public health dilemma all over the world; therefore, awareness of the disease among the public is essential, which provides a positive impact on early detection of breast cancer (2). The World Health Organization has recorded that the number of deaths in 2020 reached 685,000 worldwide. Also, in the same year, 2.3 million cases of breast cancer were diagnosed, and this made it the most common cancer in the world. According to data from the Global Cancer Observatory (GCO) website and a 2022 study approved by the World Health Organization, breast cancer ranks first in terms of infection rates compared to other cancers. This makes it one of the most widespread and deadly cancers worldwide (3). Breast cancer is a complex and heterogeneous disease characterized by the abnormal proliferation of breast tissue, leading to tumor formation. Although the main causes of breast cancer in women are still unclear, nonhereditary causes and risk factors remain the predominant cause. These include early menarche, hormone intake, nutrition, alcohol consumption, smoking, and obesity, all of which are generally reported as risk factors for developing breast cancer (4).

Although the breast cancer epidemiology studies are very limited. However, previous studies consistently reported that BC is the most common cancer (n=1440, 23.2%), followed by lung cancer (n=938, 15.1%), and colorectal cancer (n=939, 15.1%) (5). Libyan females, when diagnosed with BC, usually presenting at a relatively younger age, and an advanced stage of III/IV (6,7).

Currently, estrogen and progesterone receptor expressions are the most important and valuable predictive factors. Expression of ER is present in 80-90% of patients with breast cancer, while expression of PR appears in 70-80% of cases. Over-expression of HER2-neu is present in 15-20% of cases (8). Testing for steroid receptors such as ER and PR by immunohistochemistry is the well-known standard of care. The level of ER and PR positivity increases with age, reaching its highest levels in postmenopausal women (9). Breast cancers patients whose malignancy is deficient in ER and PR do not benefit from hormonal treatment (10). Moreover, HER2/neu oncogene expression is also important in breast cancer tumorigenesis. The HER2/neu receptor is a member of the epidermal growth factor receptor family of receptor tyro-sine kinases, which are important mediators of proliferation and differentiation of cells (11). Positive HER2/neu has been considered to be a negative predictor of response to hormonal therapy, adjuvant radiotherapy, and adjuvant chemotherapy (12). The aim of this study is to analyze the demo-graphical profile of BC patients and evaluate the steroid receptor status and their association with the grading of breast cancer.

Methods

This was a retrospective study conducted in the Department of the National Cancer Institute Sabratha (NCI), West Libya. It is well-attended by patients who are referred from all over the country, especially the Western region. The study was approved by the Institutional Ethics Review Committee and the Research Ethics Committee at the National Cancer Institute in Sabratha under reference number (3/475)

A total of 124 BC (female) cases were diagnosed between November 2024 and March 2025 and registered with NCI were enrolled. All study participants with breast cancer were clinically diagnosed and referred to the laboratory for blood assessment. Informed consent was taken from all the patients. Participants were analyzed for age, residence, marital status and tumor characteristics like histological grade and hormonal receptor status (ER, PR, HER2/neu receptors). The tumor grade was classified according to the Scarff Bloom and Richardson histological system.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 27) and Graph Pad Prism 7. Descriptive statistics, including means and standard deviations, were computed to summarize the continuous variables, while frequencies and percentages were calculated for categorical variables. Chi-square tests were performed to assess associations between categorical variables, such as hormone receptor status (ER, PR, HER2) and tumour laterality or co-expression. The level of statistical significance was set at $P < 0.05$ for all analyses.

Results

Distribution of subjects by socio-demographic factors

Breast cancer patients were categorized in different age groups from 25-35 years to 65-75 years (Table 1). The mean age was 49.7y. A statistical significance was found between age groups. The highest percentage, 33.1%, was in the age range of 45-55y. Women with breast cancer were divided into four groups according to marital status; the result showed a significant difference between the four categories ($P < 0.001$). The result showed married women were the highest at 73.37%. Furthermore, patients were also analyzed according to family history into first degree, second degree and no relationship. The result showed a significant difference between these groups ($P < 0.001$). Women with breast cancer were divided into three groups in relation to BMI: normal weight, overweight and obese. There was a significant difference ($P < 0.001$) among these groups, and the obesity group was the highest percentage (55.4%). There are also significant differences regarding the grade of tumor ($P < 0.001$) among these patients, and most patients with breast cancer were in grades II and III.

Table 1: Clinicopathological parameters of participants' understudy

Variable	Value	Chi- square	*P* value
Age (years); Mean SD			
Age group n (%)	49.7 ± 9.0 y		
25-35	6 (4.8)		
35-45	31 (25.0)		
45-55	41 (33.1)	47.290	< 0.001
55-65	39 (31.5)		
65-75	7 (5.6)		
Marital status n(%)			
Single	22 (17.74)		
Married	91 (73.37)	160.710	< 0.001
Divorced	5 (4.03)		
Widow	6 (4.84)		
Family history n (%)			
First degree	26 (20.9)	58.081	
Second degree	17 (13.7)		< 0.001
No relationship	81 (65.3)		
BMI n (%)			
Normal weight	13 (20.0)	14.431	
Overweight	16 (24.6)		< 0.001
Obesity	36 (55.4)		
Grade n (%)			
I	10 (8.93)		
II	51 (45.54)	30.496	< 0.001
III	51 (45.45)		

Distribution of estrogen receptor, progesterone receptor, and HER2 status in BC patients
Data relating to steroid receptor and HER2 status are shown in Table 2. The distribution of ER-positive (79.5%) cases is highly significantly higher than ER-negative (20.5%) (P<0.0001). Similarly, comparison of PR distribution showed PR-positive (71.6%) are significantly higher against PR-negative (28.4%) (P < 0.0001). In contrast, the distribution of HER-positive (32.1%) was significantly lower than HER-2 negative (67.9%) (P < 0.001).

Table (2): Distribution of estrogen receptor, progesterone receptor and HER2 status in BC patients

Variable	Categories	N (%)	Chi square	*P* value
ER	Positive	93 (79.5	40.68	<0.0001
	Negative	24 (20.5)		
PR	Positive	83 (71.6	21.56	< 0.001
	Negative	33 (28.4)		
HER2	Positive	36 (32.1)	14.29	< 0.001
	Negative	76 (67.9)		

Estrogen (ER), progesterone (PR) receptors and human epidermal growth factor receptor-2 (HER2) were analyzed, and a chi-square test was conducted to determine whether the distribution between them is significant (P<0.0001).

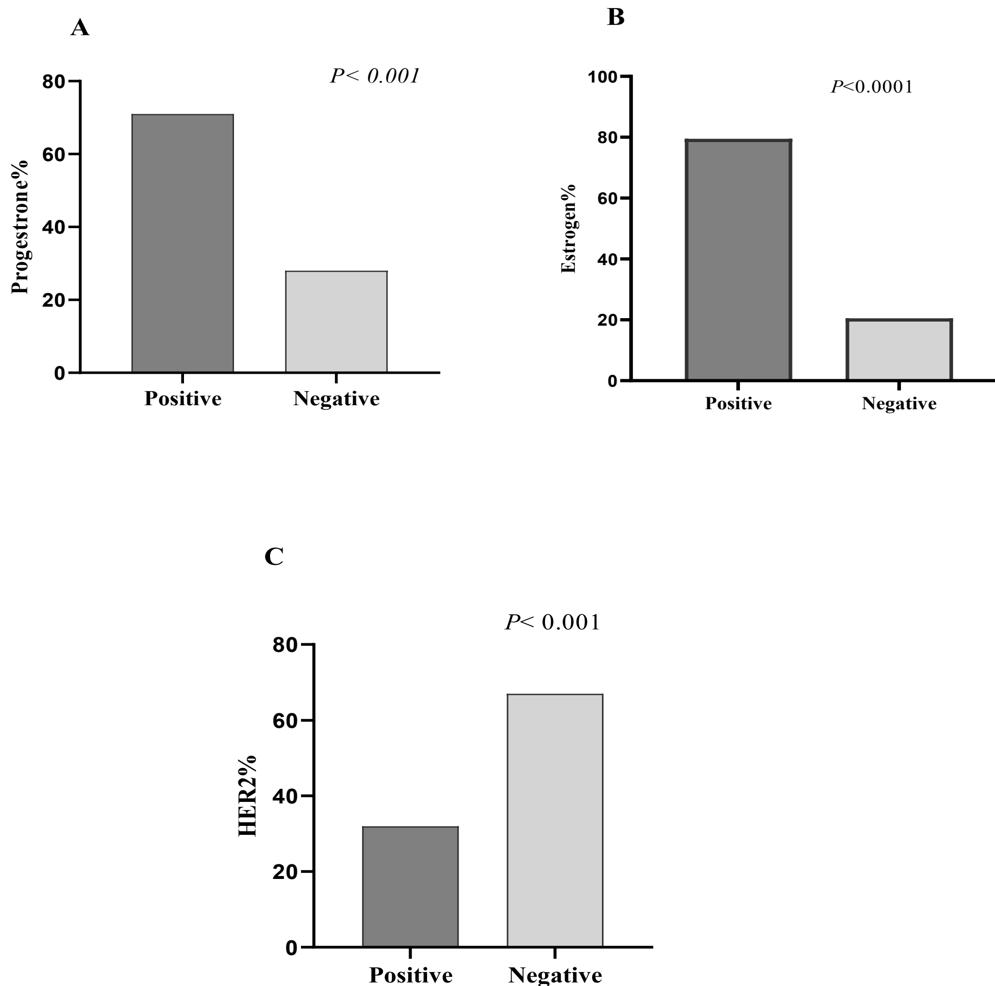

Figure (1): Distribution of HER2 receptor (A), estrogen receptor (B) and progesterone receptor (C)status in BC patients

Association between estrogen receptor (ER) and HER2 status
Table 3 presents the relationship between estrogen receptor (ER) status and HER2 expression among breast cancer patients. The results showed that among ER-positive patients, 24.8% were also HER2-positive, while

54.7% were HER2-negative. Conversely, among ER-negative cases, 9.4% were HER2-positive, and 11.1% were HER2-negative. This result indicates that the association was not statistically significant (*P*=0.177).

Table (3). Association between estrogen receptor (ER) and HER2 status

ER	**HER2**		**Chi - square**	**P value**
	Positive	**Negative**		
	N (%)	**N (%)**		
Positive	29 (24.8)	64 (54.7)	1,820	0.177
Negative	11 (9.4)	13 (11.1)		
Total	40 (34.2)	77 (56.8)		

Steroid receptors estrogen (ER) and human epidermal growth factor 2 (HER2) were analyzed. A chi-square test of independence was conducted to determine whether there was a significant association.

Association between progesterone receptor (PR) and HER2 status

Table 4 displays the relationship between progesterone receptor (PR) status and HER2 expression in breast cancer patients. Among individuals with PR-positive status, 21.4% were also HER2-positive, and 50.94% were HER2-negative. In contrast, among PR-negative individuals, 12.8% were HER2-positive, and 15.4% were HER2-negative. There was no significant association between PR expression and HER2.

Table (4). Association Between Progesterone Receptor (PR) and HER2 Status

PR	**HER2**		**Chi square**	***P value***
	Positive	**Negative**		
	n(%)	**n(%)**		
Positive	25(21.4)	59(50.94)	2.894	0.089
Negative	15(12.8)	18(15.4)		
Total	40(34.2)	77(56.8)		

Steroid receptors progesterone (PR) and human epidermal growth factor 2 (HER2) were analyzed. A chi-square test of independence was conducted to determine whether there was a significant association.

Association grading of tumor with ER, PR and HER2

Table (4) shows that among those with grade I tumors, 9.2% were ER-positive and none were ER-negative. For grade II, 39.4% were ER-positive and 7.3% ER-negative. In grade III, 31.2% were ER-positive and 12.8% ER-negative (P = 0.062), indicating that the result approached but did not reach statistical significance at the conventional level of ($P < 0.05$).

Table (4) Association grading of tumor with ER

Grade	**ER n(%)**		**Chi-square**	**P value**
	Positive	**Negative**		
I	10 (9.2)	0 (0.0)	5.573	0.062
II	43 (39.4)	8 (7.3)		
III	34 (31.2)	14 (12.8)		
Total	87 (79.8)	22 (20.2)		

Table (5) shows that among grade I patients, 9.2% were PR-positive and none were PR-negative. In grade II, 38.5% were PR-positive and 8.3% were PR-negative. In contrast, grade III patients included 24.8% PR-positive and 19.3% PR-negative cases (P = 0.002). This result indicates that PR status is significantly associated with the grade of breast cancer at diagnosis. The findings suggest that PR positivity is more common in earlier grades of breast cancer, particularly grade I and II, while PR negativity is more frequent in advanced (grade III) tumors.

Table (5) Association grading of tumour with PR

Grade	PR n (%)		Chi- square	*P* value
	Positive	Negative		
I	10 (9.2)	0 (0.0)	12.627	0.002
II	42 (38.5)	9 (8.3)		
III	27 (24.8)	21 (19.3)		
Total	79 (72.5)	30 (27.5)		

Table 6 shows that among grade I patients, 3.7% were HER2-positive and 5.5% were HER2-negative. In grade II, 11.9% were HER2-positive and 34.9% HER2-negative, while in grade III, 15.6% were HER2-positive and 28.4% HER2-negative. No statistically significant (P = 0.465), indicating no significant relationship between HER2 expression and breast cancer grade in this sample.

Table (6): Association of grading of tumor with HER2

Grade	HER2 n(%)		Chi -square	P value
	Positive	Negative		
I	4 (3.7)	6 (5.5)	1.533	0.465
II	13 (11.9)	38 (34.9)		
III	17 (15.6)	31 (28.4)		
Total	34 (31.2)	75 (68.8)		

Discussion

This study explored the association between age, gender, obesity, and family history, as well as steroid hormone levels, and the risk of breast cancer. The findings of this study demonstrate a clear age-related pattern in breast cancer incidence, with the highest percentage between the ages of 45 and 55 years (33.1%), followed by the ages of 55 and 65 years (31.5%), whereas the lowest percentage of patients was between the ages of 25 and 35 years (4.8%). There was a statistically significant difference between age groups ($P <$ 0.001). The calculated mean age at diagnosis was 51 years, underscoring the predominance of the disease among older adults.

A previous study in Brazilian breast cancer patients suggested that postmenopausal status is one factor associated with the development of breast cancer (13). It has been suggested that breast cancer is a disease of older women, and its incidence increases with age. The majority of postmenopausal women having dense breast tissue was a predominant risk factor among all women (14). The current data are consistent with previous epidemiological data from Libya, which reported similar median age values (15), and are also supported by studies conducted in the Gulf Cooperation Council countries; these data (16) reinforce the established association between older age and an increased risk of breast cancer.

The researcher concluded from the results obtained that the incidence of breast cancer was significantly higher among married women compared to other marital status categories. Specifically, married women accounted for 73.39% of cases, followed by single women (17.74%), widows (4.84%), and divorcees (4.03%). These findings are similar to previous research conducted in Central Africa, where the previous study concurred with the researcher's findings. It turned out that one possible explanation for these previous findings is the age distribution pattern typically associated with marital status, as married women are more likely to develop breast cancer. The results of this previous study indicate that marital status, particularly marriage may be associated with an increased risk of breast cancer (17).

Analysis of family history of breast cancer revealed a statistically significant association (P < 0.001). The statistical results indicated that 65.3% of patients reported no family history of the disease, while 20.9% had a first-degree relative and 13.7% had a second-degree relative with breast cancer. These results are consistent with a previous study conducted in Iran (18), which reported that a family history of breast cancer did not represent a statistically significant association with the disease. Based on these results, the researcher concluded that family history is not associated with breast cancer. However, these results can be justified by the small sample size and the possibility that some cases refrained from disclosing their history due to privacy concerns. Therefore, genetic background, in this context, does not appear to be a significant or reliable risk factor for breast cancer.

Furthermore, this study explored the association between body mass index (BMI) and breast cancer risk, revealing that 55.4% of cases were classified as obese, 24.6% as overweight, and 20% as having a normal BMI. These findings suggest a significant correlation between obesity and an elevated risk of breast cancer, particularly in postmenopausal women. The decline in estrogen levels following menopause is believed to contribute to increased adiposity and elevated BMI, both of which are recognized risk factors. Supporting

evidence from an African study also demonstrated a postmenopausal rise in BMI and a corresponding increase in breast cancer risk (19). Previous studies are inconsistent with our results and have further substantiated this relationship (20, 21).
Measurement of breast cancer grade indicates how quickly cancer cells may grow and spread compared to the normal cells. The current study investigated the breast cancer grade in BC patients. The findings of this study underscore the significance of tumour grading in the diagnosis and management of breast cancer. The result showed that 45% of cases were diagnosed at grade II and 46% at grade III, whereas only 8.8% were identified at grade I. This distribution highlights a critical gap in early detection, suggesting that delayed diagnosis remains a major challenge. The results emphasise the essential role of public awareness and timely screening in facilitating early-grade diagnosis and improving treatment outcomes. A study reported a high prevalence of late-grade diagnoses, which can impact treatment options and survival rate (22). Moreover, a global comparative study found a higher prevalence of early-grade diagnoses in developed countries, a trend attributed to greater health awareness, organized screening programs, and active educational campaigns by healthcare professionals (23). These disparities underscore the impact of systemic public health measures on early cancer detection and outcomes.
The distribution of hormones and HER2 receptors was analysed. estrogen receptor (ER) and progesterone receptor (PR) positive cancers were significantly more frequent than their negative counterparts, whereas HER2-positive cancers were less prevalent than HER2-negative cases. Our study is similar to previous studies that showed the rate of ER- and PR-positive receptor expression is higher. In the European and American populations, 60–80% of patients were found with positive receptor expression (24) Furthermore, the study described an inverse correlation of Her2/neu expression with ER and PR expression; this may be because women who overexpress Her2/neu may be resistant to tamoxifen, which is also correlated with a previous study (25).
The association between tumour grade and expression of PR and ER receptors showed grade II was more common in our study, followed by grades III and I, similar to a previous study (25). In our study, PR correlated well with grade II (P=0.0021). ER expression was also higher in grade II, but the result was not statistically significant (P=0.062). Though, HER2/neu expression did not show a significant association with tumour grade. In breast cancer, tumour grade is an important predictor of tumour behavior. The study revealed the association between tumour size and an expression of PR (P=0.0021). However, HER2/neu expression did not reveal any correlation with tumour size. Our results are correlated well with previous studies (26, 27). Indicated that non-reactivity of hormonal receptors increases with growth in tumour size (25).

Conclusion
Over a period of up to six months from November 2024 to March 2025, a total of 124 BC cases (124 females) with a mean age of 49.7 ± 9.0 years were diagnosed with breast cancer. Significant association was found between age group, marital status, family history, BMI and tumour grade. Analysis of hormone status expression revealed positive expression of PR and ER was significantly more common among women with breast cancer. Tumour grades 11 and III were common among these patients, and tumour grade was significantly correlated with expression of PR status. These results of findings could have clinical importance in breast cancer treatment.

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Conflict of interest. Nil

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