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Expression Patterns of ER, PR, Her2/neu, and Ki67 in Sudanese Breast Cancer Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Tumor markers are crucial indicators for breast cancer treatment and follow-up. Thus, this study attempted to explore the expression patterns of ER, PR, Her2/neu, and Ki67 in Sudanese breast cancer patients.
Methodology: This study was a retrospective descriptive analysis conducted in El-Obeid city, Sudan. Records of 190 patients were obtained, including 110 with malignant lesions and 79 with benign breast lesions, from two histopathology laboratories.
Results: Approximately 37% of patients were ER/PR positive, whereas 31% of cases tested for ER, PR, and Her2/neu were classified as triple negative. Ki-67 expression exhibited significant variability among breast lesions. Invasive ductal carcinoma (IDC) exhibited the highest expression of estrogen receptors (ER) at 59%, followed by progesterone receptors (PR) at 56%, and HER2 positivity at 53.8%.
Conclusion: Breast cancer cases in Sudan are prevalent, characterized by ER/PR positivity, triple-negative status, and elevated Ki-67 expression. The predominant histological type of breast cancer is invasive ductal carcinoma. Women under the age of 45 exhibit a higher susceptibility to breast cancer. A significant number of patients exhibit advanced stages of the disease. Sudan advocates for the prevention and early detection of breast cancer.

Keywords: Breast cancer; invasive ductal carcinoma; estrogen receptors; progesterone receptors; triple-negative breast cancer.

1. INTRODUCTION

Experts estimate that 2.3 million new cases of breast cancer will occur globally in the next years. It ranks sixth in terms of mortality and accounts for 11.7% of cancer cases [1]. The most prevalent type of cancer in Sudan during the 1967–2010 cancer spike was breast cancer (BC). Khartoum, North Kordufan, the Nile River, Northern, Gezira, and the White Nile had the highest rates. The majority of cancer cases occur in young women, with 40% of those under 45 having late-stage progressive illness, compared to 3.5–4% of men [2].

Mutations and abnormal amplification of oncogenes and anti-oncogenes, such as BRCA1 and BRCA2, have an effect on breast cancer development. Immunohistochemical expression of hormone receptors classifies breast cancer into four subtypes: luminal A, luminal B, HER2-positive, and triple-negative. MiRNAs and mutations may improve classification, according to recent studies [3].

These subtypes can be broken down into four groups based on the hormone receptors they express: ER+, PR+, HER2+, and triple-negative (TNBC), which doesn't have any of the above receptors. Since 70–75% of invasive breast carcinomas exhibit high levels of estrogen receptor (ER), it is a key diagnostic marker. Over 50% of ER-positive breast cancer patients express the progesterone receptor (PR), while ER-negative individuals rarely express it. ER regulates PR expression; hence, physiological PR values reveal ER function. Breast cancer cells widely express ER and PR, which serve as diagnostic and prognostic indicators. Higher PR expression is associated with better overall survival, time to recurrence, and time to treatment failure or progression, while lower levels are associated with more aggressive disease and a worse prognosis [4]. Human epidermal growth factor receptor 2 (HER2) expression accounts for 15–25% of breast tumors and is key to treatment selection. Early breast cancer development involves HER2 overexpression. By 50%–80%, HER2 promotes metastatic or recurring breast cancer detection. Serum HER2 levels may be a viable real-time tumor marker. HER2 amplification turns on too many proto-oncogenic signaling pathways, which leads to cancer cells multiplying out of control and worse outcomes for HER2+ patients. A shorter disease-free duration is also associated with HER2 overexpression. The cell proliferation marker Ki67 antigen is useful for detecting cell proliferation. Ki67's proliferative activities indicate cancer aggressiveness, treatment response, and recurrence. Thus, Ki-67 is critical for treatment selection and recurrence monitoring. It may be prognostic. Low survival rates are associated with high Ki67 expression [4]. BC is clinically and molecularly heterogeneous. Tumor size, histological tumor grade, and lymph node metastases no longer help early-detected breast cancer patients in the age of individualized medicine. Technology has enhanced our comprehension of tumor growth and the impact of therapy on genetics. The

development of prognostic and predictive molecular biomarkers has helped doctors choose treatments. By customizing treatment, they've optimized it and prevented over-, under-, and incorrect treatment. Prognostic markers help clinicians choose treatments by predicting tumor aggressiveness and invasiveness [5]. Breast cancer is growing rapidly in Sudan, necessitating reliable tumor marker profiling. Due to the ongoing conflict, doctors routinely treat individuals who lack these indicators. Thus, this study examined Sudanese breast cancer molecular characteristics and prevalence to aid treatment.

2. MATERIALS AND METHODS

Kordofan Histopathology Center and El-Obeid International Hospital, two reputable institutions offering histopathology services in the northern part of Kordofan State, conducted this retrospective descriptive analysis. The study comprised 190 participants, of whom 110 had malignant lesions and 79 had benign breast lesions. We performed a comprehensive analysis on histopathology reports from January 2019 to April 2024. The expressions of tumor markers were identified using immunohistochemistry.

Statistical analysis: We compiled and arranged all demographic data, clinical information, and histopathological data into a data sheet. We imported the data into SPSS version 24 and Microsoft Excel 2016 for analysis. We conducted an analysis to generate frequencies, charts, and cross-tabulations.

3. RESULTS

This study included 111 breast cancer patients ranging in age from 23 to 90 years, with a mean age of 50±13 years and a standard deviation of ±STD$^{=}$. The majority of patients, 108 (97.3%), were females, with only three (2.7%) being males. The majority of the 111 study subjects with breast cancer were between the ages of 50 and 64 (36.9%), followed by 35 and 49 (32.4%) and 65 and 79 years.

Table 1 and Fig. 1: Out of 108 subjects, 61/108 (56.4%) had positive ER staining and 47/108 (43.5%) had negative ER staining, 41/107 (38.3%) had positive PR staining and 66/107 (61.6%) had negative PR staining, 26/100 (26%) had positive Her2 staining, and 74/100 (74%) were negative for Her2.

Invasive ductal carcinoma showed the highest expression of ER (36/61, 59%), PR (23/41, 56%), and Her2 (14/26, 53.8%). Followed by infiltrating ductal carcinoma, 7/61 (11.4%) tested positive for ER, 4/13 (30.7%) for PR, and 3/12 for Her2. In invasive lobular carcinoma, 6/10 (60%) of patients tested positive for ER, 5/10 (50%) for PR, and 4/10 (40%) for Her2. In 33 patients, Ki-67 expression varied between breast lesions, with some having a high expression (>20%).

Table 2 and Fig. 2 shows that grade 2 had the highest ER expression (24/39, 61.5%), followed by grade 3 with 13/39, 33.3%. Grade 3 had the highest negative staining for ER (16/28, 57%), followed by grade 2 (11/28, 25.3%). PR staining was positive in 14/25 (56%) cases in grade 2, followed by 9/25 (36%) in grade 3. PR had the highest percentage of negative staining (21/42, or 50%) in grade 2, followed by 20/42, or 47.6%, in grade 3. Her2 staining was positive (7/14(50%) in grade 3 and 6/14(42.8%) in grade 2. The most negative staining for Her2 occurred in grade 2 (28/52, 53.8%), followed by grade 3 (22/52, 42.3%).

Table 1. Distribution of immunohistochemical markers (ER, PR, and Her2/neu) and histological diagnosis of breast cancer

Variable	ER		Total	PR		Total	Her2		Total
	-ve	+ve		-ve	+ve		-ve	+ve	
Diagnosis									
Invasive ductal carcinoma	28	36	64	41	23	64	46	14	60
Invasive lobular carinoma	4	6	10	5	5	10	6	4	10
Infiltraing ductal Carcinoma	6	7	13	9	4	13	9	3	12
Others	9	12	21	11	8	19	13	5	18
Total	47	61	108	66	41	107	74	26	100

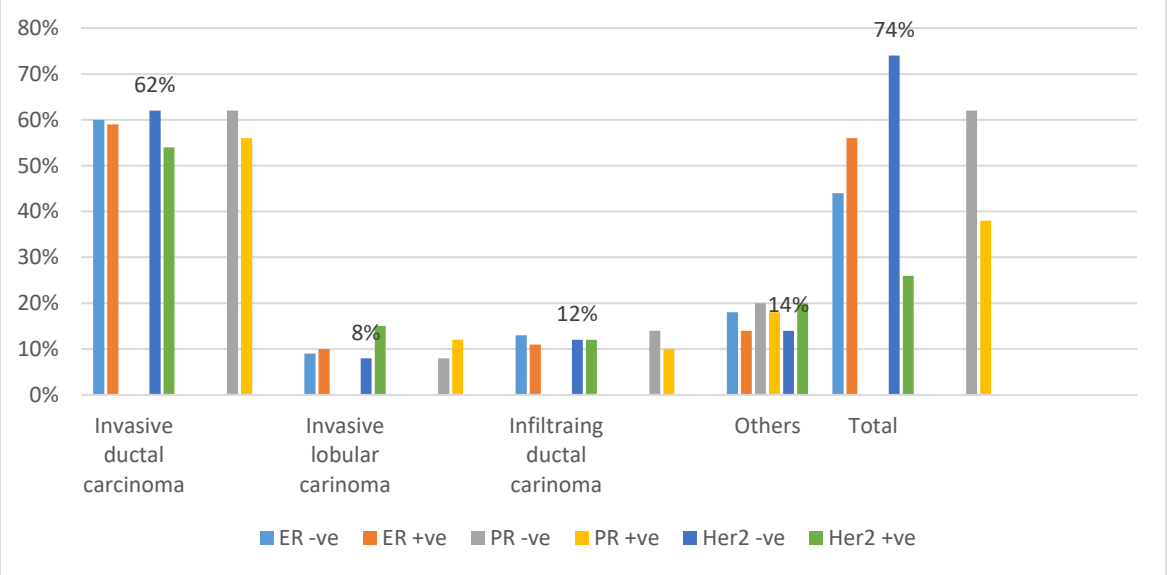

Fig. 1. Discerption of immunohistochemical markers (ER, PR, and Her2/neu) and histological diagnosis

Table 2. Distribution of immunohistochemical markers (ER, PR, and Her2/neu) and histological grade of tumors

Variable	ER		Total	PR		Total	Her2		Total
	-ve	+ve		-ve	+ve		-ve	+ve	
Histological Grade of tumor									
Grade1	1	2	3	1	2	3	2	1	3
Grade 2	11	24	35	21	14	35	28	6	34
Grade 3	16	13	29	20	9	29	22	7	29
Total	28	39	67	42	25	67	52	14	66

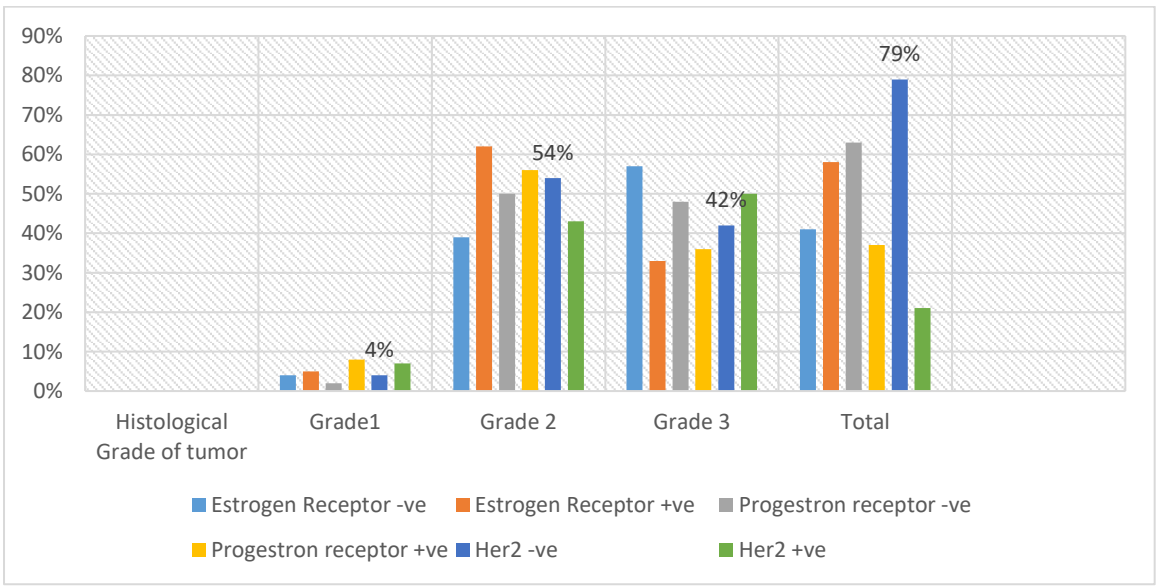

Fig. 2. Description of immunohistochemical markers (ER, PR and Her2/neu) and histopathological grade of tumors

Table 3. Distribution of expression of tumor markers (ER, PR, Her2/neu, and Ki67).

Variable	PR		Total	Her2/neu		Total	KI67		Total
ER	-ve	+ve		__-ve	+ve		<20%	>20%	
Negative	45	2	47	33	11	44	7	6	13
Positive	21	40	61	41	16	57	10	10	20
Total	66	42	108	74	27	101	17	16	33
Her2/neu									
Negative	45	16	61	0	0	0	0	0	0
Positive	29	11	40	0	0	0	0	0	0
Total	74	27	101	0	0	0			

Table 4. distribution of immunohistochemical markers (ER, PR, and Her2/neu) and tumor behaviors

Variable	Non-Metastatic	Metastatic	Total
ER			
Negative	8	4	12
Positive	15	2	17
Total	23	6	29
PR			
Negative	15	5	20
positive	8	1	9
Total	23	6	29
Her2			
Negative	13	6	19
Positive	9	0	9
Total	22	6	28

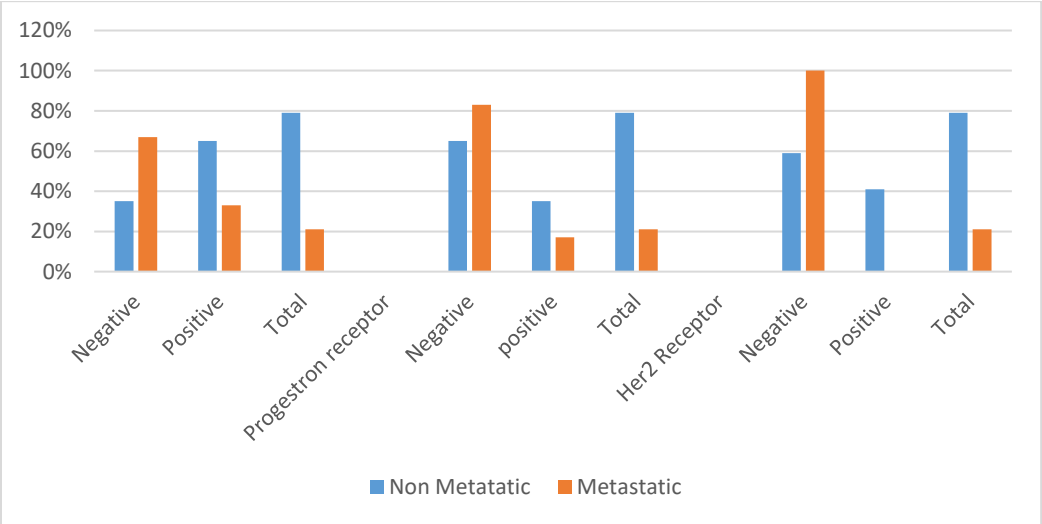

Fig. 3. Description of immunohistochemical markers (ER, PR, and Her2/neu) and tumor behaviors

As shown in Table 3, of the 108 patients tested for ER, 61/108 (56%) were positive and 47/108 (43%) were negative. Of the 108 instances tested for PR, 42 (39%) were positive, while 66 (61%) were negative. Out of 101 Her2/neu tested cases, 27/101 (26%) were positive, while 74/101 (73%) were negative. Out of the 108 patients tested for ER and PR, 40/108 (37%) were ER and PR positive, 45/108 (42%) were negative for ER and PR, 21/108 (19%) were positive for ER but negative for PR, and 2/108 (2%) were PR positive and ER negatiOut of 101 patients tested for ER, PR, and Her2/neu, 28 (27%) were luminal A subtype (ER/PR+HER2-), 10 (9.9%) were luminal B (ER/PR+HER2+), 32 (31.6%) were triple negative (ER/PR-HER2-)

HER2+, and 10 (9.9%) were Her2+ (ER/PR-HER2+). +). Ki67 expression was found to be high (>20%) in 16/33 samples, while low (<20%) in 17/33 samples.

Table 4 it is shown in Fig. 3 that 15/17 (88.2%) of primary lesions stained positively for ER, 8/9 (88.8%), and 9/9 (100%), respectively. In metastatic lesions, only 2/17 (11.7%), 1/9 (11.1%), and none of the lesions stained positively for HER2. Ki-67 expression was high in 9/33 (27.2%) primary lesions, but only in 1/33 (3%) metastatic lesions.

4. DISCUSSION AND CONCLUSION

New research reveals a considerable spread of breast cancer in younger adults, with 7-10% of women diagnosed before the age of 40, despite an age-related increase. Breast cancer is a complex disease, and standard prognostic markers are inadequate in individualized care. Advances in technology have increased our understanding of genetic variables and treatment outcomes. Molecular biomarkers aid in the customization, optimization, and avoidance of over-, under-, and inappropriate treatment [5]. Immunohistochemical profiles of these 101 carcinomas revealed that ER receptors were positive in 56% of the cases, while Omer's study from Sudan found that the rate of ER-positive tumors was 33% [1]. 37% of patients showed ER and PR coexpression. We concluded that the majority of patients with breast cancer in western Sudan who participated in the study had hormone receptor expression, classified their cancer as hormone receptor positive, and were likely to respond to hormonal therapy, given that 37% of cases were ER/PR positive [1]. 18% [1] of the studies found PR-positive tumors, while 39% of the individuals in our study tested positive for PR. About 70–75% of invasive breast carcinomas have very high levels of ER expression [3]. Our results are in line with other studies that have shown that the estrogen receptor (ER) is a key diagnostic factor. We observed the highest ER expression in invasive ductal carcinoma (59%). 34 percent of the 61 instances were ER+/PR-, which contradicts the form. A survey of the National Cancer Database (NCDB) from 2004 to 2015 revealed that 13.7% of ER+ breast cancers had an ER+/PR phenotype. It is possible to tell the difference between ER+/PR- cancers and ER+ and ER-low tumors and between ER−/PR+ carcinomas and ER− carcinomas by looking at PR expression [6]. Progesterone receptor (PR) loss, as a downstream gene target of the estrogen receptor (ER), is usually associated with a poor prognosis in breast cancer. Our findings support earlier research indicating that the ER+/PR+ phenotype accounts for 9.7% of ER-positive breast cancer. The ER-PR+ subtype has the same outcomes as ER-PR-malignancies. On the other hand, the ER+PR- and ER-PR+ single hormone receptor-positive subtypes are more likely to have bad features and a lower survival rate than the ER+PR+ subtype [7]. In the current study, 12.8% of patients had this trait, compared to 25.5% in the other study [8]. Our research indicates that 37% of ER and PR coexpression occurs. Gezira University's Wad Medani investigation revealed that only 10 instances (11%) of ER and PR coexpression occurred between 2016 and 2022 [1]. We discovered that more than three-quarters of the study's breast cancer patients in western Sudan expressed hormone receptors, were hormone receptor positive, and would most likely respond to hormonal therapy because 37% of cases were ER/PR positive. The current investigation found that 27 out of 101 malignant cases, or 26%, were positive for her2/neu expression. This study's HER2 positivity rate of 26% aligns with another Sudanese study that reported Her2 positivity at 27% [1]. These results are consistent with another study that found 22.9% of subjects exhibited positive her2/neu expression [9]. It was possible to molecularly classify breast cancer cases by looking at the relationship between hormone receptor response and Her-2/neu status. The four types of breast cancer we looked into were Luminal-A (27%), luminal-B (9.9%), Her2/neu (9.9%), and triple-negative (31.6%). This was based on the link between hormone receptor responsiveness and Her2/neu status [9]. The percentage of triple-negatives is consistent with West African countries: Nigeria (46.7%), Senegal (46.7%), Togo (37.6%), and Ganah (44%), North African countries Egypt (44.79%) and Sudan (34.5%), East African Kenya (36.7%), and Rwanda (37.7%) [1]. Higher prevalence was observed in West African nations such as Nigeria (63%), Senegal (46.7%), and Ganah (82.20%), as well as one research from North Africa, Tunisia (66.25%). In contrast, Congo (4.20%), Kenya (20%), Ethiopia (23%), Botswana (21.1%), and South Africa (21.7%) reported a lower frequency of triple-negative infections. Demographic variance alone cannot explain this difference in triple-negative frequency across Africa; therefore, we strongly recommend a validated technique for measuring hormone status, including pre- and post-analytical quality control

[1]. TNBC is considered a highly invasive BC, with a shorter survival time, increased mortality, recurrence, and metastasis when compared to other BC subtypes. TNBC's aggressiveness, early recurrence, and lack of specific targets present significant therapeutic management problems, with a threefold increased risk of distant recurrence within five years [10]. The study found that nearly 49% of the participants exhibited high Ki67 expression (>20%), which is similar to a previous study from Sudan that also found high Ki67 expression (50%) [1]. We recommended frequent use of Ki76 evaluation to determine the prognosis of triple-negative breast cancer, as it has become more widely available and reasonably priced. Ki67 serves as a proliferation marker, and a high Ki67 percentage could potentially impact the treatment of receptor-negative malignancies. This is because chemotherapy more effectively targets dividing cells than non-dividing ones in these tumors. Ki67, as an independent factor, can predict a poor prognosis for stage I triple-negative tumors [1]. Her2 staining was positive in grade 3 (50%), which is consistent with Iqbal's findings; the Her2+ subtype had the largest proportion of grade III lesions [11]. According to our findings, the majority of Western Sudanese breast cancer patients are hormone receptor positive, which means they most likely responded well to hormonal therapy. The frequent subtypes of breast cancer include triple negative, with high Ki67 expression, which is consistent with findings from other research conducted in Sudan and Africa. Because of the importance of socioeconomic status in the current war, these findings were considered when making treatment decisions. Additionally, this information encourages political decision-makers to consider ways to reduce the death rate from breast cancer by reducing racial disparities in access to high-tech screening programs and improving management through collaboration between the health system, community shareholders, and supporting organizations.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Officials from the Kordofan Histopathology Center and the El-Obeid Oncology Center have given permission to retrieve the data.

The Human Ethics Committee of the Prof. Medical Research Consultancy Center approved the study protocol.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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