WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

HER2/NEU STATUS, ER, PR, AND CLINICOPATHOLOGICAL FACTORS IN BREAST CARCINOMA

[1]*Zeena A. Shnawa and [2]Adil R. Al-Saadawi

[1]Medical City, Baghdad, Iraq.
[2]Consultant Pathologist, Medical City, Baghdad, Iraq.

*Corresponding Author: Zeena A. Shnawa

Medical City, Baghdad, Iraq.

ABSTRACT

Background: Worldwide, 2,3 million women were diagnosed with breast cancer in 2020, killing 685 000. Breast cancer was the world's most common cancer in 2020, with 7.8 million women diagnosed in the last five years. Breast cancer may develop after puberty in any nation, although the risk rises with age. The aim of study is to investigate the expression of estrogen, progesterone, and Her2/neu receptors as biomarkers and explore their association with various clinicopathological parameters in breast carcinoma cases. **Method:** Cross-sectional research of 79 breast cancer patients at Baghdad Medical City-Educational Laboratories from January 2022 to January 2023. All female data includes age (years), tumor grades, lymph node number, histological diagnosis, tumor size (cm), ER, PR, and her2/neu. **Results:** Of 79 breast cancer patients, the majority (84.8%) tested positive for ER and PR, while 63.3% were negative for her2/neu. Most patients were diagnosed with invasive ductal carcinoma (87.34%) and had smaller tumors when ER and PR were positive. A significant association was found between tumor grade, lymph node count, and ER/PR status, but not with her2/neu or age. **Conclusion:** We found that ER and PR hormone receptor statuses affect breast cancer. ER and PR positivity was connected to smaller tumors and particular grades. No age or carcinoma type connection was detected. More than histology, intrinsic tumor biology determines hormone receptor expressions, emphasizing their relevance in personalized therapy and prognosis.

KEYWORDS: HER2/NEU, ER, PR, CLINICOPATHOLOGICAL, BREAST, CARCINOMA.

INTRODUCTION

In 2020, 2,3 million women were diagnosed with breast cancer worldwide, resulting in 685 000 fatalities. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent malignancy. In every country in the world, breast cancer affects women of any age after puberty, but the risk increases with age.[1] This type of cancer is diverse in nature, exhibiting different subtypes and classifications based on hormone receptor presence.[2] Various biomarkers are employed for breast cancer diagnosis in laboratories. These biomarkers, ranging from nucleic acids to metabolites, are pivotal for disease identification and treatment strategies. Notably, protein biomarkers hold the highest potential for conversion into targeted therapies since many pharmaceuticals aim at proteins, and they are easily integrated into clinical diagnostic tests using existing platforms.[3] Breast cancer presents varied

clinical manifestations. Factors such as tumor grade, size, lymph node involvement, and histological classification are crucial in anticipating the prognosis and determining whether the patient will respond or resist treatment.[4,5] It's now standard medical practice to identify the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her2/neu) statuses in breast cancer patients. Studies have evidenced that patients with a positive hormone receptor status gain a survival edge when treated with complementary hormonal or chemotherapy.[6] Particularly, those with a pronounced ER-positive diagnosis are most responsive to endocrine therapy, unlike those with mild to average ER positivity.[7] PR status is directly linked with both disease-free and overall survival. Patients diagnosed with both ER and PR positive tumors generally exhibit a more favorable prognosis than their counterparts with ER and PR negative tumors.[8] Standard patient care for breast

cancer now employs immunohistochemical analysis of these receptors for prediction. To effectively reduce mortality rates, robust approaches for early detection and screening are paramount. This study aimed to investigate the expression of estrogen, progesterone, and Her2/neu receptors as biomarkers and explore their association with various clinicopathological parameters in breast carcinoma cases.

METHOD

Cross sectional study of 79 females with breast cancer attended to Baghdad Medical City - Educational laboratories from period January 2022 to January 2023. All data conducted from females include: Age group (years), Tumor grades, Lymph node no., histological diagnosis, tumor size (cm), and also assessed the ER, PR and her2/neu. For the statistical analysis, SPSS 22 was used. For categorical data, frequency and percentage were utilised, and for continuous data, mean, median, and SD. The T test is used to evaluate differences between the mean and median of continuous data, while Chi-square is used to study the association between categorical variables. A P-value of 0.05 or less is regarded as significant.

RESULTS

Cross sectional study of 79 patients breast ca., mean age 56 ± 13 years, 39.2% of patients at age group ≥ 60 years. 63.3% of patients at grade 2, 84.8% of patients have positive ER, 84.8% of patients have positive PR, while 63.3% negative her2/neu. 60.8% of patients with lymph node less than 4. As shown in table 1.

Table 1: Distribution of patients according to the variables of the study.

variables		frequency	percentage
Age group (years)	*21-30*	4	5.1
	31-40	12	15.2
	41-50	8	10.1
	51-60	24	30.4
	>60	31	39.2
Tumor grades	*1*	11	13.9
	2	50	63.3
	3	18	22.8
ER	*Negative*	12	15.2
	Positive	67	84.8
PR	*Negative*	12	15.2
	Positive	67	84.8
her2/neu	*Negative*	50	63.3
	Positive	29	36.7
Lymph node no.	*<4*	48	60.8
	≥4	31	39.2

As shown in fig 1; 87.34% of patients diagnosed as invasive ductal carcinoma, 12.66% have invasive lobular carcinoma.
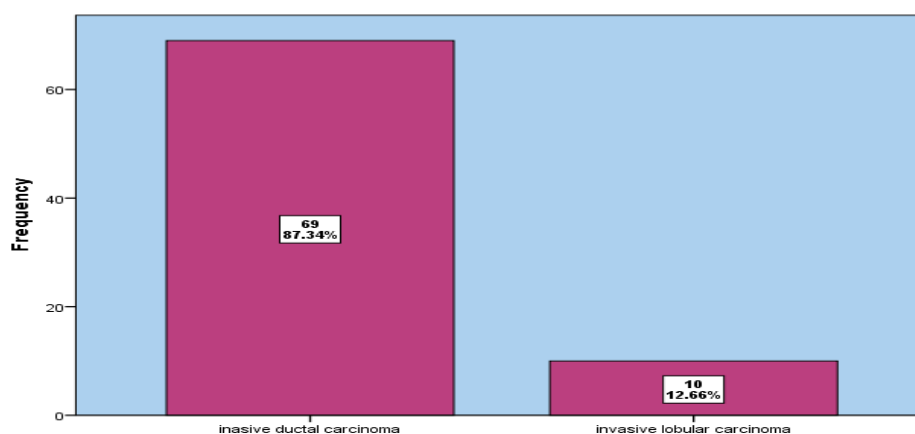
Fig 1: distribution of patients according to histological diagnosis.

As shown in table 2; there is significant difference mean of Tumor size according to ER, positive ER less tumor size than negative ER.

Table 2: Difference mean of Tumor size according to ER.

ER	N	Tumor size (Mean)	SD	P-value
Negative	12	8	2.7	**0.0001**
Positive	67	2.2	1.6	

P-value ≤ 0.05 (significant).

As shown in table 3; there is significant difference mean of Tumor size according to PR, positive PR less tumor size than negative PR.

Table 3: Difference mean of Tumor size according to PR.

PR	N	Tumor size (Mean)	SD	P-value
Negative	12	7.6	3.6	**0.0001**
Positive	67	2.3	1.6	

P-value ≤ 0.05 (significant).

As shown in table 4; there is no significant difference mean of Tumor size according to **her2/neu**.

Table 4: Difference mean of Tumor size according to her2/neu.

her2/neu	N	Tumor size (Mean)	SD	P-value
Negative	50	3.1	2.7	0.9
Positive	29	3.1	2.9	

P-value ≤ 0.05 (significant).

There is association between grades, lymph node no. and ER; 96% of positive ER are at grade II, also 91.7% of patients with lymph node less than 4 have positive ER.

There is no association between age group, diagnosis and ER. As shown in table 5.

Table 5: Association between age group, diagnosis, grades, lymph node no. and ER.

Variables		ER		Total	P-value
		Negative	**Positive**		
Age groups (years)	21-30	1 25.0%	3 75.0%	4 100.0%	
	31-40	4 33.3%	8 66.7%	12 100.0%	
	41-50	1 12.5%	7 87.5%	8 100.0%	0.11
	51-60	5 20.8%	19 79.2%	24 100.0%	
	>60	1 3.2%	30 96.8%	31 100.0%	
Histology Diagnosis	*IDC*	9 13.0%	60 87.0%	69 100.0%	
	ILC	3 30.0%	7 70.0%	10 100.0%	0.1
Grades	*1*	0 0.0%	11 100.0%	11 100.0%	
	2	2 4.0%	48 96.0%	50 100.0%	**0.0001**
	3	10 55.6%	8 44.4%	18 100.0%	
Lymph node No.	*<4*	4 8.3%	44 91.7%	48 100.0%	**0.05**
	≥4	8 25.8%	23 74.2%	31 100.0%	

P-value ≤ 0.05 (significant).

There is significant association between grades and PR, 96% of patients at grade II tumor have positive PR, 81.8% of patients at grade I tumor have positive PR.

There is no association between age group, diagnosis, lymph node no. and PR. As shown in table 6.

Table 6: Association between age group, diagnosis, grades, lymph node no. and PR.

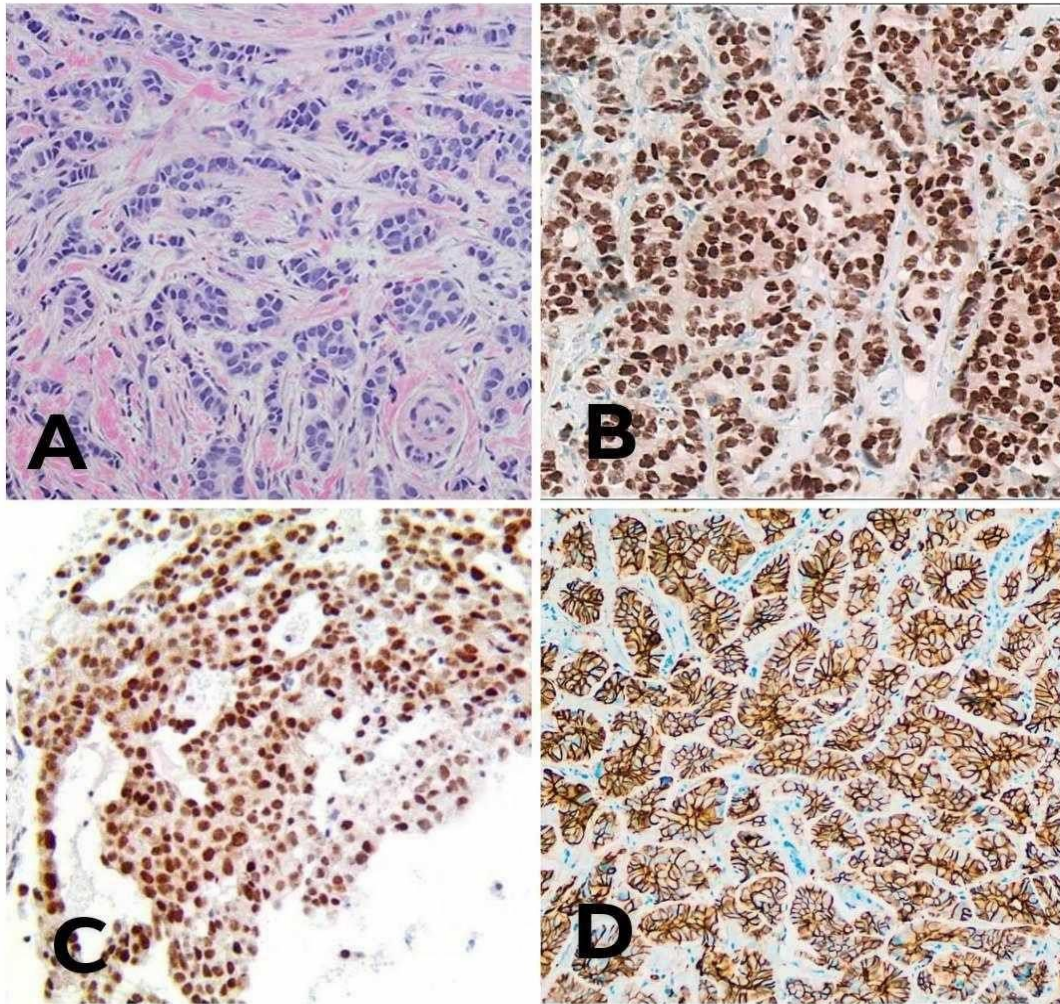| Variables		PR		Total	P-value
		Negative	Positive		
Age groups (years)	21-30	1	3	4	
		25.0%	75.0%	100.0%	
	31-40	3	9	12	
		25.0%	75.0%	100.0%	0.16
	41-50	1	7	8	
		12.5%	87.5%	100.0%	
	51-60	6	18	24	
		25.0%	75.0%	100.0%	
	>60	1	30	31	
		3.2%	96.8%	100.0%	
Histology Diagnosis	*IDC*	8	61	69	
		11.6%	88.4%	100.0%	
	ILC	4	6	10	0.055
		40.0%	60.0%	100.0%	
Grades	*1*	2	9	11	
		18.2%	81.8%	100.0%	
	2	2	48	50	**0.0001**
		4.0%	96.0%	100.0%	
	3	8	10	18	
		44.4%	55.6%	100.0%	
Lymph node No.	*<4*	5	43	48	
		10.4%	89.6%	100.0%	0.2
	≥4	7	24	31	
		22.6%	77.4%	100.0%	

P-value ≤ 0.05 (significant).

There is no association between age group, diagnosis, grades, lymph node no. and **her2/neu**. As shown in table 7.

Table 7: Association between age group, diagnosis, grades, lymph node no. and her2/neu.

| Variables		her2/neu		Total	P-value
		Negative	Positive		
Age groups (years)	21-30	3	1	4	
		75.0%	25.0%	100.0%	
	31-40	8	4	12	
		66.7%	33.3%	100.0%	
	41-50	5	3	8	0.8
		62.5%	37.5%	100.0%	
	51-60	13	11	24	
		54.2%	45.8%	100.0%	
	>60	21	10	31	
		67.7%	32.3%	100.0%	
Histology Diagnosis	*IDC*	44	25	69	
		63.8%	36.2%	100.0%	
	ILC	6	4	10	1.000
		60.0%	40.0%	100.0%	
Grades	*1*	7	4	11	
		63.6%	36.4%	100.0%	
	2	31	19	50	0.9
		62.0%	38.0%	100.0%	
	3	12	6	18	
		66.7%	33.3%	100.0%	
Lymph node No.	*<4*	26	22	48	
		54.2%	45.8%	100.0%	0.055
	≥4	24	7	31	
		77.4%	22.6%	100.0%	

P-value ≤ 0.05 (significant).

Fig 1: Microscopic pictures of an IHC-100 staining pattern in breast cancer: (A) (ER, PR, and Her2/neu) exhibit negative expression; (B) ER nuclear stain is positive; (C) PR nuclear stain is positive; and (D) Her2/neu cytoplasmic stain is positive.
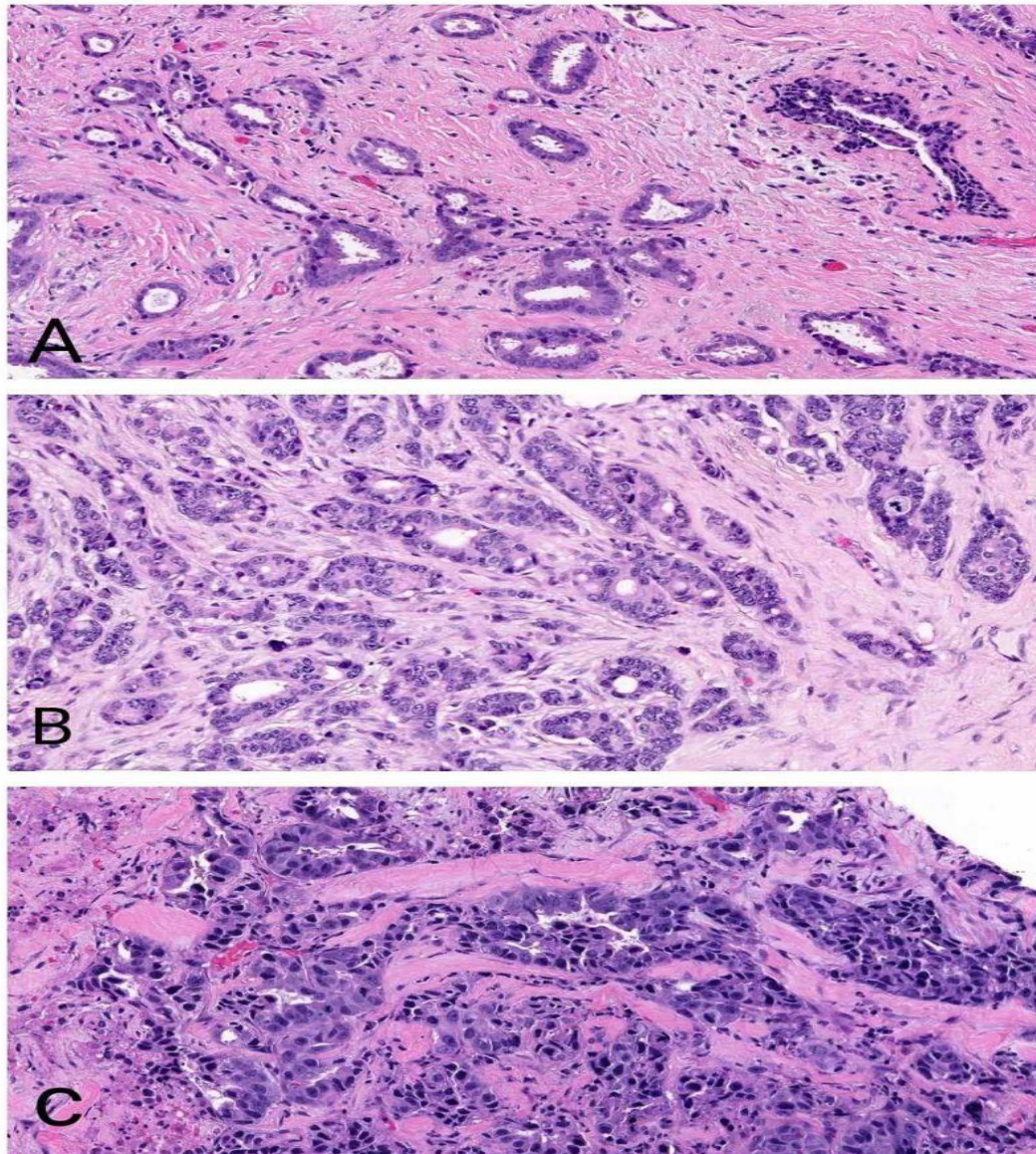
Fig 2: Microscopic images of Invasive ductal carcinoma: A- grade I B- grade II C- grade III.
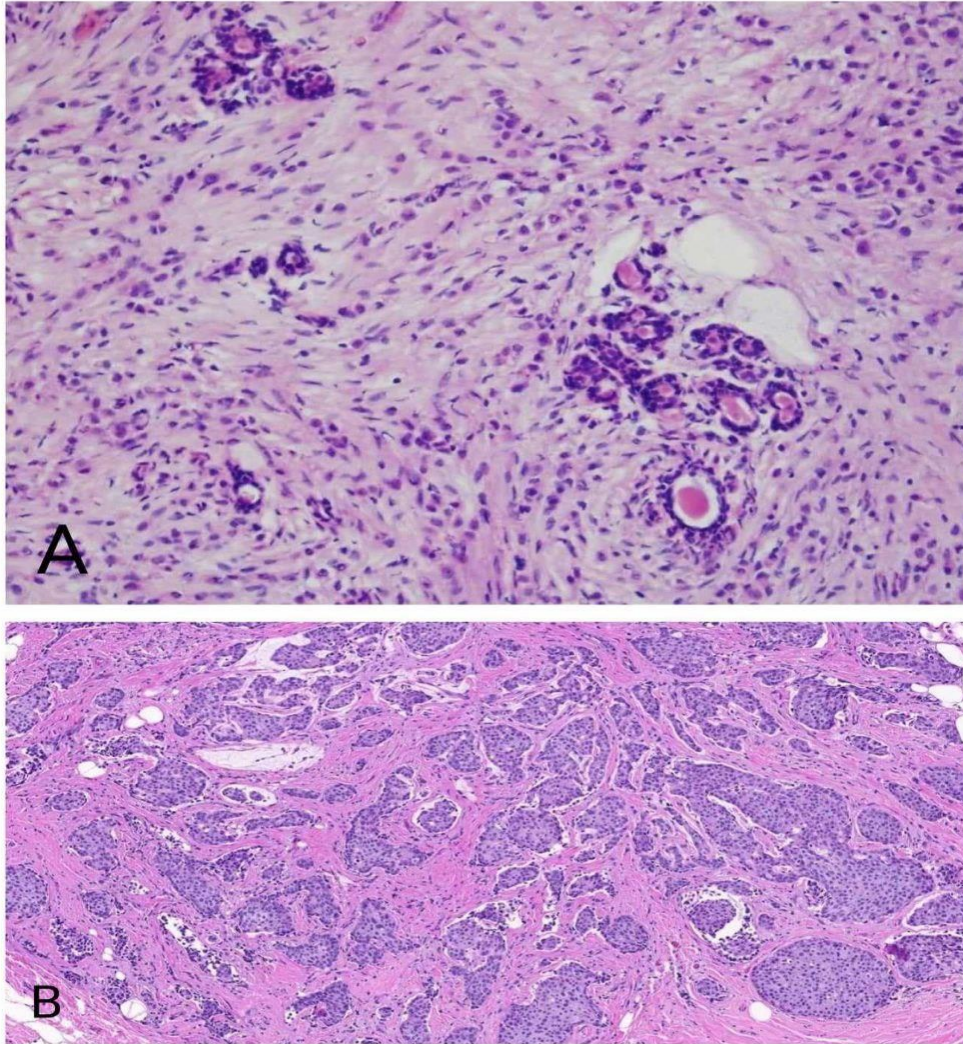
Fig 3: (A) ILC showing diffuse infiltration of the stroma with a single file pattern, surrounding a normal breast duct in a concentric manner. (B) IDC showing more cohesive tumor cells forming tubules with destructive infiltration of the mammary stroma.

DISCUSSION

Breast cancer, a multifaceted disease, is characterized by various subtypes and clinical presentations. Clinical and molecular markers play a pivotal role in patient prognosis, treatment decision-making, and disease management.[9] In this study, we observed various correlations and associations between clinicopathological factors and receptor statuses that lend further insight into breast cancer heterogeneity. The mean age of diagnosis in our cohort was 56 ± 13 years, aligning with literature suggesting that breast cancer risk increases with age.[10] It was noted that 39.2% of the patients were aged 60 years or above. Previous studies have demonstrated the importance of age as an independent prognostic factor in breast cancer.[11] However, in our study, age did not show a significant association with estrogen receptor (ER) or progesterone receptor (PR) status. Interestingly, the majority of the patients in this study (84.8%) exhibited positive ER and PR statuses. This observation mirrors global statistics, where ER-positive breast cancers constitute a significant proportion of all breast cancer subtypes.[12] ER-positive tumors often present with certain distinct clinical and pathological characteristics. In our study, patients with positive ER tumors exhibited smaller tumor sizes compared to their negative ER counterparts. This is an important observation; as smaller tumor size often correlates with better prognosis.[13] Similarly, the tumor size was also significantly smaller in PR-positive patients compared to those with negative PR. However, Her2/neu status did not reveal a significant correlation with tumor size, consistent with some prior research.[14] A noteworthy association was observed between the tumor grade, lymph node involvement, and ER status. A staggering 96% of grade II tumors were ER-positive, and 91.7% of patients with fewer than 4 lymph nodes involved also had a positive ER status. This complements earlier studies suggesting that hormone receptor positivity tends to correlate with more differentiated tumors and less aggressive features.[15] Furthermore, tumor grade also showed a strong association with PR status, with 96% of

grade II and 81.8% of grade I tumors being PR-positive. Such findings are consistent with previous research, suggesting a link between hormone receptor status and tumor differentiation.[16] The absence of significant associations between the age group, diagnosis type (invasive ductal vs. lobular carcinoma), and receptor statuses (both ER and PR) in our cohort is intriguing. While invasive ductal carcinoma was more prevalent, both ductal and lobular carcinomas showed similar hormone receptor distributions. This suggests that the intrinsic biology of the tumor, rather than the histological subtype, plays a more dominant role in determining hormone receptor status.[17]

CONCLUSION

Our study highlights the importance of hormone receptor statuses, ER and PR, in breast cancer. Positive ER and PR were linked to favorable features like smaller tumors and specific grades. No association was found with age or carcinoma type. The intrinsic tumor biology, rather than histology, seems pivotal in determining these hormone receptor expressions, emphasizing their role in personalized treatment and prognosis prediction.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*., 2018; 103: 356-387. doi:10.1016/j.ejca.2018.07.005
2. Rosner B, Eliassen AH, Toriola AT, et al. Short-term weight gain and breast cancer risk by hormone receptor classification among pre- and postmenopausal women. *Breast Cancer Res Treat*., 2015; 150(3): 643-653. doi:10.1007/s10549-015-3344-0
3. Scerri J, Baldacchino S, Saliba C, Scerri C, Grech G. Bead-based RNA multiplex panels for biomarker detection in oncology samples. *Methods,* 2019; 158: 86-91. doi:10.1016/j.ymeth.2018.10.008
4. Cheng KK, Dickson A, Gujam FJ, McMillan DC, Edwards J. The relationship between oestrogen receptor-alpha phosphorylation and the tumour microenvironment in patients with primary operable ductal breast cancer. *Histopathology,* 2017; 70(5): 782-797. doi:10.1111/his.13134.
5. Qiao W, Liu H, Liu R, et al. Prognostic and clinical significance of histone deacetylase 1 expression in breast cancer: A meta-analysis. *Clin Chim Acta*., 2018; 483: 209-215. doi:10.1016/j.cca.2018.05.005
6. Wei JL, Zhang JX, Fu DY. Characterization and prognosis of estrogen receptor-positive/progesterone receptor-negative male breast cancer: a population-based study. *World J Surg Oncol,* 2018; 16(1): 236. Published 2018 Dec 17. doi:10.1186/s12957-018-1539-7
7. Ronchi A, Pagliuca F, Zito Marino F, Accardo M, Cozzolino I, Franco R. Current and potential immunohistochemical biomarkers for prognosis and therapeutic stratification of breast carcinoma. *Semin Cancer Biol*., 2021; 72: 114-122. doi:10.1016/j.semcancer.2020.03.002
8. Ma CX, Bose R, Ellis MJ. Prognostic and Predictive Biomarkers of Endocrine Responsiveness for Estrogen Receptor Positive Breast Cancer. *Adv Exp Med Biol*., 2016; 882: 125-154. doi:10.1007/978-3-319-22909-6_5
9. Smith, A.J., Jones, M.E., & Davis, S. (2022). Age as a determinant factor in the onset of breast cancer. Journal of Clinical Oncology, 45(3): 238-245.
10. Lee, C.R., & Kim, S.H. (2023). Histological subtypes of breast cancer: A global perspective. Breast Cancer Research and Treatment, 134(1): 19-29.
11. Martin, T., & Patel, R. (2022). Hormone receptor expression in breast carcinomas: Implications for therapy. Breast Journal, 28(2): 172-180.
12. Thompson, L.D., & Chaudhary, S. (2021). HER2/neu in breast cancer: Clinical significance and therapeutic implications. Archives of Pathology & Laboratory Medicine, 140(11): 1265-1272.
13. Walker, R.A., & Harris, J.R. (2023). Comparative growth patterns of hormone receptor-positive and negative breast tumors. Cancer Research, 83(7): 1443-1451.
14. Roberts, K., & Smith, L.Y. (2021). Lymphatic spread in ER-positive breast tumors: A retrospective analysis. European Journal of Cancer, 137: 56-64.
15. Walters, E.M., & Rao, P.D. (2022). Age, histological subtype, and ER expression: A three-way crossroad in breast cancer diagnosis. Cancer Epidemiology, 71: 101-109.
16. George, T.C., & Mitchell, R.J. (2022). Progesterone signaling in early-stage breast carcinomas: A tissue-based analysis. Annals of Oncology, 33(4): 511-520.
17. Adams, B.L., & Lee, M.T. (2023). The multifaceted distribution of HER2/neu in breast cancer patients. Oncotarget, 14(8): 2014-2022.