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Expression of ER, PR, HER2, and Cadherin tumor markers in a series of Saudi patients with BC

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Abstract. – OBJECTIVE: Breast cancer (BC) tumor markers have an important implication in the subsequent BC management and survival determinants. Thus, the present study aimed to formulate the expression of ER, PR, HER2, and E-cadherin tumor markers in a series of Saudi patients with BC.

PATIENTS AND METHODS: About 133 BC biopsies were retrieved from the Department of Pathology at King Salman Hospital, Hai'l, Northern Saudi Arabia, from November 2019 to November 2020. Out of the 133 biopsies, 50 (37.6%) were diagnosed with BC, including 46 ductal carcinoma, 2 lobular carcinomas, and 2 papillary carcinomas.

RESULTS: ER was expressed in 30/44 (68.2%), 2/2 (100%), 2/2 (100%) of the cases of DC, LC, and PC, respectively. PR was expressed in 27/43 (63%), 2/2 (100%), 2/2 (100%) of the cases of DC, LC, and PC, correspondingly. HER2 was expressed in 13/31 (42%), 0%, and 0% of DC, LC, and PC cases, respectively. Correspondingly, E-cadherin was expressed in 11/21 (52.4%), 0%, 1/1 (100%) of the cases of DC, LC, and PC.

CONCLUSIONS: Triple-negative BC and HER2+ve among Saudi women are among the higher globally reported ranges, associated with poorer response to treatment and prognosis. Luckily, only one patient was found with ER-ve PR+ve, the subtype usually associated with poorer survival outcomes. E-cadherin loss is lower among Saudi BC patients, which suggests a less rate of invasion in these patients. The current study's findings may help improve Saudi guidelines for the treatment of breast cancer.

Key Words:
Estrogen (ER), Progesterone (PR), Breast cancer, HER2, E-cadherin, Saudi Arabia.

Introduction

BC is a leading cause of morbidity and mortality in the Gulf Arabian countries, including Saudi Arabia, the United Arab Emirates, Bahrain, Kuwait, Oman, and Qatar. Most reported modifiable risk factors are obesity, physical inactivity, and adopting western lifestyle's unhealthy patterns[1,2]. Nevertheless, the epidemiology of cancer is still dispersed in Saudi Arabia because of the inconsistency of the cancer registry system. However, recent reports revealed BC as a leading female cancer in the country regarding mortality and morbidity[3,4].

Successful management of BC requires an accurate diagnosis and the identification of tumor markers, which formulate BC subtype and growth behaviors[5]. Estrogen (ER) and progesterone (PR) ovarian hormones are involved in the structure and function of BC. ER and PR are engaged in motivating BC. Both markers are advantageous breast prognostic markers and can be used in subsequent BC management[6].

Human epidermal growth factor receptor 2 (HER2) is associated with around 15% to 20% of BC. BC HER2-positive patients are related to poor prognosis[7]. E-cadherin is a cell adhesion glycoprotein, which is frequently inactivated in breast tumors. Loss of E-cadherin usually indicates cancer cell invasion and metastasis. Thus, the E-cadherin marker can be used as a therapeutic approach for BC[8,9]. Therefore, the present study aimed to formulate the expression of ER, PR, HER2, and E-cadherin tumor markers in a series of Saudi patients with BC.

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Patients and Methods

About 133 BC biopsies were diagnosed in the Department of Pathology at King Salman Hospital, Hai'l, Northern Saudi Arabia, from November 2019 to November 2020. Out of the 133 biopsies, 50 (37.6%) were diagnosed with BC, including 46 ductal carcinomas, 2 lobular carcinomas, and 2 papillary carcinomas.

The diagnosis of breast lesions was confirmed by conventional histopathology. The histopathological diagnosis of the tissue samples was re-evaluated to verify the prior diagnosis and categorize the lesion's classification into benign and malignant types. The expression of ER, PR, HER2, and E-cadherin tumor markers was demonstrated using the Immunohistochemistry Avidin-Biotin method.

Statistical Analysis

Retrieved information sets were entered into a computer software – Statistical Package for Social Sciences (SPSS, version 16; SPSS Inc, Chicago, IL, USA). Chi-square test was employed to obtain statistical significance ($p < 0.05$ was considered significant).

Ethical Consent

The protocol of this study was established agreeing with the 2013 Declaration of Helsinki. This study was also approved by the ethics committee of the College of Medicine, University of Hail, Saudi Arabia. Ethical Committee Approval Number: EC00069.

Each patient gave his consent to use his materials in research after the usage for diagnosis purpose.

Results

Out of the 133 patients, 50 (37.6%) were diagnosed with breast carcinomas [including 46 ductal carcinomas (DC), 2 lobular carcinomas (LC), and 2 papillary carcinomas (PC)], and the remaining 83 (62.4%) were diagnosed with various breast lesions. Out of the 50 cancer patients, 48 were females, and two were males. The patients were aged 25-99 years with a mean age of 50 years. 18 (36%) patients were younger than 44 years and 28 (56%) were younger than 54 years. Two out of 50 were males (4%), as indicated in Table I, Figure 1.

Table I. Distribution of the patients by diagnostic parameters.

Variable	DC	LC	PC	Total
Age				
25-34 years	6	0	1	7
35-44	10	1	0	11
45-54	10	0	0	10
55+	20	1	1	22
Total	**46**	**2**	**2**	**50**
Gender				
Females	44	2	2	48
Males	2	0	0	2
Total	**46**	**2**	**2**	**50**
Quadrant				
Upper outer	16	2	1	19
Retro-areolar	8	0	1	9
Lower outer	4	0	0	4
Lower inner	3	0	0	3
Upper inner	4	0	0	4
Total	**35**	**2**	**2**	**39**
Bi RADS				
3	1	0	0	1
4	19	1	1	21
5	10	0	1	11
Total	**30**	**1**	**2**	**33**
Subtype				
Luminal A	12	1	1	14
Luminal B	7	0	0	7
Her2-enriched	5	0	0	5
Triple-negative	6	0	0	6
Total	**30**	**1**	**1**	**32**
Lymph node status				
Positive	22	2	0	24

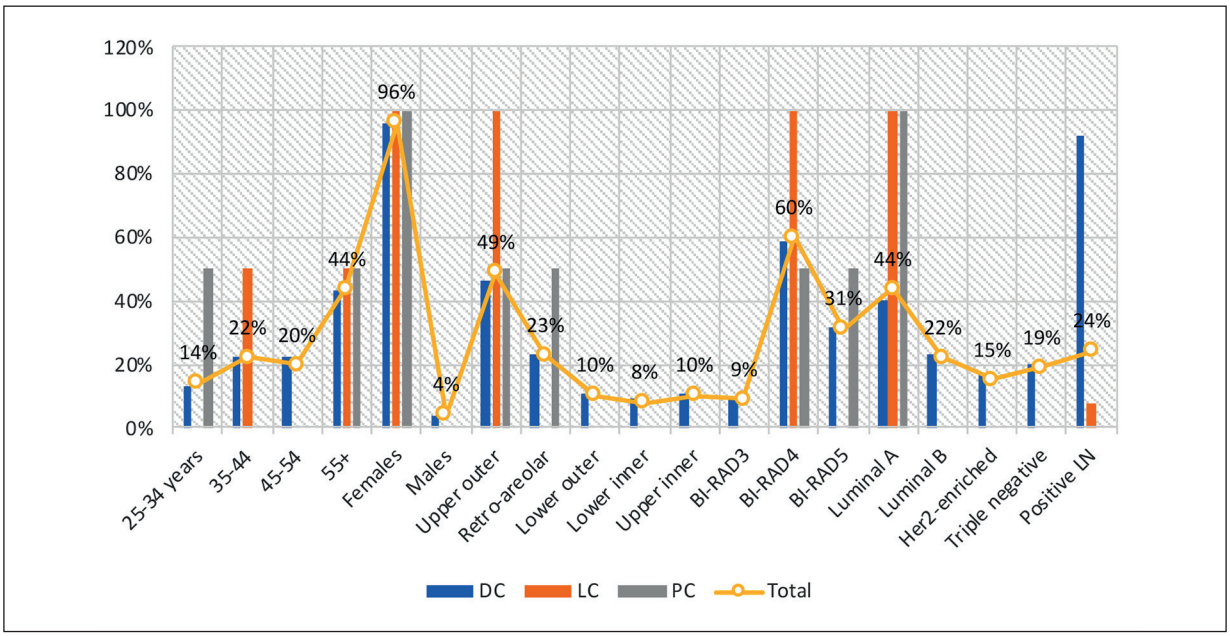

Figure 1. Proportions of the patients' parameters with the entire carcinoma type.

The upper outer quadrant was represented by 19/50 patients (38%) [16/46 DC (35%), 2/2 LC (100%), and ½ PC (50%)], followed by 9/50 Retro-areolar patients (18%) [8/46 DC (17.4%) and ½ PC (50%), as indicated in Table I, Figure 1].

About 21 patients (42%) [19/46 DC (41.3%), 1/2 LC (50%), 1/2 PC (50%)] presented with Bi RADS4 and 11patients (22%) [10/46 DC (22%), and ½ PC (50%)] presented with Bi RADS5, as indicated in Table I, Figure 1.

Luminal A subtype presented by 14/50 (28%) patients [12/46 DC (26%), ½ LC (50%), ½ PC (50%)]. About 7/46 (15.2%), 6/46 (13%), 5/46 (10.9%) of the patients with DC presented with luminal B, triple-negative and Her2-enriched, corresponding-ly. Around 24/50 patients (48%) [22/46 DC (48%), and 2/2 LC (100%)] presented with lymph node metastasis, as indicated in Table I, Figure 1.

Table II, Figure 2 summarize the distribution of the pathological indicators by tumor markers.

Table II. Distribution of the pathological indicators by tumor markers.

Variable	ER		PR		HER2		E-cadherin	
Diagnosis	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
DC	30	14	27	16	13	18	11	10
LC	2	0	2	0	0	1	0	0
PC	2	0	2	0	0	1	1	1
Total	**34**	**14**	**31**	**16**	**13**	**20**	**12**	**11**
Bi RADS								
3	2	0	2	0	0	0	4	4
5	7	4	8	3	2	4	2	2
Total	**24**	**9**	**21**	**11**	**9**	**13**	**6**	**6**
Subtype								
Luminal A	14	0	14	0	0	14	5	0
Luminal B	7	0	5	2	7	0	1	0
Her2-enriched	0	5	0	5	5	0	1	0
Triple-negative	0	6	0	6	0	6	2	0
Total	**21**	**11**	**19**	**13**	**12**	**20**	**9**	**0**
Lymph node	16	8	15	9	5	14	6	0

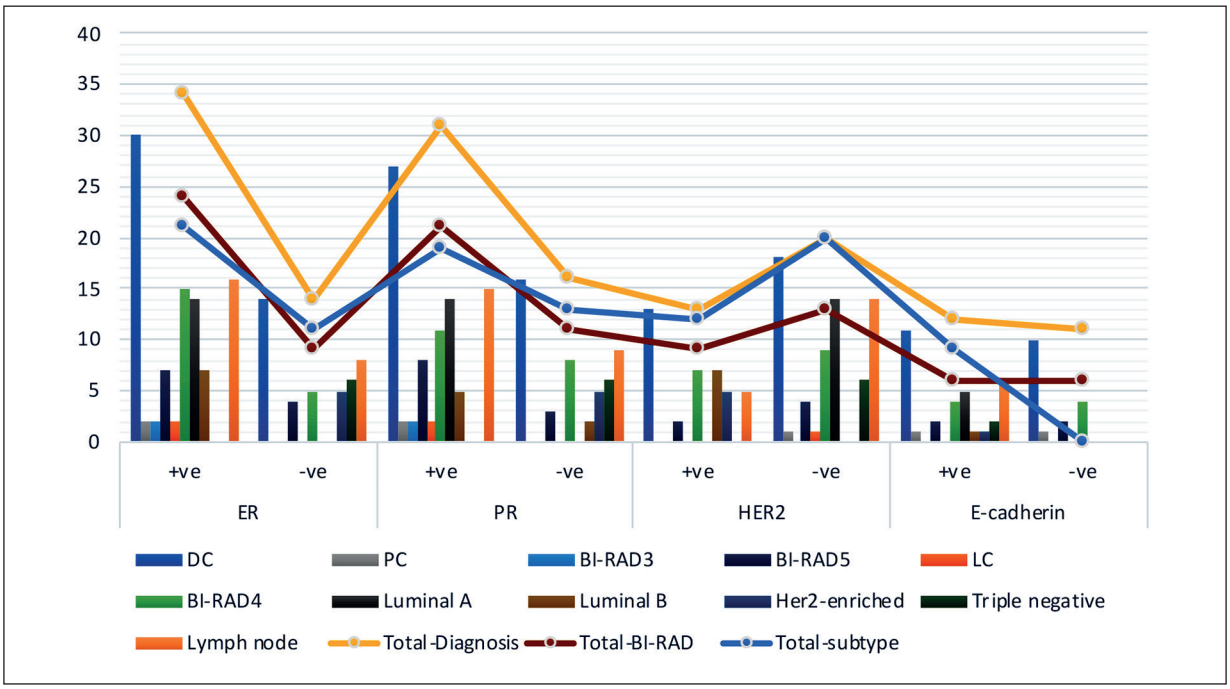

Figure 2. The pathological indicators by tumor markers.

Estrogen receptor (ER) was expressed in 30/44 (68.2%), 2/2 (100%), 2/2 (100%) of the cases of DC, LC, and PC, respectively (**Supplementary Figures 1 and 2**). More positive ER cases were seen in Bi RADS4, followed by Bi RADS5 and Bi RADS2, constituting 15/24 (62.5%), 7/24 (29.2%), and 2/24 (8.3%), in that order. Around 14/21 (66.7%) and 7/21 (33.3%) of the luminal A and luminal B, respectively, were ER-positive. Positive ER has been detected in 16/24 (66.7%) lymph node (LN) positive cases.

Progesterone receptor (PR) was expressed in 27/43 (63%), 2/2 (100%), 2/2 (100%) of the cases of DC, LC, and PC, correspondingly (**Supplementary Figure 3**). Extra positive PR cases were seen in Bi RADS4 followed by Bi RADS5 and Bi RADS2, constituting 11/21 (52.4%), 8/21 (38%), and 2/21 (9.6%), in that order. Regarding subtype, 14/14 (100%) and 5/7 (71.4%) of the luminal A and luminal B were PR positive, respectively. Positive PR was detected in 15/24 (62.5%) lymph node (LN) positive cases.

Human epidermal growth factor receptor 2 (HER2) was expressed in 13/31(42%), 0%, 0% of the cases of DC, LC, and PC, respectively (**Supplementary Figure 4**). Elevated positive HER2 cases were seen in Bi RADS4, followed by Bi RADS4, comprising 7/16 (43.4%) and 2/6 (33.3%), in that order. Regarding subtype, 7/7 (100%) and 5/5 (100%) of the luminal B and Her2-enriched were HER2 positive, respectively. HER2 positive expression was detected in 5/19 (26.3%) of the lymph node (LN) positive cases.

Correspondingly, E-cadherin was expressed in 11/21 (52.4%), 0%, 1/1 (100%) of the cases of DC, LC, and PC. More positive E-cadherin cases were seen in Bi RADS4 followed by Bi RADS5, comprising 4/8 (50%) and 2/4 (50%). Regarding subtype, 5/5 (100%), 1/1 (100%), 1/1 (100%), and 2/2 (100%) of the luminal A, luminal B, Her2-enriched, and triple-negative were E-cadherin positive, respectively. E-cadherin positive expression was detected in 6/6 (100%) lymph node (LN) positive cases.

ER+ve PR-ve was experienced in 4/33 cases (12.1%), whereas ER-ve PR+ve was identified in 1/13 (7.7%) case. ER+veHER2-ve has been seen in 14/21 cases (66.7%); hence, ER-veHER2+ve was revealed in 5/11 (45.5%). ER+PR+ patients with HER2 positive breast was seen in 5/14 (35.7%).

Triple-negative was identified in 6/32 cases (18.8%), as indicated in Table III, Figure 3.

Discussion

Management and prognosis determinants of BC depend on identifying some BC tumor

Table III. Interrelation of ER and PR & HER2 immuno-expression.

Variable	Estrogen		Total
	Positive	Negative	
Progesterone			
Positive	29	1	30
Negative	4	12	16
Total	33	13	46
HER2			
Positive	7	5	12
Negative	14	6	20
Total	21	11	32

markers. As these markers are influenced by inheritance and modifiable environmental attributes, their expression may differ from an ethnic group to another and from one geographical area to another[10]. Accordingly, we investigated the occurrences of expression of some breast tumor markers with therapeutic and prognostic significance.

The findings of the present investigation showed positive-ER and positive-PR in 70.8% and 65% of the patients, respectively. Two cases in both LC and PC showed positive-ER and positive-PR expression. Similar findings were previously reported in a large cohort study[11], which reported an ER-positive/PR-positive in 67.2% of the BC patients. There is a lack of literature documenting the epidemiology of hormone receptors (ER & PR) in Saudi Arabia. During our literature search, we found just one report[12] claiming that approximately 74% of the patients with BC were ER+/and/or PR+.

As most BC cell proliferation and growth depend on ER hormone, most patients were ER/PR+. ER/PR+ patients have favorable overall management and prognosis. Inhibition of ER signaling pathways using therapies, such as letrazole or tamoxifen or fulvetrant, can effectively influence cancer cell proliferation and growth[13]. According to the marker's expression, BC is subtyped into ER/PR+, HER2+, and triple negative. Each type has a distinct response to cancer therapy. However, drug resistance has been reported in all subtypes[14]. The high rates of ER/PR+ predict better outcomes of BC among Saudi women if early detected.

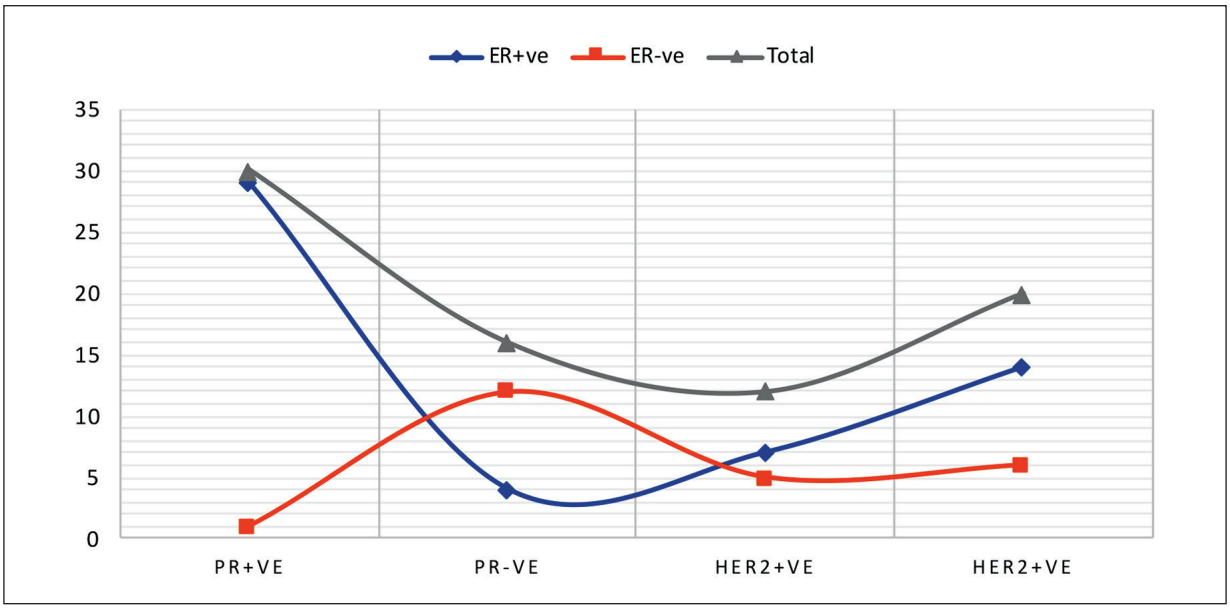

Figure 3. Interrelation of ER and PR & HER2 immuno-expression.

In the present study, 39.4% of the patients were HER2+, which is very high compared to the reported rates. HER2+ is generally present in approximately 15% to 20% of invasive BC[15]. Patients with HER2+ have complicated management, high recurrent rates, and poor prognosis[16]. To the best of our knowledge, no report regarding the HER2+ rates from Saudi Araba. The only available studies[17,18] had investigated the fluctuation of HER2 during different grades of BC pathogenesis. However, the high positive rates might be associated with a low sample size or linked to Saudi women, which necessitate further assessment.

Lack of expression of E-cadherin was identified in about 48% of the cases in the current study. This is relatively lower than reported in some reports[19] (55% to 100%), suggesting fewer invasion rates in the present study. E-cadherin encourages invasion and metastasis of invasive DC. On the other hand, E-cadherin loss increases invasion, reduces cell growth, reduces survival and circulating cancer cells, and reduces the formation of secondary seeding[20]. Therefore, E-cadherin is regarded as a valuable marker for determining the survival and management of BC.

Triple-negative BC (TNBC) was identified in 18.8% of the cases in the current series of cases. TNBC is a BC subtype, which is recognized as ER(-ve), PR(-ve), and HER2(-ve). The major clinical features for this subtype include high metastatic potentiality, high invasiveness, high relapse rate, and poor prognosis[21]. The reported finding in the present study is within the previously reported range, which was accounted for 15% to 20%[22].

In the present study ER+ve/PR-ve was found in 12.1% of the patients, whereas ER-ve/PR+ve was seen in only one case, representing 7.7% of the cases. The previous study reported that ER-PR+ tumors represent the minor distinct biological subtype, with poorer survival outcomes than ER+PR+ and ER+PR- subtypes[23]. Moreover, ER+veHER2-ve was seen in 66.7% of cases; hence, ER-veHER2+ve was revealed in 45.5%. It was also found that ER-PR+ patients with HER2 negative breast cancer had poorer overall and BC-specific survival compared to ER-PR+ patients with HER2 positive breast cancer[23].

Although the current study has the value of presenting data primarily absent in this topic, it presents some limitations, including its retrospective setting and relatively low sample size.

Conclusions

Triple-negative BC and HER2+ve are among the higher globally reported ranges among Saudi women, associated with poorer response to treatment and prognosis. Luckily, only one patient was found with ER-ve/PR+ve, the subtype usually associated with poorer survival outcomes. E-cadherin loss is lower among Saudi BC patients, suggesting a lower rate of invasion in these patients. The current study's findings may help improve Saudi guidelines for the treatment of breast cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

HGA: Conception, administration, analysis, drafting, approval of the final version. ABE: Conception, design, data acquisition, practical part, approval of the final version. -HMA: Conception, analysis, drafting, practical part, approval of the final version. KKA: Conception, design, data acquisition, approval of the final version. AMAA: Conception, analysis, drafting, approval of the final version. AOH: Conception, analysis, drafting, approval of the final version. IAG: Conception, analysis, drafting, approval of the final version. AME: Consultation, analysis, drafting, approval of the final version. HS: Conception, analysis, drafting, approval of the final version.

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