Comparison Of ER-Positive Versus ER-Negative In Breast Cancer Women And Invasive Ductal Carcinoma In The West Of Iran: A Direct Correlation With Vascular Invasion

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Abstract: Background & Objective**:** ER expression is the main indicator of potential responses to endocrine therapy, and approximately 70% of human breast cancers are hormone-dependent and ER-positive. The aim of the study is to evaluate the correlation between risk factors with ER status in breast cancer patients in the West of Iran. Methodology: In a retrospective study, 260 breast cancer women were included invasive ductal carcinoma our Clinic. A sufficient sample size was selected from any patient, and the slides were stained by hematoxylin and eosin (H & E) method. Estrogen receptor (ER) and progesterone receptor (PR) positivity were defined as ≥10% positive tumor cells with nuclear staining. Chi-square test and T-test were used to analyze the significance of correlation between the expression of ER and other parameters. Results: The patients were divided into two groups (156 patients with ER-positive group and 104 patients with ER-negative group). There was a significant difference between histological grade, nuclear grade, lymph node metastasis, tumor size and vascular invasion and also tumor markers of HER2, PR, P53 expression with ER status. Based on binary logistic regression analysis, in patients with ER-positive, more patients had vascular invasion and PR-positive, but P53 was negative. Conclusion: There was a direct correlation between vascular invasion and PR, with ER status and a reverse correlation between p53 with ER status. [Sadeghi M NJIRM 2016; 7 (1): 37-40]

Key Words: Breast cancer, Estrogen receptor, Vascular invasion, P53

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Introduction: Breast cancer is the most frequent malignancy among women who can be a leading cause of death through middle-aged women. Patients with invasive ductal carcinoma present higher lymphatic involvement and worse prognosis than fewer common types of breast carcinoma.[1] A small number of single biomarkers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), and proliferation marker Ki-67 have been used for several years to predict the prognosis of breast cancer and to guide its therapy. Ki-67 is a nuclear non-histone protein, and an antigen associated with cell proliferation.[2]

ER expression is the main indicator of potential responses to endocrine therapy, and approximately 70% of human breast cancers are hormone-dependent and ER-positive.[3] Reports that selective ER modulators reduce the occurrence of only ER positive tumors strongly support the etiological distinction between ER-positive and ER-negative breast cancers.[4] The estrogen activation of ER in ER-positive breast cancers enhances their aggressiveness, while the activation of exogenously introduced ERs into aggressive ER-negative cells diminishes their aggressiveness. The basis of the protective effect of the ER appears complex and could be due to the altered expression of genes involved in cell proliferation, differentiation and invasiveness.[5] The tumor suppressor p53 is activated by genotoxic stress to induce target genes for cell cycle arrest, DNA repair, and apoptosis.[6] Also, metastasis to the lymph nodes are an important prognostic factor, which indicate advanced disease status with the probability that cancer cells have spread to distant sites.[7] Peritumoral lymphatic vessel and vascular invasion have been demonstrated to have prognostic significance for the risk of local and distant recurrence.[8]

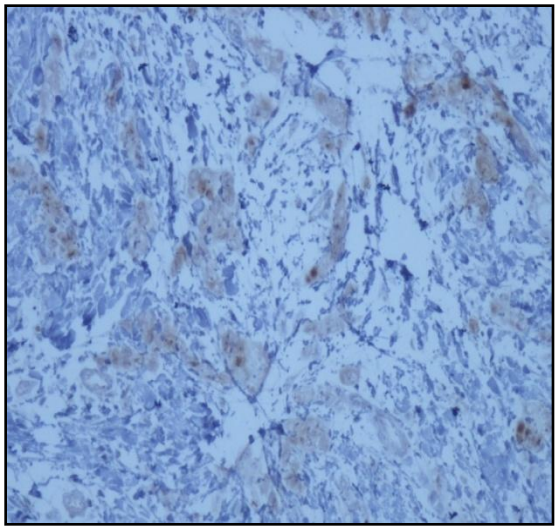
The aim of study is to evaluate the correlation between risk factors with ER status in breast cancer patients in the West of Iran.

Material and Methods: In a retrospective study, 260 breast cancer women were included invasive ductal carcinoma our Clinic, Kermanshah city, Iran, between 2012 and 2014. They received chemotherapy, radiotherapy or hormone therapy. A lot of patients underwent primary surgery. A sufficient sample size was selected from any patient, and the slides were stained by hematoxylin and eosin (H & E) method. Then 4 micron sections were prepared for staining with H & E and also for IHC (Ki67, ER, PR, p53 and HER2) staining. Estrogen receptor (ER) and progesterone receptor (PR) positivity were defined as ≥10% positive tumor cells

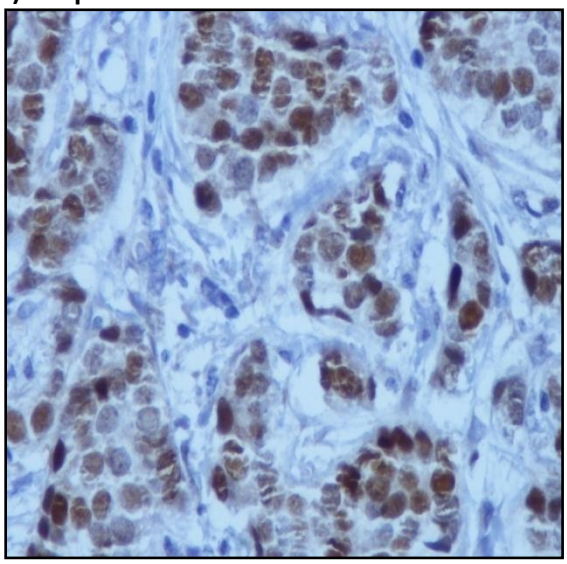
with nuclear staining (Figure 1). HER2-positive was defined as either HER2 gene amplification by fluorescent *in situ* hybridization (FISH) or scored as 3+ by IHC. In case of HER2 (2+), FISH was performed to determine HER2 positivity. Age, tumor size, lymph node metastasis, histological grade, nuclear grade and vascular invasion were other factors that determined in a lot of patients. Statistical analyses were performed using the SPSS v.19. Chi-square test and T-test were used to analyze the significance of correlation between the expression of ER and other parameters. A binary logistic regression model was selected using Akaike Information Criteria (AIC) in stepwise selection to examine the association between ER *status* and other risk factors. P-value<0.05 was considered significant.

Figure 1: (×400) the figure presents *immunohistological* staining of (A) ER-negative (B) ER-positive breast cancer tissue

(A) ER-negative



(B) ER-positive



Results:

We divided the patients into two groups (156 patients with ER-positive group and 104 patients with ER-negative group). The Table 1 shows these results based on ER status. There was a significant difference between histological grade, nuclear grade, lymph node metastasis, tumor size and vascular invasion and also tumor markers of HER2, PR, P53 expression with ER status (P<0.05).

Table 1: The baseline characteristics of breast cancer patients (n=260)

Variables	ER-positive N=156	ER-negative N=104	P-value
Mean age (year)	45.7±8.7	47.7±9.5	0.859*
Age group (year)			0.428**
≤50	96	66	
>50	60	38	
Histological grade, n=237			0.000**
I	28	19	
II	103	37	
III	13	37	
Nuclear grade, n=152			0.000**
I	17	18	
II	76	14	
III	2	25	
Lymph node metastasis, n=242			0.000**
Yes	113	42	
No	33	54	
Tumor size (cm), n=243			0.000**
<2	11	25	
≥2	133	74	
Vascular invasion, n=206			0.000**
Yes	100	35	
No	25	46	
HER2 status			0.000**
Positive	77	29	
Negative	79	75	
PR status			0.000**
Positive	138	11	
Negative	18	93	
P53 overexpression, n=231			0.000**
Positive	45	59	
Negative	90	37	
Ki67 expression			0.097**
<20%	92	52	
≥20%	64	52	

* T-test ** Chi-square test Abbreviations: ER, *estrogen* receptor; PR*, progesterone* receptor; HER2, the human epidermal growth factor.

Table 2 shows a binary logistic regression analysis to generate odds ratios, 95% CI and p-values for the association between risk factors with the expression of ER. Vascular invasion, PR status and P53 expression were prognostic factors for ER status in breast cancer patients (P<0.05). In patients with ER-positive, more patients had vascular invasion and PR-positive, but P53 was negative.

Table 2: Binary logistic regression analysis between the variables in the expression of ER status in breast cancer

Variables	P-value	OR	95% CI
Histological Grade (grades I or II vs. III)	0.568	0.69	0.19-2.43
Nuclear Grade (grades I or II vs. III)	0.119	3.05	0.74-12.49
LN involvement (positive vs. negative)	0.923	0.92	0.18-4.70
Tumor size (<2 vs. ≥2cm))	0.367	0.16	0.04-8.02
Vascular Invasion (positive vs. negative)	0.012	15.43	1.82-130.67
HER2 (positive vs. negative)	0.194	0.53	0.20-1.37
PR (positive vs. negative)	0.000	24.55	5.34-112.90
P53 (positive vs. negative)	0.003	0.09	0.01-0.43

A binary logistic regression model was selected using Akaike Information Criteria (AIC) in stepwise selection. Odds ratios are adjusted for all of the factors listed in the table. Abbreviations: CI, *confidence interval;* ER, *estrogen* receptor; PR*, progesterone* receptor; HER2, the human epidermal growth factor; OR, odds ratio; LN: lymph node.

Discussion: Despite the high frequency of breast cancer among Iranian women, the epidemiological characteristics of breast cancer among Iranian patients are yet unknown.[9] ER-negative breast cancers are a group of tumors with poor prognosis, and fewer cancer prevention and treatment strategies compared to ER-positive tumors.[10] In response to genotoxic stress; the p53 tumor suppressor induces target genes for cell cycle arrest, apoptosis, and DNA repair.[11] ER-negative tumors show a higher expression of p53[10,12] and HER2 compared to ER-positive breast cancer.[10]

A study, [13] reported that HER2 expression was inversely correlated with ER expression. In our study, HER2 expression was more in ER-positive, but p53 overexpression was more in ER-negative and these differences were statistically significant (P<0.05). In another study, the inverse correlation was between tumor grade and ER (P< 0.05) that the higher tumor grade correlates with a decrease of ER expression. [14] Therefore, the ER level does not contribute to the prediction of lymph node metastases since there was no correlation with node positivity. [15] In our study, histological grade and nuclear grade had a reverse correlation with ER status. Therefore, higher tumor grade was more in ER-negative.

There were significant differences between the Ki67 expression and ER status[16] that our study rejected this result. In a research, a significant correlation was not found between the positive lymph nodes with estrogen receptor status, [7] but another study, [17] reported that ER-negative status was significantly associated with low risk of axillary node metastasis.

Furthermore, it has been documented that patients who underwent sentinel lymph node (SLN) biopsy, showed that the prevalence of SLN metastases had an inverse relationship with a lack of PRs.[18] There is a statistically significant correlation between ER and PR status. [19] In this study, lymph node metastasis was significantly more in ER-negative status compared to ER-positive and there was a direct significant correlation between ER with PR status. Another analysis found that tumors in young women have lower ER positivity [7] that in this study, there was no correlation between age and ER status.

Conclusion: There was a direct correlation between vascular invasion and PR, with ER status and a reverse correlation between p53 with ER status. For a better result, it needs to more researches in our area with more patients.

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