Int J Cancer Manag. 2018 August; 11(8):e9492. doi: 10.5812/ijcm.9492.

Published online 2018 February 28. **Research Article**

The Differences of Age, Tumor Grade, and Her2 Amplification in Estrogen and Progesterone Receptor Status in Patients with Breast Cancer

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Received 2016 October 26; **Revised** 2017 February 04; **Accepted** 2018 February 24.

Abstract

Background: Breast cancer is the most common cancer in women. Histological grade and type of tumor are morphological findings that play a main role in breast cancer classification. Markers including Estrogen receptor (ER), progesterone receptor (PR), and Her 2 can be used in routine clinical labs to predict response or resistance to treatment for using new drugs.

Objectives: The aim of this study was to evaluate the differences in tumor characteristics in estrogen and progesterone receptor status (ER^+/PR^+, ER^+/PR^-, ER^-/PR^-, ER^-/PR^+) in patients with breast cancer.

Methods: In this study, 130 patients with primary invasive ductal breast carcinoma were chosen from Shahid Sadoughi hospital, Yazd, Iran from 2014 to 2016. The histological grade of tumor was detected according to Bloom and Richardson grading method. Her-2, estrogen receptor, and progesterone receptor were analyzed by immunohistochemistry (IHC) method through primary antibody.

Results: In this study, 73 (56.15%) and 23 patients (17.69%) were double receptor positive (DRP) and double receptor negative (DRN), respectively. ER^+/PR^- and ER^-/PR^+ were found in 30 (23.84%) and 3 (2.3%) tumors. Moreover, 65.63% and 60.52% of tumors were Her-2 negative and low grade, respectively. Significant difference was seen between Estrogen receptor/progesterone receptor according to age, Her-2 expression, and grade ($P < 0.05$).

Conclusions: The result of this study showed that hormone receptor expression is different according to age, grade, and Her-2 expression. Moreover, ER^+/PR^+ tumors had lower grade and more Her-2 negative than other hormone receptors.

Keywords: Her-2, ER, PR, Grade, Breast Cancer

1. Background

Breast cancer is the most common cancer in women (1). It is one of the most frequent malignancies among Iranian women (2). The prognosis and survival rates of breast cancer are different in women and related to characteristics including age, tumor stage, and intrinsic properties of the tumors (3). Moreover, the histological grade and type of tumor are morphological findings that play a main role in breast cancer classification (4). Markers including Estrogen receptor (ER), Progesterone receptor (PR), and Her-2 can be used in routine clinical labs to predict response or resistance to treatment for using new drugs (5-8). Her-2 neu over-expression is associated with poor clinical outcome (2) and resistance to hormonal therapy (2). The expression of Estrogen receptor and/or progesterone receptor, as prognostic factors, is predictor of response to endocrine therapy (2). Moreover, tumors with ER^+/PR^+ are hormone responsive and have a better prognosis in comparison to tumors which are ER^-/PR^- (2). The significance of ER^+/PR^- tumors, as a distinct subset of breast cancer, has been well documented (9-12). But, a debate was seen about the significance of ER^-/PR^+ tumors as a clinically and biologically distinct group of breast cancer (3).

2. Objectives

The aim of this study was to evaluate the differences in tumor characteristics in estrogen and progesterone receptor status in patients with breast cancer.

3. Methods

In this study, 130 patients with age range of 30 to 82 years old and primary invasive ductal breast carcinoma were chosen from Shahid Sadoughi hospital, Yazd, Iran in between 2014 and 2016. The haematoxylin and eosin (H

and E) was used to stain and analyze of tissue sections. The histological grade of tumor was detected by Bloom and Richardson grading method (13). Her-2, Estrogen receptor (ER), and Progesterone receptor (PR) were analyzed by immunohistochemistry (IHC) method through primary anti-body (Table 1).

Table 1. Anti-Bodies Used for Immunohistochemical Characterization of Patients with Breast Cancer

Anti-Body	Isotype	Dilution	Source
ER	Monoclonal mouse anti humanID5	Ready for use	Dako
PR	Monoclonal mouse anti human PGR 636	Ready for use	Dako
Her2	Polyclonal Rabbit anti human c-erbB2	1: 400	Dako

Then, secondary anti-body sheep anti mouse, anti-Rabbit Horseradish peroxidase (Ready to use) was used and in later stage, sections were incubated with 3, 3 diaminobenzidinetetrahydrochloride (Sigma). After counterstaining of sections with hematoxylin, they were washed in tap water, dehydrated, and mounted with glass cover slips.

3.1. Statistical Analysis

Statistical analysis was performed, using the SPSS (SPSS Inc., Chicago, Ill, USA). Pearson Chi-square test and chi square test were used for statistical analysis. P value < 0.05 was considered statistically significant.

4. Results

The status of hormone receptors of patients with breast cancer is shown in Table 2.

Table 2. The Status of Hormone Receptors in Patients with Breast Cancer

Hormone Receptor Status	No. (%)
ER^+/PR^+	73 (56.15)
ER^+/PR^-	23 (17.69)
ER^-/PR^-	31 (23.84)
ER^-/PR^+	3(2.30)
Total	130

As shown Table 2, the most tumors (56.15%) were ER^+/PR^+ and the least tumors were (2.30%) ER^-/PR^+.

Table 3 shows hormone receptor status according to Her-2 expression in these tumors.

In Table 3, 125 cases were available and 5 cases were missed value. The most HER2 negative was due to ER^+/PR^+ groups. Moreover, there was significant difference between ER/PR groups status (ER^+/PR^+, ER^+/PR^-, ER^-/PR^-, ER^-/PR^+) according to HER2 amplification status ($P < 0.05$).

Table 3. Hormone Receptor Status According to Her-2 Expression[a]

Expression of Biomarkers of ER and PR	Her-2 Positive	Her-2 Negative	P Value
ER^+/PR^+	21 (16.8)	50 (40)	0.032
ER^-/PR^-	14 (11.2)	17 (13.6)	
ER^+/PR^-	5 (4)	15 (12)	
ER^-/PR^+	3 (2.4)	0	

[a]Values are expressed as No. (%).

Table 4 shows hormone receptor status in patients with breast cancer according to age.

Table 4. Hormone Receptor Status in Patients with Breast Cancer According to Age[a,b]

Variables	Age, y		P Value
	≥ 40	< 40	
ER^+/PR^+	63 (50)	7 (5.55)	0.004
ER^-/PR^-	25 (19.84)	5 (3.96)	
ER^+/PR^-	13 (10.3)	10 (7.93)	
ER^-/PR^+	2 (1.58)	1 (0.79)	

[a]Values are expressed as No. (%).
[b]$P < 0.05$ is significant.

In Table 4, 126 cases were available and 4 cases were missed values.

The mean age of patients in DRP and DRN was 51.9 and 51.1 years old, respectively. The mean age of patients with (SRP) ER^+/PR^- and ER^-/PR^+ was 48.6 and 52.4 years old, respectively. As shown Table 4, the most number of patients in all groups were higher than 40 years old. Moreover, there was significant difference between ER/PR status (ER^+/PR^+, ER^+/PR^-, ER^-/PR^-, ER^-/PR^+) according to age ($P < 0.01$).

Table 5 shows hormone receptor status in patients with breast cancer according to grade.

From 130 cases, 4 cases were missed value. Moreover, significant difference was seen between ER/PR status (ER^+/PR^+, ER^+/PR^-, ER^-/PR^-, ER^-/PR^+) according to grade ($P < 0.05$). The lowest grade of patients with breast cancer was due to ER^+/PR^+ group.

5. Discussion

In this study, ER^+/PR^+ and ER^-/PR^- were found in 56.92% and 23.07% of tumors, respectively. Ozguzer et al., reported that ER^+/PR^+ and ER^-/PR^- were found in 40.3% and 38.4% of

Table 5. Hormone Receptor Status in Patients with Breast Cancer According to Grade[a,b]

Variables	Grade		P Value
	Low Grade	High Grade	
ER^+/PR^+	52 (40.94)	24 (18.89)	0.001
ER^-/PR^-	8 (6.2)	16 (12.5)	
ER^+/PR^-	17 (13.38)	6 (4.72)	
ER^-/PR^+	0	3	

[a] Values are expressed as No. (%).
[b] $P < 0.01$ is significant.

tumors. In the present study, ER^+/PR^- were found in 17.69% of tumors. Ozguzer reported that ER^+/PR^- were found in 16.1% of tumors in patients with breast cancer (3). It seems that ER^+/PR^- tumor is a distinct disease subtype (3). A debate has been seen about ER^-/PR^+ tumors as a clinically and biologically distinct group of breast cancer (3). In this study, 2.3% of patients were ER^-/PR^+. Bernoux and colomer also reported that ER^-/PR^+ tumors account for 2% to 8% of all breast cancers (14, 15). Ozgur et al., reported that 5.1% of patients were ER^-/PR^+. Another study reported that there is no ER^-/PR^+ breast tumors (16, 17), but some studies showed that these tumors are clinically and biologically distinct tumors (18, 19). Moreover, natural history and responsiveness to hormone therapy in patients with ER^-/PR^+ group is uncommon (20, 21). Some studies reported that ER^-/PR^+ tumors could show false-negative ER assay due to methodological problems or false-positive PR, which is resulted from cross-reaction of monoclonal anti-bodies with other antigens (3, 20, 21).

Moreover, the findings of this study showed that hormone receptor expression is different according to age, grade, and Her-2 expression. Ozguzer et al., also reported that single receptor positive such as the expression of ER^+/PR^- and double receptor positive is different in groups with regard to age, grade, and HER2 amplification (3). Arpino et al., showed that single receptor positive tumors had higher expression of Her-2 than DRP tumors (22). Ozguzer et al. in thier study obtained similar result (3). But, in our study, the lowest expression of Her-2 was seen in DRP group. Moreover, the lowest grade of tumors was seen in patients with DRP. Sundblad et al., reported that SRP tumors had higher grade in comparison to DRP (23). Ng and Chen showed that ER^-/PR^+ breast cancer happens in younger patients compared to other phenotypes (24, 25).

5.1. Conclusions

The result of this study showed that hormone receptor expression is different according to age, grade, and Her-2 expression. Moreover, ER^+/PR^+ tumors had lower grade and more Her-2 negative than other hormone receptors.

Acknowledgments

None declared.

Footnotes

Authors' Contribution: None declared.
Conflict of Interests: None declared.
Financial Disclosure: None declared.

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