Prevalence and Correlates of the Estrogen and Progesterone Receptors (ER/PR), Human Epidermal Growth Factor Receptor-2 (HER-2) and P53 in Breast Cancer: a Cross-Sectional Study

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ABSTRACT

Background & Objective: Breast cancer has a pivotal role in many deaths caused by malignancies. Epidermal growth factor receptor-2 (EGFR-2 or HER-2) and estrogen receptor (ER) have immense predictive values as prognostic factors. Breast cancers that have steroid receptors and respond to hormone therapy show a better prognosis than cancers without steroid receptors.

Materials & Methods: A retrospective cross-sectional study was performed on 500 pathology blocks of women with breast cancer sent to the pathology department of Amir-al-Momenin medical and educational center, Gerash, Iran, from 2016 to 2019. Data were analyzed by SPSS software (Version-16) via ANOVA test followed by Chi-square and t-tests. P-value <0.05 was considered as significant.

Results: The utmost type of malignancy was invasive ductal carcinoma (IDC) at 35.03%. Among ER-positive patients 59.67% were HER-2-positive. Nonetheless, among the PR-positive patients 54.74% were HER-2-positive. ER-positive patients were correlated with p53 receptor, distant metastasis and HER-2 significantly ($P<0.01$). However, PR-positive patients just correlated with p53 receptor significantly ($P<0.01$).

Conclusion: Investigated samples were more ER-negative and less PR-positive compared to similar studies. Meanwhile, ER-positive patients were HER-2-positive. Regarding the correlation with prognosis of breast cancer, especially in HER-2-positive patients, there is a need to perform profound screening programs for HER-2 in breast cancer patients, especially with histopathological characteristics of invasive ductal carcinoma.

Keywords: Breast Cancer, HER-2, P53, Prevalence, Prognosis

Introduction

Among malignancies, breast cancer is considered one of the utmost factors which cause death in women globally. In accordance with the World Health Organization (WHO), more than 1.2 million new breast cancer cases were discerned annually, and more than 500,000 human die every year owing to this cancer **(1-4)**. Breast cancer accounts for 21.4% of all malignancies diagnosed in Iran. The outbreak of breast cancer is pretty high in Iran **(5)**. The occurrence age of breast cancer in Iranian women is 35-44 years **(3)**. Since the onset and clinical course of malignancies are various in different patients, it is important to know the factors that directly and indirectly affect the prognostic and treatment policies. Prognostic factors are divided into two categories of pathophysiologic features and biomarkers **(3)**. The most important pathophysiologic

features include age, tumor size (T), tumor tissue type, histologic grade of the tumor, lymph node involvement (N), and finally carcinoma metastasis (M) **(6)**.

Estrogen receptors (ER) and progesterone receptors (PR) act as ligand-dependent transcription factors in target cells **(7)**. Studies have shown that mortality rates of patients with ER/PR positive are lower, and they respond better to hormonal therapies, as anti-steroidal therapies are effective for tumors with both receptors in more than 50% of cases. Mortality rates for tumors that have one of these receptors and those that have none of them were reported as 33% and less than 10%, respectively **(3, 5)**. Findings have shown that tumors which express these two receptors had lower grade and these patients have a higher survival at each separate stage of the cancer **(5)**.

HER-2 oncogene (a receptor with tyrosine kinase activity), which is reported in 20 to 30% of cancers plays an important role in the transcriptional stimulation signal transduction by growth factor. It has also been observed that in some mutations, without the presence of its ligand, HER-2 sends a growth-promoting message. HER-2 oncogene causes overexpression of the tumor and increases the metastatic power of the carcinoma, and thereby lowers the prognosis of cancer **(3, 8, 9)**. P53, a tumor suppressor gene, plays a key role in diagnosis and repair of cellular DNA damage. If necessary, P53 also activates apoptosis in the cell, so that mutated genes do not transfer to daughter cells and thus suppress the tumor. Mutations in the p53 gene will increase the mortality results from cancer **(10)**. This study investigated the correlation between Estrogen, Progesterone receptors and p53 receptor besides epidermal growth factor receptor-2 (EGFR-2 or HER-2) as prognostic factors associated with breast cancer.

Methods

A retrospective cross-sectional study was directed at the pathology department of Amir-al-Momenin medical and educational center, Gerash, Iran. The study was performed on 500 women whose pathology blocks were sent to pathology department from 2016 to 2019.

For evaluation of the incidence of Estrogen, Progesterone and p53 receptors besides HER-2 receptor and their correlations with breast cancer prognosis, 358 pathologic blocks from 500 referred samples of patients from South and South East of Iran were analyzed. Medical records of all patients were evaluated for clinical and pathologic characteristics by an experienced oncologist and their biomarkers were entered into a checklist after consideration and confirmation. Pregnant patients and those with incomplete records and those who received any type of therapeutic intervention since their malignancy was diagnosed were excluded from study. Afterwards, the results of 358 patients were extracted from their archived documents in pathology department and were recorded. Variables that were evaluated in each patient included: age, type of tumor (ductal, lobular, ductal-lobular, modular and mucinous), tumor size (T_1: tumor in diameter of 2 cm or lower and T_2: tumor between two and five centimeters in diameter and T_3: tumor in diameter higher than 5cm, and T_4: direct invasion of tumor to chest wall or skin irrespective of diameter), Lymph node (LN) involvement [(N_0: any lymph node involvement, N_1 (1±3 lymph nodes), N_2 (4±9 lymph nodes) and N_3 (10 or more lymph nodes)] and distant metastasis; M_1(distant metastasis) and M_0(any evidence of distant metastasis in Axillary lymph node), data extracted from imaging (mammography or ultrasound) and pathology reports. Tumor markers that were evaluated in present study were estrogen receptors (both negative and positive), progesterone receptors (both negative and positive) besides HER2 oncogene (HER-2-negative and HER-2-positive) and cell proliferation markers (P53-negative and HER-2, P53-positive). Samples were evaluated by immunohistochemistry (IHC) method. In IHC, for each samples, 4 µm thick tissue slices were prepared and stained using monoclonal antibody. Slides were reported by pathologist as positive and negative. Data were analyzed by SPSS software (SPSS Inc. Chicago, Il, The USA, Version-16) by ANOVA, Chi-square, and t-test. *P* value<0.05 was considered as statistically significant.

Results

The mean ± SD age of patients was 46.04±16.1 year. The highest incidence rate of breast cancer was observed at the ages of 31-60 and under 25, however, lowest incidence rate was above 73 years, respectively. The utmost prevalent type of malignant cancers were invasive ductal carcinoma followed by lobular, ductal lobular, medullar and mucinous carcinoma, respectively (Table 1). In patients with invasive ductal carcinoma, 38% were both ER and PR-positive and 62% were both ER and PR-negative. Also, in patients with lobular carcinoma, 32% were ER/PR-positive whereas 55% ER/PR-negative. In addition, 85.3% and 79.8% of patients with ductal carcinoma and mucinous carcinoma were considered as HER-2-negative and HER-2-positive, respectively. Patients with mucinous carcinoma and medullary carcinoma had the highest rates of P53-positive and P53-negative cases at 75.5% and 87.3%, respectively (Table 1).
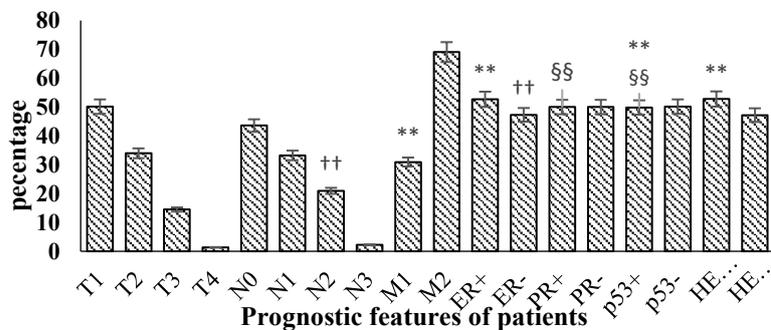
Table 1. Types of hormone receptors and types of carcinoma.

Type of carcinoma	percentage	Receptor types(percent)
Invasive ductal	35.03%	ER/PR-positivity (38%) ER/PR-negativity (62%)
Lobular	24.58%	ER/PR-positivity (32%) ER/PR-negativity (55%)
Ductal	20.9%	HER-2-negativity (85.3%)
Medullary	11.86%	P53-negativity (87.3%)
Mucinous	7.63%	P53-positivity (75.5%) HER-2-positivity (79.8%)

Only 59.67% of ER-positive and 54.74% of PR-positive patients were HER-2-positive. ER-positive patients were significantly correlated with p53 receptor, distant metastasis and HER-2 ($P<0.01$). However, ER-negative patients (54.65%) were just significantly correlated with N2 (20.95%) ($P<0.01$).

PR-positive patients were correlated with p53 receptor significantly ($P<0.01$) (Chart 1).

The frequency of prognostic features is showed in Tables 2 & Figure 1

Figure 1. Prognostic features of patients

T_1, T_2, T_3 and T_4 (tumor sizes). N0: any lymph node involvement, N_1, N_2, N_3: lymph node involvement. M_1: (distant metastasis) and M_0: (no evidence of distant metastasis). ER+ (positive estrogen receptor), ER-(negative for estrogen receptor). PR+ (positive for progesterone receptor), PR-(negative for progesterone receptor). P53+ (p53 positive), p53-(p53 negative). HER-2+ (HER-2-positive), HER-2-(HER-2-negative). **Patients with positive ER were significantly correlated with p53 receptor, distant metastasis, and HER-2 ($P<0.01$). §§Positive PR patient's correlation with p53 receptor was significant ($P<0.01$). ††Negative ER patients (54.65%) was significantly correlate with lymph node (N2) involvement ($P<0.01$).

Table 2. Prognostic features of patients

Prognostic factor	Number of patients (%)
T1	50.14
T2	33.98
T3	14.48
T4	1.39
N0	43.58
N1	33.24
N2	20.95
N3	2.23
M1	30.95
M2	69.05
ER+	52.69
ER-	47.31
PR+	50
PR-	50
p53+	49.85
p53-	50.15
HER-2 +	52.79
HER-2 -	47.21

T_1: tumor in diameter of 2 cm or less. T_2: tumor between 2 and 5 cm in diameter. T_3: tumor in diameter more than 5cm, and T_4: direct invasion of tumor to chest wall or skin irrespective of diameter). N0: no Lymph node involvement, N_1: (1±3 Lymph Nodes), N_2: (4±9 Lymph Nodes) and N_3: (10 or more Lymph Nodes. M_1: (distant metastasis) and M_0: (any evidence of distant metastasis in axillary lymph node). ER+: (positive for estrogen receptor), ER-: (negative for estrogen receptor). PR+: (positive for progesterone receptor), PR-:(negative for progesterone receptor). P53+ (P53 positive), P53-(P53 negative). HER-2+ (HER-2 positive), HER-2 - (HER-2 negative).

Discussion

In breast cancer, both the estrogen and progesterone receptors (ER and PR) are evaluated routinely to predict response to anti-estrogen therapy. Immunohistochemistry is a reliable method for examining the Estrogen and progesterone receptors [11]. In the present study, 53.4% of ER-negative patients were positive regarding HER-2. On the other hand, 48% of ER-positive patients were reported negative regarding HER-2. Also, among PR-negative patients, only 52% were positive regarding HER-2 which considered as a poor prognosis. From PR-positive patients, 52.8% were negative regarding HER-2 which were considered as good prognosis. Besides, from P53-negative patients 52.8% were negative regarding HER-2 which could be explicated as good prognosis. However, 53.4% of patients were positive regarding both factors which can be considered as poor prognosis.

Therewith, 53.1% of patients were reported negative regarding both ER and PR. Only 46.9% of ER-positive patients were PR-positive. Furthermore, 53.4% of ER-negative patients were P53-positive and 48% among ER-positive patients were P53-negative. Also, 53.4% among ER-negative patients were P53-positive and 48% among ER-positive patients were P53-negative. Astonishingly, our results regarding the correlation between HER-2 and the type of malignancy showed that estrogen and progesterone receptors (ER and PR) had a significant correlation. Regarding the relationship between age and the HER-2 receptor, a poorer prognosis was associated with younger ages (with positive HER-2). However, in other patients with positive hormone (ER and PR) receptors, a higher age range and a good prognosis were reported. It is reported

that HER-2 positive has been reported in 20 to 30% of breast cancers. In this study, the HER-2 positive rate was 52.79%, which was lower than other studies conducted in our country like investigations by Sirati *et al*. **(12)**. At the present study, no significant correlation between age with HER-2 and tumor size was seen, which is similar to studies performed by Dunnwald *et al,* and Tehrani *et al*., **(13, 14)**.

In this study, there was a significant correlation between patients with positive ER hormone receptors with p53, distant metastasis and HER-2 receptors ($P<0.01$). Whereas PR receptor had only a significant relationship with p53 ($P<0.01$). In our study, estrogen receptor linkage was more pronounced than progesterone receptors among steroid receptors. Expression of progesterone receptors is regulated by the hormone estrogen, so most tumors that are positive progesterone receptors also express estrogen receptors, which usually appear after menopause, and increase with age of tumors with estrogen receptors; while estrogen receptors are less protective in pre-menopausal patients, ER-positive tumors are less common in younger women, and may be due to malignant breast cancer in the youngers **(15)**. The pattern of receptor among patients in our study showed 52.69% ER, 50% PR positivity, which was in consistent with a study conducted by Sharon Baisil *et al.*, **(16)**.

In this study, the frequency of estrogen-positivity (52.69%) was lower than the literature, which reported 60%, but was in accordance with a study by Xu L *et al*. and Jazayeri *et al.* **(17, 18)**. Progesterone receptors prevalence in the reference literature is 50%, which is consistent with the results of our study **(19)**. In general, breast cancer cells that express estrogen receptors have normal biological activity. Survival rates in patients with positive receptors are about two to three times more likely to survive after metastatic and are more effective in patients with both estrogen and progesterone receptors. In the cell division cycle, tumor suppressor genes such as p53, play a critical role in growth stopping of damaged cells and repairing cellular DNA structure. So, if the structure of DNA is overexpressed, the cell would have to be programmed to die to prevent disruption of cell health and identifies

and destroys mutated genes **(20)**. In this study, ER negative patients were significantly associated with N2 involvement ($P<0.01$). There has been also a significant association between HER-2 and N_2 ($P<0.05$), which was in consistent with a study conducted by Tehrani *et al*., but in other studies the frequency of HER-2 positive was higher in ductal carcinoma patients **(14)**. Whereas in this study no significant difference was found. In this study, ductal carcinoma was the most common malignancy which was in line with other studies **(21, 22)**. In our study, ER-negative had a significant correlation with T1 tumor size ($P>0.05$). Moreover, ER negative had a significant correlation with HER-2 ($P>0.01$). On the other hand, it has been reported that with increasing tumor size, HER-2 positive tumors were more frequent, indicating that the patient has a worse prognosis and is more likely to have recurrence and death due to cancer **(23)**. In this study, HER-2 was positively associated with metastasis ($P>0.001$), which is consistent with some studies in this regard **(14)**.

Conclusion

Investigated samples were more ER-negative and less PR-positive compared to similar studies. Meanwhile, ER-positive patients were HER-2-positive. Regarding HER-2-positive patients and its correlation with prognosis of breast cancer, it is advised to perform much profound HER-2 screening programs for all breast cancer patients, especially for invasive ductal carcinoma.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

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