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Prevalence of Androgen Receptor in Invasive Breast Cancer and Its Association with Clinicopathologic Features in East Azarbaijan Province of Iran: A Cross-Sectional Study

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ABSTRACT

Background: Breast cancer is the most common malignancy and the leading cause of cancer-related deaths in females. Accordingly, the evaluation of new prognostic markers and therapeutic targets is of vital importance. Here, we aimed to detect androgen receptor (AR) status and define its association with clinicopathologic parameters in patients with invasive breast cancer.

Materials and Methods: In this study, AR status was studied in 104 patients with invasive breast carcinoma by immunohistochemistry. Besides, its association with clinicopathologic factors, i.e., age, menopausal status, tumor size, lymph node involvement, tumor stage, tumor grade and estrogen receptor (ER), progesterone receptor (PR), Her2/neu, Ki-67and P53 were investigated.

Results: AR was positive in 84 patients (80.8%), and its expression in ER-positive (85.7%) and PR-positive (85.6%) patients were remarkably higher than in ER-negative (46.2%) and PR-negative (50%) patients (p= 0.001 and p=0.002, respectively). AR expression was noticeably lower in Her2/neu-positive (25%) patients compared to Her2/neu-negative (87.9%) ones (p=0.000). AR expression was also higher in patients with smaller, earlier stage, and low mitotically active tumors, but the association was not statistically significant.

Conclusion: The expression of AR in patients with breast cancer was found to be high and its association with ER-positive, PR-positive, and HER2/neu-negative tumors was found to be significant. In that light, this receptor may play an important role in the determination of prognosis and targeted therapy in breast cancer.

Keywords: Invasive breast cancer; Androgen receptor; Estrogen receptor; Progesterone receptor; Her2/neu

INTRODUCTION

Breast cancer is the most common malignancy in women, with an estimated incidence of 2.4 million cases per year and the most common cause of cancer-related deaths worldwide in 2015[1]. In tandem with that, breast cancer is the most common malignancy and cause of cancer-related deaths in Iranian women with an estimated incidence of 24.5% and 14.2% in 2012, respectively [2]. This is also the case in East Azarbaijan province, where the most common cancer in women is breast cancer with an incidence of 691 cases (22.11%) in 2016 [3].

Normal breast epithelial cells and some breast cancer cells have receptors that attach to the hormones and depend on these hormones to grow. The expression of estrogen receptor (ER),

progesterone receptor (PR), and human epithelial growth factor 2 (Her2/neu) have been determined as prognostic and predictive markers in breast cancer, leading to a fundamental change in treatment methods and reducing unwanted side effects of chemotherapy [4-6]. Androgen receptor (AR), belongs to the family of nuclear steroid receptors, as do ER and PR, and has been considered as a potential biomarker in breast cancer[7].The role of AR in the development and progression of breast cancer is unclear. Some researchers have reported that the expression of AR is associated with a better prognosis[8], and, in one meta-analysis, the expression of AR was associated with a reduced risk of breast cancer recurrence[9]. Patients with ER- and AR-positive tumors have better outcomes than those with ER-negative/AR-positive status [10].

It has been tried to show a link between the expression of AR and the prognosis in breast cancer; however, there are many unanswered questions about the direction and extent of the effect of AR on the prognosis. It has been shown that the expression of AR, regardless of ER, is associated with improved overall survival (OS) and disease-free survival (DFS)[11]. Besides, AR is expressed in a significant number of ER negative, HER2/neu-positive and triple negative (TNBC) breast cancers, indicating that AR could be a new therapeutic target and a marker of good prognosis in these patients[12]. Although the expression of AR has varied widely, it has been reported that its occurrence in TNBC has a predictive value[13]. The difference in the results of different studies might be due to differences in patient populations and/or diversity of study methods. In that light, the lack of sufficient information and disagreement in various studies have led to AR being routinely not evaluated, even in patients with TNBC. Here, we aimed to assess the prevalence of AR in invasive breast cancer and its association with clinicopathologic features.

MTERIALS AND METHODS

Patients

Women with pathological proof of invasive breast carcinoma referred to the Hematology and Oncology Clinic at Tabriz University of Medical Sciences from 2010 to 2017 were included in this descriptive cross-sectional study. Inclusion criteria were invasive breast carcinoma determined by pathology and written self-consent of the participants. Exclusion criteria were carcinoma in situ (CIS) and incomplete patient records. The sample size was estimated to reach at least 81, and here we studied the mentioned parameters in 104 patients.

Study methods

Accordingly, the AR expression was assessed in 104 patients. Clinical and pathological variables including age, menopausal status, lymph node involvement, tumor size, metastasis, stage, histological type, and degree of tumor differentiation (grade) were extracted from patients' records. ER, PR, HER2/neu, Ki-67, and p53 status were also collected from patients' records. The proposed threshold by the ASCO/CAP guidelines were used for ER and PR and the HER2/neu as the positive criteria in this study. ER and PR were considered positive when at least 1% of tumor cell nuclei were stained ,regardless of staining intensity.(Although 1-10% positivity for ER is considered low positive in recent CAP guidelines)[14].

For immunohistochemistry (IHC) evaluation in HER2/neu, the results were reported semi-quantitatively in the following scale according to recent guidelines of CAP. Only one of the Her2/neu patients was 2+, who was excluded from the Her2 study due to not performing the FISH test.(14)

Negative (Score zero): No staining observed or membrane stating that is incomplete and is faint/barely perceptible and within ≤10% of tumor cells.

Negative (Score 1+): Incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells.

Equivocal (Score 2+): Weak to moderate complete membrane staining in >10% of tumor cells or complete membrane staining that is intense but within ≤10% of tumor cells.

Positive (Score 3+): Complete membrane staining that is intense and >10% of tumor cells.

Ki-67 was considered as high if ≥ 14 %(15) and P53 was considered positive if ≥ 10% of cells were stained[16].

Experimental procedures

To measure AR on paraffin samples of the patients, 4-micron sections were prepared from the blocks and IHC staining (Envision method) was performed for each section. The blocks were prepared for microscopic examination during the following steps: First, the sample was put in the oven at 60 ° C for one hour (deparaffinization). Then, rehydration and clarification were achieved using xylol and alcohol 100%, 96%, and distilled water. Consequently, inactivation of endogenous peroxidase was done using a 3% oxygenated aqueous solution and methanol. The samples were then washed with TBS buffer. Incubation of slides was done with primary specific antibodies against androgen (DAKO) at room temperature for one hour, the slides were washed with TBS buffer solution, and then Envision solution was added. The slides were accordingly, washed with TBS buffer solution again, and the 3,3'-diaminobenzidine(DAB) substrate was added. Finally, Gills-hematoxyllin cross staining was performed. The prepared slides were then examined under a light microscope and the percentage of stained cells was calculated in a field with a magnification of 400.In this study, for AR, staining more than 10% of cells(with nuclear pattern) was considered positive[17]**.**

Ethical considerations

All information was extracted from patients' records and remained strictly confidential. In this study, no intervention was performed on the patients themselves and the samples available in the laboratory and clinic archives were used. This study was approved by the Ethics Committee of TUOMS under the following code: IR.TBZMED.REC.1395.900.

Statistical analysis

Data were analyzed using SPSS 21 software. Descriptive data were expressed using frequency (%) for qualitative variables and mean±standard deviation (SD) for quantitative variables. AR was considered as a dependent variable and the relationship between AR and other variables including age, menopausal status, tumor biomarkers (ER, PR, HER2/neu, p53, Ki-67), and grade as well as clinical stage was evaluated by Pearson's chi square test. P-value less than 0.05 was considered statistically significant.

RESULTS

General findings

In this study, data on 104 patients were collected. The mean age of these 104 patients was 49.90 ± 10.95 years (min = 25, max = 80). Among patients, 55 (52.9%) were 50 years old and younger, and 49 (47.1%) were over 50 years old. The highest frequency of breast cancer was in the age group of 40-50 years followed by 50-60 years. (Figure 1).

Among 104 patients, 58 (56.9%) were in the premenopausal, and 44 (43.1%) were in the postmenopausal state. In two patients, this status was unknown due to hysterectomy without bilateral oophorectomy. Tumor histology in 102 patients (98.08%) was invasive ductal; it was invasive lobular in one patient (0.96%) and mucinous (0.96%) in another patient. The most common grade of tumor was grade 2 (76 patients (79.2%)), followed by grade 1 (16 patients (16.7%)) and grade 3 (4 patients (2.2%)), respectively (Figure 2).

The most common tumor size (T) in these patients was T2 (56 patients (54%)), followed by T1 (36 patients (35%)) and T3 (11 patients (10.7%)).In terms of lymph node involvement, the most common condition was N0 (without involvement) in 38 patients (36.9%), followed by N1 (1-3 lymph node involvement) in 29 patients (28.2%). The status of lymph node involvement in one patient was unknown. Systemic metastasis was present at the time of referral in three patients (2.9%).

The most common stage in the studied patients was stage II in 43 patients (42.2%), followed by stages III (in 37 patients (37.3%)), I (18 patients (17.6%)), and IV (three patients (2.9%)) (Figure 3).

The results showed that 91 patients (87.5%) were ER-positive, and 13 (12.5%) were ER-negative. In addition, 90 out of 104 patients (86.5%) were PR-positive, and 14 (13.5%) were PR negative. Twelve

patients (11.7%) were HER2/neu-positive, 91 patients (88.3%) were HER2/neu-negative, and one case was unknown due to lack of FISH test (Figure 4). P53 protein mutation test was done in 63 patients, which was positive in 44 patients (69.8%) and negative in 19 patients (30.2%). Ki-67 was positive (high) in 38 patients (43.2%) and negative (low) in 50 patients (56.8%). However, this test was not performed in 16 patients. Six patients (5.8%) were found to be negative for all three HER2/neu, PR, and ER receptors (TNBC group). AR was positive in 84 patients (80.8%) and negative in 20 patients (19.2%).

Association of AR incidence with other variables age

In patients over 50 years of age, 40 were AR-positive (81.6%), and 9 (19.4%) were AR-negative. In patients aged 50 years and younger, 44 were AR-positive (80%), and 11 (20%) were AR-negative. AR positivity was not significantly associated with age (p = 0.83).

Menopausal status

In premenopausal patients, 47 patients (81%), and in postmenopausal patients, 36 patients (81.8%) were AR-positive. There was no significant relationship between AR positivity and menopausal status (p = 0.92).

Tumor grade

The number of AR-positive patients was highest in grade 2 (n=66, 86.8%) and lowest in grade 3 tumors (n=2, 50%)). However, this association was not statistically significant (p = 0.05).

Tumor staging

We found that 32 cases (88.9%) in the T1 group, 43 cases (76.8%) in the T2, and 8 cases (72.7%) in the T3 group were AR-positive. However, there was no statistically significant difference between these groups (p = 0.28). Moreover, 30 cases (78.9%) in N0, 25 cases (86.7%) in N1, 19 cases (82.6%) in N2, and 10 cases (76.9%) in N3 were AR-positive. There was no statistically significant relationship between AR status and lymph node involvement (p = 0.85). We showed that 17 patients (94.4%) in stage I, 33 patients (76.6%) in stage II, 31 patients (81.6%) in stage III, and two patients (66.7%) in stage IV were AR-positive. No meaningful relationship was detected between the tumor stage and AR status (p = 0.38).

Receptor status

Of 91 ER-positive patients, 87 patients (85.7%) and of 13 ER-negative patients, 6 patients (46.2%) were AR-positive. The prevalence of AR was higher in ER-positive patients, which was statistically significant (p = 0.00). Moreover, out of 90 PR-positive patients, 77 (85.6%), and out of 14 PR-negative patients, 7 (50%) were AR-positive. AR was more prevalent in PR-positive patients, and this relationship was found to be statistically significant (p = 0.00). Besides, of 12 Her2/neu-positive patients, 3 (25%), and of 91 Her2/neu-negative patients, 80 (87.9%) were AR-positive. As a result, the prevalence of AR was lower in Her2/neu-positive patients, and this relationship was found to be statistically significant (p = 0.00).

P53 and Ki-867

In patients with and without P53 mutation, out of 44 and 19 cases, 38 (86.4%) and 13 (68.4%) were AR-positive, respectively. The prevalence of AR was higher in patients with P53 mutation; however, the association was not significant (p = 0.09). In Ki-67-positive patients, out of 38 patients, 29 (76.3%) were AR-positive, and in Ki-67-negative patients, 42 (84%) were AR-negative. Therefore, the prevalence of AR was lower in Ki-67-positive patients. The association was not statistically significant, though (p = 0.36). Accordingly, in TNBC patients, out of six cases, four (66.6%) were AR-positive, which was not statistically significant (p = 0.36) (Table1).

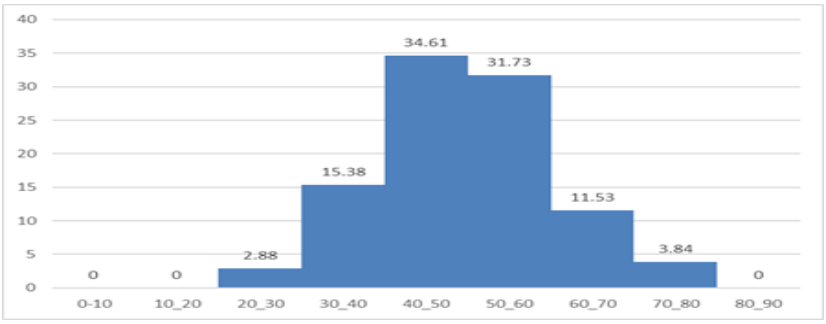

Figure 1. Prevalence of breast cancer in different age decades

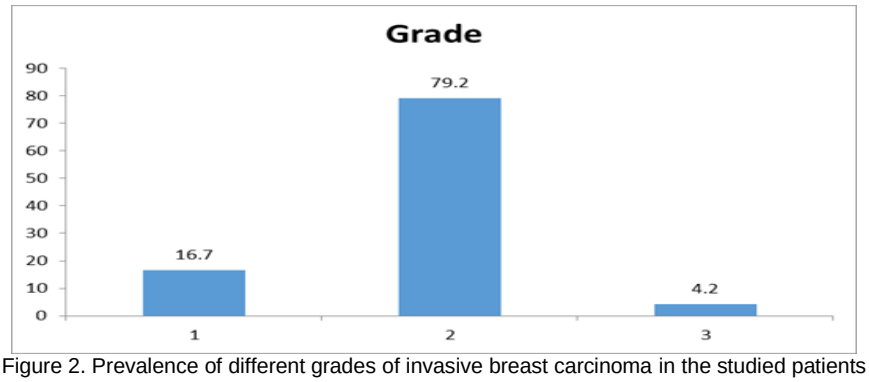

Figure 2. Prevalence of different grades of invasive breast carcinoma in the studied patients

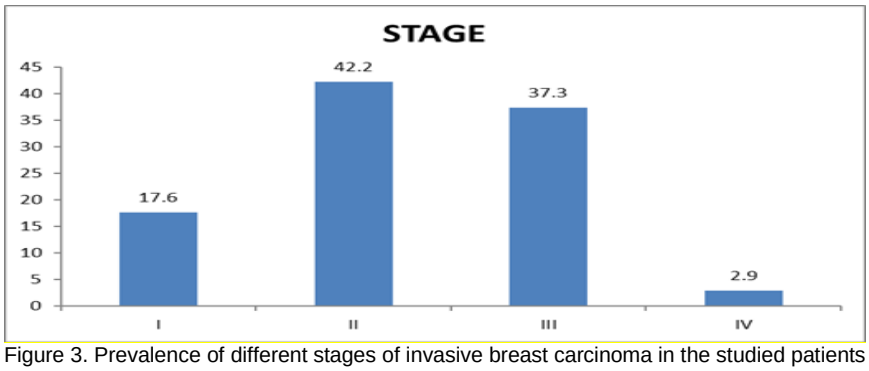

Figure 3. Prevalence of different stages of invasive breast carcinoma in the studied patients

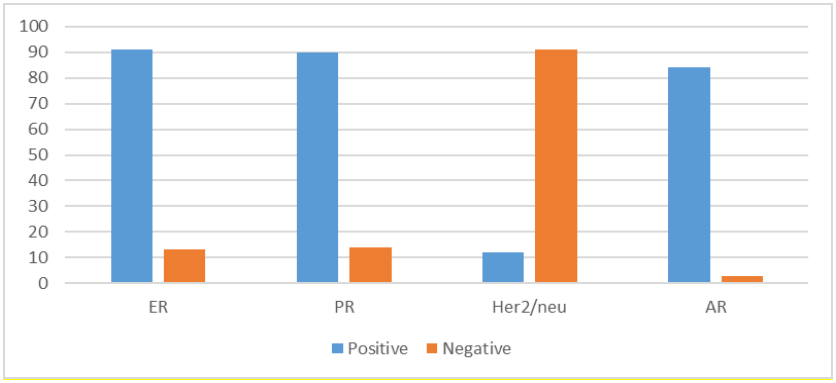

Figure 4. Receptor status in studied patients

DISCUSSION

Traditional histopathologic factors, including tumor size, axillary lymph node involvement, and histologic differentiation, along with new biomarkers including steroid hormone receptors and Her2/neu, are valuable predictors and determinants of prognosis in breast cancer having heterogeneous properties[18]. However, it is difficult to predict the outcome of all breast cancers using old histopathologic factors. Thus, accreditation and evaluation of new biomarkers are necessary to determine their significant usefulness in developing prognostic algorithms and dealing with the disease[19]. AR is one of these new biomarkers.

Due to the importance of the expression of AR in breast cancer and its relationship with other predictive and prognostic factors, this study was performed.

In this study, AR status was determined in 104 patients and was found to be positive in 80.8% of them. Several studies reported AR expression in 60-80% of breast cancers, but both lower incidence (34% and 56%) [20,21] and higher incidence (91%) have been reported in some studies[22].

The mean age of patients in this study was 49.9 ± 10.95 years, and the maximum prevalence of breast cancer was observed in the 4th and 5th decades of life. In a study in Iran on 3010 patients from 1998 to 2014, the mean age of the patients was 49.1 ± 11.6 years, with a maximum age prevalence in the 4th and 5th decades of life, which is similar to our study, a decade younger than the global maximum age[23].

In addition, in our study, the expression of AR was not significantly associated with age, menopause, and lymph node involvement. The expression of AR in smaller tumor size (T1) and in stage I patients was higher, but this difference was not statistically significant. Moreover, the expression of AR was reported to be higher in ER/PR positive and lower in Her2/neu-positive patients, and the relationship was statistically significant. However, as the number of TNBC patients was low (six patients, 5.8%) in this study, its relationship with AR expression was not statistically significant. In a study of 400 consecutive invasive breast carcinomas of any type (ductal, lobular, apocrine, micro-papillary, tubular, and special types) in the United States, AR, ER, PR, and Her2/neu were found to be positive in 87.8%, 83%, 73.75%, and 10.25% of the patients, respectively; the results of which were almost similar to those of our study. Similar to our findings, this study reported a strong and significant positive relationship between the expression of AR and ER, as well as PR, but no significant relationship between AR and Her2/neu expressions was observed [24]. In a study performed on 335 patients in China, the prevalence of AR expression was 72.5%. Furthermore, 53.2% of the patients were reported to be ER/PR-negative and AR-positive. In line with our findings, this study showed that AR was an independent prognostic factor in patients with invasive breast cancer of any type (hazard ratio: 0.309, 95% confidence interval: 0.192–0.496; P< 0.001). The majority (61.0%) of basal-like breast cancers revealed loss of AR expression (P< 0.001), which accompanied a poor prognosis[25].

In another study on 980 patients in China, the incidence of AR expression was 77%, which was significantly associated with the expression of ER and PR, as well as smaller tumor size and low Ki-67 [26]. The latter association was also found between the incidence of AR and ER and PR expressions in Thai patients [27]. The results of studies done in Isfahan and Dubai also showed that higher AR expression was accompanied by a better prognosis in invasive breast cancer patients [28, 29].

Although the incidence of AR was significantly higher in ER-positive patients compared to ER-negative patients, AR was also reported to be positive in a significant number of TNBC patients, in which AR can be potentially used as a goal for treatment. Likewise, it seems reasonable to consider AR as an alternative target in patients with ER-positive or Her2/neu-positive patients who tend to be resistant to targeted therapies against these receptors.

In our study, the relationship between AR and P53 mutation and Ki-67 expression was also implicitly investigated. Although the expression of AR was lower in patients with high expression of Ki-67 and P53 mutations, the association was not significant. It has been found that patients with AR-negative and high Ki-67 levels have a significant correlation with poor outcomes. Thus, the use of IHC expression of AR along with Ki67 as prognostic markers in TNBCs may

help to stratify TNBC patients into different prognostic classes[30]. Moreover, the expression of AR in patients with locally advanced cancer was found to be associated with a greater response to neoadjuvant chemotherapy[31]. Anestis et al. suggested that preliminary clinical research using AR-targeted drugs, which have already been FDA-approved for prostate cancer, has given promising results for AR-positive breast cancer patients [32].

Another study showed that the relatively high amount of AR-positive tumors (36%) among 50 TNBC patients is a significant outcome supporting the routine evaluation of AR in at least all TNBCs and apocrine carcinomas as a potential target for treatment[24].

Numerous anti-androgen drugs are being studied in clinical trials as monotherapy or combination with cytotoxic drugs and other cyclic inhibitors. A study by Hilborn et al. investigated the effect of tamoxifen on the reduction of recurrence in ER-negative and AR-positive patients and suggested AR can predict tamoxifen treatment benefit in patients with ER-negative tumors and TNBC[33]. Overall, as it seems that AR expression has a significant effect on the prognosis and treatment of breast cancer, it should be carefully determined in these patients.

CONCLUSION

In conclusion, the results of this study showed that the expression of AR in patients with breast cancer was found to be high, and its association with ER-positive, PR-positive, and Her2/neu-negative tumors was found to be significant. In that light, this receptor may play a vital role in the determination of prognosis and targeted therapy in breast cancer.

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