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Androgen Receptor Expression in Triple-Negative Breast Cancer

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ABSTRACT

Background: Triple-negative breast cancer (TNBC) accounts for 15 to 20% of all breast cancers. These patients do not benefit from hormone therapy and other targeted treatments of breast cancer. Recently, researchers proposed the use of androgen receptor (AR)-targeted therapies in this subset of patients. The rate of AR expression in TNBC patients varies from 0 to 53%. AR positivity is associated with a better outcome for breast cancer patients. The purpose of this study was to evaluate AR status in TNBC patients and its association with other demographic and pathologic features.

Methods: This cross-sectional study was conducted in the Cancer Institute of Iran, affiliated with Tehran University of Medical Sciences, in 2015. Archived formalin-fixed, paraffin-embedded breast tumor blocks were evaluated to determine the AR status of the tumors. Demographic and pathologic characteristics of the patients were retrieved from the department of pathology database. Data were analyzed with SPSS 18.0.

Results: Seventy-seven TNBC patients with the mean age of 45.3 ± 11.5 were assessed. Twenty-six patients (34%) showed AR expression, and 51 patients (56%) did not have AR expression. There was no significant correlation between AR status and age, tumor size, histopathologic type of tumor, or lymph node involvement. However, AR positivity had a statistically significant association with a lower tumor grade and lymphovascular invasion (P = 0.029 and P = 0.01, respectively).

Conclusion: TNBC patients with AR expression tend to have lower tumor grades and higher rates of lymphovascular invasion.

Introduction

The American Institute for Cancer Research (AICR) reported 18 million newly diagnosed cancer cases worldwide in 2018. Lung cancer and breast cancer are the most prevalent cancers (excluding non-melanoma skin cancers) in men and women, respectively.[1] Breast cancer accounted for 25.4% of newly diagnosed cancers in women in 2018.[1] The first cause of cancer death in women in developing countries is breast cancer. In Iran, breast cancer contributes to 24.6% of all cancers and is the fifth cause of death in Iranian women.[2]

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression are important predictive and prognostic factors for the management of breast cancer and are the basis of molecular classification of breast cancer subtypes.[3] Triple-negative breast cancer (TNBC) is pathologically defined as breast tumors that do not express ER, PR, and HER2.

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TNBC accounts for 15% to 20% of all types of breast cancer. It is a very aggressive tumor subtype with poor prognosis, as patients with TNBC do not benefit from hormone therapy and trastuzumab-based targeted therapy, and the only available systemic treatment for them is chemotherapy.[4]

As there is an absence of a well-defined targeted therapy for TNBC, recent gene expression studies focus on androgen receptors (ARs) in these patients.[5-8] AR expression prevalence in all subtypes of breast cancer is approximately 70% to 90%, but it varies from 0 to 53% in TNBC patients.[7-8]

Androgen signaling was first studied in prostate tumor cells, and flutamide -an androgen blocker- was used for prostate cancer treatment. The association between AR and breast cancer was demonstrated for the first time in the rat in 2001.[9] This sparked interest in the use of androgen-blocking agents in the treatment of breast cancer. Bicalutamide, an androgen-blocking agent, has been studied in the breast cancer setting. It had paradoxical effects on ER-positive breast cancer and caused apoptosis in ER-negative breast cancer.[10-12] Although positive androgen receptor is associated with poorer response to neoadjuvant chemotherapy, it may be associated with better prognosis in TNBC patients.[7] Novel androgen-blocking agents are introduced and can be beneficial for the treatment of AR-positive TNBC patients.

In this study, we evaluated AR status in TNBC patients in the Cancer Institute of Iran and its association with other demographic and pathologic features of the tumor.

Methods

Study Design

This was a cross-sectional study conducted in the Cancer Institute, affiliated with Tehran University of Medical Sciences in 2015. All patients diagnosed with TNBC between 2019 and 2014 were included. The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences.

Triple-negative breast tumors were identified in the pathology database of Cancer Institute and the paraffin blocks were selected for AR staining. Patients' demographic data were retrieved from the pathology department database. Demographic data included age at diagnosis, histopathologic tumor type, tumor size (mm), grade, lymphovascular invasion status and the number of involved axillary lymph nodes. Androgen receptor status was assessed as mentioned below.

Androgen receptor

Archived formalin-fixed, paraffin-embedded breast tumor blocks were collected from the pathology department and Hematoxylin and Eosin staining was used to confirm the diagnosis and select the appropriate blocks. A commercially available antibody (Monoclonal Mouse Anti-Human AR, Clone 441 Isotype: IgG1 Kappa; Dako, Denmark) was used to determine the AR status. Microwave heating was used for antigen retrieval in all cases. Then, the slides were assessed and scored by the same pathologist using a light microscope. If more than 10% of tumor nuclei were stained, AR status was considered positive. Cytoplasmic and membrane staining were considered negative for the androgen receptor.

Statistical Analyses

Data were analyzed with SPSS 18.0 statistical software (SPSS Inc, Chicago, IL, USA). For evaluating qualitative variables, the chi-square and the Fisher exact tests were used. Also, quantitative variables were compared between the two groups using an independent *t* test. P values less than 0.05 were considered significant.

Results

Seventy-seven TNBC pathology blocks were collected and assessed for AR status. All patients were female, with the mean age of 45.3 ± 11.5 years at the time of diagnosis. AR expression was positive in 26 patients (34%), and 51 patients (56%) were AR-negative. Demographic and pathological characteristics of patients are shown in Table 1.

AR-negative status was more commonly observed in TNBC patients with higher tumor grade (P = 0.029). Also, lymphovascular invasion was associated with an AR-positive status (P = 0.010). Table 2 shows the distribution of demographic and pathological characteristics in AR-positive and AR-negative tumors.

Table 1. Demographic and Pathological Characteristics

Variables		N(%)
Age, mean ± SD, y		45.3 ± 11.5
Tumor size, mean ± SD, mm		17 ± 36.5
Histopathologic type	IDC	64 (83%)
	Medullary	7 (9%)
	Papillary	3 (4%)
	Metaplastic	3 (4%)
Tumor grade	I	2 (3%)
	II	28 (36%)
	III	47 (61%)
Lymphovascular invasion	Yes	50 (65%)
	No	27 (35%)
Lymph node metastasis	Yes	31 (40%)
	No	36 (60%)
Androgen receptor	Positive	26 (34%)
	Negative	51 (56%)

Discussion

This study showed that the frequency of AR expression in TNBC patients was 34%. There was no statistically significant association between AR

status and age, tumor size, histopathologic type of tumor, or lymph node involvement, although lower tumor grade and lymphovascular invasion were associated with a positive AR status.

These findings are similar to other studies. The prevalence of AR-positive status in TNBC tumors has been reported in various studies. In two recent review articles, AR expression rate in TNBC varied from 0% to 53%.[7,8] A study from Iran examined the AR status in breast tumors in 2014 and found an AR expression rate of 64.3% in all tumors and 50% in TNBC cases.[13] However, there were only 12 cases of TNBC in their study, which makes their results less accurate for this subgroup of patients.[13]

Age has been associated with an AR-positive status in some studies.[13,14] Two recent studies reported the association of AR-positive status with older age at the time of diagnosis.[14,15] On the contrary, the previously mentioned study in Iran reported that patients with AR-positive tumors were younger than AR-negative patients.[13] However, most studies declared that age does not appear to affect the AR positivity.[16,17]

The current study did not show any association between tumor size and AR status. However, other studies reported that the smaller tumors were more likely to be AR-positive.[15,17] Another study from Iran did not show any significant association between tumor size and AR status.[13]

Some studies have reported a significantly lower rate of AR expression in metaplastic, mucinous, and medullary subtypes of breast cancer.[14,15] In the study by Choi *et al*., the authors concluded that AR positivity was distinctively associated with an apocrine histopathologic type (P = 0.001).[14] Our study did not show any association between the histopathologic type and AR expression. The most common histopathological type of tumors in our study was invasive ductal carcinoma, and the frequency of other types was not adequate for accurate evaluation.

In the present study, AR expression was associated with a lower tumor grade. This finding is similar to other studies. Park *et al.* reported that the expression of AR was significantly higher in tumors with lower grades (P < 0.001).[20] In other studies, a significant association was found between AR positivity and a lower tumor grade.[14,18]

Lymphovascular invasion is a predictor of more aggressive tumor behavior and might be associated with higher rates of AR expression. Our results are in concord with other studies showing that AR positivity is related with lymphovascular invasion.[16,19,20] However, there are other studies that found an inverse correlation between AR positivity and lymphovascular invasion.[17]

Lymph node involvement is one of the important predictive and prognostic factors for outcomes of breast cancer patients.[8,21] We did not find a statistically significant association between AR expression and lymph node involvement (P = 0.231). Also, most studies confirmed the lack of a significant relationship between AR expression and lymph node involvement.[13,14,20] In one study by Rakha *et al.*, there was a significant association between AR expression and lymph node involvement (P = 0.03).[19]

We did not have the data on Ki-67 for our study sample. Other studies have reported inconsistent results regarding AR status and Ki-67 relationship. A study by Pistell and colleagues evaluated 81 TNBC patients, and only 18.8% were AR-positive. AR positivity was associated with higher Ki-67 expression (P < 0.001) and lymphovascular invasion (P = 0.01) in their study.[17] However, the study by Park *et al*. did not show any association between AR status and Ki-67.[20]

In conclusion, AR positivity is associated with a lower tumor grade and positive lymphovascular invasion in TNBC. Further studies with larger study samples are required to evaluate the impact of AR status on patient outcome and the use of AR-based hormonal manipulations in TNBC patients.

Conflict of Interest

The authors have none to declare.

Table 2. Comparing demographic and pathological characteristics between AR-positive and AR-negative groups

variables		Positive (N=26)	Negative (N=51)	P Value
Age, mean ± SD, y		46 ± 10	45 ± 12	0.700
Tumor size, mean ± SD, mm		37 ± 19	34 ± 14	0.500
Histopathologic type	IDC	22 (85%)	42 (82%)	0.759
	Medullary	3 (11%)	4 (8%)	
	Papillary	0 (0%)	3 (6%)	
	Metaplastic	1 (4%)	2 (4%)	
Tumor grade	I	1 (4%)	1 (2%)	**0.029**
	II	14 (54%)	14 (27%)	
	III	11(42%)	36 (71%)	
Lymphovascular invasion	Yes	22 (85%)	28 (55%)	**0.010**
	No	4 (15%)	23 (45%)	
Lymph node metastasis	Yes	13 (50%)	18 (35%)	0.213
	No	13 (50%)	33 (65%)	

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