

Androgen receptor expression in hormone-negative breast cancers and its prognostic significance

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Background/aim

Breast carcinoma is a common, yet heterogeneous aggressive disease affecting relatively young patients. The androgen receptor (AR) is expressed in majority of breast cancers and across the main breast cancer subtypes. The aim of this study was to evaluate AR expression in hormone-negative breast cancer subtypes.

Materials and methods

Sixty cases of breast cancer were involved in this study; the samples were received in the Department of Pathology of Kasr El-Aini Hospital, Cairo University, Egypt. The expression of AR and human epidermal growth factor receptor-2 receptors were studied by immunohistochemistry in 60 formalin-fixed paraffin-embedded selected hormone-negative breast cancer surgical specimens. The immunohistochemistry expression of the marker was correlated with the clinicopathological variables.

Results

Of the hormone-negative cases, 61.6% show positive AR expression, 89% of which are invasive duct carcinoma, 68.3% are associated with ductal carcinoma *in situ*, and 55% are human epidermal growth factor receptor-2-enriched subtype. A significant correlation was found between the AR expression and tumor type. There is no evident significant correlation with tumor grade, multicentricity or lymphovascular invasion.

Conclusion

The AR has recently emerged as a useful marker for the further refinement of breast cancer subtype classification. Antiandrogens are thought to markedly enhance treatments and to be the first targeted therapy in hormone-negative breast cancer cases.

Keywords:

androgen receptor, hormone-negative breast cancer, immunohistochemistry, triple-negative breast cancer

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Introduction

According to The National Cancer Registry Program (NCRP) in Egypt, breast cancer was ranked as number one regarding female malignancies constituting 38.8% of the total recorded malignancies in the period between 2008 and 2011 [1].

Breast cancer remains the most common cancer among women worldwide with the ongoing challenge to find improved methods of classifying its subtypes [2]. Breast cancer is classified into five basic intrinsic subtypes based on gene expression: luminal A [estrogen receptor (ER) +/progesterone receptor (PR)+/human epidermal growth factor receptor-2 (HER2-)], luminal B (ER+/PR+/HER2+), triple-negative TNBC/basal-like (ER-/PR-/HER2-), HER2-enriched breast cancer (ER-/PR-/HER2+), and normal breast like type [3,4].

Androgens, although classified as male hormones, are also expressed in the female body. Androgen receptor (AR), ER, and PR are nuclear steroid hormone

receptors. AR acts as transcription factors regulating gene expression and thus they are considered as critical components of signaling pathways [5,6].

The prognostic and predictive values of ER and PR expression in breast cancer are widely recognized together with their therapeutic applications; however, the role of AR in breast cancer is ambiguous. In physiological conditions, testosterone is the main active androgen in women. In the breast tissue, testosterone is converted either to dihydrotestosterone or under estrogen deprivation conditions it converts to estrogen agonist 17 β -estradiol (E2).

Mammary epithelial cells express AR with opposite status of ER/PR expression depending on the cell type,

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where metaplastic apocrine cells show AR expression but not ER/PR. On the other hand, 5–30% of luminal epithelial cells show a status of coexpression. This indicates that the signaling effect of AR is different across breast cancer subtypes [7].

Recently, potent, AR-directed therapies have been introduced as adjuvant therapy in prostatic carcinoma. A similar role for AR blockers in the treatment of breast carcinoma is looked for. According to certain studies AR expression was detectable in 75% of breast cancers [6]. This work aimed to study AR expression in ER/PR-negative breast cancers to clarify its prognostic role to provide a hormonal targeted therapy for this sector of patients.

Materials and methods

The study sample

A retrospective study on breast cancer surgical specimens was done. The samples were received in the Department of Pathology of Kasr El-Aini Hospital, Cairo University, Egypt. Detailed history and clinical data were taken for each of them. The institutional ethics committee of National Research Centre, Cairo (No. 18004), approved the study.

Sixty cases of hormone-receptor-negative breast cancers were retrieved as paraffin-embedded blocks, that is, triple-negative/basal-like breast (HER2 negative) ($n=27$) and HER2-enriched breast cancers (HER2 positive) ($n=33$). They underwent modified radical mastectomy and conservative breast surgery. The studied cases consisted of 46 cases of infiltrating duct carcinoma (IDC), eight cases of infiltrating lobular carcinoma, and six cases of medullary carcinoma.

The cases were graded according to WHO criteria. The presence of lymph node metastasis and N stage were reviewed. Estrogen and progesterone receptors, HER2 reactivity was obtained from patient charts. Two sections of 4 μ m thickness were cut from each block. One section was stained with hematoxylin and eosin for histopathological evaluation and grading. The other section was mounted on positively charged glass slides for immunohistochemical staining using antiandrogen antibody.

Immunohistochemistry

AR expression was examined in all tissues using the streptavidin-biotin technique. Sections were deparaffinized, hydrated, and incubated in 3%

hydrogen peroxide for 30 min to block the internal peroxidase activity. Antigen retrieval was done by microwave pretreatment for 10 min in 0.01 M citrate buffer. Subsequently, the sections were incubated at 4°C overnight with anti-AR (antiandrogen; rabbit monoclonal androgen receptor (ab108341 1 : 25 dilution) purchased from Abcam Co. (UK). These steps were followed by 60 min incubation with biotinylated secondary antibody (code 3024; Dako, Copenhagen, Denmark) at room temperature, avidin-biotin peroxidase complex for 50 min at room temperature and finally diaminobenzidine for 3–5 min. The slides were counterstained with hematoxylin, dehydrated, and mounted.

Tumors exhibiting more than 1% of tumor cells nuclear staining for ER and PR of any intensity were considered positive (performed at Kasr El-Aini Medical School), according to the method of Hammond *et al.* [8].

HER2 is considered positive when a uniform intense membrane staining of greater than 30% of tumor cells was detected, according to the method of Mrklic *et al.* [9], using kits of anti-ErbB antibody (EPR19547-12) purchased from Abcam Co..

AR immunoreactivity was considered positive if more than 10% of tumor cells showed nuclear staining [10]. In the negative control group, 1% bovine serum albumin was used in place of the primary antibody.

Statistical analysis

Data were statistically described in terms of mean $\pm$ SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Mann-Whitney *U*-test for independent samples for comparing two groups and Kruskal-Wallis test for comparing more than two groups. For comparing categorical data, χ^2 test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using the computer program SPSS (2006, statistical package for the social sciences; SPSS Inc., Chicago, Illinois, USA) release 15 for Microsoft Windows.

Results

A total of 60 formalin-fixed paraffin-embedded breast cancer surgical specimens of infiltrating breast

carcinoma were included. The clinicopathological characteristics are presented in Table 1. The mean age is 48.58 years; mean tumor size is 4.29 cm. Forty-six (76.7%) cases were IDC, eight (13.3%) cases were infiltrating lobular carcinoma, and the remaining six (10%) cases were medullary carcinoma. According to WHO, 68.3% of cases (41 out of 60 cases) were of nuclear grade II and 31.7% cases (19 out of 60 cases) were of nuclear grade III. On reviewing nodal staging, 15 cases of N0, nine cases of N1, 14 cases of N2, 22 cases of N3. Seventy percent were associated with desmoplastic reaction, 68.3% of cases showed ductal carcinoma *in situ* (DCIS), and 23.3% of cases were associated with lymphovascular invasion. Only 20% of cases showed multicentric lesions. Twenty-seven cases were of triple-negative subtypes (ER-,

PR-, HER2-) and the remaining 33 cases were of HER2 enriched subtypes (ER-, PR-, HER2+) as shown in Table 1.

Immunohistochemical expression of androgen receptor

The present results indicated that AR was positively expressed in 61.6% of cases (37 cases) and the remaining 23 (38.3%) cases were negatively stained for AR with a cut-off point of 10% (Fig. 1, Table 1). Moreover, the statistical analysis using Fisher's exact test showed that there was a significant correlation between AR expression and tumor type, as 71.7% (33 cases/46) of the IDC cases and, 50% (four cases/eight) of the lobular carcinoma cases were positively stained for AR ($P=0.002$) (Table 2, Figs. 2 and 3). All medullary carcinoma cases were negatively stained for AR expression. There was a borderline significant correlation between AR expression and axillary lymph nodes status ($P=0.09$); only 40% of patients with N0 showed positive AR expression (six cases/15), while 68.89% (31 cases/45) of nodal metastatic cases showed positive expression for AR (Table 2).

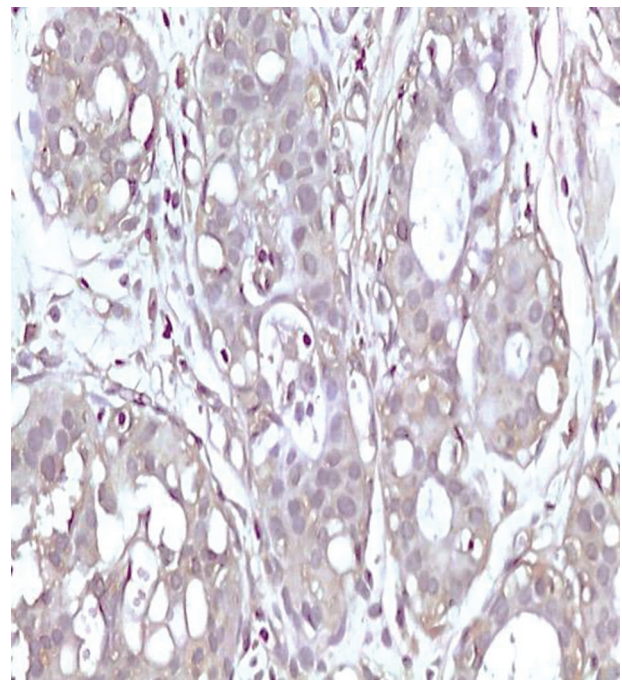
The present results recorded nonsignificant correlation between AR expression and multicentricity in the studied group ($P=0.55$), where 64.58% of monofocal cases and 50% of multicentric cases showed positive AR expression (Table 2). There was a significant

Table 1 Clinicopathological characteristics and immunohistochemical results of breast cancer cases

Prognostic factors	n=60 [n (%)]
Tumor type	
IDC	46 (76.7)
ILC	8 (13.3)
MED	6 (10)
Operation	
CBS	11 (18.3)
MRM	49 (81.7)
N stage	
N0	15 (25)
N1	9 (15)
N2	14 (23.3)
N3	22 (36.7)
Multicentricity	
Negative	48 (80)
Positive	12 (20)
Nuclear grade	
I	41 (68.3)
II	19 (31.7)
LVI	
Negative	46 (76.7)
Positive	14 (23.3)
DCIS	
Negative	19 (31.7)
Positive	41 (68.3)
HER2	
Negative	27 (45)
Positive	33 (55)
Androgen	
Negative	23 (38.3)
Positive	37 (61.6)
Descriptive statistics (mean±SD)	
Age	48.58±9.431
Tumor size	4.29±2.177

CBS, conservative breast surgery; DCIS, ductal carcinoma *in situ*; HER2, human epidermal growth factor receptor-2; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; LVI, lymphovascular invasion; MED, medullary carcinoma; MRM, modified radical mastectomies.

Fig. 1



Androgen receptor-negative nuclear immunostaining in normal breast ducts (original magnification ×400).

Table 2 Association between androgen with different prognostic parameters in breast cancer cases

Prognostic factors	Androgen intensity count (n=60)	
	Negative	Positive
Tumor type		
IDC ^a	13	33
ILC	4	4
MED	6	0
N stage		
N0	9	6
N1	3	6
N2 ^a	4	10
N3 ^a	7	15
Multicentricity		
Negative	17	31
Positive	6	6
Nuclear grade		
I	18	23
II	5	14
LVI		
Negative	19	27
Positive	4	10
DCIS		
Negative ^a	12	7
Positive ^a	11	30
HER2		
Negative ^a	6	21
Positive	17	16

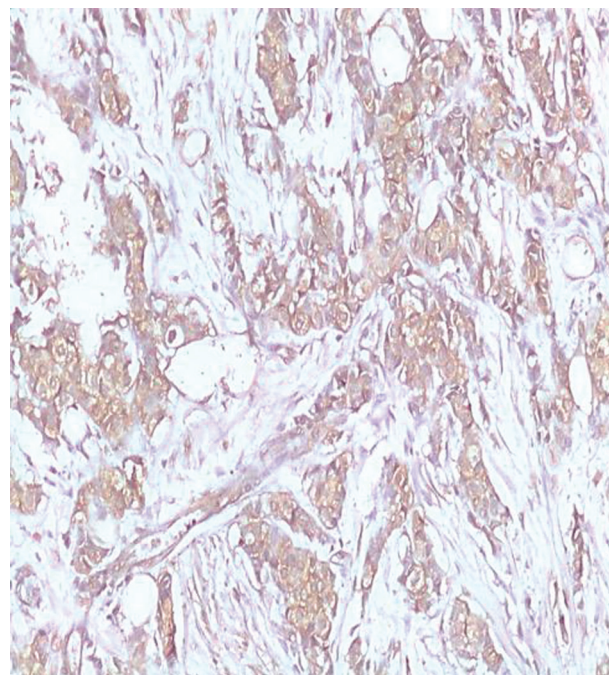
^aSignificant difference using χ^2 at *P* value less than 0.05. CBS, conservative breast surgery; DCIS, ductal carcinoma *in situ*; HER2, human epidermal growth factor receptor-2; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; LVI, lymphovascular invasion; MED, medullary carcinoma; MRM, modified radical mastectomies.

correlation between AR positivity and associated DCIS ($P=0.016$), where 73.17% (30 cases/41 cases) of cases with ductal carcinoma *in situ* and only 36.8% (seven cases/19) of cases without DCIS showed positive androgen expression.

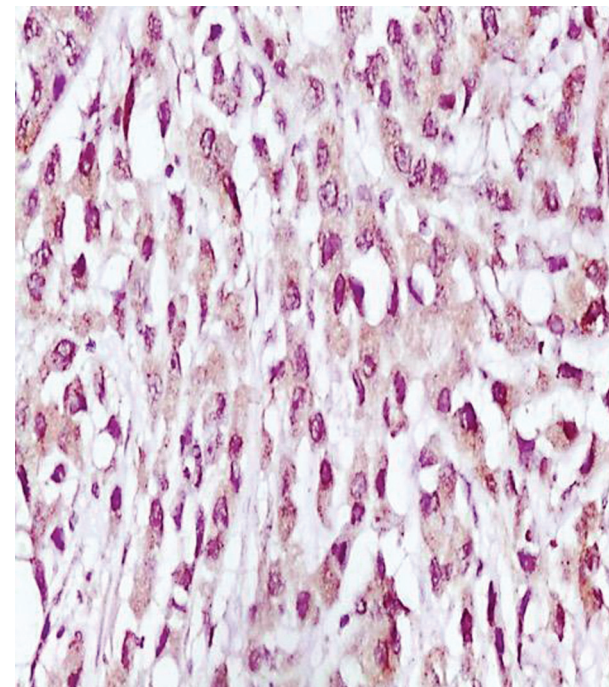
On the other hand, AR expression was nonsignificantly correlated with lymphovascular invasion ($P=0.58$) or tumor grade ($P=0.67$) (Table 2). There was a significant inverse correlation between HER2 expression and AR positivity ($P=0.03$) where 77.78% (21 cases/27) of triple-negative breast cancer subtype (HER2 negative) and 48% (16 cases/33) of HER2-enriched subtype (HER2 positive) were positively stained for AR (Table 2).

Discussion

Breast cancer is a highly heterogeneous disease. The clinical classification of breast cancers based on the expression of ER, PR, and HER2 are broadly divided into four groups, ER+/PR+/HER2-, ER+/PR-

Fig. 2

Androgen receptor-positive immunostaining in invasive ductal carcinoma. Tumor cells show greater than 10% nuclear staining (original magnification $\times 200$).

Fig. 3

Androgen receptor-positive immunostaining in invasive lobular carcinoma (original magnification $\times 400$).

+HER2+, ER-/PR-/HER2+, and ER-/PR-/HER2- (also known as TNBC). ER and HER2 serve as prognostic markers and direct therapeutic strategies [3,4,11].

Despite these number of categories grouped by different studies, breast tumors fall primarily into three major classes, that is, luminal, HER2 overexpression, and TNBC, where triple-negative tumors are the most heterogeneous [4].

Among these intrinsic subtypes, HER2 overexpression and TNBC are of particular interest due to the aggressive clinical course they follow and the lack of standard, targeted hormone therapy and these are the selected categories included in the present study.

The development and progression of breast cancer depends on the action of steroid hormones; there is evidence that androgens may increase breast cancer risk either directly, by increasing cellular growth and proliferation via the AR, or indirectly, through their aromatization to estrogens [12].

However, there is also in-vivo and in-vitro evidence that androgens may protect the breast from estrogen-induced stimulation of premalignant cells, possibly by competitive blockage of the estrogen receptor, and also by inducing antiproliferative and proapoptotic effects in the cell [13].

The frequency of AR expression in breast cancers is highly variable with a varying range of 6.6–75% [11,14–18]. In the present study, AR expression is noted in 61.67% of the selected hormone-negative cases. In some studies, 70–90% of primary breast cancers are AR positive [10,19]. In contrast, a meta-analytical study by Francisco and his team showed that AR expression was 74.8 and 31.8% in ER-positive and ER-negative tumors, respectively, indicating the importance of ER status for the prognostic role of AR [20].

The discrepancy could be attributed to the variability among reported studies in terms of source of the primary antibody, the methodology of testing, number of patients, and the AR positivity cut-off ($\geq 1\%$ vs. $>10\%$). Here we applied a cut-off point of greater than 10% since the since this higher cut-off point showed increased specificity [20].

The majority of the cases expressing AR (89%) are ductal in origin and the remaining 11% are lobular. None of the included medullary carcinoma cases expressed AR. Moreover, there seem to be a significant correlation between AR expression and associated DCIS. This could be attributed to the normal AR expression in metaplastic apocrine cells and luminal epithelial cells [7].

Jézéquel *et al.* [21] used gene expression profiling to subclassify TNBC: a luminal androgen receptor (LAR subtype), a basal-like subtype, and a basal-enriched subtype. LAR subtype is distinguished by increased AR expression compared with other TNBC molecular subtypes [22]. This molecular characterization definitely helps to develop targeted therapy [23].

In our study the statistical analysis of the AR shows no evidence of significant correlation between AR expression and some prognostic factors namely the multicentricity, tumor grade, and lymphovascular invasion. However, it is significantly expressed in lower grade tumors (grade I vs. grade II), which goes with previous studies based on unselected breast cancer cohorts that have shown AR to be related to ER and PR expression and to be a marker of low-grade, well-differentiated disease [24–26]. Also previous studies have shown that positivity by AR immunostaining is a favorable prognostic factor and is associated with a lower clinical stage and lower histologic grade in TNBC [19,27]. However, this favorable prognostic significance of AR is not uniform across the literature. Controversy exists, with discordant findings among certain studies. Hu *et al.* [5] have shown AR expression to be associated with increased mortality among women with ER-negative and TNBC tumors.

Similarly, Park *et al.* [11] have suggested worse outcomes in AR+/ER- breast cancers.

Francisco and his team through their extended meta-analytical study concluded that AR expression in female breast cancer is associated with better overall survival and disease-free survival irrespective of the coexpression of ER [20]. Choi *et al.* [28] findings have reported AR expression to be a significant predictor of worse disease-free survival and overall survival in TNBC without lymph node involvement.

Our results on the selected cases show borderline correlation between nodal metastasis and AR expression. These results are comparable to Choi and colleagues' findings as they could not identify AR as a prognostic marker in patients with TNBC and lymph node metastasis [9,28]. However, this is contradictory to the findings by McGhan and colleagues, Choi and colleagues, Rakha and colleagues, and Sutton and colleagues, who suggested AR expression to be associated with lymph node metastasis in TNBC [15,20,28–30].

Despite the establishment of AR expression, the function of AR in breast cancer is still being elucidated. Androgens seem to have either an inhibitory or a stimulatory effect on breast cancer cell lines depending on the coexpression of other steroid hormone receptors [30].

Conclusion

The present work found a variable relationship between AR and established prognostic factors. AR has recently emerged as a useful marker for the further refinement of breast cancer subtype classification. The expression of AR in breast carcinoma has shed new light on the signaling consequences of AR. This allows us to harness the clinical availability of new potent AR antagonists to potentially improve current therapies especially in hormone-negative patients. Based on promising early clinical data, we anticipate that the newer, more potent antiandrogens will significantly improve outcomes and likely will be the first targeted therapy.

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Conflicts of interest

There are no conflicts of interest.

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