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RESEARCH

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Androgen receptor expression and clinical characteristics in breast cancer

Dan-dan Wang[1†], Lin-hong Jiang[2†], Jian Zhang[1†], Xiu Chen[1], Hong-lei Zhou[1], Shan-liang Zhong[3*] and He-da Zhang[1*]

Abstract

Objective To investigate the relationship between the expression of androgen receptor (AR) and clinical characteristics in breast cancer.

Patients and methods The clinical records of all 432 patients tested for AR in our institution between January 2020 and May 2023 were reviewed. Clinical characteristics, age, menopausal status, tumor node metastasis (TNM) stage, distant metastasis, pathological complete response (pCR), histopathological features histological grade, estrogen receptor (ER), progesterone receptor, Her-2, Ki-67, and molecular subtype were registered for all patients.

Results About 377 (87.27%) of the 432 patients had AR expression.

No significant difference in AR expression was found with age, menopausal status, TNM stage of primary tumor, or pCR. AR was positively and significantly associated with the histological grade, and recurrence. The AR expression was significantly related with molecular subtypes, including ER, PR Her-2, Ki67 and molecular subtype. ER (OR = 10.489, 95%CI: 5.470–21.569), PR (OR = 7.690, 95%CI: 3.974–16.129, Her-2 (OR = 10.489, 95%CI: 2.779–23.490 and tumor recurrence (OR = 0.110, 95%CI: 0.031–0.377 were significant independent risk factors affecting AR expression.

Conclusions AR expression can serve as a reliable basis for judging the clinical molecular types and poor prognosis for breast cancer. AR may be a novel biomarker and target in AR-positive breast cancer depending on significant difference in AR expression among different molecular types of breast cancer.

Keywords Breast cancer, Androgen receptor, Estrogen receptor, Clinical characteristics

Introduction

Breast cancer is the most common malignancy and the first leading cause of cancer-related death in women worldwide. It is highly heterogeneous at molecular and clinical levels [1]. The main breast cancer subtypes include luminal A, Luminal B, Her-2-enriched and basal-like type, and normal-like type, depending on molecular profiles and several biomarkers [2]. Estrogen receptor (ER) and progesterone receptor (PR) as sex steroid hormone receptors are important biological markers for prognosis prediction in breast cancer. Androgen receptor (AR), another sex steroid hormone receptor family, is expressed in 70%-90% of breast cancer patients. The AR expression varies among breast cancer subtypes, and

†Dan-dan Wang, Lin-hong Jiang and Jian Zhang contributed equally to this work.

He-da Zhang is the first corresponding author.

*Correspondence:
Shan-liang Zhong
slzhong@njmu.edu.cn
He-da Zhang
zhanghedazhd@163.com
[1] Department of General Surgery, the First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Jiangsu 210029, P. R, China
[2] Department of Radiation Oncology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
[3] Center of Clinical Laboratory Science, the Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, 42 Baiziting, Jiangsu 210029, P. R, China

accounts for a large proportion in ER-positive tumors [3]. AR is a ligand-activated transcription factor. Increasing research shows AR played a dominant role in the development of breast cancer. AR can reportedly accelerate cell proliferation of ER-negative breast cancer and triple-negative breast cancer (TNBC) [4–6]. The main reason is that AR competes with ER for binding to androgen-responsive elements, leading to tumor cell growth [2]. The synergy between Her-2 and AR is reinforced by a positive feedback loop mechanism, which promotes Her-2 transcriptional upregulation and then activates related downstream pathways, accelerating AR-positive tumor growth [3, 7]. Additionally, AR promotes tamoxifen resistance probably by regulating cyclin D1 expression and promoting cell cycle progression [8]. However, some studies show serum androgen is positively associated with breast cancer risk whether in premenopausal or postmenopausal women [9–12]. Moreover, high AR expression is correlated with better disease-free survival (DFS) and overall survival (OS) [13]. Therefore, the existing views concerning the prognostic value of AR in different breast cancer subtypes are controversial.

Although some research shows AR-target drugs are effective for AR-positive breast cancer, the patients who exactly benefit from AR-target therapies remain uncertain. The aim of this study was to investigate the clinical characteristics of AR in breast cancer, and to evaluate the prognostic value and provide a therapeutic tool for breast cancer.

Patients and methods

Totally 432 breast cancer patients receiving surgical resection at the First Affiliated Hospital of Nanjing Medical University between January 2020 and May 2023 were enrolled This study was approved by Ethics Committee of the Hospital (Ethics code 2022-SR-473).

Immunohistochemistry(IHC)

For IHC assay, the breast cancer tissue slides were incubated with the indicated primary antibodies (anti-AR, Clone number: EP120; ZSGB-BIO) overnight at 4℃. And then chromogenic detection was performed through a DBA detection kit (Kit-2031, Maixin, China). Data were obtained and analyzed by two experienced doctors of the pathology department of our hospital. and AR scores were presented as levels (0, none; 1+, weak; 2+, moderate; 3+, strong) and the percentage of stained nuclei and divided into five groups (0: < 5%; 1:6%-25%; 2:26%-50%; 3:51%-75%; and 4–75%). Finally, the score was expressed as (staining intensity × percentage of positively stained cells).

Criteria for pathological results

The ER/PR status criterion is that ≥ 1% stained tumor nucleus is positive. The Her-2 status criteriona is that immunohistochemistry (IHC) confirms 3+or 2+(Fish confirm IHC) is positive. Ki67 is expressed in positive cells to calculate the percentage [14]. The 8th edition of Breast cancer TNM Staging Atlas from the American Joint Committee on Cancer (AJCC).

Statistical analysis

Statistical analysis was performed on SPSS 22.0. Associations between AR expression and clinicopathological features were assessed using Chi-square or Student's t-test and analysis of variance (ANOVA). Significant risk factors were used to predict AR expression using a multivariate logistic regression model. $p < 0.05$ was deemed as significant.

Results

AR expression in breast *cancer* tissue specimens

Of the 432 cases of ranged from 23 to 81 years (52.15 ± 11.10). Fifty five (12.7%) of the 432 patients were AR-negative and 377 (87.3%) patients were AR-positive (Table 1).

Relationship between AR expression and clinical features

Overall, 87 patients received neoadjuvant chemotherapy, among which 14 patients showed pathological complete response (pCR) (10 AR^+ patients, 4 AR patients), and 73 patients were non-pCR (58 AR^+ patients, 15 AR patients). In our series, AR expression was not significant in pCR ($p = 0.5057$, Table 1). Furthermore, no significant correlations were observed between AR expression and age, menopausal status, tumor size, lymph node, distant metastasis or tumor stage (Table 1).

In addition, 11 patients relapsed during follow-up. Our series showed a significant difference in AR expression and poor prognosis ($p = 2.503e-05$, Table 1). According to histological grade, there were significant differences in AR expression ($p = 0.001363$, Table 1).

Relationship between AR expression and molecular typing of breast *cancer* tissues

In all patients, 206 (47.7%) patients belonged to Luminal type, 83 (19.2%) patients were HR+/Her-2+, 54 (12.5%) patients were HR-/Her2+, and 82 (19.0%) patients were TNBC (Table 2). AR expression was related to the presence of ER (p=5.357e-15), PR (p=9.594e-11) and Her-2 (p= 8.408e-05). AR expression was also significantly

Table 1 Clinical characteristics of breast cancer patients according to AR status

Variable	Patients	AR + (%)	AR-(%)	χ2	*p*
Age					
≤ 50	184	154(83.7%)	30(16.3%)	3.6825	0.05499
> 50	248	223(89.92%)	25(10.08%)		
Menopausal status					
Premenopausal	195	167(85.64%)	28(14.36%)	0.84737	0.3573
Postmenopausal	237	210(88.61%)	27(11.39%)		
T stage of primary tumor					
T1	178	159(89.33%)	19(10.67%)	3.5689	0.3119
T2	213	185(86.85%)	28(13.15%)		
T3	25	19(76%)	6(24%)		
T4	16	14(87.5%)	2(12.5%)		
N of primary tumor					
N0	210	182(86.67%)	28(13.33%)	1.257	0.7394
N1	152	135(88.82%)	17(11.18%)		
N2	43	38(88.37%)	5(11.63%)		
N3	27	22(81.48%)	5(18.52%)		
Distant Metastases					
Metastases	3	2(66.67%)	1(33.33%)	1.154	0.2827
None	429	375(87.41%)	54(12.59%)		
Stage					
I	111	98(88.29%)	13(11.71%)	1.7648	0.94
IIA	149	130(87.25%)	19(12.75%)		
IIB	83	73(87.95%)	10(12.05%)		
IIIA	51	43 (84.31%)	8(15.69%)		
IIIB	10	9(90%)	1(10%)		
IIIC	25	22(88%)	3(12%)		
IV	3	2(66.67%)	1(33.33%)		
pCR					
pCR	14	10(71.43%)	4(28.57%)	0.44303	0.5057
non-PCR	73	58(79.45%)	15(20.55%)		
Histological grade					
G1	4	4(100%)	0	13.197	**0.00136**
G2	163	155(95.09%)	8(4.91%)		
G3	229	191(83.41%)	38(16.59%)		
Recurrence					
No	421	372(88.36%)	49(11.64%)	17.762	**2.503e-05**
YES	11	5(45.45%)	6(54.55%)		

associated with Ki-67 (p= 0.0458) and histological subtype (p<2.2e-16) (Table 2).

Expression difference of AR in TNBC and non-TNBC tissues

Among the patients, 82 (18.98%) patients were TNBC with 44 AR-positive cases (53.66%), and 350 (95.14%) patients were non-TNBC with 333 AR-positive cases (95.14%). AR expressions were significantly different between the TNBC group and the non-TNBC group (p < 2.2e-16) (Table 3).

Multivariate analysis with significant factors

Multivariate logistic regression confirmed ER, PR and Her-2 as independent predictors for AR expression (p < 0.05). In addition, AR expression was significantly related to tumor recurrence (p < 0.05) (Table 4).

Discussion

Breast cancer is hormone-dependent and routinely examined with ER/PR and AR, ER belong to the nuclear receptor superfamily [15–17]. Although AR has the same

Table 2 Relationship between the expression of AR and molecular typing characteristics

Variable	Patients	AR + (%)	AR-(%)	χ2	*p*
ER					**5.357e-15**
ER +	293	281(95.6%)	12(4.1%)	61.125	
ER-	139	96(69.06%)	43(30.94%)		
PR					**9.594e-11**
PR +	259	248(95.75%)	11(4.25%)	41.903	
PR-	173	129(74.57%)	44(25.43%)		
Her-2					**8.408e-05**
Her-2 +	135	131(97.04%)	4(2.96%)	18.767	
Her-2-	290	239(82.41%)	51(17.59%)		
Unknown	7	7(100%)	0		
Ki67					**0.0458**
≤ 14	39	38(97.44%)	1(2.56%)	3.9888	
> 14%	393	339(86.26%)	54(13.74%)		
Subtype					**< 2.2e-16**
Luminal stype	206	194(94.17%)	12(5.83%0	103.44	
HR-Her-2 +	54	49(90.74%)	5(9.26%)		
HR + Her-2 +	83	83(100%)	0		
TNBC	82	44(53.66%)	38(46.34%)		

Table 3 Difference analysis of AR expression in triple negative and non-triple negative breast cancer tissues

Variable	Patients	AR(%)	
TNBC	N	+	-
non-TNBC	350	333(95.14%)	17(4.86%)
TNBC	82	44(53.66%)	38(46.34%)
χ2		102.9	
P		**< 2.2e-16**	

structure as ER/PR and is more extensively expressed AR is far less understood than ER and PR. We investigated the AR expression in breast cancer patients and correlated it with clinical-pathological characteristics.

We observed AR expression in about 87.3% ($n = 377/432$) of the cases in our cohort. This large proportion of AR expression is consistent with the literature. Research AR plays an important role in the pathogenesis of breast cancer, and is expressed in more than 70% breast cancer patients [18]. Other studies show the presence of AR in ER-positive breast cancer is correlated with tumor size, and histopathological grading [19, 20]. However, our investigation found AR expression was significantly associated with independent risk factors (e.g., ER, PR, Her-2 and Ki-67), but not with clinical-pathological characteristics (e.g., age, menopausal status, tumor size, lymph node, distant metastasis tumor stage) in breast cancer patients. This result may suggest AR is correlated with the histological subtype, and can be adopted as a potential biomarker.

The AR positive rate in ER-positive breast cancers is 66.9%, which is consistent with the reported rate of 60%-90% [17, 20, 21]. However, some studies indicate AR may act as a tumor suppressor in this sub-type [22, 23]. Meanwhile, AR expression is correlated with ER. One of the most likely mechanisms is that AR can competitively combine estrogen responsive elements to inhibit the transcriptionally active components of ER [22]. In addition, AR can directly bind to p300, a coactivator for competitive binding with ER, and then inhibits the function and downstream signaling pathways of ER [22], thus suppressing tumor growth in luminal breast cancer. Indeed, AR is also regarded as a good prognostic factor. For instance, the presence of AR in ER-positive breast cancer patients shows a better prognostic outcome in terms of DFS and OS [24, 25]. In HR + /Her2-T_2N_0 breast cancer, AR-positive patients have better DFS and lower risk of recurrence. In addition, AR negativity predicts a worse curative effect for adjuvant chemotherapy and endocrine therapy [13]. We did not discover significant relations between AR expression and time-to-event outcomes, which is because we did not follow up our patients for a long time and we will follow up full life.

AR expression accounts for 60% in Her-2-positive breast cancer patients, but the AR expression rate is low in this sub-type in our work, which may be related to the small sample size. Moreover, AR expression in Her-2-positive breast cancer patients predicts a worse prognosis, which may be involved in mediating Wnt/β catenin and Her-2 signaling pathways [26]. To the delight, we are conducting clinical trials on enzalutamide combined with trastuzumab for Her-2^+/AR^+ breast cancer patients, and hope to achieve good results.

As we know, TNBC have high heterogeneity and lacks target therapy, such as Her-2 and HR that predict poor prognosis and early metastasis. However, more than 50% of TNBC cases express AR, and more evidences suggest AR to be a solid target. Thike et Al. (2014) found AR-positive TNBC was related to better DFS [27]. Howeverother studies present opposite results. For instance, a clinical study with 559 TNBC cases shows AR negativity is correlated with a better prognostic outcome in terms of OS. For TNBC patients without lymph node metastasis, AR-positive patients also have a higher risk of death and recurrence [20, 24, 28]. Therefore, we are required to confirm the clinical role of AR. A. Di Leone disclosed that AR overexpression in TNBC showed a lower Ki67 rate and was related to a lower rate of pCR in neoadjuvant chemotherapy [29]. Currently, researchers pay more attention to TNBC to ensure long survival. In this aspect,

Table 4 Logistic regression analysis of AR expression and clinico-pathological factors

Factor	B	SE	Wald	OR	95%CI	p
	0.55254	0.29035	3.62141			
Age	1	2	5	1.737662	[0.9849–3.0899]	0.05704
menopaus	0.26548	0.28896	0.84407			0.35823
e	1	3	8	1.304059	[0.7389–2.3053]	3
T	-0.23631 0.20025	4 0.32777	3 0.37327	0.789533	[0.4192–1.4587]	9 0.54122
N	9	5	8	1.221719	[0.6485–2.3625]	3
M	-1.24479	1.23336 3	1.01862 3	0.288	[0.0271–6.2588]	0.31284 6
Stage	-0.09692	0.38399 1	0.06371	0.907626	[0.4192–1.9121]	0.80072 5
ER	2.3503	0.34722 4	45.8170 4	10.48872	[5.4701–21.5687]	**1.3E-11**
PR	2.03991 1	0.3541	33.1871 1	7.689922	[2.9743–16.1293]	**8.37E09**
Her-2	1.94426 5	0.53049 6	13.4322 1	6.988494	[2.7786–23.4905]	**0.00024 7**
Ki67	-1.80057	1.02360 5	3.09425	0.165205	[0.0092–0.7873]	0.07856 9
Stype	19.4194 7	1180.40 6	0.00027 1	2.71E + 0 8	[2.91E-13- 2.9E + 182]	0.98687 4
pCR	0.43610 2	0.65871 7	0.43830 8	1.546667	[0.3827–5,3731]	0.50794
Grade	-12.6021	727.698 9	0.0003	3.36E-06	[NA-3.92E + 30]	0.98618 3
Recurrence	-2.2094	0.62431	12.5241 1	0.109767	[0.0306–0.3773]	**0.00040 2**

AR-target therapy gives the choice for TNBC, which also need more clinical trials.

In summary, in-depth research on targeted therapy and combination therapy for breast cancer is demanded. Routine assessment of AR may help better personalize treatment for breast cancer, and can be used as a potential therapeutic target and novel biomarker in breast cancer. Furthermore, extensive research containing a large substantiation in patients, and more controlled prospective clinical trials are needed to validate the results.

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None.

Authors' contributions
HDZ and SLZ designed the study and wrote the manuscript. DDW and LHJ primarily wrote the manuscript and prepared the tables. JZ and XC made substantial contributions to the acquisition and analysis of data. JZ and HLZ made contributions to the analysis and interpretation of data and revised the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
In this research were approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Ethics code 2022-SR-473), which deemed that written informed consent was not necessary due to the retrospectiveness of the research and the concealment of patient information.

Competing interests
The authors declare no competing interests.

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