original article

Annals of Oncology 22: 1288–1294, 2011
doi:10.1093/annonc/mdq586
Published online 25 November 2010

Expression of androgen receptor in breast cancer and its significance as a prognostic factor

Q. Yu[1,2], Y. Niu[1]*, N. Liu[1], J. Z. Zhang[3], T. J. Liu[1], R. J. Zhang[1], S. L. Wang[1], X. M. Ding[1] & X. Q. Xiao[1]

[1]*Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital;* [2]*Department of Oncology, Jinghai Hospital, Tianjin;* [3]*Department of Pathology, Beijing 306 Hospital, Beijing, China*

Received 29 April 2010; revised 8 June 2010; accepted 27 August 2010

Background: Breast cancer is an extraordinarily hormone-dependent tumor. This study was to evaluate androgen receptor (AR) status and its significance in breast cancer in Chinese women.

Methods: Three hundred and thirty-five consecutive cases of invasive ductal breast carcinoma, 34 ductal carcinoma *in situ* (DCIS), and 82 DCIS adjacent to invasive tissues were involved in this study. The expression of AR was analyzed by immunohistochemistry and compared with patient outcome, and its implications were evaluated in five molecular subgroups of invasive ductal carcinoma (IDC) and in DCIS lesions.

Results: AR expression was related to that of estrogen receptor ($P < 0.001$) and progesterone receptor ($P = 0.035$) but not correlated with the other conventional parameters. AR retained independent prognostic significance (hazard ratio 0.309, 95% confidence interval, 0.192–0.496; $P < 0.001$). The majority (61.0%) of basal-like breast cancers showed loss of AR expression ($P < 0.001$), which had poor prognosis. The percentage of AR-positive cases was significantly higher in DCIS adjacent to IDC group than in pure DCIS and IDC groups (93.9%, 79.4%, and 72.5%; $P = 0.046$ and $P < 0.001$, respectively).

Conclusions: Our data suggest that AR may provide another specific definition of breast cancer subtypes and reveal a potential role in DCIS progression. These findings may help develop new therapies.

Key words: androgen receptor, basal-like subgroup, biological characteristics, breast cancer, clinicopathological characteristics, ductal carcinoma *in situ*

introduction

Growth of breast cancer is known to be in an extraordinarily hormone-dependent manner. The critical role of estrogen receptor (ER) and progesterone receptor (PR) in the pathogenesis of breast cancer is well recognized, and they are considered important in regulating cell proliferation and differentiation. Therefore, antiestrogen therapy has been used to successfully treat some cancers. In contrast to patients with hormone receptor-positive disease, patients with ER-negative and PR-negative tumors gain little or no benefit from antiestrogen therapy. The targeted therapy with trastuzumab [antihuman epidermal growth factor receptor-2 (HER-2) monoclonal antibody] is limited to those patients with HER-2-positive disease. However, those with triple-negative breast cancer (ER−, PR−, and HER-2−) lack any effective targeted therapies.

Correspondence to: Prof Y. Niu, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, West Huanhu Road, Ti Yuan Bei, He Xi District, Tianjin 300060, China.
Tel: +86-22-27303428; Fax: +86-22-23359337; E-mail: yunniu2000@126.com

Some biochemical and immunohistochemical data have indicated the presence of androgen receptor (AR) in breast cancer tissues, and AR is expressed in a considerable proportion of cases [1–3]. Particularly, AR expression has also been reported in almost 50% of patients with ER-negative breast cancer [4, 5], even the sole receptor in 25% of metastatic breast tumors [6]. Agrawal et al. [7] indicate that AR is the most frequently detected steroid receptor in breast cancer cells. Identifying the underlying mechanisms of AR is crucial in the design of appropriate therapies for estrogen-insensitive neoplasms. However, the role of AR in breast cancer etiology and progression has been less profoundly studied and remains as an unanswered question [8]. There have been variable results regarding the clinical significance of cells expressing AR in breast cancer. For example, androgen signaling plays a crucial role in breast homeostasis, negating the proliferative effects of estrogen signaling in the breast. In addition, androgens have been hypothesized to influence risk of breast cancer through several possible mechanisms, including their conversion to estradiol or their binding to the ER and/or AR in the breast. It is clear from both clinical and experimental settings that their

effects may be mediated, in part, by binding to the AR. Peters et al. [9] assessed AR status in a cohort of 215 invasive ductal breast carcinomas; they conclude that, by binding to a subset of estrogen-responsive element, the AR can prevent activation of target genes that mediate the stimulatory effects of 17β-estradiol on breast cancer cells. On the other hand, there is also scientific evidence that androgens can directly stimulate the growth of human breast cancer cell lines. Furthermore, a cell line model for the molecular apocrine subtype of breast cancer, MDA-MB-453, demonstrates a proliferative response to androgen in an ER-independent manner, which can be reversed by using the antiandrogen agent flutamide [10]. Hence, AR is central to the initiation and growth of breast cancer and to its response to hormone therapy.

In recent years, gene expression profiling has been used to classify the breast cancers into five major subtypes: luminal A, luminal B, HER-2 overexpressing, basal-like, and normal-like subtypes [11]. The five subtypes were identified on the basis of different gene expression, genomic alterations, as well as clinical characteristics and outcome. Subsequent studies have shown that breast carcinomas can also be divided into five similar subgroups using immunohistochemical analysis with a limited panel of molecular markers (e.g. ER, PR, HER-2, and basal cytokeratins (CK), such as CK5/6, CK14) [12]. These subgroups have distinguishing features closely associated with subtypes defined by gene expression profiling, including distinct clinical outcomes [13].

The aim of the present study was to detect the expression of AR by immunohistochemistry in breast cancer in Chinese women; to correlate AR expression with patient outcome, the degree of differentiation, ER, PR, and HER-2 status; and to evaluate its implications in five major subtypes of invasive ductal carcinoma (IDC) and in ductal carcinoma in situ (DCIS). This study may provide relevant diagnostic and prognostic information that complement clinical variables in order to propose the most adapted treatment.

materials and methods

patient characteristics

A total of 335 consecutive cases of invasive ductal breast carcinoma were collected in this study, with a mean age of 52.5 years, who underwent mastectomy at Tianjin Medical University Cancer Institute and Hospital from January 2004 to May 2004. Among these cases, 82 samples contained both IDC and DCIS components, which were also taken as DCIS adjacent to IDC group (median age 53.5 years) for comparative analysis. Thirty-four cases of pure DCIS (median age 56 years) with partial mastectomy were also involved in this study. All the patients had been treated according to modern guidelines, including the use of adjuvant chemotherapy for IDC, irradiation for lymph node metastasis, and endocrine therapy for ER-positive/PR-positive tumors. We retrospectively reviewed 66-month follow-up data. The follow-up contacts were carried out at 3-month intervals over the first year, 6-month intervals during the second year, and at 12-month intervals there after. The medical work-up consisted of regular physical checkups, imaging tests such as chest X-ray, bone scan and/or ultrasound, and to look for recurrences, second primary breast cancers, or metastatic disease. The study protocol was approved by the Hospital Human Ethical Committee. Informed consent was obtained from all patients before their surgery and the examination of the specimens.

immunohistochemical assay and evaluation of the staining

Formalin-fixed paraffin-embedded tissue sections (5 μm) were deparaffinized in xylene and rehydrated in a graded series of ethanol. The slides were treated with methanol containing 0.3% hydrogen peroxide to block any endogenous peroxidase activity. Heat-mediated antigen retrieval with the pressure cooker method was used for all staining. Specific antibodies were used for immunohistochemical studies on serial tissue sections from each case. Primary antibodies used in this study included ER (SP1, 1: 200 dilution; ZETA), PR (SP2, 1: 200 dilution; ZETA), HER2 (CB11, 1: 100 dilution; Invitrogen), AR (AR441, 1: 100 dilution; LabVision), CK5/6 (D5/16B4, 1: 200 dilution; Invitrogen) and CK14 (LL002, 1: 200 dilution; LabVision).

The immunostaining was scored by two pathologists, who were blinded to patients' clinicopathologic characteristics and outcomes. For each antibody, the location of immunoreactivity, percentage of stained cells, and intensity were determined. The evaluation of each protein expression was determined from the mean of the individual cases. AR, ER, and PR stains were assessed using Allred scores [14]. CK5/6 and CK14 stains were considered positive if any cytoplasmic and/or membranous staining was observed, whereas HER-2+ was defined as strong membrane staining in >30% of the tumor cells. The immunohistochemical subtyping of breast cancer was previously described [12, 15–18], which was best matched with the gene expression patterns. Briefly, the subtype definitions were as follows: luminal A (ER+ and/or PR+ and HER-2−), luminal B (ER+ and/or PR+ and HER-2+), HER-2 overexpressing (ER−, PR−, and HER-2+), basal-like (ER−, PR−, HER-2−, CK5/6+, and/or CK14+), and normal like (negative for all five markers).

We assessed the correlation of AR immunoreactivity with existing parameters, such as age, tumor size, nodes, histological grade, stage, ER, PR, HER-2 status, and clinical progression, and then evaluated the implications of AR in five major subtypes of IDC, in DCIS components adjacent to IDC and in pure DCIS lesions of the breast. Disease-free survival data were available in all patients.

statistical analyses

Statistical analysis was carried out using SPSS 13.0 statistical software. The correlation analyses between the immunophenotypes and the various clinicopathological and biological factors were examined by the χ^2 test, and P values <0.05 were considered significant. Disease-free survival curves were generated according to the Kaplan–Meier method. The differences between the curves were assessed using the log-rank test. Multivariate analysis was carried out with Cox regression analysis.

results

In this series of 335 patients with IDC, two died of acute cerebral accident and six lost to follow-up. Among 327 cases with follow-up data, a greater percentage (72.5%) of cases displayed nuclear immunoreactivity for AR, and AR expression was found in 53.2% (58/109) of ER− and PR− cases. Immunohistochemical staining of each protein marker in breast cancer tissues is illustrated in Figure 1. AR expression was related to that of ER ($P < 0.001$) and PR ($P = 0.035$) but showed no relation to other parameters, such as age, tumor size, nodes, histological grade, stage, and HER-2 status in this surgically treated cohort (Table 1).

With a follow-up period of 66 months for the 327 invasive ductal breast cancer patients analyzed in this study, the disease-free survival was 78.0% (255/327), while the other 22% (72/327) patients were died or survived with local relapse or distant

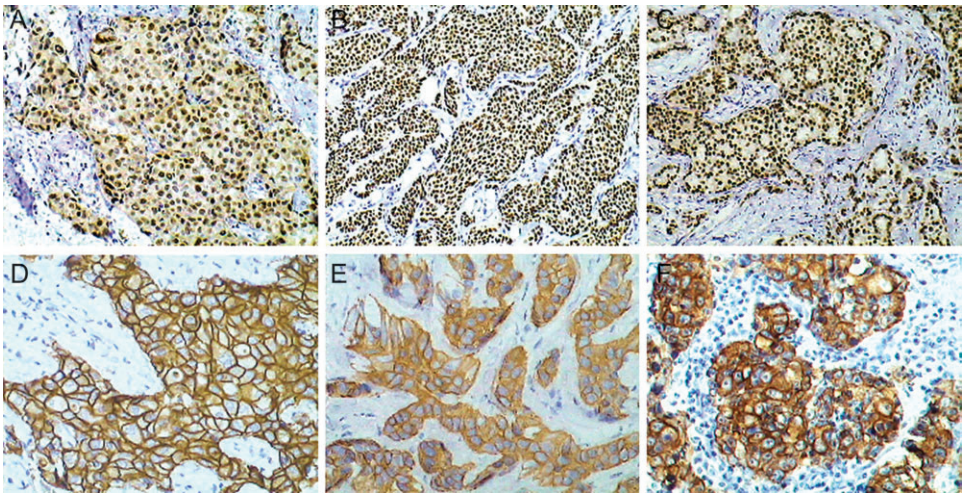

Figure 1. Immunohistochemical staining of each protein in breast cancer tissues. (A) Immunohistochemical staining of androgen receptor revealed nuclear staining in IDC, original magnification ×100. (B) Immunohistochemical staining of ER revealed nuclear staining in IDC, original magnification ×100. (C) Immunohistochemical staining of PR revealed nuclear staining in IDC, original magnification ×100. (D) The tumor showed strong membrane staining of HER-2, original magnification ×200. (E) Diffuse cytoplasmic and membrane staining of CK5/6, original magnification ×200. (F) Diffuse cytoplasmic staining of CK14, original magnification ×200.

metastasis. The log-rank test was used to evaluate the association between AR expression and survival. The survival curve is presented in Figure 2 and shows a median disease-free survival of 52.056 months [95% confidence interval (CI), 47.946–56.165 months] in the AR-negative group and 59.954 months (95% CI, 58.005–61.902 months) in the AR-positive group. There was a significant association of AR expression with cancer-specific survival ($P < 0.001$). Patients with AR expression had a more favorable disease-free survival than those without expression. The multivariate model using the Cox regression test is shown in Table 2. AR retained independent prognostic significance [(HR) 0.309, 95% CI, 0.192–0.496; $P < 0.001$] along with CerB2 status (HR 1.655, 95% CI, 1.011–2.708; $P = 0.045$) and stage (HR 5.695, 95% CI, 3.634–8.925; $P < 0.001$). The significant influence on disease-free survival for age, tumor size, lymphonode, histological grade, ER, and PR status was not confirmed in multivariate analysis.

Among 327 invasive cancers, 52.9% were luminal A, 13.8% luminal B, 13.1% HER-2 overexpressing, 12.5% basal-like, and 7.6% normal-like subtype. AR expression was more common in luminal A (83.8%). Also, 75.6% of luminal B, 55.8% of HER-2 overexpressing, and 72.0% of normal-like cancers showed expression of AR. However, we found that the basal-like subgroup showed lack of AR expression in 25 of 41 cases (61.0%), whereas only 16 of 41 (39.0%) were positive (Table 3). In 66-month interval, occurrence rate of relapse, distant metastasis or death was 44.0% (11/25) for those AR-negative tumors of the basal-like subgroup: three (12.0%) with disease-related death, one (4.0%) local relapse, and seven (28.0%) developing distant metastasis, whereas patients with tumors positive for AR had significantly lower risk of relapse [2 of 16 (12.5%)] in this basal-like subgroup (Table 4). The expression of AR was significantly associated with improved survival. Figure 3 shows the disease-free survival curve of 41 patients with basal-like breast cancer ($P = 0.036$). AR was also significantly associated with improved survival in luminal A, luminal B, and normal-like subgroups ($P = 0.006$, $P = 0.013$, and $P = 0.010$, respectively) (data not shown). Their occurrence rate of relapse distant metastasis, or death of the three subgroups for those AR-negative and AR-positive tumors was 32.1% versus 12.4%, 54.5% versus 17.6%, and 57.1% versus 11.1% ($P = 0.019$, 0.044, and 0.032, respectively). While for the HER-2 overexpressing subgroup of breast cancer, the occurrence rate was 26.3% versus 37.5% ($P = 0.437$), and no significant difference was found between AR expression and the disease-free survival in survival analysis ($P = 0.382$).

For those in situ components adjacent to invasive carcinomas, 77 of 82 (93.9%) samples were positive for AR. Whereas in pure DCIS, 27 of 34 (79.4%) cases were AR positive (Figure 4). The percentage of AR-positive cases was significantly higher in DCIS adjacent to invasive carcinoma group than in pure DCIS group ($P = 0.046$). Similar significance was observed between DCIS adjacent to invasive carcinomas and IDC lesions (93.9% versus 72.5%, $P < 0.001$). This is demonstrated in Table 5.

discussion

AR is a member of the steroid hormone receptor family of ligand-activated nuclear transcription factors, which share a common structure with other receptors, such as the estrogen, progesterone, glucocorticoid, retinoid, mineralocorticoid and thyroid hormone receptors [19]. The AR binds to androgen response elements located in the promoter and enhancer regions of target genes, resulting in concomitant recruitment of co-regulatory proteins and formation of an active transcription complex. The fact that sex steroid hormones and their receptors act in concert has led investigators to study the expression of AR and evaluate the role of AR signaling in patients with breast cancer.

Our data clearly showed that AR expression was a common feature of invasive and noninvasive breast carcinoma in

Table 1. Relationship between AR expression and Clinicopathological and biological characteristics of invasive ductal breast cancer

Clinicopathological and biological characteristics	Total cases	AR positive		*P* value
		Cases	%	
Age (years)				
<35	5	5	100.0	0.275
≥35 to <49	169	125	74.0	
≥50	153	107	69.9	
Tumor				
T1	80	63	78.8	0.311
T2	216	151	69.9	
T3 + T4	31	23	74.2	
Lymphonode				
N0	151	106	70.2	0.626
N1	126	95	75.4	
N2 + N3	50	36	72.0	
Stage				
I	59	48	81.4	0.137
II	206	142	68.9	
III	62	47	75.8	
Histological grade				
G-1	50	37	74.0	0.371
G-2	220	163	74.1	
G-3	57	37	64.9	
ER				
Negative	157	86	54.8	<0.001
Positive	170	151	88.8	
PR				
Negative	180	122	67.8	0.035
Positive	147	115	78.2	
HER-2				
Negative	239	179	74.9	0.107
Positive	88	58	65.9	

AR, androgen receptor.

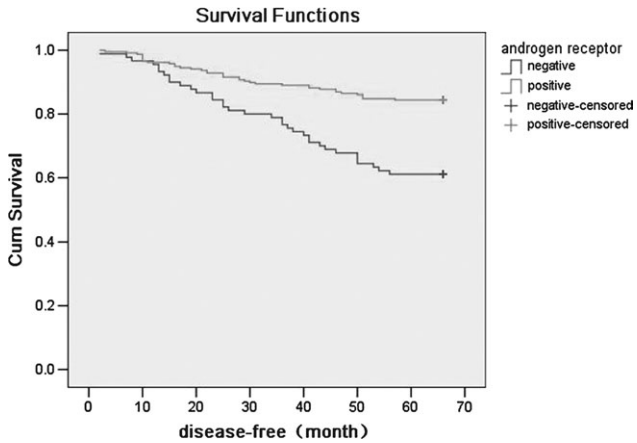

Figure 2. Disease-free survival curve of 327 patients with IDC of the breast ($P < 0.001$).

a Chinese women population. Among 327 interpretable cases with invasive ductal breast carcinoma, 72.5% were positive for AR expression. And AR was also found in 53.2% of ER− and PR− breast cancers; these tumors were conventionally classified as receptor 'negative' based on estrogen and PR measurements, still contained notable amounts of AR. Accordingly, the androgen-signaling pathway may play a critical role in breast carcinogenesis. This study further indicated that AR was related to ER and PR expression in IDCs. The parameters, such as age, tumor size, nodes, histological grade, stage, and HER-2 expression, are significantly conventional prognostic factors. In contrast, AR expression did not correlate with these parameters. Moreover, the presented data showed that patients whose tumors contained AR expression had a somewhat more favorable prognosis than those whose tumors did not expressed. A multivariate analysis was also carried out and indicated AR as an independent prognostic marker. These revealed the inhibitory effect of AR on breast tumor growth.

Triple-negative breast cancer has recently been recognized as an important subgroup of breast cancer with a high risk and the aggressive clinical behavior. Relying on the three-biomarker classifier (ER, PR, and HER-2) to define breast tumors loses significant information to predict their outcome compared

Table 2. Cox regression analysis for predictors of breast cancer disease-free survival in 327 patients

Variables	*P* value	Hazard ratio	95% CI	
			Lower	Upper
CerB2	0.045	1.655	1.011	2.708
AR	<0.001	0.309	0.192	0.496
Stage	<0.001	5.695	3.634	8.925

AR, androgen receptor; CI, confidence interval.

Table 3. Expression of AR in five molecular subgroups of IDC of the breast

Subgroups	Total cases	AR positive	
		Cases	%
Luminal A	173	145	83.8
Luminal B	45	34	75.6
HER-2 overexpressing	43	24	55.8
Basal like	41	16	39.0
Normal like	25	18	72.0
Total	327	237	72.5

Using the χ^2 test, $P < 0.001$. AR, androgen receptor.

Table 4. AR expression in each prognostic subcategory of basal-like breast cancers

Prognostic subcategories	AR negative ($N = 25$)		AR positive ($N = 16$)	
	Cases	%	Cases	%
Relapse	1	4.0	1	6.25
Distant metastasis	7	28.0	1	6.25
Death	3	12.0	0	0
Total	11	44.0	2	12.5

AR, androgen receptor.

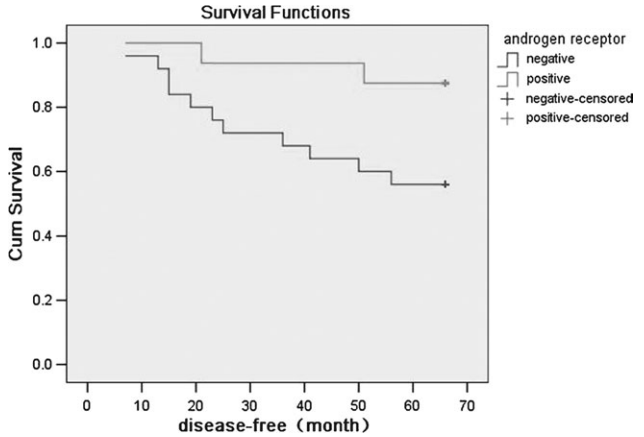

Figure 3. Disease-free survival curve of 41 patients with basal-like breast cancer ($P = 0.036$).

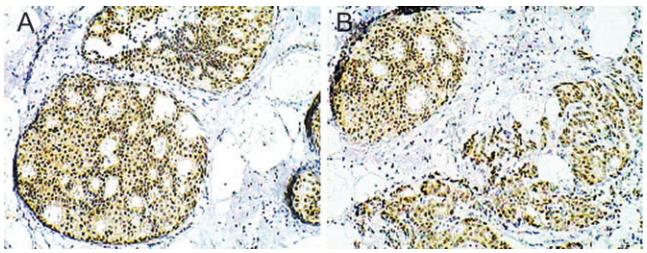

Figure 4. Immunohistochemical staining of androgen receptor (AR) in ductal carcinoma *in situ* (DCIS) of the breast. (A) Immunohistochemical staining of AR in pure DCIS. (B) Immunohistochemical staining of AR in DCIS components adjacent to IDC, original magnification ×100.

Table 5. AR expression in DCIS components adjacent to IDC, in pure DCIS and IDC lesions of the breast

Groups	Total cases	AR positive	
		Cases	%
DCIS adjacent to IDC	82	77	93.9
Pure DCIS	34	27	79.4
IDC	327	237	72.5

Using the χ^2 test, statistically significant differences: DCIS adjacent to IDC group versus pure DCIS group, $P = 0.046$; DCIS adjacent to IDC group versus IDC group, $P < 0.001$. AR, androgen receptor.

with the five-marker panel whose outcome more closely matches that expected by gene expression profiling [20–22]. Previous DNA microarray and immunohistochemical analyses have shown that most triple-negative tumors possess a basal phenotype and have a clinical behavior similar to basal-like behavior [23], which are characterized by the absence of ER, PR, and HER2 expression, together with expression of the basal markers, and generally do not respond to ER-targeted treatments. In recent years, scientists have begun looking for new targets in these 'triple-negative' cancers. One that has been identified is the AR.

We determined the expression rates of AR in five molecular classifications and evaluated its importance in these subgroups, especially in basal-like cancer. As shown in Table 2, in fact, in luminal A cancers, 145 of 173 (83.8%) cases were positive for AR, also 34 of 45 (75.6%) in luminal B, 24 of 43 (55.8%) in HER-2 overexpressing, and 18 of 25 (72.0%) in normal-like subgroup demonstrated positive for AR, whereas in basal-like cancers, 61.0% showed loss of AR expression ($P < 0.001$), which potentially explained the poor prognosis of this group. Although so called the 'same' triple-negative phenotype, the basal-like tumors, with the presence of CK5+ and/or CK14+, showed less frequent AR expression than normal-like subgroup. Furthermore, as shown in Table 4, a trend to a higher risk of relapse among the basal-like patients was observed, which led us to consider that lack of AR expression was significantly correlated with a more advanced disease. Our data revealed that patients whose tumors were positive for CK5/6 and/or CK14+ but loss of AR had a high probability of disease recurrence: among 11 of 25 (44.0%) patients, three (12.0%) died of disease, one (4.0%) was with relapse, and seven (28.0%) developed distant metastasis, whereas patients with tumors positive for AR had significantly lower risk of relapse [2 of 16 (12.5%)] in this basal-like subgroup. Also, Figure 3 demonstrated this tendency. A joint association might exist between AR and CK5/6 or CK14 expression. Further data are needed in order to clarify their biological signification and correlation between CK5/6, CK14, and AR in breast cancer.

Similarly, the AR was significantly associated with improved survival in luminal A, luminal B, and normal-like subgroups. The occurrence rate of relapse, distant metastasis or death of these three subgroups for those AR-negative and AR-positive tumors was 32.1% versus 12.4%, 54.5% versus 17.6%, and 57.1% versus 11.1%, respectively. While for the HER-2 overexpressing subgroup, the occurrence rate was 26.3% versus 37.5%. These data suggest that AR may also be a predictive factor in luminal A, luminal B, and normal-like subgroups. Interestingly, in HER-2 expressing subgroup, the recurrence rate of AR-negative tumors was slightly lower than that of AR-positive tumors, and no significant difference was found between the AR expression and the disease-free survival in survival analysis. Future studies are needed to examine the molecular mechanism underlying these findings. Our results provide an evidence that AR has prognostic and predictive value in these molecular subtypes. By adding AR as a positive marker, better outcome group can be identified. Thus, AR may provide another specific definition of breast cancer subtypes that better predicts patient survival.

Here, our data showed that there were significantly higher percentage of cases with AR expression in DCIS components adjacent to invasive carcinomas than in pure DCIS and IDC lesions of the breast, suggesting that AR might correlate with tumor transformation of DCIS to IDC, probably in the early phases of tumor progression. However, this mechanism seems to be complex. Shibuya et al. [24] indicated that intratumoral concentrations of 5a-dihydrotestosterone as well as estradiol were increased in DCIS, and androgen-producing enzymes, 5a-reductase type 1 (5aRed1), were abundantly expressed. They also showed that 5aRed1 immunoreactivity was significantly associated with Ki-67 labeling index, which is closely correlated with the S-phase fraction and mitotic index. Gonzalez et al. [2] found that AR-positive tumors had a higher percentage of cases positive for matrix metalloproteinase (MMP)-1, -7, -11, and

tissue inhibitor of metalloproteinase-2 in their malignant cells, when compared with AR-negative tumors. Further, there has been sufficient evidence from model systems to suggest that MMPs are apparently involved in both breast tumor initiation and dissemination [25]. It is interesting that the MMPs expression patterns display variability in different cellular type, tumor grade, and different stage [25, 26]. These suggest that AR may be able to regulate MMPs and contribute to an invasive potential of breast cancer cells. Additionally, Boddy et al. [27] found that the presence of AR was also significantly related with hypoxia-inducible factors (HIF), such as HIF-1a and HIF-2a, and with the key angiogenesis factor, vascular endothelial growth factor expression. It has been proved that upregulation of HIF-1a is an early event in human carcinogenesis [28]. Likewise, in breast DCIS lesions, a high level of HIF-1 was statistically significantly associated with increased microvessel density and potentially associated with more aggressive tumors [29]. These findings all suggest the importance of AR in the invasive transformation and increased proliferation of breast cancer. González et al. [30] also indicated that AR expression might represent an independent predictive factor in DCIS of the breast. Thus, complexity of androgens and AR in carcinogenesisis was compounded by the observation of specific inhibitory actions and growth stimulatory. To our knowledge, one possible explanation for the understanding of the complexity was that the tumor type, stage, and other growth factors might influence the activity of androgens and AR in either a proliferative or inhibitory direction. Also, in this current study, we found that rate of AR expression in IDC was lower than that in DCIS adjacent to IDC group. This may imply that cell divisions are most active in the evolution of DCIS into IDC and subsequently fall when cancer cells invade into the stroma. Next, some factors other than AR involved in the progression may play critical role.

Our findings are leading to a new understanding of the pathogenesis of breast cancer and to the generation of new targets for diagnosis, prognosis, and prediction of therapeutic response. Koo et al. [31] analyzed AR immunohistochemical staining on chemotherapy response in 47 cases of triple-negative breast cancer. The results showed that cases with AR expression had higher cell death rates than those without in 5-fluorouracil and methotrexate chemotherapy. Toth-Fejel group's findings showed that in ER−, AR+ breast cancer cells, dehydroepiandrosterone sulfate substantially inhibited growth by 22% via the AR [32]. Therapeutic comediation of receptors may provide effective treatment of ER− and AR+ breast cancers. In an ongoing study [33], it is already apparent that AR inhibition with bicalutamide (an antiandrogen agent) can stabilize disease in ER−, and PR− breast cancer if AR+. It was supported that the AR might be taken as a therapeutic target for these patients. Our results also imply that there will be higher rate of normal-like and relatively lower rate of basal-like patients may become potential candidates to respond well to AR-targeted therapy.

Since AR expression has important consequences on the prognosis and treatment of breast cancer, its presence should be precisely determined. Although we are still in the very early phase of clinical development, further studies of more cases and long-term prognostic valuation of different AR assays in patients comprising operable breast cancers should be carried out. The development of new strategies and drugs that can suppress or activate AR signaling will probably result in important clinical benefits.

funding

Scientific and Technological Development Fund (09JCYBJC 10100) of Tianjin Scientific and Technological Committee; National Natural Science Foundation of China (30872519); Program for Changjing Scholars and Innovative Research Team in University (TRT0743).

disclosure

The authors declare no conflicts of interest.

references

1. Shidham VB, Komorowski RA, Machhi JK. Androgen receptor expression in metastatic adenocarcinoma in females favors a breast primary. Diagn Pathol 2006; 1: 34.
2. Gonzalez LO, Corte MD, Vazquez J et al. Androgen receptor expression in breast cancer: relationship with clinicopathological characteristics of the tumors, prognosis, and expression of metalloproteases and their inhibitors. BMC Cancer 2008; 8: 149.
3. Riva C, Dainese E, Caprara G et al. Immunohistochemical study of androgen receptors in breast carcinoma. Evidence of their frequent expression in lobular carcinoma. Virchows Arch 2005; 447: 695–700.
4. Nahleh Z. Androgen receptor as a target for the treatment of hormone receptor-negative breast cancer: an unchartered territory. Future Oncol 2008; 4: 15–21.
5. Agoff SN, Swanson PE, Linden H et al. Androgen receptor expression in estrogen receptor-negative breast cancer. Immunohistochemical, clinical, and prognostic associations. Am J Clin Pathol 2003; 120: 725–731.
6. Lea OA, Kvinnsland S, Thorsen T. Improved measurement of androgen receptors in human breast cancer. Cancer Res 1989; 49: 7162–7167.
7. Agrawal AK, Jeleń M, Grzebieniak Z et al. Androgen receptors as a prognostic and predictive factor in breast cancer. Folia Histochem Cytobiol 2008; 46: 269–276.
8. Nicolas Diaz-Chico B, German Rodriguez F, Gonzalez A et al. Androgens and androgen receptors in breast cancer. J Steroid Biochem Mol Biol 2007; 105: 1–15.
9. Peters AA, Buchanan G, Ricciardelli C et al. Androgen receptor inhibits estrogen receptor-alpha activity and is prognostic in breast cancer. Cancer Res 2009; 69: 6131–6140.
10. Doane AS, Danso M, Lal P et al. An estrogen receptor-negative breast cancer subset characterized by a hormonally regulated transcriptional program and response to androgen. Oncogene 2006; 25: 3994–4008.
11. Sørlie T, Tibshirani R, Parker J et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003; 100: 8418–8423.
12. Rakha EA, El-Rehim DA, Paish C et al. Basal phenotype identifies a poor prognostic subgroup of breast cancer of clinical importance. Eur J Cancer 2006; 42: 3149–3156.
13. Tang P, Skinner KA, Hicks DG. Molecular classification of breast carcinomas by immunohistochemical analysis: are we ready? Diagn Mol Pathol 2009; 18: 125–132.
14. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol 1999; 17: 1474–1481.
15. Nielsen TO, Hsu FD, Jensen K et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 2004; 10: 5367–5374.

16. Rakha EA, El-Sayed ME, Green AR et al. Prognostic markers in triple-negative breast cancer. Cancer 2007; 109: 25–32.
17. Carey LA, Perou CM, Livasy CA et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006; 295: 2492–2502.
18. Kuroda H, Ishida F, Nakai M et al. Basal cytokeratin expression in relation to biological factors in breast cancer. Hum Pathol 2008; 39: 1744–1750.
19. Evans R. The steroid and thyroid hormone receptor super family. Science 1988; 240: 889–895.
20. Perou CM, Sørlie T, Eisen MB et al. Molecular portraits of human breast tumours. Nature 2000; 406: 747–752.
21. Sorlie T, Wang Y, Xiao C et al. Distinct molecular mechanisms underlying clinically relevant subtypes of breast cancer: gene expression analyses across three different platforms. BMC Genomics 2006; 7: 127.
22. Cheang MC, Voduc D, Bajdik C et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 2008; 14: 1368–1376.
23. Bidard FC, Conforti R, Boulet T et al. Does triple-negative phenotype accurately identify basal-like tumour? An immunohistochemical analysis based on 143 'triple-negative' breast cancers. Ann Oncol 2007; 18: 1285–1286.
24. Shibuya R, Suzuki T, Miki Y et al. Intratumoral concentration of sex steroids and expression of sex steroid-producing enzymes in ductal carcinoma in situ of human breast. Endocr Relat Cancer 2008; 15: 113–124.
25. Duffy MJ, Maguire TM, Hill A et al. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast Cancer Res 2000; 2: 252–257.
26. Köhrmann A, Kammerer U, Kapp M et al. Expression of matrix metalloproteinases (MMPs) in primary human breast cancer and breast cancer cell lines: new findings and review of the literature. BMC Cancer 2009; 9: 188.
27. Boddy JL, Fox SB, Han C et al. The androgen receptor is significantly associated with vascular endothelial growth factor and hypoxia sensing via hypoxia-inducible factors HIF-1a, HIF-2a, and the prolyl hydroxylases in human prostate cancer. Clin Cancer Res 2005; 11: 7658–7663.
28. Zhong H, Semenza GL, Simons JW et al. Up-regulation of hypoxia-inducible factor 1alpha is an early event in prostate carcinogenesis. Cancer Detect Prev 2004; 28: 88–93.
29. Bos R, Zhong H, Hanrahan CF et al. Levels of hypoxia-inducible factor-1 alpha during breast carcinogenesis. J Natl Cancer Inst 2001; 93: 309–314.
30. Gonzalez LO, Corte MD, Junquera S et al. Expression of androgen receptor and two androgen-induced proteins (apolipoprotein D and pepsinogen C) in ductal carcinoma in situ of the breast. Histopathology 2007; 50: 866–874.
31. Koo JS, Jung W, Jeong J. The Predictive Role of E-cadherin and androgen receptor on in vitro chemosensitivity in triple-negative breast cancer. Jpn J Clin Oncol 2009; 39: 560–568.
32. Toth-Fejel S, Cheek J, Calhoun K et al. Estrogen and androgen receptors as comediators of breast cancer cell proliferation: providing a new therapeutic tool. Arch Surg 2004; 139: 50–54.
33. Traina TA, Wolff AC, Giri D et al. Androgen receptor inhibition for the treatment of AR+/ER-/PR- metastatic breast cancer. Breast Cancer Symposium, San Francisco, CA, October 8–10, 2009 (Abstr 251).