

Expression of androgen receptors in primary breast cancer

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Received 16 September 2009; accepted 29 September 2009

Background: To investigate the clinicopathological significance of androgen receptor (AR) expression in primary breast cancers.

Patients and methods: We evaluated AR using immunohistochemistry from 413 whole sections from January 2008 to March 2009 and analyzed the relationship between AR and clinicopathological parameters. Tumors with $\geq 10\%$ nuclear-stained cells were considered to be positive for AR. The differences among variables were calculated by chi-square test.

Results: The expression rate of AR was 72.9% higher than those of estrogen receptors (ER) and progesterone receptors. AR expression was significant in patients with no elevated preoperative serum cancer antigen 15-3 levels, smaller tumor size, lower histologic grade and hormone receptor-positive and non-triple-negative breast cancer. However, AR expression was observed in 35% of triple-negative cancers. Metaplastic, medullary and mucinous types of carcinomas showed less AR expression. In the ER-negative subgroup, AR was significantly correlated with human epidermal growth factor receptor type 2 (HER-2) overexpression.

Conclusions: AR is expressed in a significant number of breast cancers and is associated with lower tumor burden and favorable differentiation. There are many issues to be further investigated such as whether AR is an independent prognostic factor, whether it is a therapeutic target for the triple-negative breast cancers and whether it is associated with HER-2 signaling in ER-negative tumors.

Key words: androgen receptor, breast cancer, estrogen receptor negative, HER-2 signal pathway

introduction

The development and progression of breast cancers are highly dependent on the action of steroid hormones including estradiol. Therefore, evaluation of estrogen receptor (ER) and progesterone receptor (PgR) expression in breast cancer patients is important in order to assess the biology of the tumor, predict outcomes and select management strategies such as hormonal therapy [1, 2].

In recent years, improvement in the understanding of the molecular biology of cancer has led to the identification of new molecular targets and the development of targeted therapies, for example, human epidermal growth factor receptor type 2 (HER-2) and trastuzumab [3, 4]. Trastuzumab has proven beneficial in breast cancer patients with overexpressed HER-2 in the metastatic or adjuvant setting in randomized clinical trials [5]. Various classes of targeted anticancer agents that block the cellular signaling pathways are still in the early phase of clinical trials, but the USA Food and Drug Administration

has approved some agents such as lapatinib and bevacizumab. As a result, the number of novel targeted therapies is expected to increase [6].

Traditional histopathologic factors including tumor size, axillary lymph node metastasis and histologic grade, as well as new biomarkers including steroid hormone receptors and HER-2 are valuable as predictive and prognostic factors in breast cancer [7–9]. However, breast cancers have heterogeneous features. It is difficult to predict outcomes in all breast cancer patients using traditional histopathologic factors and the same biomarkers. The validation of new emerging biomarkers is required to determine whether they are significantly beneficial for making a prognosis and guiding management algorithms [1].

The androgen receptor (AR) is one such newly emerging biomarker [10]. Many breast cancers express AR. Since AR belongs to the nuclear steroid hormone receptor family, it shows high structural, functional and topographic similarity to ER and PgR [8, 11, 12]. However, AR has not been well characterized in terms of its role as a predictive or a prognostic factor and the clinical significance of its expression in breast cancer patients remains unknown.

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Table 1. Relationships between AR expression and clinicopathological factors

Factors	AR positive (%, n = 301)	AR negative (%, n = 112)	P value
Age (years)			0.096
≤35	12 (4.0)	9 (8.0)	
>35	289 (96.0)	103 (92.0)	
Body mass index			0.335
<25	244 (81.1)	86 (76.8)	
≥25	57 (18.9)	26 (23.2)	
Menopause status			0.970
Premenopausal	178 (59.1)	66 (58.9)	
Postmenopausal	123 (40.9)	46 (41.1)	
Preoperative CEA (ng/ml)			0.480
≤3.88	285 (94.7)	104 (92.9)	
>3.88	16 (5.3)	8 (7.1)	
Preoperative CA 15-3 (U/ml)			0.042
≤20.11	291 (96.7)	103 (92.0)	
>20.11	10 (3.3)	9 (8.0)	
Histologic type			0.030
Ductal	266 (88.4)	95 (84.8)	
Lobular	15 (5.0)	3 (2.7)	
Mucinous	5 (1.7)	7 (6.3)	
Medullary	1 (0.3)	3 (2.7)	
Tubular	3 (1.0)	0 (0)	
Papillary	9 (3.0)	2 (1.8)	
Others ^a	2 (0.7)	2 (1.8)	
T stage			0.035
Tis	48 (15.9)	18 (16.1)	
T1	187 (62.1)	56 (50.0)	
T2–3	66 (21.9)	38 (33.9)	
N stage			0.626
N0	229 (76.1)	80 (71.4)	
N1	56 (18.6)	27 (24.1)	
N2	11 (3.7)	3 (2.7)	
N3	5 (1.7)	2 (1.8)	
TNM stage			0.137
Stage 0	47 (15.6)	18 (16.1)	
Stage 1	148 (49.2)	42 (37.5)	
Stage 2	90 (29.9)	46 (41.1)	
Stage 3	16 (5.3)	6 (5.4)	
Histologic grade (n = 382)			<0.001
<i>In situ</i> carcinoma			
Nonhigh grade	22 (7.9)	6 (5.8)	
High grade	21 (7.5)	12 (11.7)	
Invasive carcinoma			
G1	74 (26.5)	13 (12.6)	
G2	117 (41.9)	39 (37.9)	
G3	45 (16.1)	33 (32.0)	

^aOther types were two apocrine and two metaplastic carcinomas. All apocrine carcinomas expressed AR and all metaplastic carcinomas did not.

AR, androgen receptor; CEA, carcinoembryonic antigen; CA 15-3, cancer antigen 15-3; TNM, tumor–node–metastasis.

The aim of this study was to investigate the relationship between AR expression and clinicopathological factors in primary breast cancer patients.

Table 2. Results of immunohistochemistry according to AR expression

Factor	AR positive (%, n = 301)	AR negative (%, n = 112)	P value
ER			<0.001
Negative	65 (21.6)	65 (58.0)	
Positive	236 (78.4)	47 (42.0)	
PgR			<0.001
Negative	91 (30.2)	66 (58.9)	
Positive	210 (69.8)	46 (41.1)	
HER-2			0.052
Negative	235 (78.1)	97 (86.6)	
Positive	66 (21.9)	15 (13.4)	
Triple negative ^a			<0.001
Non-triple negative	279 (92.7)	71 (63.4)	
Triple negative	22 (7.3)	41 (36.6)	
Ki-67 (n = 406)			0.806
Negative	109 (39.1)	43 (38.4)	
Positive	185 (62.9)	69 (61.6)	

^aTriple negative represents tumors that are negative for ER, PgR and HER-2 by immunohistochemical staining.

AR, androgen receptor; ER, estrogen receptor; PgR, progesterone receptor; HER-2, human epidermal growth factor receptor type 2.

patients and methods

We reviewed the data of 652 breast cancer patients who were treated at the Department of Surgery, Yonsei University College of Medicine in Seoul, Korea, from January 2008 to March 2009. Among them, 457 cases (70.1%) were consecutively evaluated for AR expression. We excluded 44 patients who had received neoadjuvant chemotherapy and were diagnosed with recurrent breast cancers at the time of operation. A total of 413 cases (63.3%), including four synchronous bilateral breast cancers, were analyzed. The mean age at diagnosis for the study cohort (n = 413) was 50.3 ± 10.1 years, which was not very different from 50.0 ± 10.2 years for the patients overall (N = 652). Data regarding patient demographics and histopathology of primary tumor were obtained by reviewing medical records. Postmenopausal status was defined as prior bilateral oophorectomy or serum follicle stimulating hormone levels >30 mIU/ml. Cut-off values of the preoperative serum tumor marker carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA 15-3) were determined to be 3.88 ng/ml and 20.11 U/ml, respectively, which are both within the 95th percentile of healthy individuals [13]. Tumor stage was on the basis of criteria of the Sixth American Joint Committee on Cancer. Histologic type and grading followed the World Health Organization classification.

We evaluated AR, ER, PgR, HER-2 and Ki-67 expression in primary breast cancer from formalin-fixed, paraffin-embedded whole sections of surgically resected breast cancer specimens using immunohistochemistry (IHC). Primary antibodies for AR (clone AR441; Dako, Glostrup, Denmark), ER (clone SP1; NeoMarkers for Lab Vision, Fremont, CA), PgR (clone PgR 636; Dako), HER-2 (polyclonal; Dako) and Ki-67 (clone MIB-1; Dako) were used. Briefly, 4 μm-thick sections of formalin-fixed, paraffin-embedded tissues were deparaffinized and rehydrated. After treatment with 3% hydrogen peroxide solution for 10 min to block endogenous peroxidases, the sections were pretreated in 10 mM citrate buffer (pH 6.0) for antigen retrieval in a microwave oven for 20 min. The aforementioned primary antibodies were incubated, and then, the sections were processed with EnVision™ Detection Systems (Dako) according to the manufacturer's instructions and 3, 3'-diaminobenzidine tetrahydrochloride was used as a chromogen. The sections were counterstained with hematoxylin. These

Table 3. Comparison of AR expression with HER-2 overexpression stratified by ER status

	ER-positive tumors (<i>n</i> = 283)			ER-negative tumors (<i>n</i> = 130)		
	AR positive (%, <i>n</i> = 236)	AR negative (%, <i>n</i> = 47)	<i>P</i> value	AR positive (%, <i>n</i> = 65)	AR negative (%, <i>n</i> = 65)	<i>P</i> value
HER-2			0.279			<0.001
Negative	202 (85.6)	43 (91.5)		33 (50.8)	54 (83.1)	
Positive	34 (14.4)	4 (8.5)		32 (49.2)	11 (16.9)	

AR, androgen receptor; ER, estrogen receptor; HER-2, human epidermal growth factor receptor type-2.

Table 4. Comparison of AR expression with HER-2 overexpression by ER status according to the guidelines for HercepTest™

	ER-positive tumors (<i>n</i> = 240)			ER-negative tumors (<i>n</i> = 118)		
	AR positive (%, <i>n</i> = 201)	AR negative (%, <i>n</i> = 39)	<i>P</i> value	AR positive (%, <i>n</i> = 59)	AR negative (%, <i>n</i> = 59)	<i>P</i> value
HER-2			0.297			<0.001
Negative	167 (83.1)	35 (89.7)		27 (45.8)	48 (81.4)	
Positive	34 (16.9)	4 (10.3)		32 (54.2)	11 (18.6)	

AR, androgen receptor; ER, estrogen receptor; HER-2, human epidermal growth factor receptor type 2.

IHC methods are routinely carried out in the Department of Pathology at our institution.

Tumors with $\geq 10\%$ nuclear-stained cells were considered positive for AR, ER, PgR and Ki-67 expression. HER-2 immunohistochemical staining was scored from 0 to 3+ according to the guideline indicated for HercepTest™ (Dako) [14]. HER-2 IHC was considered positive when strong (3+) membranous staining was observed, whereas cases with 0 to 2+ were regarded as negative. However, FISH test using the PathVysion HER-2 DNA Probe Kit (Abbott, IL) was carried out according to the manufacturer's protocols in 30 cases with equivocal (2+) staining, and three cases with HER-2 gene-to-chromosome 17 ratio >2.2 were designated as HER-2 overexpression. Triple-negative breast cancer was defined by lack of expression of ER, PgR and HER-2 by IHC.

The differences between the discrete variables were evaluated by chi-square test. Fisher's exact test was used when appropriate. For the comparison of the means in the case of continuous numerical data, the independent samples *t*-test was used. A *P* value <0.05 was considered statistically significant. SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL) was used for all statistical analyses.

results

The median age at diagnosis for the study cohort was 49 years (range 26–84 years). AR was found in 72.7% (48 of 66) of cases of *in situ* carcinoma and in 72.9% (253 of 347) of invasive carcinoma. Overall, 72.9% of breast cancers expressed AR. The positive rates for ER, PgR, HER-2 and Ki-67 were 68.5%, 62.0%, 19.6% and 61.5%, respectively.

The relationship between AR expression and clinicopathological factors is summarized in Table 1. AR-negative tumors showed higher rates of elevated preoperative serum CA 15-3 levels with statistical significance ($P = 0.042$). Most types of tumor frequently express AR. However, in some types of tumor such as metaplastic, medullary and mucinous carcinoma, the negative rates of AR are high ($P = 0.030$). AR was significantly expressed in patients with smaller tumor size ($P = 0.035$) and lower histologic grade ($P < 0.001$). There were

no statistically significant differences between AR expression and age at diagnosis, body mass index, menopausal status, preoperative serum CEA levels, lymph node involvements and tumor–node–metastasis stage.

The results of IHC for AR expression are shown in Table 2. AR was significantly expressed in ER-positive ($P < 0.001$), PgR-positive ($P < 0.001$) and non-triple-negative breast cancers ($P < 0.001$). However, AR expression was observed in 50% (65 of 130) of ER-negative and in 35% (22 of 63) of triple-negative cancers. There were no statistically significant differences between AR expression and HER-2 or Ki-67 positivity.

Breast cancers represent heterogeneous features in terms of ER status, and we evaluated the association of AR expression with HER-2 overexpression by ER status (Table 3). In ER-negative tumors, AR expression was significantly correlated with HER-2 overexpression ($P < 0.001$). In ER-positive tumors, however, there was no relationship between AR expression and HER-2 overexpression ($P > 0.05$). In our study, HER-2 overexpression was defined as all cases with 3+ staining by IHC and three cases with 2+ staining by IHC and subsequent FISH test of HER-2 gene amplification. On the basis of these definitions, patients ($n = 55$) who showed 2+ staining by IHC but did not have a subsequent FISH test were considered non-negative for HER-2 overexpression. For strict subgroup analysis by ER status, we excluded those patients who did not satisfy the guidelines indicated for HercepTest™ [14]. In that analysis, AR expression was also significantly correlated with HER-2 overexpression in ER-negative tumors ($P < 0.001$) but not in ER-positive tumors ($P = 0.297$) (Table 4).

discussion

Despite public education for cancer prevention, increased proportions of early diagnosis and advanced management of cancer, ~200 000 women will develop breast cancer and >40 000 women will die of breast cancer in the United States

this year [15]. A number of known and unknown mechanisms may play critical roles in the breast carcinogenesis, progression and metastasis, which may be related to breast cancer outcomes. Although some biomarkers including ER and HER-2 are well known predictive or prognostic factors in breast cancer, it is important to identify and validate new biomarkers for better prediction and prognostication [16, 17].

AR, one of the new biomarkers, is a member of the steroid receptor subfamily that also includes ER. However, the role of AR in breast cancer is still uncertain. There is some evidence supporting a role for AR in the pathogenesis and outcome of breast cancer. AR is expressed in >70% of breast carcinomas and positive rates of AR are comparable with or higher than those of ER or PgR [10, 18, 19]. In our study, AR was expressed in 72.9% of breast cancers, which is higher than the expression rates of both ER and PgR in breast cancer. In addition, epidemiologic studies have reported significant associations between increased serum androgen levels and the risk of breast cancer [20, 21].

It has been shown that AR is frequently expressed in some types of breast carcinoma, including apocrine or lobular carcinoma, and less expressed in other types such as mucinous carcinoma, although these studies were conducted on small sample sizes [22–25]. Our study showed similar results. AR positivity of the ductal type was 73.7%. Higher positive rates of AR were shown in apocrine (100%), tubular (100%), lobular (83.3%) and papillary (81.8%) types and higher negative rates in metaplastic (0%), medullary (25%) and mucinous (41.7%) types. These results are somewhat limited by our small sample size.

It has been documented that AR expression is related to positive prognostic factors, including smaller tumor size, lack of lymph node metastasis, lower histologic grade and ER expression and that it serves as a prognostic and predictive factor in breast cancer [8, 9, 11, 18, 26]. Our results also show that AR is associated with smaller size, lower histologic grade, ER or PgR expression and non-triple-negative breast cancer. Although the impact of AR on breast cancer outcomes has not been clearly established, this result may provide evidence that AR is a good prognostic marker. Since AR expression has recently been evaluated from whole sections using IHC at our institution, the follow-up period is still too short to assess the impact of AR as a predictive and a prognostic factor. We are going to evaluate the predictive and prognostic function of AR in the near future.

It has been indicated that AR is expressed in some proportion of triple-negative breast cancers and that it might have a role as a prognostic marker and a therapeutic target in this subgroup [9, 12, 19, 27]. In our study, one third of the triple-negative cancers showed AR negativity. It is well known that ER-negative breast cancers show aggressive biologic features and have limited benefits to hormone therapy. In those cases, chemotherapy or targeted therapy are the mainstays of adjuvant treatment. New biomarkers and additional effective treatment guidelines are necessary to predict or to improve outcomes in these subgroups. In studies of prostate cancers, cross talk between AR and HER-2 pathways is indicated [28]. In ER-negative tumors, functional cross talk of AR with the HER-2 signaling pathway has been shown in *in vitro* and gene

expression profile studies [29, 30]. We analyzed AR expression by ER status, and 50% of ER-negative tumors expressed AR. AR positivity was significantly correlated with HER-2 overexpression in ER-negative tumors, but not in ER-positive tumors, even though HER-2 overexpression is defined according to the guidelines for HercepTest™. Therefore, it is still unknown whether AR provides a benefit as a prognostic factor or a therapeutic molecular target and how AR and HER-2 signaling pathway are related in these special subgroups.

In conclusion, AR is expressed in a significant number of most types of breast cancers, except in metaplastic, medullary and mucinous carcinoma, and is more frequently expressed than ER and PgR. AR is also associated with lower tumor burdens and favorable differentiation. In addition, AR is expressed in a significant number of triple-negative breast cancers, which indicates that AR could be a new target for the treatment of triple-negative cancers. Many issues regarding AR expression in breast cancer should be further assessed, including the relationship of HER-2 signaling pathway in ER-negative breast cancers.

funding

Faculty research grant, Yonsei University College of Medicine (6-2008-0151); Brain Korea 21 Project for Medical Science, Yonsei University; Korea Science and Engineering Foundation, Korean government (Ministry of Education, Science and Technology) (R13-2002-054-03001-0).

acknowledgements

A major part of this study will be presented at the 32nd Annual San Antonio Breast Cancer Symposium poster session, 9–13 December 2009 in San Antonio, TX.

disclosure

The authors declare that we have no relevant conflicts of interest.

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