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ORIGINAL PAPER

# Androgen receptor expression is a predictive marker in chemotherapy-treated patients with endocrine receptor-positive primary breast cancers

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**Abstract**
*Purpose* The androgen receptor (AR) is intensively discussed as a prognostic and/or predictive marker in breast cancer patients.
*Methods* We evaluated the value of AR mRNA expression with the Affymetrix HG-U 133A array in 3 different cohorts: a cohort of breast cancer patients who received adjuvant treatment (cohort A; $n = 165$), a cohort of untreated breast cancer patients (cohort B; $n = 200$) and a cohort of chemotherapy-treated breast cancer patients with estrogen receptor (ER)-positive tumors (cohort C; $n = 223$).
*Results* AR mRNA expression was associated with lower grading (Grades 1 and 2) as well as ER and progesterone receptor (PgR) positivity in all cohorts. In the treated cohort (cohort A), low androgen receptor expression was associated with shorter event-free survival (OR 2,34, 95 % CI 1.01–5.43, $p = 0.047$) which was not seen in the untreated cohort B. Subgroup analysis revealed that shorter survival of patients with low AR mRNA expression was observed mainly in the ER-positive subgroup of patients treated with adjuvant chemotherapy. In the validation cohort C we could confirm a benefit of chemotherapy for the group of tumors with high AR mRNA expression (5-year event-free survival (EFS) 74 % versus 57 %, $p = 0.013$). In this cohort, low AR mRNA expression was associated with shorter event-free survival also in multivariate analysis (OR 2.86, 95 % CI 1.29–6.35, $p = 0.010$) adjusted for HER2, ki-67, tumor size, age and tumor grade.
*Conclusions* We provide evidence that AR expression is associated with chemotherapy responsiveness in ER-positive patients.

**Keywords** Androgen receptor · Breast cancer · Prognosis · Prediction

## Introduction

The androgen receptor (AR) is a member of the nuclear superfamily and is known to be involved in a complex network of signaling pathways that collectively regulate cell proliferation (Liao and Dickson 2002; Yeh et al. 2003). There is emerging evidence that the androgen signaling pathway plays a critical role in normal and malignant breast tissue (Peters et al. 2009). In particular, AR is expressed in normal breast epithelial cells and in approximately 70–90 % of invasive breast carcinomas (Gonzalez et al. 2008). AR is frequently co-expressed with the ER and PgR (Kuenen-Boumeester et al. 1996), but is less frequent in HER2-positive tumors (Collins et al. 2011; Ogawa et al. 2008). The emerging role of AR in breast cancer patients is

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due to results supporting the prognostic value of AR in both ER-positive and ER-negative tumors (Agoff et al. 2003; Castellano et al. 2010; Hu et al. 2011; Park et al. 2011). Forty-five percent of triple-negative breast cancers express AR. AR has been identified as a potential new therapeutic target in this subset of patients with limited therapeutic options (Ogawa et al. 2008). There is some evidence that AR could also serve as a predictive marker, mainly for response to endocrine treatment (Park et al. 2012). The antiproliferative effect of aromatase inhibitors may be increased by the inhibitory effect of androgen via AR (Macedo et al. 2006; Ogawa et al. 2008). AR expression could be a significant factor in the prediction of therapeutic response to systemic therapies in ER-positive breast cancers (Agoff et al. 2003; Rakha et al. 2007). AR expression adds independent information toward achieving a pathological complete response (pCR) after neoadjuvant TAC (Docetacel, Adriamycin, Cyclophosphamide) chemotherapy (Loibl et al. 2011). Nevertheless, the biological role of the AR expression in breast cancer is not clear nor are the consequences for making therapy decisions depending on the AR expression in breast cancer therapy.

The aim of this study was to investigate whether AR expression has a prognostic or rather a predictive value in breast cancer patients.

We evaluated the role of AR expression in a cohort of untreated breast cancer patients and compared results with a cohort of breast cancer patients who received adjuvant chemotherapy treatment. In order to verify our findings in the treated cohort, we determined the effect of AR in a third cohort of chemotherapy-treated breast cancer patients with ER-positive tumors.

## Materials and methods

### Finding cohort A

Tissue samples of 165 patients with primary breast cancer were collected during surgery, snap-frozen and stored in liquid nitrogen. All patients were treated for breast cancer at the University Medical Center Hamburg Eppendorf, Germany, between 1992 and 2002. Patient selection was based upon availability of tumor tissue. Patients gave written informed consent to access their tissue and review their medical records according to our investigational review board and ethics committee guidelines.

The median age of the patients at surgery was 51.7 years (range 29–76 years). The median time of follow-up was 80 months; 65 % of patients ($n = 105$) had received taxane-free chemotherapy in the adjuvant setting, 57 % endocrine treatment ($n = 94$) and 39 % ($n = 64$) had received both. No radiotherapy or neoadjuvant chemotherapy had been performed prior to surgery. None of the patients had received trastuzumab treatment.

### Finding cohort B

Two hundred patients did not receive any systemic therapy in the adjuvant setting. This population-based cohort consisted of lymph node-negative breast cancer patients, treated at the Department of Obstetrics and Gynaecology of the Johannes Gutenberg University Mainz between 1988 and 1998. Patients did not receive adjuvant treatment according to former treatment standards. The median age of the patients at surgery was 60 years (range 34–89 years). The median time of follow-up was 92 months. Patients were treated either with modified radical mastectomy ($n = 75$) or breast conserving surgery followed by irradiation ($n = 125$) and did not show evidence of regional lymph node or distant metastases at the time of surgery.

### Validation cohort C

We combined a database of 223 patients with ER-positive primary tumors who received chemotherapy for breast cancer. We included 75 patients from the datasets Frankfurt which have been described previously (Karn et al. 2010) as well as 148 ER-positive patients treated with chemotherapy from publicly available datasets from Gene Expression Omnibus (GSE2603, $n = 34$; GSE12276, $n = 18$; GSE16391, $n = 19$; GSE19615, $n = 42$) and ArrayExpress (E_TABM_158, $n = 35$). ER, PgR and HER2 status were based on gene expressions from microarray as previously described (Karn et al. 2010).

Detailed patient characteristics of all cohorts are listed in Table 1.

### RNA isolation

Approximately 50 mg of frozen breast tumor tissue was pulverized in liquid nitrogen. RLT-Buffer (QIAGEN, Hilden, Germany) was added, and the homogenate was centrifuged through a QIAshredder column (QIAGEN). From the eluate, total RNA was isolated by the RNeasy Kit (QIAGEN) according to the manufacturer's instructions. RNA yield was determined by UV absorbance, and RNA quality was assessed by analysis of ribosomal RNA band integrity on an Agilent 2100 Bioanalyzer RNA 6000 LabChip kit (Agilent Technologies, Palo Alto, CA).

### Microarray analysis

The Affymetrix (Santa Clara, CA) HG-U133A array and GeneChip System™ was used to quantify the relative

**Table 1** Clinical and histopathological characteristics in all cohorts

| | Cohort A (treated) | | Cohort B (untreated) | | Cohort C (ER-positive, treated) | |
|---|---|---|---|---|---|---|
| | Number of cases | Total % | Number of cases | Total % | Number of cases | Total % |
| Age | | | | | | |
| ≤40 | 12 | 7.3 | 8 | 4.0 | 45 | 20.2 |
| 40–70 | 138 | 83.7 | 145 | 72.5 | 168 | 75.3 |
| ≥70 | 15 | 9 | 47 | 23.5 | 10 | 4.5 |
| Event (*) | | | | | | |
| No | 108 | 65.5 | 154 | 77 | 160 | 71.5 |
| Yes | 57 | 34.5 | 46 | 23 | 63 | 28.5 |
| Grade | | | | | | |
| 1 | 12 | 7.3 | 29 | 14.5 | 27 | 12.1 |
| 2 | 66 | 4 | 136 | 68 | 91 | 40.8 |
| 3 | 84 | 50.9 | 35 | 17.5 | 70 | 31.4 |
| Unknown | 3 | 1.8 | 0 | | 35 | 15.7 |
| pN | | | | | | |
| 0 | 119 | 72.1 | 200 | 100 | 74 | 33.2 |
| 1,2,3 | 46 | 27.9 | 0 | 0 | 130 | 58.3 |
| Unknown | | | | | 19 | 8.5 |
| Estrogen receptor | | | | | | |
| Negative | 41 | 24.9 | 37 | 81.5 | 0 | 0 |
| Positive | 118 | 71.5 | 163 | 18.5 | 223 | 100 |
| Unknown | 6 | 3.6 | 0 | | 0 | |
| Progesterone receptor | | | | | | |
| Negative | 59 | 35.8 | 56 | 28.0 | 58 | 24.7 |
| Positive | 100 | 60.6 | 144 | 72.0 | 165 | 64.3 |
| Unknown | 6 | 3.6 | 0 | | 0 | |
| Chemotherapy | | | | | | |
| No | 60 | 36.4 | 0 | 0 | 200 | 100 |
| Yes | 105 | 63.6 | 223 | 100 | 0 | 0 |

(*) defined as relapse or metastasis

transcript abundance in breast cancer tissues. Starting from 5 μg total RNA, labelled cRNA was prepared using the Roche Microarray cDNA Synthesis, Microarray RNA Target Synthesis (T7) and Microarray Target Purification Kit, according to the manufacturer's instructions. Arrays were analyzed using MAS5 algorithm (Affymetrix Microarray Suite 5.0 software) with global scaling of each array to a mean target intensity of 500. Samples with suboptimal average signal intensities (i.e., scaling factors >25) or GAPDH 3′/5′ ratios >5 were relabelled and rehybridized on new arrays.

## Statistical analysis

Correlations between mRNA expression and clinical or histological tumor parameters were calculated by Spearman analysis using the PASW statistics 19 (SPSS Inc, Chicago, Illinois, USA). For prognostic parameters, the following groups were compared: Tumor size less than 5 cm (pT1 + 2) versus more than 5 cm (pT3 + 4), G1/G2 versus G3; node-positive versus node-negative tumors; ER/PgR-positive versus ER/PgR-negative tumors; age <56 years versus 56 years and older. For survival analyses, the cohorts were stratified into quartiles according to Affymetrix expression values of AR mRNA. Survival analyses were then performed for all quartiles. The cutoffs that resulted in the most significant difference in outcome were used. For AR, the lower 25 % of values were compared with the higher 75 %. Event-free survival was computed from the date of surgery to the date of first metastasis or recurrence. Survival curves were compared with the logrank test. Univariate as well as multivariate $p$ values for the respective risk factors in the survival model were obtained by a Cox proportional hazards model. All tests were performed at a significance level of $p = 0.05$ (two-sided).

## Results

### Androgen receptor expression in finding cohort A and B

Two different probesets for measuring AR expression are present on the Affymetrix U133A microarray (probeset 211621_at and 211110_s_at). In cohort A (treated) and cohort B (untreated), median AR expression values were 666 (range 25–2,018) and 735 (34–5,286) for probeset 211110_s_at and 307 (36–891) and 442 (3–2,009) for probeset 211621_at, respectively. We found a strong correlation between both probesets ($r = 0.86$, $p < 0.001$) and therefore selected probeset 211110_s_at for all subsequent analyses. AR mRNA expression did not differ between treated and untreated patients.

The patient cohorts were stratified into quartiles according to AR mRNA expression. The lower 25 % of patients were compared with the higher 75 % of patients. As shown in Table 2, high AR mRNA expression was associated with lower grading (Grades 1 and 2) as well as ER and PgR positivity in all cohorts. In the lymph node-negative group of patients with no adjuvant systemic therapy (cohort B), only grading correlated with shorter event-free survival in the multivariate analysis (OR 2,63, 95 %-CI-1.37–5.0, $p = 0.004$, Table 3), whereas in cohort A (treated) low AR expression was associated with shorter event-free survival (OR 2,34, 95 %-CI-1.01–5.43, $p = 0.047$, Table 3) as well as positive nodal status (OR 3.08, 95 % CI 1.15–8.23, $p = 0.025$, Table 3).

Kaplan–Meier analyses of disease-free survival according to AR mRNA expression were performed separately for the subgroups of ER-positive and ER-negative breast cancers (Cohort A). As shown in Fig. 1, poor survival of patients with tumors displaying low AR mRNA expression was observed in the ER-positive subgroup (5-year event-free survival (EFS) 60 vs. 82 %, $p = 0.02$, Fig. 1a), while no significant difference among ER-negative breast cancers was detected (5-year EFS 57 vs. 59 %, $p = 0.079$, Fig. 1b). To analyze a potential predictive effect of AR mRNA expression, we performed analysis separately for the patients with or without adjuvant chemotherapy in Cohort A. We detected a significant difference in EFS only among those 104 patients who received adjuvant chemotherapy (5-year EFS 53 vs. 78 %, $p = 0.009$, Fig. 2). In contrast, this difference was not seen for endocrine treatment (5-year EFS 59 vs. 84 %, $p = 0.10$, data not shown).

### Androgen receptor expression in validation cohort C

In the validation cohort C (223 ER-positive chemotherapy-treated patients), we could confirm the effect of low AR mRNA expression on shorter event-free survival in a larger group of patients with ER-positive tumors who received chemotherapy. A benefit of chemotherapy was observed among the group of tumors with high AR mRNA expression (5-year event-free survival (EFS) 74 % versus 57 %, $p = 0.013$). A good response to chemotherapy has been reported to be associated with high proliferation of tumors. Therefore, we also examined a potential association of AR expression and proliferation by analyzing the correlation of AR and Ki-67 expression. However, as shown in Fig. 3, we detected no significant correlation of these two parameters ($r = 0.05$, $p = 0.43$, Fig. 3). Moreover, in a multivariate analysis, low AR mRNA expression remained a significant predictor of shorter event-free survival (OR 2.86, 95 % CI 1.29–6.35, $p = 0.010$, Table 4) when adjusted for HER2, Ki-67, tumor size, age and tumor grade in patients of validation cohort C.

## Discussion

Our data suggest that AR is rather a predictive than a prognostic marker in breast cancer patients. In patients that did not receive any systemic treatment, the AR had no additional prognostic information. In contrast, in the two chemotherapy-treated cohorts, low AR mRNA expression was associated with shorter event-free survival.

In all cohorts, AR expression correlated inversely with grading. Although grading was associated with event-free survival in the untreated cohort, interestingly, AR remained the only significant predictor of shorter event-free survival in treated patients adjusted for grading. In addition, we could show no correlation between AR and Ki-67 which supports a biological role of the AR independent from proliferation.

A potential drawback of our study is its retrospective nature and assessment of a biomarker that was not prospectively defined. In addition, AR could be determined only on RNA level since paraffin embedded tissue was not available from most patients.

Regarding AR positivity, immunohistochemical analysis reveals AR positivity in 65–80 % of breast cancer patients (Hu et al. 2011). A correlation between staining intensity and mRNA expression of the protein exists (Rabiau et al. 2011). Therefore, in our view, a classification into low and high AR mRNA expression by using quartiles seems to be justified.

At present, AR is mainly discussed as a prognostic marker in breast cancer patients (Hu et al. 2011; Park et al. 2011; Yu et al. 2011). Recently published data assume that AR might be a predictive marker for response to endocrine treatment in breast cancer patients (Lundin et al. 2011). Gonzalez et al. could show in a group of breast cancer patients, that in ER-positive patients, the outcome was

**Table 2** Patients' and histopathological characteristics according to androgen receptor mRNA expression

| | Cohort A (treated) | | | Cohort B (untreated) | | | Cohort C (ER-positive, treated) | | |
|---|---|---|---|---|---|---|---|---|---|
| | AR low (q1) | AR high (q2-4) | *p* value | AR low (q1) | AR high (q2-4) | *p* value | AR low (q1) | AR high (q2-4) | *p* value |
| Age | | | | | | | | | |
| ≤40 | 5 | 7 | n.s. | 3 | 4 | n.s. | 11 | 34 | n.s. |
| 40–70 | 33 | 108 | | 30 | 97 | | 43 | 125 | |
| ≥70 | 4 | 11 | | 10 | 32 | | 2 | 8 | |
| Grade | | | | | | | | | |
| Low (G1 and 2) | 10 | 68 | 0.002 | 32 | 133 | <0.001 | 21 | 97 | 0.005 |
| High (G3) | 29 | 55 | | 18 | 17 | | 25 | 45 | |
| pT | | | | | | | | | |
| 1 and 2 | 37 | 114 | n.s. | 49 | 145 | n.s. | 9 | 57 | n.s. |
| 3 and 4 | 4 | 9 | | 1 | 5 | | 0 | 9 | |
| pN | | | | | | | | | |
| 0 | 26 | 93 | n.s. | 50 | 150 | n.a. | 8 | 66 | 0.002 |
| 1,2,3 | 14 | 33 | | | | | 39 | 91 | |
| Estrogen receptor | | | | | | | | | |
| Negative | 22 | 19 | <0.001 | 20 | 17 | <0.001 | | | n.a. |
| Positive | 16 | 102 | | 30 | 133 | | 52 | 154 | |
| Progesterone receptor | | | | | | | | | |
| Negative | 26 | 33 | <0.001 | 26 | 30 | <0.001 | 19 | 36 | 0.075 |
| Positive | 12 | 88 | | 24 | 120 | | 36 | 126 | |
| HER2 | | | | | | | | | |
| Positive | 7 | 22 | 0.59 | 5 | 21 | 0.48 | 5 | 17 | 1 |
| Negative | 21 | 65 | | 44 | 121 | | 38 | 107 | |

**Table 3** Event-free survival (multivariate analysis) in finding cohorts A (untreated) and B (treated)

| Parameter | Cohort A (treated, $n = 165$) | | | Cohort B (untreated, $n = 200$) | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95 % CI | *p* value | Odds ratio | 95 % CI | *p* value |
| AR mRNA (low) | 2.34 | 1.01–5.43 | 0.047 | 1.04 | 0.55–1.96 | 0.9 |
| Age | 1.44 | 0.68–3.02 | 0.33 | 1.19 | 0.67–2.11 | 0.54 |
| Tumor size (T3 + 4) | 0.92 | 0.39–2.16 | 0.85 | 0.79 | 0.63–1.82 | 0.79 |
| Nodal status (pos.) | 3.08 | 1.15–8.23 | 0.025 | | | |
| Grading (G3) | 1.83 | 0.86–3.89 | 0.12 | 2.6 | 1.37–5.03 | 0.004 |
| ER-negative | 1.78 | 0.98–3.20 | 0.055 | 1.25 | 0.62–2.51 | 0.53 |
| Chemotherapy (no) | 2.15 | 0.83–5.56 | 0.12 | | | |

more favorable with higher AR levels (cutoff was median) determined by reverse-phase protein arrays. As only a minority of ER-positive patients had also received chemotherapy, the authors conclude that AR might be a predictive marker for endocrine treatment (Gonzalez-Angulo et al. 2009). In the study published by Castellano et al., the AR was evaluated in ER-positive tumors by immunohistochemistry and was counted as positive in 71 % of patients. However, 42 % of patients in this study had received chemo-endocrine treatment and a prognostic role of AR could be basically seen in those patients (Castellano et al. 2010), which is in line with our results. In contrast to our findings, Park et al. described no effect of low AR expression levels on chemotherapy benefit in ER-positive patients and concluded that patients with low AR expression could be ideal candidates for chemotherapy treatment (Park et al. 2012). Inversely, we found that the impact of AR did not depend on endocrine treatment, although it was more prominent in ER-positive tumors. Therefore, we conclude that AR predicts response to adjuvant chemotherapy rather than to endocrine treatment with the worst response in patients with low AR expression. According to

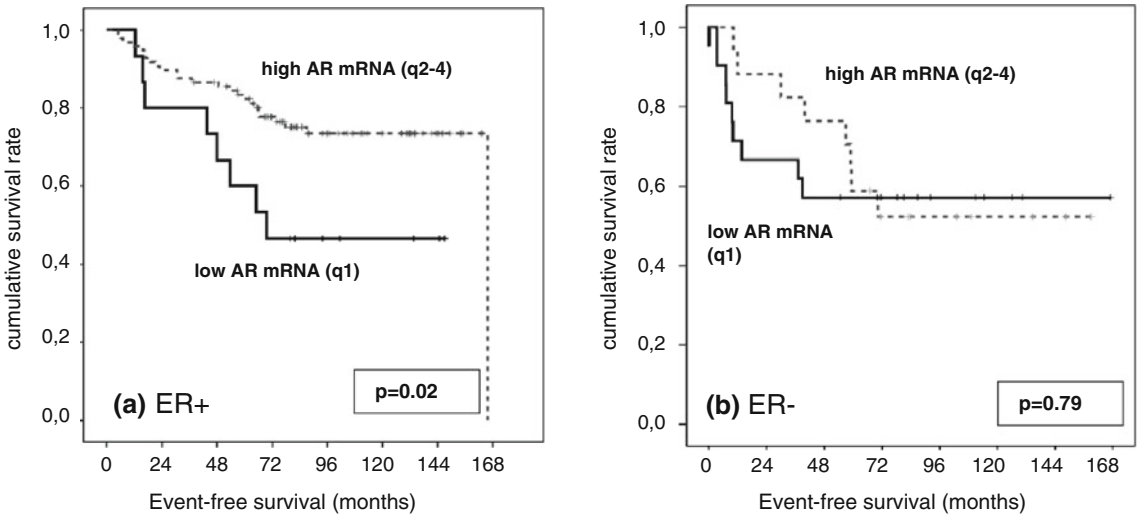


**Fig. 1** Event-free survival in ER-positive (**a**) and ER-negative (**b**) patients with high and low AR mRNA levels in cohort A

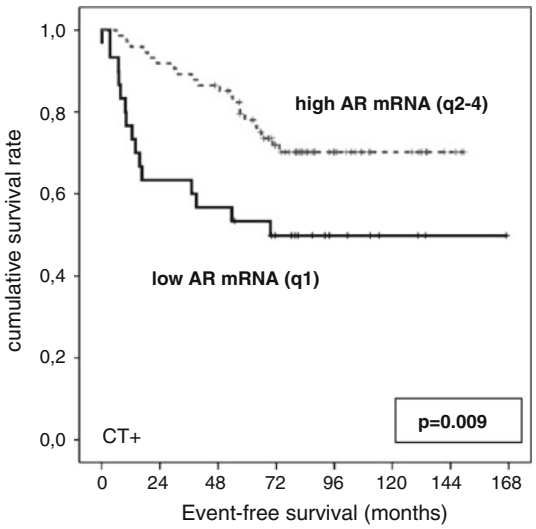


**Fig. 2** Event-free survival in chemotherapy-treated patients with high and low AR mRNA levels in cohort A

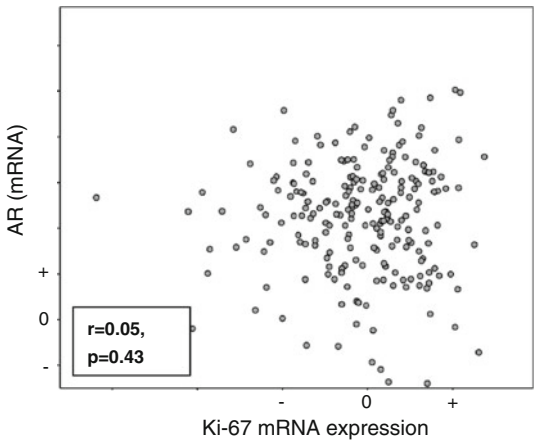


**Fig. 3** Correlations between AR and ki-67 mRNA expression in Cohort C ($r = 0.05$, $p = 0.43$)

data from the neoadjuvant Gepartrio trial, Loibl et al. also reported that low AR expression determined by immunohistochemistry was associated with shorter disease-free and overall survival in 673 patients receiving chemotherapy with TAC (Loibl et al. 2011).

Currently, AR antagonists are under evaluation in the treatment of castration-resistant prostate cancer (Ryan and Tindall 2011). New compounds like abiderone acetate were described to be of clinical efficacy (Fizazi et al. 2012; Logothetis et al. 2012). The role of AR antagonists was not studied in breast cancer so far. One very recently suggested direction in preclinical and clinical research is the use of AR antagonists in triple-negative breast cancer (McNamara et al. 2012; Naderi et al. 2011). As in our cohorts patients with low AR expression had less benefit of chemotherapy,

**Table 4** Event-free survival in validation cohort C (ER-positive chemotherapy-treated patients)

| Parameter | Cohort C (n = 223) | | |
|---|---|---|---|
| | Odds ratio | 5 %-CI | *p* value |
| AR mRNA (low) | 2.86 | 1.29–6.35 | 0.01 |
| Age | 0.9 | 0.35–2.15 | 0.76 |
| Tumor size (T3 + 4) | 0.63 | 0.24–1.92 | 0.42 |
| Grading (G3) | 1.32 | 0.53–3.28 | 0.55 |
| Ki-67 (low) | 0.65 | 0.22–1.89 | 0.42 |
| HER2 (positive) | 2.2 | 0.78–6.41 | 0.14 |

the use of AR antagonists in this group of patients seems questionable. However, an interaction between AR and ER has been described (Peters et al. 2009), and hypermethylation of the AR promoter might lead to the loss of AR expression (Peters et al. 2012). In the neoadjuvant setting, a

change of AR mRNA expression levels before and after chemotherapy in tumor tissue could be demonstrated (Chintamani et al. 2010). Therefore, a biological role of AR in ER-positive patients might be clinically relevant in the context of upcoming therapeutic concepts targeting the AR.

In conclusion, we provide evidence that there is an important interaction between AR expression, ER-status and chemotherapy responsiveness in breast cancer patients.

**Conflict of interest** All authors declare that they have no conflict of interest.

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