Androgen Receptor Expression and Outcomes in Early Breast Cancer: A Systematic Review and Meta-Analysis

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Background

The androgen receptor (AR) is expressed frequently in breast cancer, but its prognostic significance is unclear. Preclinical data suggest that expression of AR may modify clinical outcomes in early breast cancer with improved prognosis in estrogen receptor (ER)–positive disease and poorer prognosis in ER-negative disease.

Methods

A systematic review of electronic databases was conducted to identify studies published between 1946 and July 2012 and to explore the association between AR expression and overall survival (OS) and disease-free survival (DFS) in women diagnosed with early breast cancer. The odds ratios (OR) for OS and DFS at 3 and 5 years were calculated and then weighted and pooled in a meta-analysis with Mantel–Haenszel random-effect modeling. All statistical tests were two-sided.

Results

Nineteen studies with a total of 7693 women were included. AR expression was documented in 60.5% of patients. ER-positive tumors were more likely to express AR- than ER-negative tumors (74.8% vs 31.8%, χ² P < .001). Compared with tumors without AR expression, those expressing AR were associated with improved OS at both 3 and 5 years (OR = 0.47, 95% confidence interval [CI] = 0.39 to 0.58, P < .001; and OR = 0.40, 95% CI = 0.29 to 0.56, P < .001). The absolute differences in the probability of OS at 3 and 5 years were 6.7% (95% CI = 3.5% to 9.8%) and 13.5% (95% CI = 7.5% to 19.6%), respectively. Results for 3- and 5-year DFS were similar. Coexpression of the ER did not influence OS at 3 or at 5 years.

Conclusions

Expression of AR in women with breast cancer is associated with better OS and DFS irrespective of coexpression of ER.


Multiple studies have confirmed that expression of the estrogen receptor (ER) and progesterone receptor (PR) is associated with better outcome in women with breast cancer (1,2). More recently, attention has focused on the role of androgens and the androgen receptor (AR) as prognostic markers and as therapeutic targets in breast cancer (3–5).

Therapeutic use of the androgen fluoxymesterone for women with advanced breast cancer was described more than 50 years ago with reported response rates of 14% to 53% (6–9). Its use in combination with tamoxifen has also been studied, although clinical benefit was not observed (10,11). As a result of a lack of biological understanding of the anticancer effects of androgens, inconsistent clinical data, undesirable toxicities such as virilization, and the development of aromatase inhibitors, enthusiasm for their use as treatment for breast cancer diminished.

More recently, in vitro data have shown that the effects of androgens may be dependent on the expression of AR. High concentrations of the androgen 5α-dehydro-testosterone have seen shown to cause inhibition of proliferation and cell survival and an increase of apoptosis in human breast cancer cell lines expressing both ER and AR (12). Activation of AR with dihydrotestosterone in such cell lines decreased estrogen-dependent signaling to a similar magnitude as that seen with tamoxifen (13). The proposed mechanism for these findings is that after ligand binding AR translocates to the nucleus where it competes with ER and PR for binding to the estrogen-related elements and thereby inhibits estrogen-dependent signaling (Figure 1A) (14,15). One might therefore expect that expression of AR would be associated with reduced cell survival and promotion of apoptosis.

Data describing the effect of AR expression in breast cancer cells without coexpression of ER are sparse. It has been hypothesized that signaling through AR replaces estrogen-dependent signaling as the major determinant of steroid-related gene expression. This signaling can exert a stimulatory effect through the androgen responsive element, thereby stimulating transcription of steroid-responsive genes (Figure 1B) (16). Preclinical studies have demonstrated that androgens can lead to proliferation of AR-expressing breast cancer cell lines and promote tumor formation in animal models (17). In one study, ER-negative/AR-positive tumors have also been associated with higher nuclear grade, increased risk of recurrence and distant metastasis, and adverse survival (18). The ER-negative/AR-positive phenotype may also possess a specific
molecular signature such as the molecular apocrine tumor (18). However, independent validation of this signature is required because hierarchical clustering has been shown to have only modest interobserver reproducibility (19).

The magnitude and direction of association between AR expression and clinical outcome in both ER-positive and ER-negative breast cancer is unclear. We report a systematic review and a meta-analysis of the influence of AR expression on clinical outcomes in early breast cancer. We also assess the influence of AR in subgroups determined by expression of other receptors such as ER and HER2/neu. Based on preclinical data, we hypothesized that expression of AR would modify clinical outcomes in early breast cancer with an improved prognosis seen in ER-expressing tumors and a worse prognosis in ER-negative disease.

**Methods**

**Data Sources and Searches**

An electronic search of the following databases was undertaken: Medline (host: OVID) from 1946 to July 2012, EMBASE (host: OVID) from 1946 to July 2012, and Cochrane Central Register of Controlled Trials (from inception Oct 2000 until July 2012).
search was limited to English language articles. The search terms included “breast neoplasms,” “androgen,” and “androgen receptor.” Citation lists of retrieved articles were manually screened to ensure sensitivity of the search strategy.

**Study Selection**
Inclusion criteria were studies in early breast cancer (as defined by individual reports) with availability of overall survival (OS) data for 3 and/or 5 years or disease-free survival (DFS) data for 3 and/or 5 years. There was no restriction based on study methodology. Exclusion criteria included studies in metastatic disease and duplicate publications. One reviewer (P. de Gouveia) evaluated all the titles and abstracts identified by the search strategy, and all potentially relevant publications were retrieved in full. Two independent reviewers (E.E. Vera-Badillo and P. de Gouveia) then assessed the articles for study eligibility. Inter-reviewer agreement was assessed using Cohen’s kappa coefficient. Disagreement was resolved by consensus.

**Endpoints of Interest**
OS at 3 and 5 years were the primary endpoints. Where not available, data for DFS at 3 and 5 years were collected. Tumors were classified by ER and HER2/neu expression status using cutoffs as defined by individual studies.

**Data Extraction**
Data were collected using predesigned abstraction forms. The following details were extracted by 2 reviewers (E.E. Vera-Badillo and P. de Gouveia): number of patients, technique used to quantify ER and AR, and cutoff to determine ER and AR positivity. Survival data were extracted from tables or the body of eligible articles or estimated from Kaplan–Meier curves where applicable (20).

**Statistical Analysis**
Data were presented descriptively as means and proportions. Differences between groups were tested using the \( \chi^2 \) test. The relative frequency of death or disease recurrence at 3 or 5 years between AR-positive and AR-negative tumors was presented as an odds ratio (OR) with its 95% confidence interval (CI). Data were extracted from the primary publications and combined into a meta-analysis using RevMan 5.1 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Estimates of odds ratios were weighted and pooled using the Mantel–Haenszel random-effect model. Statistical heterogeneity was assessed using the Cochran’s \( Q \) and \( I^2 \) statistics. Differences between subgroups were assessed using methods described by Deeks et al. (21). Sensitivity analyses were carried out for different analytical methods and cutoffs for defining ER and AR expression as well as for potential heterogeneity in the definition of early (vs metastatic) breast cancer. All statistical tests were two-sided, and statistical significance was defined as \( P \) less than .05. No correction was made for multiple statistical testing.

**Results**
Of the 1918 abstracts identified initially, 50 full text articles were retrieved for detailed evaluation. All these studies used a retrospective cohort design. Thirty-one articles were excluded (see Figure 2) and 19 studies were included in the analysis. The kappa coefficient for agreement was 0.96. Data were available for OS at both 3 and 5 years from 14 studies. For DFS, 10 studies provided data at 3 years, and 12 studies provided data at 5 years.

Characteristics of included studies are shown in Table 1. The median and range of age between studies was representative of an early breast cancer, population with individual studies reporting median age of between 49 and 61 years. There was heterogeneity in study populations; 15 studies (78.9%) included women with both ER-positive and ER-negative breast cancer, two studies (10%) included only women with ER-expressing tumors, and two studies (10.5%) included only women with ER-negative tumors. Definition of ER expression was reported in 13 studies (68.4%). Among these, ER-positive disease was defined as 10% or greater staining in eight studies (42.1%), as greater than 5% staining in one study (5.3%) and as 1% or greater staining in two studies (10.5%). Of the 7693 patients included in eligible studies, 4658 patients (60.5%) had AR expression (AR-positive). Among ER-positive tumors, 74.8% also showed expression of AR, where among ER-negative cancers, AR expression was seen in 31.8% of cases (\( \chi^2 P < .001 \)). Among PR-positive tumors, 77.0% showed expression of AR, but for PR-negative cancers, only 51.4% expressed AR (\( \chi^2 P < .001 \)). The association between AR and Ki-67 was explored in four studies (21.1%). All studies used a 10% cutoff to define high Ki-67 expression. There was a highly statistically significant association between AR expression and low Ki-67 (\( \chi^2 P < .001 \)). There was no association between the presence of AR expression and tumor size (\( P = .12 \)), nodal status (\( P = .78 \)), tumor grade (\( P = .17 \)), lymphovascular invasion (\( P = .19 \)), or use of adjuvant chemotherapy (\( P = .12 \)) or adjuvant endocrine treatment (\( P = .12 \)).

Analysis of AR was carried out using immunohistochemistry (IHC) in 15 studies (78.9%), radioimmunoassay in three studies (15.8%), and reverse-phase protein array in one study (5.3%). Among studies using IHC, positive results were determined as AR expression (A). Sensitivity analyses were associated with a statistically significant improvement in OS (OR = 0.47; 95% CI = 0.39 to 0.58; \( P < .001 \)) (see Figure 3A). This translated to an absolute difference in 3-year OS of 6.7% (95% CI = 3.5% to 9.8%). The association of AR expression and improved 3-year OS appeared independent of coexpression of ER, with similar magnitudes of effect observed for studies including only ER-positive patients (OR = 0.45; 95% CI = 0.29 to 0.69), those including only ER-negative patients (OR = 0.38; 95% CI = 0.13 to 1.10) and those with patients unselected for ER expression (OR = 0.47; 95% CI = 0.36 to 0.61). There was no statistically significant difference between these subgroups (\( P = .93 \)).
A total of 10 studies reported data for DFS at 3 years. There was no evidence of statistically significant heterogeneity between studies (Cochran’s Q $P = 0.83$; $I^2 = 0\%$). Compared with tumors without AR expression, those with AR expression were associated with a statistically significant improvement in DFS ($OR = 0.43$; 95% CI = 0.35 to 0.52; $P < .001$) (see Figure 3B). This translated to an absolute difference in 3-year DFS of 8.8% (95% CI = 5.2% to 12.3%). The association of AR expression and improved 3-year DFS was similarly independent of coexpression of ER, with similar magnitudes of effect observed for studies including only ER-positive patients ($OR = 0.42$; 95% CI = 0.31 to 0.57), those including only ER-negative patients ($OR = 0.32$; 95% CI = 0.15 to 0.70), and those with patients unselected for ER expression ($OR = 0.40$; 95% CI = 0.32 to 0.52). There was no statistically significant difference between these subgroups ($P = .83$) (see Figure 4).

Five-Year OS and DFS
A total of 14 studies reported data for OS at 5 years. There was statistically significant heterogeneity between studies (Cochran’s Q $P < .001$; $I^2 = 72\%$), which resulted from the inclusion of one study (22) with outlying data. Of interest, this study did not report the cutoff used for determination of AR expression, and we were unable to retrieve this information from other sources. When all studies were included, there was a statistically significant association between AR expression and improved 5-year OS compared with no AR expression ($OR = 0.40$; 95% CI = 0.29 to 0.56; $P < .001$) (see Figure 5A). This translated to an absolute difference in 5-year OS of 13.5% (95% CI = 7.5% to 19.6%). Exclusion of the one study with outlying data eliminated the heterogeneity (Cochran’s Q $P = .57$; $I^2 = 0\%$) but retained the statistically significant association between AR expression and improved 5-year OS compared with no AR expression ($OR = 0.51$; 95% CI = 0.43 to 0.61; $P < .001$).

Similar to the 3-year OS data, the association between AR expression and improved 5-year OS was also independent of coexpression of ER, with similar magnitudes of effect observed for studies including only ER-positive patients ($OR = 0.49$; 95% CI = 0.36 to 0.66), those including only ER-negative patients ($OR = 0.59$; 95% CI = 0.28 to 1.25), and those with patients unselected for ER expression ($OR = 0.39$; 95% CI = 0.19 to 0.83). There was no statistically significant difference between these subgroups ($P = .75$).

A total of 12 studies reported data for DFS at 5 years. There was again evidence of statistically significant heterogeneity between studies (Cochran’s Q $P < .001$; $I^2 = 91\%$). This resulted from general interstudy heterogeneity without evidence that this was a consequence of inclusion of studies with outlying data. Compared with tumors without AR expression, those with AR expression were associated with a statistically significant improvement in DFS ($OR = 0.34$; 95% CI = 0.21 to 0.56; $P < .001$) (see Figure 3B). This translated to an absolute difference
Table 1. Characteristics of studies included in the meta-analysis*

<table>
<thead>
<tr>
<th>References</th>
<th>No.</th>
<th>Age, median (range)</th>
<th>Population</th>
<th>Method and definition of ER+</th>
<th>Follow up, months</th>
<th>Technique for AR assessment</th>
<th>Antibody</th>
<th>Definition of AR+</th>
<th>Magnitude</th>
<th>Location</th>
<th>AR+, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carreno et al. 2007 (41)</td>
<td>25</td>
<td>61 (27–92)</td>
<td>ER+/ER−</td>
<td>IHC ≥10%</td>
<td>39</td>
<td>IHC</td>
<td>AR411 DAKO (mouse)</td>
<td>≥10%</td>
<td>NR</td>
<td>16 (64)</td>
<td></td>
</tr>
<tr>
<td>Honma et al. 2012 (23)</td>
<td>403</td>
<td>56 (32–81)</td>
<td>ER+ only</td>
<td>IHC ≥10%</td>
<td>11</td>
<td>IHC</td>
<td>AR27 Novocastra (mouse)</td>
<td>≥10%</td>
<td>Nuclear</td>
<td>212 (53)</td>
<td></td>
</tr>
<tr>
<td>Hu et al. 2011 (4)</td>
<td>1467</td>
<td>61 (39–75)</td>
<td>ER+/ER−</td>
<td>NR</td>
<td>168</td>
<td>IHC</td>
<td>AR 441 DAKO</td>
<td>≥10%</td>
<td>Nuclear</td>
<td>1155 (79)</td>
<td></td>
</tr>
<tr>
<td>Kuenen-Boumeester et al. 1996 (42)</td>
<td>153</td>
<td>55 (29–88)</td>
<td>ER+/ER−</td>
<td>IHC ≥10%</td>
<td>46</td>
<td>IHC</td>
<td>F39.3 (mouse)</td>
<td>≥10%</td>
<td>Nuclear</td>
<td>1288 (84)</td>
<td></td>
</tr>
<tr>
<td>Park et al. 2010 (24)</td>
<td>931</td>
<td>49.3 (NR)</td>
<td>ER+/ER−</td>
<td>NR</td>
<td>NR</td>
<td>IHC</td>
<td>AR441 Thermo Scientific (mouse)</td>
<td>≥10%</td>
<td>NR</td>
<td>1155 (79)</td>
<td></td>
</tr>
<tr>
<td>Yu et al. 2011 (43)</td>
<td>327</td>
<td>52.5 (NR)</td>
<td>ER+/ER−</td>
<td>IHC ≥10%</td>
<td>66</td>
<td>IHC</td>
<td>AR441 Lab Vision (mouse)</td>
<td>≥10%</td>
<td>Nuclear</td>
<td>541 (58)</td>
<td></td>
</tr>
<tr>
<td>Castellano et al. 2010 (44)</td>
<td>859</td>
<td>NR</td>
<td>ER+ only</td>
<td>IHC ≥1%</td>
<td>82</td>
<td>IHC</td>
<td>AR411 DAKO (mouse)</td>
<td>≥1%</td>
<td>NR</td>
<td>609 (71)</td>
<td></td>
</tr>
<tr>
<td>Gonzalez et al. 2008 (45)</td>
<td>111</td>
<td>NR</td>
<td>ER+/ER−</td>
<td>NR</td>
<td>87.5</td>
<td>IHC</td>
<td>AR411 DAKO</td>
<td>≥1%</td>
<td>NR</td>
<td>83 (75)</td>
<td></td>
</tr>
<tr>
<td>Loibl et al. 2011 (46)</td>
<td>673</td>
<td>NR</td>
<td>ER+/ER−</td>
<td>IHC ≥10%</td>
<td>60.5</td>
<td>IHC</td>
<td>F39.4.1 Biogenex (mouse)</td>
<td>≥1%</td>
<td>NR</td>
<td>358 (53)</td>
<td></td>
</tr>
<tr>
<td>Luo et al. 2010 (47)</td>
<td>137</td>
<td>49 (25–80)</td>
<td>TNBC</td>
<td>NR</td>
<td>NR</td>
<td>IHC</td>
<td>AR411 DAKO</td>
<td>&gt;1% or moderate staining</td>
<td>Nuclear</td>
<td>38 (28)</td>
<td></td>
</tr>
<tr>
<td>Micello et al. 2010 (48)</td>
<td>226</td>
<td>58.7 (24–97)</td>
<td>ER/PR− only</td>
<td>IHC ≥10%</td>
<td>116.4</td>
<td>IHC</td>
<td>AR27 Novocastra (mouse)</td>
<td>≥1%</td>
<td>Nuclear</td>
<td>128 (57)</td>
<td></td>
</tr>
<tr>
<td>Peters et al. 2012 (49)</td>
<td>73</td>
<td>54 (30–94)</td>
<td>ER+/ER−</td>
<td>IHC ≥1%</td>
<td>NR</td>
<td>IHC</td>
<td>Anti-AR Biocare Medical</td>
<td>≥1%</td>
<td>Nuclear</td>
<td>41 (56)</td>
<td></td>
</tr>
<tr>
<td>Agoff et al. 2003 (50)</td>
<td>88</td>
<td>54.9 (26–91)</td>
<td>ER+/ER−</td>
<td>IHC ≥5%</td>
<td>25</td>
<td>IHC</td>
<td>F39.4.1 Biogenex (mouse)</td>
<td>≥5%</td>
<td>NR</td>
<td>51 (58)</td>
<td></td>
</tr>
<tr>
<td>Peters et al. 2009 (13)</td>
<td>215</td>
<td>55 (24–87)</td>
<td>ER+/ER−</td>
<td>IHC ≥10%</td>
<td>NR</td>
<td>IHC</td>
<td>AR-U407 NEN Life Sciences Products (rabbit)</td>
<td>≥75%</td>
<td>Nuclear</td>
<td>116 (54)</td>
<td></td>
</tr>
<tr>
<td>Agrawal et al. 2008 (22)</td>
<td>488</td>
<td>54.3 (32–79)</td>
<td>ER+/ER−</td>
<td>NR</td>
<td>NR</td>
<td>IHC</td>
<td>AR411 DAKO</td>
<td>NR</td>
<td>Nuclear</td>
<td>212 (43)</td>
<td></td>
</tr>
<tr>
<td>Bryan et al. 1984 (51)</td>
<td>840</td>
<td>NR</td>
<td>ER+/ER−</td>
<td>NR</td>
<td>NR</td>
<td>RIA</td>
<td>R1881 New England Medical</td>
<td>&gt;5 fmol/mg</td>
<td>NR</td>
<td>396 (47)</td>
<td></td>
</tr>
<tr>
<td>Langer et al. 1990 (52)</td>
<td>61</td>
<td>NR</td>
<td>ER+/ER−</td>
<td>RIA 10 fmol/mg</td>
<td>48</td>
<td>RIA</td>
<td>R1881 New England Medical</td>
<td>≥10 fmol/mg</td>
<td>NR</td>
<td>24 (39)</td>
<td></td>
</tr>
<tr>
<td>Collett et al. 1996 (53)</td>
<td>269</td>
<td>NR</td>
<td>ER+/ER−</td>
<td>RIA 15 fmol/mg</td>
<td>50.4</td>
<td>RIA</td>
<td>R1881 Medical Systems</td>
<td>≥43 fmol/mg</td>
<td>NR</td>
<td>137 (51)</td>
<td></td>
</tr>
<tr>
<td>Gonzalez-Angulo et al. 2009 (54)</td>
<td>347</td>
<td>59 (23–89)</td>
<td>ER+/ER−</td>
<td>RPPA 2470 arrayer Aushon Biosystems</td>
<td>log mean centered value ≥ 0.0852</td>
<td>RIA</td>
<td>R1881 Medical Systems</td>
<td>NR</td>
<td>174 (50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* AR+ = androgen receptor positive; ER+ = estrogen receptor positive; ER− = estrogen receptor negative; IHC = immunohistochemistry; NR = not reported; RIA = radioimmunoassay; RPPA = reverse-phase protein array; TNBC = triple negative breast cancer.
in 5-year DFS of 20.7% (95% CI = 8.7% to 32.7%). The association of AR expression and improved 5-year DFS was once again independent of coexpression of ER, with similar magnitudes of effect observed for studies including only ER-positive patients (OR = 0.41; 95% CI = 0.20 to 0.83), those including only ER-negative patients (OR = 0.39; 95% CI = 0.13 to 1.16), and those with patients unselected for ER expression (OR = 0.27; 95% CI = 0.11 to 0.71). There was no statistically significant difference between these subgroups (P = .79).

**Sensitivity Analyses**

Removal of studies using radioimmunoassay or reverse-phase protein array did not influence results for 3-year or 5-year OS (OR = 0.43, 95% CI = 0.31 to 0.60; OR = 0.37, 95% CI = 0.25 to 0.55, respectively). Similarly, removal of the single study (13) that was an outlier with regard to definition of AR expression by IHC (75% vs 1%–10% for other studies) did not substantially affect the association between AR expression and favorable 3-year and 5-year OS compared with no AR expression (OR = 0.48, 95% CI = 0.36 to 0.79).

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**Figure 3.** Patient outcome at 3 years by androgen receptor (AR) expression. A) Three-year overall survival. B) Three-year disease-free survival. Odds ratios in reference to AR expression compared with no AR expression for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated pooled effect (labeled total). Estimates of odds ratios were weighted and pooled using the Mantel–Haenszel random-effect model. Statistical heterogeneity was assessed using Cochran’s Q and P statistics. All P values are two-sided.
0.62; OR = 0.36, 95% CI = 0.23 to 0.55, respectively). Exclusion of these studies did not reduce heterogeneity for 5-year OS (Cochran's

Among studies using IHC, use of different cutoffs for AR over-expression was not statistically different; the association between AR over-expression and outcome was similar for both the 1% and 10% thresholds, and the test for subgroup difference did not meet statistical significance for either 3-year or 5-year OS (P = .62 and P = .09, respectively). Similarly, use of difference cutoffs for ER expression was not associated with a statistically significant test for subgroup difference for either 3-year or 5-year OS (P = .51 and P = .32, respectively).

Corresponding authors of papers using the IHC cutoff of ≥10% for AR positivity were contacted to retrieve any available data using the ≥1% cutoff. Responses were received from three authors (4,23,24). For one study, 5% of the study cohort had AR expression between 1% and 9%, increasing the proportion of patients considered positive from 58% to 63% (Byeong-Woo Park and Seho Park, personal communication). Using the 1% rather than 10% cutoff for AR led to marginally different values of median OS

Figure 4. Three-year overall survival (OS) by androgen receptor (AR) expression based on coexpression of estrogen receptor (ER). Odds ratios in reference to AR expression compared with no AR expression for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated pooled effect (labeled total). Estimates of odds ratios were weighted and pooled using the Mantel–Haenszel random-effect model. Statistical heterogeneity was assessed using Cochran's Q and I² statistics. Test of subgroup differences relates to the test of heterogeneity between the three cohorts of ER expression as defined by Deeks et al. (21). All P values are two-sided.
and DFS but did not change the statistical significance. Of the two other authors who responded, one did not have any further information available (Rong Hu, personal communication), and another described that the association between AR and outcome was smaller, but was unable to provide updated data (Naoko Honma, personal communication).

Among studies using IHC, there did not appear to be any difference between those where assessment was made using nuclear compared with nonnuclear staining. The odds ratios for 3-year OS for nuclear vs nonnuclear assessment were 0.42 (95% CI = 0.30 to 0.59) and 0.17 (95% CI = 0.02 to 1.55), and the test for subgroup difference was 0.43. Similar data were seen for 5-year OS (OR = 0.55, 95% CI = 0.44 to 0.70 vs OR = 0.35, 95% CI = 0.19 to 0.62; subgroup difference $P = .14$).

Although the definition of early vs metastatic breast cancer has been relatively standard over time, between 1987 and 2002,

### Figure 5. Five-year patient outcome by androgen receptor (AR) expression. **A** Five-year overall survival. **B** Five-year disease-free survival. Odds ratios in reference to AR expression compared with no AR expression for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval. The diamonds represent the estimated pooled effect (labeled total). Estimates of odds ratios were weighted and pooled using the Mantel–Haenszel random-effect model. Statistical heterogeneity was assessed using Cochran’s $Q$ and $I^2$ statistics. All $P$ values are two-sided.
patients with supraclavicular nodal metastases at diagnosis of breast cancer were classified as having metastatic disease (23). Before and after this time, these patients were considered to have early breast cancer. Exclusion of studies published during this time did not affect the association between AR-expression with either 3-year or 5-year OS (OR = 0.46, 95% CI = 0.36 to 0.58; OR = 0.38, 95% CI = 0.27 to 0.54, respectively). Furthermore, there was no apparent improvement in heterogeneity for 5-year OS (Cochran’s Q P < .001; F = 73%).

Only two studies, which involved a total of 78 patients, reported the influence of AR expression in HER2/neu-positive breast cancer. In these studies, there was no statistically significant effect of AR expression for either OS or DFS (OR = 1.58, 95% CI = 0.09 to 27.26, \( P = .75 \); OR = 0.92, 95% CI = 0.34 to 2.52, \( P = 0.87 \), respectively). As a consequence of this very small sample size, a meaningful analysis of the role of AR on outcome in women with HER2/neu-positive breast cancer was not possible.

Discussion
Various studies have attempted to describe the association of AR expression and outcome in early breast cancer. However, there remain unanswered questions about the direction and magnitude of effect of AR on outcome and whether the outcome is consistent among different subgroups. Here, we report a systematic review of 7693 patients included in 19 different studies. Our review shows that the expression of AR is a marker of good prognosis, with approximately a doubling of OS at 3 and 5 years. This effect appeared independent of coexpression of ER.

Based on preclinical findings of the effects promoted by the AR in breast cancer cell lines, we hypothesized better outcomes in women with tumors expressing both ER and AR compared with those expressing ER but not AR. Results of this review support this hypothesis. Preclinical data for ER-negative/AR-positive breast cancer suggest a poor prognosis, but the results of this review refute this. This finding may be explained by the association of AR with low proliferative activity as measured by Ki67 expression (26).

Among HER2-overexpressing breast tumors, AR can be highly expressed (18). AR expression appears more frequently in ER-negative and HER2-overexpressing tumors compared with those that also express ER (27). An interaction between AR and HER2 has been suggested (28). In this analysis, there were too few women with HER2-overexpressing tumors to definitively evaluate any association between AR expression and outcome in women with HER2/neu-positive breast cancer.

Our results are of clinical relevance in view of the emergence of new drugs targeting AR. Despite an association with good outcome, targeting of breast tumors expressing AR may be beneficial, similar to the effects of pharmacologic targeting of ER. Bicalutamide, a nonsteroidal antiandrogen, has been evaluated in metastatic breast cancer in a multicenter phase II trial of women with ER-negative/PR-negative breast cancer (<10% by IHC) and AR expression (>10% by IHC); 26 patients were treated with bicalutamide, and 21 were evaluated for response. Of these, 19% achieved complete or partial response or stable disease for longer than 6 months (3). These data warrant further investigation.

In women with ER-positive metastatic breast cancer, treatment with sequential lines of endocrine therapy (eg, tamoxifen, aromatase inhibitors, or fulvestrant) leads to development of resistance to ER-targeted therapy (29). Numerous mechanisms explaining this resistance have been suggested, including cross-talk with or increased expression of components of growth receptor pathways, especially those belonging to the epidermal growth factor superfamily or to insulin growth factor receptors. Other postulated mechanism include aberrant activation of other growth factor signaling pathways, overexpression of myc, cycline E1, and cycline D1, epigenetic modification, as well as mutations, deletions, and truncations in the ERα gene (30–35). In the presence of a nonfunctional ER, AR may be the primary driver of downstream signaling for cell growth (36). Pharmacological antagonism of AR has potential to reverse this signaling (36).

Two novel agents, enzalutamide, an irreversible inhibitor of AR-dependent signaling, and abiraterone, an inhibitor of the 17 α-hydroxylase/C17,20 lyase that inhibits synthesis of androgens, have become available for treatment of prostate cancer (37,38) and may have activity against breast cancer. Abiraterone, by inhibiting formation of adrenal androgens, may also lead to a reduction in circulating estrogens in postmenopausal women by reducing the substrate for aromatase. Cancer Research UK is conducting a trial of abiraterone acetate in postmenopausal women with advanced or metastatic breast cancer. This phase I/II open-label study is evaluating the safety, endocrine effects, and antitumor activity in patients with ER- and AR-expressing tumors (NCT00755885) (39). A further industry-sponsored multicenter study is evaluating the efficacy of abiraterone and prednisone with or without exemestane in postmenopausal women with ER-positive metastatic breast cancer after progression on nonsteroidal aromatase inhibitor therapy, regardless of AR expression (NCT01381874) (40).

There are several limitations of our study. First, this is a systematic review and meta-analysis of the literature, and therefore, we were only able to extract population-level rather than individual patient-level data. This reduced our ability to test for associations between variables in specific subgroups and also limited our ability to assess for sources of heterogeneity. Second, there was marked heterogeneity in patient populations, methods for assessing AR, definition of AR positivity, and follow-up of patients. For 5-year OS, the interstudy heterogeneity in effect size was influenced by a single outlying study, but for 5-year DFS, no clear source for heterogeneity was identified. Random-effects modeling and sensitivity analyses were conducted to address this heterogeneity, but these statistical methods may not be sufficient, and there is uncertainty about the accuracy of our 5-year DFS results. Finally, data on OS and DFS were extracted from text, figures, and tables of articles. We were unable to extract or model hazard ratios, so we have reported odds ratios for OS and DFS instead. Odds ratios provide a less robust measure of time to event outcomes because they do not take into account the time to an event of interest, but it was the only feasible method with the data available.

In conclusion, AR expression appears to be associated with improved OS and DFS regardless of ER expression. In view of the prognostic significance of AR, its association with activity of androgen therapy, and initial clinical data showing biologic activity of
targeting of AR, further studies evaluating therapeutic targeting of AR are warranted. The selection of ER-negative and AR-positive patients, as well as ER-positive and AR-positive patients who have developed endocrine resistance, would likely enrich for patients with activated AR-related pathways.

References


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I. Diaz-Padilla holds an employee position with Novartis AG; however, this meta-analysis was written before he commenced this appointment.

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