ORIGINAL RESEARCH

DOI: 10.37047/jos.2022-94227

Prognostic Value of Androgen Receptor Expression in Premenopausal Women with Estrogen Receptor-Positive Breast Cancer

Hasan Çağrı YILDIRIM[a], Meral ÜNER[b], Tuğba YILDIRAN ÖZMEN[c], Elvin CHALABIYEV[a], Deniz Can GÜVEN[a], Fatih KUŞ[a], Arif AKYILDIZ[a], Feride YILMAZ[a], Serkan YAŞAR[a], Yasemin EVLENDİ[c], Ömer DİZDAR[a], Şuayib YALÇIN[a], Ayşegül ÜNER[b], Sercan AKSOY[a]

[a]Division of Medical Oncology, Hacettepe University Institute of Cancer, Ankara, Türkiye
[b]Department of Pathology, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[c]Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye

ABSTRACT Objective: The prognosis of breast cancer in premenopausal women is variable and depends on the interactions between several biological factors. The androgen receptor (AR) could be one of the prognostic variables associated with survival in these patients; however, the data about this is scarce. The aim of the study was to examine the relationship between AR expression and survival outcomes in patients with estrogen receptor (ER)-positive premenopausal invasive breast carcinoma. **Material and Methods:** We analyzed the AR expression in premenopausal women with ER-positive invasive breast carcinomas and correlated this expression pattern with several clinical and pathological parameters, such as tumor size, lymph node status, progesterone receptor (PgR) status, and human epidermal growth factor receptor type 2 (HER-2) overexpression and evaluated the association of these parameters with survival using univariate analyses. Immunohistochemical analysis for AR, PgR, and HER-2, and semiquantitative evaluation of staining were performed. **Results:** AR expression was demonstrated in 61.44% of patients. There was no statistically significant association of AR with age, tumor size, lymph node status, stage, and PgR/HER-2 status (p values=0.758, 0.346, 0.604, 0.175, 0.070, 0.728, respectively). AR expression was not a prognostic factor for disease-free survival and overall survival in women with ER-positive cancer. **Conclusion:** AR expression was not associated with tumor size or ER/PgR/HER-2 status. Although AR expression has prognostic significance in triple-negative breast cancer, it is not a prognostic marker in hormone-positive premenopausal breast cancer.

Keywords: Premenopausal breast cancer; androgen receptor expression; prognostic marker

Globally, breast cancer is the most common type of cancer among women and is the second most common cause of death from cancer among women.[1] It is a heterogeneous entity with various clinical, histological, immunohistochemical (IHC), and genetic features. The course of the disease and the treatment algorithm depend on the histopathological type and grade of the tumor, size of the primary tumor, lymph node involvement, presence of metastases, expression of hormone receptors, and human epidermal growth factor receptor type 2 (HER-2) expression. Markers such as the Ki-67 index, E-Cadherin expression level, TP53 mutation, and Cathepsin D expression level have been found to have prognostic importance in breast cancer.[2-5]

In the pathogenesis of breast cancer, androgens induce cell proliferation, similar to estrogen and progesterone. It is known that androgen receptor (AR) expression is seen in 34 to 91.1% of women with breast cancer.[6-9] AR+ expression is more common in estrogen receptor (ER) + positive breast cancer, and tumors expressing ER and AR are reported to have a better prognosis compared to ER-negative tumors.[10-12] In the study by Castellano et al., AR positivity was found to be a good prognostic factor for overall surival in ER-positive patients. However, the proportion of premenopausal patients in this study was small.[13]

In this study, we sought to determine the impact of AR expression on disease-free survival (DFS) and

Correspondence: Hasan Çağrı YILDIRIM
Division of Medical Oncology, Hacettepe University Institute of Cancer, Ankara, Türkiye
E-mail: hasan-cagri@windowslive.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 07 Nov 2022 ***Received in revised form:*** 25 Feb 2023 ***Accepted:*** 27 Feb 2023 ***Available online:*** 08 Mar 2023

2452-3364 / Copyright © 2023 by Turkish Society of Medical Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

overall survival (OS) in women with premenopausal ER-positive breast cancer.

MATERIAL AND METHODS

Premenopausal women who underwent surgery for primary breast cancer and later received adjuvant chemotherapy were included in the study. In all, 83 women were included. Electronic medical records were used to obtain the data of the subjects. The epidemiological and pathological characteristics of the enrolled subjects were extracted from the data. Follow-up duration was counted from the date of the definitive surgery until death or last follow-up. The best representative/typical morphology of each tumor was identified on the hematoxylin-eosin slides. Subsequently, 6 tissue microarrays (TMAs) were constructed, including one core (3 mm in diameter) of each tumor from paraffin-embedded blocks corresponding to the counterpart of the marked areas. IHC staining for AR (clone AR 441, 1:200, retrieval ER2 30', DBS, Pleasanton, CA) was performed using Leica BOND-MAX, ElabscienceIHC/ISH automated immune-stainer from the unstained slides of TMA sections (4-5 mm thick). IHC ER, progesterone receptor (PgR), and HER-2 (ERBB2) staining scores were reported by various pathologists based on the College of American Pathologists guidelines.

Statistical analyses were conducted using version 20 of the Statistical Package for Social Sciences, IBM, United States of America. Independent t-tests were applied for the comparison of continuous variables. The χ^2 test was used to analyze categorical variables. Continuous variables are reported as means and standard deviations. Cox proportional hazard analysis was employed to evaluate the probability of recurrence or mortality in relation to the prognostic variables. The cumulative survival rates were determined using the Kaplan-Meier approach. p values below 0.05 were considered statistically significant.

All procedures were performed in accordance with the ethical guidelines set by the institutional and national research committees, as well as the Helsinki statement from 1964 and its later changes or other equivalent ethical guidelines. The Hacettepe University Ethics Committee (date: November 2, 2021, no: GO-22732) approved the project. Consent was obtained from the patients included in the study or their relatives.

RESULTS

A total of 83 premenopausal women with ER+ primary invasive breast carcinomas were included; the mean age of the cohort was 40.01±7.71 years. AR expression was detected in 61.44% of patients (51 out of 83). The median follow-up duration was 127.93 months.

AR expression was unrelated to tumor size (p=0.346), lymph node status (p=0.604), stage (p=0.175), PgR (p=0.070), HER-2 status (p=0.728), or tumor grade (p=0.751) (Table 1). Age (>40 vs. <40 years, p=0.98), tumor size [p=0.757, hazard ratio (HR): 0.84, confidence interval (CI) 95%: 0.285-2.493, T1-2 vs. T3-4], lymph node status (p=0.186, HR: 0.56, CI 95%: 0.244-1.314, N0-1 vs. N2-3), PgR status (p=0.815, HR=0.84, CI 95%: 0.195-3.615, negative vs. positive), stage (p=0.378, HR=0.68, CI 95%: 0.297-1.584, Stage 1-2 vs. Stage 3) were not independently associated with OS. HER-2 positive patients had shorter survival than HER-2 negative patients (median OS 35.41 months vs. NA, p<0.001, HR: 0.27, CI 95%: 0.172-0.428).

There were 25 relapses and 22 deaths during the follow-up period. In Kaplan-Meier log-rank analysis, there was no statistically significant difference in DFS and OS between the groups with an without AR expression (Figure 1, Figure 2). The median DFS could not be achieved in both groups (p=0.876, HR: 0.93 CI 95%: 0.41-2.10). Median OS could not be reached in AR+ and AR- groups (p=0.610 HR: 0.61 CI 95%: 0.26-1.42).

DISCUSSION

In our study, we found no correlation of AR expression with age, tumor size, lymph node involvement, and HER-2 expression in premenopausal women with hormone receptor-positive breast cancer. Similarly, we found that AR expression had no effect on DFS and OS.

It is known that AR plays a role in the pathogenesis of cancer in several organs, including the prostate.[14] Its effect on breast cancer has also been investigated for a long time, and studies have been done

TABLE 1: Descriptive statistics of women with AR+ and AR- negative tumor.

	Total (n=83)	AR+ (n=51)	AR- (n=32)	p values (AR+ vs AR-)
Age	40.01±7.98	40.00±7.44	40.04±8.90	0.758
Tumor size classification				
1	22 (26.25%)	11 (21.6%)	11 (34.4%)	0.346
2	45 (54.2%)	31 (60.8%)	14 (43.8%)	
3	15 (18.1%)	8 (15.7%)	7 (21.9%)	
4	1 (1.2%)	1 (2%)	0 (0%)	
Lymph node status				
Na	1 (1.2%)	0 (0%)	1 (3.1%)	0.604
0	19 (22.9%)	10 (19.6%)	9 (28.1%)	
1	34 (41%)	22 (43.1%)	12 (37.5%)	
2	16 (19.3%)	11 (21.6%)	5 (15.6%)	
3	13 (15.7%)	8 (15.7%)	5 (15.6%)	
Stage				
1	9 (10.8%)	3 (5.9%)	6 (18.8%)	0.175
2	39 (47%)	26 (51%)	13 (40.6%)	
3	35 (42.2%)	22 (43.5%)	13 (40.6%)	
Progesterone receptor				
Positive	78 (94%)	50 (98.1%)	28 (87.5%)	0.070
Negative	5 (6%)	1 (1.9%)	4 (12.5%)	
HER-2				
Positive	9 (10.8%)	5 (9.8%)	4 (12.5%)	0.728
Negative	74 (89.2%)	46 (90.2%)	28 (87.5%)	
Grade				
1	4 (4.8%)	3 (5.8%)	1 (3.1%)	0.751
2	39 (46.9%)	26 (50.9%)	13 (40.6%)	
3	35 (42.1%)	21 (941.1%)	14 (43.7%)	
Missing	5 (6.0%)	1 (1.9%)	4 (1.25%)	
Surgery type				
Breast conserving surgery	23 (27.8%)	12 (23.5%)	11 (34.3%)	0.320
Mastectomy	60 (72.2%)	39 (76.5%)	21 (65.6%)	
Radiotheapy				
Presence	72 (86.7)	45 (88.2%)	27 (84.3%)	0.742
Absence	11 (13.3)	6 (11.8%)	5 (15.7%)	
Chemotherapy				
Presence	83 (100%)	51 (100%)	32 (100%)	1
Absence				

AR: Androgen receptor; HER-2: Human epidermal growth factor receptor type 2.

with antiandrogen treatments in the past.[15] Yu et al. suggest that AR offsets the proliferative effects of ER in healthy breast tissue; hence, the aberrations in AR could accelerate carcinogenesis in the breast.[16]

While some studies found a relationship between AR expression and age, tumor size, and lymph node involvement, no such relationship was found in our study, as in the study by Agrawal et al.[17-19] However, in these studies, no subgroup analysis according to menopausal status was performed.

In a comprehensive meta-analysis, AR expression is found in 74.8% of ER-positive breast cancer, while it is 31.8% in ER-negative breast cancer.[10] Though AR positivity was associated with DFS and OS, no analysis according to the menopausal status of patients was performed.[10] Castellano et al. reported that AR expression was a good prognostic factor for OS in ER-positive patients; however, the proportion of premenopausal patients was very low in this study.[13] Similarly, Yang et al. reported that AR ex-

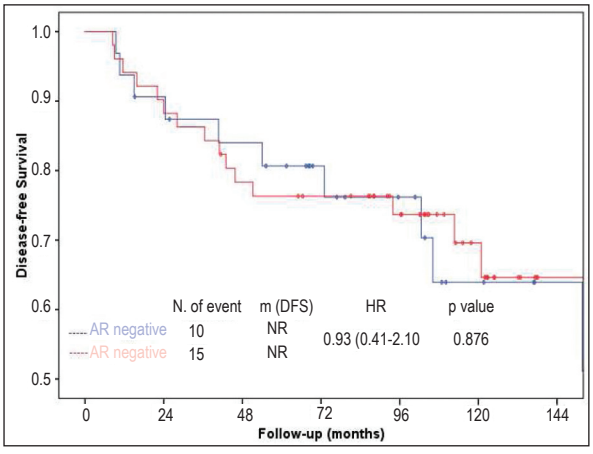


FIGURE 1: Relationship between androgen status and DFS.
DFS: Disease-free survival; HR: Hazard ratio; AR: Androgen receptor.

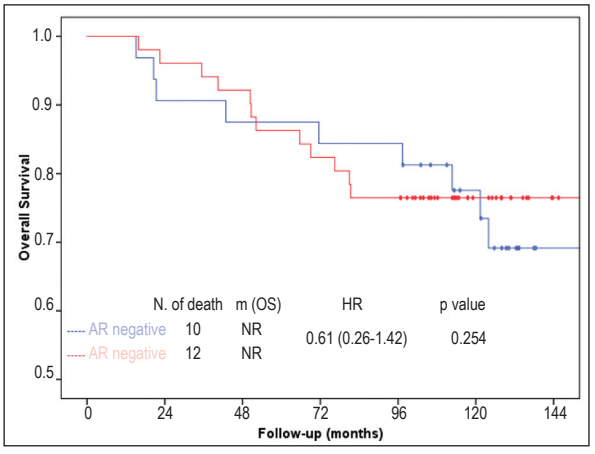


FIGURE 2: Relationship between androgen status and OS.
OS: Overall survival; HR: Hazard ratio; AR: Androgen receptor.

pression was a good prognostic factor for OS; however, no analysis according to the menopausal status was performed.[20] We could not find any study in the literature on the prognostic significance of AR positivity in premenopausal women with hormone receptor-positive breast cancer. In our study, no relationship was found between AR positivity and DFS and OS in patients with hormone receptor-positive breast cancer.

The lack of any targeted therapy in triple-negative breast cancer and its poor prognosis compared to other subtypes led to the investigation of AR-targeted therapies for this type of cancer. Good outcomes were obtained in studies with bicalutamide and enzalutamide.[21-23]

In hormone receptor-positive breast cancer, AR receptor positivity is thought to play a role in tamoxifen resistance.[24] In the trial in which the combination of abiraterone acetate with exemestane was evaluated, no DFS contribution could be observed.[25] The preclinical study of enzalutamide reported that it might be effective in hormone-positive breast cancer.[26] In Phase 1/2 studies, abiraterone acetate revealed anticancer activity in patients with postmenopausal ER and AR-positive metastatic breast cancer with androgen and estradiol concentrations below the analytical limit. After 24 weeks of therapy, 22% of patients achieved disease stability.[27]

In Phase 1/2 studies, abiraterone acetate revealed anticancer activity in patients with postmenopausal ER and AR-positive metastatic breast cancer with androgen and estradiol concentrations below the analytical limit. In 24 weeks of therapy, 22% of patients achieved disease stability.

In the Phase 2 study about abiraterone and prednisone treatment in advanced triple-negative breast cancer, all patients who responded to the treatment were postmenopausal.[28]

Our study included premenopausal women with hormone-positive breast cancer who received adjuvant chemotherapy and endocrine therapy; thus, it was a homogeneous group. Premenopausal females lacked data about the influence of ARs positivity on prognosis. Prospective studies with larger numbers of patients are needed to demonstrate the prognostic effect of ARs in premenopausal ER-positive early-stage breast cancer.

CONCLUSION

Although AR expression has prognostic importance in postmenopausal hormone-positive breast cancer patients, it has no effect on prognosis in premenopausal patients because of physiological differences between premenopausal and postmenopausal women.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that pro-

vides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hasan Çağrı Yıldırım, Meral Üner, Tuğba Yıldıran Özmen;* ***Design:*** *Hasan Çağrı Yıldırım, Elvin Chalabiyev, Deniz Can Güven, Fatih Kuş;* ***Control/Supervision:*** *Hasan Çağrı Yıldırım, Arif Akyıldız, Feride Yılmaz, Yasemin Evlendi, Şauyip Yalçın;* ***Data Collection and/or Processing:*** *Hasan Çağrı Yıldırım, Arif Akyıldız, Feride Yılmaz, Yasemin Evlendi, Şauyip Yalçın;* ***Analysis and/or Interpretation:*** *Ömer Dizdar, Ayşegül Üner, Fatih Kuş, Arif Akyıldız;* ***Literature Review:*** *Hasan Çağrı Yıldırım, Şauyip Yalçın, Sercan Aksoy;* ***Writing the Article:*** *Hasan Çağrı Yıldırım, Deniz Can Güven, Feride Yılmaz, Serkan Yaşar;* ***Critical Review:*** *Hasan Çağrı Yıldırım, Yasemin Evlendi, Öer Dizdar;* ***References and Fundings:*** *Hasan Çağrı Yıldırım, Sercan Aksoy;* ***Materials:*** *Hasan Çağrı Yıldırım, Serkan Yaşar, Feride Yılmaz.*

REFERENCES

1. Miller KD, Nogueira L, MariottoAB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin.2019;69(5):363-385. [Crossref] [PubMed]
2. Lal P, Tan LK, Chen B. Correlationof HER-2 status with estrogen and progesterone receptors and histologic features in 3,655invasive breast carcinomas. Am J Clin Pathol. 2005;123(4):541-546. [Crossref] [PubMed]
3. Mallon E, Osin P, Nasiri N, BlainI, Howard B, Gusterson B. The basic pathology of human breast cancer. J Mammary Gland BiolNeoplasia. 2000;5(2):139-163. [Crossref] [PubMed]
4. Koo JS, Jung W, Jeong J. Thepredictive role of E-cadherin and androgen receptor on in vitro chemosensitivity intriple-negative breast Cancer. Jpn J Clin Oncol. 2009;39(9):560-568. [Crossref] [PubMed]
5. Sørlie T, Wang Y, Xiao C, et al.Distinct molecular mechanisms underlying clinically relevant subtypes of breast cancer: geneexpression analyses across three different platforms. BMC Genomics. 2006;7:127. [Crossref] [PubMed] [PMC]
6. Ogawa Y, Hai E, Matsumoto K, IkedaK, Tokunaga S, Nagahara H, et al. Androgen receptor expression in breast cancer:relationship with clinicopathological factors and biomarkers. Int J Clin Oncol.2008;13(5):431-435. [Crossref] [PubMed]
7. Agrawal AK, Jeleń M, GrzebieniakZ, Zukrowski P, Rudnicki J, Nienartowicz E. Androgen receptors as a prognostic andpredictive factor in breast cancer. Folia Histochem Cytobiol. 2008;46(3):269-276. [Crossref] [PubMed]
8. Miller WR, Telford J, Dixon JM,Hawkins RA. Androgen receptor activity in human breast cancer and its relationship withoestrogen and progestogen receptor activity. Eur J Cancer Clin Oncol. 1985;21(4):539-542. [Crossref] [PubMed]
9. Søreide JA, Lea OA, Varhaug JE, Skarstein A, Kvinnsland S. Androgenreceptors in operable breast cancer: relation to other steroid hormone receptors,correlations to prognostic factors and predictive value for effect of adjuvant tamoxifentreatment. Eur J Surg Oncol. 1992;18(2):112-118. [PubMed]
10. Vera-Badillo FE, Templeton AJ, deGouveia P, et al. Androgen receptor expression and outcomes in early breast cancer: asystematic review and meta-analysis. J Natl Cancer Inst. 2014;106(1):djt319. [Crossref] [PubMed]
11. Park S, Koo JS, Kim MS, et al.Androgen receptor expression is significantly associated with better outcomes in estrogenreceptor-positive breast cancers. Ann Oncol. 2011;22(8):1755-1762. [Crossref] [PubMed]
12. Hu R, Dawood S, Holmes MD, et al.Androgen receptor expression and breast cancer survival in postmenopausal women. Clin CancerRes. 2011;17(7):1867-1874. [Crossref] [PubMed] [PMC]
13. Castellano I, Allia E, AccortanzoV, et al. Androgen receptor expression is a significant prognostic factor in estrogenreceptor positive breast cancers. Breast Cancer Res Treat. 2010;124(3):607-617. [Crossref] [PubMed]
14. Koochekpour S. Androgen receptorsignaling and mutations in prostate cancer. Asian J Androl. 2010;12(5):639-657. [Crossref] [PubMed] [PMC]
15. Kennedy BJ. Fluoxymesteronetherapy in advanced breast cancer. N Engl J Med. 1958;259(14):673-675. [Crossref] [PubMed]
16. Yu Q, Niu Y, Liu N, et al.Expression of androgen receptor in breast cancer and its significance as a prognosticfactor. Ann Oncol. 2011;22(6):1288-1294. [Crossref] [PubMed]
17. Shim HS, Jung WH, Kim H, Park K,Cho NH. Expression of androgen receptors and inhibin/activin alpha and betaA subunits inbreast apocrine lesions. APMIS. 2006;114(5):352-358. [Crossref] [PubMed]
18. Gatalica Z. Immunohistochemicalanalysis of apocrine breast lesions. Consistent over-expression of androgen receptoraccompanied by the loss of estrogen and progesterone receptors in apocrine metaplasia andapocrine carcinoma in situ. Pathol Res Pract. 1997;193(11-12):753-758. [Crossref] [PubMed]
19. Riva C, Dainese E, Caprara G, etal. Immunohistochemical study of androgen receptors in breast carcinoma. Evidence of theirfrequent expression in lobular carcinoma. Virchows Arch. 2005;447(4):695-700. [Crossref] [PubMed]
20. Yang Y, Min A, Lee KH, et al.Prognostic role of androgen receptor expression in surgically resected early breast cancerpatients. J Breast Cancer. 2020;23(2):182-193. [Crossref] [PubMed] [PMC]
21. Arce-Salinas C, Riesco-MartinezMC, Hanna W, Bedard P, Warner E. Complete response of metastatic androgen receptor-positivebreast cancer to bicalutamide: case report and review of the literature. J Clin Oncol.2016;34(4):e21-24. [Crossref] [PubMed]
22. Gucalp A, Tolaney S, Isakoff SJ,et al; Translational Breast Cancer Research Consortium (TBCRC 011). Phase II trial ofbicalutamide in patients with androgen receptor-positive, estrogen receptor-negativemetastatic Breast Cancer. Clin Cancer Res. 2013;19(19):5505-5512. [Crossref] [PubMed] [PMC]
23. Traina TA, Miller K, Yardley DA,et al. Enzalutamide for the treatment of androgen receptor-expressing triple-negative breastcancer. J Clin Oncol. 2018;36(9):884-890. [Crossref] [PubMed] [PMC]
24. De Amicis F, Thirugnansampanthan J, Cui Y, et al. Androgen receptor overexpression induces tamoxifen resistance in humanbreast cancer cells. Breast Cancer Res Treat. 2010;121(1):1-11. [Crossref] [PubMed] [PMC]
25. O'Shaughnessy J, Campone M, BrainE, et al. Abiraterone acetate, exemestane or the combination in postmenopausal patients withestrogen receptor-positive metastatic breast cancer. Ann Oncol. 2016;27(1):106-113. [Crossref] [PubMed] [PMC]
26. Cochrane DR, Bernales S, JacobsenBM, et al. Role of the androgen receptor in breast cancer and preclinical analysis ofenzalutamide. Breast Cancer Res. 2014;16(1):R7. [Crossref] [PubMed] [PMC]
27. Ng CHM, Macpherson I, Rea D, etal. Phase I/II study of abiraterone acetate (AA) in estrogen receptor (ER) or androgenreceptor (AR) positive metastatic breast cancer (MBC). European Society for Medical OncologyCongress; 2012. [Crossref]
28. Bonnefoi H, Grellety T, Tredan O,et al. A phase II trial of abiraterone acetate plus prednisone in patients withtriple-negative androgen receptor positive locally advanced or metastatic breast cancer(UCBG 12-1). Ann Oncol. 2016;27(5):812-818. [Crossref] [PubMed]