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Breast Cancer

Androgen Receptor Expression in ER and PR Negative Breast Cancer—A Study from a Tertiary Hospital in Northern India

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Abstract

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Objectives Breast cancer is the leading cause of cancer-related deaths in women. Estrogen (ER) and progesterone receptor (PR) status and Her2 overexpression are major determinants in therapeutic decision making. Triple-negative breast cancers (TNBCs) have limited treatment options. Androgen receptor (AR) expression opens up therapeutic avenues for these patients. The aim of this article was to study the immunohistochemical expression of ARs in ER and PR Negative breast carcinomas and to correlate AR expression with various clinical, histopathological, and other immunohistochemical parameters.

Materials and Methods It is a cross-sectional study including 105 ER and PR Negative cases of breast carcinoma. Clinical parameters, histopathology, and immunohistochemical expression of AR, Her2, and Ki67 were analyzed in all cases.

Results AR expression was observed in 63.8% of ER and PR Negative breast cancers. In this group, AR expression was strongly associated with Her2 co-expression (89.2%) as compared to TNBCs (45.8%); p-value = 0.0002. Significant correlation was also observed between AR expression and tumor necrosis (p-value = 0.034) and postmenopausal status ($p = 0.007$).

Conclusion Our study shows that significant proportion of ER and PR Negative breast carcinomas (ER- PR- Her2+ and TNBCs) show AR expression. We strongly recommend routine evaluation of all hormone receptor-negative breast carcinomas for AR status by immunohistochemistry.

Keywords

- androgen
- breast carcinoma
- estrogen
- Her2
- TNBC

Introduction

Breast cancer is the most prevalent malignancy in women worldwide with 2.26 million new cases diagnosed each year.[1] It is also the most common cancer in Indian women comprising 26.3% of all malignancies and is the leading cause of cancer related death.[1]

Breast cancer is a heterogenous disease with different clinical outcomes for same stage and histopathological category.[2] Evaluation by immunohistochemistry (IHC) for estrogen receptor (ER), progesterone receptor (PR) and Her2 guides therapeutic decision making and also provides prognostic information.[3]

Approximately 65 to 75% of breast carcinomas are ER/PR positive that respond to hormonal therapies and have a favorable prognosis.[4] Her2 expression is seen in 12 to 20% of breast carcinomas and these show response to therapies targeting Her2 receptors like transtuzumab. However, targeted therapies

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are unaffordable for a significant proportion of the population in low- and middle-income countries.[4,5]

Triple-negative breast cancers (TNBCs) comprise 10 to 15% of breast carcinomas.[6] This subgroup is more aggressive with higher frequency of relapses, a higher risk of development of metastasis, and poor overall survival.[7] Their mainstay of treatment is chemotherapy in combination with surgery and radiation therapy. Clinical trials and studies are underway for newer therapeutic targets for this subgroup such as androgen targeted therapy, tyrosine kinase inhibitors, poly ADP-ribose polymerase-1 inhibitors, antiangiogenic factors, immune checkpoint inhibitors, and histone deacetylase inhibitors. In addition, the PI3K/AKT/mTOR pathway is another proposed target for the treatment of TNBCs.[8,9]

Androgen receptor (AR) is a sex steroid hormone receptor and plays an important role in breast carcinogenesis.[10] Previous studies have shown that the overall expression of AR in breast cancer ranges from 60 to 89%.[11] It is seen in 74.8% of ER-positive tumors conferring them a better outcome.[12,13] About 32.8% of ER-negative tumors are AR-positive.[12] The estimated AR expression in TNBCs is about 10 to 32%.[14] It is a good prognostic indicator and predicts response to chemotherapy within the TNBC subgroup.[15] AR expression is associated with improved overall survival at both 3 and 5 years.[12] The molecular apocrine carcinoma (MAC) subgroup of TNBCs invariably expresses AR and responds favorably to taxanes.[16]

AR positivity potentially opens up an avenue of therapeutic target with antiandrogen therapy that may benefit patients with TNBCs. AR-targeted therapies may also be important for breast cancers that have developed resistance to current hormone and Her2 directed therapies.[17]

Aims and Objectives

1. To study the IHC expression of AR in ER and PR Negative breast carcinomas.
2. To correlate AR expression with various clinical, histopathological, and other IHC parameters.

Materials and Methods

The cross-sectional study was carried out at a tertiary care teaching hospital in Northern India using convenience sampling.

IHC for AR was done using the HRP HiDef 2-step polymer detection kit, Cell Marque, United States using a dilution of 1:100 for AR antibody (SP107 clone, Rabbit monoclonal). American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines were followed for IHC interpretation of ER, PR, and Her2. For AR, similar to ASCO/CAP guidelines for interpreting ER/PR IHC, nuclear expression of more than or equal to 1% tumor cells was taken as positive. The AR assessment was done individually by two pathologists, KSK and SS. Any discordances were mutually discussed and consensus reached. Statistical analysis was done using percentages, chi-squared and Fisher's exact tests. Where ever data for a particular variable was missing or not applicable, it was excluded from analysis.

Selection Criteria

Inclusion criteria: Cases of breast carcinoma negative for ER and PR were included in the study (►Fig. 1).
Exclusion criteria: Cases in which the biopsied tissue was inadequate for evaluation were excluded (►Fig. 1).

Results

A total of 575 patients of breast cancer were diagnosed during the study period. Of these IHC data was available for 295 cases. ER was positive in 63.7% of cases ($n = 188$) and PR was positive in 46.1% ($n = 136$) of cases. Her2 data was available in 263 cases of which 20.9% were positive ($n = 55$), 19.4% ($n = 51$) were equivocal, and the rest were negative.

There were 105 cases of ER and PR Negative breast carcinomas that were included in the study. Of these, 45 were core biopsies, 44 mastectomy specimens, 7 lumpectomies, 5 wedge biopsies, and 4 were metastatic-site biopsies. All cases were women with a mean age of 52.8 ± 11.5 years. Invasive ductal carcinoma was the most common histological type of breast cancer comprising 95 cases (89.5%). Other histological types included lobular ($n = 1$), metaplastic ($n = 4$), medullary ($n = 4$), and micropapillary ($n = 1$) carcinomas (►Fig. 2).

The overall AR positivity was 63.8%. Thirty-seven cases were Her2 positive, 59 were negative, and 9 equivocal on IHC. The data on Her2 testing by fluorescence in situ hybridization was not available (►Figs. 3–5).

The various clinicopathological parameters are shown in ►Table 1.

The various clinicopathological parameters assessed in relation to AR expression are presented in ►Table 2.

The AR-positive group had a mean age of 54.7 ± 11.6 years, while the AR-negative subgroup presented earlier at a mean age of 49.47 ± 10.6 years. AR expression studied in relation to menopausal status showed higher rate of AR positivity in the postmenopausal subgroup with a statistically significant p-value of 0.007.

A statistically significant association was seen between necrosis and AR expression. Presence of tumor necrosis was associated with higher AR expression with a p-value of 0.034. Twelve cases out of 105 had received neoadjuvant chemotherapy prior to surgery. Necrosis was present in all of these cases.

A significant association was seen between AR expression and Her2 overexpression with a p-value of 0.00002. Of the 37 Her2-positive cases, AR expression was seen in 33 (89.2%) cases (►Table 2).

The assessment of AR expression with tumor size and pathological nodal metastasis status was available in 44 and 48 cases, respectively. The AR expression did not correlate with these two parameters; however, this analysis was limited by small number.

Of the total 105 cases of ER and PR Negative breast cancers, 59 were TNBCs. In the TNBC subgroup, 27 cases

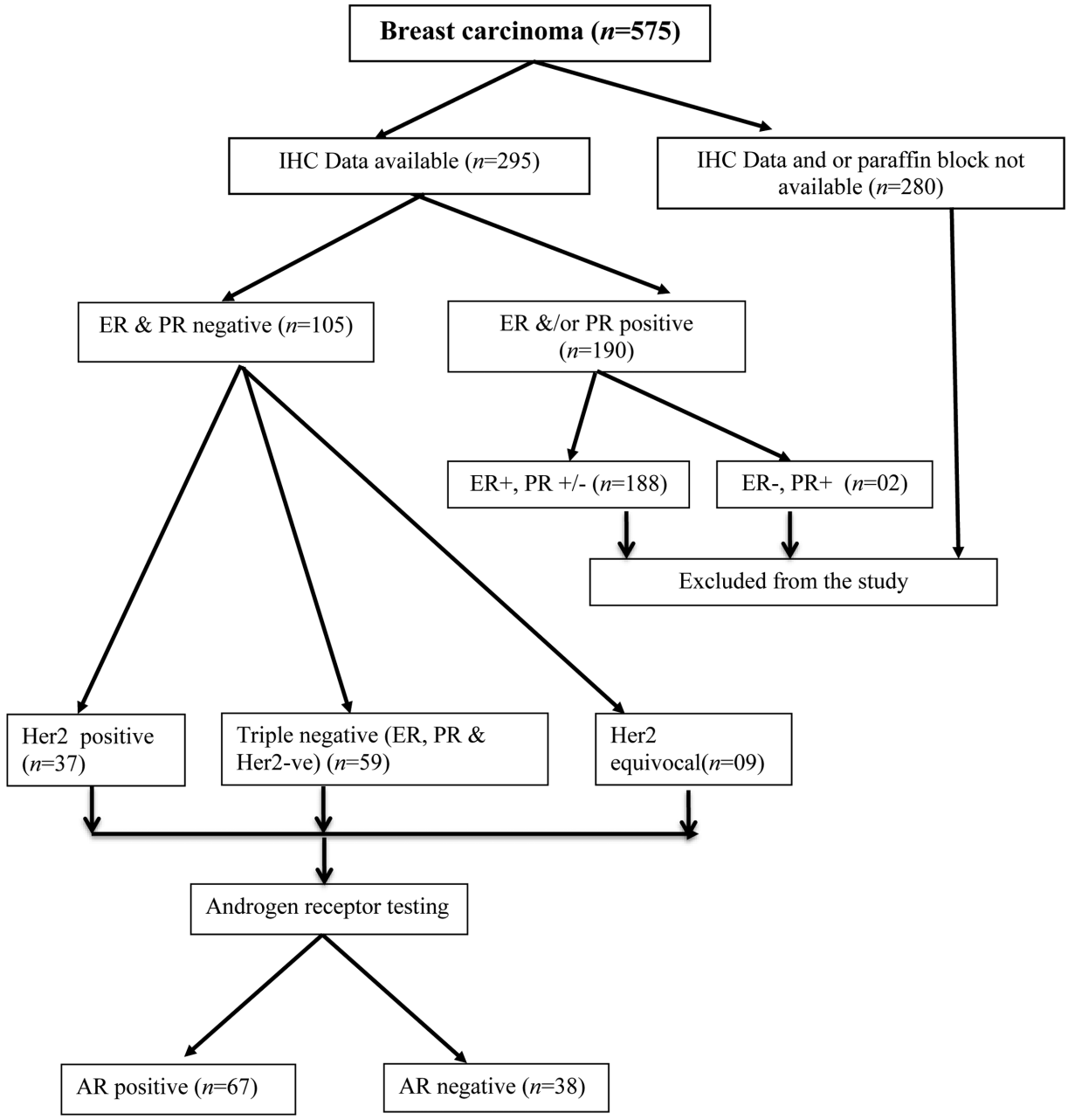

Fig. 1 Inclusion and exclusion criteria.

(45.8%) showed AR expression. A trend of higher AR positivity was appreciated with increasing tumor diameter, higher tumor grade, presence of tumor necrosis, presence of nodal metastasis, and postmenopausal status. However, due to small sample size *p*-values were not significant in subgroup analysis.

Discussion

Limited data is available on AR expression in ER and PR Negative tumors as a group. However, several studies have been carried out which have assessed AR expression in ER-negative tumors and PR-negative tumors separately. In this study, AR expression was seen in 63.8% of the hormone receptor-negative cases that is a little higher compared to a study by Micello et al that showed 56.6% AR positivity (►Table 3).[18] A comparison of various studies showing AR expression in ER-/PR- and only ER tumors is shown in ►Table 3. The higher percentage of AR positivity in the current study was probably due to a lower cutoff for AR expression (≥1%) and could partly also reflect geographic variation. However, using 10% cutoff for AR positivity, the percentage of AR-positive cases decreased to 58% which is comparable to that observed by Micello et al.[18]

Mean age of the ER/PR-negative breast cancer patients in this study was 52.8 ± 11.5 years. The AR-positive group had a higher mean age as compared to other studies. In study by Micello et al, the mean age of ER/PR-negative subgroup was

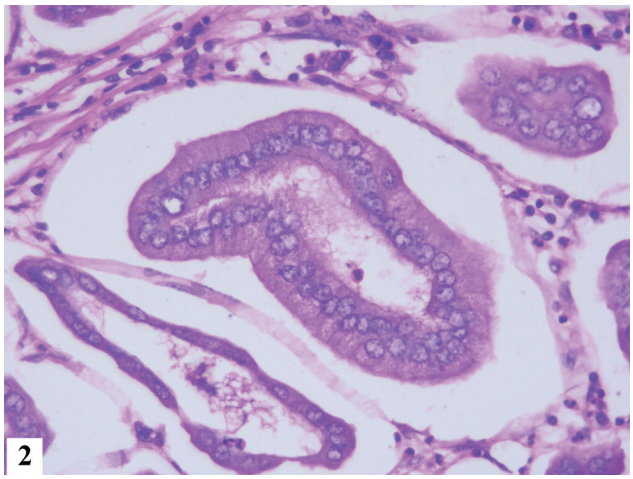

Fig. 2 Micropapillary breast carcinoma, hematoxylin and eosin 400x.

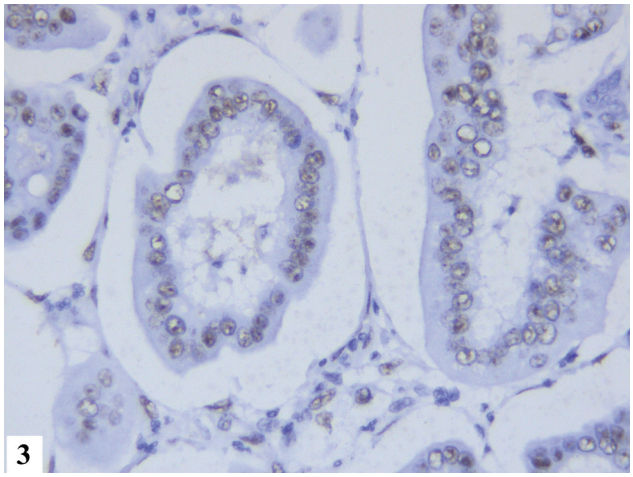

Fig. 3 Micropapillary breast carcinoma showing androgen receptor positivity, immunohistochemistry 400x (same case as ►**Fig. 2**).

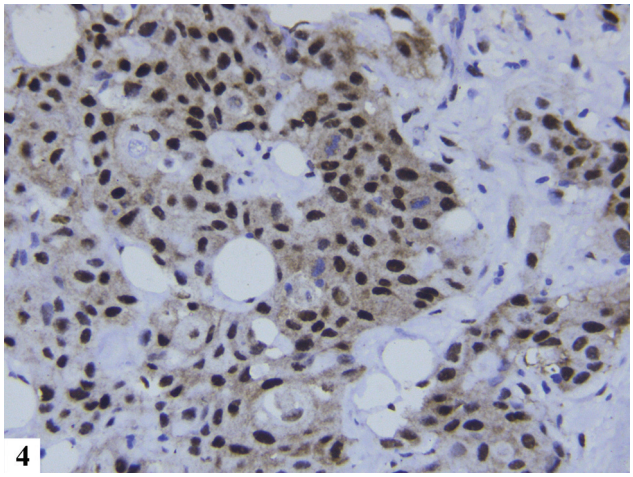

Fig. 4 Androgen receptor expression in breast carcinoma, immunohistochemistry 400x.

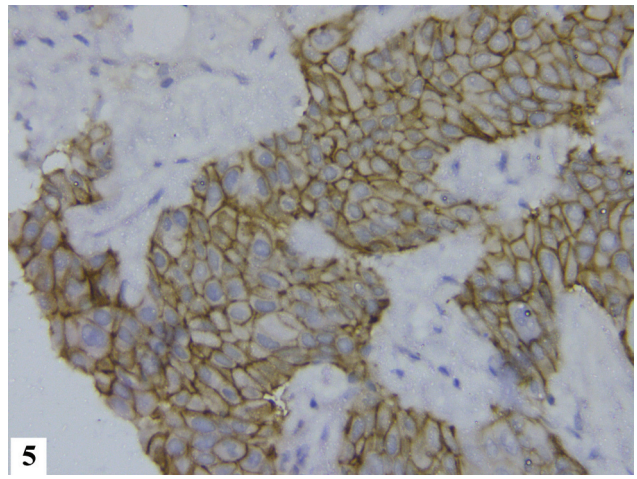

Fig. 5 Her2-positive breast carcinoma, immunohistochemistry 400x (same case as ►**Fig. 4**).

Table 1 Clinicopathological parameters in ER and PR Negative breast cancers

Clinicopathological Parameter	Number (%)
AR expression ($n = 105$)	
AR positive	67 (63.8)
AR negative	38 (36.2)
HER2 expression ($n = 105$)	
HER2 positive	37 (35.2)
HER2 equivocal	9 (8.6)
HER2 negative	59 (56.2)
Grade ($n = 105$)	
Grade 2	13 (12.4)
Grade 3	92 (87.6)
Tumor size[a] ($n = 44$)	
T1	6 (13.6)
T2	27 (61.4)
T3 and T4	11 (25)
Nodal metastasis[b] ($n = 48$)	
Nodal metastasis present	29 (60.4)
Nodal metastasis absent	19 (39.6)
Necrosis ($n = 105$)	
Present	88 (83.8)
Absent	17 (16.2)
Menopausal status ($n = 105$)	
Premenopausal	29 (27.6)
Perimenopausal	5 (4.8)
Postmenopausal	71 (67.6)

Abbreviations: AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.
[a]T1 $\leq$ 2 cm; T2 > 2 - $\leq$5 cm; T3 and T4 > 5 cm. Included cases in which pathological tumor size was available.
[b]Included cases in which the pathological nodal status was available.

Table 2 Clinicopathological parameters in relation to AR expression

Parameters	AR positive	AR negative	Total	*p*-Value
	Number (%)	Number (%)		
Menopausal status ($n = 100$)[a]				
Premenopausal	12 (41.4)	17 (58.6)	29	0.007
Postmenopausal	50 (70.4)	21 (29.6)	71	
Family history ($n = 64$)[b]				
Present	4 (50)	4 (50)	8	1.0
Absent	31 (55.4)	25 (44.6)	56	
Parity ($n = 67$)[c]				
≤2	19 (63.3)	11 (36.7)	30	0.921
>2	23 (62.2)	14 (37.8)	37	
Tumor size in cm ($n = 44$)[d]				
≤2	2 (33.3)	4 (66.7)	6	0.274
>2–≤5	16 (59.3)	11 (40.7)	27	
>5	8 (72.7)	3 (27.3)	11	
Nodal metastasis ($n = 48$)[e]				
Present	21 (72.4)	8 (27.6)	29	0.08
Absent	9 (47.4)	10 (52.6)	19	
Grade ($n = 105$)[e]				
II	8 (61.5)	5 (38.5)	13	1.0
III	59 (64.1)	33 (38.9)	92	
Necrosis ($n = 105$)				
None	7 (41.2)	10 (58.8)	17	0.034
Present	60 (68.2)	28 (31.8)	88	
Her2 ($n = 96$)[f]				
Positive	33 (89.2)	4 (10.8)	37	0.00002
Negative	27 (45.8)	32 (54.2)	59	
Ki67 ($n = 36$)[g]				
≤50	9 (69.2)	4 (30.8)	13	1.0
>50	16 (69.6)	7 (30.4)	23	

Abbreviation: AR, androgen receptor.
[a]Five perimenopausal cases excluded from statistical analysis (Case number inadequate for statistical significance)
[b]Included only the cases in which the clinical information was available.
[c]Included only the cases in which the clinical information was available.
[d]Included cases in which pathological tumor size was available. Core biopsies excluded.
[e]Included cases in which the pathological nodal status was available.
[f]Nine cases equivocal for HER2 expression were excluded from statistical analysis.
[g]Ki67 IHC was not available for 69 cases.

65.8 ± 8.67.[18] This late presentation of cancer may be attributed to geographical variation. The percentage of AR expression was higher in presence of nodal metastasis (72.4%) with a *p*-value of 0.08. Similar to this study, Micello et al found increasing AR expression with nodal involvement (*p*-value <0.034).[18]

The findings of a higher mean tumor size in AR-positive group are in agreement with the study by Micello et al; however, association was not statistically significant.[18] In contrast, study by Agoff et al observed decrease in AR expression with increasing tumor size.[19]

In this study, necrosis was associated with higher AR expression with a significant *p*-value of 0.034. It has not been evaluated in the other two studies.

There was no significant association of AR expression with tumor grade, family history, or lymph node metastasis. Micello et al found significant association with lymph node metastasis and Agoff et al found significant association with tumor grade and tumor size.[18,19]

A comparison of clinicopathological parameters in relation to AR expression with other relevant studies is presented in ►Table 4.

Table 3 Comparison of AR expression in ER-negative breast cancers in various studies

Study	Total cases	AR positivity (%)	AR-positive criterion
Present study (ER−/PR−)	105	63.8	≥1%
Micello et al (ER−/PR−)[18]	226	56.6	≥10%
Agoff et al (ER−)[19]	69	49	≥5%
Safarpour et al (ER−)[20]	67	47.8	≥1%
Collins et al (ER−)[14]	512	43.9	≥10%
Park et al (ER−)[21]	130	50	≥10%

Abbreviations: AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.
AR expression and clinicopathological parameters

Table 4 A comparison of AR expression with various clinicopathological parameters

Clinicopathological parameter	Present study (ER−/PR−)	Micello et al (ER/PR−)[18]	Agoff et al (ER−)[a,19]
Menopausal status	Significant *p*-value 0.007	–	Significant *p*-value <0.001
Lymph node metastasis	Not significant *p*-value 0.08	Significant *p*-value < 0.034	Not significant *p*-value 0.9
Tumor grade	Not significant *p*-value 1.0	Not significant *p*-value 0.89	Significant *p*-value < 0.03
Tumor size	Not significant *p*-value 0.274	Not significant *p*-value 0.38	Significant *p*-value < 0.03[a]
Family history	Not significant *p*-value 1.0	–	Not significant *p*-value 0.4
Necrosis	Significant *p*-value 0.034	–	–

Abbreviations: AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor.
[a]Significant association was observed with decreasing tumor size.

AR and Her2 Expression

Her2 overexpression showed strong association with AR expression (p-value = 0.00002). Several other studies have also found a highly significant statistical association between higher AR expression in the Her2 expressing ER/PR-negative tumors[18,19] (►Table 5).

AR function is modified by coexpression of ER and Her2 through complex molecular interplay leading to variable prognostic outcomes. It is postulated that AR in the ER-positive tumors has antiproliferative action as opposed to proproliferative effect in ER-negative breast cancers.[22] A cross-talk exists between AR and ER via which they inhibit each other's activity. AR also mediates the ligand-dependent activation of the Wnt and Her2 signaling pathways.[23]

Complex cross-talk exists between AR and Her2 receptors in the absence of interplay of ER expression.[23] AR upregulates Her2/Her3 signaling pathway leading to downstream activation of myelocytomatosis oncogene.[24] AR activates PI3K via FOXA1 and Wnt/ β-catenin pathways. Addition of Her2 inhibitor along with Flutamide (AR antagonist) causes a higher degree of proliferative inhibition of tumor cells.[23]

AR-targeted therapies are a newly emerging therapeutic options for the treatment of TNBC. These include inhibition of androgen synthesis, inhibition of co-activators, use of non-androgenic AR binding hormones, activation of membrane

Table 5 Her2 expression and AR expression in the hormone receptor negative group

Study	Her2+ (%)		Her2− (%)		*p*-Value
	AR+	AR−	AR+	AR−	
Present	89.2	10.8	45.8	54.2	0.00002
Micello et al[18]	76.7	23.3	30.4	69.6	$<10^{-10}$
Agoff et al[19]	81.2	18.8	38.5	61.5	0.003
Park et al[21]	74.4	25.6	37.9	62.1	<0.001

Abbreviation: AR, androgen receptor.

AR, and medroxyprogesterone acetate. Clinical trials have been completed for use of CYP17 inhibitors, seviteronel for treatment of TNBC, and abiraterone acetate for MAC. Clinical trials are underway for use of ribociclib and bicalutamide in AR+ TNBC and palbociclib in combination with bicalutamide for the treatment of AR+ metastatic breast cancer. The use of enzalutamide with paclitaxel before surgery in treating patients with stage I to III AR-positive TNBC and feasibility study of adjuvant enzalutamide for the treatment of early stage AR (+) TNBC are also being studied. Trial for combination of enobosarm with pembrolizumab for AR-positive metastatic TNBC is underway.[25]

AR targeting drugs may be used as second line agents for Her2-positive breast cancers. Combination of enzalutamide with transtuzumab is in phase 2 of clinical trial for the treatment of metastatic or locally advanced Her2 +/AR+ breast cancer.[26]

Conclusion

- AR expression was seen in 63.8% of ER and PR Negative breast carcinomas.
- Within this group, AR expression had strong association with Her2 positivity and was also expressed in 45.8% of TNBCs.
- Androgen expression by IHC should be analyzed in all ER and PR receptor-negative breast carcinomas.

Authors' Contributions

Kanwardeep Kwatra, Pamela Alice Kinsley, and Sumeet Sidhu helped in planning and conceptualization and designing. Sumeet Sidhu and Kanwardeep Kwatra conducted and reported the study and analyzed and interpreted the data. Sumeet Sidhu acquired the data.

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Conflict of Interest

None declared.

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