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Evaluation of Androgen Receptor in Breast Carcinoma and its Correlations with Er, Pr, Her2/Neu, Triple Negative Receptor Status and Clinical Parameters

Avanish Kumar Saxena[1*], Mayank Agarwal[2], Juhi Singhal[3], Amrita Gupta[4]

[1]Professor; [2]Senior Resident; [3]Associate Professor, Department of Surgery; [4]Assistant Professor, Department of Anaesthesia, S.N Medical College, Agra, UP, India.

ABSTRACT

Background: *Breast cancer is the second most common malignancy in Indian women. Among the members of the steroid receptor superfamily the role of estrogen and progesterone receptors (ER and PR) is well established in breast cancer in predicting the prognosis and management of therapy, however, little is known about the clinical significance of androgen receptor (AR) in breast carcinogenesis. The present study was aimed to evaluate the expression of AR in breast cancer and to elucidate its clinical significance by correlating it with other hormonal receptors and clinical parameters.*

Methods*: It was a prospective study which include 30 patients of histopathologically proven breast cancer admitted to department of surgery at S.N Medical College Agra .Expression of AR, ER, PR, HER2/ neu receptor by immunohistochemistry (IHC) and clinical parameters were studied.*

Results*: AR expression is related to ER(P<0.015), PR(p<0.008) and triple negative breast cancer patients (p <0.008). There is significant correlation between AR and menopausal status(p<0.006) while no significant correlation was found with age and parity.*

Conclusions*: Since there is significant association of AR in triple negative and post-menopausal women so we can say that AR expression possibly help in confirming their predictive role for therapeutic response in breast cancer patients*

Key words*: Androgen Receeptor, Estrogen Receptor, Triple Negative , Breast Cancer*

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Corresponding Author
Dr. Avanish Kumar Saxena, 89, Vimal Vatika, Karmyogi Enclave, Kamla Nagar, Agra.

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INTRODUCTION

The prevalence of breast cancer in India is increasing. It constitutes 25-30% of all malignancies and it is second most common malignancy after cancer cervix in females in India but in urban areas it is most prevalent malignancy in women and its incidence rate is continuously increasing. Moreover since 50% breast cancer patients in India present with advanced disease (stages 3 and 4) and younger patients have relatively more aggressive disease, there are poor survival outcomes in Indian patients.

Due to hormonal changes at puberty, the ductal epithelial cells transform and develop the potential for proliferation and differentiation.[1] Steroid hormones stimulate breast cell proliferation by binding to their respective receptors, resulting in the clonal propagation of normal as well as tumour cells.

AR is known to have a role in normal prostate development and progression of prostate cancer.AR has also been involved in differentiation, development and regulation of

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breast cell growth. Androgen may influence breast cancer risk indirecty through their conversion to estradiol or by competing for steroid binding proteins, or directly by binding to the AR.[2]

Bicalutamide is a nonsteroidal antiandrogen therapy used to treat metastatic prostate cancer. A phase II trial of bicalutamide is currently enrolling women with ER−/PR−/AR+ breast cancers (ClinicalTrials.gov Identifier NCT00468715). Although there are no published studies of AR targeted therapy and breast cancer survival, taken together these data suggest that AR status may have a clinically important role in terms of prognosis and treatment for women with triple negative breast cancer.

It has been shown that AR expression correlates well with ER expression as well as PR expression. Hence the co-expression status of receptors may identify more accurately those patients with breast cancer.[3]

There is scientific consensus that breast cancer is a systemic disease and multimodality treatment is needed to cure or prevent residual cancer after surgery. The three well-established systemic treatments for breast cancer are chemotherapy, hormonal therapy and biological targeted therapy apart from surgery.

Systemic chemotherapy is generally considered to have the highest efficacy against breast cancer, but it can cause serious side effects for the patient. Compared to chemotherapy, hormonal treatment has fewer side effects, but it can only be used if the breast tumor cells express the estrogen receptor (ER). The biological targeted therapies are relatively new weapon to fight breast cancer but due to their high cost they are less affordable for developing countries.[4,5] Currently, there are two types of hormonal treatments available for ER responsive breast cancer which use either an anti-ER drug (e.g., tamoxifen) or an aromatase inhibitor (e.g., letrozole). The biological targeted therapies are relatively new weapon to fight breast cancer but due to their high cost they are less affordable for developing countries.[6,7]

The effect of tamoxifen and medroxy progesrone acetate are meditiated by AR.[8,2] Mortality and morbidity are higher for patients with triple negative breast cancer,

Most patients with triple negative breast cancers express AR so androgens can indeed inhibit breast cancer cell growth via the AR.[9,10]

This study was done to evaluate the expression of AR in cases of breast carcinoma patients and its correlation with ER, PR, HER-2neu and triple negative receptor status and to establish the correlation between AR receptor and following clinical parameters of patient i.e Age, menopausal status and parity.

METHODS

This was a prospective study done on 30 patients histologically proven cases of breast cancer patients coming to surgery O.P.D between January 2014 to July 2015. This study was carried out in Department of General Surgery, S.N Medical College, Agra.

All histologically proven breast cancer patients were included in the study. patients who were excluded from the study were Metastatic breast cancer patients. Male breast cancer patients. Benign and inflammatory breast lesions. All inoperable advanced breast malignancies Recurrent breast lump in a previously operated case of carcinoma breast.

The institutional clearance and informed consent was taken from patient. Clinical assessment of all cases was carried out and clinical details like age, menopausal status, tumour size, lymph node status and stage by TNM staging were recorded. Patients underwent mastectomy or core biopsy according to stage of disease and immunohistochemistry was performed for biomarkers AR, ER, PR, and HER2/neu from Tata Memorial Hospital Bombay because this facility is not available in our college. When greater than 10% of tumor cells expressed the marker, the cases were labeled as positive. All post-operated samples were transferred in 10% fomalin to department of pathology in our college for histopathological examination. The association of androgen receptor with age, parity and menstrual status was also determined**.**

Statistical analysis was done using graph pad software. The association of factors like age, menstrual status and parity was carried out using chi square test and Fisher exact test to measure the strength of association. Risk ratio along with 95%confidence interval was also estimated p<.05 was considered statistically significant.

RESULTS

Table 1 showed that large number of patients were in 41-50-year age group, 70% of patients were post-menopausal and 80% were parous.

Table 2 showed that ER, PR, HER2/neu receptor was positive in 63.33%, 66.67%, 46.67% cases respectively. Androgen receptor was positive in 80% cases. Ten patients (33.33%) were triple negative. (Graph 1)

Table 3 showed correlation of AR with other receptors and clinical parameters. AR expression is significantly related to ER (P<0.015), PR (p<0.008) and triple negative breast cancer patients (p <0.008). There is significant correlation between AR and menopausal status (p<0.006) while no significant correlation was found with age and parity.

Table 1: Clinical parameters of patients

Characteristics		Number (n)	Percentage (%)
Age (years)	≤30	2	6.67
	31-40	7	23.33
	41-50	16	53.33
	>50	5	16.67
Menstrual status	Premenopausal	9	30.00
	Postmenopausal	21	70.00
Parity	Nullipara	6	20.00
	Parous	24	80.00

DISCUSSION

In hormone dependent tissue like breast and prostate steroid hormones play an important role in pathophysiology of tumours. Steroids have mitogenic effect.[11] Role of estrogen and progesterone and its receptor is well established in carcinogenesis so direct or indirect inhibition of these receptors is the mainstay of treatment of breast cancer. Another important hormone is androgen that is also very important for estrogen biosynthesis. Synthetic progesterone also mediates its effect by binding to AR. While the disruption of androgen action by synthetic progesterone may have negative effect on breast tissue, breast homeostasis is maintained by the balance between estrogen and signalling. So, AR is emerging as important biomarker. There is an emerging evidence that androgen receptor is additional target in breast cancer treatment.[9,12]

Table 2: Receptors

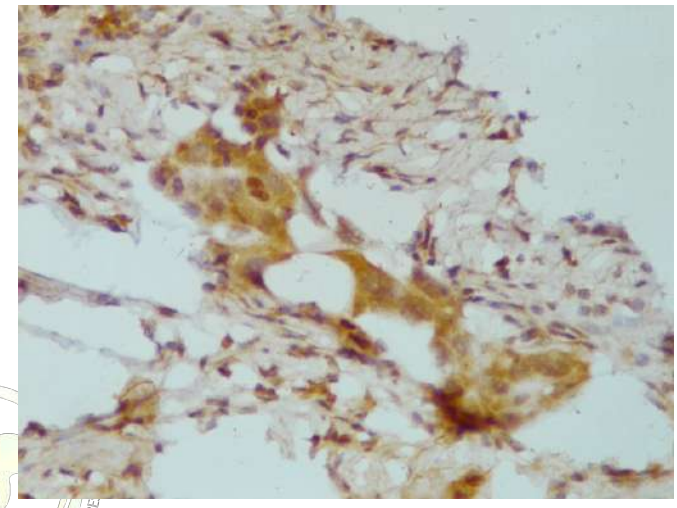
		Number (n)	Percentage (%)
ER	Positive	19	63.33
	Negative	11	36.67
PR	Positive	20	66.67
	Negative	10	33.33
Her2neu	Positive	14	46.67
	Negative	16	53.33
AR	Positive	24	80
	Negative	6	20
Triple negative(ER,PR,HER2/neu)		10	33.33
Non triple negative		20	66.67

Table 3: Comparison of AR with other receptors and clinical parameters

FACTORS		ANDROGEN RECEPTOR		P VALUE
		POSITIVE	NEGATIVE	
AGE(years)	<30	1	1	0.151
	31-40	4	3	
	41-50	15	1	
	>50	4	1	
Menopausal Status	Premenopausal	5	4	**0.006**
	Postmenopausal	19	2	
Parity	Nullipara	4	2	0.570
	parous	20	4	
ER	Positive	18	1	**0.015**
	Negative	6	5	
PR	Positive	19	1	**0.008**
	Negative	5	5	
Her2neu	Positive	12	2	0.656
	Negative	12	4	
Hormonal status	Triple negative	5	5	**0.008**
	Non-triple negative	19	1	

In our study like Raina et al.[13] the breast cancer patients were younger at age of diagnosis. The mean age of presentation of breast cancer in India is found to be less than 50 which is less than that in western countries. This suggest that breast cancer occurs at younger age group in India as compared to western countries.

In this study ER, PR is present in two third of cases which is similar to western countries.[14] Her2/neu is present in 46.6% of cases which is much higher as compared to western countries in which it is present in 19% of cases.[15,16] AR /ER ratio also influences breast tumour response to hormone treatment.[17] This differential finding between breast cancer type in asian and western countries may result from population stratification bias and difference of demographic data.[18,19]



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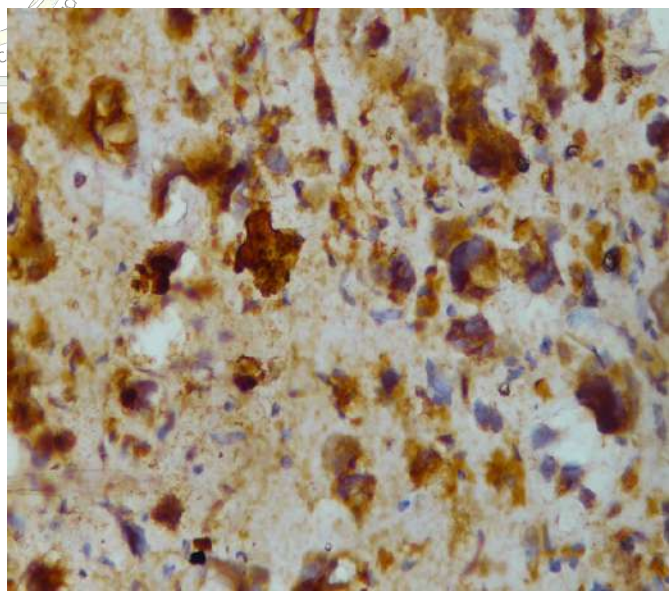

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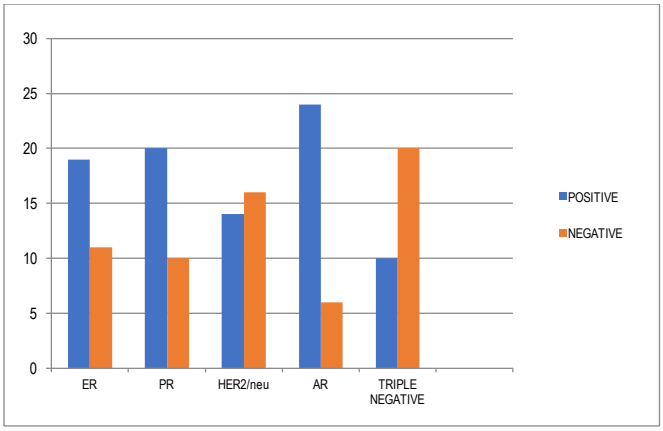
Fig 1&2: IHC staining for AR in breast tumour cells showing nuclear staining for androgen receptor and cytoplasmic staining(400x).

AR is present in 80% of cases and is significantly associated with ER (P <.015) PR (p<.008) and not associated with HER2/neu.[3,20] In ER negative patients AR is present in 20% of cases ER- cases not responding to treatment are treated with medroxyprogesterone acetate which mediates its action by binding to AR.[21]

Triple negative breast cancer (ER^-, PR^-, $HER2/neu^-$) was significantly correlated with AR ($p< .008$) and AR expression in triple negative patients is 16.67% .

There are studies which state that androgen can inhibit the growth of hormone negative breast cancer if there is strong expression of AR.[22,23] It occurred because of conversion of androgen to estrogen by the aromatase enzyme.[24] These androgens also induce apoptosis regardless of ER,PR status. So, AR antagonist could be used for AR positive tumours regardless of ER status.



Graph: Pattern of Receptor Expression in Our Study

Ogawa et al like our study showed that menstrual status is significantly associated with AR expression. AR expression is more in post-menopausal women.

AR expression is not related other parameters like age and parity.

Hence our observation could lead to basis of possibility of AR expression as prognostic factor and could be used therapeutically in triple negative cases. Main limitation our study is that there were less number of patients

CONCLUSION

Hence, we conclude that breast cancer express AR which is significantly associated with ER and PR but not HER2/neu. AR is also significantly expressed in triple negative cases and in postmenopausal women. Further studies are required to determine whether AR could be therapeutic target in triple negative and postmenopausal women.

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