Original Article

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Receptor Status and Menopause in Breast Cancer: A Prospective Study to Analyze the Association

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ABSTRACT

Introduction: Receptor status has a strong bearing on breast cancer prognosis and management. The probability of ER, PR, and HER2/neu positivity depends on age, menopause, and other factors. This study was done to develop a database to assess the receptors status in relation to menopause in Jaipur district.

Methodology: A prospective study was conducted in women diagnosed and treated with breast cancer. A total 250 women were included each in premenopausal and postmenopausal group. ER, PR, and HER2/neu receptors were assessed prior to treatment. Analysis on receptors and clinical and pathological parameters were carried out in each group.

Results: ER, PR, and HER2/neu were positive in 145, 128, 139 premenopausal women and 116, 106, 82 postmenopausal women, respectively. Triple negative breast cancers were detected in 38 premenopausal and 68 postmenopausal women. Receptor negative group had higher ratio of lymphovascular invasion. Premenopausal women had higher ratio of perineural invasion and DCIS component.

Conclusion: Receptor reactivity changes with age and menopausal status and has a prognostic as well as predictive role. We had contradictory findings with postmenopausal women being more triple receptor negative. Larger databases are needed to consolidate the results and observe the trend in this geographical region.

INTRODUCTION

Analysis of receptors, namely estrogen receptor (ER), progesterone receptor (PR) and HER 2/ neu has become a standard practice in management of breast cancer. These are valuable in prognosis and predicting the behavior of breast carcinoma. Receptor positivity varies according to the age and menopause status of patients. ER and PR positive tumors are better differentiated and have a relatively better prognosis.[1] An association exists between amplification and/or over expression of HER 2/neu and various features of advanced breast carcinoma including lack of steroid receptor expression.[2]

The overall prevalence of triple negative breast cancer (TNBC) is 11%-20% and varies in different parts of the world.[3] There is no database from Jaipur district that evaluated the receptor status in breast cancer patients. TNBC is a clinical challenge because of its predominance in younger age, aggressive behavior and poor prognosis with dearth of response to endocrine or targeted therapy.[4] The objective of this study was to assess the rate of ER, PR, and HER-2/neu reactivity in premenopausal and postmenopausal women with breast cancer and to study the clinical and pathological parameters in relation with menopause.

METHODS

The study was conducted in the Department of Surgical Oncology at a government medical college from February 2015 to December 2016. Female patients with pathologically proven breast cancer were included and divided into two groups with respect to menopause. Women aged above 50 years were included in post-menopausal group, based on study on Indian women.[5] Sample size was calculated to be 250 in each group at α error 0.005 and study power 80%, assuming proportion of

PR positivity among pre and post menopausal patients to be 0.47 and 0.347, respectively.

All the eligible patients had their receptor status evaluated either on core biopsy tissue or mastectomy specimen. Haematoxylin and eosin stained slides were examined under low power and high power and observations were recorded. Representative section of tumor and adjacent normal breast tissue (internal control) were processed for ER, PR, and HER 2/neu immune-histochemical staining. For ER, PR staining, section was taken on histogrip-coated slides. Citrate buffer did antigen retrieval and slides were stained by monoclonal antibodies against the estrogen and progesterone receptor by LSAB (labeled strptaviden biotin) system (ER clone ID5 and PR clone IA6, DAKO). All red scoring for ER and PR reviewed immune-stained slides. For HER 2/neu staining, after antigen retrieval, slides were stained with polyclonal antibody against HER 2/neu (DAKO) oncoprotein by envision system.

RESULTS

A total of 500 women with breast cancer were included, 250 in premenopausal group and 250 in postmenopausal group. Mean age at presentation was 47.1 years (age range 24-83 years). Core cut biopsy was mainly used for diagnosis in 234 premenopausal and 229 postmenopausal women. Rest of the women presented with carcinoma detected after lumpectomy done elsewhere. Fifty-five patients received neo-adjuvant chemotherapy and had receptor status evaluation prior to chemotherapy. ER positivity was seen in 145/250 of premenopausal group and 116/250 in postmenopausal group. PR positivity was present in 128/250 of premenopausal group and 106/250 in postmenopausal group. HER2/neu receptor was positive in 139 premenopausal women as compared to 82 postmenopausal women. But this included both HER 2/neu 3+ and equivocal 2+ scores. If only 3+ score was taken into consideration, HER2/neu positivity was found in 72/250 premenopausal and 58/250 postmenopausal women. All three receptors (ER/PR/HER2/neu) were negative in 38/250 premenopausal women and 68/250 postmenopausal women. Patients' clinical and pathological characteristics, and receptor status are given in tables 1, 2 and 3 respectively. Table 4 depicts relationship between hormone receptor status and menopause.

DISCUSSION

The prognosis of breast carcinoma is related to various clinical and pathological factors. Amongst all, receptor status is most acceptable in predicting prognosis, response to treatment, and the potential use of hormonal and targeted therapy.

Table1: Clinical characteristics of pre and post menopausal groups

	Groups	
	Premenopausal (N=250)	**Postmenopausal (N=250)**
Presentation		
Lump	235	220
Pain	10	16
Ulceration	05	14
Mammography	141	101
BIRADS 2	10	6
BIRADS 3	30	18
BIRADS 4	52	25
BIRADS 5	49	52
MRM	190	214
BCS	60	36
NACT	21	34

BIRADS: Breast Imaging Reporting and Data System; MRM: Modified Radical mastordectomy; BCS: Breast Conservative Surgery; NACT : Neo-adjuvant Chemotherapy

Table 2: Pathological characteristics of pre and post menopausal groups

	Premenopausal group (N=250)	Postmenopausal group (N=250)
Tumor		
T1	64	48
T2	113	73
T3	55	95
T4	18	34
Lymph node metastasis Stage	158	155
IA	30	29
IIA	58	28
IIB	29	32
IIIA	94	105
IIIB	18	42
IIIC	21	14
LVI	176	137
DCIS/LCIS	111	74
PNI	132	96

LVI : Lymphovascular Invasion; DCIS/LCIS : Ductal Carcinoma in Situ/Lobular Carcinoma in Situ; PNI: Perineural Invasion

Table 3: Receptor status of pre and post menopausal groups

	Premenopausal group (N=250)	Postmenopausal group (N=250)
ER+	145	116
PR+	128	106
HER2/neu+	139 (72 (3+); 67 (2+))	82 (58 (3+); 24(2+))
TNBC	38	68

TNBC : Triple Negative Breast Carcinoma

Database from worldwide have shown varying proportions of receptor positivity related to age, race, ethnicity, genetic mutations, menopausal status etc. Knowing the trend and epidemiology assists in predicting the tumor biology in a respective group of patients and planning the treatment guidelines. Estrogen is an important mitogen exerting its activity by binding to its receptor (ER) and found in 50-80% of breast cancers. PR is a surrogate marker of a functional ER and valuable in predicting the behavior of breast carcinoma. It is expressed in 60-70% invasive breast carcinomas with a higher positivity in older age and postmenopausal women.[6] Patients with larger tumors, poorly differentiated morphology, higher axillary lymph node metastases, and higher stage have more chance of an ER and PR negative status.[7] Overall 52% ER positivity and 47% PR positivity was observed in this entire cohort, which matches with other Indian series.

Group analysis reveal 58% of premenopausal group and 46.4% of postmenopausal group cases expressed ER positivity. Statistically significant association was found between estrogen receptor expression and premenopausal women which was also observed in few other studies.[5,8] Similarly, PR positivity was more in premenopausal group (51.2% v/s 42.4%) with a statistically significant association present between them. The finding concurs with those of Rajan et al[5] and Pourzand A et al.[9] As expected, estrogen receptor and progesterone receptor show positive association in both premenopausal and

postmenopausal group but the higher receptor positivity was not anticipated in premenopausal women.

HER 2/neu proto-oncogene is amplified and or over expressed in approximately in 25-30% of invasive primary breast cancers. HER 2/neu+ over expression can be detected by IHC analysis and fluorescent in situ hybridization techniques. The association between HER 2/neu gene amplification and poor prognosis was first determined in 1987.[10] We included only IHC analysis in our study due to unavailability of FISH technique in our center and cost issues. Overall HER2/neu positivity was 44.2%, which comprised 2+ and 3+ scores; however only 3+ score was present in 26.2% cases.

We found 55.6% (28.8%, 3 + score) cases from premenopausal group and 32.8% (23.2%, 3 + score) cases from postmenopausal group showed HER2/neu receptor positivity. The frequency of HER2/neu positivity varies among Indian studies and is not correlated with menopausal status. Munjal et al[11] and Vaidyanathan et al[12] reported around 41% HER2/neu positivity overall. In contrast, Haung HJ et al[13] showed only 17.7% positivity, Lal P et al[14] showed 26.89% and Moses Embroise et al[15] showed 27.10% HER2/neu positivity respectively in their studies.

The findings in our study show that HER2/neu expression decreases with menopausal status of the patient and there was significant association between HER2/neu and menopausal status. Literature shows mixed findings correlating HER2/neu expression with age.[13,16,17] The correlation between hormone receptors and HER2/neu has been reported in many published studies. There is well-established inverse relationship between the expression of ER, PR, and HER2/neu amplification in both preclinical and clinical studies. This inverse relationship has been linked with the fact that estrogens and its receptor are required to suppress HER2/neu. ER and HER2/neu signaling are inversely related through a transcriptional repression of HER2/neu by estradiol binding to ER.

Surprisingly, hormone receptor status of either group did not show association with HER2/neu receptor. Premenopausal group had more of luminal B and HER2/neu enriched tumors while postmenopausal group had predominance of luminal A and TNBCs. Similar findings were shared by other studies done previously.[18-20] Triple negative breast cancer carries poor prognosis and ought to predominate in younger age group knowing the fact that young breast cancer is aggressive.[21] We had contradictory finding here also with 15.2% of premenopausal women having TNBC as compared to 27.2% of postmenopausal women likewise Aapro M et al.[22] The variations in receptor status in this study could be due to small sample size and observer/laboratory related factors.

On comparison between the clinical and pathological features in both the groups of women classified by state of menopause, in our study no statistically significant difference in tumor size and lymphatic spread was observed. However, premenopausal group had majority of early breast cancer (119/250) while post-menopausal group had mostly locally advanced breast cancers (161/250). This could be explained by lack of breast awareness and pendulous breast in older women.

Lymphovascular invasion was present in 183 cases of premenopausal women group and 161 cases of postmenopausal women group. There was no statistically significant relation in LVI and menopausal status but LVI was detected higher in receptor negative patients. Young Ju Song[23] in their study showed association of LVI with Estrogen receptor alone. Few studies have reported that LVI is also related with HER2/neu over expression.[24,25]

In our study, perineural invasion had significant association with menopausal status, being more in premenopausal group (30% v/s 21%) in contrast with study done by the Duraker N et al.[26] Same study has also shown significant association between PNI and hormone receptor status, which concurs with our finding. But association between PNI and HER2/neu was statistically insignificant as noticed by them. DCIS/LCIS component was detected in 111 cases of premenopausal group and 74 cases of postmenopausal group. There is association seen between DCIS/LCIS component and menopausal status as shown by MacKenzie TA et al[27] in their study which strongly associated it with premenopausal phase. Rao C et al[28] did not find significant association between DCIS/LCIS component and hormonal receptor status. On the contrary, Dobrescu A et al[29] demonstrated a strong concordance between hormone receptor status of breast tumors containing DCIS and contiguous invasive cancer. The receptor status and their relation to menopause detected in our study differ from observations made by others and needs a larger regional database as well as standardization of techniques for confirmation of the

trend.

Limitations of the study: Other markers important in classifying the molecular subtypes of breast cancer like Ki67 and cytokeratins were not assessed in this study. They have an established role in prognosis and should be done in a standardized manner.

CONCLUSION

Receptor status evaluation is critical in management of breast cancer. The study demonstrated higher ER, PR and HER2/neu positivity in pre-menopausal women despite the increased rate of early breast cancers in this group. Also the parameters of poor prognosis like LVI, PNI and DCIS were at higher rate in premenopausal women. TNBCs presumed to be in younger age, involved more postmenopausal women.

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