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Research Article

MOLECULAR SUBTYPING OF INVASIVE BREAST CANCER AND ITS RELATION TO COMMON RISK FACTORS: A HOSPITAL BASED STUDY

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ABSTRACT

Background: Breast cancer is the most common cancer among Indian women. Majority of our patients do not have the traditional risk factors, and present in a locally advanced stage which progresses despite treatment. Studies have shown that it can be stratified in molecular subtypes by using a panel of immunohistochemical markers for estrogen, progesterone and HER 2neu receptor, which is closely related to its prognosis. **Aim:** This study was done to determine the prevalence of various molecular subtypes in our patients and its relation to various risk factors. Materials and **Method:** 446 breast cancer patients treated at Mahavir Cancer Sansthan, Patna from January 2015 toDecember 2015 were retrospectively analysed for their age, parity, history of breast feeding, menopausal status, height, weight, ER, PR & HER2neu receptor status. They were then classified in four molecular subgroups, Luminal A, Luminal B, Triple negative and HER2neu positive cancers and its relation to menopausal status and body mass index was analysed. **Observations and Results:** 68.38% patients were premenopausal with a mean age of 47.12 years. 24.38% patients were obese or overweight, with an average BMI of 22.38. Luminal A subtype followed by Triple Negative subtype was found in 37% and 29% of the patients respectively. The prevalence of Triple Negative subtype was more in premenopausal and overweight patients. **Conclusion:** Overall prevalence of triple negative subtype in our patient population is high esp. among premenopausal overweight patients.

INTRODUCTION

Breast cancer is the most common cancer among women worldwide with nearly 1.7 million new cases diagnosed in 2012 and 5.2 lakh deaths. Even in India, breast cancer is the most commonly diagnosed cancer among women. In 2012, an estimated 144,937 new patients were diagnosed with breast cancer in India, and about 70,218 women died of the disease. Age-standardized 5-year breast cancer survival for Indian women diagnosed with breast cancer is 60% compared with 80% in Western countries. [1]

Breast tumors with similar histopathological appearances can exhibit divergent clinical presentations, disease aggressiveness and treatment responsiveness. These differences are probably due to the limitation of the current classification and anatomical staging of breast cancers, based mainly on morphology and imaging. Recent developments in the field of molecular oncology have shown that breast cancer is a heterogeneous disease with different biologic subtypes that are recognized by gene expression profiling studies. [2,3] Several studies have shown that breast carcinomas may be stratified in subtypes similar to those defined by expression profiling using a panel of immunohistochemical (IHC) markers. [4] The four major molecular subtypes of breast cancer include Luminal A (ER and/or PR positive and HER2neu negative), Luminal B (ER and/or PR positive and HER2neu positive), Triple Negative or TNBC (ER negative, PR negative and HER2neu negative) and HER2 type (ER negative, PR negative and Her2neu positive). Usually, patients with TNBC tend to present at a younger age, have large size tumors and poor prognosis than patients with ER/PR receptor positive disease. [5] Apart from their prognostic and predictive values, a widespread use of this molecular classification of breast cancer will also lead to new etiological insights and eventually better ways of prevention and therapies that are targeted towards a particular molecular type of breast cancer.

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To control the high burden and mortality of breast cancer in India, we need population-based database of our patients. Both epidemiological and clinical studies are required to assess the risk factors, clinical and molecular profile along with the outcome analysis of our breast cancer patients. This study was done to assess the molecular subtypes and their correlation to the common risk factors, of the breast cancer patients being treated at a tertiary cancer Centre in east India.

Aims and Objectives

1. To determine the prevalence of Luminal A, Luminal B, Triple Negative and HER2neu positive molecular subtypes of breast cancer in our patients.
2. To correlate the molecular subtypes in reference to the menopausal status of these patients.
3. To correlate the molecular subtypes in reference to the body mass index of these patients.

METHODS AND MATERIAL

This study is a retrospective analysis of breast cancer patients treated at a tertiary cancer centre in east India from Jan, 2015 to Dec,2015. The study population included 446 biopsy proven invasive breast cancer patients who also underwent ER, PR, HER2neu receptor status analysis. For the given study, these patients were evaluated for their age, parity, breast feeding, menopausal status, height, weight and ER, PR & HER2neu receptor status. Level of ER and PR was expressed as a product of the percentage of epithelial cells stained and intensity of staining through immunohistochemistry (IHC). The cut off value of ER and PR -positive disease was defined as nuclear staining of ≥1% of the epithelial component of the tumour. A positive HER2 result was IHC staining of 3+ (uniform, intense membrane staining of 30% of invasive tumour cells) or a FISH ratio of more than 2.2. Patients with an IHC score of 2+, with no additional evaluation were considered as HER2 neu negative. Patients were classified as Luminal A (ER and/or PR positive and HER2neu negative), Luminal B (ER and/or PR positive and HER2neu positive), Triple Negative or TNBC (ER negative, PR negative and HER2 neu negative) and HER2 type (ER negative, PR negative and Her2 neu positive).

For statistical analysis, percentage of patients in these four groups were calculated. Patients were further subdivided into two groups on the basis of menopausal status; premenopausal and postmenopausal group and prevalence of the four molecular subtypes were calculated in both the groups. The group was also subdivided into two groups on the basis of body mass index, BMI (wt in kg/ht^2 in meters) into overweight (BMI ≥ 25) and normal weight (BMI < 25) and prevalence of the four molecular subtypes were calculated in both the groups. The statistical significance was calculated using Two sample t-test between proportions.

RESULTS AND OBSERVATIONS

A total of 446 patients were evaluated for the present study. The age ranged from 24 to 82 years with a mean age of 47.12 years. About two-third of the patients (68.38%) were in the premenopausal age group. Only 4 patients were nulliparous, while others had children, out of which about 96% had breastfed their children.

The average height of the patients was calculated to be 157.25 cm with a range from 133 to 182 cm. The weight of the patients ranged from 32 to 94 kg with an average of 55.10 kg. The average BMI was 22.38 with a range from 12.40 to 42.44. Among 446 patients, 109 (24.38%) were overweight with BMI between 25 to 30, 20 (4.47%) were obese with BMI more than 30 and rest 317 (71.07%) had a BMI of less than 25.

Among the patients less than or equal to 50 years of age, only 83 out of 305 (27.21%) patients were overweight or obese. 70 of these patients (22.95%) were in the overweight category and 13 (4.26%) were obese.

Among the elderly patients which is more than 50 years of age, about 33% of the patients were overweight with 5% in the obese category.

Overall, 221 patients (49.55%) were ER positive, 212 (47.53%) were PR positive and 151 (33.85%) were HER2neu positive.
The molecular classification of the patients is shown in Table: 1.

Table 1 Showing overall molecular classification of the patients.

Molecular Subtype	Number	Percentage
Luminal A	165	36.99%
Luminal B	74	16.59%
TNBC	130	29.14%
HER2 neu Positive	77	17.26%

Luminal A was seen in about 37% of the patients and was the commonest molecular type in our patients. This was followed by Triple negative type in about 29% of the patients. Luminal B and HER2neu positive type were each seen in about 17% of the patients.

The patients were divided into two groups according to their Body Mass Index. The percentage of patients with Luminal A and HER2Positive type of cancer were almost similar. However, the percentage of patients with Luminal B type cancer decreased from 18.29% to 12.4% (p-value= 0.1299, not significant) as the BMI increased to more than 25. Further the percentage of patients with Triple Negative breast cancer increased from 27.76% to 32.55% as the BMI increased to more than 25. Again p-value was not significant (0.3134). The distribution among the molecular types according to body mass index is shown in Table:2.

Table 2 Showing molecular classification in context to BMI

Molecular Subtype	BMI ≥ 25		BMI < 25		p-value
	No.	Percent	No.	Percent	
Luminal A	48	37.2%	117	36.9%	0.9526
Luminal B	16	12.4%	58	18.29%	0.1299
TNBC	42	32.55%	88	27.76%	0.3134
HER2Positive	23	17.82%	54	17.03%	0.8415

TNBC= Triple Negative Breast Cancer

The patients were also divided into two groups according to their menopausal status. The percentage of patients with Luminal B and HER2Positive type of cancer were almost similar. However, the percentage of patients with Luminal A type cancer increased from 36.06% in the premenopausal group to 39% in the postmenopausal group (p-value= 0.5503, not significant). Further the percentage of patients with Triple Negative breast cancer decreased from 30.81% in the

premenopausal group to 25.53% in the postmenopausal group. Again p-value was not significant (0.2549).The distribution among the molecular types based on the menopausal status of the patients is shown in Table:3.

Table 3 Showing molecular classification in context to Menopausal status

Molecular Subtypes	Premenopausal		Postmenopausal		p-value
	No.	Percent	No.	Percent	
Luminal A	110	36.06%	55	39%	0.5503
Luminal B	49	16.06%	25	17.73%	0.6597
TNBC	94	30.81%	36	25.53%	0.2549
HER2Positive	52	17.04%	25	17.73%	0.8579

TNBC= Triple Negative Breast Cancer

DISCUSSIONS

This study of 446 patients of invasive breast cancer showed the mean age at presentation to be 47.12 years only. Various other epidemiological studies done in India also suggest that the disease peaks at 40-50 years in Indian women. [6-9] Data also shows that breast cancer occurs at a younger premenopausal age in Indian and Asian women compared to western women who get it more than a decade or more later. [10] In our study two third of the patients were in the premenopausal age group. A study by Chopra *et al* also highlights around 61% breast cancer cases in the premenopausal age group. [11]

In this study the most common molecular subtype was luminal A representing 37%, which is compatible with study done by Munjal K *et al* [12] and Fan *et al* [13] but much lower than Yang *et al* [14] and Spitale A *et al* [15] which showed around 70% of the patients to be of Luminal A type.

This was followed by TNBC patients representing about 29% of the patients. Triple negative breast cancer is an aggressive subtype that is defined by lack of expression of ER and PR as well as absence of over expressed or amplified HER2. TNBC accounts for approximately 12% to 17% of all invasive breast cancers in Western populations. TNBC occurs more frequently in younger women and is associated with higher histologic grade and more advanced disease. [16,17] Prevalence of TNBC in India is reported to be higher than that observed in Western populations; however, there is considerable variation in prevalence rates reported by studies from the region. A recent meta-analysis of 17 Indian studies that involved 7,237 patients was done by Sandhu *et al* to get an estimate of the prevalence of triple negative breast cancer in India. Overall prevalence of TNBC in the north, south, east, and west of the country was 28%, 34%, 30%, and 31%, respectively and the combined prevalence was 31% (95% CI, 27% to 35%). [18] Our prevalence rate of TNBC is also comparable to those seen in African American women. [19] As TNBC is known to be more aggressive than other breast cancer subtypes, higher prevalence of TNBC could be a cause for the high mortality rate of breast cancer patients in India.

Multiple factors have been hypothesized as the probable cause for higher prevalence of TNBC reported by studies conducted among Indian patients with breast cancer. These could be the early age of onset of breast cancer; lifestyle factors, such as diet and obesity; reproductive factors, such as multiparity; socioeconomic status; and screening behaviors. Another important factor could be a potential genetic susceptibility of Indians to TNBC [17,20]

To identify these proposed determinants of the high prevalence of TNBC in our patients we did subgroup analyses based on the body mass index which represented physical activity and obesity in these patients and the menopausal status which was closely related to age of the patients.

Prevalence of Luminal A and HER2 Positive type of cancer showed almost no difference with change in body mass index. However, the percentage of patients with Luminal B type cancer decreased from 18.29% to 12.4% as the BMI increased to more than 25 and the percentage of patients with Triple Negative breast cancer increased from 27.76% to 32.55% as the BMI increased to more than 25. However, this finding was not statistically significant with a p-value of 0.13 and 0.31 respectively for the difference in the prevalence of Luminal B and TNBC respectively. Kwan *et al*. [21] confirmed that women with TNBC were more likely to be overweight (OR=1.82, 95% CI 1.03–3.24) or obese (OR=1.97, 95% CI 1.03–3.77) if premenopausal. Similarly, Trivers *et al*. [22] also reported that women with TNBC were more likely to be obese than normal/ underweight (OR=1.89, 95% CI 1.22–2.92). While these studies supported an association between TNBC and obesity, Stead *et al*. [23] reported that TNBC was equally common in obese and non-obese patients (29% versus 31%) and considering all patients, as BMI increased, the proportion of TNBC decreased (p = 0.08)

When the patients were analysed in context to their menopausal status the prevalence of Luminal B and HER2Positive type of cancer were almost similar in both premenopausal and postmenopausal group. However, the prevalence of Luminal A type cancer increased from 36.06% in the premenopausal group to 39% in the postmenopausal group (p-value= 0.5503, not significant). Further the prevalence of patients with Triple Negative breast cancer decreased from 30.81% in the premenopausal group to 25.53% in the postmenopausal group. Again p-value was not significant (0.2549). Our results are similar to that reported by Kwan *et al* who found that compared with luminal A breast cancer cases, TNBC cases tended to be younger at diagnosis (P< 0.0001) [21].

Another finding in our patients was the very high prevalence of multiparity as only 4 out of 446 patients were nulliparous. Using data from 155723 women enrolled in the Women's Health Initiative, Phipps *et al*. [24] suggested that nulliparity was associated with decreased risk of TNBC [hazard ratio (HR)=0.61, 95% CI 0.37–0.97], and among parous women, the number of births was positively associated with the risk of TNBC.

Thus, we see that there is a high prevalence of TNBC in our patients. Though we could not find any significant association of this high prevalence multiparity, young premenopausal women with high body mass index could be the probable factors.

CONCLUSION

The molecular classification of breast cancer based on a panel of immunohistochemical (IHC) markers for ER, PR and HER2neu expression should be used routinely in breast cancer patients as it is helpful in clinical management of the patient. Besides, pooling of population based data on the prevalence and determinants of the molecular subtypes of breast cancer

will certainly help in better understanding the etiological factors responsible for advanced and aggressive type of disease presentation, which is seen commonly in our patients.

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