Original Article

A Comparative Analysis of Body Mass Index with Estrogen Receptor, Progesterone Receptor and Human Epidermal Growth Factor Receptor 2 Status in Pre- and Postmenopausal Breast Cancer Patients

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Abstract

Background: Breast cancer is now the most common cancer among Indian women. Recent studies have suggested a possible link between risk factors like high BMI and molecular subtypes of breast cancer. Studies from Western and Asian population have shown varying relationship between post- menopausal obesity and expression of ER, PR, Her2-neu receptors in breast cancer patients. **Aim:** This study was done with an aim to explore if overweight or obesity as defined by BMI and status of ER, PR and Her2-neu receptors differ in Indian pre-menopausal and post-menopausal breast cancer patients. **Methods and Material:** This is a retrospective analysis of 446 breast cancer patients treated at Mahavir Cancer Sansthan, Patna from July to December 2019. Their case records were evaluated and data regarding age, menopausal status, height, weight and ER, PR & HER2-neu receptor status were extracted for analyses. **Statistical Analysis:** Chi-square test was used to compare categorical variables between the pre-menopausal and post-menopausal group. **Results:** The prevalence of obesity in the post-menopausal group was 2.3% more than the pre-menopausal group (*P*-value = 0.24). As compared to the pre-menopausal group, there was an increase in the ER/PR positivity in the post-menopausal group by 3.41% (*P*-value = 0.47) and in the Her2-neu positivity by 6.38% (*P*-value = 0.15). As compared to the pre-menopausal group, there was further increase in the ER/PR positivity in the post-menopausal group by 6.85% (*P*-value = 0.40) in sub-group of patients with BMI ≥ 25kg/m^2. **Conclusions:** Our study showed slightly increased incidence of obesity in post-menopausal breast cancer patients. Overweight post-menopausal patients also had a higher percentage of ER/PR receptor positivity and lower percentage of Triple negative breast cancer. The percentage of Her2-neu receptor positivity was more in post-menopausal patients. A high BMI was found to be associated with a lower Her2neu positivity.

Keywords: *Body mass index, estrogen receptor, human epidermal growth factor receptor 2-neu, postmenopausal group, progesterone receptor*

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Introduction

Breast cancer is the most common female cancer in the world, with an estimated 2,088,849 new cases and 626,679 deaths reported in 2018.[1] Although the age-standardized incidence rate of breast cancer in India is lower (24.7/lac) than the western countries (84.9/lac in the USA), because of the large population, the burden of breast cancer is high and increasing day by day.[2,3] With an annual incidence of approximately 162,468 new cases of breast cancers reported in 2018, it has now become the most common cancer in India. The number of deaths reported from breast cancer in 2018 in India was 87,090.[2]

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Many risk factors are presumed to increase the chance of having breast cancer. Among them, hormonal factor like exposure to estrogen has been implicated as an important contributor in the genesis of breast cancer. Most breast cancers are intimately linked with exposure to estrogen, particularly endogenous estrogen.[4] With an increase in the age, there is a sharp decline in the level of endogenous estrogen secreted from the ovaries and adipose tissue becomes the main source of estrogen production in postmenopausal women. Hence, being overweight or obese with the presence of excessive adipose tissue results in high level of estrogen in the body and is an established risk factor for the development of postmenopausal breast cancer.[5-7] However, an analysis of seven prospective cohort studies shows that high body mass index (BMI) was negatively correlated to breast cancer risk among premenopausal women, while it was positively associated with breast cancer risk among postmenopausal women.[8,9] Further, multiple studies from western populations have suggested that excess endogenous estrogen due to obesity contributes to an increased risk of both estrogen receptor (ER) and progesterone receptor (PR)-positive breast cancer in postmenopausal women, probably explained by the hormonally mediated mechanism of these subtypes.[10] However, studies from Asian population done in China and Japan shows a low prevalence of obesity and ER/PR positivity.[11,12] Human epidermal growth factor receptor 2 (HER2)-neu oncogene is an another important prognostic and predictive marker of breast cancer, which is found to be overexpressed in about 15%–43% of breast cancers.[13,14] An epidemiological study done in the Mediterranean population showed that obesity-related postmenopausal breast cancers had a high rate of HER2-neu overexpression.[15] The relationship between elevated BMI and the presence of ER, PR, and/or HER2 in the breast cancer tissue of postmenopausal patients requires further evaluation in Indian patients. Further, there are issues regarding the best BMI classification for the Asian/Indian population. Various studies have proposed lower cutoff values for defining overweight and obesity among Indians than the WHO guidelines, but there is still no uniformity among health researchers regarding its use.[16,17] Due to the scarcity of literature, we decided to continue with the standard WHO guidelines for defining overweight and obesity in our present study which was done with an aim to explore if combined overweight and obesity as defined by BMI and status of ER, PR, and HER2-neu receptors differ in our pre- and postmenopausal breast cancer patients.

Materials and Methods

This is a retrospective analysis of breast cancer patients treated at Mahavir Cancer Sansthan, Patna, from July to December 2019. The study population included 446 biopsy-proven invasive breast cancer patients. Their case records were evaluated and data regarding age, menopausal status, height, and weight and ER, PR, and HER2-neu receptor status were extracted for analyses.

Menopausal Status: Menopausal status was assessed based on the last menstrual period from the patient's medical record. Premenopausal patients were defined as women with regular menses before receiving chemotherapy. Patients with amenorrhea for more than 12 months before receiving chemotherapy were considered postmenopausal. Patients with an amenorrhea for <12 months were included in the premenopausal group. Patients with a history of hysterectomy and/or bilateral oophorectomy were excluded from the study.

Immunohistochemistry methods

The status of ER, PR, and HER2-neu in breast cancer tissues was determined by standardized immunohistochemistry. The 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 cutoff value of ER and PR-positive disease was defined as nuclear staining of ≥1% of the epithelial component of the tumor. A positive HER2 result was IHC staining of 3+ (uniform, intense membrane staining of 30% of invasive tumor cells) or a fluorescent *in situ* hybridization ratio of more than 2.2. Patients with an IHC score of 2+, with no additional evaluation were considered as HER2-neu negative.

Body mass index categories

BMI was calculated as weight (kg) divided by height squared (m^2). It was categorized as per the WHO criteria into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30.0 kg/m^2) category.

Statistical analysis

Data was entered into Microsoft Excel sheet and categorized into pre- and postmenopausal group. The percentage of patients in different BMI categories and receptor status was calculated for both the groups. Chi-square test was used to compare categorical variables between the pre- and postmenopausal group. $P < 0.05$ was considered to be statistically significant.

Results

A total of 446 breast cancer patients were included in the study. The age ranged from 24 to 80 years, with a mean age of 47 years. Two hundred and fifty-seven (57.62%) of the patients were in the premenopausal group as compared to 189 (42.37%) in the postmenopausal group. The mean ages of the patients were 40 years and 59 years in the premenopausal and postmenopausal

groups, respectively. The average BMI of all the patients was 22.37. Overall, 83 (18.60%), 210 (47.08%), 133 (29.82%), and 20 (4.48%) were in the underweight, normal weight, overweight, and obese category, respectively. An analysis of the receptor status showed that239, 151, and 130 patients were ER/PR positive, HER2-neu positive, and triple negative, respectively. A total of 74 patients in the group were positive for ER/PR and HER2-neu receptors [Table 1].

In the premenopausal group, patients in the underweight, normal weight, overweight, and obese category were 45 (17.5%), 124 (48.24%), 79 (30.73%), and 9 (3.5%) as compared to 38 (20.10%), 86 (45.5%), 54 (28.6%), and 11 (5.8%) in the postmenopausal group, respectively. The prevalence of obesity in the postmenopausal group was 2.3% more than the premenopausal group (P = 0.24) [Table 2].

The analyses of receptor status showed that the number of patients in ER/PR positive, HER2-neu positive, and triple Negative group were 134 (52.14%), 80 (31.12%), and 81 (31.51%) in the premenopausal group as compared to 105 (55.55%), 71 (37.5%), and 49 (25.92%) in the postmenopausal group, respectively. As compared to the premenopausal group, there was an increase in the ER/PR positivity in the postmenopausal group by 3.41% (P = 0.47) and in the HER2-neu positivity by 6.38% (P = 0.15). However, the number of patients with triple-negative breast cancer (TNBC) was more in the premenopausal group by 5.59% (P = 0.19) [Table 3].

Similar analyses of receptor status in different BMI categories showed that the number of patients in ER/PR-positive, HER2-neu-positive, and triple-negative group was 156 (53.24%), 101 (34.47%), and 81 (27.64%) in patients with BMI <25 kg/m^2 as compared to 83 (54.24%), 50 (32.67%), and 49 (32.02%) in patients with BMI more than or equal to 25 kg/m^2, respectively. ER/PR positivity was higher by 1.0% and HER2-neu positivity was lower by 1.8% in patients with BMI ≥25 kg/m^2, while the proportion of patients with TNBC was more in patients who were overweight or obese by 4.38% (P = 0.334) [Table 4].

The subset analyses of only overweight and obese patients showed that the number of patients in ER/PR-positive, HER2-neu-positive, and triple-negative group was 40 (45.45%), 25 (28.40%), and 33 (37.50%) in the premenopausal group as compared to 34 (52.30%), 23 (35.38%), and 19 (29.23%) in the postmenopausal group, respectively. As compared to the premenopausal group, there was further increase in the ER/PR positivity in the postmenopausal group by 6.85% (P value = 0.40) and in the HER2-neu positivity by 6.98% (P = 0.35). The number of patients with TNBC also increased in the premenopausal group by 8.27% (P = 0.28) [Table 5].

Further, subset analyses of non overweight or obese patients showed that the number of patients in ER/PR-positive, HER2-neu–positive, and triple-negative group was 94 (55.62%), 55 (32.54%), and 48 (28.40%) in the premenopausal group as compared to 71 (57.25%), 48 (38.70%), and 30 (24.19%) in the postmenopausal group, respectively. As compared to the premenopausal group, there was a slight increase in the ER/PR positivity in the postmenopausal group by 1.63% (P = 0.781) and in the HER2-neu positivity by 6.16% (P = 0.276). However, the number of patients

Table 1: Baseline characteristics of breast cancer patients

Parameters	Number of patients (n=446), n (%)
Age (years)	
Range	24-80
Mean	47
Menopausal status	
Premenopausal	257 (57.62)
Postmenopausal	189 (42.37)
BMI	
Range	12.5-42.4
Mean	22.37
BMI category (kg/m^2)	
Underweight (<18.5)	83 (18.60)
Normal weight (18.5-24.9)	210 (47.08)
Over weight (25-29.9)	133 (29.82)
Obese (≥30.0)	20 (4.48)
Receptor status	
ER/PR +ve, Her2-neu -ve	165 (36.99)
ER/PR +ve, Her2-neu +ve	74 (16.59)
ER/PR -ve, Her2-neu +ve	77 (17.26)
ER/PR -ve, Her2-neu -ve	130 (29.14)

ER: Estrogen receptor, PR: Progesterone receptor, Her2-neu: Human epidermal growth factor receptor, BMI: Body mass index

Table 2: Distribution of body mass index in premenopausal and postmenopausal breast cancer patients

BMI category (kg/m^2)	Premenopausal (n=257), n (%)	Postmenopausal (n=189), n (%)	Difference (%)	P
Underweight (<18.5)	45 (17.5)	38 (20.10)	2.6	0.48
Normal weight (18.5-24.9)	124 (48.24)	86 (45.5)	2.74	0.56
Over weight (25-29.9)	79 (30.73)	54 (28.6)	2.13	0.62
Obese (≥30.0)	9 (3.5)	11 (5.8)	2.3	0.24

BMI: Body mass index

Table 3: Distribution of receptor status in premenopausal and postmenopausal breast cancer patients

Receptor status	Premenopausal (*n*=257), *n* (%)	Postmenopausal (*n*=189), *n* (%)	Difference (%)	*P*
ER/PR +ve	134 (52.14)	105 (55.55)	3.41	0.47
Her2-neu +ve	80 (31.12)	71 (37.5)	6.38	0.15
TNBC	81 (31.51)	49 (25.92)	5.59	0.19

ER: Estrogen receptor, PR: Progesterone receptor, Her2-neu: Human epidermal growth factor receptor, TNBC: Triple-negative breast cancer

Table 4: Distribution of receptor status of breast cancer patients in relation to body mass index

Receptor status	BMI		Difference (%)	*P*
	<25 kg/m^2 (*n*=293), *n* (%)	≥25 kg/m^2 (*n*=153), *n* (%)		
ER/PR +ve	156 (53.24)	83 (54.24)	1.0	0.840
Her2-neu +ve	101 (34.47)	50 (32.67)	1.80	0.703
TNBC	81 (27.64)	49 (32.02)	4.38	0.334

ER: Estrogen receptor, PR: Progesterone receptor, Her2-neu: Human epidermal growth factor receptor, TNBC: Triple-negative breast cancer, BMI: Body mass index

Table 5: Distribution of receptor status in premenopausal and postmenopausal breast cancer patients with body mass index (≥25 kg/m^2)

Receptor Status	Premenopausal (*n*=88), *n* (%)	Postmenopausal (*n*=65), *n* (%)	Difference (%)	*P*
ER/PR +ve	40 (45.45)	34 (52.30)	6.85	0.40
Her2-neu +ve	25 (28.40)	23 (35.38)	6.98	0.35
TNBC	33 (37.50)	19 (29.23)	8.27	0.28

ER: Estrogen receptor, PR: Progesterone receptor, Her2-neu: Human epidermal growth factor receptor, TNBC: Triple-negative breast cancer

Table 6: Distribution of receptor status in premenopausal and postmenopausal breast cancer patients with body mass index (<25 kg/m^2)

Receptor status	Premenopausal (*n*=169), *n* (%)	Postmenopausal (*n*=124), *n* (%)	Difference (%)	*P*
ER/PR +ve	94 (55.62)	71 (57.25)	1.63	0.781
Her2-neu +ve	55 (32.54)	48 (38.70)	6.16	0.276
TNBC	48 (28.40)	30 (24.19)	4.21	0.421

ER: Estrogen receptor, PR: Progesterone receptor, Her2-neu: Human epidermal growth factor receptor, TNBC: Triple-negative breast cancer

with TNBC was higher by 4.21% in the premenopausal group (P = 0.421) [Table 6].

Discussion

Breast cancer incidence and mortality are rapidly growing worldwide. It is the most frequently diagnosed cancer among women in 154 countries of the world and leading cause of death due to cancer in 100 countries.[1] In India, one of the emerging economies of the world, there is not only an increase in the number of cancer cases but also a change in the distribution of common cancer types. Till few years back, it was infection and poverty-related cancer like cervical cancer which was the major cancer affecting Indian women. However, recent data from GLOBOCON show that lifestyle-related cancer like breast cancer is now the leading cancer among Indians.[18]

The median age at diagnosis for breast cancer among Indian women has been generally reported between 40 and 50 years, which is about 6–18 years younger than their western counterparts.[19] Similarly, the mean age of our breast cancer patients was found to be 47 years, with 58% of the patients in the premenopausal group as compared to only 42% in the postmenopausal group. This younger age at onset in the Asian population has been studied and analyzed in various studies. Jarrahi *et al*. proposed the age-period-cohort effect as a probable explanation to this observation. They concluded that the rapid change of breast cancer risk profiles related to westernized lifestyle such as low parity, insufficient breastfeeding, and weight gain is observed more commonly in younger women, which has resulted in a higher incidence of breast cancer in the younger generation.[20] A high young population density in our country may also contribute to a younger age of onset of these patients.[21]

Breast cancer is a disease with multiple and often complex risk factors. Several reproductive and lifestyle

factors are known to increase the risk of developing breast cancer.[22] Obesity as defined by BMI is one of the important lifestyle factors that have been linked to breast cancer.[9] The average BMI of our patients was found to be 22.37 kg/m^2. About one-third of the patients, which were 34.23% in the premenopausal group and 34.4% in the postmenopausal group, were in the overweight or obese category (BMI more than 24.9 kg/m^2). However, the subgroup analyses showed that 5.8% of the patients in the postmenopausal group were obese as compared to only 3.5% in the premenopausal group. Although the difference of 2.3% was not significant, it did suggest that postmenopausal breast cancer patients are more likely to be obese than premenopausal patients in our population.

There is sufficient evidence supporting that high BMI is positively associated with breast cancer risk among postmenopausal women and negatively correlated to breast cancer risk among premenopausal women.[8,9] A meta-analysis of 31 studies with 3,318,796 participants by Chen *et al*. was conducted to find the different effects of BMI on the risk of breast cancer among premenopausal and postmenopausal women. It concluded that BMI had different effects on premenopausal and postmenopausal breast cancer risk. However, contrary to previous studies, a high BMI was not found to be associated with a decreased risk in premenopausal women and it recommended more research to understand these differences.[23] The exact mechanism of the association between high BMI and breast cancer remains unclear, though the production of endogenous estrogen from excessive adipose tissue has been postulated to stimulate proliferation of breast epithelial cells and initiate carcinogenesis.[24]

Further, breast cancer is a heterogeneous disease with different molecular subtypes which can be identified clinically on the basis of status of ER, PR, and HER2-neu receptor. These molecular subtypes are not only used as a prognostic indicator but are also important in clinical decision-making.[25,26] In our study, there was an increase in the ER/PR positivity in the postmenopausal group by 3.41% (P = 0.47) and in the HER2-neu positivity by 6.38% (P = 0.15). However, the number of patients with TNBC was more in the premenopausal group by 5.59% (P = 0.19). Increasing evidence suggests that breast cancer subtypes defined by the expression of ER, PR, and HER2 represent distinct biological entities of breast carcinoma and it has been hypothesized that differing receptor status may reflect different etiological mechanisms as seen in premenopausal and postmenopausal women.[27,28] Studies have suggested that risk factors operating through hormonal mechanisms are differentially correlated with hormone-related receptor expression.[29] A study by Islami *et al*. reported that breastfeeding is associated with a lower incidence of hormone receptor negative and TNBC.[30] As such, overweight or obesity may be more closely associated with ER and PR positivity because of the hormonally mediated mechanism of these subtypes.[31] The subset analyses of our patients with BMI ≥25 kg/m^2 showed a further increase in the ER/PR positivity in the postmenopausal group as compared to the premenopausal group by 6.85% (P = 0.40) but almost similar difference in HER2-neu positivity which was 6.98% (P = 0.35). However, the number of patients with TNBC further increased in the premenopausal group by 8.27% (P = 0.28). Similar trend, but with a narrowed difference was seen in the receptor status of patients with BMI <25 kg/m^2.

A systematic review of literature done by Althuis *et al*. analyzing the etiology of hormone receptor defined breast cancer concluded that postmenopausal obesity was more consistently associated with increased risk of hormone receptor positive, both ER and PR than hormone receptor-negative tumors, possibly reflecting increased estrogen synthesis in adipose stores.[10] Similar results were reported in the Shanghai Breast Cancer Study evaluating Asian patients. They found that high BMI in postmenopausal breast cancer patients was associated with an increased risk of the ER- and PR-positive subtype.[29] However, a study done in Japanese women showed that breast cancer risk with postmenopausal obesity was modified by PR status alone, although this was not statistically significant.[12] Another Asian study done in Chinese women showed that among postmenopausal Chinese women with elevated BMI, there was an increased proportion of PR-positive breast cancer and the proportion of ER-positive cancer did not vary with increasing BMI in postmenopausal women.[32]

Our study showed a marginally higher ER/PR positivity and lower HER2-neu positivity in overweight and obese patients. HER2-neu oncogene encodes an epidermal growth factor receptor family like growth protein and its over expression is associated with early disease recurrence, relative treatment resistance, and poor prognosis.[33,34] A study done in the Mediterranean population has shown that obesity was related with postmenopausal breast cancer overexpressing HER2-neu oncoprotein.[15] However, few other studies have found an inverse relationship between HER2-neu expression and BMI. They have postulated that higher level of estrogen associated with obesity causes downregulation of HER2-neu receptors.[35]

TNBC is known to be associated with aggressive pathology and poor survival. While factors related to

reproductive history and triple-negative breast cancer risk have been well studied and documented, there are only a few studies on the association between BMI and TNBC .[36] Some studies have reported a modest positive association between BMI and triple-negative breast cancer risk in younger women. The probable pathway suggested is the state of chronic low-grade inflammation associated with obesity.[37]

This is probably one of the few studies analyzing the correlation of BMI, menopausal status, and receptors in breast cancer patients in a cohort of patients from eastern India. The study has its own limitations as it is a retrospective, single-center analysis with a small sample size using the WHO criteria for defining overweight and obesity. Use of different classification systems for overweight and obesity like the Modified Criteria for Asian Indians and waist circumference could modify the results. Other limitations of the study include presence of other probable risk factors such as parity, age at first childbirth, and breastfeeding which were not considered in the statistical analysis.

Conclusion

In summary, the result of our study showed a slightly increased incidence of overweight and obesity in postmenopausal breast cancer as compared to premenopausal patients. Further postmenopausal patients with a BMI ≥25 kg/m^2 had a higher percentage of ER/PR receptor positivity and lower percentage of TNBC. The percentage of HER2-neu receptor positivity was more in postmenopausal patients but similar in both overall and obese subgroup analyses. Patients with a high BMI were also found to have a low percentage of HER2-neu positivity. We suggest more studies with a large sample size focused on evaluating modifiable risk factors and molecular subgroups to provide causal insights for observed association and to form targeted prevention strategies.

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Conflicts of interest

There are no conflicts of interest.

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