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ORIGINAL ARTICLE

Association of BMI with Breast Cancer: An Experience at a Tertiary Healthcare in a Developing Country

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ABSTRACT

Objective: Breast carcinoma is the most common invasive cancer in females, and second leading cause of global cancer mortality.[1] The incidence of this disease remains high in our population. It is therefore essential to identify and control common risk factors. This case-control study was conducted to determine the relationship between BMI and breast cancer.

Materials and Methods: A prospective case control study was performed between the time duration of September 2021 till February 2022. A total no of 158 patients, out of which 79 of them were part of the control group, while the remaining 79 had breast cancer were included in this study. Patient's BMI and other risk factors were contrasted with these groups using stata 14.2.

Results: Multivariate logistic regression analysis revealed that of the preoperative factors; age greater than 40 years(95%CI, 1.01 4.87), and postmenopausal status (95%CI, 1.10 9.70) were all independently associated with higher incidence of breast cancer in our women. BMI association with breast cancer was also considered significant with 95% confidence interval around 1 (95%CI, 0.20 1.14). Family history and breast cancer had no independent associated with each other. When only the tumor stage were compared, higher stage of disease was associated with delayed presentation.

Conclusions: higher BMI, low parity and higher number of miscarriages cumulatively predispose the postmenopausal women of this region to higher risk of breast cancer.

INTRODUCTION

Breast carcinoma is the most common invasive cancer in females, and second leading cause of global cancer mortality.[1] Pakistan also suffers the heavy burden of this disease. 1.78 million new cancer cases were reported for 2020 in Pakistan, out of which 14.5% were breast cancer.[1] The incidence of this disease remains high in our population. It is therefore essential to identify and control common risk factors.

Excess body weight has been documented to contribute to development of many human cancers, including breast carcinoma. Existing literature suggests a strong relationship of high Body Mass Index (BMI) with developing breast cancer, especially after menopause. [2] High BMI leads to an increase in adipose cells in body causing to increased conversion of androstenedione to estrone.[3] After menopause fat cells remain the only source of estrogen leading to increased exposure and subsequent risk of breast cancer.[3] Breast neoplastic cells can have ER, PR tumour receptors on their surface, which when attach to circulating estrogen and progesterone hormones in blood, promote tumour cell proliferation. Obesity is also associated with increased insulin resistance, which leads to higher levels of leptin and inflammatory cytokines, which can stimulate cell proliferation through various mechanisms[3]. Adiponectin is an adipocyte specific protein, which down regulates tumor cell proliferation and up regulates apoptosis. Insulin resistance secondary to obesity is inversely associated with adiponectin, hence promotes tumor cell proliferation.[3]

Breast cancers is classified into four molecular subtypes based on presence of Estrogen/ Progesterone Receptors and Her2 over-expression.[4] Luminal B (ER/PR +, HER2+) is the most common subtype of breast carcinoma in our population.[4] The tumor is also categorized on basis of rate of Ki-67, which is considered high if >10%. Although the literature has not statistically associated Ki-67 levels with ER, PR and Her2 statuses; however, it associates Ki-67 expression with higher disease stages.[5]

The rationale of this study is to evaluate the association between BMI and breast cancer in our women and its effects on increasing the incidence and poor prognosis of the disease. This study is expected to add evidence to obesity-breast cancer linkage. Although advanced stage at presentation, lack of awareness about Breast Cancer and limited access to available screening and treatment options are contributing factors to disparate mortality rate.[6] obesity being a modifiable risk factor of breast cancer, measures can be taken to decrease the prevalence of this disease in our society, or at least in first degree relatives, by altering BMI.

METHODS

A prospective case control study was performed between the time duration of September 2021 till February 2022 in the breast outpatient clinic after the approval from the Institutional Review Board, IRB-2034/DUHS/Approval/2021/452. The study was conducted at Dow University Hospital, DUHS Karachi, Pakistan. During the research phase a total no of 158, histopathologically confirmed patients were asserted coming to the clinic, out of which 79 of them were part of the control group and had benign diseases, while the remaining 79 had breast cancer as confirmed by the histopathology. Written informed consent was obtained from the following patient, who was also subjected to a Performa interview. Furthermore, the patient's medical record number was noted and subsequently followed.

The STATA version 14.2 was employed to retrieve the data and carry out pertinent statistical analysis. The body weight was determined using the ZT-160 height and weight scale, which has a minimum scale division of 100 grams and a minimum height range of 0.5 cm. At the time of weight assessment, all patients were without shoes and dressed simply. Co-investigators took measurements in the breast clinic under the lead investigator's supervision.

These BMI and other risk factors were contrasted with the subsequent quantitative and qualitative breast cancer characteristics. Patients with breast cancer who have already undergone breast surgery, chemotherapy, radiation, or hormonal therapy were excluded. All previously treated breast cancer patients who experienced recurrence were further excluded.

Statistical Analysis: Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as means and standard deviations. T-test was used to compare continuous variables, while Chi-square tests was used to compare categorical variables with cases and controls.(Table 1)

The patients were categorized into groups based on presence of breast cancer. The two groups were analyzed for their differences in baseline characteristics and presentation. The patients with breast cancer were also categorized and evaluated for associations of their characteristics with Age, BMI, menstrual status and family history using both univariable and Multivariable logistic regression. (Table 2)

Anova and chi square tests were used while comparing breast cancer stages with continuous and categorical variables respectively. (Table 3)

RESULTS

This case control study was directed on absolute no of 158 women patients as of now biopsied for breast disease. All patients of >25 years of age were included from stage I to stage IV metastatic disease at the time of diagnosis. The quantity of patients analyzed as benign disease were accounted for as 79, albeit the patients bringing about breast cancer on biopsy were 79. The results were found out through reports of diagnostic procedures. The factors of interest taken into account include demographic variables, comorbidities, menstrual history with family history. Control group incorporate healthy women presenting to breast center for screening reason, both pre-and post-menopausal, without any proof of breast malignant growth on history, breast assessment, ultrasound, mammogram or biopsy. In each part of the cohort, the control group taken was unified with biopsy demonstrating benign illnesses still in risk of developing Breast cancer.

The dissemination of the chosen qualities of breast cancer cases and controls is introduced in Table A. Mean age in years, for controls were found to be 40.4 ± 8.6, although for cases were of around 49.6 ± 12.0 showing the significantly low p-value of <0.001 at median age. There was a statistically significant difference (p= 0.015) between BMI of case (27.7 ± 5.9) and control group (29.9 ± 5.7) and clinically this was not a significant difference as both lie in the overweight category, according to CDC guidelines[7].

Nulliparity (p <0.001) and increased number of miscarriages (p <0.001) were significantly associated with breast cancer. Presence of breast cancer in the family observed in the control group was 31.7% out of which most were first degree relatives. While in the cancer group, 12.1% patients were having family history of breast cancer, out of which most of them were their immediate family members. Co-morbidities i.e. DM and HTN showed no statistical significance with breast cancer. Ages at menarche, menopause and first born child were also compared in both case and control groups, but showed no statistical significance (p- value >0.05). Post-menopausal women were mostly in the cancer group as compared to the control group (8.7%), with a clinically significant p-value of < 0.05.

Table B shows association of risk factors with breast cancer by univariate regression analysis, comparing age, BMI, menstrual status and family history. Among all subjects, age greater than 40 years increased the risk of breast cancer compared with women less than 40 years (OR 2.51; 95%CI, 1.30-4.82; P<0.05). Similarly risk of breast cancer was greater in post-menopausal women (OR 4.02; 95%CI, 1.48-10.9; P<0.05). BMI and family history association with breast cancer was not clearly understood.

Multivariate logistic regression analysis revealed that of the preoperative factors; age greater than 40 years(95%CI, 1.01 - 4.87), and postmenopausal status (95%CI, 1.10 - 9.70) were all independently associated with higher incidence of breast cancer in our women. BMI association with breast cancer was also considered significant with 95% confidence interval around 1 (95%CI, 0.20 - 1.14). Family history and breast cancer had no independent associated with each other.(Table B)

The delayed presentation of breast cancer is a troublesome issue in breast cancer management. We compared the breast cancer stage at which the patients presented to us at the time of selection with various risk factors (Table C). This comparison revealed that delayed presentation resulted in advanced cancer stage (p<0.05). Another pairwise comparison was performed between the different stages using the Fisher-protected LSD test and revealed no patients with stage I disease, while patients with longer duration of symptoms had mainly stage II and III disease. (P-value <0.05)

Table 1: Association of risk factors with Breast cancer cases and controls.

Risk factors	Benign (N= 79)	Cancer (N= 79)	P value
Age	40.4 ± 8.6	49.6 ± 12.0	<0.001*
Marital status Married Single Widowed	 68 (87.1 %) 07 (9.0%) 03(3.9%)	 65 (82.53%) 11(13.9%) 03(3.8%)	 0.642**
BMI	29.9 ± 5.7	27.7 ± 5.9	0.0153*
Duration of symptoms (months)	7.2 ± 10.6	6.7 ± 6.4	0.7533*
HTN	21 (26.6%)	28 (38.9%)	0.107**
DM	10 (12.7%)	15 (21.7%)	0.141**
History of trauma Yes No Maybe	 2 (2.53%) 77 (97.47 %) 00	 3 (4.35%) 65 (94.20%) 01(1.45%)	 0.462**
Parity Nulliparous <3 Kids >3 Kids	 20 (25.3%) 28 (26.5%) 31 (39.2%)	 50 (73.5%) 18 (26.5%) 0	 <0.001**
Miscarriages NIL 1-3 >3	 56 (70.9%) 22 (27.85%) 27.85 (1.3%)	 19 (27.9%) 24 (35.3%) 35.29 (36.8%)	 <0.001**
Age at menarche	13.2 ± 1.0	13.2 ± 1.5	0.9460*
Menstrual cycle Regular Irregular Post-menopausal	 58 (84.1%) 5 (7.3%) 6 (8.7%)	 40 (60.6%) 7 (10.6%) 18 (27.3%)	 0.014**
Menstrual status Pre-menopausal Post-menopausal	 63 (91.30%) 6 (8.7%)	 48 (72.7%) 18 (27.3%)	 0.005**
Age at menopause	43.1 ± 5.2	54.9 ± 64.7	0.4587 *
Age at first born <30yrs >30yrs	 46 (92%) 4 (8%)	 36 (94.7%) 2 (5.26%)	 0.614**
Addiction Nil Smoking Betel nut Naswar	 78 (98.73%) 0 1 (1.27%) 0	 0 2 (50%) 1 (25%) 1 (25%)	 <0.001**
Family history of Breast Ca? Yes No	 25 (31.7%) 54 (68.4%)	 10 (12.1%) 69 (87.3%)	 0.004**
Relation with family member with breast cancer Immediate family First degree relative Second degree relative	 4 (16%) 16 (64%) 5 (20%)	 7 (87.5%) 1 (12.50 %) 0	 0.001**

Table 2: Association between risk factors and breast cancer; univariate and multirate analysis

Risk factors	Univariate Analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
Age <40yrs >40yrs	 2.51 (1.30 - 4.82)	 2.21(1.01 - 4.87)
BMI <25kg/m^2 >25kg/m^2	 0.41 (0.19 - 0.86)	 0.48 (0.20 - 1.14)
Menstrual status Pre-menopausal Post-menopausal	 4.02 (1.48 - 10.9)	 3.30(1.10 - 9.70)
Family history of Breast Ca? No Yes	 0.31 (0.14 - 0.71)	 0.24 (0.10 - 0.63)

Table 3: Comparison between breast cancer stages and Risk factors

Breast cancer	Stage I (N=0)	Stage II (N=43)	Stage III (N=18)	Stage IV (N=18)	P – value
Age	NIL	49.2 ± 12.8	50.5 ± 12.2	50.7 ± 10.1	0.3807***
BMI	NIL	28.8 ± 6.6	25.1 ± 4.7	27.4 ± 4.6	0.1510***
Duration	NIL	4.3 ± 5.5[a]	8.35 ± 5.8[a]	8.2 ± 6.5	0.0245***
Parity					
Nulliparous		27 (79.4%)	13 (72.2%)	8 (57.1%)	0.352**
Less than 3 Kids	NIL	7 (20.6%)	5 (27.9%)	6 (42.9%)	
More than 3 Kids		0	0	0	
Miscarriages					
NIL		12 (35.3%)	4 (22.2%)	3 (21.4%)	
1-3	NIL	13 (38.2%)	7 (38.9%)	2 (14.3%)	0.104**
>3		09 (26.5%)	7 (38.9%)	9 (64.3%)	
Menstrual status					
Pre-Menopausal		23 (71.9%)	13 (72.2%)	9 (64.3%)	0.883**
Post-menopausal	NIL	8 (25.0%)	5 (27.9%	5 (35.7%)	
Family history of Breast Ca?					
Yes	NIL	7 (16.7%)	2 (11.1%)	1 (5.9%)	0.649**
No		35 (83.3%)	16 (88.9%)	16 (94.1%)	
[a] on comparison (LSD < 0.05)					

DISCUSSION

The results of this study suggest that higher BMI are associated with greater chances of breast cancer. Older age and post-menopausal status has an add-on effect on increased risk of having breast cancer. Our study also provide evidence that multi-parity and lower number of miscarriages has protective effect against breast cancer.

Maintaining moderate weight throughout adult life may be beneficial for breast cancer survival in women and this appears to hold for all ethnic groups.[8] Chang et.al[9] proposed that progressive weight gain throughout adulthood drives progression of chronic diseases to manifest at an earlier age. There are several potential mechanisms involved in alteration of normal breast tissue growth, that are triggered by higher adipocyte levels in body, leading to increased prevalence of breast cancer among women.

Excessive adiposity stimulates low-grade inflammation, oxidative stress and proinflammatory cytokines. Obesity increases circulating insulin concentrations, alters adipocytokine proteins, sex steroid hormones and binding proteins. Hence forth leading to increasing tumor growth, angiogenesis and metastasis. Greenlee et.al conducted a study on Post mastectomy breast tissue and concluded that higher levels of breast white adipose tissue inflammation were found in patients with higher BMI. [10] Anthony et.al. proposed that breast cancer chances are even increased in obese men due to conversion of testosterone to estrogen by aromatase in adipose tissue.[11]

Neuhouser et.al[12] also showed that most of the higher stage patients were morbid obese with BMI >35 kg/m^2. While in our study most of the higher stage patients were overweight with BMI between 25-30 kg/m^2. This variation of BMI can be due to variation in eastern and western population lifestyle. But still showing association of higher BMI with breast cancer. Copson et.al.[13] showed that Obesity can complicates outcomes in breast cancer pateints, even in youngsters.[13] Despite adjustment for this, obesity still independently predicts disease free interval and overall survival in breast cancer pateints.[13] Even there are higher chances of cancer recurrence in patients with higher BMI.[14]

Postmenopausal status was an independent factor associated with breast cancer in our study. This was also supported by Park. Et.al study suggesting that postmenopausal women who are metabolically unhealthy or have central adiposity are may be at increased risk for breast cancer despite having a normal BMI.[15]

In contrary to our study, Neuhouser et.al.[12] and Engkakul et.al.[16]showed that Obesity was associated with more advanced disease including larger tumor size, positive lymph nodes and regional/distant stage at diagnosis. while in our study higher stage of disease was associated with delayed presentation(Table C). Nattenmüller et.al[17] suggested that obesity is related to risk of breast tumors with lower aggressiveness (hormone positive,her2 negative disease) while our study showed no significant difference among subtypes of breast cancer according to BMI . Henceforth supporting Sayed et.al study that also stated that BMI, either overall or by menopausal status, did not vary significantly by ER status.[18]

The positive points of our study is we included patients who have not underwent any management related intervention at time of BMI recording. This is a prospective study in which parity, family history, breast feeding was also included. A unique strength of this study was ages were approximately same in each group as compared to other studies leading to a better comparison.

Though this study has strengths derived from being a prospective case control study, it also has some limitations. Patients included in our study usually presented late to clinic since duration of start of symptoms henceforth no stage I cancer patient could be included in this study. In this study timing of weight gain and onset of breast cancer was also not compared.

In conclusion, we provide evidence that delayed presentation lead to higher stage and a greater disease burden. Lower chances of afferent surgery and increased chances of neo adjuvant chemo and extensive surgeries. Such data point to the need of promoting lifestyle modification consonant with weight management and control and the potential need for more vigilant screening among women who manifest higher BMI.

Additional studies that investigate, the timing of weight gain and onset of breast cancer, are needed to confirm these findings.

CONCLUSION

Obesity, low parity and higher number of miscarriages cumulatively predispose the postmenopausal women of this region to higher risk of breast cancer. Obesity is recognized as a preventable life style risk factor for cancer and as such healthy diet and regular physical activity should be promoted across the lifespan.

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