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RESEARCH ARTICLE

THE ROLE OF BODY MASS INDEX (BMI) AS AN INDEPENDENT RISK FACTOR AND PROGNOSTIC FACTOR IN BREAST CANCER – A HOSPITAL BASED EPIDEMIOLOGICAL STUDY

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ABSTRACT

Objectives: To study the role of Body Mass Index as an independent risk factor and prognostic factor in breast cancer.

Methods: A hospital based epidemiological study was conducted in a tertiary care hospital in India involving 50 patients with a diagnosis of breast cancer who visited the Medical Oncology outpatient department for a period of 3 months. 50 age matched controls who had no detectable breast cancers were selected as controls. Their body mass index was calculated. Data including stage of breast cancer, lymph node status and presence of metastasis, histological type, grade of the tumour and hormone receptor status. (ER, PR and Her 2 neu) were tabulated. Additional information regarding menstrual, menopausal status, co-morbidities like Diabetes mellitus, hypertension and epilepsy was also gathered.

Results: The mean age of patients was 53.8 years and that of controls was 49.08 years. 56 % of cases and 44% of controls were post menopausal. 20 patients and 10 controls were diabetic; 14 patients and 9 controls were hypertensive and 2 patients and 2 controls had hypothyroidism. The odds ratio which quantifies the risk of association of breast cancer and obesity is 0.339 in premenopausal women and 0.045 in post menopausal women. The number of triple negative breast cancers was more in I and II classes of body mass index. Obesity grade 2 and 3 were also associated with advanced disease, including larger tumor size, positive lymph nodes, regional and/or distant stage and deaths after breast cancer.

Conclusion: There is a statistically significant association between obesity and breast cancer in post menopausal women but the same is not applicable in pre menopausal women.

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INTRODUCTION

Obesity is increasingly becoming a major public health problem in developing countries. It is defined as an accumulation of adipose tissue that is of sufficient magnitude to impair health. Excess weight is best assessed by body mass index or BMI, which is a surrogate marker for underlying obesity. The normal BMI range is 18.5 to 25 kg/m^2 (Torre *et al*., 2015). According to World Health Organization (WHO) people can be divided into the following categories based on BMI. Approximately 7% of cancers in women are associated with obesity (van den Brandt *et al*., 2000). In women, a BMI greater than 25kg/m^2 correlated strongly with an increased incidence of carcinomas of esophagus, endometrium, gall bladder, breast and kidneys. A proposed hypothesis for such an association is explained by the presence of hyperinsulinemia and peripheral insulin resistance in obese individuals (Roberts *et al*., 2010). Insulin at high concentrations has multiple effects on cell growth.

i. Activation of phosphatidyl inositol 3 kinase, β catenin and RAS
ii. Hyperinsulinemia causes increase in insulin like growth factor 1, which is a mitogenic and anti apoptotic agent, which activates many of the cell growth pathways.
iii. Obesity increases the synthesis of estrogen from androgen precursors through an effect on adipose tissue aromatases.
iv. Insulin increases androgen synthesis in ovaries and enhances estrogen availability in obese persons by inhibiting production of sex hormone binding globulin in liver.

BMI	Classification
< 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	overweight
30.0–34.9	class I obesity
35.0–39.9	class II obesity
≥ 40.0	class III obesity

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Obese women under the age of 40 have a decreased risk as a result of anovulatory cycles and lower progesterone levels. In contrast, post menopausal obese women have an increased risk, which is attributed to the synthesis of estrogen in fat deposits (Schmidt *et al*., 2015).

MATERIALS AND METHODS

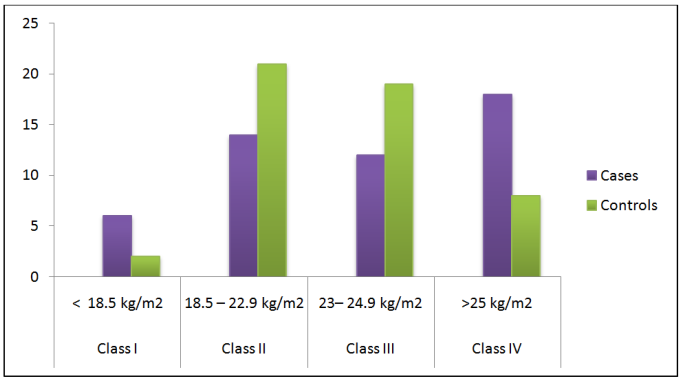
A case control study was carried out at our tertiary care hospital. This was a single institution study drawn from patients who attended the medical oncology outpatient department over a period of three months. The women accompanying the patients and a few voluntary women who had no detectable breast cancers were selected as controls. The study protocol was approved by the Institutional Human Ethics Committee. Informed consent was obtained from every patient and control and the patients were asked to enter the details provided in a questionnaire. Results of their heights and weights were entered. As a relative indicator of body weight, Body Mass Index was calculated as weight in kilograms divided by square of height in meters. The patients and controls were categorized into 4 classes based on BMI.

Class I – BMI < 18.5 kg/m^2
Class II – BMI 18.5 – 22.9 kg/m^2
Class III – BMI 23 – 24.9 kg/m^2
Class IV – BMI > 25 kg/m^2

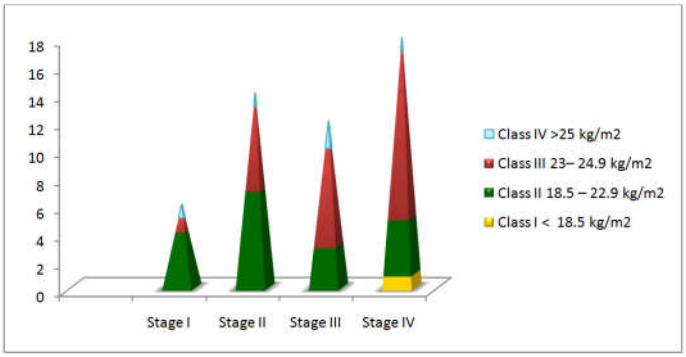
Data including stage of breast cancer, lymph node status and presence of metastasis was obtained from the case records of the patient. The histopathology reports were analyzed for recording the histological type, grade of the tumour and hormone receptor status (ER, PR and Her 2 neu).

Additional information regarding menstrual, menopausal status, co-morbidities like Diabetes mellitus, hypertension and epilepsy was also gathered. The results were tabulated and analyzed using SPSS (Statistical Package for the Social Sciences). The relationship between body mass index and risk of breast cancer was evaluated using odds ratio and the p value was calculated.

Bar diagram showing the distribution of cases and controls among different classes of body mass index



Bar diagram depicting the relation between stages of breast cancer and classes of body mass index



Body mass index in premenopausal women – Cross tabulation

Group	BMI ≤ 24.9 kg/m^2	BMI > 25.0 kg/m^2	P value	Confidence interval	Odds ratio
Cases	15 (68.2%)	7 (31.8%)			
Controls	23 (82.1%)	5 (17.9%)	0.23	0.131-0.877	.339

Table 1. Age distribution of cases and controls in various classes of BMI

Age Range	Class I < 18.5 kg/m^2		Class II 18.5 – 22.9 kg/m^2		Class III 23– 24.9 kg/m^2		Class IV >25 kg/m^2	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
21-30	0	0	0	1	0	1	0	0
31-40	1	0	1	6	2	5	2	3
41-50	1	1	4	6	1	2	5	2
51-60	2	1	5	4	4	6	9	1
61-70	1	0	0	3	5	4	2	3
71-80	1	0	3	0	0	0	0	0
>80	0	0	0	2	0	0	0	0

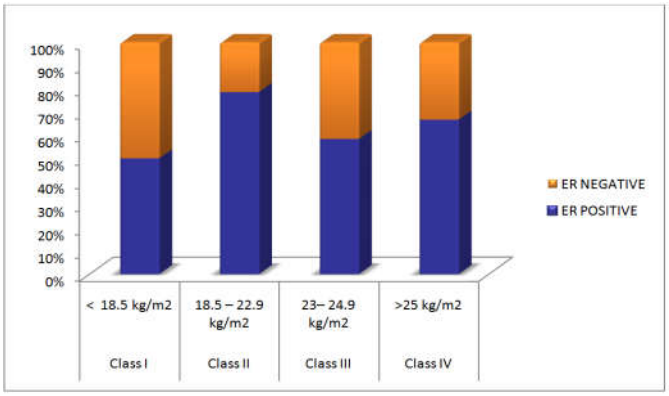
RESULTS AND OBSERVATION

50 women diagnosed with breast cancer during a period of 3 months were taken as cases and 50 women without a history of breast cancer were taken as controls. The mean age of patients was 53.8 years and that of controls was 49.08 years. 56 % of cases and 44% of controls were post menopausal. 20 patients and 10 controls were diabetic; 14 patients and 9 controls were hypertensive and 2 patients and 2 controls had hypothyroidism.

Body mass index in post menopausal women – Cross tabulation

Group	BMI ≤ 24.9 kg/m^2	BMI > 25.0 kg/m^2	P value	Confidence interval	Odds ratio
Cases	17 (60.7%)	11 (39.3%)			
Controls	19 (86.4%)	3 (13.6%)	0.045	0.058-1.024	.045

Histogram showing estrogen receptor expression in various classes of BMI



The odds ratio which quantifies the risk of association of breast cancer and obesity is .339 in premenopausal women and .045 in post menopausal women.

DISCUSSION

Overweight and obesity are current escalating public health issues. The prevalence of obesity in females has accelerated over the past decade in many developing countries. Obesity is an established risk factor for cancer and cancer related deaths, including that of breast cancers. Several studies show that a significantly stronger association is obvious between increased body mass index (BMI) and higher breast cancer incidence. Increased levels of estrogens due to excessive aromatization activity of the adipose tissue, over expression of pro-inflammatory cytokines, insulin resistance and hyper activation of insulin-like growth factors (IGFs) pathways, adipocyte-derived adipokines, hypercholesterolemia and excessive oxidative stress contribute to the development of breast cancer in obese women. Lopez *et al*. (2017) conducted a cross-sectional study of 849 women diagnosed with breast cancer in Columbian patients. Participant's body weight, height, and body mass index were collected at the time of diagnosis. Patients were classified following the Center for Disease control's (CDC) criteria: underweight (BMI $<$ 18.5 kg/m2), normal (18.5 $\leq$ BMI $<$ 25 kg/m2), overweight (25 $\leq$ BMI $<$ 30 kg/m2), and obese (BMI $\geq$ 30 kg/m2). Their data revealed that an association between BMI and menopausal status was not statistically significant in the study population. In the current study, the odds ratio of association was .339 with a p value of 0.23 in premenopausal women, which is not significant. However, the odds ratio in post menopausal women was .045 with a p value of .045 which is significant. Obese breast cancer patients are often associated with advanced stage disease, larger tumors, and axillary lymph node-positive status, partly due to delayed diagnoses and technical difficulties in palpation of the tumors. In a study conducted by Turkos *et al*. (2013), obese patients compared with normal-weight women were older at diagnosis and more often had high grade tumor with lymphovascular invasion. According to the molecular subtypes, overall survival and disease free survival were significantly shorter in obese patients with triple negative breast cancer. Obesity and lymphovascular invasion were found to be independent prognostic factors for TNBC mortality. In our study also we found that more number of obese breast cancer patients presented with stage III or IV disease, although the association was not statistically significant.

The study done by Sahin *et al*. (2017) BMI was an independent factor in patients with BC, with an association indicating a decreased incidence for luminal-like subtype and increased incidence for triple-negative subtype among premenopausal patients. However, this significance was not found in postmenopausal patients. Accordingly, a plausible etiological heterogeneity in BC might play a role among immunohistochemical subtypes in every life stage of women. Makama *et al*. (2017) published an association study of established breast cancer reproductive and lifestyle risk factors with tumour subtype defined by the prognostic 70-gene expression signature. Using prognostic gene expression profiles, they found that specific reproductive factors like higher parity was associated with low-risk (good prognosis) tumours. Also, longer duration of breastfeeding was associated with high-risk (poor prognosis) tumours. Neuhouser *et al*. (2015) performed a randomized control study and detected that A BMI of 25.0 or higher was strongly associated with risk for estrogen receptor-positive and progesterone receptor-positive breast cancers but was not associated with estrogen receptor-negative cancers. In our study we found that there was no significant difference in the distribution of estrogen receptor positive tumours and Her 2 neu positive tumours in obese and non obese patients. However, the number of triple negative breast cancers was more in I and II classes of body mass index. Obesity grade 2 and 3 were also associated with advanced disease, including larger tumor size, positive lymph nodes, regional and/or distant stage and deaths after breast cancer. An article by Schmitz *et al*. (2013) proposes that obesity and related co morbid conditions pose an increased risk for common adverse treatment effects, including breast cancer–related lymphedema, fatigue, poor health–related quality of life, and worse functional health. But we did not notice any significant difference in the post treatment morbidity among obese and non obese individuals.

Limitations of our study

The sample size of our study is limited to derive a statistically significant association of obesity and malignancy. The follow up was for a period of 6 months to one year and so the response of obese and non obese patients to the various treatment strategies could not be compared.

Conclusion

There is a valid association between obesity and breast cancer in post menopausal women but the same is not applicable in pre menopausal women. There is no significant difference in the size, histological type and immunohistochemical profile of breast cancers in obese and non obese patients, although the incidence of triple negative cancers was high in class I and class II BMI individuals. However obese patients presented with more advanced stages, possibly due to delay in detection.

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