Ref: Ro Med J. 2024;71(2)
DOI: 10.37897/RMJ.2024.2.7

Associations between body mass index and hormonal receptor, HER2/neu receptor, as well as other clinical characteristics of breast cancer

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ABSTRACT

Background. Obesity is a growing problem in the world. Correlations have been found between increasing body mass index (BMI) and breast cancer (BC). BC has multiple predictive and prognostic factors like hormonal receptors, human epidermal growth factor 2 receptor, stage of the disease and grade. Obesity may be differentially related to the risk of different subtypes given the various potential mechanisms underlying its association with breast cancer. The study aims to analyze the association between BMI, BC histopathologic, ER, PR and HER2/neu receptors expression, tumor size axillary nodes involvement, metastasis and nuclear grade.

Methods. A cross sectional study was conducted involving 256 cases with breast cancer. Oncology teaching hospital based BC cases had been interviewed and data collected regarding weight and height, estrogen and progesterone receptors status, human epidermal growth factor 2 receptor, stage of the disease, grade of tumor at time of diagnosis, and categorize the cases to pre and postmenopausal state and then subdivided according to body mass index (normal, overweight, obese) and compared between three groups.

Results. Overweight/obese people showed a significant statistical effect with estrogen and progesterone receptors, positive p value = 0.026, 0.007 respectively, larger tumor size, p value =0.035, and more lymph node involvement, p-value =0.031 in post-menopausal women, while premenopausal cases did not show significant statistical effect regarding the above-mentioned variables. Body mass index difference did not show a significant statistical effect on human epidermal growth factor 2 receptor, metastasis at diagnosis, tumor grade in both pre and postmenopausal cases.

Conclusion. Body mass index difference affects postmenopausal BC cases rather than premenopausal as overweight/obese cases presented with more estrogen and progesterone receptors positive, larger tumor size and more lymph node involvement.

Keywords: postmenopausal, breast cancer, human epidermal growth factor 2 receptor expression, tumor size, HER2/neu

INTRODUCTION

BC is the most common cancer in the world and the leading cause of cancer-related deaths in women [1]. Breast tumors have long been classified according to morphological features, histological type, and stage; the majority of breast cancers are invasive ductal carcinoma (75%), invasive lobular carcinoma (10%), or a combination of these [2,3]. The histological classification system of BC is a semi quantitative morphological assessment consisting of percentage tumor size, degree of nuclear pleomorphism, and mitotic number in a predetermined area. Based on the scores for these features, three numbers indicate the difference in BC: low, medium and high [1]. Identification of molecular markers such as expression of estrogen receptor (ER), progesterone receptor (PR), and human growth factor 2 (HER2/neu) has also provided value as a predictor of prognosis in women diagnosed with BC [1].

ER and PR are poor markers, but are highly predictive of response to endocrine therapy. ER functions as a ligand-induced transcription factor that

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Article History:
Received: 29 April 2024
Accepted: 20 June 2024

regulates gene expression through interactions with hormone receptors [1].

HER2 is a member of the epidermal growth factor receptor (EGFR) tyrosine kinase family, which includes four transmembrane receptor proteins: EGFR-1, HER2, HER3, and HER4. Receptor activation through ligand binding or by ligand-independent effects results in homo- or heterodimerization of receptor proteins that stimulate cell growth, cell survival, migration, and angiogenesis. Overexpression of the 185 kd HER2 protein results from gene amplification, which is found in approximately 20% of breast cancer cases. HER2 status is defined by the ASCO/CAP guidelines updated in 2013 [3].

Obesity is an important public health problem. The prevalence of overweight and obesity in Iraq was 61.1% and 76% [1,2]. These high figures are explained by economic development, urbanization and social development, which lead people to eat more, and are associated with a sedentary lifestyle. Changes in these conditions have led to obesity [1]. Body weight can be measured as body weight relative to height or can be measured by body fat distribution. BMI (weight in kg/height in m^2) or type of obesity with central or peripheral fat distribution are the two most commonly used and clinically relevant classifications to determine the degree of obesity [1].

BMI is an indicator of body fat for most people. It is used as a screening tool to determine whether an adult is at a healthy weight. What matters is how much you weigh according to your height. A BMI between 18.5 and 25 kg/m² indicates normal weight. A BMI below 18.5 kg/m² is considered underweight. A BMI between 25 kg/m² and 29.9 kg/m² is considered overweight. A BMI of 30 kg/m² or more is considered obese [1].

Obesity has been identified as a risk factor for BC in postmenopausal women [1,2]. Estrogen is produced mainly by female sperm through the aromatization of testosterone and androstenedione by aromatase. Adipose tissue also produces aromatase; Therefore, the conversion of androgens to estrogens in postmenopausal men and women depends on the type of fatty tissue. Estrogen signaling has many effects that are thought to promote tumor growth: it can induce cell proliferation, inhibit apoptosis, and induce angiogenesis [2]. Additionally, it is associated with low levels of sex hormone binding globulin, which increases free estradiol and is associated with many cancers [1].

Several studies report that obesity poses a risk of BC in pregnant women, with the risk decreasing by approximately 10% per 5 kg per m^2 [1,2]. The effect is particularly pronounced in tumors expressing (ER) and/or (PR). In contrast, the risk of ER/PR breast cancer increases threefold (80% increased risk per 5 kg increase per m^2) [3].

The study aims to analyze the association between BMI, BC histopathologic, ER, PR and HER2/neu receptors expression, tumor size axillary nodes involvement, metastasis and nuclear grade.

METHODS

Study design

Hospital based cross sectional study was conducted to evaluate the effect of BMI on BC case regarding ER, PR, HER2/neu status, as well as tumor size, lymph node status, metastasis, grade of tumor at time of diagnosis for BC women.

Study population

A sample of a 256 BC cases who were diagnosed on basis of histopathology obtained from mastectomy, breast conserving surgery and Tru-cut biopsy from breast mass or metastatic site.

Immunohistochemistry for ER, PR and HER2/neu expression evaluated by either oncology teaching hospital pathology department lab or private pathology clinic lab.

Staging of the disease had been done by different methods of image modalities or by histopathology of the metastatic site.

Data collection

The study started on 1st of January, 2018, and ended on the 31st of December, 2018. BC cases sample were collected by direct interview during the visits for regular follow up in the oncology clinic from the teaching hospital.

Data collection at time of diagnosis was taken from the registry book of the cases. Age, menopausal status, weight, height, ER and PR status, HER2/neu status, grade, tumor size, lymph node involvement, metastasis and grade data were analyzed. Cases sample was divided to premenopausal and postmenopausal state, then subdivided according to their BMI into normal weight index <25, over weight 25-30, and obese >30.

Inclusion criteria

All BC cases with complete documents regarding study variables – either newly diagnosed or coming for regular treatment schedule or follow up in the oncology clinic of the teaching hospital – were included in the study.

Exclusion criteria:

1. Cases with family history of breast cancer
2. History of thyroid disease
3. History of steroid use

Ethical consideration

The research was approved by the scientific and ethical committee in Iraqi board of medical specialties.

Statistical analysis

For the purpose of statistical analysis, Chi-Square and Fisher's exact tests were applied and any p-value, for an association/ difference, equals or below 0.05 was considered significant for statistical association/difference. These two tests were applied using the Statistical Package for Social Sciences (SPSS), version 23.

RESULTS

The total number of cases included in this study was 256 –124 cases in premenopausal state and 132 in postmenopausal state, at time of diagnosis. The percentages of estrogen positive and progesterone positive were obviously higher in all sampled cases with more relevance in postmenopausal cases. Regarding HER2/neu receptors, about two-thirds were negatives in pre and postmenopausal cases. In premenopausal cases more than half of the cases were T2 disease (57.4%). Regarding the lymph node involvement, the cases sample was distributed between N0, N1 and N2. Most of the cases (80.6%) presented the non-metastatic disease. Postmenopausal cases presented in the similar way with the T2 diseases had the highest percentage (59.1%), but with higher percentage of N3 (15.9%) and metastatic disease (25.8%). Concerning the grade of tumor, intermediate grade was seen in (60.5%) of premenopausal cases and (66.7%) in postmenopausal cases. Low grade had the least percentage in both groups. In premenopausal cases, 18 (14.5%) had a normal BMI, 45 (36.3%) were over weight, and 61 (49.2%) obese. Whereas in postmenopausal cases, 11 (8.3%) were normal weight, 37 (28.0%) over weight, and 84 (63.6%) obese. In overall, the percentage of obesity was high in all the sampled cases, but more obesity was seen in postmenopausal cases.

Table 1 shows that there was no significant statistical association between BMI and ER in premenopausal cases as the p=0.875. Whereas in postmenopausal women there was a significant statistical association between BMI and ER positive p=0.026.

TABLE 1. BMI with estrogen receptors in premenopause cases

	PREMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
ER + VE	13 (15.1%)	32 (37.2%)	41 (47.7%)	86 (100%)
ER - VE	5 (13.2%)	13 (34.2%)	20 (52.6%)	38 (100%)
	18	45	61	124
p = 0.875				TOTAL

An increased BMI induced an increase of the percentage of cases with ER positive, as shown in Table 2.

TABLE 2. BMI with estrogen receptors in post menopause cases

	POSTMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
ER + VE	8 (6.8%)	30 (25.6%)	78 (67.5%)	117 (100%)
ER - VE	3 (20%)	7 (46.7%)	5 (33.3%)	15 (100%)
	11	37	84	132
P = 0.026				TOTAL

Table 3 and Table 4 demonstrate the relation between BMI and PR receptors which presented in similar trend of ER in relation to BMI. As there is no significant statistical association between PR receptors and BMI in premenopausal women, p=0.379, and significant statistical association in postmenopausal cases, p=0.007.

TABLE 3. BMI with progesterone receptors in premenopause cases

	PREMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
PR + VE	15 (17.4%)	30 (34.9%)	41 (47.7%)	86 (100%)
PR – VE	3 (7.9%)	15 (39.5%)	20 (52.6%)	38 (100%)
	18	45	61	124
p = 0.379				TOTAL

TABLE 4. BMI with progesterone receptors in postmenopause cases

	POSTMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
PR + VE	7 (6.1%)	29 (25.4%)	78 (68.4%)	114 (100%)
PR – VE	4 (22.2%)	8 (44.4%)	6 (33.3%)	18 (100%)
	11	37	84	132
p = 0.007				TOTAL

TABLE 5. BMI association with tumor size in premenopausal cases

	PREMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
T1	4 (20%)	5 (25%)	11 (55%)	20 (100%)
T2	8 (11.3%)	25 (35.2%)	38 (53.5%)	71 (100%)
T3	6 (24%)	11 (44%)	8 (32%)	25 (100%)
T4	0 (0.0%)	3 (50%)	3 (50%)	6 (100%)
	18	44	60	122
p = 0.354				TOTAL

There was no significant statistical effect of BMI on HER2/neu whether in pre or postmenopause cases, p-values were 0.687, 0.486 respectively. There was no significant statistical association between BMI and tumor size in premenopausal women (Table 5), the highest percentage of T1 and T2 was seen in >30 BMI, while the highest percentage of T3 was seen in 25-30 BMI. Meanwhile, T4 showed equal percentages in 25-30 and >30 BMI, p= 0.354 (Table 5).

On the other hand, postmenopausal group showed a significant statistical association between BMI and tumor size, as demonstrated in Table 6. Where T2, T3, T4 showed the highest percentage when the BMI was over 30., p=0.035 (Table 6).

TABLE 6. BMI association with tumor size in postmenopausal cases

	POSTMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
T1	1 (7.1%)	9 (64.3%)	4 (28.6%)	14 (100%)
T2	5 (6.4%)	19 (24.4%)	54 (69.2%)	78 (100%)
T3	3 (10%)	6 (20%)	21 (70%)	30 (100%)
T4	2 (20%)	3 (30%)	5 (50%)	10 (100%)
	11	37	84	132
p = 0.035				TOTAL

In premenopausal cases no significant statistical association between BMI and number of lymph node involvement was shown (Table 7).

TABLE 7. BMI association with lymph node staging in premenopausal cases

	PREMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
N 0	9 (25%)	13 (36.1%)	14 (38.9%)	36 (100%)
N 1	4 (11.8&)	14 (41.2%)	16 (47.1%)	34 (100%)
N 2	4 (9.8%)	14 (34.1)	23 (56.1%)	41 (100%)
N 3	1 (9.1%)	3 (27.3%)	7 (36.6%)	11 (100%)
	18	44	60	122
p = 0.435				TOTAL

Note: 2 cases are missing due to lack of local staging

Table 8 demonstrated the significant statistical association between BMI and lymph node staging in postmenopausal cases, p-value=0.031. In the sample collected, N2 and N3 were 0.0% in BMI <25, while N2 was 67.6%, and N3 was 80% in BMI >30.

Neither pre nor postmenopausal women had shown any statistically significant association between the BMI and BC metastasis at the time of diagnosis (Tables 9 and 10). M0 percentage was higher in all sampled cases.

TABLE 8. BMI association with lymph node staging in postmenopausal cases

	POSTMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
N 0	5 (14.7%)	6 (17.6%)	23 (67.6%)	34 (100%)
N 1	6 (14.6%)	15 (36.6)	20 (48.8%)	41 (100%)
N 2	0 (0.0%)	12 (32.4%)	25 (67.6)	37 (100%)
N 3	0 (0.0%)	4 (20%)	16 (80%)	20 (100%)
	11	37	84	132
p = 0.031				TOTAL

TABLE 9. BMI association with metastasis at presentation in premenopausal cases

	PREMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
M 0	15 (15%)	35 (35%)	50 (50%)	100 (100%)
M 1	3 (12.5%)	10 (41.7%)	11 (45.8%)	24 (100%)
	18	45	61	124
p = 0.823				TOTAL

TABLE 10. BMI association with metastasis at presentation in postmenopausal cases

	POSTMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
M 0	9 (9.2%)	25 (25.5%)	64 (65.3%)	98 (100%)
M 1	2 (5.9%)	12 (35.3%)	20 (58.8%)	34 (100%)
	11	37	84	132
p = 0.507				TOTAL

Table 11 showed no significant statistical association between BMI and tumor grade in premenopausal cases as p=0.372.

TABLE 11. BMI association with tumor grade in premenopausal cases

	PREMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
LOW	2 (20%)	1 (10%)	7 (70%)	10 (100%)
INTERMEDIATE	12 (16%)	27 (36%)	36 (48%)	75 (100%)
HIGH	4 (10.3%)	17 (43.6%)	18 (46.2%)	39 (100%)
	18	45	61	
p = 0.372				TOTAL

The postmenopausal cases also show no significant statistical association between BMI and tumor grade p-value 0.768 as shown in Table 12.

TABLE 12. BMI association with tumor grade in postmenopausal cases

	POSTMENOPAUSE			
	BODY MASS INDEX			
	<25	**25-30**	**>30**	
LOW	1 (10%)	2 (20%)	7 (70%)	10 (100%)
INTERMEDIATE	7 (8%)	23 (26.1%)	58 (65.9%)	88 (100%)
HIGH	3 (8.8%)	12 (35.3%)	19 (55.9%)	35 (100%)
	11	37	84	132
p= 0.768				TOTAL

DISCUSSION

In our study, regarding BMI association with ER/PR receptors we observed that ER/PR positive BC is statistically significant with BMI in postmenopausal women, over weight and obese cases tend to presented with ER/PR positive more often. This result was observed in many previous studies [2-5].

In premenopausal cases our results is in agreement with Govind Babu et al. [6], Dalton et al. [7] and Biglia et al. [8] in that BMI does not have statistical effect on ER/PR receptors, while White et al. [9] report that obesity is associated with lower ER positive BC risk before menopause.

This endocrine setting may explain the strong association between obesity and positive ER/PR cancers, but available data are not yet consistent, especially in young children. During menopause, the systemic estrogen level is not affected by peripheral aromatization because estrogen is produced mainly by the ovaries. Obesity does not appear to play a significant role in cancer development in young women who are more likely to develop benign tumors, and many authors have reported that the obese have a lower risk of BC before menopause compared to menopause [2].

There are few case-control studies examining the effect of immune factors on HER-2 expression in postmenopausal breast cancer. Most found an association between BMI and post-BC menopause risk overall, but no association between BMI and HER2-positive cancers [2], in this study there was no statistical significant effect of BMI on HER2/neu receptors in both pre and postmenopausal cases as in Biglia et al. [8]. On the other hand, Nikos Tsakountakis et al. [10] shows that HER2/neu positive cases is more when BMI >30 kg/m.

There is general consensus that obese and overweight cases most likely presented with larger tumor size and more axillary lymph nodes involvement this may be explained by hypothesis first, that overweight/obese women have large breasts, so it can be difficult to detect masses in these women because masses are difficult to find in large breasts. This hypothesis is supported by several studies showing a link between breast size and breast cancer [2,11]. Secondly, obesity may be associated with a more advanced stage at diagnosis because of an underlying endocrinological abnormality related to tumor progression. Some studies suggest that locally increased estrogen levels promote tumor growth [2,12].

In the results of our study the postmenopausal women presented with larger tumor size and more lymph node involvement when being overweight or obese. While premenopausal women stage not shown to be affected by BMI.

Abrahamson et al. [13], Loi et al. [14] and Ewertz et al. [15] demonstrate that tumor size and lymph node involvement both affected by obesity, in the other hand CUI et al. [16], Rinella et al. [17] and Li et al. [18] showed the same effect of BMI on tumor size but not for lymph node involvement as our study in regard to premenopausal cases.

The non-significant association effect of BMI on tumor size and lymph node in premenopausal cases could not be explained by early detection of the disease in Iraq as Alwan et al. [19] showed that 90.6% of the cases detected the lumps by themselves, regrettably, only 32% sought medical advice within the first month after detection.

This may be due to the reported association between obesity and risk of premenopausal BC [2,3]. An analysis of 7 studies involving 337,819 women and 4,385 breast cancer patients showed a differential association between BMI and premenopausal risk, comparing women with BMI>31 kg/m^2 with women with BMI=21 kg/m^2. Or information on risk factors for BC such as menstrual history, reproductive history, hormonal contraceptive use, and health factors were not available for analysis. It is possible that these factors are also related to the BC stage at measurement and thus our results may be biased on these potential risk factors were not included in the study.

Overweight/obesity seems not to affect the distant metastasis at diagnosis as it was not statistically significant in our study which is in concordance with CUI et al. [16] the effect of overweight/obesity confirmed to be affect the distant recurrence of the disease, Loi et al. [14] showed that the risks of developing metastases post 10 years was significantly raised by 46% for cases with a BMI=30 kg/m^2 or more.

The small sample size and the short time of cohort were limitations for this study. In addition, the low socioeconomic status of participants was also an obstacle as well as the lack of awareness and survey programs in our localities.

CONCLUSION

The body weight of women seems to be a risk factor of development of BC cases mostly in postmeno-

pausal period rather than premenopausal. Overweight/obese postmenopausal women tend to have ER/PR receptors positive, larger tumor size and more lymph node involvement. Prospective study required to analyze the effect of obesity on prognosis of BC cases. Menstrual history, reproductive history, hormone use history and lifestyle factors need to be included in further study as they may affect obesity and characters of BC cases. Larger sample and data from multi-centers in Iraq are required to be included in future studies.

Conflict of interest: none declared.
Financial support: none declared.

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