Body Mass Index (BMI) As a Prognostic Factor in Breast Cancer

Emad Sadaka and Samar Galal

Clinical Oncology Department, Faculty of Medicine, Tanta University, Egypt
emad_sadaka@hotmail.com

Abstract: Background/Aim: Breast cancer is the most common malignancy and the second most common cause of cancer death in females. So, there is a continuous need for the development and search for new prognostic factors which will aid in therapy. Studies in breast cancer have shown conflicting data about the prognostic significance of body size, ranging from no prognostic significance to adverse outcome. The aim of this work is to correlate obesity with clinic-pathologic findings and patient survival to assess its prognostic significance. **Patient & Methods:** From January 2002 through December 2007, a series of 243 patients with non-metastatic invasive breast carcinomas were eligible for this study. All female patients were analyzed for correlation of obesity with clinicopathologic findings and patient survival to assess its prognostic significance. **Results:** Older patients (>50 years) (p=0.001), post-menopausal (p<0.01) patients with higher T stage (p=0.01), higher nodal stage (p<0.01), invasive ductal carcinoma (IDC) (p=0.01) and higher tumor grade (p<0.01) were more likely to have significantly higher body mass index (BMI) of >30 kilograms/m^2. There were no significant difference as regards the correlation between BMI and either hormonal status (p=0.192) or HER2 status (p=0.085).Univariate & multivariate analysis revealed that high BMI was significantly associated with a shortened DFS and OS. **Conclusion:** Body mass index appears to be potentially useful indicator of poor prognosis in breast cancer patients and it was found to be an independent prognostic factor, thus can be used to detect cases with aggressive biological behavior that can benefit from more aggressive therapy.
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1. Introduction

Breast cancer is known to be one of the most common female cancers in industrialized countries around the world. Also, the number of women suffering from breast cancer in developing countries has recently been increasing. Breast cancer is also the most common cause of death in cancer patients[1].

Body size may be related to prognosis in women with breast cancer. This relationship was first reported by Abe *et al.*[2], who studied obesity in Japanese women with breast cancer. After this several other investigators have studied the effect of body size on prognosis in breast cancer. Many investigators have found adverse effects associated with increased body size, whereas others have reported no effect[3].

Breast cancer is known to be one of the most common cancers and the most common cause of death in female around the world[1]. Abe *et al.*[2] studied the relation between obesity and body size in Japanese women with breast cancer. After this several other investigators have studied the effect of body size on prognosis in breast cancer. Many investigators have found adverse effects associated with increased body size, whereas others have reported no effect [3].

Evidence accumulated during the last 30 years suggests that obese women have a poorer prognosis than lean women after treatment for breast cancer [4]. Women who are overweight, obese, or gain weight after a breast cancer diagnosis are atgreater risk for certain therapy related complications as well as for breast cancer recurrence and death compared with lighter women. Obesity also is associated with hormonal profiles thought to favor breast cancer growth[5,6].Women who are obese may be diagnosed at a more advanced stage of disease, with larger tumors, and more often with nodal involvement, but multivariate analyses have demonstrated an independent prognostic effect on the risk of recurrence, disease-free survival, and overall survival[7,8].

National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, claimed that obesity did not affect the risk of recurrence or breast cancer mortality but was associated with increased risks of contralateral breast cancer, other primary cancers, and overall mortality[9].

Ewertz*et al.*[10] studied the effect of obesity on the prognosis of breast cancer and they found that obesity is an independent prognostic factor for developing distant metastases and for death as a result of breast cancer; the effects of adjuvant therapy seem to be lost more rapidly in patients with breast cancer and obesity[10].

In the current study, we correlated the body mass index in breast invasive carcinoma with the

clinicopathologic findings and patient survival to assess the prognostic significance of this variable.

2.Patientand Methods

Patient Characteristics& inclusion criteria:

Review of patients' medical records presented to Clinical Oncology Department, Tanta University Hospital throughout the period from January 2002 to December 2007, identified 243 female patients with invasive breast cancer whose weight and height were available and who had no distant metastases at the time of diagnosis. All of these patients were eligible for this study.

From January 2002 through December 2007, a series of 243 patients with non-metastatic invasive breast carcinomas were eligible for this study. Medical record (MR) review of patients presenting to Clinical Oncology Department, Tanta University Hospitalidentified 243 patients whose weight and height were available and who had no distant metastases at the time of diagnosis.

Initial clinical stage of all patients was coded according to the staging criteria proposed by the 2003 sixth edition of the American Joint Committee on Cancer[11]. Before inclusion to this study, the following evaluations should be available for each patient as complete physical examination, chest radiography, bilateral mammography, ECG, ultrasonography of breasts, axillary fossa, abdomen, and pelvis, complete blood count, and routine biochemical tests to make an exact staging.

Eligibility criteria for this analysis included female gender, an initial diagnosis of primary breast cancer without distant metastases, and complete data on the following: Weight, height, age, tumour size, number of involved axillary lymph nodes, status of oestrogen receptor (ER), progesterone receptor (PR) as well as ERBB2 and recurrence information. The medical records (MR) of all patients were reviewed and patients with a previous malignancy were not eligible.Follow-up ended at April 10, 2013.

Body mass index review

Weight and height of the eligible patients were retrieved from the MR in the archive of Clinical Oncology Department, Tanta University Hospital, Faculty of Medicine, Tanta University. Data on height and weight at diagnosis were used to compute body mass index (BMI: weight in kilograms divided by the square of height in meters). Patients were classified according to BMI into three groups: group (A) patients with a BMI of <25 kg/m^2, group (B) BMI of 25-29 kg/m^2 and group (C) BMI of ≥30 kg/m^2. Patients with BMI ≥30 kg/m^2 considered as obese patients.

Treatment and Follow-Up

All patients received either preoperative or adjuvant chemotherapy and 153 (62.96%) patients received adjuvant radiation therapy to the chest wall and draining lymphatic following surgery. One hundred seventy eight (73.25%) underwent modified radical mastectomy for their primary tumor, and 65 (26.75%) underwent a breast conserving surgery **(**BCS). Combination chemotherapy consisted of either: 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) in 137 (56.38%)patients, 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) in 82 (33.74%) patients, or sequential FEC with taxanes in 24 (9.88%) patients.

Regarding radiation therapy, patients received a median dose of 50 Gy in 2-Gy fractions delivered 5 days/weekto the chest wall and draininglymphatic, followed by a 10-Gy boost for those underwent BCS , also in 2-Gy fractions delivered 5 days/week, bringing the total dose to tumor bed to 60 Gy.

Endocrine therapy included primarily in the form of tamoxifen10 mg twice daily was introduced to 102 patients, whereas 90 patients received aromatase inhibitors. (Total number of patients receiving endocrine therapy = 192)

Patients were followed up on a regular basis after completion of treatment through patients' clinic visits at the Clinical Oncology Department, Tanta University Hospital every 3 months during the first two years, every 6 months during the next 3 years and once a year thereafter. Follow-up studies included physical examination, routine lab, biopsy from any suspected lesion, mammography, breast and abdomino-pelvic sonography and/or computed tomography (CT) scan, as well as bone scan.

Statistical Analysis

Patients were followed up until April 10, 2013. At the time of analysis, the median follow-up for the entire group was 62.5 months (range, 3.030 to 134.970 months). The primary endpoints in this study were the effect of BMI on overall-survival (OS) anddisease-free survival (DFS) rates. Overall-survival (OS) rates were calculated from the time of diagnosis to the time of the last follow-up visit or death using the method of Kaplan and Meier[12].Disease-free survival (DFS) was defined as the time from initial treatment to the earliest occurrence of an event, including loco regional, visceral and bone relapse. Those without any evidence of event were censored at the last date they were known to be alive. The variables analyzed were age at diagnosis, tumor status, menopausal status, tumor nuclear grade (grade 3 versus grade 1–2), histologic type, type of chemotherapy, and radiation (yes versus no). SPSS Statistical package (version 9.0) was used for data analysis. Mean and standard deviation were estimates of quantitative data. Chi-square/ Fischer exact were tests of proportion independence. Kaplan-Meier method was used for estimating survival and log rank to compare curves [12].

Cox-regression analysis was used to estimate odds of recurrence & its 95% CI on univariatelevel and to evaluate independent prognostic variables affecting OS and DFS. *P*-value is significant at 0.05 levels.

3.Results

Patient characteristics:

The study included 243 female patients with invasive breast carcinoma with their age ranging from 29 to 69 years (median, 52 years) at the time of diagnosis. Their tumors ranged in size from 1.5 cm to 11 cm. The majority of cases were T3, node positive and grade II. They showed hormonal receptor positivity in 177 cases (72.83%) and HER-2 positivity in 34 cases (13.99%). Maximal follow-up was 134.970 months with a median of 62.5 months. The demographic data and their relation to body mass index were summarized in table 1.Older patients (> 50 years) were more likely to have significantly higher BMI than patients aged less than 50 years old (p=0.001). Furthermore, post-menopausal (P<0.01) patients with higher T stage (p=0.01), higher nodal stage (p<0.01), IDC pathology (p=0.01) and higher tumor grade (P<0.01) were more likely to have significantly higher BMI of >30 kilograms/m^2. There were no significant difference as regards the correlation between BMI and either hormonal status (p=0.192) or HER2 status (p=0.085).

Table (1): Correlation between patient characteristics and BMI

Factors	BMI			*p*
	(A) <25 52 (100%)	**(B) 25-29 95 (100%)**	**(C) ≥30 96 (100%)**	
Age				
<50	38 (73.1)	48 (50.5)	38 (39.6)	0.001
≥50	14 (26.9)	47 (49.5)	58 (60.4)	
Menstruation				
Premenopausal	38 (73.1)	35 (36.8)	27 (28.1)	<0.001
Post-menopausal	14 (26.9)	60 (63.2)	69 (71.9)	
T				
1	10 (19.2)	6 (6.3)	10 (10.4)	
2	24 (46.2)	26 (27.4)	32 (33.3)	0.01
3	12 (23.1)	52 (54.7)	41 (42.7)	
4	6 (11.5)	11 (11.6)	13 (13.5)	
N				
0	15 (28.8)	7 (7.4)	8 (8.3)	
1	8 (15.4)	14 (14.7)	6 (6.3)	<0.001
2	26 (50)	39 (41.1)	32 (33.3)	
3	3 (5.8)	35 (36.8)	50 (52.1)	
Pathology				
IDC	43 (82.7)	82 (86.3)	93 (96.9)	0.01
ILC	9 (17.3)	13 (13.7)	3 (3.1)	
Grade				
I	6 (11.5)	7 (7.4)	7 (7.3)	<0.001
2	32 (61.5)	53 (55.8)	30 (31.3)	
3	14 (26.9)	35 (36.8)	59 (61.5)	
Hormonal receptors				
+ve	39 (75)	73 (76.8)	65 (67.7)	0.192
-ve	8 (15.4)	16 (16.8)	27 (28.1)	
Unknown	5 (9.6)	6 (6.3)	4 (4.2)	
Her-2				
+ve	7 (13.5)	17 (17.9)	10 (10.4)	0.085
-ve	29 (55.8)	54 (56.8)	44 (45.8)	
Unknown	16 (30.8)	24 (25.3)	42 (43.8)	

BMI, Body mass index; T, tumor size; N, nodal stage; IDC, Invasive duct carcinoma; ILC, Invasive lobular carcinoma; *p*significant<0.05

Relationships to survival:

To evaluate the prognostic significance of BMI, it was analyzed in relation to DFS and OS. BMI was significantly associated with a shortened DFS (Figure 1). The 5 years DFS, for group of patients with BMI of >25 kg/m^2 was 78.75% and it was 71.44% for the group of patients with BMI of25-29 kg/m^{2}while for the group of patients with BMI of ≥30 kg/m^2 it was 63.52% (p= 0.025). Thus,non-obese patients had a significant better 5 years DFS.

Similarly grade (p<0.001), hormonal receptors status (p<0.001), tumor status (p=0.009), nodal status (p=0.006), menstrual status (p=0.003), her 2 receptors status (p=0.006) and age (p<0.001) were significantly related to DFS in univariate analysis (Table 2). On the other hand, type of chemotherapy and pathologic type were not significantly related to DFS in univariate analysis. In multivariate analysis, BMI was independently related to this end point (p= 0.002).

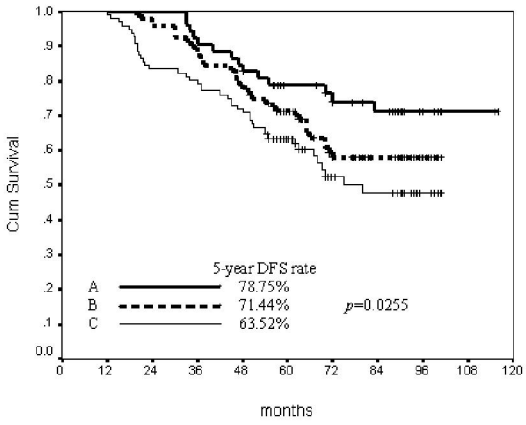

Fig (1): DFS survival rate according to BMI

Table (2): Univariate& multivariate analysis of factors affecting DFS rate

Factors		Univariate		Multivariate	
		5-year DFS	p	HR (95%CI)	p
Age	<50 ≥50	59.46% 80.67%	**0.0003**	-	NS
Menstruation	Premenopause Menopause	55.78% 79.69%	**0.0009**	0.42 (0.21 – 0.87)	**0.0198**
T	1 2 3 4	80.77% 79.12% 65.42% 50.00%	**0.0091**	-	NS
N	0 1 2 3	86.67% 78.57% 71.02% 59.87%	**0.0064**	-	NS
Pathology	IDC ILC	69.21% 75.16%	0.9190	-	-
Grade	I 2 3	85.00% 79.77% 56.44%	0.0001	1.49 (1.02 – 2.17)	**0.0386**
Hormonal receptors	+ve -ve Unknown	84.05% 31.37% 33.33%	<0.0001	3.64 (2.59 – 5.09)	**<0.0001**
Her-2	+ve -ve Unknown	73.53% 79.29% 53.66%	0.0045	-	NS
BMI	(A) (B) (C)	78.75% 71.44% 63.52%	0.0255	1.69 (1.21 – 2.34)	**0.0018**

In terms of OS, the univariate analysis of prognostic factors demonstrated that, the most important prognostic factors were tumor size (p = 0.001), tumor grade (p<0.001), age (p=0.001), hormonal receptors status (p< 0.001), HER-2 receptor status (p<0.001), lymph node status (p<0.001) and menstrual status (p<0.001) (Table 3).

The hazard ratios in the multivariate Cox model show that patients whose BMI>30 kilograms/m^2 have increased risk of death compared to non-obese women. Also in multivariate analysis, menstrual status (p= 0.001), nodal status (p= 0.007), tumor grade (p<0.001), and hormonal receptor status (p<0.001), were found to be independent prognostic factors (Table 3).

Table (3): Univariate& multivariate analysis of factors affecting OS rate

Factors		Univariate		Multivariate	
		5-year OS	*p*	HR (95%CI)	*p*
Age	<50 ≥50	71.03% 93.28%	**0.0006**	-	NS
Menstruation	Premenopause Menopause	68.93% 90.90%	**0.0001**	0.16 (0.06 – 0.45)	**0.0005**
T	1 2 3 4	88.29% 96.34% 75.55% 60.00%	**0.0007**	-	NS
N	0 1 2 3	100% 88.86% 81.23% 74.58%	**0.0002**	1.76 (1.17 – 2.66)	**0.0067**
Pathology	IDC ILC	81.96% 83.43%	0.5222	-	-
Grade	I 2 3	100% 94.72% 65.21%	**<0.0001**	3.37 (1.93 – 5.88)	**<0.0001**
Hormonal receptors	+ve -ve Unknown	95.43% 38.14% 73.33%	**<0.0001**	5.01 (3.21 – 7.84)	**<0.0001**
Her-2	+ve -ve Unknown	82.35% 92.88% 65.61%	**<0.0001**	-	NS
BMI	(A) (B) (C)	95.94% 82.99% 73.85%	**0.0024**	2.20 (1.43 – 3.39)	**0.0003**

The Kaplan–Meier survival curves demonstrate the better prognosis for non-obese patients (The 5 years OS, for group A was 95.95% and it was 83.03% for group B while for group C it was 73.86% (p= 0.002)) (Fig. 2).

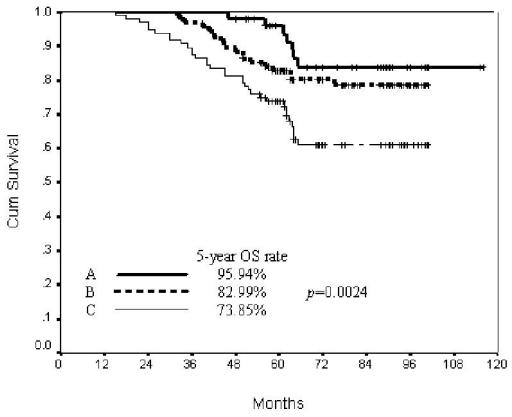

Fig (2): OA survival rate according to BMI

4.Discussion

Contradictory results have been reported in the literature concerning the role of obesity in breast cancer and its prognostic impact.

Earlier investigators denied the prognostic significance of obesity and refute its correlation with decreased survival [13].

Many factors affect the prognosis of breast cancer including race[14], age[15,16], menopausal status[17], metastasis to the axillary lymph nodes[18], estrogen receptors status[19]. Others have studied the effect of BMI on breast cancer prognosis and they found adverse effects associated with increased body size, whereas others have reported no effects[20].

However, more recent reports revealed a bad prognostic impact of obesity in breast cancer in correlation with a shorter DFS and OS[4,7,8]. Their findings are in keeping with those of the present study. Several mechanisms have been raised to explain the association between obesity and poor prognosis. Some reports suggested that obesity leads to poor prognosis by increasing circulating plasma level of estrogen, insulin and insulin-like growth factor that promote tumor growth. Obese patients tend to have larger tumors and more positive nodes.

The findings of the present study point to the presence of obesity as a prognostic factor in breast carcinoma patients. Higher BMI of >30kilograms, was significantly correlated with an aggressive phenotype that was characterized by higher histologic grade, larger tumor size, more lymph node metastasis.The univariate and multivariate analysis indicated a strong correlation between the presence of obesity and a shorter DFS and OS. There were no significant

difference as regards the correlation between BMI and neither hormonal status nor HER2 status.

The prognostic value of obesity in breast cancer was proved by other investigators as well. deAzambuja*et al.*[21] and Ewertz*et al.*[10] conducted two relatively large studies of 2887 patients and 53,816 patients respectively. deAzambuja*et al.*[21]evaluated in a retrospective analysis 2,887 node-positive BC patients enrolled in the BIG 02-98 adjuvant study. He observed that, obesity remained an independent prognostic factor for OS and DFS.

Ewertz*et al.*[10] studied the effect of obesity in breast cancer outcome and they showed that patients with a BMI of 30 kg/m^2 or more were at increased risk of developing distant metastases as well as increase in the risk of dying as a result of breast cancer. They concluded that obesity is an independent prognostic factor for developing distant metastases and for death as a result of breast cancer; the effects of adjuvant therapy seem to be lost more rapidly in patients with breast cancer and obesity. Our finding of a significant relationship between obesity and DFS and OS in breast carcinoma patients has also been observed by Kawai*et al.* [22], whostudied the body mass index and survival after breast cancer diagnosis in 653 Japanese women. They suggest that higher BMI was associated with an increased risk of mortality, especially among premenopausal patients or among patients with hormonal receptor positive tumors. However, Lee*et al.*[13] could not verify the same relation on breast cancer patients.

In conclusion, BMIwas found to be an independent prognostic factor in multivariate analysis and appears to be potentially useful indicator of bad prognosis in breast carcinoma patients.So, it can be used to predict cases with aggressive biological behavior that can benefit from more aggressive therapy. However, larger number of cases and longer follow up period are necessary to confirm their independent prognostic value in a multivariate analysis.

Corresponding author:
EmadSadaka, lecturer of Clinical Oncology, At Clinical Oncology department, Tanta University, emad_sadaka@hotmail.com

References

1- Ryu SY, Kim C-B, NamCM*et al.*(2001).Is Body Mass Index the Prognostic Factor in Breast Cancer?: A Meta-Analysis. J Korean Med Sci; 16: 610-4

2- Abe R, Kumagi N, Kimura M, *et al.*(1976). Biological characteristics of breast cancer in obesity. Tohoku J Exp Med; 120: 351-9.

3- Goodwin PJ, Boyd NF (1990). Body size and breast cancer prognosis: a critical review of the evidence. Breast Cancer Res Treat; 16:205-14.

4- Chlebowski RT, Aiello E, McTiernan A (2002). Weight loss in breast cancer management. J ClinOncol; 20:1128-1143.

5- Chlebowski RT, Aiello E, McTiernan A (2002).Weight Loss in Breast Cancer Patient Management. J ClinOncol,; 20 (4): 1128-1143.

6- Calle EE, Rodriguez C, Walker-Thurmond K, *et al.*(2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med; 348:1625-1638.

7- Majed B, Moreau T, Senouci K, *et al.*(2008). Is obesity an independent prognosis factor in woman breast cancer? Breast Cancer Res Treat; 111:329- 342.

8- Berclaz G, Li S, Price KN, *et al.*(2004). Body mass index as a prognostic feature in operable breast cancer: The International Breast Cancer Study Group experience. Ann Oncol; 15:875-884.

9- Dignam JJ, Wieand K, Johnson KA, *et al.*(2003). Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst 95:1467-1476.

10- Ewertz M, Jensen M-B, Gunnarsdo´ttir K (2011): Effect of Obesity on Prognosis after Early-Stage Breast Cancer. J ClinOncol 29:25-31.

11- Singletary SE, Allred C, Ashley P *et al.*(2003). Staging system for breast cancer: revisions for the 6th edition of the AJCC Cancer Staging Manual. SurgClin North Am; 83: 803–819.

12- Kaplan EL, Meier P (1958): Nonparametric estimation from incomplete observations. J Am Stat Assoc.; 53: 457-481.

13- Lee K-H, Keam B, Im S-A, *et al.*(2012): Body Mass Index Is Not Associated with Treatment Outcomes of Breast Cancer Patients Receiving Neoadjuvant Chemotherapy: Korean Data. J Breast Cancer; 15(4): 427-433

14- Galanis DJ, Kolonel LN, Lee J, *et al.*(1998). Anthropometric predictors of breast cancer incidence and survival in a multi-ethnic cohort of female residents of Hawaii, United States. Cancer Causes Control; 9: 217-24.

15- Velentgas P, Daling JR (1994). Risk factors for breast cancer in younger women. J Natl Cancer InstMonogr; 16: 15-24.

16- Rutqvist LE, Wallgren A (1983). Influence of age on outcome in breast carcinoma. ActaRadiolOncol; 22: 289-94.

17- Ursin G, Longnecker MP, Haile RW, *et al.*(1995) : A Meta-Analysis of Body Mass Index and risk of premenopausal breast cancer. Epi- demiology; 6: 137-41.

18- Fisher B, Bauer M, Wickerham DL, *et al.*(1983). Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. Cancer; 52: 1551-7.

19- Manni A (1983). Hormone receptors and breast cancer. N Engl J Med; 309: 1383-5.

20- Goodwin PJ, Boyd NF (1990). Body size and breast cancer prognosis: a critical review of the evidence. Breast Cancer Res Treat; 16: 205-14.

21- de Azambuja E, McCaskill-Stevens W, Francis P, *et al.* (2010): The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial ,Breast Cancer Res Treat,119:145–153.

22- Kawai M, Minami Y, Nishino Y*et al.*(2012): Body mass index and survival after breast cancer diagnosis in Japanese women. BMC Cancer, 12:149.

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