RESEARCH ARTICLE

Effects of Obesity on Presentation of Breast Cancer, Lymph Node Metastasis and Patient Survival: A Retrospective Review

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Abstract

Background: As data on the relation between obesity and lymph node ratio are missing in the literature, we here aimed to assess the impact of obesity on this parameter and other clinicopathological features of breast cancer cases and patient survival. Materials and Methods: Medical data of 646 patients, all referred to two centers in Tehran, Iran, were reviewed. Factors that showed significant association on univariate analysis were entered in a regression model. Kaplan-Meier and Cox-regression were employed for survival analysis. Results: Obesity was correlated with the expression of estrogen and progesterone receptor (p=0.004 and p=0.039, respectively), metastasis to axillary lymph nodes (p=0.017), higher lymph node rate (p<0.001) and larger tumor size (p<0.001). The effect of obesity was stronger in premenopausal women. There was no association between obesity and expression of human epidermal growth factor receptor. Three factors showed independent association with BMI on multivariate analysis; tumor size, estrogen receptor and lymph node ratio. Obesity was predictive of shorter disease-free survival with a hazard ratio of 3.324 (95%CI: 1.225-9.017) after controlling for the above-mentioned variables. Conclusions: The findings of this study support the idea that obese women experience more advanced disease with higher axillary lymph node ratio, and therefore higher stage at the time of diagnosis. Furthermore, obesity was associated with poorer survival independent of lymph node rate.

Keywords: Breast cancer - body mass index - lymph node ratio - survival - Iran

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Introduction

Breast cancer is the most common cancer and leading cause of death among women worldwide (Parkin et al., 2005; Jemal et al., 2011). Many of risk factors which are known to develop breast cancer are related to estrogen, e.g. early menarche, late menopause and hormone replacement therapy (HRT) (Key et al., 2001; Weiss et al., 2002; Van Leeuwen and Rookus, 2003; Ritte et al., 2013). Protective factors include child bearing and breastfeeding (Jernström et al., 2004; Andrieu et al., 2006; Stuebe et al., 2009; Jordan et al., 2010). Besides these predisposing risk factors, there some other factors such as obesity and age that can negatively affect the survival of patients with breast cancer (Chlebowski et al., 2002; Han et al., 2004).

To assess the modifiable risk factors for breast cancer, the roll of obesity has become the matter of discus in different studies, as it can be the greatest modifiable risk factor after tobacco use. Several studies reported the survival of breast cancer in obese women; all of them concluded that obesity is correlated with poorer survival and higher chance of recurrence (Chlebowski et al., 2002; Rock and Demark-Wahnefried, 2002; Berclaz et al., 2004). The exact reason remain unclear, but different hypothesis have been established for the poorer survival in obese women, for instance obese women undergo less screening (Wee et al., 2004) thus have higher advanced disease at presentation, obese women have more chance of developing second primary cancer (Li et al., 2009), obese women receive reduced doses of chemotherapy due to prevention of side effects and toxicity (Griggs et al., 2005) and finally obese women have more biologically aggressive tumor (Cui et al., 2002; Protani et al., 2010).

With the aforementioned in mind that obese women have more aggressive tumor at the time of diagnosis, we investigate this hypothesis using recently introduced parameter; lymph node ratio (LNR). LNR can show the quantity of metastasis to axillary lymph nodes; hence aggressive tumors must have higher range of LNR. Previous studies disclosed that higher LNR (>0.2) is associated with poorer survival (van der Wal et al., 2002; Vinh-Hung et al., 2009). To our knowledge, assessing the correlation between obesity and LNR is lacking in literature. We aimed to evaluate this association in addition to other biological features of breast cancer in Iranian women. We used body mass index (BMI) as an index, further assessing correlations with LNR, tumor size, hormone status, lymph node metastasis and survival.

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Materials and Methods

To initiate this retrospective study medical record of women with diagnosis of breast cancer in two referral centers (Imam Khomeini hospital and Kaviani breast disease institute) in Tehran, Iran between 2003 and 2011 were reviewed. Detailed information was obtained from electronic registration database (PegahSoft Co-Hakim software). Study was designed and conducted in accordance with the Declaration of Helsinki. Information which gathered for each patient consisted of demographic information, fertility history, height and weight, tumor features (size, lymph node metastasis) and hormone status (estrogen receptor (ER), progesterone receptor (PR), human epithelial growth factor 2 (HER2)).

BMI was calculated as weight divided to the square of height. Patients were divided into three groups based on the national institute of health (NIH) classification for obesity: normal weight (BMI<24.9), over weight (25<BMI<29.9) and obese (BMI>30).

In this study, lymph node ratio (LNR) (defined as the number of involved nodes by tumor divided to total number of resected lymph nodes during surgery) was used to evaluate BMI association with the quantity of lymph node metastasis. Patients were divided into two groups; high range of LNR (LNR>0.2) and low LNR (LNR<0.2). In evaluating HER-2 status, immunohistochemical score of 0 or +1 were considered as HER-2 negative and score of +2 or +3 were considered as HER-2 positive.

Statistical analysis

Statistical analyses were performed using SPSS software for windows, version 17 (SPSS Inc. Chicago, IL, USA). Continuous variables are expressed in mean±standard deviation. Categorical variables (i.e. menopausal status) are presented in percents. In order to reduce the impact of missing data, if the value of some variables were unknown the patients were excluded from the analysis of that variable but remain for the others. So it is obvious that the sample size was not equal in each analysis. Chi-square test was used to assess the correlation between BMI and tumor size, lymph node metastasis, LNR, ER, PR and HER2. Factors that showed significant association in univariate analysis were put in logistic regression model to identify independent correlations. Kaplan-Meier was employed to perform survival analysis. Assessing the impact of different characteristics on survival was done by using Cox proportional-hazards regression model. In all tests, the p-value of less than 0.05 was considered as significant.

Results

In this retrospective study, a total of 646 women with breast cancer were enrolled. Mean age of study participant was 49.62±11.48 years (ranging from 21-88). Among the patients, 324 (50.2%) were per-menopause and 322 (49.8%) were post-menopause. Median follow-up time was 1.92 years, ranging from 0-8 years. Among the patients which fertility history of them was available; 538 (95.2%) have became pregnant for at least one time. The family history of breast cancer was positive in 131 (20.5%) patients.

Patients were divided into three groups based on their BMI; normal weight group consisted of 213 (33.0%) patients, overweight group consisted of 276 (42.73%) and 157 (24.3%) women were in obese group. Characteristics of each group are presented in Table 1.

Comparing tumor features between three groups, higher range of BMI accompanied with larger tumor size (p<0.001), increased risk of lymph node metastasis (p=0.017) and higher LNR (p<0.001).

Assessing hormone status between different BMI groups, ER and PR was correlated with BMI and obese women had higher chance of being receptor positive (p=0.004 and p=0.039, respectively). Status of HER2 was not correlated with obesity (p=0.150). tumor features of each group are presented in Table 2.

Furthermore the correlations between BMI and tumor features were evaluated in premenopausal and postmenopausal groups. Tumor size and LNR was correlated with BMI in both groups. HER-2 was not associated with obesity either in premenopausal or postmenopausal patients. ER and PR had greater relation with obesity in premenopausal cases (Table 3).

Comparing tumor features between overweight and normal weight patients showed that the only significant correlation was observed between tumor size and BMI (Table 2), therefore no multivariate analysis were done to compare these groups. On the other hand, factors were put in a regression model to determine intercorrelations between clinicopathological features comparing obese versus normal weight patients. The results of multivariate analysis are presented in Table 4.

Kaplan-Meier analysis revealed that patients with higher range of BMI had lower disease-free survival (p=0.025) (Figure 1). Cox-regression model showed that BMI was an independent predictor of shorter disease-free survival, respective to ER, tumor size and LNR with

Table 1. Demographic Information for the Study Groups

	Normal weight N=213	Over weight N=276	Obese N=157
BMI*	22.67±1.84	27.30±1.48	33.50±4.06
Age*	47.71±12.54	46.57±10.41	52.23±11.34
Age at menarche*	13.66±1.55	13.34±1.44	13.30±1.56
Age at first pregnancy*	23.53±4.93	22.54±5.39	20.90±5.20
Menopausal status			
Pre-menopause	126 (59.2%)	133 (48.2%)	65 (41.4%)
Post-menopause	87 (40.8%)	143 (51.8%)	92 (58.6%)
Unknown	0 (0%)	0 (0%)	0 (0%)
Gravidity			
Yes	160 (75.1%)	232 (84.1%)	146 (93.0%)
No	12 (5.6%)	11 (4.0%)	4 (2.5%)
Unknown	41 (19.2%)	33 (12.0%)	7 (4.5%)
Smoking			
Yes	10 (4.7%)	10 (3.5%)	8 (5.1%)
No	197 (92.5%)	256 (96.0%)	149 (94.9%)
Unknown	6 (2.8%)	1 (0.4%)	0 (0%)
Family history of BC			
Yes	49 (23.0%)	57 (20.7%)	25 (15.9%)
No	159 (74.6%)	217 (78.6%)	132 (84.1%)
unknown	5 (2.3%)	2 (0.7%)	0 (0%)

*Mean±SD

Table 2. Tumor Features among Study Groups, with Associated p value and Odds Ratio of Obese and Over Weight Versus Normal Weight Patients

		Normal weight n=213	Over weight n=276	OR[a] (95% CI)	Obese n=157	OR[b] (95% CI)	P value[c]
Tumor size	<2cm	82 (38.5%)	80 (29.0%)	Referent	27 (17.2%)	Referent	<0.001
	2-5cm	77 (36.2%)	124 (44.9%)	1.651 (1.085-2.510)	67 (42.7%)	2.643 (1.533-4.555)	
	>5cm	31 (14.6%)	56 (20.3%)	1.852 (1.083-3.165)	45 (28.7%)	4.409 (2.345-8.288)	
	Unknown	23 (10.8%)	16 (5.8%)		18 (11.5%)		
Lymph node metastasis							
	No	99 (46.4%)	122 (44.2%)	Referent	53 (33.8%)	Referent	0.017
	Yes	109 (51.2%)	145 (52.5%)	1.122 (0.780-1.613)	102 (65.0%)	1.817(1.183-2.790)	
	Unknown	5 (2.3%)	9 (3.3%)		2 (1.3%)		
ER	Negative	82 (38.5%)	81 (29.3%)	Referent	31 (19.7%)	Referent	0.004
	Positive	127 (59.6%)	173 (62.7%)	1.379 (0.940-2.023)	109 (69.4%)	2.270 (1.396-3.691)	
	Unknown	4 (1.9%)	22 (8.0%)		17 (10.8%)		
PR	Negative	76 (35.7%)	103 (37.3%)	Referent	38 (24.2%)	Referent	0.039
	Positive	102 (47.9%)	156 (56.5%)	1.128 (0.766-1.663)	93 (59.2%)	1.824 (1.128-2.948)	
	Unknown	35 (16.4%)	17 (6.2%)		26 (16.6%)		
HER2	Negative	73 (34.3%)	115 (41.7%)	Referent	69 (43.9%)	Referent	0.150
	Positive	76 (35.7%)	77 (27.9%)	0.688 (0.446-1.062)	44 (28.0%)	0.655 (0.398-1.079)	
	unknown	64 (30.0%)	84 (30.4%)		44 (28.0%)		
LNR	<0.2	134 (62.9%)	158 (57.2%)	Referent	64 (40.8%)	Referent	<0.001
	>0.2	74 (34.7%)	109 (39.5%)	1.249 (0.859-1.816)	91 (58.0%)	2.575 (1.679-3.948)	
	unknown	5 (2.3%)	9 (3.3%)		2 (1.3%)		

*LNR, lymph node ratio; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2. [a]Odds ratio calculated for comparing over weight versus normal weight patients. [b]Odds ratio calculated for comparing obese versus normal weight patients. [c]P value calculated comparing all three groups

Table 3. Tumor Features Correlation with BMI in Pre- and Postmenopausal Women

		Premenopausal				Postmenopausal			
		Normal weight N= 126	Over weight N= 133	Obese N= 65	P value	Normal weight N=87	Over weight N= 143	Obese N= 92	P value
Tumor size	< 2cm	50 (39.7%)	34 (25.6%)	12 (18.5%)	0.012	30 (34.4%)	46 (32.2%)	15 (16.3%)	0.004
	2-5cm	45 (35.7%)	58 (43.6%)	25 (38.5%)		34 (39.2%)	66 (46.2%)	42 (45.7%)	
	>5cm	20 (15.9%)	33 (24.8%)	19 (29.2%)		11 (12.6%)	23 (16.0%)	26 (28.2%)	
	Unknown	11 (8.7%)	8 (6.0%)	9 (13.8%)		12 (13.8%)	8 (5.6%)	9 (9.8%)	
Lymph node metastasis	No	60 (47.6%)	52 (39.1%)	22 (33.9%)	0.091	39 (44.9%)	70 (49.0%)	31 (33.7%)	0.043
	Yes	64 (50.8%)	77 (57.9%)	42 (64.6%)		45 (51.7%)	68 (47.5%)	60 (65.2%)	
	Unknown	2 (1.6%)	4 (3.0%)	1 (1.5%)		3 (3.4%)	5 (3.5%)	1 (1.1%)	
ER	Negative	50 (39.7%)	37 (27.8%)	12 (18.5%)	0.019	32 (36.8%)	44 (30.8%)	19 (20.7%)	0.128
	Positive	75 (59.5%)	87 (65.4%)	48 (73.8%)		52 (59.8%)	86 (60.1%)	61 (66.3%)	
	Unknown	1 (0.8%)	9 (6.8%)	5 (7.7%)		3 (3.4%)	13 (9.1%)	12 (13.0%)	
PR	Negative	43 (34.1%)	52 (39.1%)	9 (13.8%)	0.003	33 (37.9%)	51 (35.7%)	29 (31.5%)	0.528
	Positive	64 (50.8%)	76 (57.1%)	47 (72.4%)		38 (43.7%)	80 (55.9%)	46 (50.0%)	
	Unknown	19 (15.1%)	5 (3.8%)	9 (13.8%)		16 (18.4%)	12 (8.4%)	17 (18.5%)	
HER2	Negative	43 (34.2%)	51 (38.3%)	27 (41.5%)	0.930	30 (34.5%)	64 (44.8%)	42 (45.7%)	0.082
	Positive	41 (32.5%)	44 (33.1%)	23 (35.4%)		35 (40.3%)	33 (23.1%)	21 (22.8%)	
	Unknown	42 (33.3%)	38 (28.6%)	15 (23.1%)		22 (52.2%)	46 (32.1%)	29 (31.5%)	
LNR	<0.2	81 (64.3%)	74 (55.6%)	28 (43.1%)	0.018	53 (60.9%)	84 (58.7%)	36 (39.1%)	0.002
	>0.2	43 (34.1%)	55 (41.4%)	36 (55.4%)		31 (35.6%)	54 (37.8%)	55 (59.8%)	
	Unknown	2 (1.6%)	4 (3.0%)	1 (1.5%)		3 (3.5%)	5 (3.5%)	1 (1.1%)	

*LNR, lymph node ratio; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2

Table 4. Multivariate Analysis of Factors that Showed Significant Association in Univariate Analysis

		Odds ratio	95% confidence interval lower	Upper
Tumor size:	2-5cm	2.438	1.310	4.540
	>5cm	4.755	2.192	10.313
ER		1.896	1.055	3.409
PR		1.701	0.969	2.988
Lymph node metastasis		0.650	0.278	1.520
LNR		3.837	1.661	8.866

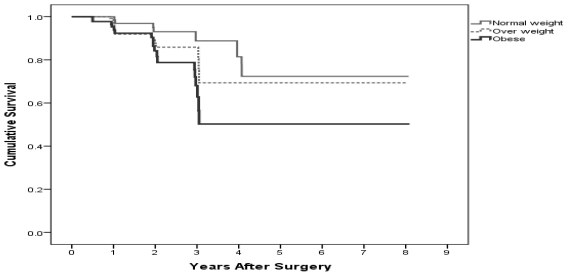

Figure 1. Disease-free Survival of Normal, Over Weight and Obese Patients

hazard ratio of 3.324 (95%CI: 1.225-9.017). Analysis was repeated using LNR as continuous variable to ensure that results are not affected by considering LNR as a categorical. Regardless of how analyzed (>0.2 or continuous) obesity had independent effect on disease-free survival.

Discussion

The cause for worsen survival and more aggressive biological tumor features that has been observed in obese women in not clear, but it is hypothesized that activated macrophage in adipose tissue release large amount of proinflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (Olefsky and Glass, 2010). This secretion activity results in subclinical inflammation which can be responsible for cancer development (Morris et al., 2011). IL-6 has mitotic and anti-apoptotic effect and higher levels of IL-6 is associated with poorer survival (Bachelot et al., 2003). However, previous studies did not concluded in same results regarding the idea that obese women's tumor has more aggressive phenotype; obesity did not show association with triple negative breast cancer (Maiti et al., 2010), in contrary it was correlated with larger tumor size (Ove Mæhle et al., 2001) and more lymphovascular invasion (Gillespie et al., 2010).

We investigated 646 Iranian patients to evaluate the effect of obesity on biological features of breast cancer. Our results revealed that BMI is in association with larger tumor size, more involvement of axillary lymph nodes by tumor cells, more chance of axillary lymph node metastasis, expression of PR and ER and shorter disease-free survival but higher range of BMI was not predictor of HER-2 expression.

Our results were in consistent with previous studies that showed expression of PR is more frequent in obese women (Esfahlan et al., 2011). Ove Maehle et al. revealed that obese women have higher chance of having PR positive and ER positive tumor. Also they reported that large tumors (>2.0 cm) were more common among obese women and this relationship was more prominent in patients with PR negative or ER-PR negative tumors (Ove Mæhle et al., 2001).

The status of ER in obese women was a matter of controversy in different studies. A case-control study was conducted in Japan to evaluate the effect of post-menopausal obesity on breast cancer risk according to hormone status. Yoo et al. (2001) concluded that obese post-menopausal women have an increased risk of developing breast cancer and this risk is more prominent in ER positive and PR positive breast cancer. Enger et al. (2000) showed there is an association between obesity and ER/PR positive breast cancer in post-menopausal women. Daling et al. (2001) conducted a population based follow up study of 1177 women with invasive ductal carcinoma (IDC) who were younger than 45 years, their results showed that obese women are more likely to have ER negative breast cancer. Gillespie et al. (2010) did not observed any association between BMI and ER or PR expression. Our results revealed that there is an association between BMI and expression of estrogen and progesterone receptor, but this association was not observed in postmenopausal women.

Our results were in accordance with Porter et al. (2006) study that revealed lymph node metastasis is more common in obese women compared to normal weight women. The association between obesity and higher chance of lymph node metastasis was reported by different authors (Deglise et al., 2010; Singh et al., 2011). Also, our results were in agreement with the idea that obese patients are at increased risk having of larger tumor size (Ove Mæhle et al., 2001; Ewertz et al., 2011). LNR has shown better prognostic value compared to traditional classification of axillary metastasis in TNM staging system (Woodward et al., 2006), as the former methods is depended to total number of removed nodes. More than 10 lymph nodes must be involved by tumor cells to considered patients as having pN3 disease (Singletary et al., 2002). Therefore, in patients that fewer lymph nodes (less than 10) is harvested and examined during operation it is difficult to make an accurate staging. LNR was introduced so the total number of lymph nodes could be taken into account when making clinical decision about axillary lymph node involvement (Vinh-Hung et al., 2009). According to data available in literature, LNR more 0.2 is correlated with worsen survival of patients with breast cancer (Van der Wal et al., 2002). Our study showed that obesity is associated with higher rang of LNR.

Our findings regarding the greater effect of obesity in premenopausal women goes in good accordance with the results of a meta-analysis conducted by portani et al. (2010), though, in their study, the difference failed to reach statistical significance.

As the association between BMI and expression of ER and PR is a matter of controversy in literature, further studies must be conducted using large breast cancer registry database to determine the impact of obesity on these important prognostic factors.

In conclusion, our results revealed that obesity is associated with higher chance of estrogen and progesterone receptor expression, lymph node metastasis, larger tumor size and higher range of LNR. Although obese patients had higher LNR but obesity was an independent predictor of shorter disease-free survival. This indicates that axillary lymph node metastasis is not responsible for poorer survival in these patients and the underlying cause is still unknown. Further studies are warranted to identify the cause of poorer breast cancer survival in obese patients.

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