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Body mass index and prognosis of breast cancer

An analysis by menstruation status when breast cancer diagnosis

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Abstract

Objective: To examine whether obesity/overweight is a risk predictor for breast cancer recurrence and death by menopausal status in a retrospective study.

Methods: We performed a retrospective analysis of 1017 breast cancer patients treated in our hospital from January 2004 to December 2012. Three groups were divided according to body mass index (BMI) when breast cancer diagnosis: normal weight, BMI < 25.0 kg/m^2; overweight, 25.0≤BMI < 30.0 kg/m^2; and obesity, BMI≥30.0 kg/m^2. The clinicopathological characteristics and clinical outcomes of patients within 5 years following breast cancer diagnosed were analyzed. Subgroup analyses of BMI on breast cancer prognosis were analyzed according to the menopausal status when breast cancer diagnosis. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Overweight and obesity groups were associated with larger size tumors, older age, increased proportion of postmenopausal patients and less patients choosing anthracycline and/or taxane regimen. The 5-year disease-free survival (DFS) and overall survival (OS) decreased in overweight and obese patients ($P < .001$), and both overweight and obesity were independent predictors for increased risks of breast cancer relapse and death ($P < .001$). When stratified by menopausal status, both overweight and obesity were associated with reduced 5-year DFS and OS in postmenopausal patients ($P < .050$), and multivariate analysis showed that the risk of relapse and breast cancer mortality in these 2 groups also increased ($P < .050$). Among premenopausal patients, the risks of relapse and death were significantly increased in obesity group rather than overweight group by multivariate analysis.

Conclusion: Overweight and obesity might be independently associated with poorer prognosis for breast cancer patients, and the effects of overweight on the breast cancer prognosis seem to be related to menopausal status.

Abbreviations: BMI = body mass index, CIs = confidence intervals, DFS = disease-free survival, ER = estrogen receptor, HER2 = human epidermal growth factor receptor-2, HRs = hazard ratios, OS = overall survival, PR = progesterone receptor, TNBC = triple-negative breast cancer.

Keywords: body mass index, breast cancer, menopausal, mortality, obesity, overweight, relapse

1. Introduction

Nowadays, obesity or overweight has become an emerging health concern worldwide with over 500 million adults were obese and 958 million were overweight in 2008,[1,2] and overweight or obesity was also reported to be a risk factor for increased incidence of various forms of cancer.[3,4] Breast cancer remains the most common malignant neoplasm among women,[5] and being overweight or obese in adults is correlated with a greater risk of breast cancer.[6] Besides its established role as a risk factor, there is now widespread consensus on the importance of obesity or overweight as a negative prognostic factor for breast cancer.[7,8]

In 2004, Berclaz et al[9] have reported that obesity or overweight is associated with a poor prognosis after breast cancer treatment, and other studies also suggested that obesity at the time of cancer diagnosis or pre-diagnosis is associated with poor prognosis for breast cancer patients.[10,11] In addition, it has been demonstrated that breast cancer patients with higher body mass index (BMI) estimated as obesity or overweight have a worse prognosis disease regardless of tumor subtype.[12] However, a large retrospective study including stage I-III triple-negative breast cancer (TNBC) patients found that overweight (BMI 25–29.9 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) at diagnosis did not affect disease-free survival (DFS) or overall survival (OS),[13] and Kwan et al[14] also did not find any association between BMI and risk of breast cancer recurrence or mortality after nearly 8-year follow-up.

According to previous study, the effects of higher BMI on prognosis of breast cancer may be associated with menopausal status.[15] Berclaz et al[9] demonstrated that elevated BMI is significantly associated with a worse prognosis of breast cancer, especially for premenopausal and perimenopausal patients, and Kawai et al[16] found that higher BMI (BMI ≥25.8 kg/m^2) was associated with an increase in mortality for premenopausal

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patients. In a cohort study, obese postmenopausal women at diagnosis were at increased risk of breast cancer mortality compared to normal weight women after 6-year follow-up, while being overweight did not affect survival.[17] Another study found that both obesity and overweight were associated with a non-significant higher risk of recurrence and breast cancer death for premenopausal women, and obesity was associated with a significant higher risk of breast cancer death (not for recurrence), but overweight was not a prognosis predictor for postmenopausal women.[18]

To date, the relationship between obesity/overweight and outcomes of breast cancer patients has not been well defined. To our knowledge, the association between obesity/overweight and risk of breast cancer recurrence and death in Chinese women according to menopausal status is less well understood mechanistically. In our study, we presented the analysis of the link between BMI and prognosis of breast cancer, and the stratification analysis was also conducted according to menopausal status when breast cancer diagnosis.

2. Methods

2.1. Patient selection

Data in the study were extracted from the hospital recording statistics in the Affiliated Changzhou No. 2. People's Hospital with Nanjing Medical University from January 2004 to December 2012. We collected primary and adjuvant treatment from medical records: surgery, radiation, chemotherapy, and specific hormonal therapy. We examined a number of potential confounding variables including age when breast cancer diagnosis, stage at diagnosis, tumor size, lymph node evaluation, estrogen receptor (ER) or progesterone receptor (PR) expression, human epidermal growth factor receptor-2 (HER2) expression, pathological subtype, and histological grade. Survival data, which included date of breast cancer diagnosis, surgery, relapse, death and last follow-up, were collected in this cohort. The diagnostic of breast cancer was based on the pathological diagnosis. Patients who did not perform surgery were excluded. We further excluded patients who were without complete medical records, dying from other

Table 1

Comparison of clinicopathological characteristics among breast cancer patients according to the body mass index (kg/m^2).

	BMI < 25 (N1 = 474) n %		BMI ≥ 25, < 30 (N2 = 351) n %		BMI ≥ 30 (N3 = 192) n %		*P*
Age at diagnosis, ys							**<.001**
≤35	94	19.8	39	11.1	19	9.9	
36-65	348	73.4	263	74.9	142	74.0	
≥66	32	6.8	49	14.0	31	16.1	
Menopausal status							**<.001**
Premenopausal	315	66.5	188	53.6	98	51.0	
Postmenopausal	159	33.5	163	46.4	94	49.0	
Lymph node metastasis							**.095**
0	273	57.6	194	55.3	102	53.6	
1–3	148	31.2	105	29.9	52	27.1	
≥4	53	11.2	52	14.8	37	19.3	
Tumor size, cm							**<.001**
≤ 2	216	45.6	128	36.5	54	28.1	
>2, ≤5	208	43.9	178	50.7	105	54.7	
>5	50	10.5	45	12.8	33	17.2	
Pathological subtype							.517
Invasive ductal cancer	371	78.3	286	81.5	154	80.2	
Others	103	21.7	65	18.5	38	19.8	
Histological grade							.836
I	81	17.1	58	16.5	31	16.1	
II	306	64.6	225	64.1	118	61.5	
III	87	18.3	68	19.4	43	22.4	
Estrogen receptor							.496
Negative	179	37.8	138	39.3	82	42.7	
Positive	295	62.2	213	60.7	110	57.3	
Progesterone receptor							.632
Negative	169	35.7	128	36.5	76	39.6	
Positive	305	64.3	223	63.5	116	60.4	
HER2							.420
Negative	351	74.1	271	77.2	150	78.1	
Positive	123	25.9	80	22.8	42	21.9	
Chemotherapy regimen							**.036**
Anthracycline and/or taxane	260	54.9	170	48.4	86	44.8	
Others	214	45.1	181	51.6	106	55.2	
Radiotherapy							.962
Yes	143	30.2	109	31.1	59	30.7	
No	331	69.8	242	68.9	133	69.3	
Hormone therapy							.118
Yes	349	73.6	250	71.2	126	65.6	
No	125	26.4	101	28.8	66	34.4	

BMI = body mass index, HER2 = human epidermal growth factor receptor-2.

causes within 5 years of breast cancer diagnosis and lost follow-up. A total of 1344 breast cancer patients were treated with surgery in our hospital. We further excluded 327 patients for the following reasons: without complete medical records (n=146), unable to determine the menopausal status (n=42), death for other reasons (n=63), and lost to follow-up (n=76). The final analytic cohort consisted of 1017 women.

All study participants provided written informed consent and the study protocol and procedures were approved by the institutional review boards at the Affiliated Changzhou No. 2 People's Hospital with Nanjing Medical University.

Table 2

Univariate analysis of 5-year survival for all patients.

Characteristics	n	5-year DFS %	5-year DFS *P*	5-year OS %	5-year OS *P*
BMI, kg/m^2			**<.001**		**<.001**
<25	474	87.3		92.8	
≥25, <30	351	79.8		86.9	
≥30	192	74.5		81.8	
Age at diagnosis, ys			**.070**		.560
≤35	152	77.6		87.5	
36-65	753	83.8		89.2	
≥66	112	78.6		86.6	
Menopausal status			.311		.222
Premenopausal	601	83.4		89.7	
Postmenopausal	416	80.8		87.3	
Lymph node metastasis			**<.001**		**<.001**
0	570	87.7		94.2	
1–3	305	79.3		85.6	
≥4	142	66.9		73.2	
Tumor size, cm			**<.001**		**<.001**
≤ 2	398	90.5		94.5	
>2, ≤5	491	80.2		88.0	
>5	128	64.8		73.4	
Pathological subtype			.557		.384
IDC	811	82.0		88.3	
Others	206	83.5		90.3	
Histological grade			**<.001**		**<.001**
I	170	91.2		96.5	
II	649	82.6		89.1	
III	198	73.7		80.8	
ER			**.045**		**.026**
Positive	618	84.1		90.5	
Negative	399	79.4		86.0	
PR			**.032**		**.064**
Positive	644	84.2		90.1	
Negative	373	79.1		86.3	
HER2			.642		.719
Positive	245	81.2		89.4	
Negative	772	82.6		88.5	
Chemotherapy			.692		.829
Anthracycline and/or taxane	516	82.8		89.0	
No	501	81.8		88.4	
Radiotherapy			**.004**		**.003**
Yes	311	77.2		84.2	
No	706	84.6		90.7	
Hormone therapy			**.002**		**.002**
Yes	725	84.6		90.6	
No	292	76.7.		83.9	

BMI=body mass index, DFS=disease-free survival, ER=estrogen receptor, HER2=human epidermal growth factor receptor-2, IDC=invasive ductal cancer, OS=overall survival, PR=progesterone receptor.

2.2. Group definitions

We calculated BMI as weight in kilograms divided by height in square meters. BMI was categorized according to WHO standard: normal weight, BMI < 25.0 kg/m^2; overweight, 25.0≤BMI < 30.0 kg/m^2; and obesity, BMI≥30.0 kg/m^2. Patient's weight and height were recorded before surgery. Three groups were divided according to BMI when breast cancer diagnosis: normal weight group (474), overweight group (351), and obesity group (192). Furthermore, a stratified analysis about relationship between BMI and prognosis of breast cancer was conducted in line with menopausal status when breast cancer diagnosed. Menopausal status was defined by 1 year of amenorrhea, or previous bilateral oophorectomy. In the present study, a total of 416 breast cancer patients were postmenopausal, and 601 breast cancer patients were premenopausal. The differences in clinicopathologic characteristics and 5-year breast cancer outcomes between 3 groups were compared.

2.3. Follow-up and outcomes

Follow-up has been maintained by reviewing clinical charts and by contacting patients via telephone or mail. Events used for the

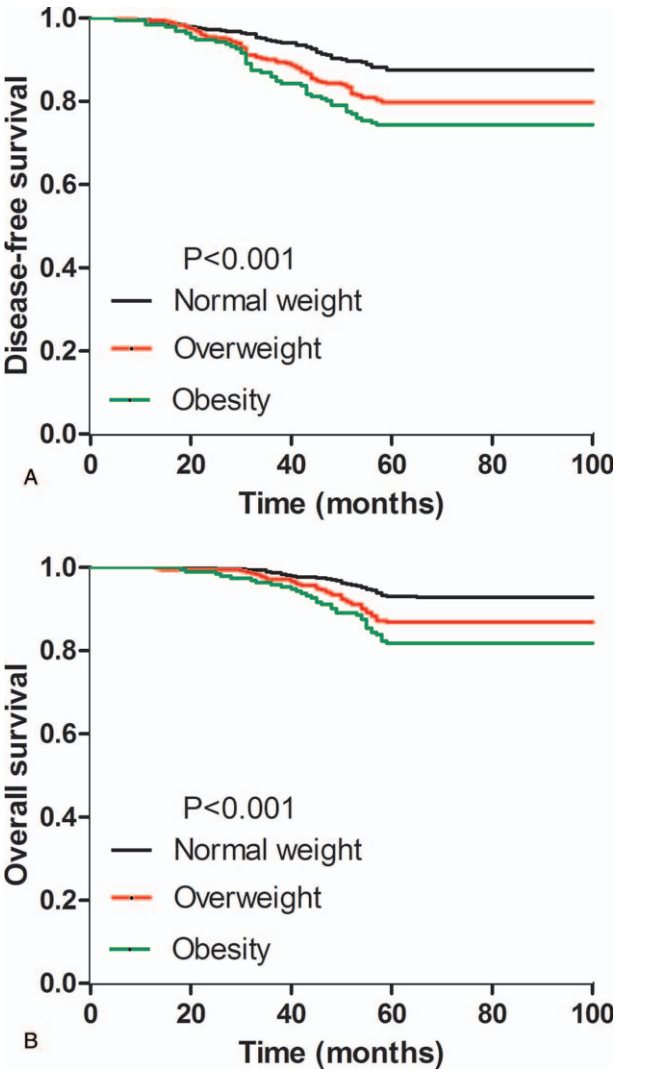

Figure 1. Kaplan–Meier analysis of 5-year survival outcomes for breast cancer patients according to BMI. A, Disease-free survival. B, Overall survival. Statistically significant differences between the groups were estimated by log-rank test.

analysis were 5-year mortality of breast cancer or relapse including local, regional and contralateral breast cancer or distant breast cancer recurrence. Survival status was censored at the date of last contact or 31 December 2017 (last follow-up). DFS defined as the time of diagnosis to development of first evidence of recurrence (distant metastasis or local regional recurrence) or date of last follow-up. OS was defined as from the time of diagnosis to last follow-up or time of mortality from breast cancer (patients dying from other causes within 5 years of breast cancer diagnosis were excluded).

2.4. Statistical analysis

In our study, the associations between different BMI groups and clinicopathologic characteristics of breast cancer patients were analyzed by the chi-square test. The Kaplan–Meier methods were used to calculate 5-year DFS and OS, and the significance was tested by log-rank test. Factors with $P < .10$ in univariate analysis were included in the multivariate Cox model for multivariate analysis. Multivariable Cox proportional hazard models were used to estimate the adjusted hazard ratios (HRs) of different BMI groups. In multivariate analysis, the normal weight group was regarded as a reference for calculating the HR of BMI. Stratified analyses were conducted to explore whether the effects of obesity or overweight on prognosis of breast cancer were modified by menopausal status. All statistical analyses were carried out with SPSS software (version 17.0), and $P < .05$ were considered statistically significant.

3. Results

3.1. Clinical characteristics of patients in study groups

The median follow-up time for this study was 80 months (13–140 months). Of the 1017 breast cancer patients, 474 were normal weight, 351 patients were overweight, and 192 were obesity. The clinicopathological features of these 3 groups were summarized in Table 1. The older age (≥66 years) tended to distribute in overweight (14.0%) and obesity (16.1%) groups compared to normal weight group (6.8%) ($P < .001$). Besides, the larger size of tumors and postmenopausal patients were more likely to distribute ($P < .001$) in overweight and obesity groups, and less patients chose anthracycline and/or taxane to be chemotherapy regimen in these 2 groups ($P = .036$). Lymph node metastasis, pathological subtype, histological grade, ER and PR status, HER2 status, the percentages of patients receiving radiotherapy, and hormone therapy were not significantly different among these 3 groups (Table 1).

3.2. 5-Year DFS and OS

In total, 180 patients suffered from breast cancer relapse within 5 years after breast cancer diagnosis, and the number of recurrent patients was 60, 71, and 49 in the normal weight group, overweight group, and obesity group, respectively. The 5-year DFS and breast cancer relapse rate for the whole cohort were 82.3% (837/1017) and 17.7% (180/1017), respectively. A total of 115 patients died of breast cancer, 34 patients were in the normal weight group, 46 cases were in the overweight group, and 35 cases were in the obesity group. The 5-year OS and breast cancer mortality rate were 88.7% (902/1017) and 11.3% (115/1017), respectively. The Kaplan–Meier analysis showed that there was a significant difference in the DFS and OS between the three groups (Table 2). The DFS was 87.3, 79.8, 74.5% for normal weight, overweight, and obesity groups, respectively ($P < .001$) (Table 2, Fig. 1a). The OS was 92.8, 86.9, 81.8% for normal weight, overweight, and obesity groups, respectively ($P < .001$) (Table 2, Fig. 1B). The 5-year DFS in the premenopausal and postmenopausal groups were 83.4% and 80.8% ($P = .311$) (Table 2). The 5-year OS in the premenopausal and postmenopausal groups were 89.7% and 87.3% ($P = .222$) (Table 2).

Table 3

Multivariate Cox proportional hazards model for survival in all patients.

Characteristics	5-Year breast cancer relapse			5-Year breast cancer mortality		
	HR	95% CI	P	HR	95% CI	P
BMI, kg/m^2						
≥25,<30 vs <25	1.630	1.150–2.311	**.006**	1.747	1.120–2.725	**.014**
≥30 vs <25	1.888	1.281–2.783	**.001**	2.052	1.262–3.336	**.004**
Age at diagnosis, years						
36–65 vs ≤35	0.574	0.389–0.846	**.005**		NA	
≥66 vs ≤35	0.686	0.400–1.178	0.172			
Lymph node status						
1–3 vs 0	1.541	1.089–2.181	**.015**	2.299	1.452–3.641	**<.001**
≥4 vs 0	2.492	1.550–4.005	**< .001**	4.515	2.473–8.245	**<.001**
Tumor size, cm						
≤ 2 vs >5	0.295	0.176–0.494	**<.001**	0.319	0.171–0.595	**<.001**
>2, ≤5 vs >5	0.562	0.369–0.855	**.007**	0.544	0.333–0.888	**.015**
Histological grade						
I vs III	0.358	0.200–0.641	**.001**	0.220	0.092–0.525	**.001**
II vs III	0.748	0.532–1.051	.095	0.697	0.462–1.050	.084
ER						
Negative vs Positive	1.022	0.678–1.540	.916	1.180	0.705–1.975	.528
PR						
Negative vs Positive	1.054	0.716–1.553	.790	0.926	0.560–1.530	.763
Radiotherapy						
Yes vs No	0.674	0.438–1.035	.071	0.601	0.354–1.018	.058
Hormone therapy						
Yes vs No	0.756	0.464–1.232	.262	0.707	0.382–1.309	.270

BMI = body mass index, CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, NA = not applicable, PR = progesterone receptor.

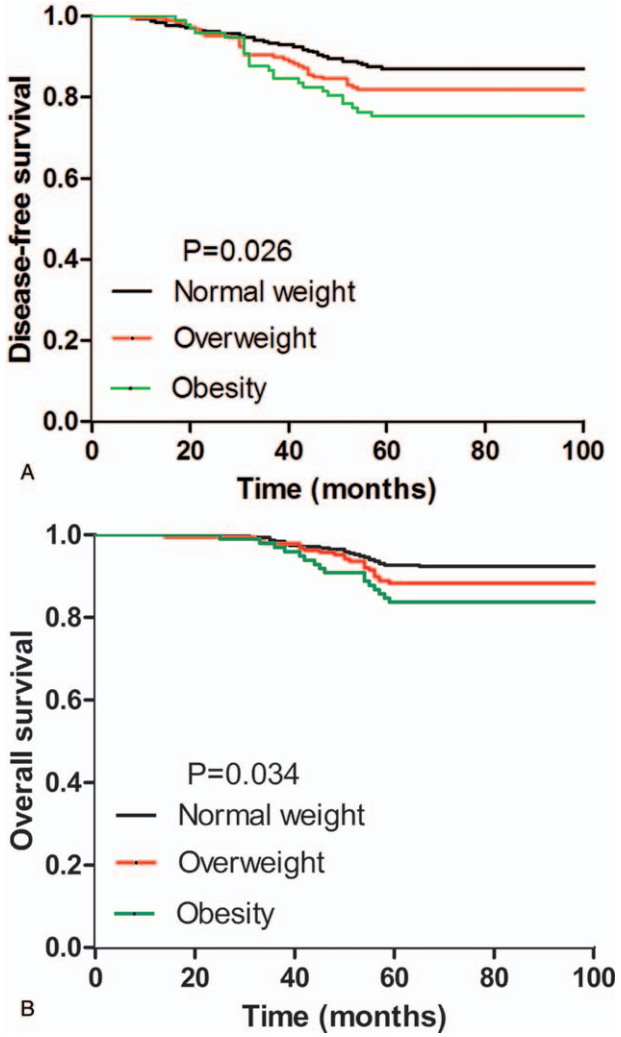

Figure 2. Kaplan–Meier analysis of 5-year survival outcomes for premenopausal breast cancer patients according to BMI. A, Disease-free survival. B, Overall survival. Statistically significant differences between the groups were estimated by log-rank test.

3.3. BMI and breast cancer relapse and mortality risks for all patients

All factors were included in the univariate analysis, and the 5-year DFS and OS were significantly different in terms of lymph node status, tumor size, histological grade, expression of ER and PR, radiotherapy, and hormone therapy ($P<.05$) (Table 2). In multivariate analysis, when compared with normal weight patients, the risks of 5-year breast cancer relapse (HR, 1.630; 95% confidence interval [CI], 1.150–2.311; $P=.006$) and mortality (HR, 1.747; 95% CI, 1.120–2.725; $P=.014$) for the overweight patients were significantly increased after adjusted for other variables, and the 5-year risks of breast cancer relapse (HR, 1.888; 95% CI, 1.281–2.783; $P=.001$) and mortality (HR, 2.052; 95% CI, 1.262–3.336; $P=.004$) were also significantly increased in obesity group after adjusting for age, lymph node status, tumor size, histological grade, ER, PR, radiotherapy, and hormone therapy (Table 3).

3.4. BMI and prognosis of breast cancer for premenopausal patients

In univariate analysis, both the 5-year DFS and OS were significantly different among the 3 groups for premenopausal patients. The DFS was 86.7, 81.9, 75.5% for normal weight, overweight, and obesity groups, respectively ($P=.026$) (Fig. 2A), and the OS was 92.4, 88.3, 83.7% for normal weight, overweight, and obesity groups, respectively ($P=.034$) (Fig. 2B) (Table 4). Besides, the 5-year DFS and OS were significantly different in terms of age, lymph node status, tumor size, histological grade, radiotherapy, and hormone therapy (Table 4). By multivariate analysis, the 5-year risks of breast cancer relapse (HR, 1.824; 95% CI, 1.096–3.037; $P=.021$) and mortality (HR, 1.948; 95% CI, 1.029–3.687; $P=.041$) were

Table 4

Univariate analysis of 5-year survival for premenopausal patients (n = 601).

Characteristics	n	5-Year DFS %	5-Year DFS *P*	5-Year OS %	5-Year OS *P*
BMI, kg/m^2			**.026**		**.034**
<25	315	86.7		92.4	
≥25,<30	188	81.9		88.3	
≥30	98	75.5		83.7	
Age at diagnosis, ys			**.019**		.282
≤35	152	77.6		87.5.90.4	
36-65	449	85.3			
Lymph node metastasis			**<.001**		**<.001**
0	349	88.8		94.8	
1–3	172	77.9		85.5	
≥4	80	71.3		76.3	
Tumor size, cm			**<.001**		**<.001**
≤ 2	253	90.9		94.9	
>2, ≤5	282	79.8		87.9	
>5	66	69.7		77.3	
Pathological subtype			.991		.541
IDC	477	83.4		89.3	
Others	124	83.1		91.1	
Histological grade			**.051**		**.033**
I	102	91.2		95.1	
II	386	82.6		89.9	
III	113	78.8		84.1	
ER			.209		.186
Positive	357	84.9		91.0	
Negative	244	81.1		87.7	
PR			.294		.320
Positive	392	84.4		90.6	
Negative	209	81.3		88.0	
HER2			.398		.829
Positive	153	81.0		90.2	
Negative	448	84.2		89.5	
Chemotherapy			.765		.133
Anthracycline and/or taxane	305	83.0		87.9	
No	296	83.8		91.6	
Radiotherapy			**.008**		**.004**
Yes	186	77.4		84.4	
No	415	86.0		92.0	
Hormone therapy			**.029**		**.069**
Yes	435	85.3		91.0	
No	166	78.3.		86.1	

BMI = body mass index, DFS = disease-free survival, ER = estrogen receptor, HER2 = human epidermal growth factor receptor-2, IDC = invasive ductal cancer, OS = overall survival, PR = progesterone receptor.

significantly increased in obesity group compared to normal weight group after adjusting for confounding factors. However, the 5-year risks of relapse (HR, 1.462; 95% CI, 0.926–2.308; $P = .103$) and mortality (HR, 1.619; 95% CI, 0.904–2.898; $P = .105$) were non-significantly increased for overweight group after adjusting for age, lymph node status, tumor size, histological grade, radiotherapy, and hormone therapy (Table 5).

3.5. BMI and prognosis of breast cancer for postmenopausal patients

When compared to the normal weight group, the 5-year DFS and OS of overweight and obesity groups for postmenopausal patients were significantly decreased. As shown in Table 6, the 5-year DFS was 88.7, 77.3, 73.4% for normal weight, overweight, and obesity groups, respectively ($P = .003$) (Fig. 3A); the 5-year OS was 93.7, 85.3, 79.8% for normal weight, overweight, and obesity groups, respectively ($P = .003$) (Fig. 3B). Additionally, the 5-year DFS and OS were significantly different in terms of lymph node status, tumor size, histological grade, PR expression, and hormone therapy ($P < .05$) (Table 6). By multivariate analysis, 5-year risks of relapse (HR, 1.884; 95% CI, 1.066–3.331; $P = .029$) and mortality (HR, 2.210; 95% CI, 1.040–4.696; $P = .039$) were increased for overweight group after adjusting for lymph node status, tumor size, histological grade, ER, PR, chemotherapy, and hormone therapy (Table 7). The 5-year risks of breast cancer relapse (HR, 2.031; 95% CI, 1.091–3.782; $P = .026$) and mortality (HR, 2.493; 95% CI, 1.117–5.564; $P = .026$) were also increased in obesity group after adjusting confounding factors (Table 7).

4. Discussion

Obesity and overweight in adults have been reported to be correlated with a greater risk of breast cancer,[6,19] while the studies that evaluated influence of overweight and obesity on breast cancer survival have yielded mixed findings.[20,21] In an effort to address this gap, we conducted a retrospective study to elucidate the relationship between obesity and breast cancer prognosis.

In our study, we found that overweight and obese breast cancer patients were associated with larger size tumors compared to normal weight patients. Additionally, patients tended to be older, the proportion of postmenopausal patients was increased, and lesser patients choose anthracycline and/or taxane to be chemotherapy regimen in overweight and obesity groups. There were also several studies demonstrating that obese women develop aggressive breast cancer with a significantly larger size compared to normal weight women,[22,23] and patients with BMI ≥ 25 kg/m^2 tended to be older and to have larger tumor size,[24] postmenopausal patients were more distributed in patients with higher BMI (BMI≥ 25.8 kg/m^2).[16] Interestingly, some authors claimed that women with higher BMI undergo less screening so tend to have more advanced disease at presentation.[25]

We also found that overweight and obesity were independent predictors for increased risks of 5-year breast cancer relapse and mortality for the whole cohort. In a previous study from America, after 5-year follow-up, the authors calculated that HRs for risks of recurrence was 1.18 (95% CI 1.02–1.36) in overweight patients and breast cancer mortality was 1.23 (95% CI 1.00–1.52) in the obese group relative to the normal weight, while overweight did not influence recurrence and obesity wasn't a predictor for breast cancer mortality.[20] In a study including African TNBC patients, overweight was significantly related to breast cancer mortality (HR 2.903, 95% CI: 1.551–5.432) and recurrence (HR 1.899, 95% CI: 1.05- 3.433) by multivariable analysis.[26] Another study found that the risks of developing distant metastasis were significantly increased for Danish obese patients, while both obesity and overweight women had higher risk of breast cancer mortality relative to normal weight women.[27] However, Kawai et al [18] reported that obesity was an independent risk factor for breast cancer death (HR: 1.47; 95% CI: 1.11–1.93) but not for recurrence, and overweight had no association with breast cancer prognosis. Nevertheless, in another study from America, Kwan et al[14] observed that overweight or obesity was not associated with increased risk of

Table 5

Multivariate Cox proportional hazards model for survival in premenopausal patients.

Characteristics	5-Year DFS			5-Year OS		
	HR	95% CI	*P*	HR	95% CI	*P*
BMI, kg/m^2						
≥25,<30 vs <25	1.462	0.926–2.308	.103	1.619	0.904–2.898	.105
≥30 vs <25	1.824	1.096–3.037	**.021**	1.948	1.029–3.687	**.041**
Age at diagnosis, years						
36–65 vs ≤35	0.581	0.380–0.888	**.012**	NA		
Lymph node status						
1–3 vs 0	1.704	1.078–2.694	**.023**	2.547	1.374–4.723	**.003**
≥4 vs 0	2.047	1.056–3.967	**.034**	4.189	1.798–9.759	**.001**
Tumor size, cm						
≤ 2 vs >5	0.376	0.184–0.767	**.007**	0.402	0.170–0.951	**.038**
>2, ≤5 vs >5	0.761	0.416–1.390	.374	0.705	0.350–1.422	.329
Histological grade						
I vs III	0.400	0.186–0.863	**.019**	0.297	0.110–0.801	**.016**
II vs III	0.896	0.557–1.442	.651	0.642	0.365–1.131	.125
Radiotherapy						
Yes vs no	0.991	0.552–1.780	.976	0.938	0.440–2.002	.869
Hormone therapy						
Yes vs no	0.722	0.474–1.101	.131	0.682	0.403–1.154	.154

BMI = body mass index, CI = confidence interval, DFS = disease-free survival, ER = estrogen receptor, HR = hazard ratio, NA = not applicable, OS = overall survival, PR = progesterone receptor.

Table 6

Univariate analysis of 5-year survival for postmenopausal patients (n = 416).

Characteristics	n	5-Year DFS		5-Year OS	
		%	*P*	%	*P*
BMI, kg/m^2			**.003**		**.003**
<25	159	88.7		93.7	
≥25,<30	163	77.3		85.3	
≥30	94	73.4		79.8	
Age at diagnosis, ys			.444		.733
36-65	304	81.6		87.5.86.6	
≥ 66	112	78.6			
Lymph node metastasis			**<.001**		**<.001**
0	221	86.0		93.2	
1–3	133	81.2		85.7	
≥4	62	61.3		69.4	
Tumor size, cm			**<.001**		**<.001**
≤ 2	145	89.7		93.8	
>2, ≤5	209	80.9		88.0	
>5	62	59.7		69.4	
Pathological subtype			.392		.542
IDC	334	79.9		86.8	
Others	82	84.1		89.0	
Histological grade			**<.001**		**<.001**
I	68	91.2		98.5	
II	263	82.5		87.8	
III	85	67.1		76.5	
ER			**.093**		**.056**
Positive	261	83.1		89.7	
Negative	155	76.8		83.2	
PR			**.048**		.119
Positive	252	83.7		89.3	
Negative	164	76.2		84.1	
HER2			.826		.820
Positive	92	81.5		88.0	
Negative	324	80.6		87.0	
Chemotherapy			.344		**.051**
Anthracycline and/or taxane	211	82.5		90.5	
Others	205	79.0		83.9	
Radiotherapy			.176		.212
Yes	125	76.8		84.0	
No	291	82.5		88.7	
Hormone therapy			**.024**		**.010**
Yes	290	83.4		90.0	
No	126	74.6.		81.0	

BMI = body mass index, ER = estrogen receptor, HER2 = human epidermal growth factor receptor-2, IDC = invasive ductal cancer, OS = overall survival, PR = progesterone receptor.

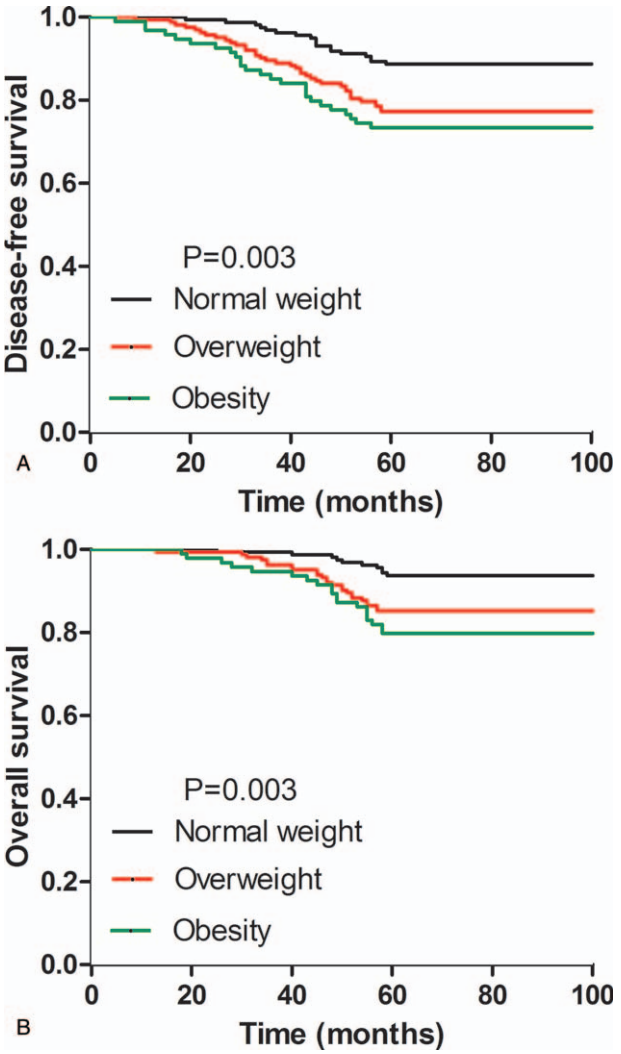

Figure 3. Kaplan–Meier analysis of 5-year survival outcomes for postmenopausal breast cancer patients according to BMI. A, Disease-free survival. B, Overall survival. Statistically significant differences between the groups were estimated by log-rank test.

recurrence and breast cancer mortality compared to normal weight, a report from the Korean Breast Cancer Society demonstrated similar results.[21]

Although the association between obesity/overweight and the prognosis of breast cancer patients remains controversial, it has been reported that impact of BMI on prognosis of breast cancer may relate to menopausal status.[15] To identify this issue, we conducted a stratified analysis according to the menopausal status.

In stratified analysis, we found that being overweight was associated with increased risks of breast cancer relapse and mortality within 5 years after breast cancer diagnosis for postmenopausal but not for premenopausal women, and obesity was an independently poor predictor for breast cancer relapse and mortality regardless to menopausal status. Similar to our study, Reeves et al[4] have reported that obesity and overweight were related to increased breast cancer progression and mortality primarily in British postmenopausal women. A meta-analysis of 82 studies that included 213,075 breast cancer patients demonstrated that obesity was associated with higher risk of breast cancer mortality (HR, 1.41; 95% CI, 1.29–1.53) in both premenopausal (HR, 1.75; 95% CI, 1.26–2.41) and postmenopausal (HR, 1.34; 95% CI, 1.18–1.53) women,[28] similar results were found by Niraula et al.[29] A study from Japan found that obesity and overweight were associated with a nonsignificant higher risk of recurrence and breast cancer death for premenopausal women, and obesity but not overweight was associated with a significant higher risk of breast cancer death for postmenopausal women (not for recurrence),[18] results from a cohort study also suggest that obesity (not overweight) was an independent poor prognostic predictor for American postmenopausal breast cancer patients.[17] However, some authors[9] found that overweight or obesity is significantly associated with a shorter OS and DFS for premenopausal and perimenopausal patients. Besides, another study including American breast cancer

Table 7

Multivariate Cox proportional hazards model for survival in postmenopausal patients.

Characteristics	5-Year DFS			5-Year OS		
	HR	95% CI	*P*	HR	95% CI	*P*
BMI, kg/m^2						
≥25,<30 vs <25	1.884	1.066–3.331	**.029**	2.210	1.040–4.696	**.039**
≥30 vs <25	2.031	1.091–3.782	**.026**	2.493	1.117–5.564	**.026**
Lymph node status						
1–3 vs 0	1.257	0.734–2.154	.405	2.085	1.042–4.172	**.038**
≥4 vs 0	1.800	1.001–3.237	**.050**	2.611	1.238–5.502	**.012**
Tumor size, cm						
≤ 2 vs >5	0.326	0.161–0.658	**.002**	0.346	0.146–0.819	**.016**
>2, ≤5 vs >5	0.551	0.319–0.950	**.032**	0.554	0.290–1.060	**.074**
Histological grade						
I vs III	0.342	0.137–0.854	**.021**	0.105	0.014–0.803	**.030**
II vs III	0.654	0.394–1.085	.100	0.822	0.441–1.532	.537
ER						
Negative vs Positive	1.111	0.555–2.225	.766	1.172	0.482–2.848	.726
PR						
Negative vs Positive	1.071	0.604–1.899	.814		NA	
Chemotherapy						
A /T vs others		NA		0.652	0.370–1.150	.140
Hormone therapy						
Yes vs No	0.853	0.392–1.855	.688	0.690	0.278–1.713	.424

A/T = anthracycline and/or taxane, BMI = body mass index, CI = confidence interval, DFS = disease-free survival, ER = estrogen receptor, HR = hazard ratio, NA = not applicable, OS = overall survival, PR = progesterone receptor.

patients also stated that overweight or obesity was positively associated with recurrence in premenopausal rather than postmenopausal women.[15] Moreover, some studies indicated that overweight is an independent prognostic factor for increased breast cancer mortality and recurrence in premenopausal TNBC women, while similar results were not found in postmenopausal women.[26,30]

Although the effects of BMI on breast cancer prognosis are still controversial, the possible mechanisms have been disclosed as follow. Some authors reported that in postmenopausal patients with higher BMI, increased synthesis of peripheral estrogen in adipose tissue and reduced sex hormone binding globulin might be responsible for the poor breast cancer prognosis due to enhanced aromatase activity may induce and stimulate the growth of abnormal mammary cells,[31,32] and higher BMI women may not fully benefit from aromatase inhibitors in postmenopausal women.[33] Furthermore, women with higher BMI and older age may withstand comorbidities and chemotherapy dose reduction due to concerns about toxicity,[34] and women with higher BMI may present increased levels of insulin, insulin-like growth factor, and hormones with potent mitogenic activity.[35] Besides, paracrine secretion of interleukin-6 and tumor necrosis factor-alpha and the establishment of a pro-inflammatory micro-environment may promote tumor growth, metastasis.[36] Several cytokines produced by obese adipose tissue may promote the progression of breast cancer via upregulating breast cancer stem cells, inhibiting the antitumor immunity and stimulating breast tumor angiogenesis.[37] Thus higher BMI might induce the development of breast cancer.

Our study found that obesity at diagnosis was related to poor prognosis of breast cancer irrespective of menopausal status, while overweight was only associated with prognosis of postmenopausal patients. However, our study has some limitations. Firstly, there is an active debate regarding the limitations of BMI to define obesity and overweight categories for various populations.[38] Secondly, negative effects of weight change on breast cancer prognosis have been reported,[39,40] the association limited to BMI when cancer diagnosis may attenuate over time, but we did not dynamically monitor changes in body weight in breast cancer patients. Thirdly, obese patients are thought to have a higher risk of comorbid conditions, but our study did not include information on comorbidities. Finally, the sample size was small relatively, follow-up period was short, and we did not adjust other potential confounders. The limitations mentioned above may partly bring about the discrepancy in our study.

In conclusion, our study adds to the literature by showing a link of obesity, menopausal status, and breast cancer prognosis. However, further studies with larger sample sizes and more comprehensive design are urgently warranted.

Author contributions

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