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Obesity and Weight Change in Relation to Breast Cancer Survival

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Abstract

The authors evaluated the prognostic effects of obesity and weight change after breast cancer diagnosis. A total of 5042 breast cancer patients aged 20–75 were identified through the population-based Shanghai Cancer Registry approximately 6 months after cancer diagnosis and recruited into the study between 2002 and 2006. Participants were followed by in-person interviews supplemented by record linkage with the Shanghai Vital Statistics Registry database. Anthropometric measurements were taken and information on sociodemographic, clinical, and lifestyle factors was collected through in-person interviews. During the median follow-up of 46 months, 442 deaths and 534 relapses/breast cancer-specific deaths were documented. Women with body mass index (BMI) ≥30 at diagnosis had higher mortality than women with 18.5≤BMI<25; the multivariate adjusted hazard ratios (HRs) were 1.55 (95% confidence interval (95% CI): 1.10–2.17) for total mortality and 1.44 (95% CI: 1.02–2.03) for relapse/disease-specific mortality. Similar results were found for pre- and post-diagnostic obesity. Women who gained ≥5kg or lost >1kg had higher mortality than those who maintained their weight. No association was observed between waist-to-hip ratio and mortality. Our study suggests that obesity and weight change after diagnosis are inversely associated with breast cancer prognosis. Weight control is important among women with breast cancer.

Keywords

Body mass index; central obesity; weight change; breast cancer; survival

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The current obesity epidemic is a major public health concern in the US and many other countries, affecting over 66 million American adults and 400 million people worldwide (1). Obesity in the general population is related to high mortality and high risk for the development of many diseases, including cardiovascular disease, diabetes, and cancer (1, 2). Breast cancer is the most common cancer among women in the world. Approximately 4.4 million women worldwide are currently living with breast cancer (3, 4), two million of whom are in the U.S., and this population is growing (4). Obesity and weight gain after breast cancer diagnosis are profound issues for women with breast cancer and are attributable to disruption of the endocrine system, fitness level, and comorbidities resulting from cancer, cancer-related treatments, and lifestyle factors (5–10). Given the increasing

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number of women living with breast cancer and the growing prevalence of obesity, understanding the effect of obesity and weight gain on breast cancer prognosis is important.

Although a large body of research has suggested that general obesity or increased body mass index (BMI) in women diagnosed with breast cancer may be related to unfavorable prognosis (6–9, 11–26), the evidence is not entirely consistent (6, 15, 27–33). Studies on the role of central obesity, mainly measured by waist-to-hip ratio (WHR), have been limited and inconsistent (8, 9, 12, 15, 34, 35). Furthermore, less is known about the association of post-diagnosis weight change with breast cancer prognosis (20, 25, 36–38). Generally, most prior studies have focused on specific groups of breast cancer patients or stages of disease (28, 39), post-menopausal women (8, 29, 30), or have had small sample sizes (8, 16, 19, 29–32, 34). Tumor characteristics such as disease stage and hormone receptor status are well-established prognostic factors for breast cancer (9), and women with severe comorbidities have higher mortality than their comparatively healthier counterparts (40). Whether these prognostic factors modify the association of body size with breast cancer prognosis remains unclear, partly due to lack of power and missing information in most existing studies.

To elucidate these issues, in this report, we describe a comprehensive evaluation of the association of breast cancer survival with general and central obesity at the time of breast cancer diagnosis and weight change after diagnosis in a population-based cohort study of 5043 pre- and post-menopausal women diagnosed with stage 0-IV breast cancer.

MATERIALS AND METHODS

The Shanghai Breast Cancer Survival Study (SBCSS) is a population-based cohort study. Through the Shanghai Cancer Registry, 6299 women were identified approximately 6 months after breast cancer diagnosis and were invited to participate in the study between April 1, 2002 and December 31, 2006. Of these, 5042 women provided written, informed consent and enrolled in the SBCSS (participation rate: 80.0 %). Reasons for non-participation included refusals (12.0%), moving (2.7%), out of town (1.4%), inability to locate potential participants (1.3%), and other miscellaneous reasons (2.6%). Information on survival status was collected during the follow-up interviews and by linkage with the Shanghai Vital Statistics database. The SBCSS was approved by the institutional review boards of all institutions involved in this study.

In-person interviews were conducted approximately 6, 18, 36, and 60 months after diagnosis using structured questionnaires. Information on demographics, cancer diagnosis and treatment, comorbidity, family history of breast cancer, menstrual and reproductive history, exercise participation, dietary intake, tea consumption, alcohol consumption, cigarette smoking, complementary and alternative medicine use, and quality of life were collected. Postmenopausal status was defined as having no menstruation during the preceding 12 months or more, excluding lapses caused by pregnancy or breast-feeding, and having hormone-induced menopause.

Anthropometric measurements were taken twice according to a standard protocol by trained interviewers at the baseline interview (approximately 6 months after cancer diagnosis). Weight was measured to the nearest 0.1 kg, using a digital weight scale that was calibrated every 6 months. Height and circumferences were measured to the nearest 0.1 cm. Waist circumference was measured at 2.5 cm above the umbilicus and hip circumference at the level of maximum width of the buttocks with the subject in a standing position. A tolerance limit of 1 kg was set for the weight measurement and 1 cm for height and circumference measurements. A third measurement was taken if the difference of the first two measurements was greater than the tolerance limit. Body mass index (BMI; weight in

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kilograms divided by the square of height in meters) and waist-to-hip ratio (WHR; waist circumference divided by hip circumference) were calculated. Participants were also asked to report their weight at 1 year prior to diagnosis and at diagnosis. Weight at approximately 18 months after diagnosis was measured by trained interviewers using a standard protocol. The corresponding BMIs and weight changes were calculated.

Habitual dietary intake was assessed using an abbreviated 29-item food frequency questionnaire that was designed to measure the intake of meats, cruciferous vegetables, and soy food. Details about the full-scale dietary assessment questionnaire have been described elsewhere (41). The nutrient content of each food item was estimated based on the Chinese Food Composition Tables 2002 (42).

Disease- and treatment-related information was collected, including stage of tumor-node metastasis (TNM) at diagnosis, estrogen receptor (ER) and progesterone receptor (PR) status, type of surgery, chemotherapy, radiotherapy, immunotherapy, and tamoxifen use. Additionally, medical charts were reviewed to verify diagnosis, treatment, and disease stage information. ER and PR status were included in the analyses in the following joint categories: ER+/PR+ (receptor-positive), ER−/PR− (receptor-negative), and ER−/PR+ or ER+/PR− (mixed). A Charlson comorbidity index was created for each woman based on a validated comorbidity scoring system (43) and the diagnostic codes from the International Classification of Disease (ICD-9) (44).

Statistical analysis

The endpoints for the study were any death, for overall survival and cancer recurrence or metastasis or death related to breast cancer for disease-free survival analyses. With age as the time scale (45), multivariate Cox proportional hazards models were employed to evaluate the associations of BMI, WHR, and weight changes with overall and disease-free survival rates. Entry time was defined as the age at diagnosis and exit time was defined as the age at death or censoring. BMI was categorized according to the World Health Organization (WHO) guidelines (46): underweight, <18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; and obese, ≥30 kg/m^2. Weight changes during the following time periods were evaluated: from 1 year pre-diagnosis to 6 and 18 months post-diagnosis and from diagnosis to 18 months post-diagnosis. Women were categorized as losing weight (lost more than 1 kg), maintaining weight (weight change of ±1 kg), moderate weight gain (gained 1–5 kg), and substantial weight gain (gained weight ≥5 kg). Student's t test was used to evaluate the difference in weight change by exercise participation and chemotherapy, radiotherapy, and tamoxifen use. Pearson correlation analyses were conducted to calculate correlation coefficients (r) for weight, BMI, and WHR with adjustment for age at diagnosis.

Differences in sociodemographic and clinical characteristics across baseline BMI categories were evaluated using analysis of variance (ANOVA) for continuous variables and/or the χ^2 test for categorical variables. The adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were derived from Cox models. The following covariates were related to the exposure (body size) or outcome (mortality) and were adjusted for in the multivariate models: age at diagnosis, time interval from diagnosis to study recruitment, education, income, marital status, menopausal status, menopausal symptoms, exercise participation, dietary intake of meats, cruciferous vegetables and soy protein, comorbidity, type of surgery, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, TNM stage, and ER/PR status. Stratified analyses were conducted to explore whether the associations of obesity at diagnosis or weight change between diagnosis and 18 months post-diagnosis with overall and or disease-free survival were modified by TNM stage, ER/PR status, comorbidity,

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menopausal status, exercise participation, or pre-diagnostic obesity. Effect modification was examined by using a multiplicative scale.

Trend tests were performed by entering the categorical variables as continuous parameters in the corresponding models. All tests were performed by using Statistical Analysis Software (SAS, version 9.1; SAS Institute, Inc., Cary, North Carolina). The significance levels were set at $P<0.05$ for two-sided analyses.

RESULTS

During the median follow-up of 46 months after cancer diagnosis, 442 deaths and 534 breast cancer-specific deaths were documented among the participants. For the disease-free survival analysis, 53 breast cancer cases were excluded because they had metastasized disease before or at the study enrollment. Overall, 27.8% of women were overweight (25≤BMI<30) and 5.2% were obese (BMI≥30) at 1-year pre-diagnosis. The corresponding prevalence rates of overweight and obesity were 26.6% and 5.1% at diagnosis, and 29.7% and 5.6% at 6 months post-diagnosis, respectively. The mean weight changes with standard deviations (SDs) from pre-diagnosis to 6 and 18 months post-diagnosis were 0.8±4.1 kg (median: 0.5 kg) and 1.5±4.6 kg (median: 1.0 kg), and from diagnosis to 6 and 18 months post-diagnosis were 1.0±3.7 kg (median: 1.0 kg) and 1.7±4.4 kg (median: 2.0 kg), respectively. The age-adjusted correlation coefficient between BMI and WHR was 0.44. Weight before diagnosis was highly correlated with weight at diagnosis (r=0.97) and weight at 6 months post-diagnosis (r=0.90). The correlation coefficient between weight at diagnosis and weight at 6 months post-diagnosis was 0.92 (all $P<0.001$).

Distributions of baseline sociodemographic and clinical characteristics by baseline BMI are shown in Table 1. Obese women tended to be older at diagnosis, postmenopausal, and physically inactive, and were less likely to have received chemotherapy or immunotherapy. Obesity was more common in women with higher WHR, women who gained more weight between diagnosis and 6 months post-diagnosis, and women with higher dietary intake, a higher comorbidity index, and later disease stage. No differences were found regarding family history of breast cancer, age at menarche, radiotherapy, tamoxifen use, ER/PR status, or other lifestyle factors.

Table 2 presents associations of BMI and WHR with mortality after adjustment for potential confounders. Women who were obese at 1-year pre-diagnosis or at diagnosis had higher mortality than normal-weight women. The multivariate adjusted HRs for total mortality were 1.58 (95% CI: 1.13–2.22) for women who were obese (BMI≥30) at 1 year pre-diagnosis and 1.55 (95% CI: 1.10–2.17) for women who were obese at diagnosis, and the HRs for relapse/disease-specific mortality were 1.39 (95% CI: 0.98–1.97) and 1.44 (95% CI: 1.02–2.03), respectively. We found similar positive associations of total mortality and relapse/disease-specific mortality with obesity at 6 months post-diagnosis. Further adjustment for WHR did not alter the results. WHR was not significantly related to mortality with or without adjustment for BMI in pre- or post-menopausal women.

A U-shaped association of weight change with mortality was observed (Table 3). Compared with women who maintained their weight (±1 kg), those who gained ≥5kg from pre-diagnosis to 18 months post-diagnosis had an HR of 1.71 (95% CI: 1.12–2.60) for total mortality and 1.90 (95% CI: 1.23–2.93) for relapse/disease-specific mortality. Women who lost weight (>1kg) had higher total mortality (HR: 2.41; 95% CI: 1.62–3.58) and relapse/disease-specific mortality (HR: 1.60; 95% CI: 1.03–2.48). Similar but attenuated associations were observed when weight change over the 18-month post-diagnosis period was considered.

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Table 4 presents stratified analyses of obesity at diagnosis and mortality by TNM stage, ER/PR status, comorbidity, and exercise participation at baseline. Among women with TNM stage 0-II breast cancer, obesity at diagnosis was related to higher total mortality (HR: 1.53; 95% CI: 0.98–2.39) and relapse/disease-specific mortality (HR: 1.67; 95% CI: 1.09–2.55). Similar results were also observed for women with stage III–IV disease. Tests for multiplicative interaction between obesity and TNM stage were not significant. Analysis stratified by ER/PR status showed that the association was more apparent among women with ER/PR-negative breast cancer than women with ER/PR-positive or mixed cancer. However, the two latter groups had small numbers and interactions were not significant. The effect of obesity on breast cancer mortality appeared to be more apparent among women with more severe comorbidities and among non-exercisers, however, the interactions were not significant. The association of obesity with mortality varied little by menopausal status (data not shown).

Table 5 presents associations of weight change with mortality stratified by pre-diagnostic BMI. The associations of weight change with total and relapse/disease-specific mortality appeared to be slightly stronger among women with lower BMI (BMI<25) than women with higher BMI (BMI≥25), although the tests for multiplicative interaction were not significant. We did not find that the association varied by exercise participation, comorbidities, menopausal status, TNM stage, or ER/PR status (data not shown).

DISCUSSION

In this large, population-based cohort study of women diagnosed with breast cancer, we found that obesity prior to or at cancer diagnosis and weight gain after cancer diagnosis were inversely associated with breast cancer prognosis. Weight loss after cancer diagnosis was also related to higher breast cancer mortality, even after adjustment for baseline BMI and other potential confounders.

A number of studies have evaluated the adverse prognostic effect of general obesity before breast cancer diagnosis (8, 9, 18, 20, 22, 25, 33, 38, 47) or at the time of or shortly after a diagnosis of breast cancer (12, 19, 21, 24–27, 30, 31, 35, 39). In our study, we found that women who were obese 1 year prior to cancer diagnosis had 1.6 times higher total mortality than normal-weight women and had 1.4 times higher relapse/disease-specific mortality, similar to several previous reports on obesity at 1 year pre-diagnosis (9, 18, 22, 25). We also found that obesity at diagnosis was significantly associated with higher total and relapse/disease-specific mortality, consistent with most prior studies. Our findings suggest that general obesity is an independent prognostic factor for poorer breast cancer outcomes.

Obesity may delay the diagnosis of breast cancer and thus, may compromise prognosis because of the presence of more advanced tumors and more severe comorbidities at diagnosis as observed in our and other studies (16, 21, 40). In our study, the obesity-mortality association appeared to be more apparent in women with severe comorbidities, although the interaction was not significant. The association of obesity with breast cancer mortality persisted after adjustment for disease stage, comorbidities, and other potential confounders. Two other studies have indicated that this association is stronger among women with early-stage disease than among women with advanced-stage disease (9, 20). We did not find that disease stage modified the effect of body size on mortality from breast cancer, consistent with the findings of Whiteman *et al.* (7).

It has been suspected that the effect of obesity on breast cancer prognosis may be stronger in women with estrogen receptor-positive tumors than women with estrogen receptor-negative tumors (48, 49). However, two previous studies reported no difference in the obesity-

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survival association by hormone receptor status (9, 22). The Nurses' Health Study (NHS) had small number of ER/PR negative breast cancer and therefore lacked adequate power to examine differences by receptor status (20). Our study suggested a significant association of obesity with overall and disease-free survival among both women with ER/PR-negative and ER/PR-positive breast cancer. No interaction was observed between obesity and ER/PR status.

Of interest, we found that the adverse effect of obesity on breast cancer survival was more apparent among women who did not participate in exercise at study enrollment, although no significant interaction was observed. Abrahamson *et al.* found that the detrimental effects of body size on breast cancer survival were restricted to women with low recreational activity levels (35). Exercise may counter the adverse effect of obesity on breast cancer prognosis, but further research is warranted.

The limited research on the association between central obesity and breast cancer prognosis has resulted in mixed findings (8, 9, 12, 15, 29, 34, 35). In a cohort study of 1254 young US women diagnosed with breast cancer, Abrahamson *et al.* found that total mortality was 1.5 times higher for women in the highest quartile of WHR at 4 months post-diagnosis than for women in the lowest quartile of WHR with 8–10 years of follow-up (35). Another 10-year follow-up study of 603 breast cancer patients in Canada showed that elevated WHR at 2 months after surgery but before adjuvant treatment was related to breast cancer mortality in postmenopausal women but not in premenopausal women (34). In our study, we found no significant association between WHR and breast cancer mortality in either pre- or post-menopausal women, which is consistent with our earlier study (12) and other research (8). However, the follow-up period of our study is relatively short. Further follow-up of the cohort, as is planned, would help disentangle whether WHR is associated with long-term prognosis of breast cancer.

A few studies have evaluated the prognostic effect of weight gain after breast cancer diagnosis with mixed findings (20, 25, 36–38). We found that both substantial weight gain and weight loss after diagnosis increased the risk for total mortality and relapse/disease-specific mortality, even after adjustment for baseline BMI. Pre-diagnostic BMI did not significantly modify the effect of weight change, similar to the findings of Nichols *et al.* (25). In the NHS, the association of weight gain with breast cancer mortality was evident only among women who were normal weight but not overweight or obese (BMI≥25) at baseline (20). The discrepancy may be due, in part, to differences in the characteristics of the study populations or exposure assessments (weight change vs. BMI change). The adverse effect of weight change on mortality observed in our study varied little by menopausal status, which is consistent with a previous study (25), but did not support the findings by Camoriano *et al.* (36), which suggested that weight gain was only detrimental for premenopausal breast cancer patients. Substantial weight gain in the first several years post-diagnosis may be an independent prognostic factor for breast cancer.

Several mechanisms have been proposed to explain the adverse effect of body size on breast cancer prognosis (10, 11, 50). For example, adult BMI and weight gain reflect the accumulation of adipose tissue, and obesity is related to high circulating levels of estrone, estradiol, and free estradiol (51). Because of the increased activity of aromatase enzymes in adipose tissue and the inhibition of synthesis of sex hormone–binding globulin, increased level of circulating and local free estradiol may stimulate residual neoplastic cells to grow (52). Another possible mechanism relates to insulin and insulin-like growth factors (IGF-I, IGF-II), which stimulate the synthesis of sex steroid hormones and increase cell proliferation and decrease apoptosis (53). Chronic hyperinsulinaemia decreases concentrations of IGF binding protein, which increases bioavailable or free IGF-I with concomitant changes in the

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cellular environment (mitogenesis and anti-apoptosis) that favor tumor formation (50). Fasting serum insulin concentration may be directly linked to an increase in both distant recurrence and death in women previously treated for breast cancer (14).

Our study has several strengths. First, this was a large, population-based survival study specifically designed to evaluate the effect of lifestyle factors (e.g., obesity) on breast cancer survival. This design, plus the high response rate, minimized selection bias. Second, detailed information on sociodemographic, anthropometric, clinical, and lifestyle factors were collected, which allowed a comprehensive evaluation of the effect of body size on breast cancer prognosis with proper adjustments for potential confounders and evaluation of effect modifiers. Third, anthropometric measurements were taken at study recruitment by trained interviewers who were retired medical professionals and information on weight at cancer diagnosis was collected through review of medical charts. Our study also has limitations. We used self-reported weight 1-year before cancer diagnosis and at diagnosis. However, self-reported weight at diagnosis was highly correlated with measured weight at diagnosis (correlation coefficient: 0.92), suggesting that self-reported weight information in our study is reliable. We observed a similar pattern when measured weight was analyzed. Also, the follow-up period was relatively short. Our ongoing follow-up with the cohort will allow an examination of the long-term effect of body size on breast cancer prognosis. Additional limitations include the possibility of residual confounding and the drop-outs from the study during the follow-up.

In conclusion, this large, population-based cohort study indicates that obesity prior to or at cancer diagnosis and substantial weight gain or weight loss after breast cancer diagnosis are independently and inversely associated with overall and disease-free survival rates among women with breast cancer. Given that cancer-related treatments and physical impairments make breast cancer survivors more prone to obesity, further research is warranted to develop effective strategies for weight control among breast cancer patients and survivors to improve their survival.

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Table 1

Sociodemographic and Medical Characteristics of Breast Cancer Cases, by Body Mass Index (BMI) at Study Enrollment

Characteristics	Total[a] (N=5042)	BMI category[a]				P value[b]
		<18.5 (N=149)	18.5–24.9 (N=3112)	25.0–29.9 (N=1498)	≥30.0 (N=283)	
Age at diagnosis (year)	53.5 (10.0)	49.7 (11.2)	52.2 (9.7)	55.5 (9.9)	58.6 (9.9)	<0.001
Age at menarche (year)	14.4 (1.6)	14.4 (1.6)	14.4 (1.6)	14.4 (1.7)	14.3 (1.7)	0.886
Time interval from diagnosis to study enrollment (month)	6.5 (0.7)	6.5 (0.8)	6.5 (0.7)	6.5 (0.7)	6.5 (0.8)	0.332
Waist-to-hip ratio	0.83 (0.05)	0.77 (0.05)	0.82 (0.05)	0.86 (0.05)	0.88 (0.05)	<0.001
Weight change: diagnosis to 6-month post-diagnosis	1.0 (3.6)	−1.5 (3.1)	0.8 (3.4)	1.5 (3.9)	1.6 (4.7)	<0.001
Education level (%)						
<High school	46.4	29.5	42.9	52.6	60.4	<0.001
High school	37.6	49.7	39.8	33.9	26.9	
>High school	16.0	20.8	17.3	13.5	12.7	
Household income (%)						
<1000 (yuan/month)	57.3	61.1	55.0	60.0	66.8	<0.001
1000–1999 (yuan/month)	30.7	28.2	31.5	30.6	24.4	
≥2000 (yuan/month)	12.0	10.7	13.5	9.4	8.8	
Marital status: married or living with partner (%)[c]	87.9	80.5	89.0	87.6	81.3	<0.001
Post-menopausal (%)[c]	51.1	38.9	46.1	58.8	72.1	<0.001
Menopausal symptoms (%)[c]	71.5	74.5	72.9	69.4	65.4	0.007
Charlson index of comorbidity ≥1 (%)[c]	20.0	18.1	17.0	24.4	29.7	<0.001
Family history of breast cancer (%)[c]	5.6	3.4	5.6	6.0	4.6	0.485
Meat intake (g/d)	82.8 (57.8)	71.2 (48.4)	82.1 (57.7)	85.2 (58.6)	83.1 (57.1)	0.027
Cruciferous vegetable intake (g/d)	74.5 (52.7)	64.2 (48.1)	73.3 (48.4)	77.7 (60.1)	76.2 (57.2)	0.005
Soy protein intake (g/d)	11.3 (8.6)	10.1 (10.5)	10.9 (8.0)	12.1 (9.3)	12.4 (9.1)	<0.001
Exercise participation (%)[c]	64.6	64.4	64.7	65.8	56.5	0.029
Tea consumption (%)[c]	23.8	22.2	22.9	25.4	26.2	0.215
Alcohol consumption (%)[c]	3.1	3.4	2.9	3.5	2.5	0.583
Cigarette smoking (%)[c]	2.6	3.4	2.3	3.0	4.2	0.142
Mastectomy (%)[c]	93.9	88.6	94.0	93.7	96.1	0.020

Characteristics	Total[a] (N=5042)	BMI category[a]				P value[b]
		<18.5 (N=149)	18.5–24.9 (N=3112)	25.0–29.9 (N=1498)	≥30.0 (N=283)	
Chemotherapy (%)[c]	91.2	89.9	92.1	89.9	87.6	0.011
Radiotherapy (%)[c]	32.1	36.2	32.2	32.5	26.9	0.182
Immunotherapy (%)[c]	14.7	20.8	15.1	14.2	9.5	0.012[d]
Tamoxifen use (%)[c]	52.0	47.7	52.8	50.5	53.4	0.356[d]
ER/PR status (%)						
Positive (ER+ PR+)	49.9	52.4	49.7	49.6	53.7	0.692[d]
Negative (ER− PR−)	27.6	26.2	28.2	26.8	26.5	
Mixed (ER+PR−/ER−PR+)	20.4	20.1	20.4	21.0	17.0	
Unknown	2.1	1.3	1.8	2.7	2.8	
TNM stage (%)						
0-I	36.4	42.3	37.7	35.3	25.4	<0.001[d]
IIA	32.6	33.6	32.6	32.2	35.0	
IIB	16.6	10.1	16.1	17.6	20.9	
III–IV	9.8	9.4	8.8	10.9	15.2	
Unknown	4.6	4.7	4.9	4.0	3.5	

[a]Unless specified, means (SDs) are presented.

[b]For tests of differences among women with different body mass index (BMI) status.

[c]Compared with women who had no corresponding characteristics.

[d]Unknown group was excluded from χ^2 test.

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Table 2

Associations of Body Mass Index and Waist-to-hip Ratio With Total and Relapse/disease-specific Mortality

	Total mortality				Relapse/disease-specific mortality			
	No. of subjects (n=5042)	No. of events (n=442)	Adjusted		No. of subjects (n=4989)	No. of events (n=481)	Adjusted	
			HR	95% CI			HR	95% CI
BMI 1-year before diagnosis[a]								
<18.5	180	18	1.44	0.88, 2.37	174	17	1.18	0.71, 1.96
18.5–24.9	3198	253		1.00	3176	281		1.00
25.0–29.9	1400	126	1.02	0.81, 1.27	1381	143	1.08	0.88, 1.34
≥30.0	264	45	1.58	1.13, 2.22	258	40	1.39	0.98, 1.97
BMI at diagnosis[a]								
<18.5	207	22	1.45	0.92, 2.28	203	21	1.21	0.76, 1.91
18.5–24.9	3238	258		1.00	3213	284		1.00
25.0–29.9	1341	118	0.99	0.79, 1.24	1323	135	1.06	0.86, 1.31
≥30.0	256	44	1.55	1.10, 2.17	250	41	1.44	1.02, 2.03
BMI at 6 months post-diagnosis[a]								
< 18.5	149	11	0.95	0.51, 1.74	148	13	1.01	0.57, 1.77
18.5–24.9	3112	255		1.00	3088	270		1.00
25.0–29.9	1498	136	0.97	0.78, 1.20	1473	151	1.06	0.87, 1.30
≥30.0	283	40	1.33	0.94, 1.87	280	47	1.49	1.08, 2.06
WHR (quartile)[b]								
<0.796	1261	98		1.00	1252	105		1.00
0.796–0.832	1261	83	0.78	0.58, 1.05	1253	105	0.96	0.72, 1.27
0.833–0.869	1248	109	0.97	0.73, 1.30	1234	120	1.00	0.76, 1.33
≥0.870	1272	152	1.22	0.91, 1.63	1250	151	1.17	0.88, 1.56
P value for trend			0.057				0.226	

Abbreviations: HR, hazard ratio; BMI, body mass index; WHR, waist-to-hip ratio.

[a]Adjusted for age at diagnosis, education, income, marital status, comorbidity, exercise participation, intake of meats, cruciferous vegetable, and soy protein, time interval from diagnosis to study enrollment, menopausal status, menopausal symptoms, surgery, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, tumor-node metastasis stage, and estrogen/progesterone receptor status.

[b]Further adjusted for BMI at 6 months post-diagnosis.

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Table 3

Associations of Weight Change From Pre-diagnosis to 6 and 18 Months Post-diagnosis With Total and Relapse/disease-specific Mortality

Weight change (kg)	Total mortality				Relapse/disease-specific mortality			
	No. of subjects	No. of event	HR	95% CI	No. of subjects	No. of event	HR	95% CI
Pre-diagnosis to 6 months post-diagnosis[a]								
	n=5042	n=442			n=4989	n=481		
<−1	1348	141	1.21	0.92, 1.60	1329	138	1.13	0.87, 1.48
−1 ~ 1	1196	88		1.00	1185	95		1.00
1 ~ 5	1684	141	1.14	0.87, 1.50	1670	152	1.10	0.85, 1.43
≥5	814	72	1.11	0.80, 1.53	805	96	1.31	0.97, 1.75
Pre-diagnosis to 18 months post-diagnosis[a]								
	n=4561	n=291			n=4422	n=251		
<−1	1030	93	2.41	1.62, 3.58	983	57	1.60	1.03, 2.48
−1 ~ 1	883	35		1.00	866	32		1.00
1 ~ 5	1552	94	1.89	1.27, 2.82	1513	90	1.97	1.30, 2.97
≥5	1096	69	1.71	1.12, 2.60	1060	72	1.90	1.23, 2.93
Diagnosis to 18 months post-diagnosis[b]								
	n=4561	n=291			n=4422	n=251		
<−1	907	85	2.16	1.48, 3.16	861	45	1.04	0.68, 1.58
−1 ~ 1	889	41		1.00	876	45		1.00
1 ~ 5	1669	92	1.35	0.93, 1.97	1628	92	1.21	0.84, 1.73
≥5	1096	73	1.54	1.03, 2.29	1057	69	1.30	0.88, 1.92

Abbreviations: HR, hazard ratio; 95% CI: 95% confidence interval.

[a]Adjusted for age at diagnosis, pre-diagnostic body mass index, education, income, marital status, comorbidity, exercise participation, intake of meats, cruciferous vegetable, and soy protein, time interval from diagnosis to study enrollment, menopausal status, menopausal symptoms, type of surgery, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, tumor-node metastasis stage, and estrogen/progesterone receptor status.

[b]Adjusted for similar variables as above, except that the variable ‘pre-diagnosis body mass index’ was changed to ‘body mass index at diagnosis’.

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Table 4

Associations of Body Mass Index at Diagnosis With Total and Relapse/disease-specific Mortality, Stratified by Tumor-node Metastasis Stage, Estrogen/progesterone Receptor Status, Comorbidity, and Exercise Participation at Baseline

	Total mortality				Relapse/disease-specific mortality			
	Total	No. of events	Adjusted		Total	No. of events	Adjusted	
			HR	95% CI			HR	95% CI
Stratified by TNM[a]								
TNM 0-II stage	n= 4318	n= 276			n=4302	n=317		
BMI at diagnosis								
<18.5	176	13	1.24	0.70, 2.21	176	15	1.12	0.65, 1.92
18.5–24.9	2786	163		1.00	2781	189		1.00
25.0–29.9	1147	75	0.98	0.74, 1.31	1137	85	1.04	0.80, 1.36
≥30.0	209	25	1.53	0.98, 2.39	208	28	1.67	1.09, 2.55
TNM III-IV stage	n=494	n=145			n=462	n=145		
BMI at diagnosis								
<18.5	22	6	1.42	0.58, 3.47	19	5	1.26	0.46, 3.42
18.5–24.9	289	84		1.00	271	83		1.00
25.0–29.9	146	38	0.93	0.61, 1.37	138	45	1.05	0.71, 1.55
≥30.0	37	17	1.99	1.08, 3.65	34	12	1.51	0.78, 2.94
P value for interaction		*0.913*				*0.913*		
Stratified by ER/PR[b]								
ER+PR+ (positive)	n=2518	n=141			n=2508	n=170		
BMI at diagnosis								
<18.5	101	6	1.28	0.55, 2.98	100	4	0.58	0.20, 1.65
18.5–24.9	1607	88		1.00	1604	106		1.00
25.0–29.9	670	36	0.83	0.55, 1.26	664	45	0.95	0.65, 1.38
≥30.0	140	11	0.95	0.49, 1.85	140	15	1.25	0.70, 2.22
ER-PR− (negative)	n=1393	n=185			n=1370	n=189		
BMI at diagnosis								
<18.5	63	11	1.81	0.93, 3.50	61	12	1.90	1.00, 3.61
18.5–24.9	907	102		1.00	894	106		1.00

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	Total mortality				Relapse/disease-specific mortality			
	Total	No. of events	Adjusted		Total	No. of events	Adjusted	
			HR	95% CI			HR	95% CI
25.0–29.9	352	50	1.22	0.85, 1.74	345	49	1.11	0.77, 1.58
≥30.0	71	22	2.26	1.37, 3.75	70	22	2.03	1.22, 3.37
ER+PR−/ER−PR+ (Mixed)	n=1026	n=89			n=1015	n=107		
BMI at diagnosis								
<18.5	39	3	1.32	0.38, 4.56	39	4	1.31	0.44, 3.93
18.5–24.9	665	56		1.00	660	64		1.00
25.0–29.9	287	26	0.86	0.52, 1.42	282	35	1.04	0.66, 1.62
≥30.0	35	4	0.73	0.24, 2.23	34	4	0.85	0.28, 2.57
P value for interaction		*0.351*				*0.279*		
Stratified by comorbidity[c]								
Comorbidity index=0	n=4036	n=337			n=3997	n=388		
BMI at diagnosis								
<18.5	179	17	1.19	0.71, 1.98	176	17	1.02	0.61, 1.69
18.5–24.9	2716	212		1.00	2698	245		1.00
25.0–29.9	981	85	0.91	0.70, 1.19	966	102	1.01	0.79, 1.29
≥30.0	160	23	1.28	0.81, 2.01	157	24	1.25	0.80, 1.94
Comorbidity index=1	n=1006	n=105			n=992	n=92		
BMI at diagnosis								
<18.5	28	5	5.84	2.11, 16.1	515	39	4.86	1.62, 14.6
18.5–24.9	522	46		1.00	27	4		1.00
25.0–29.9	360	33	1.20	0.75, 1.93	357	33	1.28	0.79, 2.09
≥30.0	96	21	1.95	1.10, 3.48	93	17	2.26	1.21, 4.25
P value for interaction		*0.146*				*0.122*		
Stratified by exercise[d]								
Exercise participation	n=3255	n=248			n=3235	n=285		
BMI at diagnosis								
<18.5	133	15	1.82	1.05, 3.16	132	14	1.42	0.81, 2.49
18.5–24.9	2105	147		1.00	2095	174		1.00

	Total mortality				Relapse/disease-specific mortality			
	Total	No. of events	Adjusted		Total	No. of events	Adjusted	
			HR	95% CI			HR	95% CI
25.0–29.9	882	71	1.01	0.75, 1.35	874	82	1.01	0.76, 1.32
≥30.0	135	15	1.13	0.64, 1.98	134	15	0.99	0.57, 1.73
No exercise participation	n=1787	n=194			n=1754	n=196		
BMI at diagnosis								
<18.5	74	7	1.16	0.52, 2.59	71	7	0.93	0.41, 2.10
18.5–24.9	1133	111		1.00	1118	110		1.00
25.0–29.9	459	47	0.94	0.66, 1.35	449	53	1.12	0.79, 1.58
≥30.0	121	29	1.86	1.19, 2.89	116	26	1.91	1.20, 3.04
P value for interaction		*0.200*				*0.293*		

Abbreviations: TNM, tumor-node metastasis; BMI: body mass index; ER/PR, estrogen/progesterone receptor; HR, hazard ratio; 95% CI: 95% confidence interval.

[a]Adjusted for age at diagnosis, education, income, marital status, comorbidity, exercise participation, intake of meats, cruciferous vegetable, and soy protein, time interval from diagnosis to study enrollment, menopausal status, menopausal symptoms, type of surgery, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, TNM stage, and ER/PR status.

[b]Adjusted for similar variables as in model ‘a’, except that the variable ‘ER/PR status’ was changed to ‘TNM stage’.

[c]Adjusted for similar variables as in model ‘a’, except that the variable ‘comorbidity’ was change to ‘TNM stage’.

[d]Adjusted for similar variables as in model ‘a’, except that the variable ‘exercise’ was change to ‘TNM stage’.

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Table 5

Associations of Weight Change from Diagnosis to 18 months Post-diagnosis With Total Mortality and Relapse/disease-specific Mortality, Stratified by Pre-diagnostic Body Mass Index[a]

	Total mortality				Relapse/disease-specific mortality			
	Total	No. of events	Adjusted		Total	No. of events	Adjusted	
			HR	95% CI			HR	95% CI
Pre-diagnostic BMI<25	n=3036	n=175			n=2953	n=151		
Weight change (Kg)								
<−1	434	41	2.69	1.60, 4.52	411	19	1.13	0.61, 2.08
−1 ~ 1	553	23		1.00	547	24		1.00
1 ~ 5	1179	54	1.18	0.72, 1.96	1156	58	1.19	0.73, 1.95
≥5	870	57	1.65	1.00, 2.73	839	50	1.37	0.82, 2.28
Pre-diagnostic BMI≥25	n=1525	n=116			n=1469	n=100		
Weight change (Kg)								
<−1	473	44	2.00	1.13, 3.53	450	26	1.02	0.56, 1.86
−1 ~ 1	336	18		1.00	329	21		1.00
1 ~ 5	490	38	1.69	0.95, 3.01	472	34	1.24	0.71, 2.19
≥5	226	16	1.51	0.74, 3.05	218	19	1.33	0.69, 2.58
P value for interaction		*0.182*				*0.952*		

Abbreviations: BMI, body mass index; HR, hazard ratio; 95% CI: 95% confidence interval.

[a]Adjusted for age at diagnosis, education, income, marital status, comorbidity, exercise participation, intake of meats, cruciferous vegetable, and soy protein, time interval from diagnosis to study enrollment, menopausal status, menopausal symptoms, type of surgery, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, tumor-node metastasis stage, and estrogen/progesterone receptor status.