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Body mass index and weight change in relation to triple-negative breast cancer survival

Ping-Ping Bao[1], **Hui Cai**[2], **Peng Peng**[3], **Kai Gu**[4], **Yinghao Su**[5], **Wei Lu**[6], **Xiao-Ou Shu**[7], and **Ying Zheng**[8,*]

[1]Shanghai Municipal Center for Disease Control & Prevention, No. 1380 Zhong Shan Road (W), Shanghai 200336, China

[2]Division of Epidemiology, Department of Medicine and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Vanderbilt University, Nashville, Tennessee 37203, USA

[3]Shanghai Municipal Center for Disease Control & Prevention, No. 1380 Zhong Shan Road (W), Shanghai 200336, China

[4]Shanghai Municipal Center for Disease Control & Prevention, No. 1380 Zhong Shan Road (W), Shanghai 200336, China

[5]Division of Epidemiology, Department of Medicine and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Vanderbilt University, Nashville, Tennessee 37203, USA

[6]Shanghai Municipal Center for Disease Control & Prevention, No. 1380 Zhong Shan Road (W), Shanghai 200336, China

[7]Division of Epidemiology, Department of Medicine and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Vanderbilt University, Nashville, Tennessee 37203, USA

[8]Shanghai Municipal Center for Disease Control & Prevention, No. 1380 Zhong Shan Road (W), Shanghai 200336, China

Abstract

Background—To evaluate the influence of body mass index (BMI), weight change on triple-negative breast cancer (TNBC) prognosis in a population-based prospective cohort study.

Material and Methods—The current analysis included 518 participants diagnosed with TNBC in Shanghai Breast Cancer Survival Study. Weight at 1-year prior to cancer diagnosis, at diagnosis and at 6-, 18- and 36-month after cancer diagnosis and height at 6-month after cancer diagnosis were assessed. Disease-free survival (DFS) and overall survival (OS) were evaluated in relation to BMI and weight change using Cox proportional hazard models.

Results—Mean weight change from pre-diagnosis to 18-month and 36-month post-diagnosis was 1.5 kg (SD: 4.6) and 1.5 kg (SD: 4.8), respectively. Obesity at 1-year pre-diagnosis was associated with higher risk of total mortality and recurrence/disease-specific mortality, with HRs of 1.79

*Correspondence to: Ying Zheng, Shanghai Municipal Center for Disease Control &Prevention, No.1380 Zhongshan Road(W), Shanghai 200336, China. Phone: +86-021-62758710; zhengying@scdc.sh.cn.

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(95% CI 1.06-3.03) and 1.83 (95% CI 1.05-3.21), respectively. Compared with stable weight, weight loss ≥ 5% at 18- or 36-month post-diagnosis was associated with higher risk of total mortality and recurrence/disease-specific mortality. Respective HRs were 2.08 (95% CI 1.25-3.46) and 1.42 (95% CI 0.77-2.63) for OS, and 2.50 (95% CI 1.45-4.30) and 2.17 (95% CI 1.14-4.12) for DFS. Weight gain ≥ 5% at 18- or 36-month post-diagnosis was associated with a non-significant increased risk of death.

Conclusions—The results suggested stable weight was associated with a favorable prognosis of TNBC. Emphasis on maintaining stable weight after cancer diagnosis for TNBC patients should be considered.

Keywords

triple-negative breast cancer; body-mass index; weight change; survival outcomes; prognosis

Introduction

Studies have suggested that obesity at the time of cancer diagnosis or pre-diagnosis was associated with poor prognosis for breast cancer all types combined [1-6]. Triple-negative breast cancers (TNBCs), namely negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2), accounts for 10-20% of breast cancers and it is characterized by aggressive clinical behavior and lack of effective targeted therapies and worse prognosis [7]. Limited research has evaluated the association of obesity at diagnosis or pre-diagnosis on TNBC prognosis and findings are mixed [8-14].

Weight gain is a common and persistent problem in breast cancer patients, especially those who are younger, closer to ideal body weight and who have been treated with chemotherapy [15]. Several studies [16-18] have demonstrated that weight gain post-diagnosis increases the risk of all-cause mortality and recurrence, including a report from our study [19]; whereas other studies found no relation [20-22]. The majority of previous studies have suggested that weight loss is associated with poorer breast cancer outcomes [16-20, 22]. To our knowledge, no studies have examined whether changes in weight after cancer diagnosis influence outcomes of TNBC. Given the limited treatment options and the little information on prognostic factors of TNBC, the prognostic effects of weight change may be of particular relevance for its outcome and the clarification may provide a chance to improve the survival rate through weight control.

In an effort to address this gap, we conducted a comprehensively study to elucidate the relationship between BMI, weight change post-diagnosis, and TNBC prognosis, using data from a population-based prospective cohort study Shanghai Breast Cancer Survival Study (SBCSS).

Material and Methods

Study participants were women who were diagnosed with a primary breast cancer and enrolled in SBCSS, a population-based cohort study in Shanghai, China. Details of the study design and method have been reported elsewhere [23-24]. Briefly, through the population-

based Shanghai Cancer Registry, 6,299 eligible cases were identified approximately 6 months after cancer diagnosis, and 5,042 were enrolled (participation rate, 80.0%) and completed baseline interviews between March 2002 and April 2006. Of these participants, 532 patients were TNBC based on information abstracted from the medical chart and the test done in the Vanderbilt Molecular Epidemiology Lab [25]. For this analysis, we excluded patients with non-invasive breast cancer (TNM stage 0, n=13) and stage IV breast cancer (n=1). The final cohort consisted of 518 patients.

In-person interviews by trained interviewers who were mostly retired medical professionals were performed approximately 6 months by using a standardized questionnaire. The baseline survey covered demographic characteristics, cancer diagnosis and treatment, reproductive history, exercise participation, dietary intake, tea consumption, cigarette smoking, use of complementary and alternative medicine, cancer therapies, and quality of life. Medical record charts were reviewed to verify clinical information and treatment. All participants were asked to report whether they participated in regular exercise between cancer diagnosis and the date of their interview. A Charlson comorbidity index was created for each woman based on a validated comorbidity scoring system [26], and the diagnostic codes were obtained from the International Classification of Disease, Ninth Revision, Clinical Modification [27]. Anthropometric measurements (height, weight, waist and hip circumference) were measured by trained interviewersaccording to a standard protocol at the baseline survey (approximately 6 months after cancer diagnosis) and the details have been described previously [19]. In short, weight was measured to the nearest 0.1 kg using a digital weight scale. Height and circumferences were measured at 2.5 cm above the umbilicus and hip cirsumference at the level of maximum width of the buttocks with subject in a standing position. Participants were also asked to report their pre-diagnosis weight around 1 year before dagnosis and weight at diagnosis.

The cohort has been being followed up by in-person interviews at 18 months, 36 months, 60 months, and 120 months after cancer diagnosis to update exposure information including weight and collect data on disease progression and survival status. The follow-up rate for the 18-, 36-, and 60-month post-diagnosis interview was 91%, 84%, and 77%, respectively. The 120-month interview is ongoing, with 2393 cases having completed the interview to date. Information on survival status was also collected and ascertained by periodical linkage with the Shanghai Vital Statistics database.

Weight at approximated 18 months, 36 months and 60 months after diagnosis was measured by trained interviewers using the same standard protocol. For subjects with missing data at a specific survey, we substituted the information with the mean values assessed at adjacent surveys. BWI was calculated by dividing weight by height squared (kg/m^2).

Change in weight from pre- to post-diagnosis was calculated by subtracting the weight measurements took at one year pre-diagnosis from that took at post-diagnosis surveys. The relative percent of weight changes between pre-diagnosis and each follow-up survey post-diagnosis was evaluated [(weight at follow-up – weight pre-diagnosis) / weight pre-diagnosis×100]. This current study was focused on the weight change between 1-year pre-diagnosis and 18- or 36-month post-diagnosis to allow sufficient time for patients to recover

from the treatment related immediate weight change. A positive and negative value was indicative of weight gain and loss, respectively.

The SBCSS was approved by the institutional review boards of all institutions involved in this study and the participants provided written informed consent prior to interview.

Statistical analysis

BMI was categorized according to Chinese standard: underweight, < 18.5 kg/m^2; normal weight, 18.5 - 23.9 kg/m^2; overweight, 24.0 - 27. 9kg/m^2; and obese ≥ 28.0 kg/m^2. A weight change of < 5% of the pre-diagnosis weight was considered as weight stable (reference); weight gain and loss were defined as a ≥ 5 % change.

The means and standard deviations for the socio-demographic and clinical characteristics were calculated. Differences in these characteristics across baseline BMI categories were evaluated using analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. The endpoints for the analysis were any death for overall survival overall (OS) and cancer recurrence/metastasis or death related to breast cancer for disease-free survival (DFS). Survival status was censored at the date of last in-person contact or December 31, 2013 (the most recent for linkage to the Vital Statistics database). For disease-free analysis, censoring occurred at date of last in-person contact or date of death for non-breast cancer death. Multivariable Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) in association with BMI and weight change using age as time scale [28]. Entry time was defined as age at diagnosis and exit time was defined as age at the event or censoring. The following covariates were adjusted for in the multivariate models: age at diagnosis, education level, menopausal status, Charlson comorbidity index, exercise participation, TNM stage, type of surgery received, chemotherapy, and radiotherapy. Stratified analyses were conducted to explore whether the associations of pre-diagnostic obesity or weight change post-diagnosis were modified by TNM stage, menopausal status, comorbidity, exercise participation, or pre-diagnostic obesity.

Tests for trend were performed by entering the category variable as continuous parameters in the models. Multiplicative interactions were tested for using -2 log likelihood ratio test statistics, which compared models with and without the interaction terms. All analyses were performed using SAS version 9.3. Tests of statistical significance were based on two-sided probability and p-values < 0.05 were considered statistically significant.

Results

During the median follow-up of 9.1 years (range: 0.6 - 11.8 years) after cancer diagnosis, 128 deaths and 112 recurrences or breast cancer deaths were documented among 518 TNBC patients. The mean age at cancer diagnosis was 53.4 years (standard deviation, SD: 10.6). Overall, 30.9% of women were overweight (BMI: 24.0 - 27.9 kg/m^2) and 12.0% were obese (BMI ≥ 28.0 kg/m^2) at 1-year prior to cancer diagnosis. The corresponding prevalence rates of overweight and obesity were 29.3% and 11.0% at diagnosis, 35.3% and 12.6% at 6-month post-diagnosis, and 39.0% and 14.4% at 18-month post-diagnosis, respectively. The mean

weight at 1-year pre-diagnosis, diagnosis, 6-month post-diagnosis, 18-month post-diagnosis, 36-month post-diagnosis, and 60-monthpost-diagnosis was 59.2 kg (SD: 9.4), 58.8 kg (SD: 9.3), 60.0 kg (SD: 9.2), 60.7 kg (SD: 9.4), 60.3 kg (SD: 9.2), and 60.1 kg (SD: 9.5), respectively. The mean weight changes and SDs from pre-diagnosis to 6-, 18-, and 36-month post-diagnosis were 0.8 ± 4.0 kg (median: 1.0 kg), 1.5 ± 4.6 kg (median: 1.0 kg), and 1.5 ± 4.8 kg (median: 1.0 kg), respectively.

Table 1 shows the distribution of patient characteristics by baseline BMI. Obese patients tended to be older, postmenopausal, and to have higher WHR. There was no significant difference among BMI groups with regards to time interval from diagnosis to study enrollment, level of education, marriage status, Charlson comorbidity index, tea consumption, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, or tumor stage.

BMI pre-diagnosis and TNBC prognosis

Table 2 displays associations of BMI and WHR with mortality after adjustment for potential confounders. Women who were obese (BMI ≥ 28.0 kg/m^2) at 1-year pre-diagnosis had higher mortality than normal weight women. The adjusted HRs were 1.79 (95% CI 1.06-3.03) for total mortality and 1.83 (95% CI 1.05-3.21) for recurrence/disease-specific mortality. No such association was found for women who were obese at diagnosis or 6-month post-diagnosis. WHR at diagnosis was not significantly associated with mortality, with and without adjustment for BMI at 6-month post-diagnosis.

Further stratified analyses showed that the association of obesity at pre-diagnosis and mortality did not varied by TNM stage, menopausal status, comorbidity, or exercise participation (data not shown).

Weight change post-diagnosis and TNBC prognosis

Table 3 and Table 4 present associations of weigh change at 18- and 36-month post-diagnosis with total mortality and recurrence/disease-specific mortality of TNBC, respectively. Compared with women who maintain the weight (change within 5%), those who lost weight from pre-diagnosis to 18-month post-diagnosis (≥ 5%) had HRs of 2.08 (95% CI 1.25-3.46) for total mortality and 2.50 (95% CI 1.45-4.30) for recurrence/disease-specific mortality. Similarly, weight loss at 36-month post-diagnosis was associated with TNBC survival with HRs of 1.42 (95% CI 0.77-2.63) for OS and 2.17 (95% CI 1.14-4.12) for DFS. Weight gain ≥ 5% at 18-month or at 36-month post-diagnosis was not significantly related to OS or DFS.

We further investigated if the associations of weight change with mortality were modified by pre-diagnostic BMI, menopausal status, TNM stage, comorbidities, and exercise participation. The associations of weight change with mortality appeared to be pronounced among women who were premenopausal, or women with higher BMI, although the tests for multiplicative interaction were not significant. The prognostic effect of weight change was not modified by exercise participation, TNM stage, and comorbidities (data not shown).

In sensitivity analysis, all models were run excluding the 8 women who died within the first year of diagnosis, and results were not substantially altered (data not shown).

Discussion

In this population-based prospective cohort study of women diagnosed with TNBC, we found that obesity prior to diagnosis was associated with worse outcomes. We also found that maintaining stable weight post-diagnosis was related to favorable prognosis.

Evidence from observational studies has consistently shown that obesity at the time of cancer diagnosis is associated with a poorer survival for all types of breast cancer combined [1-6]. Chan et al. conducted a systemic review that included 82 follow-up breast cancer studies showed that compared with normal weight women before diagnosis, the summary relative risks of total mortality were 1.41 (95% CI 1.29-1.53 for obese, 1.07 (95% CI 1.02-1.12) for overweight and 1.10 (95% CI 0.92-1.31) for underweight women [6].

The limited studies that evaluated influence of BMI on TNBC survival have yielded mixed findings [8-12]. The largest retrospective study published so far, including 2311 women with stage I-III TNBC tumors, found no difference in DFS or OS across BMI groups at diagnosis [12]. Similar null association between BMI at cancer diagnosis with TNBC survival was also observed in two retrospective studies of TNBC patients [8, 11]. However, a retrospective study including 5,683 operable BC patients enrolled in four randomized clinical trials [13] indicated that the magnitude of the negative effect of severe obesity at diagnosis on survival outcomes was similar across the three BC subtypes (ER/PR-positive/HER2-negative, HER2- positive, triple-negative). In our study, we found that obesity pre-diagnosis was related to a significant association with TNBC mortality and other subtypes. This association appeared to be stronger among women who were premenopausal, consistent with Turkoz's report [14], which indicated obesity at diagnosis was associated with worse prognosis among premenopausal TNBC patients. The difference in the study design, the characteristics of study populations, or time of BMI assessment may be partly contributed to the discrepancy. BMI taken at diagnosis and shortly after diagnosis may be affected by cancer and associated treatment. Differences in effect may be also attributed to comorbid conditions that are associated both with obesity and with poorer prognosis.

The association of weight gain with higher mortality risk of breast cancer has been reported previously [16-18], including the SBCSS study [19], although the evidence is not entirely consistent [20-22]. Weight loss has also been associated with worse prognosis [16-20, 22]. We have previously reported in a pooling project [20] that weight loss ≥ 10% was related to a 40% increased risk of death (HR, 1.41; 95% CI 1.14-1.75) among American women with breast cancer and over three times the risk of death (HR, 3.25; 95% CI 2.24-4.73) in Chinese women with breast cancer. To our knowledge, no study has specifically evaluated the association of change in weight with TNBC outcomes. We found that weight maintenance in the first few years after diagnosis was associated a favorable outcome and weight loss was associated with higher risk of morality, especially among premenopausal women.

Several potential biological mechanisms have been proposed to explain the relationship between obesity and breast cancer prognosis, including changes in glucose metabolism, high circulating levels of estrogen, increased insulin and insulin-like growth factors and inflammatory factors [5, 29-30], as well as its influence on other medical conditions such as

diabetes and heart disease [15]. Another possibility is that compared with normal weight patients, obese patients are more likely to be undertreated, which may contribute to the poorer survival [33]. We found a similar association pattern for all breast cancer and TNBC and there was no significant difference in the prognostic role of obesity by subtype detected. It has been suggested that hyperinsulinemia correlated with BMI, recurrence, and breast cancer mortality, regardless of hormone receptor status [31]. A meta-analysis in 2012 also found no evidence of the prognostic role of obesity varying by ER/PR status [32]. Much remains to be learned about the role of obesity and weight gain in survival after the diagnosis of TNBC and more studies is needed to clarify the association. Regardless, our finding that the influence of weight gain was predominantly seen for premenopausal breast cancer patients, if confirmed, would help to identify higher risk TNBC patients for proper intervention.

For our observed risk of higher mortality among TNBC survivors who lose weight, one of potential explanation is that it may be an early marker of caner cachexia or pre-cachexia, which results in not only weight loss but substantial loss of lean body mass [20, 34]. It is hypothesized that exaggerated loss of lean body mass in cancer survivors may be related to chronic inflammation, insulin resistance, and decreases in physical activity [34]. In addition, weight loss may be an early marker of comorbid overweight women, which appeared to be at risk for weight loss, and the comorbidity may also be related to receiving less chemotherapy, experiencing more toxicity of treatment, and thus higher risk of mortality [20, 35]. Unfortunately, we were unavailable to carry out more in depth stratified analyses such as by comorbidity and treatment cycle due to the limited sample size or lack of variability. We were further hampered because no information was collected on whether weight loss was intentional. Our findings that weight loss may be an important prognostic value for TNBC survivors raised a question about the safety of intentional weight loss in the first few years post-diagnosis among TNBC survivors, particularly among populations such as Chinese women who had relatively low prevalence of obesity. More studies are needed to evaluated the prognostic effect of weight loss among TNBC patients and clarify the related biologic mechanisms.

It should be noted that our study has some limitations. First, although we had collected weight information at each follow-up survey, we had limited power to comprehensively estimate the influence of long-term weight change on TNBC survival. Further researches with extended follow-up period and larger sample size are warranted to examine the influence of weight change during longer period post-diagnosis in TNBC prognosis. Second, the findings were from Chinese population and this raises a concern whether the finding of our study can be directly extrapolated to other populations. Additionally, the study did not have sufficient power to evaluate interactions.

In summary, this population-based prospective cohort study found that obesity at 1-year pre-diagnosis was associated with worse outcomes. Weight loss during first 3 years post-diagnosis was related to a poor prognosis. These patients may require closer surveillance and proper intervention to maintain stable weight.

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Table 1

Socio-demographic and medical characteristics of TNBC by BMI at study enrollment

Characteristics	Total [a]	BMI category				*P* value [b]
		<18.5(n=17)	18.5-23.9(n=253)	24.0-27.9(n=183)	≥28.0(n=65)	
Age at diagnosis(year)	53.37(10.59)	48.74(11.77)	52.08(10.45)	53.92(10.23)	58.05(10.36)	<0.01
Time interval from diagnosis to study enrollment (month)	6.51(0.71)	6.43(0.43)	6.48(0.73)	6.53(0.72)	6.54(0.68)	0.84
Waist-to-hip ratio	0.83(0.05)	0.77(0.05)	0.82(0.05)	0.85(0.05)	0.86(0.05)	<0.01
Education level (%)						
<high school	48.65	23.53	48.22	47.54	60.00	
High School	36.68	58.52	37.15	38.80	23.08	
≥ high school	14.67	17.65	14.62	13.66	16.92	0.11
Married (%)[c]	88.03	76.47	90.51	86.89	84.52	0.20
Post-menopausal (%)[c]	53.09	35.29	48.22	54.64	72.31	<0.01
Charlson comorbidity index≥1(%)[c]	21.04	5.88	19.76	23.60	23.08	0.33
Exercise participation (%)[c]	66.80	64.71	68.77	62.84	70.77	0.52
Tea consumption (%)[c]	21.62	17.65	19.37	20.77	33.85	0.08
Mastectomy (%)[c]	95.56	94.12	95.65	95.63	95.38	0.92
Chemotherapy(%)[c]	94.40	94.12	95.44	92.35	92.31	0.18
Radiotherapy(%)[c]	27.41	29.41	26.88	28.42	26.15	0.98
Immunotherapy(%)[c]	17.76	29.41	18.97	29.41	17.58	0.26[d]
Tamoxifen use(%)[c]	21.62	23.53	21.74	21.31	21.54	0.99
Stage						
I	30.89	41.18	30.43	29.51	33.85	
II	55.60	47.06	54.55	58.47	53.85	
III	10.23	5.88	11.86	8.74	9.23	
unknown	3.28	5.88	3.16	3.28	3.08	0.95[d]

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

[b] The p values were obtained using the χ^2 test and Fisher's exact test

[c] Compared with women who had no corresponding characteristic

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

Table 2

Association of BMI and WHR with total mortality and recurrence/disease-specific mortality among TNBC

	Total mortality			Recurrence/disease-specific mortality		
	Total	**No. of Event**	**HR (95%CI)[a]**	**Total**	**No. of Event**	**HR (95%CI)[a]**
BMI at 1 year before diagnosis						
< 18.5	25	6	1.15(0.47,2.8)	25	5	1.26(0.48,3.27)
18.5-23.9	271	56	1.00	271	52	1.00
24.0-27.9	160	44	1.20(0.79,1.82)	160	35	1.23(0.78,1.94)
≥ 28.0	62	22	1.79(1.06,3.03)	62	20	1.83(1.05,3.21)
BMI at diagnosis						
<18.5	30	8	1.16(0.54,2.50)	30	7	1.28(0.57,2.89)
18.5-23.9	279	60	1.00	279	53	1.00
24.0-27.9	152	43	1.19(0.79,1.81)	152	36	1.38(0.88,2.17)
≥ 28.0	57	17	1.36(0.78,2.40)	57	16	1.53(0.84,2.77)
BMI at 6 months after diagnosis (baseline)						
<18.5	17	3	0.80(0.25,2.61)	17	2	0.53(0.13,2.22)
18.5-23.9	253	56	1.00	253	50	1.00
24.0-27.9	183	49	1.21(0.81,1.80)	183	42	1.15(0.75,1.77)
≥ 28.0	65	20	1.36(0.80,2.30)	65	18	1.40(0.80,2.45)
WHR at diagnosis						
<0.80	130	33	1.00	130	27	1.00
0.80-	115	23	0.71(0.41,1.25)	115	23	0.92(0.51,1.65)
0.83-	134	28	0.66(0.39,1.13)	134	23	0.67(0.37,1.22)
≥0.87	139	44	0.93(0.56,1.54)	139	39	1.11(0.64,1.91)
P for trend			0.89			0.83

[a]Adjusted for age at diagnosis (continuous variable), education (<high school, high school, >high school), Charlson comorbidity index (0, ≥ 1), menopausal status at baseline (yes, no),exercise participation at baseline (yes, no), type of surgery received, chemotherapy (yes, no), radiotherapy (yes, no), and TNM stage (I, II, III, unknown)

Table 3

Associations of weight change from pre-diagnosis to 18-month post-diagnosis with TNBC survival, stratified by pre-diagnostic BMI and menopausal status

	Weight change from pre-diagnosis to post-diagnosis [a]						
	Stable within 5%		Gain (≥ 5 %)		Loss (≥ 5 %)		*P* for interaction
	Total/Event	HR	Total/Event	HR (95% CI)	Total/Event	HR (95% CI)	
Total mortality							
Total	247/45	1.00	184/38	1.26(0.80,2.00)	42/27	2.08(1.25,3.46)	
Stratified by pre-diagnostic BMI							
<24.0	121/19	1.00	142/25	1.13(0.60,2.13)	27/12	1.73(0.74,4.04)	
≥24.0	125/25	1.00	42/13	1.88(0.92,3.85)	42/15	2.15(1.09,4.26)	0.48
Stratified by menopausal status at baseline							
Premenopausal	99/8	1.00	118/24	2.84(1.23,6.58)	20/7	6.22(2.13,8.13)	
Postmenopausal	148/37	1.00	66/14	0.95(0.50,1.80)	49/20	1.64(0.91,2.98)	0.46
Recurrence/disease-specific mortality							
Total	247/37	1.00	184/35	1.32(0.81,2.15)	69/25	2.50(1.45,4.30)	
Stratified by pre-diagnostic BMI [a]							
<24.0	121/17	1.00	142/25	1.30(0.67,2.50)	27/10	1.80(0.72,4.52)	
≥24.0	125/20	1.00	42/10	1.91(0.85,4.31)	42/15	2.65(1.28,5.46)	0.86
Stratified by menopausal status at baseline							
Premenopausal	99/9	1.00	118/23	2.38(1.08,5.25)	20/8	7.26(2.62,20.11)	
Postmenopausal	148/28	1.00	65/12	1.01(0.50,2.05)	49/17	1.92(0.98,3.79)	0.59

[a]HRs from Cox regression models and adjusted for age at diagnosis (continuous variable), education (<high school, high school, >high school), Charlson comorbidity index (0, ≥ 1), menopausal status at baseline (yes, no), exercise participation at baseline (yes, no), type of surgery received, chemotherapy (yes, no), radiotherapy (yes, no), and TNM stage (I, II, III, unknown)

Table 4

Associations of weight change from pre-diagnosis to 36-month post-diagnosis with TNBC survival, stratified by pre-diagnostic BMI and menopausal status

	Weight change from pre-diagnosis to post-diagnosis [a]						
	Stable within 5%		Gain (≥ 5 %)		Loss (≥ 5 %)		*P* for interaction
	Total/Event	HR	Total/Event	HR (95% CI)	Total/Event	HR (95% CI)	
Total mortality							
Total	221/32	1.00	170/26	1.28(0.73,2.22)	74/17	1.42(0.77,2.63)	
Stratified by pre-diagnostic BMI [a]							
<24.0	119/17	1.00	128/17	0.89(0.42,1.90)	26/5	0.77(0.26,2.28)	
≥24.0	102/15	1.00	42/9	1.76(0.72,4.30)	48/12	1.86(0.81,4.26)	0.85
Stratified by menopausal status at baseline							
Premenopausal	91/6	1.00	109/15	2.00(0.75,5.36)	22/3	1.27(0.27,5.90)	
Postmenopausal	130/26	1.00	61/11	1.08(0.52,2.28)	52/14	1.39(0.70,2.77)	0.32
Recurrence/disease-specific mortality							
Total	221/24	1.00	170/26	1.40(0.77,2.55)	74/18	2.17(1.14,4.12)	
Stratified by pre-diagnostic BMI							
<24.0	119/13	1.00	128/19	1.29(0.58,2.87)	26/6	1.35(0.46,3.98)	
≥24.0	102/11	1.00	42/7	1.50(0.54,4.20)	48/12	2.49(0.99,6.23)	0.65
Stratified by menopausal status at baseline							
Premenopausal	91/7	1.00	109/15	1.45(0.57,3.71)	22/5	2.23(0.62,8.03)	
Postmenopausal	130/17	1.00	61/11	1.39(0.61,3.16)	52/13	2.03(0.94,4.38)	0.75

[a]HRs from Cox regression models and adjusted for age at diagnosis (continuous variable), education (<high school, high school, >high school), Charlson comorbidity index (0, ≥ 1), menopausal status at baseline (yes, no), exercise participation at baseline (yes, no), type of surgery received, chemotherapy (yes, no), radiotherapy (yes, no), and TNM stage (I, II, III, unknown)