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Pre- to post-diagnosis weight change and associations with physical functional limitations in breast cancer survivors

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Abstract
Purpose We investigated pre- to post-diagnosis weight change and functional limitations in a cohort of breast cancer survivors.
Methods A cohort of 1,841 early-stage breast cancer survivors provided information on pre- and post-diagnosis weight and physical function on average 2 years post-diagnosis. The mean number of limitations for each BMI category and each weight change category were compared using the Wilcoxon test. Cross-sectional associations between weight change, from 1 year prior to diagnosis to 2 years post-diagnosis, and functional limitations were determined using logistic regression.
Results Women with BMI≥30 kg/m^2 had significantly higher physical limitations compared to women with BMI<25 kg/m^2 (2.06 vs 0.96 for moderate/severe limitations, 3.92 vs 3.27 for mild limitations, 1.31 vs 0.47 for lower body limitations, and 0.76 vs 0.49 for all other limitations; $P<0.0001$). Women who reported a large weight gain (≥10 % of pre-diagnosis weight) were more likely to report any limitation (OR=1.79; 95 % confidence interval (CI)=1.23–2.61), a moderate/severe limitation (OR=2.30; 95 % CI=1.75–3.02), and a lower body limitation (OR=2.05; 95 % CI=1.53–2.76) compared to women who maintained weight within 5 % of pre-diagnosis weight. However, associations between weight loss and functional limitations depended on pre-diagnosis BMI and comorbidity status. Among women without comorbidity, large weight loss (≥10 % of pre-diagnosis weight) in normal-weight women was associated with higher risk of functional limitations, whereas among overweight/obese women, large weight loss appeared to be associated with a lower risk of limitations. Among women with comorbidity, moderate weight loss in overweight/obese women was associated with a higher risk of a moderate/severe physical limitation.
Conclusions Large weight gain was associated with a higher risk of physical functional limitations, but associations between weight loss and functional limitations may depend on initial BMI and comorbidity status.
Implications for Cancer Survivors In this study we found that both weight loss and weight gain among breast cancer survivors were associated with a higher risk of physical functional limitations. Weight maintenance, therefore, may be an important factor in preventing and/or reducing the risk of functional decline in breast cancer survivors.

Keywords Breast cancer · Functional limitations · Weight change · Functional status

Introduction/background

With the exception of non-melanoma skin cancer, breast cancer is the most common cancer among women in the USA. Approximately 12 % of American women will develop invasive breast cancer [1]. Fortunately, due to improvements in treatment and early detection, survival rates for women diagnosed with breast cancer have continued to increase since 1990 [2]. As a result of increased survival rates, focus in the medical community has shifted towards improving quality of life and overall health among survivors.

One factor that has been proven to negatively affect both quality of life and overall health among breast cancer survivors is poor functional status. In 2010, Braithwaite et al. found that breast cancer survivors who reported one or more functional limitations at baseline had a significantly higher risk of death from all causes than those reporting no functional limitations [3]. Functional status is measured here as an individual's physical function and is defined by the National Palliative Care Research Center as "an individual's ability to perform normal daily activities required to meet basic needs, fulfill usual roles, and maintain health and well-being" [4]. Functional limitations

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are defined as reported difficulties performing everyday tasks and, as such, contribute to a decline in an individual's functional status [3]. Functional status as a predictor of mortality has also been demonstrated in studies involving older non-cancer populations. Using a functional status questionnaire, Reuben et al. found that participants who had greater difficulty performing intermediate activities of daily living had a greater risk of death independent of other variables [5].

Elucidating possible causes of functional limitations among breast cancer survivors is of particular interest because cancer survivors have been found to be more likely to report functional limitations than women without cancer. In 2006, Sweeney et al. found that among a cohort of 25,719 elderly women, cancer survivors were significantly more likely to report difficulty performing heavy house work, walking half a mile, and walking up and down stairs compared to their cancer-free peers [6]. Additionally, a study by Kroenke et al. found that in comparison to age-matched controls without breast cancer, women diagnosed with breast cancer experienced a significantly greater decline in physical function over a 4-year period [7].

Research in non-cancer populations has shown that weight change may influence physical functional limitations. Some have found that weight loss is associated with an increased risk of disability/functional limitations [8], whereas others have found that weight gain is associated with increased risk of developing functional limitations [9, 10]. Others have found that both weight gain and weight loss are associated with increased risk of disability [11–15].

Considering the effect of weight change on physical function in non-cancer populations, the impact of weight change on physical function in breast cancer survivors is of particular interest since studies have found that it is common for women to gain weight after a breast cancer diagnosis. In a review of the literature, Denmark-Wahnefried et al. found that 50–96 % of all early-stage breast cancer patients on adjuvant chemotherapy experience some weight gain [16]. Although breast cancer patients most commonly gained between 2.5 and 6.2 kg, Denmark-Wahnefried et al. observed that it was not unusual for breast cancer patients to gain upwards of 10 kg [16]. Weight loss following a cancer diagnosis has also been described in the literature. In 1980, Dewys et al. investigated the prevalence of weight loss among cancer patients stratified by cancer type. Dewys et al. found that cancers such as gastric cancer and pancreatic cancer were associated with a much higher frequency of weight loss than cancers with a more favorable prognosis such as non-Hodgkins lymphoma and breast cancer (87 % of patients with gastric cancer experienced weight loss compared to 32 % of patients with non-Hodgkins lymphoma and 36 % of patients with breast cancer) [17].

If the association between weight change and functional status observed in previous studies in non-cancer populations exists for breast cancer patients, then significant weight gain or weight loss in breast cancer survivors may place them at particularly high risk for functional limitations. Therefore in the current study, we were interested in determining if body size or change in body size predicts the development of functional limitations within the Life After Cancer Epidemiology (LACE) population.

Materials and methods

LACE cohort

The LACE cohort consists of 2,264 women from the western USA who were diagnosed with invasive breast cancer between 1997 and 2000. Participants were recruited primarily from the Kaiser Permanente Northern California (KPNC) Cancer Registry (82 %) and the Utah Cancer Registry (12 %). The remaining 6 % is comprised of women who declined participation in the Women's Healthy Eating and Living (WHEL) trial, a dietary intervention trial aimed at reducing risk of recurrence among breast cancer survivors [18].

A total of 2,586 women were initially enrolled in LACE. Subsequent review confirmed 2,264 women as eligible based on eligibility criteria. To be eligible for the study, women had to be between 18 and 70 years of age at enrollment, have been diagnosed with stage-I (≥1), stage-II, or stage-IIIa breast cancer, have completed their breast cancer treatment (with the exception of adjuvant therapy), be free of recurrence (according to mammography and clinical examination), and have had no other cancers within the 5 years prior to enrollment. Additional details of the LACE cohort have been previously described [19]. The analysis in the present study was restricted to the 1,841 (79 %) women who provided information on prediagnosis BMI and functional status.

Assessment of functional limitations

Women were asked whether they were able to perform certain daily activities in the past month via a baseline questionnaire that was completed, on average, 21 months following breast cancer diagnosis. Daily activities included pushing objects like a living room chair; stooping, crouching, or kneeling; getting up from stooping, crouching, or kneeling position; lifting or carrying items under 10 lbs (like a bag of potatoes); lifting or carrying items over 10 lbs (like a heavy bag of groceries); reaching or extending your right arm above your shoulder; reaching or extending your left arm above your shoulder; writing or handling small objects; standing in place for 15 min or longer; sitting for long periods (e.g.,1 h); standing up after sitting in a chair; walking alone, up and down a flight of stairs; and walking two to three neighborhood blocks. This questionnaire was based on the Framingham Disability Study [20], Established Populations for Epidemiologic Studies of the Elderly [21], and functional status measures used by Nagi [22], Rosow, and Breslau [23]. This measure of

functional limitations has been previously validated against direct measures of physical function [24], and the items included on the questionnaire were both upper and lower body functions, as well as measures of endurance, strength, muscular range of motion, and small muscle dexterity. Responses for each daily activity fell into one of two categories: "Level of Difficulty" or "In the past month, I did not do because…" for "Level of Difficulty", participants selected from four choices: "A Lot," "Some," "A Little," or "None." For those participants who selected "In the past month, I did not do because…" were prompted to choose from the following reasons: "Dr.'s Orders," "Not able to do," or "Never Do."

Functional limitation outcomes

In this study, we categorized women as having no, any, mild, or moderate/severe limitations. The first category, "no limitations," consisted of women who responded "None" to the "Level of Difficulty" question for all 13 daily activities. Participants who selected "A Lot," "Some," "A Little," or "In the past month, I did not do because" of "Dr.'s Orders" or "Not able to do" on at least one of the 13 daily activities fell under the category "with any limitation." Participants who responded "Some" or "A Little" for "Level of Difficulty" on at least one of the 13 daily activities were considered to have mild limitations. Participants who responded "A Lot" or "In the past month, I did not do because" of "Dr.'s Orders" or "Not able to do" on at least one of the 13 daily activities were considered to have moderate/severe limitations.

Lower body limitations were defined as difficulty performing any of the following daily activities: stooping, crouching, or kneeling; getting up from stooping, crouching, or kneeling position; standing in place for 15 min or longer; standing up after sitting in a chair; walking alone, up and down a flight of stairs; and walking two to three neighborhood blocks. All other limitations consisted of difficulty performing any daily activities not mentioned above (i.e., pushing objects like a living room chair; sitting for long periods (e.g., 1 h); lifting or carrying items under 10 lbs, (like a bag of potatoes); lifting or carrying items over 10 lbs (like a heavy bag of groceries); reaching or extending your right arm above your shoulder; reaching or extending your left arm above your shoulder; writing or handling small objects).

Weight measurements

Weight 1 year prior to diagnosis and weight at study entry were self-reported at the time of study entry. The validity of self-reported weight measurements has been studied previously and has been proven suitable for use in epidemiological studies [24]. Percent weight change was calculated using the formula: 100 × (weight at study entry−weight at 1 year pre-diagnosis)/(weight at 1 year pre-diagnosis). Weight change was categorized into the following categories: large gain (≥10 % weight gain), large loss (≥10 % weight loss), moderate gain (5–10 % weight gain), moderate loss (5–10 % weight loss), and stable (<5 % weight change). Pre-diagnosis BMI was calculated using self-reported pre-diagnosis weight and the formula: weight (kg)/height (m^2). BMI categories defined by the WHO standards were used: normal weight (<25 kg/m^2), overweight (25–30 kg/m^2), obese (≥30 kg/m^2), and underweight (<18.5 kg/m^2) [25]. However, because few women were characterized as underweight (n=14) and no woman reported BMI<15.0 kg/m^2, we collapsed the normal weight and underweight categories.

Covariates

Covariates were also assessed on the baseline questionnaire including race, education, smoking status, pre-diagnosis BMI, age, and the existence of comorbidities, among others. Comorbidities reported at baseline included arthritis, other cancers, cardiovascular disease, diabetes, high cholesterol, hypertension, thyroid disorders, gall bladder disease, intestinal polyps, irritable bowel syndrome, osteoporosis, and depressive symptoms. Factors selected a priori as possible confounders in the relationship between weight change and functional limitations were entered as covariates in the analysis. Covariates included in the analysis were the following: (1) the existence of one or more comorbidities, (2) obesity (pre-diagnosis), (3) race, and (4) age. We also considered adjusting for time between diagnosis and study entry, and smoking, but adjustment for these factors did not materially affect associations and so these were dropped from the analysis.

Statistical analysis

Differences in means and proportions of each potential covariate between women with and without limitations were compared using Kruskal-Wallis tests for continuous variables and chi-squared tests for categorical variables. Information regarding functional status was collected on the baseline questionnaire and this information was used to perform logistic regression. Logistic regression was used to estimate the relative odds and 95 % confidence interval (CI) of each functional limitation outcome (any vs no functional limitation, moderate/severe vs mild/no functional limitation, or any vs no lower body functional limitation) for women in each weight change category compared to women who maintained weight within 5 % of their pre-diagnosis weight. Additionally, logistic regression was used to evaluate the association of weight change and the relative odds of any vs no or a moderate/severe vs no/mild functional limitation stratified by dichotomous pre-diagnosis BMI (<25 or ≥25 kg/m^2) and comorbidity status (0 or ≥1 comorbidity).

Results

Characteristics of study population

Women with physical functional limitations were older, had lower levels of education, were more likely to be obese (BMI≥30 kg/m^2), were more likely to be past or current smokers, were more likely to have a comorbidity, and were less likely to receive chemotherapy (Table 1).

Number of functional limitations by BMI and weight change categories

The number of functional limitations differed significantly according to pre-diagnosis BMI, with women in the obese category (BMI≥30) having a significantly higher mean number of limitations than women in the normal weight category (BMI<25) (2.06 vs 0.95 for moderate/severe limitations $P<0.0001$, 3.92 vs 3.26 for mild limitations $P<0.0001$, 1.31 vs 0.47 for lower body limitations $P<0.0001$, and 0.76 vs 0.48 for all other limitations $P<0.0002$, Kruskal-Wallis test; Table 2). Additionally, the number of functional limitations differed by weight change category, with women in the large gain category having a significantly higher number of moderate/severe limitations, lower body limitations, and "all other" limitations (all limitations except lower body limitations) than women in the stable weight category (1.62 vs 1.21 for moderate/severe limitations $P=0.0002$, 0.85 vs 0.71 for lower body limitations $P=0.01$, and 0.76 vs 0.51 for all other limitations $P=0.0001$, Kruskal-Wallis test; Table 2).

Women in the moderate loss category also reported a significantly higher number of moderate/severe limitations, lower body limitations, and "all other" limitations compared to stable weight women (1.80 vs 1.21 for moderate/severe limitations 0.0002, 1.00 vs 0.71 for lower body limitations $P=0.01$, and 0.80 vs 0.51 for all other limitations $P=0.0001$, Kruskal-Wallis test; Table 2).

Weight change and risk of functional limitations

After adjusting for age, pre-diagnosis BMI, comorbidities, and race, we found that large weight gain was associated with a greater risk of any functional limitation (OR=1.79, 95 % CI=1.23–2.61), a moderate/severe limitation (OR=2.30, 95 % CI=1.75–3.02), and a lower body limitation (OR=2.05, 95 % CI=1.53–2.76) compared to those who reported stable weight (Table 3). We did not find any significant associations among women who reported gaining between 5 and 10 % of their body weight and functional status. Additionally, we found that moderate weight loss was associated with a significantly greater risk of a lower body limitation (OR=1.50, 95 % CI=1.04–2.16) (Table 3).

Table 1 Characteristics of study population by functional limitations

Characteristics	Without limitations (n=284)	With any limitation (n=1,557)	P value
Age at diagnosis, no. (%)			
<50	104 (36.6)	317 (20.4)	<0.0001
50–64	131 (46.1)	725 (46.6)	
65–79	49 (17.3)	515 (33.1)	
Education, no. (%)			
≤4 years high school	62 (21.8)	436 (28.0)	<0.0001
Some college	77 (27.1)	602 (38.7)	
College	68 (23.9)	228 (14.7)	
Graduate degree	77 (27.1)	289 (18.6)	
Race and/or ethnicity, no. (%)			
White	227 (79.9)	1,273 (81.8)	0.8195
Black	14 (4.9)	64 (4.1)	
Hispanic	15 (5.3)	85 (5.5)	
Asian/Pacific Islander	20 (7.0)	86 (5.5)	
Other	8 (2.8)	49 (3.2)	
Body mass index, no. (%)			
<18.5	5 (1.8)	9 (0.6)	<0.0001
<25	169 (59.5)	669 (43.0)	
25–30	68 (23.9)	485 (31.2)	
>30	42 (14.8)	394 (25.3)	
Cigarette smoking, no. (%)			
Never	174 (61.3)	815 (52.4)	0.0057
Past/Current	110 (38.7)	741 (47.6)	
Comorbidity count, no. (%)			
0	177 (62.3)	575 (36.9)	<0.0001
≥1	107 (37.7)	982 (63.1)	
Adjuvant tamoxifen, no. (%)			
No	65 (22.9)	338 (21.8)	0.6454
Past	16 (5.6)	110 (7.1)	
Current	203 (71.5)	1,106 (71.2)	
Chemotherapy, no. (%)			
No	105 (37.0)	687 (44.2)	0.0246
Yes	179 (63.0)	869 (55.9)	
Radiotherapy, no. (%)			
No	98 (34.5)	585 (37.6)	0.3254
Yes	186 (65.5)	972 (62.4)	
Surgery, no. (%)			
Conserving	148 (52.1)	774 (49.7)	0.4566
Mastectomy	136 (47.9)	783 (50.3)	
Stage, no. (%)			
I	138 (48.6)	731 (47.0)	0.6308
IIA	93 (32.8)	516 (33.2)	
IIB	48 (16.9)	260 (16.7)	
III	5 (1.80)	49 (3.2)	
Lymph node positivity, no. (%)			
No	184 (65.0)	992 (64.0)	0.7327
Yes	99 (35.0)	559 (36.0)	
ER positivity, no. (%)			
No	58 (20.6)	266 (17.2)	0.1725
Yes	224 (79.4)	1,281 (82.8)	

Table 1 (continued)

Characteristics	Without limitations (n=284)	With any limitation (n=1,557)	P value
PR positivity, no. (%)			
No	90 (31.9)	446 (30.1)	0.5474
Yes	192 (68.1)	1,081 (69.9)	
HER2 positivity, no. (%)			
No	220 (84.9)	1,163 (83.6)	0.5927
Yes	39 (15.1)	228 (16.4)	
Total physical activity, mean Met-h/week	62.58	49.95	

Weight change and functional limitations stratified by BMI and comorbidity status

In Table 4, we examined the association between weight change and functional limitations stratified by pre-diagnosis BMI and comorbidity status. Among women without comorbidity and a pre-diagnosis BMI<25 kg/m^2, a large weight gain was associated with a greater risk of any functional limitation (OR=2.16, 95 % CI=1.21–3.85) as well as a moderate/severe limitation (OR=2.75, 95 % CI=1.57–4.82) compared to those with stable weight. Additionally, we found that large weight loss among these women was associated with a greater risk of a moderate/severe functional limitation (OR=3.79, 95 % CI=1.29–11.13). Among women without comorbidity who were overweight or obese prior to diagnosis, a large weight gain was associated with a greater risk of any functional limitation (OR=3.69, 95 % CI=1.39–9.75) as well as a moderate/severe functional limitation (OR=3.07, 95 % CI=1.59–5.94). However, although non-significant, there was a suggestion that large weight loss in overweight/obese women was related to a lower risk of a functional limitation (Table 4).

Among women with comorbidities, a large weight gain in normal-weight women was associated with a greater risk of any limitation (OR=2.01, 95 % CI=1.17–3.44). By contrast, a large weight gain or a moderate weight loss in overweight/obese women, but not other categories of weight change, was associated with a greater risk of limitations (large gain and any limitation: OR=1.74, 95 % CI=1.08–2.81; large gain and moderate/severe limitation: OR=1.85, 95 % CI=1.15–2.98; moderate loss and any limitation: OR=1.50, 95 % CI=0.92–2.46; moderate loss and moderate/severe limitation: OR=1.70, 95 % CI=1.04–2.77).

Discussion

In this study, large weight gain between 1 year pre-diagnosis and 2 years post-diagnosis was associated with a greater risk of functional limitations post-diagnosis. Women who reported gaining 10 % or more of their pre-diagnosis body weight were approximately two times more likely to report any functional limitation, a moderate/severe limitation or a lower body limitation, compared with those who maintained stable weight, regardless of pre-diagnosis BMI and comorbidity status. By contrast, the results for weight loss and physical function were less consistent. Among women without comorbidity, a large weight loss was associated with a higher risk of functional limitations in normal-weight women but a potentially lower risk of limitation in overweight/obese women. In women with comorbid conditions, moderate weight loss in overweight/

Table 2 Number of functional limitations by pre-diagnosis BMI and weight change categories

		Number of mild limitations	Number of moderate/severe limitations	Number of lower body limitations	Number of all other limitations
	Number	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Limitations by BMI category					
<25 (normal)	852	3.26 (3.0)	0.95 (2.1)	0.47 (1.2)	0.48 (1.1)
25–<30 (overweight)	553	3.85 (3.0)	1.34 (2.3)	0.77 (1.4)	0.58 (1.1)
≥30 (obese)	436	3.92 (2.9)	2.06 (3.0)	1.31 (1.8)	0.76 (1.5)
P value		<0.0001	<0.0001	<0.0001	0.002
Limitations by weight change category					
Stable weight (<5 % change)	875	3.56 (3.0)	1.21 (2.4)	0.71 (1.4)	0.51 (1.1)
Moderate loss (5–10 % loss)	177	3.59 (2.8)	1.80 (2.8)	1.00 (1.6)	0.80 (1.5)
Large loss (≥10 % loss)	128	3.85 (3.2)	1.32 (2.3)	0.70 (1.4)	0.63 (1.2)
Moderate gain (5–10 % gain)	299	3.32 (2.9)	1.07 (2.1)	0.66 (1.4)	0.40 (1.0)
Large gain (≥10 % gain)	362	3.80 (3.1)	1.62 (2.6)	0.85 (1.5)	0.76 (1.4)
P value		0.34	0.0002	0.01	0.0001

P value is for the Kruskal-Wallis test

Table 3 Likelihood of developing a functional limitation by weight change categories

Weight change category	Mild/moderate/severe (any) vs no functional limitations: OR (95 % CI)[a]			Moderate/severe vs mild/no functional limitations: OR (95 % CI)[a]			Any vs no lower body functional limitations: OR (95 % CI)[a]		
	Number of cases	Number of controls		Number of cases	Number of controls		Number of cases	Number of controls	
Stable (<5 % change) (n=875)	706	140	Reference	308	567	Reference	227	648	Reference
Moderate loss (5–10 % loss) (n=177)	147	21	1.26 (0.76–2.09)	78	99	1.31 (0.92–1.85)	66	111	1.50 (1.04–2.16)
Large loss (≥10 % loss) (n=128)	100	20	0.86 (0.50–1.47)	52	76	1.11 (0.75–1.66)	36	92	0.91 (0.58–1.41)
Moderate gain (5–10 % gain) (n=299)	233	57	0.92 (0.65–1.32)	97	202	1.01 (0.76–1.36)	77	222	1.20 (0.87–1.64)
Large gain (≥10 % gain) (n=362)	297	46	1.79 (1.23–2.61)	167	195	2.30 (1.75–3.02)	115	247	2.05 (1.53–2.76)

[a] Adjusted for age, race, pre-diagnosis obesity, and comorbidities

obese women was associated with a higher risk of a moderate/severe limitation. Substantial weight gain may compromise physical function, whereas the potential influence of weight loss on functional limitations may depend on BMI and co-morbidity status prior to breast cancer diagnosis. To our knowledge, this is the first study investigating the association between weight change and functional status among breast cancer survivors.

Our findings for weight gain and functional limitations in this population were consistent with those in non-cancer populations. Several studies have examined the correlation between weight change and functional status among non-cancer populations. A 2005 study by Houston et al. tracked weight change and functional status among 11,177 participants (men and women). They found that African-American and White women who gained greater than 13.6 kg between young adulthood and middle age were at a twofold increased risk for developing mild functional limitations and at a fivefold increased risk for developing severe functional limitations compared to women who maintained a stable weight (women who gained or lost 4.5 kg or less). Additionally, White women who experienced a large weight gain were at a threefold or higher risk for developing difficulties performing activities of daily living (ADL, activities included walking from one room to another on the same level, getting in or out of bed, eating or drinking from a glass, and dressing oneself) and at a twofold increased risk for developing difficulties performing instrumental activities of daily living (IADL, activities included doing chores around the house, preparing meals, and managing money) compared to stable-weight women [10]. Another study that followed 40,098 women for a period of 4 years found that women who gained 9 kg (19.84 lb) or more experienced a 5–11-point decrease in physical function. These women were also 2.05 times more likely to develop physical role limitations (i.e., their physical health limited their ability to perform their work or other usual roles) [9].

Additionally, our data show that a large weight gain was associated with a significantly greater risk of lower body limitations compared to weight maintenance. This finding is also consistent with previous studies examining the relationship between weight change and lower body limitations. A study following 1,737 Mexican American men and women found that participants who gained 5 % or more of their initial weight had a 1.39-fold increased risk for developing a lower body ADL limitation and a 1.23-fold increased risk for developing a walking limitation compared to stable weight participants [14]. Another study of 475 nuns found that an annual weight gain of 3 % or higher was associated with an increased risk of becoming dependent standing (relative risk=2.0) [15]. Of note, we did not observe any increased risk of functional limitations of women who gained between 5 and 10 % of their pre-diagnosis body weight, gains more commonly seen among breast cancer survivors.

Table 4 Association between weight change and functional limitations stratified by pre-diagnosis BMI and comorbidity status

Weight Change Category	Number of cases	Number of controls	Mild/moderate/severe (any) vs no functional limitations: OR (95 % CI)[a]	Number of cases	Number of controls	Moderate/severe vs no/mild functional limitations: OR (95 % CI)[a]
BMI<25 without comorbidity						
Stable (<5 % change)	146	65	Reference	36	175	Reference
Large gain (≥10 %)	87	20	2.16 (1.21–3.85)	35	72	2.75 (1.57–4.82)
Large loss (≥10 %)	13	3	1.97 (0.53–7.29)	7	9	3.79 (1.29–11.13)
Moderate gain (5–10 %)	58	21	1.30 (0.72–2.35)	14	65	1.12 (0.56–2.24)
Moderate loss (5–10 %)	18	9	0.87 (0.36–2.06)	5	22	1.08 (0.38–3.10)
BMI<25 with comorbidity						
Stable (<5 % change)	179	26	Reference	74	131	Reference
Large gain (≥10 %)	73	15	2.01 (1.17–3.44)	43	45	1.54 (0.85–2.77)
Large loss (≥10 %)	13	2	1.95 (0.67–5.65)	8	7	1.47 (0.47–4.53)
Moderate gain (5–10 %)	64	11	1.13 (0.65–1.98)	28	47	1.18 (0.64–2.18)
Moderate loss (5–10 %)	27	2	1.03 (0.46–2.34)	11	18	0.97 (0.39–2.44)
BMI≥25 without comorbidity						
Stable (<5 % change)	108	28	Reference	36	100	Reference
Large gain (≥10 %)	64	6	3.69 (1.39–9.75)	31	39	3.07 (1.59–5.94)
Large loss (≥10 %)	16	9	0.57 (0.22–1.50)	2	23	0.29 (0.06–1.33)
Moderate gain (5–10 %)	38	11	1.02 (0.45–2.32)	10	39	0.78 (0.35–1.74)
Moderate loss (5–10 %)	27	5	1.50 (0.51–4.41)	7	25	0.85 (0.33–2.17)
BMI≥25 with comorbidity						
Stable (<5 % change)	302	21	Reference	162	161	Reference
Large gain (≥10 %)	92	5	1.74 (1.08–2.81)	58	39	1.85 (1.15–2.98)
Large loss (≥10 %)	66	6	0.97 (0.58–1.63)	35	37	0.91 (0.53–1.55)
Moderate gain (5–10 %)	82	14	0.92 (0.58–1.46)	45	51	1.11 (0.69–1.77)
Moderate loss (5–10 %)	84	5	1.50 (0.92–2.46)	55	34	1.70 (1.04–2.77)

[a] Adjusted for age and race

By contrast, findings for weight loss and functional limitations were non-linear and less consistent. Mixed findings could be due in part to chance; numbers of women in the group with extreme weight changes, particularly weight losses, were relatively small. However, non-linearity across categories of weight loss also appeared related to the varied associations by pre-diagnosis BMI and comorbidity status which may be due to differences in intentionality of weight loss and disease status. Weight loss which is unintentional or occurs secondary to disease, for example, through fatigue-related reductions in exercise or the sarcopenic effects of treatment [26], may result in losses of muscle mass [27, 28] along with fat mass, leading to corresponding declines in function [29]. This may help to explain losses in function in the normal-weight women, who may already have low absolute levels of muscle mass, and the overweight/obese women with comorbid conditions.

However, the potentially reduced risk of a functional limitation in overweight/obese women without comorbidity suggests that weight loss may have been intentional and that muscle loss and thus loss in physical function may be minimized if weight loss occurs in the context of healthy diet and exercise. Findings from the RENEW trial, a randomized controlled trial involving a population of long-term cancer survivors, lend some support for this hypothesis; Morey et al. found that a decline in physical function was less pronounced in participants who were assigned to 12-month home-based diet and exercise program compared to participants assigned to the control arm (wait-listed for 12 months), despite a mean weight loss that was twice that of those in the control group [30].

The fact that the higher risk of a limitation occurred among normal-weight women with large weight loss and among overweight/obese women with moderate weight loss was due to the fact that overweight and obese women had to lose substantially more weight than normal-weight women to be classified as having lost >10 % of their pre-diagnosis body weight. In fact, when we analyzed associations for absolute weight change and functional limitations, we noted a linear graded pattern across categories of weight loss (data not shown) providing support for this idea.

Strengths of this study include the large sample size of a well-defined population of breast cancer survivors as well as measures of weight prior to and following diagnosis. A limitation of this study is that pre-diagnosis weight was assessed retrospectively leading to the potential for recall bias. The consistency of our results with other studies in non-cancer populations that show that both weight loss and weight gain may compromise physical function, however, lends credibility to these findings. Other study limitations include a lack of a second measure of functional status and the lack of information on body composition among women included in the analyses. A study by Sternfeld et al. found that a higher fat mass was associated with an increased risk of functional limitations while a higher lean mass-to-fat mass ratio was associated with a decreased risk of functional limitations [31]. These data suggest that body composition may provide additional insight that cannot be deduced from BMI alone. Although we were unable to incorporate this information into the present study, since we did not have information on body composition for the women included in our analysis, we believe it would be of value for future studies to consider body composition as an additional variable when examining functional limitations.

In summary, in this study, we found that large pre- to post-diagnosis weight gain in a population of breast cancer survivors was associated with a higher risk of a functional limitation. Moreover, in normal-weight women and in overweight/obese women with comorbidity, weight loss was also associated with higher functional limitations. Future research should investigate the impact of weight change on changes in physical function with more complete knowledge about the contexts in which weight change occurs and possible interventions to maintain or improve physical function.

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Conflict of interest The authors declare that they have no conflict of interest.

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