Body Mass Index Before and After Breast Cancer Diagnosis: Associations with All-Cause, Breast Cancer, and Cardiovascular Disease Mortality

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Abstract

Background: **Factors related to improving outcomes in breast cancer survivors are of increasing public health significance. We examined postdiagnosis weight change in relation to mortality risk in a cohort of breast cancer survivors.**

Methods: **We analyzed data from a cohort of 3,993 women with ages 20 to 79 years living in New Hampshire, Massachusetts, or Wisconsin with invasive nonmetastatic breast cancers diagnosed in 1988 to 1999 identified through state registries. Participants completed a structured telephone interview 1 to 2 years after diagnosis and returned a mailed follow-up questionnaire in 1998 to 2001 that addressed postdiagnosis weight and other factors. Vital status information was obtained from the National Death Index through December 2005. Hazard ratios and 95% confidence intervals were estimated from Cox proportional hazards models and adjusted for prediagnosis weight, age, stage, smoking, physical activity, and other important covariates.**

Results: **During an average 6.3 years of follow-up from the postdiagnosis questionnaire, we identified 421 total deaths, including 121 deaths from breast cancer and 95 deaths from cardiovascular disease. Increasing postdiagnosis weight gain and weight loss were each associated with greater all-cause mortality. Among women who gained weight after breast cancer diagnosis, each 5-kg gain was associated with a 12% increase in all-cause mortality (P = 0.004), a 13% increase in breast cancer–specific mortality (P = 0.01), and a 19% increase in cardiovascular disease mortality (P = 0.04). Associations with breast cancer mortality were not modified by prediagnosis menopausal status, cigarette smoking, or body mass index.**

Conclusion: **These findings suggest that efforts to minimize weight gain after a breast cancer diagnosis may improve survival.** (Cancer Epidemiol Biomarkers Prev 2009;18(5):1403–9)

Introduction

Previous studies have explored the relations of weight, weight change, and body mass index (BMI) with breast cancer incidence (1-3). Among postmenopausal women, increasing adiposity is associated with a greater risk for developing breast cancer. Because adipose tissue is the major source of estrogen after menopause, this relation is thought to be due in part to the greater concentrations of circulating estrogens in obese postmenopausal women (4). Among premenopausal women, increasing adiposity is associated with a reduced risk for developing breast cancer. This association may be related to a greater number of anovulatory menstrual cycles in obese premenopausal women or to other endogenous hormonal factors.

Breast cancer mortality relative to weight change and BMI before and at a breast cancer diagnosis has also been investigated. Results generally suggest that greater prediagnosis body mass and adult weight gain are associated with increased mortality risk, particularly among premenopausal women (5-12). However, the relation of weight change and body mass after diagnosis with subsequent risk for death has been examined in fewer studies (13-19), most constrained by a small sample size (13-16).

Advances in breast cancer diagnosis and treatment have greatly enhanced survival from this disease. More than 2 million women in the United States currently live with a history of breast cancer (20). Factors that may be related to risk for dying from breast cancer, heart disease (the leading cause of death among U.S. women (21)), and other causes are of substantial interest to breast cancer survivors. To examine the impact of postdiagnosis weight change and body mass, we used data from the Collaborative Women's Longevity Study (CWLS), a

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cohort study focused on nutritional, lifestyle, and reproductive influences on breast cancer survival.

Materials and Methods

Parent Study Populations. As described elsewhere (22-25), participants in the present study had previously enrolled in one of three consecutive population-based case control studies (1988-1991, 1992-1995, 1997-1999). Briefly, eligibility criteria for cases in the original studies included an incident diagnosis of invasive breast cancer; residence in New Hampshire, Massachusetts (excluding metropolitan Boston), or Wisconsin; and a publicly available telephone number. Study participants completed a structured 45-min telephone interview conducted within 1 to 2 y of diagnosis. The study interview addressed known and suspected risk factors for breast cancer development. Additional information, including tumor staging, histology, and treatment status, was collected from state cancer registries. Study protocols were approved by institutional review boards at the University of Wisconsin-Madison and the Harvard School of Public Health.

CWLS Cohort. All surviving cases in the original studies (n = 14,621) with a known address were sent a questionnaire by mail in 1998 to 2001 and asked to enroll in the CWLS. The questionnaire addressed recent (within the past year) postdiagnosis weight, physical activity, diet, medication history, alternative therapies, and quality of life. After 3 wk, women who had not returned the questionnaire received a reminder telephone call and a second mailing was sent to all nonrespondents. Following these efforts, a total of 5,791 questionnaires were returned (40% of the 14,621 eligible women sent questionnaires); these women serve as the baseline population for this cohort.

BMI and Weight Change Assessment. Prediagnosis BMI (kg/m^2) was calculated from weight (kg) and height (m) self-reported in the original studies. For cases enrolled during 1988 to 1991, weight was reported as of 5 y before the breast cancer diagnosis. For cases enrolled during 1992 to 1995 and 1997 to 2001, weight was reported ~1 y before diagnosis. In all three studies, prediagnosis height was reported as maximum adult height. Postdiagnosis BMI (kg/m^2) was calculated from current weight and height values in the CWLS questionnaire. BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese (>30 kg/m^2; ref. 26). Weight change was calculated by subtracting the prediagnosis weight of the participant from her current weight as reported in the CWLS questionnaire. Approximate quartiles of weight gain were created with even numbers for ease of interpretation, and the reference group was defined as remaining within 2 kg of prediagnosis weight.

Outcome Ascertainment. Among women in the CWLS, vital status information was obtained through December 31, 2005. Information on date and underlying cause of death were collected through linkage to National Death Index records. Analyses were conducted for three categories of deaths according to the International Classification of Disease 10 code: breast cancer (code C50), cardiovascular disease (codes I00-99), or all causes (27).

Statistical Analysis. For this analysis, several exclusions were applied. To avoid the influence of disease on postdiagnosis body weight, we excluded women with metastatic or unknown stage of disease at diagnosis (n = 649), those who reported a breast cancer recurrence before CWLS enrollment (n = 553), and those reporting unintentional weight loss of >5% body weight (n = 262) in the CWLS questionnaire. Unintentional weight loss was identified through the response of the participant to the question "Did you lose this weight deliberately (Yes/No/Didn't lose weight)." We also excluded women with missing information on weight change (n = 184) or who reported disease or treatment interference with diet (n = 128). Questionnaires from 22 women contained implausible values for weight and were not included in the analysis. The final cohort was comprised of 3,993 women. To further limit the potential influence of treatment on postdiagnosis body weight and weight gain, we did subgroup analyses restricted to women diagnosed at least 5 y before the CWLS enrollment (n = 2,275).

Person-time of follow-up was calculated from the date of return of the CWLS questionnaire (1998-2001) until the date of death or administrative censoring at end of the study period (December 31, 2005). Hazard ratios and 95% confidence intervals (95% CI) were estimated from multivariable Cox proportional hazards models (28). Proportional hazards assumptions were assessed by incorporating a term for the product of survival time and weight change in multivariate regression models; the likelihood ratio test indicated no evidence of departure from this assumption (P > 0.9). Final models included terms for age at diagnosis (5-y categories), stage of disease (local or regional), state of residence (Massachusetts, New Hampshire, Wisconsin), time between diagnosis and CWLS enrollment, family history of breast cancer, postdiagnosis cigarette smoking, total recreational physical activity at CWLS follow-up (metabolic equivalent task-hours per week: ≤2.7, 2.8-7.9, 8.0-20.9, ≥21.0), and postdiagnosis menopausal status. Models examining weight change since diagnosis also included a term for prediagnosis weight. Breast cancer treatment modality and postmenopausal hormone use did not influence hazard ratio estimates and were not included in regression models.

Effect modification of BMI and weight change associations with mortality was evaluated according to age, prediagnosis cigarette smoking, menopausal status, and stage of diagnosis. Cross-product terms were included in models to assess statistical interaction via likelihood ratio tests. All reported P values are two sided. All analyses were done with SAS 9.1 (SAS Institute, Inc.).

Results

Cohort members enrolled in the CWLS an average of 5.8 years after breast cancer diagnosis (range, 1-16; SD, 3.1). Approximately 10% of women enrolled in the cohort within 2 years of diagnosis; 33% had survived 2.1 to 4.9 years before enrollment, 44% had survived 5 to

9.9 years, and 13% had survived ≥10 years. Women who responded to the CWLS questionnaire (n = 5,791) were similar to nonresponders (n = 8,709) with respect to age, breast cancer stage, reproductive history, and alcohol consumption at diagnosis. However, women who returned the CWLS questionnaire were generally more educated, more likely to have a prediagnosis BMI in the reference range and to have used postmenopausal hormones before diagnosis, and were less likely to be current smokers than nonparticipants. Mortality was higher among nonparticipants compared with participants. Approximately 25% of study nonparticipants died of any cause between 1999 and 2005 compared with 15% of study participants. Similarly, breast cancer deaths were reported for 8.9% of nonparticipants versus 6.3% of CWLS participants (Table 1).

At the time of cohort enrollment, study participants were 25 to 87 years of age. Women who did not report losing or gaining >2 kg since their breast cancer diagnosis tended to have a lower BMI and be more physically active at follow-up compared with women who reported weight loss or gain (Table 2). Women who reported staying approximately the same weight since before their breast cancer diagnosis were also slightly more likely to have localized breast cancer at diagnosis. Mean age at breast cancer diagnosis and the proportion of postmenopausal women decreased across increasing categories of weight change (from 10-50 kg weight loss to weight gain of ≥10 kg). Family history of breast cancer and postdiagnosis alcohol consumption were similar across categories of weight change.

After an average 6.4 years of follow-up (range, 1-8; SD, 1.2), we identified 421 deaths from any cause. There were 121 deaths from breast cancer and 95 deaths from cardiovascular disease, jointly accounting for 51% of all deaths. Other leading causes of death included chronic lung disease (14%) and other malignant cancers (18%). In the subgroup of women who enrolled in CWLS ≥5 years after a diagnosis of invasive breast cancer, we identified 298 all-cause deaths, 58 breast cancer deaths, and 77 cardiovascular deaths. Hazard ratios and 95% CIs for all-cause, breast cancer, and cardiovascular disease mortality according to BMI and weight change are presented in Table 3.

All-Cause Mortality. We observed elevated hazard ratios for all cause mortality among underweight and obese women. Women categorized as obese (BMI ≥ 30 kg/m^2) before a breast cancer diagnosis had a 52% increase in all-cause mortality risk (95% CI, 1.17-1.98). Increasing amounts of weight gain and weight loss were associated with greater all-cause mortality. Compared with women who remained within 2 kg of their prediagnosis weight, women who lost 2.1 to 10.0 kg had 1.39 times greater mortality (95% CI, 1.04-1.86) and women who lost >10 kg had 2.66 times greater mortality (95% CI, 1.73-4.07; Table 3).

Hazard ratios did not change significantly for weight gain categories of 2.1 to 6.0 kg and 6.1 to 10.0 kg (compared with −2 to 2 kg). However, women who gained >10 kg had a 70% increase in all-cause mortality (95% CI, 1.21-2.41). We observed positive trends for increasing mortality risk according to increasing levels of weight loss and gain. In subanalyses restricted to women who remained approximately the same or lost weight, each 5 kg of weight loss was associated with a 24% increase in mortality risk (P = 0.004). Similarly, in models restricted to women who remained within 2 kg of their prediagnosis weight or gained weight, each 5 kg weight gain was associated with a 12% increase in mortality risk (P = 0.004; Table 3). Hazard ratio estimates remained

Table 1. Select characteristics among participants and nonparticipants in the CWLS

Characteristic at diagnosis	CWLS participants (n = 5,791)	CWLS nonparticipants (n = 8,709)
Age at diagnosis, mean y (SD)	58.4 (10.0)	59.2 (11.0)
Breast cancer stage at diagnosis, %		
Local	64.1	62.5
Regional	24.7	26.9
Distant	0.6	1.4
Unknown	10.6	9.2
Age at menarche, mean y (SD)	12.7 (1.5)	12.8 (1.6)
Age at first live birth, mean y (SD)	24.4 (4.4)	24.3 (4.5)
Parity, mean (SD)	2.7 (1.8)	2.6 (1.8)
Postmenopausal, %	71.9	72.0
Postmenopausal hormone use, %*	38.9	33.2
Education = 12 y, %	91.2	83.1
BMI, %†		
Underweight	1.4	1.9
Normal weight	50.3	46.5
Overweight	30.9	30.6
Obese	16.4	18.7
Smoking history, %		
Never	47.5	48.4
Former	34.8	28.9
Current	17.2	21.4
Alcoholic drinks per wk, mean (SD)	0.5 (0.8)	0.4 (0.9)
Mortality, %		
All-cause deaths	15.2	25.2
Breast cancer deaths	6.3	8.9

*Among postmenopausal women.
†BMI categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese (≥30 kg/m^2).

Table 2. Select characteristics among participants in the CWLS by weight change category

	Weight change from breast cancer diagnosis to CWLS follow-up (kg)				
	−50 to −10.1 (*n* = 114)	−10.0 to −2.1 (*n* = 608)	−2.0 to 2.0 (*n* = 1,037)	2.1 to 10.0 (*n* = 1,682)	10.1 to 103 (*n* = 552)
Characteristics at diagnosis*					
Age, mean y (SD)	62.6 (9.2)	62.2 (9.0)	59.9 (9.5)	57.1 (9.6)	52.9 (9.1)
BMI, mean kg/m^2 (SD)	32.0 (5.7)	27.0 (4.9)	24.4 (4.1)	25.0 (4.4)	26.1 (5.2)
Ethnicity, % White	98.3	98.9	98.8	98.7	98.2
Breast cancer stage at diagnosis, %					
Local	73.7	74.0	74.9	72.1	68.3
Regional	26.3	26.0	25.1	27.9	31.7
First-degree family history of breast cancer, %	16.7	21.6	20.6	20.2	18.5
Education ≥12 y, %	84.2	88.5	93.2	93.2	92.4
Characteristics at follow-up†					
Postmenopausal, %	91.2	91.5	86.8	81.3	72.3
BMI, mean kg/m^2 (SD)	26.5 (5.6)	25.8 (4.9)	24.9 (4.3)	27.3 (4.7)	32.8 (6.4)
Smoking history, % current	13.2	7.7	10.1	9.8	7.4
Alcohol, mean drinks/d (SD)	0.2 (0.5)	0.4 (0.7)	0.5 (0.8)	0.5 (0.9)	0.4 (0.7)
Total recreational physical activity,‡ mean MET-h/wk (SD)	12.9 (18.1)	15.9 (22.4)	18.6 (24.3)	16.8 (21.3)	12.1 (16.9)
Energy intake,‡ mean kcal/d (SD)	1,583 (575)	1,726 (588)	1,713 (513)	1,703 (528)	1,741 (623)
Hormone therapy, % current	1.8	2.8	2.1	2.0	2.5
Years from diagnosis to follow-up survey, mean (SD)	6.4 (3.0)	6.0 (2.8)	5.1 (2.9)	5.7 (3.2)	6.9 (3.4)

Abbreviation: MET, metabolic equivalent task.
*Data obtained by parent case-control studies.
†Data obtained by CWLS questionnaire.
‡Year before enrollment in CWLS.

largely unchanged in additional models that adjusted only for age, state, and time between diagnosis and enrollment (hazard ratio, 1.24/5-kg loss; hazard ratio, 1.12/5-kg gain) or for all covariates listed in Table 3 except stage (hazard ratio, 1.25/5-kg loss; hazard ratio, 1.12/5-kg gain). All-cause mortality associations with BMI and weight change were not modified according to age, menopausal status, cigarette smoking, stage of diagnosis, or prediagnosis BMI.

Among the subgroup of ≥5 year survivors, prediagnosis BMI remained associated with increased all-cause mortality risk (hazard ratio, 1.42; 95% CI, 1.03-1.95 comparing obese versus normal BMI). Similarly, increasing amounts of weight gain were associated with greater risk for all-cause mortality in this group (hazard ratio, 1.11; 95% CI, 1.01-1.22 for each 5-kg gain). Women who reported losing ≥10 kg since diagnosis had elevated hazard ratios for all-cause mortality compared with women who remained within 2 kg of their prediagnosis weight (hazard ratio, 3.19; 95% CI, 2.01-5.05; data not shown).

Breast Cancer Mortality. We observed positive associations between postdiagnosis BMI, weight gain levels, and breast cancer–specific mortality. Risk for death from breast cancer was 2.28 times greater for women classified as obese at CWLS enrollment compared with those with a BMI in the reference range (95% CI, 1.43-3.64). Breast cancer mortality increased by 78% among women who gained >10 kg between diagnosis and CWLS enrollment (95% CI, 1.01-3.14). For each 5-kg gain in weight, breast cancer mortality increased by 13% (P = 0.01). There was no suggestion of any increase in breast cancer mortality among women who lost weight (Table 3). These estimates were virtually identical in alternate models with that adjusted only for age, state, and time between diagnosis and enrollment or for all covariates listed in Table 3 except stage.

We observed no evidence of effect modification according to age, menopausal status, cigarette smoking, stage of diagnosis, or prediagnosis BMI for breast cancer mortality. Data were sparse among ≥5 year survivors, and results were not statistically significant (data not shown).

Cardiovascular Disease Mortality. Cardiovascular disease mortality was also associated with greater BMI and weight gain. The hazard ratio estimate for obese BMI 1 to 5 years before breast cancer diagnosis was 2.45 (95% CI, 1.46-4.11) compared with BMI in the reference range. Obese women postdiagnosis had a cardiovascular disease mortality rate 1.65 times that of women with a normal BMI (95% CI, 0.97-2.83). In analyses restricted to women who reported staying within 2 kg of their prediagnosis weight or who gained weight, each 5 kg weight gain was associated with a 19% increase in cardiovascular disease mortality (P = 0.04; Table 3). Among 5-year survivors, obesity 1 to 5 years before breast cancer diagnosis was associated with a >2-fold excess in cardiovascular disease mortality (hazard ratio, 2.27; 95% CI, 1.25-4.11); however, hazard ratio estimates for other measures of BMI and weight change were not statistically significant in this limited subgroup (data not shown).

Discussion

In this study, we observed elevated mortality associated with greater body mass and increasing levels of weight gain after breast cancer diagnosis across all-cause, breast cancer, and cardiovascular disease categories. In our data, the relation between weight change and all-cause mortality seemed to be U shaped (increasing mortality risk associated with higher levels of weight gain and

loss); however, breast cancer mortality associations suggested a more linear relationship. Our findings generally suggest a positive trend between weight gain and mortality; however, the ~70% to 75% increase in the hazard ratio for all-cause, breast cancer, and cardiovascular disease deaths was consistent and statistically significant only for the most extreme category of weight gain >10 kg.

In a recent report, Caan and colleagues (19) identified a positive association between greater levels of weight loss and increased all-cause mortality in a study on 1,692 women diagnosed with early stage invasive breast cancer during 1997 to 2000. Our data support this finding. Caan et al. (19) reported a 2-fold increase in the hazard ratio for all-cause mortality according to weight loss of ≥10% of the prediagnosis weight of the participant (hazard ratio, 2.1; 95% CI, 1.3-3.4) relative to women who stayed within 5% of their prediagnosis weight. The increased all-cause mortality hazard ratio associated with weight loss was particularly evident among women who reported a BMI in the obese range 1 year before diagnosis (hazard ratio, 2.8; 95% CI, 1.4-5.6). Weight loss and mortality associations did not vary according to smoking status. Unexplained weight loss is generally known to be associated with increased mortality, often representing reverse causation from underlying conditions such as pulmonary disease or undiagnosed cancer (29). Our exclusion of women with unintentional weight loss of >5% body weight was designed to address this issue; however, the exclusion criteria may not have fully eliminated weight loss due to pre-existing disease. Alternatively, the increase in all-cause mortality associated with greater weight loss may reflect a true phenomenon that warrants further investigation.

Our results are also highly similar to those of Caan et al. (19) with respect to prediagnosis BMI and mortality risk associations. Compared with women with normal BMI at one year prediagnosis, overweight and obese women had borderline significant hazard ratios for breast cancer death of 1.4 and 1.6, respectively. Hazard ratios for all-cause mortality according to overweight and obese BMI were 1.2 (95% CI, 0.8-1.7) and 1.6 (95% CI, 1.1-2.3) compared with normal BMI (19).

Over the 7-year follow-up, Caan et al. (19) did not observe elevated hazard ratios for breast cancer and all-cause mortality in relation to postdiagnosis weight gain. Weight change was calculated by subtracting a woman's weight at 1 year prediagnosis from her weight at study entry. The average time between diagnosis and study entry was 1.9 years (range, 0.25-6.86), with a resulting mean weight change of 1.7 kg (SD, 7.6). Notably, time between diagnosis and study enrollment, average weight gain, and the number of deaths reported (90 breast cancer deaths; 160 all-cause deaths) were substantially lower compared with our study population (19).

In an analysis of data from 5,204 women enrolled in the Nurses Health Study and diagnosed with breast cancer, weight gain after diagnosis was associated with an increased risk for all-cause and breast cancer mortality only in nonsmoking women with BMI values <25 kg/m^2

Table 3. Hazard ratio and 95% CIs for all-cause, breast cancer, and cardiovascular disease mortality according to BMI and weight change since diagnosis

Characteristic	Cohort	All-cause mortality		Breast cancer mortality		CVD mortality	
	n	Deaths*	HR (95% CI) †	Deaths*	HR (95% CI) †	Deaths*	HR (95% CI) †
Prediagnosis BMI, kg/m^2							
Underweight (<18.5)	62	11	1.75 (0.94, 3.25)	2	0.93 (0.22, 3.85)	4	4.15 (1.44-12.0)
Normal (18.5-24.9)	2,058	178	1	50	1	36	1
Overweight (25.0-29.9)	1,228	137	1.13 (0.90, 1.42)	45	1.48 (0.98, 2.24)	27	1.05 (0.63, 1.74)
Obese (≥30)	639	93	1.52 (1.17, 1.98)	24	1.42 (0.86, 2.36)	28	2.45 (1.46, 4.11)
Postdiagnosis BMI, kg/m^2							
Underweight (<18.5)	42	10	1.57 (0.82, 3.02)	1	1.10 (0.15, 8.09)	1	0.58 (0.08, 4.34)
Normal (18.5-24.9)	1,497	140	1	31	1	30	1
Overweight (25.0-29.9)	1,373	133	0.91 (0.72, 1.16)	37	1.34 (0.83, 2.18)	30	0.99 (0.59, 1.66)
Obese (≥30)	977	122	1.27 (0.99, 1.64)	48	2.28 (1.43, 3.64)	29	1.65 (0.97, 2.83)
Weight change since diagnosis, kg ‡							
−50 to −10.1	114	33	2.66 (1.73, 4.07)	2	0.64 (0.15-2.79)	6	1.08 (0.42, 2.78)
−10.0 to −2.1	608	93	1.39 (1.04, 1.86)	14	0.90 (0.47, 1.72)	24	1.02 (0.58, 1.80)
−2.0 to 2.0	1,037	98	1	28	1	27	1
2.1 to 6.0	1,127	88	0.98 (0.73, 1.31)	30	0.98 (0.58, 1.65)	18	0.79 (0.43, 1.44)
6.1 to 10.0	555	48	1.06 (0.75, 1.51)	20	1.28 (0.71, 2.31)	8	0.64 (0.29, 1.44)
10.1 to 103	552	61	1.70 (1.21, 2.41)	27	1.78 (1.01, 3.14)	12	1.73 (0.83, 3.62)
5-kg Decrease§			1.24 (1.07, 1.43)		0.79 (0.42-1.47)		1.02 (0.75, 1.40)
5-kg Increase‖			1.12 (1.04, 1.22)		1.13 (1.03, 1.25)		1.19 (1.01, 1.40)

Abbreviations: HR, hazard ratio; CVD, cardiovascular disease.

*Total numbers of deaths vary slightly in pre- and postdiagnosis BMI models compared with weight change models based on missing values for height that did not allow for BMI to be calculated.

†Hazard ratio adjusted for age, state, time between diagnosis and follow-up interview, family history of breast cancer, cigarette smoking, total recreational physical activity at follow-up, menopausal status, and stage.

‡Additionally adjusted for prediagnosis weight.

§Analysis restricted to women who reported staying within 2 kg of their prediagnosis weight or losing weight.

‖Analysis restricted to women who reported staying within 2 kg of their prediagnosis weight or gaining weight.

before diagnosis (17). Our data did not replicate these results. In our stratified analyses, hazard ratio estimates for breast cancer mortality associations with weight gain >2 kg (compared with staying within 2 kg of prediagnosis weight) were higher among ever smokers (hazard ratio, 1.24; 95% CI, 0.69-2.21) and women with prediagnosis BMI ≥ 25 (hazard ratio, 1.73; 95% CI, 0.86-3.48) relative to never smokers (hazard ratio, 1.13; 95% CI, 0.56-2.27) and those with BMI < 25 (hazard ratio, 0.89; 95% CI, 0.48-1.62). Tests for interaction produced P values of 0.2 and 0.5 for prediagnosis smoking and BMI, respectively.

We included data from all eligible women in the cohort irrespective of length of follow-up. In the Nurses Health Study, Kroenke et al. (17) reported similar patterns of association with postdiagnosis weight change and mortality risk when records of women with <1 year follow-up were alternately included and excluded. In our study, subgroup analyses restricted to women who had survived ≥5 years at cohort enrollment also showed similar patterns of association, and the formal test for the proportional hazards assumption supported a continued importance of body weight regardless of survival time.

With the exceptions of the findings of Caan et al. (18, 19) and the report of Kroenke et al. (17) in the Nurses Health Study cohort, previous studies on postdiagnosis weight gain and mortality have been clinical trials constrained by small sample sizes (<550 women; refs. 13-16). Among these, one study indicated an association between greater relative weight gain at 60 weeks postdiagnosis and increased mortality among premenopausal women (15). In a second study, weight gain associations with increased mortality did not persist after multivariable adjustment (14). A third trial (N = 62) noted that, although there was no direct correlation between weight gain and survival time, the five patients with weight gain >10 kg had 100% mortality at study end (median, 112 months follow-up) compared with 48% among patients with lesser weight gain (13).

Strengths of our study include the large size and availability of detailed information on potential confounders and modifying factors. In our data, treatment modality did not seem to confound the association of BMI and weight gain with mortality risk. Self-reported treatment information has been shown to be highly reliable for radiation (κ = 0.97), chemotherapy (κ = 0.96), and hormone therapy (κ = 0.92) regimens in other populations of breast cancer survivors (12). Our death ascertainment was likely complete; the National Death Index has previously been shown to be a reliable source of vital status and underlying cause of death information (30, 31). The high reproducibility of the height and weight values self-reported in the parent studies has also been previously shown (1, 2).

Some study characteristics may limit interpretation of our results. Despite the large absolute number of breast cancer survivors enrolled in the CWLS cohort, the low response rate may raise concerns about generalizability of the results. The extensive information available from the parent studies allows us the opportunity to compare women enrolled in the cohort to those who did not respond to the CWLS questionnaire. Based on data collected within two years of the breast cancer diagnosis, cohort participants were generally more highly educated and showed a healthier profile (fewer current smokers, greater proportion of BMI values in the reference range) than those who did not participate. Higher participation involving women with less optimal risk profiles would have allowed us to examine a wider range in body weights/weight change and offered greater power to examine extremes in these factors as well as dose-response. Adverse health effects associated with obesity and weight gain have been increasingly reported by the media. If participants reported their weight at follow-up differentially with regard to health status and mortality risk, our results could be affected by reporting bias.

Furthermore, we lacked information on estrogen and progesterone receptor status at breast cancer diagnosis and therefore could not consider effect modification by this factor. We also lacked information on potential changes in weight after CWLS enrollment and were unable to evaluate the temporality of changes in body weight and the development of chronic disease comorbidities. In addition, mortality information for women who emigrated from the United States would not have been captured by NDI linkage.

Finally, CWLS cohort enrollment occurred an average of 5.8 years after breast cancer diagnosis. The length of time between breast cancer diagnosis and CWLS enrollment varied among study participants. Although our analyses adjust for this period, the possibility of residual confounding cannot be eliminated. It may not be appropriate to generalize our study results to women with shorter periods of disease-free survival. Our study cohort was >98% White; as such, these findings may also not be generalizable to women of other racial groups.

Greater postdiagnosis BMI and weight gain were associated with higher rates of all-cause and breast cancer mortality. These findings suggest that avoidance of weight gain may offer women a greater chance of surviving breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body size and risk of breast cancer. Am J Epidemiol 1997;145:1011–9.
2. Trentham-Dietz A, Newcomb PA, Egan KM, et al. Weight change and risk of postmenopausal breast cancer (United States). Cancer Causes Control 2000;11:533–42.
3. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA 2006;296:193–201.
4. Siiteri PK. Adipose tissue as a source of hormones. Am J Clin Nutr 1987;45:277–82.
5. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. Cancer 1995;76:275–83.
6. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among

young women with invasive ductal breast carcinoma. Cancer 2001; 92:720–9.
7. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. J Clin Oncol 2002;20:3302–16.
8. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. J Clin Oncol 2002;20:1128–43.
9. Petrelli JM, Calle EE, Rodriguez C, Thun MJ. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control 2002;13:325–32.
10. Loi S, Milne RL, Friedlander ML, et al. Obesity and outcomes in premenopausal and postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1686–91.
11. Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Body mass and mortality after breast cancer diagnosis. Cancer Epidemiol Biomarkers Prev 2005;14:2009–14.
12. Cleveland RJ, Eng SM, Abrahamson PE, et al. Weight gain prior to diagnosis and survival from breast cancer. Cancer Epidemiol Biomarkers Prev 2007;16:1803–11.
13. Chlebowski RT, Weiner JM, Reynolds R, Luce J, Bulcavage L, Bateman JR. Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. Breast Cancer Res Treat 1986;7: 23–30.
14. Goodwin PJ, Panzarella T, Boyd NF. Weight gain in women with localized breast cancer—a descriptive study. Breast Cancer Res Treat 1988;11:59–66.
15. Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, Veeder MH. Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer. J Clin Oncol 1990;8:1327–34.
16. Levine EG, Raczynski JM, Carpenter JT. Weight gain with breast cancer adjuvant treatment. Cancer 1991;67:1954–9.
17. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 2005;23:1370–8.
18. Caan BJ, Emond JA, Natarajan L, et al. Post-diagnosis weight gain and breast cancer recurrence in women with early stage breast cancer. Breast Cancer Res Treat 2006;99:47–57.
19. Caan BJ, Kwan ML, Hartzell G, et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. Cancer Causes Control 2008;19: 1319–28.
20. Ries LAG, Melbert D, Krapcho M, et al., editors. SEER cancer statistics review, 1975-2004. Bethesda: National Cancer Institute.
21. Heron MP, Hoyert DL, Xu J, Scott C, Tejada-Vera B. Deaths: preliminary data for 2006. National Vital Statistics Reports 2008;56.
22. Newcomb PA, Storer BE, Longnecker MP, et al. Lactation and a reduced risk of premenopausal breast cancer. N Engl J Med 1994;330: 81–7.
23. Titus-Ernstoff L, Egan KM, Newcomb PA, et al. Exposure to breast milk in infancy and adult breast cancer risk. J Natl Cancer Inst 1998; 90:921–4.
24. Sprague BL, Trentham-Dietz A, Newcomb PA, Titus-Ernstoff L, Hampton JM, Egan KM. Lifetime recreational and occupational physical activity and risk of *in situ* and invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2007;16:236–43.
25. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:379–86.
26. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series. Geneva; 1995.
27. World Health Organization. International classification of diseases (ICD-10). 1994. Available at: http://www.who.int/classifications/icd/en/.
28. Cox D. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34:187–220.
29. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999;341:427–34.
30. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.
31. Calle EE, Terrell DD. Utility of the National Death Index for ascertainment of mortality among cancer prevention study II participants. Am J Epidemiol 1993;137:235–41.

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