Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2009 May ; 18(5): 1403–1409. doi:10.1158/1055-9965.EPI-08-1094.

Body mass index before and after breast cancer diagnosis: Associations with all-cause, breast cancer, and cardiovascular disease mortality

Hazel B. Nichols[1], **Amy Trentham-Dietz**[2,6], **Kathleen M. Egan**[3], **Linda Titus-Ernstoff**[4], **Michelle D. Holmes**[5], **Andrew J. Bersch**[6], **Crystal N. Holick**[7], **John M. Hampton**[6], **Meir J. Stampfer**[5,8], **Walter C. Willett**[5,8], and **Polly A. Newcomb**[6,9]

[1] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[2] Department of Population Health Sciences, University of Wisconsin, Madison, WI

[3] H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

[4] Dartmouth Medical School, Lebanon, NH

[5] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

[6]University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, Madison, WI

[7] i3 Drug Safety, Waltham, MA

[8] Departments of Epidemiology and Nutrition, Harvard School of Public Health, Boston, MA

[9] Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract

Background—Factors related to improving outcomes in breast cancer survivors are of increasing public health significance. We examined post-diagnosis 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 aged 20−79 living in New Hampshire, Massachusetts or Wisconsin with invasive, nonmetastatic breast cancers diagnosed in 1988−1999 identified through state registries. Participants completed a structured telephone interview 1−2 years after diagnosis and returned a mailed follow-up questionnaire in 1998−2001 that addressed post-diagnosis weight and other factors. Vital status information was obtained from the National Death Index through December 2005. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated from Cox proportional hazards models and adjusted for pre-diagnosis weight, age, stage, smoking, physical activity and other important covariates.

Results—During an average 6.3 years of follow-up from the post-diagnosis questionnaire, we identified 421 total deaths, including 121 deaths from breast cancer and 95 deaths from cardiovascular disease. Increasing post-diagnosis 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).

Corresponding author: Hazel Nichols 615 Regester Ave. Baltimore MD 21212 E-mail: hnichols@jhsph.edu ph. 410−487−3458 fax 608−265−5330.

Associations with breast cancer mortality were not modified by pre-diagnosis 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.

Keywords

Breast cancer; mortality; BMI; weight change; survival

Introduction

Previous studies have explored the relations of weight, weight change, and body mass index with breast cancer *incidence* (1-3). Among postmenopausal women, increasing adiposity is associated with a greater risk of developing breast cancer. As 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 of 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 body mass index *before* and *at* a breast cancer diagnosis has also been investigated. Results generally suggest that greater pre-diagnosis 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 of death has been examined in fewer studies (13-19), the majority constrained by a small sample size (13-16).

Advances in breast cancer diagnosis and treatment have greatly enhanced survival from this disease. More than two million women in the United States currently live with a history of breast cancer (20). Factors that may be related to risk of 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 post-diagnosis weight change and body mass, we used data from the Collaborative Women's Longevity Study (CWLS), a 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 (1988−91; 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-minute telephone interview conducted within 1−2 years 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.

Collaborative Women's Longevity Study cohort

All surviving cases in the original studies (N=14,621) with a known address were sent a questionnaire by mail in 1998−2001 and asked to enroll in the CWLS. The questionnaire addressed recent (within the past year) post-diagnosis weight, physical activity, diet, medication history, alternative therapies, and quality of life. After three weeks, 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.

Body mass index and weight change assessment

Pre-diagnosis body mass index (kg/m^2) was calculated from weight (kg) and height (m) self-reported in the original studies. For cases enrolled during 1988−1991 weight was reported as of 5 years before the breast cancer diagnosis. For cases enrolled during 1992−1995 and 1997−2001 weight was reported approximately 1 year before diagnosis. In all three studies, pre-diagnosis height was reported as maximum adult height. Post-diagnosis body mass index (kg/m^2) was calculated from current weight and height values in the CWLS questionnaire. Body mass index 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) (26). Weight change was calculated by subtracting the participant's pre-diagnosis weight 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 referent group was defined as remaining within 2 kg of pre-diagnosis 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 was 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 post-diagnosis 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 greater than 5% body weight (N=262) in the CWLS questionnaire. Unintentional weight loss was identified through the participant's response 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 post-diagnosis body weight and weight gain, we performed sub-group analyses restricted to women diagnosed at least 5 years 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 (HR) and 95% confidence intervals (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-year 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, post-diagnosis 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 post-diagnosis menopausal status. Models examining weight change since diagnosis also included a term for pre-diagnosis 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 body mass index and weight change associations with mortality was evaluated according to pre-diagnosis cigarette smoking, menopausal status, and postmenopausal hormone use. 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 performed with SAS 9.1 (SAS Institute Inc., Cary, NC).

Results

Cohort members enrolled in the CWLS an average of 5.8 years after breast cancer diagnosis (range 1−16, standard deviation 3.1). Approximately 10% of women enrolled in the cohort within 2 years of diagnosis; 33% had survived 2.1−4.9 years before enrollment; 44% had survived 5−9.9 years, and 13% had survived ≥10 years. Women who responded to the CWLS questionnaire (N=5,791) were similar to non-responders (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 pre-diagnosis body mass index (BMI) in the normal range and to have used postmenopausal hormones before diagnosis, and were less likely to be current smokers than non-participants. Mortality was higher among non-participants compared to participants. Approximately 25% of study non-participants died of any cause between 1999 and 2005, compared to 15% of study participants. Similarly, breast cancer deaths were reported for 8.9% of non-participants versus 6.3% of CWLS participants (Table 1).

At the time of cohort enrollment, study participants were 25−87 years of age. Women who did not report losing or gaining more than 2 kg since their breast cancer diagnosis tended to have a lower body mass index and be more physically active at follow-up compared to 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 or more). Family history of breast cancer and post-diagnosis alcohol consumption were similar across categories of weight change.

After an average 6.4 years of follow-up (range 1−8, standard deviation 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% confidence intervals for all-cause, breast cancer and cardiovascular disease mortality according to body mass index and weight change are presented in Table 3.

All-cause mortality

We observed elevated hazard ratios for all cause mortality among both 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 both weight gain and weight loss were associated with greater all-cause mortality. Compared to women who remained within 2 kg of their pre-diagnosis weight, women who lost 2.1−10.0 kg had 1.39 times greater mortality (95% CI: 1.04, 1.86) and women who lost more than 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 2.1−6.0 kg and 6.1 −10.0 kg (compared to −2 to 2 kg). However, women who gained more than 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 both increasing levels of weight loss and gain. In sub-analyses 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 pre-diagnosis 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 largely unchanged in additional models that adjusted only for age, state, and time between diagnosis and enrollment (HR=1.24 per 5 kg loss, HR=1.12 per 5 kg gain) or for all covariates listed in Table 3 except stage (HR=1.25 per 5 kg loss, HR=1.12 per 5 kg gain). All-cause mortality associations with body mass index and weight change were not modified according to age, menopausal status, cigarette smoking, stage of diagnosis, or pre-diagnosis body mass index.

Among the subgroup of ≥5 year survivors, pre-diagnosis BMI remained associated with increased all-cause mortality risk (HR=1.42; 95% CI: 1.03−1.95 comparing obese vs. normal BMI). Similarly, increasing amounts of weight gain were associated with greater risk of all-cause mortality in this group (HR=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 to women who remained within 2 kg of their pre-diagnosis weight (HR=3.19; 95% CI 2.01, 5.05) *(data not shown)*.

Breast cancer mortality

We observed positive associations between post-diagnosis body mass index, weight gain levels and breast cancer-specific mortality. Risk of death from breast cancer was 2.28 times greater for women classified as obese at CWLS enrollment compared to those with a BMI in the normal range (95% CI: 1.43−3.64). Breast cancer mortality increased by 78% among women who gained more than 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 pre-diagnosis body mass index 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 (CVD) mortality was also associated with greater body mass index and weight gain. The HR estimate for obese BMI 1−5 years before breast cancer diagnosis was

2.45 (95% CI: 1.46, 4.11) compared to BMI in the normal range. Obese women post-diagnosis had a CVD 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 pre-diagnosis weight or who gained weight, each 5 kg weight gain was associated with a 19% increase in CVD mortality (p=0.04)(Table 3). Among 5-year survivors, obesity 1−5 years before breast cancer diagnosis was associated with a more than 2-fold excess in CVD mortality (HR=2.27; 95% CI: 1.25, 4.11); however, HR 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 appeared to be U-shaped (increasing mortality risk associated with higher levels of both 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 approximately 70−75% 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 greater than 10 kg.

In a recent report, Caan and colleagues identified a positive association between greater levels of weight loss and increased all-cause mortality in a study of 1,692 women diagnosed with early stage invasive breast cancer during 1997−2000. Our data support this finding. Caan et al. reported a two-fold increase in the hazard ratio for all-cause mortality according to weight loss of ≥10% of the participant's pre-diagnosis weight (HR=2.1; 95% CI: 1.3, 3.4) relative to women who stayed within 5% of their pre-diagnosis weight. The increased all-cause mortality HR associated with weight loss was particularly evident among women who reported a BMI in the obese range one year before diagnosis (HR=2.8; 95% CI: 1.4, 5.6). Weight loss and mortality associations did not vary according to smoking status (19). 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 greater than 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. with respect to pre-diagnosis body mass index and mortality risk associations. Compared to women with normal BMI at one year pre-diagnosis, overweight and obese women had borderline significant HRs 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 to normal body mass index (19).

Over the 7-year follow-up, Caan et al. did not observe elevated HRs for breast cancer and all-cause mortality in relation to post-diagnosis weight gain. Weight change was calculated by subtracting a woman's weight at one year pre-diagnosis 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 to our study population (19).

In an analysis of data from 5,204 women enrolled in the Nurses Health Study (NHS) and diagnosed with breast cancer, weight gain after diagnosis was associated with an increased risk of all-cause and breast cancer mortality only in non-smoking women with BMI values <25 kg/m^2 before diagnosis (17). Our data did not replicate these results. In our stratified analyses, HR estimates for breast cancer mortality associations with weight gain greater than 2 kg (compared to staying within 2 kg of pre-diagnosis weight) were higher among ever smokers (HR=1.24; 95% CI: 0.69, 2.21) and women with pre-diagnosis BMI ≥25 (HR=1.73; 95% CI: 0.86, 3.48) relative to never smokers (HR=1.13; 95% CI: 0.56, 2.27) and those with BMI <25 (HR=0.89; 95% CI: 0.48, 1.62). Tests for interaction produced p-values of 0.2 and 0.5 for pre-diagnosis smoking and BMI respectively.

We included data from all eligible women in the cohort irrespective of length of follow-up. In the NHS, Kroenke et al. reported similar patterns of association with post-diagnosis weight change and mortality risk when records of women with <1 year follow-up were alternately included and excluded (17). In our study, subgroup analyses restricted to women who had survived ≥5 years at cohort enrollment also demonstrated 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 Caan et al.'s findings (18,19) and Kroenke et al.'s report in the NHS cohort (17), previous studies of post-diagnosis weight gain and mortality have been clinical trials constrained by small sample sizes (<550 women) (13-16). Among these, one study indicated an association between greater relative weight gain at 60 weeks post-diagnosis 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 5 patients with weight gain greater than 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 appear to confound the association of body mass index 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 demonstrated (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 demonstrated a healthier profile (fewer current smokers, greater proportion of BMI values in the normal 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. Additionally, 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 time 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 post-diagnosis body mass index 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.

Acknowledgements

This research was supported by grants from the Susan G. Komen Breast Cancer Foundation (POP0504234) and the National Cancer Institute (CA47147, CA47305). Preliminary data from this research were presented in a poster session at the annual Frontiers in Cancer Prevention meeting of the American Association for Cancer Research, Philadelphia, PA in December, 2007. The authors wish to thank Dr. Kala Visvanathan for her advice and support, as well as all CWLS participants, staff, and contributors.

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. [PubMed: 9169910]
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. [PubMed: 10880035]
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. [PubMed: 16835425]
4. Siiteri PK. Adipose tissue as a source of hormones. Am J Clin Nutr 1987;45:277–82. [PubMed: 3541569]
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. [PubMed: 8625103]
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. [PubMed: 11550140]
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. [PubMed: 12149305]
8. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. J Clin Oncol 2002;20:1128–43. [PubMed: 11844838]
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. [PubMed: 12074502]
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. [PubMed: 16030102]

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. [PubMed: 16103453]
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. [PubMed: 17855698]
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. [PubMed: 3516262]
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. [PubMed: 3382763]
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. [PubMed: 2199619]
16. Levine EG, Raczynski JM, Carpenter JT. Weight gain with breast cancer adjuvant treatment. Cancer 1991;67:1954–9. [PubMed: 2004310]
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. [PubMed: 15684320]
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. [PubMed: 16541317]
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
20. Ries, LAG.; Melbert, D.; Krapcho, M., et al., editors. SEER Cancer Statistics Review, 1975−2004. National Cancer Institute; Bethesda:
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. [PubMed: 8259187]
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. [PubMed: 9637142]
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. [PubMed: 17301255]
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. [PubMed: 18250341]
26. World Health Organization. Report of a WHO Expert Committee. WHO Technical Report Series. Geneva: 1995. Physical status: the use and interpretation of anthropometry..
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 Royal Stat Soc B 1972;34:187–220.
29. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999;341:427–34. [PubMed: 10432328]
30. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9. [PubMed: 6720679]
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. [PubMed: 8452128]

Table 1

Select characteristics among participants and non-participants in the Collaborative Women's Longevity Study

Characteristic at diagnosis	CWLS Participants N=5,791	CWLS Non-participants 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 years, %	91.2	83.1
Body mass index†		
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 week, 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.

†Body mass index 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 Collaborative Women's Longevity Study (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)
Body mass index, 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 years, %	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
Body mass index, 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)	1583 (575)	1726 (588)	1713 (513)	1703 (528)	1741 (623)
Hormone therapy, % current	1.8	2.8	2.1	2.0	2.5
Years from diagnosis to follow-up survey (sd)	6.4 (3.0)	6.0 (2.8)	5.1 (2.9)	5.7 (3.2)	6.9 (3.4)

*Data obtained by parent case-control studies.

†Data obtained by CWLS questionnaire.

‡Year prior to enrollment in CWLS.

Table 3

Hazard ratio (HR) and 95% confidence intervals (CI) for all-cause, breast cancer, and cardiovascular disease (CVD) mortality according to body mass index (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)[†]
Pre-diagnosis BMI[†]							
Underweight (<18.5 kg/m^2)	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 kg/m^2)	2058	178	1	50	1	36	1
Overweight (25.0−29.9 kg/m^2)	1228	137	1.13 (0.90, 1.42)	45	1.48 (0.98, 2.24)	27	1.05 (0.63, 1.74)
Obese (≤30 kg/m^2)	639	93	1.52 (1.17, 1.98)	24	1.42 (0.86, 2.36)	28	2.45 (1.46, 4.11)
		419		121		95	
Post-diagnosis BMI[†]							
Underweight (<18.5 kg/m^2)	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 kg/m^2)	1497	140	1	31	1	30	1
Overweight (25.0−29.9 kg/m^2)	1373	133	0.91 (0.72, 1.16)	37	1.34 (0.83, 2.18)	30	0.99 (0.59, 1.66)
Obese (≥30 kg/m^2)	977	122	1.27 (0.99, 1.64)	48	2.28 (1.43, 3.64)	29	1.65 (0.97, 2.83)
		405		117		90	
Weight change since diagnosis[‡]							
−50 to −10.1 kg	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 kg	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 kg	1037	98	1	28	1	27	1
2.1 to 6.0 kg	1127	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 kg	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 kg	552	61	1.70 (1.21, 2.41)	27	1.78 (1.01, 3.14)	12	1.73 (0.83, 3.62)
		421		121		95	
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)

[*] Total numbers of deaths vary slightly in pre- and post-diagnosis BMI models compared to 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 pre-diagnosis weight.

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

‖ Analysis restricted to women who reported staying with in 2 kg of their pre-diagnosis weight or gaining weight.