Published in final edited form as:
Epidemiology. 2012 March ; 23(2): 320–327. doi:10.1097/EDE.0b013e31824596a1.

POST-DIAGNOSIS CHANGE IN BODYWEIGHT AND SURVIVAL AFTER BREAST CANCER DIAGNOSIS

Patrick T. Bradshaw[1], **Joseph G. Ibrahim**[2], **June Stevens**[1,3], **Rebecca Cleveland**[3], **Page E. Abrahamson**[1], **Jessie A. Satia**[1,3,†], **Susan L. Teitelbaum**[4], **Alfred I. Neugut**[5], and **Marilie D. Gammon**[1]

[1]Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC, 27599

[2]Department of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, NC, 27599

[3]Department of Radiology, School of Medicine, University of North Carolina, Chapel Hill, NC, 27599

[4]Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY 10029

[5]Department of Medicine, College of Physicians and Surgeons, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032

Abstract

Background—Weight gain after diagnosis is common among women with breast cancer, yet results have been inconsistent among the few studies examining its effects on survival.

Methods—We examined the effects of weight gain on mortality among a cohort of 1,436 women diagnosed with a first primary breast cancer in 1996–1997, on Long Island, NY. Subjects were interviewed soon after diagnosis and again after approximately 5 years. Weight was assessed at each decade of adult life; one year before, at and one year after diagnosis; and at the time of follow-up. Mortality through the end of 2005 was assessed using the National Death Index. Proportional hazards regression was used while employing a selection model to account for missing data.

Results—Compared with women who maintained their pre-diagnosis weight (+/− 5%), those who gained more than 10% after diagnosis had worse survival (hazard ratio [HR]= 2.67; [95% credible interval=1.37–5.05]. The effect was more pronounced during the first 2 years after diagnosis (>5% gain, all-cause mortality in the first 2 years, HR = 5.87 [0.89 – 47.8] compared with after 2 years (1.49 [0.85 – 2.57]); among women overweight before diagnosis (overweight women, all-cause HR = 1.91 [0.91 – 3.88] compared with ideal-weight women, 1.39 [0.62 – 3.01)]; and for women who had gained at least 3 kilograms over adulthood before diagnosis (>= 3 kg gain before diagnosis 1.80 [0.99 – 3.26 compared with < 3 kg gain before diagnosis 1.07 [0.30 – 3.37].

Corresponding author: Patrick Bradshaw, Department of Epidemiology, CB#7435 McGavran-Greenberg Hall, School of Public Health, University of North Carolina, Chapel Hill, NC, 27599-7435; patrickb@email.unc.edu.
[†]Died February 4, 2010.

Conclusions—These results highlight the importance of weight maintenance for women after breast cancer diagnosis.

For the more than 2 million female breast cancer survivors in the United States,[1] it is important to identify modifiable factors that may improve survival. Of particular interest is the effect on survival of changes in body size after diagnosis, because weight gain among women with breast cancer is often observed in response to treatment with chemotherapy, as well as among women of younger age, women with lower pre-diagnosis body size, women who are premenopausal, and women who present with later disease stage at diagnosis.[2–7] Higher levels of adipose tissue are associated with greater circulating levels of hormones such as estrogen, insulin and related growth factors, which increase proliferation of mammary cells and are associated with breast carcinogenesis.[8–10]

Body size at or before diagnosis[4] has been related to survival, but whether weight change after diagnosis affects survival has been studied less frequently and with inconsistent results.[4,11–14] Furthermore, most previous studies have not employed longitudinal measures of post-diagnosis weight change, and thus have been unable to examine whether the effect may vary over time. The effect of changes in body size near diagnosis is a critically under-addressed issue in survivorship research. Of the few studies that have addressed this issue, most limit their approach in several key ways. First, most previous investigations have assessed weight change only once after diagnosis; multiple measurements after diagnosis times would help to elucidate the critical window of exposure in which weight change might affect survival. Second, the study populations in previous analyses have been limited to survivors 2 or more years post-diagnosis (often much more); this approach creates cohorts biased in their tendency to survive, which again fails to account for the entire survivorship experience.

A recent report from our group showed that weight gain after diagnosis was associated with greater all-cause and breast cancer-specific mortality,[15] among a cohort of women interviewed shortly after diagnosis and followed for approximately 9 years. The primary purpose of that manuscript was to describe an analytic method developed to account for missing covariate data in survival analysis. That report did not address several important issues regarding how the effect of weight change on survival may vary over time, or how the effect may be confounded by, or vary by, pre-diagnosis body size characteristics. Here we apply that method to examine the effect of post-diagnosis weight change over time on survival after breast cancer diagnosis in a large, population-based cohort of women diagnosed with breast cancer in 1996–1997 on Long Island, New York.

Methods

We used data from the Long Island Breast Cancer Study Project, which was initiated as a population-based case-control study[16] and continued as a follow-up of the cohort of case women. The study was approved by the Institutional Review Board of participating institutions.

Study Population

Cases were English-speaking adult women with a first primary *in situ* or invasive breast cancer diagnosed between 1 August 1996 and 31 July 1997, from Nassau and Suffolk counties in New York. Potentially eligible subjects were identified through participating hospitals, and their physicians were contacted to confirm the diagnosis and obtain permission to contact the patients for participation in the study. A total of 1,508 eligible cases (82%) signed informed consent in person and completed the baseline questionnaires an average of 3 months after diagnosis.[16]

At baseline, 94 case women declined to be contacted at a later date for participation in the follow-up. For the remaining cases, they or their proxy were contacted approximately 5 years after diagnosis of the first primary breast cancer. Of the 1,414 women who initially agreed to participate, 60 subsequently declined when contacted by mail, 65 declined when contacted by telephone, 18 declined due to illness, 22 were unable to complete the interview, 55 were lost to follow-up, and 96 were deceased with no identifiable proxy to complete the interview. Of the remaining 1,098 subjects for whom informed consent was obtained by telephone, 65 were omitted because they provided information only about their first course of treatment for their first primary breast cancer. Ultimately 1,033 case subjects completed the follow-up interview,[17] of which about 8% were with the proxy. The follow-up questionnaire included ascertainment of information similar to that gathered in the baseline questionnaire,[16] but relevant to the time period since diagnosis.

Outcome Assessment

Date and cause of death were determined through the National Death Index (NDI),[18] a centralized database of death records maintained by the National Center for Health Statistics, which is considered the standard source of mortality data for epidemiologic research.[19] For deceased women we constructed two indicators: (1) breast cancer- specific mortality (any breast cancer-related death, International Classification of Disease code 174.9 or C-50.9); and (2) all-cause mortality (death from any cause). Of the 1,508 cases from the parent study, there were 308 deaths as of 31 December 2005, with just over half (n=164) attributed to breast cancer.

Body Size Assessment

The baseline questionnaire[16] assessed self-reported height in inches and body weight in pounds at age 20 years and at 1 year prior to date of diagnosis. It also included assessments of weight in pounds by decade of life from 20 years through 70 years of age. The follow-up questionnaire included assessments of self-reported height and body weight in pounds at diagnosis, one year after diagnosis and at the time of the follow-up interview (or one year before death for deceased subjects for whom the questionnaire was completed by proxy). This yielded three assessments of body size at and after diagnosis.

Percent change in body weight was calculated from the year prior to diagnosis to diagnosis, 1-year after diagnosis, and the time of follow-up interview as 100*(weight at later measurement - weight one year before diagnosis)/weight one year before diagnosis.

We categorized weight change as >5% loss; maintained within (plus or minus) 5%; 5%–10% gain; and greater than 10% weight gain. These categories were selected for comparison with other reports,[11] and they correspond to weight management recommendations aimed at cancer patients.[20] To avoid small counts within strata when assessing effect modification, we combined the upper two categories of weight gain. Other body-size variables included body mass index (BMI) 1 year before diagnosis (<25 kilograms/meters^2 (kg/m^2), 25–30 kg/m^2 and >=30 kg/m^2) and adult weight change, from age 20 years to 1 year before diagnosis (>3 kg loss, maintenance within 3 kg, and >3 kg gain). These categorizations reflect those used in previous analyses of the Long Island Breast Cancer Project.[21]

Covariates

Structured questionnaires were administered by trained interviewers at baseline[16] and at follow-up. Information collected included sociodemographic characteristics, select clinical characteristics (including first course of treatment for the first primary breast cancer), and known and suspected risk and prognostic factors for breast cancer.

For case women who signed a medical record release form at baseline (97.7%), tumor stage and estrogen and progesterone receptor (ER/PR) status of the first primary breast cancer were ascertained from the medical records. At the follow-up, signed medical record release forms were obtained again, and medical records were abstracted for 598 women to obtain the details regarding complete course of treatment for the first primary breast cancer diagnosis. These data were then compared with the self-reported information obtained during the telephone follow-up interview. Kappa coefficients comparing self-report and medical records were high for all three treatment modalities examined: radiation therapy κ=0.97, chemotherapy κ=0.96 and hormone therapy κ=0.92,[21] and thus the self-reported data are included in these analyses. Data on tumor size were obtained from the New York State Cancer Registry.

Statistical Analysis

Non-response to specific questions among subjects alive at each time, coupled with non-participation in the follow-up interview, yielded missing data on weight (48%, 49% and 34% at time of diagnosis, 1-year post diagnosis and final follow-up, respectively). Given such substantial missing data, and the sensitivity of assessing body size, there was concern that body size data may be not missing at random, a condition that arises when the probability that data are missing is dependent upon the unobserved values.[22,23] In this study, the potential issue was that non-response to the follow-up questionnaire may be more likely among heavier women, who may be more psychologically sensitive to questions regarding bodyweight or who may be in poor health caused by being overweight. To address this issue, we used a selection model for proportional hazards regression with non-ignorably missing time-varying covariates.[15] The selection model describes the joint distribution of the probability that covariate data is missing (indicated by the vector of binary variables ***R***), the outcome (failure time, denoted by T) and the covariates with missing data (denoted by the vector ***Z***), some of which may vary over time, with fully-observed covariates (denoted by ***X***). This joint distribution is expressed as a sequence of conditional distributions:

$$p(\mathbf{R}, T, \boldsymbol{Z} \mid X) = p(\mathbf{R} \mid T, \boldsymbol{Z}, \mathbf{X}) \times p(T \mid \mathbf{Z}, \mathbf{X}) \times p(\boldsymbol{Z} \mid X)$$

which is used to derive the likelihood.

The probability that data were missing for weight change at each observation, $p(\mathbf{R} \mid T, \mathbf{Z}, \mathbf{X})$, was modeled as a logistic regression with age, weight change at the corresponding observation, and missingness indicators for previous observations as predictors. Note that the inclusion of the value of weight change in this model accounts for the potentially not missing-at-random nature of the data.

For the distribution of the outcome, $p(T \mid \mathbf{Z}, \mathbf{X})$, a proportional hazards regression with time-varying covariates was specified to estimate the effect of post-diagnosis weight change on time to death. Values for post-diagnosis weight change between assessed time points (e.g. years 2, 3 and 4) were approximated by linear interpolation.[15] This model included post-diagnosis change in body size, and was adjusted for age (continuous), chemotherapy (yes, no), tumor size (>= 2 cm vs. < 2cm), estrogen-receptor status (ER status; yes, no) and progesterone-receptor status (PR status; yes, no) -- all of which are confounders that identified through use of a directed acyclic graph. We present models with and without adjusting for pre-diagnosis body size, BMI one year before diagnosis (<25 kg/m^2 (referent category), >= 30 kg/m^2) and adult weight change from age 20 (> 3 kg loss, maintained within 3 kg (referent category), > 3 kg gain).

The distribution of change in body size at each time, $p(\mathbf{Z} \mid \mathbf{X})$, was modeled as a linear regression dependent upon previous change in body-size variables, as well as age, chemotherapy, menopausal status and BMI before diagnosis variables established in the literature to be consistently associated with post-diagnosis weight change.[2–7] In addition to weight change, other covariates with relatively high levels missing data included chemotherapy, tumor size, ER status and PR status, with 32.2%, 31.6%, 34.0% and 34.3% missing, respectively. Chemotherapy and tumor size were modeled as logistic regressions against age, income (< $20,000; $20,000–49,999; $50,000–89,999 and >= $90,000) and education (high school or less, some college, college graduate and post-college), while hormone receptor status indicators were modeled as logistic regressions as a function of age. Treatment and tumor characteristics were unlikely to be non-ignorably missing and therefore did not require specification of models for their missing data mechanisms.

To assess effect modification, the product of post-diagnosis weight change and menopausal status (premenopausal, postmenopausal), time (< 2 years, >= 2 years), BMI one year before diagnosis (categorized as <25 kg/m^2 and >= 25 kg/m^2) and adult weight gain from age 20 years to 1 year before diagnosis (any loss or maintain within 3 kg, gain >= 3 kg) were included. The time interaction of two years was chosen because recent studies of post-diagnosis weight change assessed women at approximately this time[11,12] and to distinguish the possible effects of weight gain shortly after diagnosis.

The ancillary models ($p(\mathbf{R} \mid T, \mathbf{Z}, \mathbf{X})$ and $p(\mathbf{Z} \mid \mathbf{X})$) are not of inferential interest and are needed only to provide unbiased estimates of the survival model. Subjects with minor amounts of missing data (menopausal status: 2% missing, pre-diagnosis BMI: 1% missing, adult weight change: 1.2% missing, education: <1% missing) and income: <1% missing) were excluded from the analysis, as these data were unlikely to influence our results. This analysis ultimately included 1,436 women, 292 of whom died during our follow-up, with 156 of these deaths attributed to breast cancer.

We employed a fully Bayesian approach to parameter estimation using the Gibbs sampler in WinBUGS 1.4[24] to sample from the joint posterior distribution of the parameters. We specified vague prior distributions: normal with mean 0 and variance 10^6 for regression coefficients, gamma with shape and inverse scale parameters of 0.001 for baseline hazards and variance parameters to generate posterior estimates that are similar to those from frequentist analysis. The sampler was run for 200,000 iterations, discarding the first 100,000 as a burn-in sample, retaining every 5th iteration to reduce serial correlation. Posterior hazard ratios (HR) and 95% posterior credible intervals were calculated by taking the anti-logarithm of the mean of the samples for the beta coefficients (log-hazard ratios) from the proportional hazards model and the 2.5th and 97.5th percentiles of these samples, respectively.

Results

Median follow-up time was 8.8 years after diagnosis with a range from 0.2 to 9.4 years. At the time of diagnosis, the age range of the women was between 25 to 98 years, with an average of 59 years, and most were postmenopausal (Table 1). Fewer than half of the women received chemotherapy treatment, and most tumors were hormone-receptor positive. Fewer than 20% of the tumors were 2 cm or larger. Among women with complete data on at least one follow-up measure of body size, 55% maintained their pre-diagnosis body size.

Mortality was increased for women who either lost or gained weight after diagnosis (Table 2). The association of moderate weight gain with mortality (all-cause posterior HR = 1.09 [95% credible interval = 0.51 – 2.18]) was somewhat greater after adjustment for pre-

diagnostic BMI and adult weight gain, and similar to the minimally adjusted model we reported previously.[15] These additional adjustments did not meaningfully change the observation, from our previous model, that mortality risk was more than doubled for large post-diagnosis weight gain (all-cause posterior HR= 2.67 [1.37–5.05]); breast-cancer-specific posterior HR=2.84 [1.15–6.65]) (Table 2). Among women who lost weight after diagnosis, the effect on survival was adverse; the estimates for all-cause (5.29 [3.48–8.09]) and breast-cancer-specific mortality (7.09 [3.93–13.4]) were similarly pronounced, even after adjusting for weight changes throughout adulthood but before diagnosis.

As shown in Table 3, the association between weight gain and survival appeared somewhat stronger among women who were premenopausal before diagnosis (all-cause posterior HR=2.29 [0.84–6.73]) compared with postmenopausal women (1.51 [0.77–2.87]). The deleterious effects of post-diagnosis weight gain appear stronger when weight is gained shortly after diagnosis (within the first 2 years after diagnosis, all-cause posterior HR=5.87 [0.89–47.8] and breast cancer-specific HR=3.75 [0.56–31.2]), although the wide credible intervals indicate imprecise estimates resulting from the low number of deaths (52 all-cause, 36 breast-cancer-specific) within the first 2 years. Weight gain after two years shows similar effects for all-cause and breast cancer-specific mortality, with moderate increases in risk of death compared with women who maintained their weight. The effect of weight gain is greater among women who were overweight and obese (BMI >= 25 kg/m^2) before diagnosis than among women of ideal weight (BMI < 25 kg/m^2) before diagnosis, with the difference being greatest for breast cancer-related deaths (BMI < 25 kg/m^2, posterior HR=1.08 [0.34–3.21] and BMI >= 25 kg/m^2, 2.76 [0.94–8.47]). The effect of weight gain on all-cause mortality may be limited to those women who gained weight before diagnosis (<3 kg gain before diagnosis, posterior HR=1.07 [0.30–3.37] and >=3 kg gain before diagnosis, 1.80 [0.99–3.26]). Due to the small number of breast-cancer-related deaths among women without pre-diagnosis weight gain (n=21), we were unable to calculate stable estimates of risk of breast-cancer-related mortality associated with post-diagnosis weight change in this subgroup. However, upon limiting the analysis to women who gained at least 3 kg before diagnosis, we observed a strong effect of post-diagnosis weight gain (HR=2.24 [0.97–5.26]), which was similar in magnitude to that observed for all-cause mortality.

Discussion

Previously reported findings on weight change after diagnosis in this cohort of 1,436 women diagnosed with *in situ* or invasive breast cancer focused on the methodologic approach for considering missing covariate data in survival analysis.[15] That previous analysis did not include adjustments for pre-diagnosis levels of BMI or adult weight change, nor did it consider effect measure modification, including how the effect may vary over time. In the analysis presented here, even after adjusting for pre-diagnosis body size, moderate increases in risk of all-cause mortality were still observed among women who gained between 5% and 10% of their pre-diagnosis weight at any time after diagnosis. Large increases in mortality risk were found among women who gained more than 10% of their pre-diagnosis weight after diagnosis. When pre-diagnosis anthropometric measures of adiposity were included in the models, the effects were essentially unchanged. The effect of weight gain on mortality appeared stronger among premenopausal women compared with postmenopausal women and for women within the first 2 years after diagnosis compared with after 2 years, although analytic precision was limited to draw firm conclusions regarding these differences. The effect of post-diagnosis weight gain on breast-cancer-specific mortality was also stronger among women who had gained weight as an adult before diagnosis.

Fat mass may promote the development of postmenopausal breast cancer because visceral adipose tissue is metabolically active[25] and affects a number of pathways that are involved

in carcinogenesis. Visceral adipose tissue is associated with increased estradiol and decreased sex hormone binding globulin (SHBG),[26] as well as increased insulin and insulin-like growth factors,[10,27] which can promote a hormonal environment that encourages proliferation of both normal and cancerous mammary cells.[8–10] Weight gain after adolescence is associated with accumulation of visceral adipose tissue, and therefore changes in body size may be relevant.[28] Similar biologic effects of increasing levels of adipose tissue on prognosis are of particular concern, as weight gain from approximately 1 kg to more than 10 kg within the first two years after diagnosis of breast cancer is well-documented.[4]

The relationship between breast cancer survival and post-diagnosis weight change is far less studied than the relationship with pre-diagnostic body size.[11–14,29–33] Although the methodology varied considerably among previous studies, findings in general for postdiagnostic weight gain have been null when modest increases in weight have been considered, with mean weight gain of less than 6 kg in the upper category.[31–33] However, greater increases in mortality have been noted with larger changes in weight or BMI, particularly in subgroups,[12,29,30] with mean weight change among subjects in the upper category typically over 10 kg. Recent findings for postdiagnostic weight gain remain inconsistent; Caan and colleagues[11] failed to find an association between post-diagnosis weight change and survival, yet Nichols et al.[13] found results more similar to those reported here. Most recently, in a Chinese cohort, Chen et al.[14] reported that weight gain of 5 kg or more during the 18 months after diagnosis was associated with poor survival, and the effect was slightly stronger for breast-cancer-specific mortality.

Differences in findings related to postdiagnostic weight gain across studies are therefore likely due to variations across studies in the study cohort (years since the first primary diagnosis, ethnicity, age/menopausal status of the patients, sample size, and length of follow-up), and in the exposure measure (number of weight assessments, and the average weight gained postdiagnosis). For example, studies with null findings have been limited by small sample sizes[31–33] and short follow-up.[31,33] Timing of the post-diagnostic weight change measures is also likely to contribute to varied findings. Unlike previous work, our study was able to utilize multiple anthropometric measures from date of diagnosis, allowing us to estimate the effect of this time-varying exposure, as well as to estimate differences in effect across relevant time periods. Our findings of a possible stronger association of post-diagnosis weight gain among premenopausal women is supported by some other studies[12,29] but not all.[13,14] The very different study populations in the latter reports (a Chinese cohort in one,[14] only non-metastatic cases interviewed one to two years after diagnosis in the other[13]) could explain this discrepancy. We found the effect of weight gain was more pronounced closer to diagnosis, which was not assessed in other studies that instead used body size measures at least 2 years following diagnosis.[11,12] The lone previous study that did assess weight change near and after diagnosis[14] analyzed weight change only as a series of fixed time exposures, which fails to account for the longitudinal aspect of this variable.

Our findings of greater mortality associated with postdiagnostic weight loss are consistent with recent reports,[11,13,14] which all report hazard ratios over 2 in the greatest category of weight loss for death from any cause. Data from the Nurses' Health Study also suggested a greater risk of death among those who lost weight, although this finding was not statistically significant.[12] It is unclear if this observed association between weight loss and survival is due to a distinct effect of the weight loss or to the fact that those who are near death are likely to be losing weight. This issue could possibly be clarified by studies with larger sample size that assessed intent of weight loss. Recent recommendations regarding weight loss for breast cancer patients[34] have been made based on the observation that greater BMI at diagnosis is associated with poor survival. However, these recommendations may be

premature, given that they are not consistent with the currently available epidemiologic evidence, including the study reported here.

Obesity at diagnosis and adult weight gain before diagnosis are established indicators of poorer prognosis,[4,34–36] although most of the studies conducted to date have not accounted for post-diagnosis changes in body size. Similarly, a recent report that utilized the Long Island breast cancer cohort observed hazard ratios ranging from 1.63 to 2.85 for women who were obese before diagnosis.[21] Additionally, our observation of a more pronounced adverse effect for post-diagnosis weight gain among women who also gained weight as an adult before diagnosis underscores the importance of avoiding increases in adiposity at any point in a woman's life trajectory.

Strengths of this study include its population-based study design and relatively large sample size. Also, an innovative analytic approach to the treatment of missing exposure and confounder data was employed. A commonly used alternative approach is the complete case analysis, which is automatically carried out by most software packages; however, it usually reduces statistical efficiency, and can yield biased effect estimates in all but the most rigid conditions. *Ad hoc* adjustment for missing data is still common in epidemiology -- such as some variant of the "missing indicator" method or improper imputation, which can perform even worse than complete case analysis.[22] Formal treatment of missing data is crucial to accurate inference, and the selection model approach employed here can account for potentially non-ignorably missing covariates, which is a situation where bias and statistical efficiency are of greatest concern.[23] Even though the methodology used here is theoretically sound, it is important to keep in mind that even the most rigorous statistical model is no substitute for having the data that were unobserved. Missing-data models rely on untestable assumptions and can be quite sensitive to changes in specification.[37]

An important strength of this analysis is that data from multiple assessments of change in body size over the follow-up experience were utilized, starting at and near diagnosis, which allowed for determination of differential effects based on timing of weight change – an assessment that until now has not been addressed. A limitation of this analysis is the use of self-reported body size measures, which leaves open the potential for measurement error. However, self-reported anthropometric measures have been shown to be highly correlated with measurements taken in a clinic setting.[38] Data from the NHANES III study showed that self-reported and measured weight are highly correlated and that older women, who make up most of this cohort, tend to report their weight accurately.[39] Also, self- and interviewer-obtained measurements have shown nearly identical associations in a recent analysis of pre-diagnosis BMI and survival after breast cancer diagnosis in a similar cohort.[40] The use of proxy interviews could also be a source of bias, although these accounted for only a small portion of our study sample (<8%), and a recent detailed report comparing the use of proxy and case assessments illustrated that proxy assessments of anthropometric measures yielded associations that were nearly identical to those completed by the case subject.[41] To address this concern, we conducted a sensitivity analysis omitting those subjects with data from proxy interviews with similar results (data not shown).

The results from our stratified models should be interpreted as exploratory given that statistical precision was reduced for subgroup analysis. The categorization of pre-diagnosis BMI and pre-diagnosis weight gain yielded a different percentage of cases in each subgroup. Notably 80% of the cohort appeared in the upper category of pre-diagnosis weight gain, which may have contributed to the differences noted, as BMI and weight gain are highly correlated.

In summary, these findings suggest that weight maintenance after breast cancer diagnosis should be encouraged, especially among women who have gained weight as an adult before diagnosis. The time period immediately after diagnosis may be especially relevant for weight maintenance, when treatment-related weight gain is common.

Acknowledgments

Funding sources: This work supported in part by National Cancer Institute and the National Institutes of Environmental Health and Sciences Grant nos. UO1CA/ES66572, P30ES10126, T32CA72319 and T32CA009330.

References

1. SEER Cancer Statistics Review, 1975–2004. [Accessed September 28, 2007] National Cancer Institute. 2006. http://seer.cancer.gov/csr/1975_2004. Updated November 2006.
2. Campbell KL, Lane K, Martin AD, Gelmon KA, McKenzie DC. Resting energy expenditure and body mass changes in women during adjuvant chemotherapy for breast cancer. Cancer Nurs. 2007 Mar-Apr;30(2):95–100. [PubMed: 17413774]
3. Demark-Wahnefried W, Rimer BK, Winer EP. Weight gain in women diagnosed with breast cancer. J Am Diet Assoc. 1997 May; 97(5):519–526. 529. quiz 527-518. [PubMed: 9145091]
4. Goodwin, PJ. Energy Balance and Cancer Prognosis, Breast Cancer. In: McTiernan, A., editor. Cancer Prevention and Management Through Exercise and Weight Control. CRC Press; 2005. p. 405-435.
5. Irwin ML, McTiernan A, Baumgartner RN, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol. 2005 Feb 1; 23(4):774–782. [PubMed: 15681521]
6. Makari-Judson G, Judson CH, Mertens WC. Longitudinal patterns of weight gain after breast cancer diagnosis: observations beyond the first year. Breast J. 2007 May-Jun;13(3):258–265. [PubMed: 17461900]
7. Rock CL, Flatt SW, Newman V, et al. Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. J Am Diet Assoc. 1999 Oct; 99(10):1212–1221. [PubMed: 10524383]
8. Adami, HA.; Hunter, D.; Trichopolous, D. Textbook of Cancer Epidemiology. New York: Oxford University Press; 2002.
9. Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control. 1996 Nov; 7(6):605–625. [PubMed: 8932921]
10. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst. 2000 Sep 20; 92(18):1472–1489. [PubMed: 10995803]
11. 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 Aug 28; 19(10):1319–1328. [PubMed: 18752034]
12. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol. 2005 Mar 1; 23(7):1370–1378. [PubMed: 15684320]
13. Nichols HB, Trentham-Dietz A, Egan KM, et al. Body Mass Index Before and After Breast Cancer Diagnosis: Associations with All-Cause, Breast Cancer, and Cardiovascular Disease Mortality. Cancer Epidemiol Biomarkers Prev. 2009 Apr 14.
14. Chen X, Lu W, Zheng W, et al. Obesity and weight change in relation to breast cancer survival. Breast Cancer Res Treat. 2010 Aug; 122(3):823–833. [PubMed: 20058068]
15. Bradshaw PT, Ibrahim JG, Gammon MD. A proportional hazards regression model with non-ignorably missing time-varying covariates. Statistics in Medicine. In press.
16. Gammon MD, Neugut AI, Santella RM, et al. The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. Breast Cancer Res Treat. 2002 Jun; 74(3):235–254. [PubMed: 12206514]
17. Fink BN, Gaudet MM, Britton JA, et al. Fruits, vegetables, and micronutrient intake in relation to breast cancer survival. Breast Cancer Res Treat. 2006 Jul; 98(2):199–208. [PubMed: 16538530]

18. Centers for Disease Control and Prevention. [Accessed February 7, 2006] What is the National Death Index?. 2006. http://www.cdc.gov/nchs/r&d/ndi/what_is_ndi.htm.
19. Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. Ann Epidemiol. 2002 Oct; 12(7):462–468. [PubMed: 12377423]
20. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin. 2006 Nov-Dec;56(6):323–353. [PubMed: 17135691]
21. Cleveland RJ, Eng SM, Abrahamson PE, et al. Weight gain prior to diagnosis and survival from breast cancer. Cancer Epidemiol Biomarkers Prev. 2007 Sep; 16(9):1803–1811. [PubMed: 17855698]
22. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol. 1995; 142(12):1255–1264. [PubMed: 7503045]
23. Little, RJA.; Rubin, DB. Statistical Analysis with Missing Data. 2nd ed.. New York: Wiley; 2002.
24. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS--a Bayesian modelling framework: concepts, structure and extensibility. Statistics and Computing. 2000; 10:325–337.
25. Matsuzawa Y, Shimomura I, Nakamura T, Keno Y, Kotani K, Tokunaga K. Pathophysiology and pathogenesis of visceral fat obesity. Obes Res. 1995 Sep; 3(Suppl 2):187S–194S. [PubMed: 8581775]
26. Kaaks, R.; McTiernan, A. Obesity and Sex Hormones. In: McTiernan, A., editor. Cancer Prevention and Management Through Exercise and Weight Control. CRC Press; 2005. p. 289-300.
27. Zimmet PZ. Hyperinsulinemia--how innocent a bystander? Diabetes Care. 1993 Dec; 16(Suppl 3): 56–70. [PubMed: 8299479]
28. Kumar NB, Lyman GH, Allen K, Cox CE, Schapira DV. Timing of weight gain and breast cancer risk. Cancer. 1995 Jul 15; 76(2):243–249. [PubMed: 8625099]
29. 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 Aug; 8(8):1327–1334. [PubMed: 2199619]
30. 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(1):23–30. [PubMed: 3516262]
31. Costa LJ, Varella PC, del Giglio A. Weight changes during chemotherapy for breast cancer. Sao Paulo Med J. 2002 Jul 4; 120(4):113–117. [PubMed: 12436158]
32. Goodwin PJ, Panzarella T, Boyd NF. Weight gain in women with localized breast cancer--a descriptive study. Breast Cancer Res Treat. 1988 Apr; 11(1):59–66. [PubMed: 3382763]
33. Heasman KZ, Sutherland HJ, Campbell JA, Elhakim T, Boyd NF. Weight gain during adjuvant chemotherapy for breast cancer. Breast Cancer Res Treat. 1985; 5(2):195–200. [PubMed: 4016284]
34. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. J Clin Oncol. 2002 Feb 15; 20(4):1128–1143. [PubMed: 11844838]
35. Barnett JB. The relationship between obesity and breast cancer risk and mortality. Nutr Rev. 2003 Feb; 61(2):73–76. [PubMed: 12674440]
36. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. J Clin Oncol. 2002 Aug 1; 20(15):3302–3316. [PubMed: 12149305]
37. Herring AH, Ibrahim JG, Lipsitz SR. Non-ignorable missing covariate data in survival analysis: a case-study of an International Breast Cancer Study Group trial. Applied Statistics. 2004; 53(2): 293–310.
38. Weaver TW, Kushi LH, McGovern PG, et al. Validation study of self-reported measures of fat distribution. Int J Obes Relat Metab Disord. 1996 Jul; 20(7):644–650. [PubMed: 8817358]
39. Kuczmarski MF, Kuczmarski RJ, Najjar M. Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Am Diet Assoc. 2001 Jan; 101(1):28–34. quiz 35-26. [PubMed: 11209581]

40. Abrahamson, PE. Recreational physical activity, body size, and breast cancer survival among young women [Dissertation]. Chapel Hill, NC: Epidemiology, University of North Carolina at Chapel Hill; 2005.

41. Campbell PT, Sloan M, Kreiger N. Utility of proxy versus index respondent information in a population-based case-control study of rapidly fatal cancers. Ann Epidemiol. 2007 Apr; 17(4): 253–257. [PubMed: 17178233]

Table 1

Characteristics of 1,436 women newly diagnosed with a first primary breast cancer between 1996 and 1997 on Long Island, NY, with follow-up assessments between 2002 and 2004.

Variable	no. (%)
Deaths through December 31, 2005	
All causes	292 (20)
Breast-cancer	156 (11)
Weight change from 1-year before diagnosis to date of diagnosis	
>5% loss	197 (26)
Maintain ±5%	458 (60)
5–10% gain	72 (10)
>10% gain	31 (4)
Missing	678
To 1-year after diagnosis	
>5% loss	168 (23)
Maintain ±5%	400 (55)
5–10% gain	95 (13)
>10% gain	64 (9)
Missing	709
To time of follow-up interview	
>5% loss	200 (21)
Maintain ±5%	414 (44)
5–10% gain	161 (17)
>10% gain	168 (18)
Missing	493
Estrogen receptor status	
Positive	701 (74)
Negative	252 (26)
Missing	483
Progesterone receptor status	
Positive	609 (64)
Negative	340 (36)
Missing	487
Chemotherapy	
Yes	404 (41)
No	573 (59)
Missing	459
Tumor size	
< 2 cm	749 (76)
>= 2 cm	234 (24)
Missing	453
BMI 1 year before diagnosis (kg/m^2)	

Variable		no. (%)
<18.5		25 (2)
18.5–24.9		639 (45)
25.0–29.9		455 (32)
>=30.0		317 (22)
Weight change from age 20 to 1 year before diagnosis		
< 3 kg gain or any loss		240 (17)
> 3 kg gain		1196 (83)
Age at diagnosis (years)[a]		
	20–29.9	10 (1)
	30–39.9	77 (5)
	40–49.9	306 (21)
	50–59.9	381 (27)
	60–69.9	340 (24)
	70–79.9	274 (19)
	80–89.9	45 (3)
	90+	3 (0)
Menopausal Status at diagnosis		
Premenopausal		462 (32)
Postmenopausal		974 (68)
Education level at diagnosis		
High school or less		688 (48)
Some college		342 (24)
College graduate		186 (13)
Post college education		220 (15)
Income at diagnosis		
< $20,000		174 (12)
$20,000–49,999		560 (39)
$50,000–89,999		427 (30)
>=$90,000		275 (19)

[a](mean=58.8 yrs [sd=2.6 yrs])

Table 2

Hazard ratios (and 95% credible intervals) for the association between post-diagnosis changes in body weight and all-cause and breast cancer-specific mortality among women newly diagnosed with a first primary breast cancer in 1996–1997 in Long Island, NY and followed through 2005.

	All-cause Mortality[a]		Breast Cancer-specific Mortality[b]	
	Model 1[c] HR (95% CI)	Model 2[d] HR (95%CI)	Model 1[c] HR (95% CI)	Model 2[d] HR (95% CI)
Post-diagnosis weight change				
>5% loss	5.30 (3.54–8.04)	5.29 (3.48–8.09)	7.25 (4.06–13.4)	7.09 (3.93–13.4)
±5% maintain[e]	1.00	1.00	1.00	1.00
5–10% gain	1.08 (0.51–2.15)	1.09 (0.51–2.18)	0.84 (0.24–2.46)	0.85 (0.24–2.46)
>10% gain	2.72 (1.40–5.09)	2.67 (1.37–5.05)	2.80 (1.13–6.50)	2.84 (1.15–6.65)

[a] 292 deaths; 1436 subjects

[b] 156 deaths; 1436 subjects

[c] Model 1 adjusted for age at diagnosis, chemotherapy treatment, ER status, PR status and tumor size. These results presented previously (Bradshaw et al.[15]).

[d] Model 2 includes covariates from Model 1 as well as BMI 1 year prior to breast cancer diagnosis and weight change from age 20 up to 1 year before breast cancer diagnosis.

[e] Reference category

Table 3

Hazard ratios (and 95% credible intervals) for the association between post-diagnosis changes in body weight and all-cause and breast cancer-specific mortality, stratified by menopausal status, time, pre-diagnosis BMI and pre-diagnosis adult weight change among women newly diagnosed with a first primary breast cancer in 1996–1997 on Long Island, NY, and followed through 2005.

Post-diagnosis weight change	All-cause Mortality[a] Hazard ratio (95% credible interval)		Breast Cancer-specific Mortality[b] Hazard ratio (95% credible interval)	
	Menopausal status at diagnosis		Menopausal status at diagnosis	
	Premenopausal (n=462)	Postmenopausal (n=974)	Premenopausal (n=462)	Postmenopausal (n=974)
>5% loss	9.16 (3.67–26.3)	4.92 (3.14–7.88)	9.90 (3.34–34.4)	6.47 (3.24–13.7)
±5% maintain[d]	1.00	1.00	1.00	1.00
>5% gain	2.29 (0.84–6.73)	1.51 (0.77–2.87)	3.09 (0.99–11.2)	0.89 (0.24–2.81)
	Time Since Diagnosis		Time Since Diagnosis	
	Before 2 years (52 deaths)	After 2 years (240 deaths)	Before 2 years (36 deaths)	After 2 years (120 deaths)
>5% loss	15.00 (3.53–99.48)	5.21 (3.41–8.06)	10.64 (2.39–71.7)	7.11 (3.77–14.0)
±5% maintain[d]	1.00	1.00	1.00	1.00
>5% gain	5.87 (0.89–47.8)	1.49 (0.85–2.57)	3.75 (0.56–31.2)	1.48 (0.62–3.44)
	Pre-diagnosis BMI		Pre-diagnosis BMI	
	< 25 (n=664)	>= 25 (n=772)	< 25 (n=664)	>= 25 (n=772)
>5% loss	7.43 (4.09–14.1)	4.75 (2.80–8.41)	7.98 (3.51–19.0)	7.84 (3.36–21.2)
±5% maintain[d]	1.00	1.00	1.00	1.00
>5% gain	1.39 (0.62–3.01)	1.91 (0.91–3.88)	1.08 (0.34–3.21)	2.76 (0.94–8.47)
	Pre-diagnosis adult weight gain		Pre-diagnosis adult weight gain	
	< 3 kg (n=240)	>= 3 kg (n=1,196)	< 3 kg[e] (n=240)	>= 3 kg (n=1,196)
>5% loss	4.18 (1.62–10.8)	6.06 (3.88–9.70)	---	8.78 (4.51–18.0)
±5% maintain[d]	1.00	1.00	---	1.00
>5% gain	1.07 (0.30–3.37)	1.80 (0.99–3.26)	---	2.24 (0.97–5.26)

[a](292 deaths/1436 subjects)

[b](156 deaths/1436 subjects)

[c]Models adjusted for pre-diagnosis BMI, pre-diagnosis adult weight gain, age at diagnosis, chemotherapy treatment, ER status, PR status and tumor size.

[d]Reference category

[e]Small number of events in this subgroup (n=21) precluded stable effect estimates.