# Body Mass and Mortality After Breast Cancer Diagnosis

**Maura K. Whiteman,[1,2] Susan D. Hillis,[2] Kathryn M. Curtis,[2] Jill A. McDonald,[2] Phyllis A. Wingo,[3] and Polly A. Marchbanks[2]**

[1]Epidemic Intelligence Service, Division of Applied Public Health Training, Epidemiology Program Office, [2]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, and [3]Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

## Abstract

**Obesity is an established risk factor for some breast cancers, but less is known about its effect on breast cancer prognosis. Understanding this relationship is important, given the increasing number of women diagnosed with breast cancer and the growing prevalence of obesity. We conducted a cohort analysis of 3,924 women ages 20 to 54 with incident breast cancer enrolled between 1980 and 1982 in the Cancer and Steroid Hormone study, a case-control study. Interview data were linked to survival information from the Surveillance, Epidemiology, and End Results Program. We used proportional hazards models to examine the relationship between breast cancer mortality and adult body mass index (BMI; calculated using usual adult weight), BMI at age 18, and weight change from age 18 to adulthood. Hazard ratios (HR) were adjusted for cancer stage and other factors. During a median follow-up of 14.6 years, 1,347 women died of breast cancer. Obese women (adult BMI ≥30.00) were significantly more likely than lean women (BMI ≤22.99) to die of breast cancer [HR, 1.34; 95% confidence interval (CI), 1.09-1.65]. Women with BMIs of 25.00-29.99 (HR, 1.25; 95% CI, 1.08-1.44) or 23.00-24.99 (HR, 1.20; 95% CI, 1.04-1.39) also had higher breast cancer mortality (*P* for trend <0.0001). BMI at age 18 and weight change were not associated with breast cancer mortality independently of other factors. Obesity could be a preventable risk factor for death among breast cancer patients. Further study is needed to determine how these findings might affect recommendations to reduce breast cancer mortality.** (Cancer Epidemiol Biomarkers Prev 2005;14(8):2009–14)

## Introduction

A large body of research has explored the associations between measures of body size and the risk of developing breast cancer. Generally, these studies suggest that obesity, estimated by body mass index (BMI) or excess weight, has opposite effects on breast cancer risk in premenopausal and postmenopausal women. Obesity tends to be associated with a modest reduction in risk of breast cancer among premenopausal women (1, 2), a phenomenon that is poorly understood but may be attributed to an increased frequency of anovulatory cycles and lower levels of serum estradiol and progesterone (3). Conversely, obesity is associated with an increased risk of breast cancer in postmenopausal women (2), likely related to higher levels of circulating bioavailable estrogen. Other aspects of body size have also been investigated for possible associations with breast cancer risk. Less consistent evidence suggests that increasing BMI at ages early in adulthood (e.g., ages 18-20) may be inversely associated with breast cancer risk (1, 4) and that adult weight gain may be positively associated with breast cancer risk in some groups of women (1, 4, 5).

Obesity is associated with an increased risk of advanced stage breast cancers (6, 7) and is associated with a hormonal profile that is thought to enhance tumor growth (8). Thus, obesity could play a role in prognosis after breast cancer diagnosis. Obesity has been reported to negatively affect breast cancer prognosis in several studies (9), but the evidence is not entirely consistent (10-12). In addition, few studies have examined BMI at earlier ages or the consequences of weight gain in adulthood with respect to breast cancer mortality. Understanding the relationship between body size and breast cancer prognosis is important because the number of women who are diagnosed with breast cancer is increasing (13), and the prevalence of obesity among women has nearly doubled during the past decade (14).

We explored the associations between mortality up to 17 years after breast cancer diagnosis and factors related to body size, including BMI as an adult, BMI at age 18 and weight change from age 18 to adulthood. To examine these associations, we linked data for breast cancer cases from the Cancer and Steroid Hormone (CASH) study, a population-based, case-control study, to survival information from the Surveillance, Epidemiology, and End Results (SEER) program. The CASH study has contributed to our understanding of body size measures as risk factors for developing breast cancer. A previous analysis from the CASH study found that among naturally postmenopausal women, the risk of breast cancer increased with increasing BMI, whereas a similar but weaker association was found in premenopausal women (15). In this report, we have used CASH data to examine body size measures as risk factors for mortality after primary breast cancer diagnosis.

## Materials and Methods

The CASH study was a multicenter, population-based, case-control study investigating the association of oral contraceptive use with breast, endometrial, and ovarian cancers. The methods have been described in detail elsewhere (16). The study received Institutional Review Board approval. Cancer cases in the CASH study were enrolled from the SEER Program in eight areas of the U.S.: the metropolitan areas of Atlanta, Detroit, San Francisco, and Seattle; the states of Connecticut, Iowa, and New Mexico; and the four urban counties of Utah.

Received 2/9/05; revised 4/21/05; accepted 5/11/05.

**Grant support:** The Cancer and Steroid Hormone Study was supported by interagency agreement 3-Y01-HD-8-1037 between the Centers for Disease Control and Prevention and the National Institute of Child Health and Human Development, with additional support from the National Cancer Institute.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Requests for reprints:** Maura K. Whiteman, Centers for Disease Control and Prevention, 4770 Buford Highway Northeast, Mailstop K-34, Atlanta, GA 30341-3724. Phone: 770-488-6293; Fax: 770-488-6391. E-mail: acq5@cdc.gov



doi:10.1158/1055-9965.EPI-05-0106

Breast cancer cases from the CASH study were women ages 20 to 54 who were diagnosed with primary breast cancer between December 1, 1980 and December 31, 1982 while residing in one of the eight study locations. Of the 5,884 women identified as meeting the case definition, 4,730 participated in the CASH study (80.4%). Reasons for nonparticipation included the inability to locate the women or to conduct an interview within 6 months (8.1%), refusal (4.1%), debilitating illness (3.6%), physician refusal (2.9%), or death (0.9%).

In the CASH study, trained interviewers administered a questionnaire to each study participant in her home within 6 months of breast cancer diagnosis. The average time between diagnosis and interview was 2.5 months. Information was collected on reproductive and contraceptive histories, medical and family histories, use of medical services, and personal characteristics and habits. The women were asked their present height, their usual weight as an adult, and their weight at age 18. BMI was calculated as weight in kilograms (kg) divided by height in meters squared ($m^2$). Weight change was calculated as the change in reported weight at age 18 to usual weight as an adult.

For analysis, adult BMI was categorized as ≤22.99, 23.00-24.99, 25.00-29.99, and ≥30.00, with the highest two categories corresponding to the WHO definitions of overweight and obese, respectively (17). BMI at age 18 was categorized as ≤21.59, 21.60-23.79, 23.80-25.49, and ≥25.50; these cut-points are based on the 25th, 75th, and 85th percentiles in the distribution of BMI among females aged 18 from the Second National Health and Nutrition Examination Survey (18). Analyses were repeated using quartiles of both adult BMI and age 18 BMI. Weight change was categorized into quintiles.

Menopausal status (premenopause, perimenopause, natural menopause, surgical menopause with no ovaries, and surgical menopause with one or two ovaries) was determined by asking about time since last menstrual period and by the presence of menopausal symptoms as described previously (15). For some analyses, menopausal status was defined as premenopause (consisting of premenopausal and perimenopausal women) or postmenopause (consisting of naturally and surgically menopausal women).

Vital status information through December 31, 1997 was obtained by linking CASH interview data with SEER public access data files (19). We successfully linked 4,536 of the 4,730 CASH breast cancer cases (95.9%) to a SEER record using matching criteria of sex, cancer site, geographic location of the SEER registry, the SEER identification number, the year of birth, and the diagnosis date (within 2 months). SEER also provided information regarding the stage of tumor at diagnosis (SEER historic stage: localized, regional, or distant disease), histologic type of tumor, and local treatment (surgery and/or radiation therapy). Survival time in SEER was defined as the time in months from the date of diagnosis to the date of death, or for those not known to have died, the time from the date of diagnosis to the date last known to be alive. For this study, we sequentially excluded women with missing weight or height information ($n = 43$), women who were diagnosed with *in situ* tumors ($n = 226$), women with unstaged tumors ($n = 38$), women with missing or unknown menopausal status ($n = 174$), women with an unknown history of benign breast disease ($n = 71$), and women who had missing information on radiation therapy ($n = 60$). A total of 3,924 women were included in this study.

We examined deaths due to breast cancer (International Classification of Diseases, Ninth Revision, codes 174.0-174.9) as the outcome. Hazards ratios (HR) and 95% confidence intervals (CI) derived from Cox proportional hazards models (20) were used to estimate the relative risk of death associated with adult BMI, age 18 BMI, and weight change. Analyses were adjusted for a set of variables selected a priori on the basis of previous literature. These factors included race (White, Black/other), radiation therapy (yes or no), history of benign breast disease (yes or no), educational level (<12, 12-15, ≥16 years), menopausal status (premenopause, perimenopause, natural menopause, surgical menopause with no ovaries, surgical menopause with one or two ovaries), and cancer stage (local, regional/distant). We also assessed the influence of additional potential confounders, including smoking, first-degree family history of breast cancer, histologic type, oral contraceptive use, postmenopausal hormone therapy use, frequency of breast examinations (before diagnosis of a breast problems including lumps, cysts, or other problems), prior mammography, number of comorbidities (diabetes, hypertension, blood clots, kidney disease, gallbladder disease, heart attack, rheumatoid arthritis, paralysis, stroke, and other cancers), parity, age at first birth, age at menarche, time since most recent birth, height, and SEER registry. None of these confounders appreciably altered the estimates from the a priori models and were, therefore, not included in the final models. Body size measures (adult BMI, age 18 BMI, and weight change), other than the measure of interest in the model, were also examined as confounders. The assumption of proportional hazards was confirmed for the included variables by testing interaction terms with time.

Trends were assessed by entering adult BMI group, age 18 BMI group, and weight change group as a single term with equally spaced category scores into the proportional hazards model. To assess whether the effect of adult BMI, age 18 BMI, and weight change on breast cancer mortality differed between subgroups of women, we examined menopausal status, age at diagnosis, cancer stage, family history of breast cancer, history of benign breast disease, oral contraceptive use, hormone therapy use (in perimenopausal and postmenopausal women), race, number of comorbidities, and age 18 BMI (in adult BMI and weight change models) as potential effect modifiers. Statistical significance of effect modifiers at the $P < 0.05$ level was determined by the log-likelihood ratio test between a full model containing the relevant interaction terms and a reduced model without the interaction terms.

## Results

Of the 3,924 women in the study cohort, 927 (23.6%) were overweight or obese, with adult BMIs of ≥25.00. When compared with women with lower adult BMIs, women with higher adult BMIs were more likely to be of an older age at diagnosis, to be postmenopausal, to be diagnosed at a later stage, to have Pap smears less than once a year, to have a greater number of comorbid conditions and were less likely to have a history of benign breast disease (Table 1). Women with higher adult BMIs were also more likely to be of a race other than White and to have fewer years of education than leaner women. There were no significant differences by adult BMI with respect to family history of breast cancer, frequency of breast examinations, previous mammography, tumor histology, or radiation therapy.

During a median follow-up of 14.6 years, 1,671 deaths occurred in the study population; of the 1,671 deaths, 1,347 (80.6%) were recorded as deaths due to breast cancer. Of the 324 deaths in the study population not coded as due to breast cancer, 31% did not have cause of death available. Our analyses with breast cancer mortality yielded similar results to those that used all-cause mortality; only those with breast cancer mortality are shown.

Compared with women with adult BMIs of ≤22.99, obese women (adult BMIs of ≥30.00) were at an increased risk of breast cancer mortality after adjusting for age at diagnosis, race, radiation therapy, history of benign breast disease, educational level, menopausal status, and cancer stage (HR, 1.34; 95% CI, 1.09-1.65; Table 2). Overweight women with adult BMIs of 25.00 to 29.99 (HR, 1.25; 95% CI, 1.08-1.44) and women with adult

**Table 1. Distribution of select characteristics according to adult BMI among women with invasive breast cancer**

| Characteristic | All ($N$ = 3,924) % | Adult BMI (kg/m$^2$) | | | |
|---|---|---|---|---|---|
| | | ≤22.99 ($n$ = 2,331), % | 23.00-24.99 ($n$ = 666), % | 25.00-29.99 ($n$ = 664), % | ≥30.00 ($n$ = 263), % |
| Age at diagnosis (y)* | | | | | |
| 20-39 | 24.8 | 27.4 | 22.4 | 19.4 | 20.9 |
| 40-45 | 23.5 | 24.9 | 21.9 | 22.0 | 19.4 |
| 46-49 | 22.1 | 22.3 | 21.6 | 20.9 | 24.3 |
| 50-55 | 29.6 | 25.4 | 34.1 | 37.7 | 35.4 |
| Race* | | | | | |
| White | 87.5 | 90.6 | 85.6 | 82.8 | 75.3 |
| Black/other | 12.5 | 9.4 | 14.1 | 17.2 | 24.7 |
| Menopausal status* | | | | | |
| Premenopause | 47.0 | 51.0 | 43.1 | 39.9 | 39.5 |
| Perimenopause | 18.0 | 16.6 | 19.1 | 20.3 | 21.7 |
| Natural menopause | 13.1 | 11.4 | 15.6 | 16.0 | 15.2 |
| Surgical menopause—no ovaries | 7.8 | 7.2 | 7.5 | 9.8 | 8.4 |
| Surgical menopause— ≥1 ovary | 14.1 | 13.8 | 14.7 | 14.0 | 15.2 |
| First-degree family history of breast cancer | 11.7 | 12.2 | 11.7 | 10.7 | 9.5 |
| Frequency of breast examinations† | | | | | |
| At least once per month | 24.5 | 23.4 | 26.9 | 25.2 | 27.0 |
| Several times a year | 26.2 | 26.4 | 26.0 | 25.3 | 27.4 |
| Once per year or less | 49.1 | 50.1 | 46.9 | 49.1 | 45.6 |
| Previous mammogram | 16.1 | 16.0 | 17.6 | 17.3 | 11.0 |
| Frequency of Pap smears* | | | | | |
| At least once per year | 72.2 | 75.3 | 71.9 | 67.3 | 57.0 |
| Less than once per year | 27.7 | 24.5 | 28.1 | 32.4 | 42.6 |
| History of benign breast disease‡ | 16.1 | 17.3 | 16.5 | 13.6 | 11.4 |
| Cancer stage at diagnosis* | | | | | |
| Local | 51.4 | 54.0 | 47.0 | 48.2 | 47.5 |
| Regional | 45.4 | 43.6 | 49.1 | 47.7 | 45.6 |
| Distant | 3.2 | 2.4 | 3.9 | 4.1 | 6.8 |
| Histologic type | | | | | |
| Ductal | 69.6 | 70.0 | 67.1 | 70.6 | 69.6 |
| Lobular | 8.6 | 9.3 | 9.5 | 6.0 | 7.2 |
| Other | 21.8 | 20.8 | 23.4 | 23.4 | 23.2 |
| Radiation therapy | 22.4 | 23.3 | 22.8 | 20.3 | 19.4 |
| Educational level (y)* | | | | | |
| <12 | 12.6 | 8.6 | 15.5 | 19.1 | 25.1 |
| 12-15 | 63.6 | 62.5 | 65.2 | 64.3 | 67.7 |
| 16+ | 23.8 | 29.0 | 19.4 | 16.6 | 6.8 |
| Number of comorbidities*,§ | | | | | |
| None | 62.8 | 71.7 | 60.5 | 47.9 | 27.8 |
| 1 | 26.7 | 22.4 | 28.2 | 35.2 | 39.9 |
| 2 | 8.0 | 4.6 | 9.0 | 13.1 | 22.4 |
| 3+ | 2.5 | 1.4 | 2.3 | 3.8 | 9.9 |

NOTE: Because of rounding or missing information, some column percentages do not add to 100.
*$P$ < 0.001: Pearson $\chi^2$ test.
†Before being diagnosed with a breast problem (lumps, cysts, or other problem).
‡$P$ < 0.05: Pearson $\chi^2$ test.
§Diabetes, high blood pressure, blood clots, kidney disease, gallbladder disease, heart attack, paralysis, rheumatoid arthritis, stroke, other cancer.

BMIs of 23.00 to 24.99 (HR, 1.20; 95% CI, 1.04-1.39) were also at a significantly increased risk of breast cancer mortality compared with women with adult BMIs of ≤22.99 (Table 2). The association between increasing adult BMI and increasing breast cancer mortality risk was also apparent after 5 years of follow-up (adjusted HR = 1.28, 1.26, and 1.49 for women with adult BMIs of 23.00-24.99, 25.00-29.99, and ≥30.00 compared with women with adult BMIs of ≤22.99, respectively) and after 10 years of follow-up (adjusted HR = 1.22, 1.31, 1.47). All results were similar when adult BMI quartiles were examined.

We also assessed whether there was evidence for a J-shaped association between adult BMI and breast cancer mortality. Women with adult BMIs of ≤18.50 did not have a breast cancer mortality risk that was significantly different from women with adult BMIs of 18.51 to 22.99 (adjusted HR, 1.07; 95% CI, 0.81-1.41). Additional analyses showed that the results in Table 2 did not change substantially when women with adult BMIs of 18.51 to 22.99 served as the reference group (data not shown).

The association between increasing adult BMI and increasing breast cancer mortality was consistent between premenopausal and postmenopausal women ($P$ for interaction = 0.9; Table 3). The association was also consistent across strata of type of menopause, age at diagnosis, BMI at age 18, oral contraceptive use, smoking, family history of breast cancer, race, cancer stage, and hormone therapy use.

There was no evidence that BMI at age 18 was associated with breast cancer mortality (Table 4). Similarly, change in weight from age 18 to usual adult weight was not associated with breast cancer mortality (Table 5). Results were similar when relative weight change (weight change divided by weight at age 18) was examined. The results for both age 18 BMI and weight change did not vary by menopausal status, age at diagnosis, adult BMI, oral contraceptive use, smoking, family history of breast cancer, race, cancer stage, number of comorbidities, or hormone therapy use.

## Discussion

Among the women in this study, adult BMI, calculated using the participants' self-report of their usual adult weight, was significantly and positively associated with breast cancer mortality. Obese women (BMI ≥30.00) experienced a breast

**Table 2. Breast cancer mortality among women with invasive breast cancer by adult BMI**

| Adult BMI (kg/m$^2$) | *N* | No. of deaths | HR* (95% CI) |
|---|---|---|---|
| ≤ 22.99 | 2,331 | 733 | 1.00 (referent) |
| 23.00-24.99 | 666 | 252 | 1.20 (1.04-1.39) |
| 25.00-29.99 | 664 | 253 | 1.25 (1.08-1.44) |
| ≥30.00 | 263 | 109 | 1.34 (1.09-1.65) |
| | | | *P* for trend <0.0001 |

*Adjusted for age at diagnosis, race, radiation therapy, history of benign breast disease, educational level, menopausal status, and cancer stage.

**Table 4. Breast cancer mortality among women with invasive breast cancer by BMI at age 18**

| Age 18 BMI (kg/m$^2$) | *N* | No. of deaths | HR* (95% CI) |
|---|---|---|---|
| ≤ 21.59 | 2,905 | 965 | 1.00 (referent) |
| 21.60-23.79 | 647 | 245 | 1.02 (0.88-1.18) |
| 23.80-25.49 | 171 | 62 | 0.93 (0.71-1.23) |
| ≥25.50 | 201 | 75 | 1.00 (0.77-1.30) |
| | | | *P* for trend = 0.9 |

*Adjusted for age at diagnosis, race, radiation therapy, history of benign breast disease, educational level, menopausal status, adult BMI, and cancer stage.

cancer mortality that was 34% higher than that of the leanest women (BMI ≤22.99). Overweight women (BMI, 25.00-29.99) and women with BMIs approaching overweight (BMI, 23.00-24.99) also experienced significantly higher breast mortality than leaner women. Neither BMI at age 18 nor weight change from age 18 to adulthood were independently associated with breast cancer mortality.

Our finding of increasing breast cancer mortality with increasing adult BMI is in accordance with a growing body of evidence suggesting that obesity could be a preventable risk factor for breast cancer mortality. A recent critical review of the topic found that, of 26 observational studies, 17 found increased BMI or body weight to be associated with a significantly increased risk of recurrent disease and/or decreased survival, 7 had null findings, and 2 reported an inverse association between body weight and recurrence (9). Generally, in studies reporting a positive association, the magnitude of the association is somewhat greater than the 34% increase in breast cancer mortality among obese women observed in this study. However, direct comparisons are complicated by differing definitions of high BMI or obesity and varying control of confounders. As in this study, the detrimental effect of obesity on breast cancer survival has been reported in both premenopausal and postmenopausal women (21-24).

The strengths of our study include the large sample size, the population-based case selection, the long period of follow-up, and the ability to assess the effect of numerous potential confounders, including reproductive history and the use of oral contraceptives and hormone therapy prior to diagnosis. Unlike other studies, this study had information regarding the frequency of breast examinations and the use of mammography that allowed us to more directly assess whether a detection delay could explain the poorer survival observed among women with increased BMIs.

Obese women are more likely to delay or avoid breast cancer screening than nonobese women.(25, 26) Additionally, palpation of tumors in obese women may be more difficult. Either scenario may lead to a detection delay and thus a later stage at diagnosis and poorer prognosis among obese women. However, in our study, frequency of breast exams and use of mammography did not differ by adult BMI and also had little effect on estimates of the association between BMI and breast cancer mortality. Furthermore, although obesity is generally associated with later stage tumors (6, 7), in our study and others (21), the effect of increased BMI on mortality is largely independent of cancer stage. Therefore, although detection delay and late stage at diagnosis may play some role in the association between high BMI and breast cancer mortality, it is unlikely to fully explain the association.

Beyond detection issues, several biological mechanisms related to enhanced growth and spread of breast cancer have been proposed to explain the adverse effect of high BMI on breast cancer prognosis. The most commonly cited mechanism involves the increased production of estrogen associated with obesity. Obese women have higher levels of circulating estrogens than leaner women, thought to be derived from aromatization of androgen in adipose tissue together with low levels of sex hormone–binding globulin (27). These higher levels of bioavailable estrogen may lead to estrogen-stimulated tumor growth. Some studies indicate that the association of BMI to breast cancer mortality or to tumors with poor prognostic characteristics is stronger or limited to women with estrogen receptor–positive tumors (28, 29), lending support to an etiologic role for excess endogenous estrogen. However, estrogen levels in premenopausal women do not vary by BMI, and ovarian-derived estrogen in premenopausal women is the main source of endogenous estrogen rather than adipose tissue (3). Therefore, whereas excess endogenous estrogen levels is a plausible explanation for the effects of increased BMI on breast cancer mortality in postmenopausal women, it is not a likely explanation for the effects of increased BMI on breast cancer mortality in premenopausal women.

In addition to the effects on endogenous estrogen levels, increased BMI may also influence breast cancer growth through its association with hyperinsulinemia. There is some evidence that the metabolic changes associated with insulin resistance, and, in particular, the related alteration in cytokine production by adipose tissue, are major contributors to the aggressive behavior of breast cancers that develop in obese women through effects on angiogenesis (30).

Another potential explanation is the possible effect of obesity on the metabolism of drugs used for systemic therapy or on the efficacy of systemic therapy. Because information on adjuvant treatment was not available in our study, we could not address this possibility. To date, few other studies have examined this hypothesis. It has been reported that obesity is not associated

**Table 3. Breast cancer mortality among women with invasive breast cancer by adult BMI and menopausal status**

| | Premenopause | | | Postmenopause | | |
|---|---|---|---|---|---|---|
| Adult BMI (kg/m$^2$) | *n* | No. of deaths | HR (95% CI)* | *n* | No. of deaths | HR* (95% CI) |
| ≤22.99 | 1,576 | 501 | 1.00 (referent) | 755 | 232 | 1.00 (referent) |
| 23.00-24.99 | 414 | 162 | 1.28 (1.07-1.53) | 252 | 90 | 1.12 (0.88-1.44) |
| 25.00-29.99 | 400 | 153 | 1.27 (1.05-1.52) | 264 | 100 | 1.23 (0.97-1.57) |
| ≥30.00 | 161 | 65 | 1.38 (1.05-1.80) | 102 | 44 | 1.32 (0.94-1.83) |
| | | | *P* for trend = 0.002 | | | *P* for trend = 0.1 |

*Adjusted for age at diagnosis, race, radiation therapy, history of benign breast disease, educational level, and cancer stage.

**Table 5. Breast cancer mortality among women with invasive breast cancer by weight change from age 18 to usual adult weight**

| Weight change (lbs) | *N* | No. of deaths | HR* (95% CI) |
|---|---|---|---|
| ≤0 | 809 | 266 | 1.00 (referent) |
| 1-10 | 998 | 310 | 0.90 (0.76-1.06) |
| 11-17 | 589 | 200 | 0.98 (0.82-1.18) |
| 18-30 | 822 | 301 | 1.02 (0.86-1.22) |
| ≥31 | 706 | 270 | 1.02 (0.82-1.27) |
| | | | *P* for trend = 0.5 |

*Adjusted for age at diagnosis, race, radiation therapy, history of benign breast disease, educational level, menopausal status, adult BMI, and cancer stage.

with a change in tamoxifen efficacy (31) and that tamoxifen metabolites do not differ by BMI (32). Although these studies do not support the hypothesis that obesity affects systemic breast cancer treatment, additional research is needed in this area.

Perhaps the most likely explanation for the increased breast cancer mortality observed in women with high BMIs is that the metabolic consequences of obesity not only act to increase generalized tumor growth but also promote the selection and growth of more aggressive cells. In a cohort study of women under age 45, Daling et al. (33) found that tumors in women with high BMIs have properties that are indicative of a rapid growth rate, including a higher mitotic count and a higher Ki-67 expression ratio. These findings may suggest that the tumors in obese women have a particularly aggressive phenotype. However, additional study is needed to establish the mechanisms through which obesity influences breast cancer prognosis.

Whereas body size earlier in life and adult weight gain have been reported to be risk factors for developing breast cancer (1, 4, 5), we found no evidence that they influence survival after breast cancer diagnosis. In our study, adult BMI was highly correlated with total adult weight gain ($r = 0.7$) and modestly correlated with age 18 BMI ($r = 0.5$). Despite this high correlation, adult BMI was a stronger predictor of breast cancer mortality than either adult weight gain or BMI at age 18. Our results also suggest that, regardless of age 18 BMI or adult weight gain, women with high adult BMI experience a higher mortality rate after breast cancer diagnosis than leaner women. Few studies have assessed the effects of body size at earlier ages or adult weight gain on breast cancer mortality. Kumar et al. (12) found that among 166 breast cancer patients followed for at least 10 years, increased weight at age 30, but not weight at ages 16, 20, or 40 was associated with breast cancer mortality. Ewertz et al. (34) found high weight at age 20 and weight loss over the 10 years before diagnosis to be poor prognostic indicators.

Adult weight gain reflects gain in android body fat, thought by some to be more metabolically important than general obesity. In our study, BMI served as a proxy for obesity; we did not have measures of body-fat distribution, such as waist-hip ratio, dual-energy X-ray absorptiometry scan, or skin-fold thickness. However, there is some inconsistency in the literature over the significance of body-fat distribution, as opposed to obesity defined by BMI in breast cancer prognosis. In our study, high adult BMI was associated with higher breast cancer mortality, whereas adult weight gain was not. This is consistent with a recent study (35) which found that BMI, but not waist-to-hip ratio, was associated with sex hormone concentrations in postmenopausal breast cancer survivors, suggesting that the overall amount of body fat may be more important than the distribution of body fat in determining hormone concentrations that may influence prognosis. However, others have found that measures of body-fat distribution, such as waist-to-hip ratio (36) and suprailiac/thigh ratio (12) may be more important indicators of breast cancer prognosis than BMI.

Our study was subject to several limitations. Height and weight values that were used to compute BMI were based on self-report. Whereas there is a high correlation between self-reported height and weight and measured height and weight, what error exists seems to be generally systematic, with an overestimation of height and an underestimation of weight, especially for women with higher weights (37, 38). Thus, our measure of BMI probably underestimated the true BMI values among obese and overweight women. In that sense, our risk estimates in obese and overweight women may be underestimates of the true association. Other studies have computed BMI based on the patient's height and weight at diagnosis, whereas this study used usual adult weight. However, the similarities between the results of this study with those from previous studies indicate that the time of height and weight assessment has little effect on the pattern of association. Furthermore, one study (22) found that the prognostic effect of BMI did not depend on the length of time between measurement and diagnosis.

Extent of disease (size, grade, and lymph node involvement) and receptor status were not available in our study because SEER did not collect this information at the time that the CASH participants were diagnosed. We were therefore unable to examine the extent to which the tumor characteristics in overweight/obese women could explain their poorer survival. An additional limitation of our study was the lack of information on possible prognostic or confounding factors occurring after breast cancer diagnosis, including post-diagnosis weight change. Finally, the upper age limit of our study population was 54 at diagnosis, whereas the majority of breast cancers occur in older women. The generalizability of our findings to older women with breast cancer is unclear, although we found that increasing BMI was associated with increasing breast cancer mortality in both premenopausal and postmenopausal women.

This investigation provides additional evidence that obesity could be a preventable risk factor for death among both premenopausal and postmenopausal breast cancer patients. The effect of obesity on breast cancer mortality seems to be largely independent of detection issues. Further study is needed to determine how these findings might affect recommendations to reduce breast cancer mortality, as the prognostic effect of weight loss in overweight/obese breast cancer patients has not been established. Regardless, all women should be encouraged to maintain a healthy weight to minimize the health risks associated with being overweight and obese (39).

## Acknowledgments

We thank Caroline Costello for her work on the data linkage and acknowledge the many contributors to the Cancer and Steroid Hormone Study, including George L. Rubin, Nancy C. Lee, Michele G. Mandel, Herbert B. Peterson, Raymond Greenberg, J. Wister Meigs, W. Douglas Thompson, G. Marie Swanson, Elaine Smith, Charles Key, Dorothy Pathak, Donald Austin, David Thomas, Joseph Lyon, Dee West, Fred Gorstein, Robert McDivitt, Stanley J. Robboy, Lonnie Burnett, Robert Hoover, Peter M. Layde, Howard W. Ory, James J. Schlesselman, David Schottenfeld, Bruce Stadel, Linda A. Webster, Colin White, Walter Bauer, William Christopherson, Deborah Gersell, Robert Kurman, Allen Paris, and Frank Vellios.

## References

1. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997;278:1407–11.
2. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000;152:514–27.
3. Potischman N, Swanson CA, Siiteri P, Hoover RN. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. J Natl Cancer Inst 1996;88:756–8.

4. Barnes-Josiah D, Potter JD, Sellers TA, Himes JH. Early body size and subsequent weight gain as predictors of breast cancer incidence (Iowa, United States). Cancer Causes Control 1995;6:112–8.
5. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 2002;13:741–51.
6. Hall HI, Coates RJ, Uhler RJ, et al. Stage of breast cancer in relation to body mass index and bra cup size. Int J Cancer 1999;82:23–7.
7. Cui Y, Whiteman MK, Flaws JA, Langenberg P, Tkaczuk KH, Bush TL. Body mass and stage of breast cancer at diagnosis. Int J Cancer 2002;98:279–83.
8. Lamar CA, Dorgan JF, Longcope C, Stanczyk FZ, Falk RT, Stephenson HE Jr. Serum sex hormones and breast cancer risk factors in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2003;12:380–3.
9. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. J Clin Oncol 2002;20:1128–43.
10. Carmichael AR, Bendall S, Lockerbie L, Prescott RJ, Bates T. Does obesity compromise survival in women with breast cancer? Breast 2004;13:93–6.
11. Obermair A, Kurz C, Hanzal E, et al. The influence of obesity on the disease-free survival in primary breast cancer. Anticancer Res 1995;15:2265–9.
12. Kumar NB, Cantor A, Allen K, Cox CE. Android obesity at diagnosis and breast carcinoma survival: evaluation of the effects of anthropometric variables at diagnosis, including body composition and body fat distribution and weight gain during life span, and survival from breast carcinoma. Cancer 2000;88:2751–7.
13. Jemal A, Clegg LX, Ward E, et al. Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. Cancer 2004;101:3–27.
14. Mack KA, Ahluwalia IB. Observations from the CDC: monitoring women's health in the United States: selected chronic disease indicators, 1991–2001 BRFSS. J Womens Health 2003;12:309–14.
15. Chu SY, Lee NC, Wingo PA, Senie RT, Greenberg RS, Peterson HB. The relationship between body mass and breast cancer among women enrolled in the Cancer and Steroid Hormone Study. J Clin Epidemiol 1991;44:1197–206.
16. Wingo PA, Ory HW, Layde PM, Lee NC. The evaluation of the data collection process for a multicenter, population-based, case-control design. Am J Epidemiol 1988;128:206–17.
17. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation of obesity. Geneva: 3–5 June, 1997.
18. Najjar MF, Rowland M. Anthropometric reference data and prevalence of overweight, United States, 1976–80. Vital Health Stat 11 1987;238:1–73.
19. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Public-Use Data (1973–1997), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2000, based on the August 1999 submission.
20. Cox DR. Regression models and life tables. J R Stat Soc Ser B 1972;34:187–220.
21. Kyogoku S, Hirohata T, Takeshita S, Nomura Y, Shigematsu T, Horie A. Survival of breast-cancer patients and body size indicators. Int J Cancer 1990;46:824–31.
22. Tretli S, Haldorsen T, Ottestad L. The effect of pre-morbid height and weight on the survival of breast cancer patients. Br J Cancer 1990;62:299–303.
23. Senie RT, Rosen PP, Rhodes P, Lesser ML, Kinne DW. Obesity at diagnosis of breast carcinoma influences duration of disease-free survival. Ann Intern Med 1992;116:26–32.
24. Tornberg S, Carstensen J. Serum β-lipoprotein, serum cholesterol and Quetelet's index as predictors for survival of breast cancer patients. Eur J Cancer 1993;29A:2025–30.
25. Wee CC, McCarthy EP, Davis RB, Phillips RS. Screening for cervical and breast cancer: is obesity an unrecognized barrier to preventive care? Ann Intern Med 2000;132:697–704.
26. Fontaine KR, Heo M, Allison DB. Body weight and cancer screening among women. J Womens Health Gend Based Med 2001;10:463–70.
27. Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001;344:276–85.
28. Maehle BO, Tretli S. Pre-morbid body-mass-index in breast cancer: reversed effect on survival in hormone receptor negative patients. Breast Cancer Res Treat 1996;41:123–30.
29. Verreault R, Brisson J, Deschenes L, Naud F. Body weight and prognostic indicators in breast cancer. Modifying effect of estrogen receptors. Am J Epidemiol 1989;129:260–8.
30. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev 2004;5:153–65.
31. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst 2003;95:1467–76.
32. Sheth HR, Lord G, Tkaczuk K, et al. Aging may be associated with concentrations of tamoxifen and its metabolites in breast cancer patients. J Womens Health 2003;12:799–808.
33. 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.
34. Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer 1991;49:526–30.
35. McTiernan A, Rajan KB, Tworoger SS, et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. J Clin Oncol 2003;21:1961–6.
36. Borugian MJ, Sheps SB, Kim-Sing C, et al. Waist-to-hip ratio and breast cancer mortality. Am J Epidemiol 2003;158:963–8.
37. Palta M, Prineas RJ, Berman R, Hannan P. Comparison of self-reported and measured height and weight. Am J Epidemiol 1982;115:223–30.
38. Rowland ML. Self-reported weight and height. Am J Clin Nutr 1990;52:1125–33.
39. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, Maryland: Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 1998.

# Body Mass and Mortality After Breast Cancer Diagnosis

Maura K. Whiteman, Susan D. Hillis, Kathryn M. Curtis, et al.

*Cancer Epidemiol Biomarkers Prev* 2005;14:2009-2014.