General and Abdominal Obesity and Survival among Young Women with Breast Cancer

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Abstract

Among postmenopausal women, obesity is linked to increased risk of breast cancer and poorer subsequent survival. For premenopausal women, obesity may reduce incidence, but less is known about its effect on prognosis, particularly for abdominal obesity. This study investigated whether general or abdominal obesity at diagnosis influenced survival in a cohort of young women with breast cancer. A population-based follow-up study was conducted among 1,254 women ages 20 to 54 who were diagnosed with invasive breast cancer between 1990 and 1992 in Atlanta or New Jersey. Women were interviewed within several months of diagnosis and asked about their weight and height at age 20 and in the year before diagnosis. Study personnel did anthropometric measures at the interview. With 8 to 10 years of follow-up, all-cause mortality status was determined using the National Death Index (n = 290 deaths). Increased mortality was observed for women who were obese [body mass index (BMI), ≥30] at the time of interview compared with women of ideal weight [BMI, 18.5-24.9; stage- and income-adjusted hazard ratio (HR), 1.48; 95% confidence interval (95% CI), 1.09-2.01]. A similar result was seen for the highest versus lowest quartile of waist-to-hip ratio (HR, 1.52; 95% CI, 1.05-2.19). Strong associations with mortality were found for women who were obese at age 20 (HR, 2.49; 95% CI, 1.15-5.37) or who were overweight/obese (BMI, ≥25) at both age 20 and the time of interview (HR, 2.22; 95% CI, 1.45-3.40). This study provides evidence that breast cancer survival is reduced among younger women with general or abdominal obesity. (Cancer Epidemiol Biomarkers Prev 2006;15(10):1871–7)

Introduction

Women under age 45, who comprise <25% of all breast cancer cases, have survival rates considerably lower than those for older women even after controlling for stage of disease (1). Although results are not consistent across studies, the poorer prognosis for young women may be explained in part by a greater likelihood of lymph node involvement, larger tumors, higher histologic grade, estrogen receptor negativity, overexpression of p53, and poorly differentiated tumors (2-6).

Younger women may present with more advanced or aggressive disease due to delayed diagnosis, as they are not generally recommended for mammography and typically have denser breasts, making it more difficult to detect cancer through self-exam, clinical exams, or mammographic screening (7). Other hypotheses offered to explain their poorer survival include higher estrogen concentrations, which may induce a more rapid tumor growth rate or a different biology of the cancer, compared with older women (8).

Although clinical markers are generally considered to be the most important prognostic factors for women with breast cancer, stage and grade have been estimated to explain only ~20% of the observed variation in survival (9). Age, race, and socioeconomic status have been found to influence survival (10, 11), but modifiable factors have generally not been well studied in relation to surviving breast cancer. Body weight is one of the few potentially modifiable factors to receive extensive attention. For postmenopausal women, high body mass index (BMI) or weight is well established as adversely affecting both the incidence of breast cancer (12) and its prognosis (13, 14). In contrast, obesity seems to reduce the risk of developing breast cancer among premenopausal women (15); less is understood about the effects of obesity on prognosis in these younger women (16).

In addition to general obesity, as indexed by the BMI, there is growing interest in the adverse health effects of abdominal fat because of its relationship with visceral fat (17) and unique hormonal profiles (18). Women with an elevated waist-to-hip ratio (WHR) or a large waist circumference, two markers of abdominal fat distribution (19), are reported to have a higher risk of several cancers (including postmenopausal breast cancer) as well as stroke, hypertension, atherosclerosis, hirsutism, insulin resistance, and type 2 diabetes mellitus (20-22) presumably due to elevated concentrations of estrogen, insulin, and triglycerides (18, 23). The effect of abdominal fat on the prognosis for breast cancer has not been well studied in either premenopausal or postmenopausal women (24, 25). In this population-based follow-up study, we investigated whether general or abdominal obesity before or near the time of diagnosis influenced survival among a cohort of younger women.

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Note: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Materials and Methods

The cohort included women ages 20 to 54 years from a five-county region of New Jersey and from metropolitan Atlanta who had been diagnosed with primary invasive breast cancer between May 1990 and December 1992 and had participated in an earlier population-based case-control study described elsewhere (26). For the parent study, incident cases were identified through rapid ascertainment systems, and in-home, structured interviews were conducted on a variety of factors related to breast cancer in young women, such as contraceptive and reproductive history, family history of breast cancer, physical activity, body size, cigarette smoking or alcohol use, and diet. Trained interviewers obtained anthropometric measures as part of the parent study (27). Interviews were completed by 86% of eligible cases at a median of 4.2 months following diagnosis. Medical records were reviewed for clinical and pathologic characteristics related to the breast cancer diagnosis. All information pertaining to anthropometric measures and the covariates included in this study was obtained from the baseline interview or medical records.

Of the 1,283 women diagnosed with invasive breast cancer who were eligible for this follow-up study, vital status data were available for 1,264 (98.5%). An additional 10 women were excluded from these analyses because they were missing both BMI and WHR, yielding a final sample of 1,254 women (6 more were missing WHR only). This study was approved by the institutional review boards of the collaborating institutions.

Anthropometric Assessment. Anthropometric measurements included weight, sitting and standing height, and waist and hip circumference. Waist circumference was measured superior to the iliac crest of the pelvis, which was usually at the level of the umbilicus. Hip circumference, defined as the maximum extension of the buttocks, usually included underclothing plus a light, loose-fitting garment. Participants were asked in the questionnaire to recall their weight and height at age 20 and their weight in the year before diagnosis. This latter time frame was used to assess usual adult weight not affected by weight gain or loss following diagnosis. Additional measurements included width of the elbow and wrist, circumference of the middle part of the upper arm, sitting height, and triceps and subscapular skinfolds.

Outcome Assessment. Vital status and, if the woman was deceased, date and cause of death were obtained through the New Jersey State Cancer Registry (New Jersey cases) and the Surveillance, Epidemiology, and End Results program (Atlanta cases), which do routine computerized linkages with the National Death Index. We found no appreciable difference in the results when we used all-cause mortality rather than breast cancer–specific mortality as the study outcome, and we report only all-cause mortality here. Breast cancer was attributed as the cause for 85% of the 290 deaths as listed on the death certificate.

Summary stage (local, distant, and regional) data were available for all women from the abstraction of the medical records at baseline. Through a separate follow-up study, we were able to acquire complete, detailed information on cancer treatment and stage (based on the American Joint Committee on Cancer protocol; ref. 28) for the Atlanta women only ($n = 824$). Similar activities were not undertaken in New Jersey.

Statistical Methods. The follow-up period started at the date of diagnosis and ended either at the date of death or at the end of the study if the woman was still alive. The study ended on January 1, 2000 for both sites with a maximum of 9.8 years of follow-up. The Kaplan-Meier (product-limit) method was used to generate survival curves for a preliminary examination of these data (29). Estimates of the hazard ratio (HR) for the risk of all-cause mortality and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards modeling (30). The results for overall and 5-year survival were similar in most cases, and the results for overall survival are reported here.

Although different cut points for the main exposures were evaluated, we report main effects by the WHO classification scheme for BMI [<18.5 (underweight), 18.5-24.9 (ideal weight), 25-29.9 (overweight), 30+ (obese); ref. 31] and waist circumference (≤79, 80-87, ≥88 cm; ref. 32). WHR and the remaining anthropometric measures are reported by quartiles of the total population. Our findings were similar when using measured BMI at interview as opposed to BMI 1 year before diagnosis, which relied on recalled weight, and thus results for the former are reported here.

We used several approaches to assess whether a history of overweight or obesity and weight change throughout adulthood would affect mortality. First, we evaluated the percentage change in body weight from age 20 to the time of interview to compare women who lost or gained weight with those who maintained a steady weight (±3% change; ref. 33). Second, we compared women who lost or gained weight from the time of diagnosis with those who maintained their weight (stayed with 3% of their weight). Finally, we assessed the effect of being either overweight or obese (BMI, ≥25) at both age 20 and the time of the interview.

For all main exposures and potential covariates, the proportional hazards assumption was evaluated by checking graphs plotting the log(−log S(t)) function against time for diverging or crossing survival curves and testing the statistical significance of time-by-covariate interaction terms (34). No violation of this assumption was found.

To assess whether any of the factors listed below modified the relationship between body size and mortality, interaction terms were tested with the likelihood ratio test using a significance level of $P = 0.10$ (35). We defined effect measure modifiers as variables whose interaction with the main exposures created joint effects that departed from perfect multiplicity. To evaluate potential modifiers, we used both BMI at interview (≥25 compared with the <25 reference group) and WHR (using the median of 0.80 as cut point with the lower category as reference) and analyzed the effects separately. We obtained similar results when using the BMI median of 24.45 as the cut point or when eliminating women with a BMI below 18.5. We report stratified results for any factor that modified the relationship between either BMI or WHR and survival.

For assessment of confounding, covariates were included in multivariate models if related to either the exposures (BMI or WHR) or outcome (mortality) in bivariate analyses. Using backward elimination, covariates were removed from multivariate models in order of the highest P. Covariates were deemed confounders and remained in the final models if they produced changes in the estimates of effect by ≥10% (36). The Mantel-Haenszel test was used to compute the P for trend for the risk of death across levels of the body size variables (37, 38).

The factors considered for confounding and effect measure modification include the following: menopausal status; age at diagnosis; race (White, non-White); stage (Surveillance, Epidemiology, and End Results summary stage defined as local, regional, distant); estrogen receptor and progesterone receptor status; study center; prior breast biopsy; family history of breast cancer (mother or sister); age at menarche; oral contraceptive use; parity; age at first live birth; number of miscarriages; number of induced abortions; lactation history; household income; education level; marital status; alcohol intake in the year before diagnosis; cigarette smoking (never, former, current); average daily total of calories, fat, fruits, or vegetables consumed in the year before diagnosis; average recreational physical activity in the year before diagnosis; the

presence of comorbidities at the time of the interview (high blood pressure, high cholesterol, thyroid disease, diabetes, gallbladder disease, colorectal polyps, or other cancers); months between diagnosis and interview; and initiation of chemotherapy or radiation therapy before interview. When evaluating either WHR or BMI as a main exposure, the other anthropometric factor was also evaluated as a potential confounder or effect modifier.

Using our criterion of a 10% change in the estimate, income and stage proved to be the only important nonanthropometric confounders; all analyses controlled for these two factors. There was also no confounding or modification of effect measures by race or age. As there was no appreciable difference in our estimates when evaluating by menopausal status, we do not show the results stratified by this factor or with the postmenopausal women omitted.

To more completely explore possible confounding by stage or treatment, we conducted a separate analysis restricted to the Atlanta women, for whom we acquired complete treatment and American Joint Committee on Cancer staging data through a separate follow-up study. We found no confounding or modifying effects of treatment status (surgery, chemotherapy, radiation, or hormone therapy) in the relationship between body size and mortality. Our results for the main effects, however, were somewhat attenuated (~13%) when adjusting for American Joint Committee on Cancer stage (I, IIA, IIB, etc.) in place of summary stage (local, regional, distant; data not shown).

Results

Selected characteristics of the study population by BMI and WHR status at the time of the interview are presented in Table 1. Compared with the lower BMI or WHR group, women who were overweight or obese (BMI, ≥25) or had a higher WHR (>0.80) were slightly older, diagnosed with a higher stage of disease, less educated, and of lower income status. The women in the higher categories for BMI or WHR were also more likely to be non-White and have a family history of breast cancer.

The Pearson correlation coefficient between BMI and WHR was fairly low (r = 0.34), but it was high between BMI and waist circumference (0.84) and hip circumference (0.83). The main results for the association between the anthropometric measures of interest and all-cause mortality are shown in Table 2. Adjustment of BMI for WHR (or vice versa) in addition to stage and income tended to decrease the estimates for the highest levels of these anthropometric measures from those adjusted only for the latter two variables.

In a fully adjusted comparison with women of ideal weight (BMI, 18.5-24.9), a modest increase in mortality was observed for women who were overweight (BMI, 25.0-29.9) at age 20 (HR, 1.41; 95% CI, 0.93-2.16) or at the time of interview (HR, 1.34; 95% CI, 1.01-1.79). The association was somewhat stronger for women who were obese (BMI, 30+) at interview (HR, 1.48; 95% CI, 1.09-2.01), and the estimate was much higher, although less precise, for women who were obese at age 20 (HR, 2.49; 95% CI, 1.15-5.37). Being underweight (BMI, <18.5) resulted in opposite effects at the two time periods, with an inverse association at age 20 (HR, 0.74; 95% CI, 0.53-1.05) and a positive relationship at interview (HR, 1.91; 95% CI, 0.93-3.93), although few were underweight at the later period. Weight alone (unadjusted for height) at interview seemed to predict mortality after adjusting for WHR (HR, 1.34; 95% CI, 0.95-1.89, for highest versus lowest quartile).

No difference in mortality was observed between women who gained weight and those who maintained a steady weight from age 20 to the time of the interview after controlling for BMI at the time of the interview. Women who lost >3% of their body weight during that interval had an increase in mortality (HR, 1.95; 95% CI, 1.01-3.77). Results were very similar when we defined weight maintenance as remaining within 5% of weight from the earlier period or when we evaluated absolute weight gained or lost; only those who lost weight experienced elevated mortality (data not reported here).

A modestly increased mortality was observed for those who were not overweight (BMI, <25) at age 20 but became overweight or obese (BMI, ≥25) by the time of interview when the reference group was those who were never overweight or obese (HR, 1.35; 95% CI, 1.04-1.75). Using the same referent, there was a substantially higher mortality for women who were overweight or obese at both time periods (HR, 2.22; 95% CI, 1.45-3.40). No relationship was observed between mortality and the number of times that women gained and lost ≥15 pounds since age 20 (data not shown). These results did not change appreciably with additional adjustment for age.

Analysis of WHR at interview found that mortality was elevated only in the highest quartile, where the HR (versus the lowest quartile) of 1.52 (95% CI, 1.05-2.19) was similar to the finding reported above for obese women (by BMI) versus women of ideal weight. The results for WHR were also similar to those for quartile of waist circumference alone (data not shown). When evaluating waist circumference by WHO categories, a strong association with mortality was observed for the highest category (≥88 cm) only (HR, 1.75; 95% CI, 1.20-2.55). There was no association between hip circumference and mortality.

There was no difference in mortality between those who maintained their weight between diagnosis and interview and those who gained weight, but a slight trend toward increased mortality was found for women who lost weight (HR, 1.27; 95% CI, 0.93-1.74). Adjustment for chemotherapy initiated by the time of the interview did not alter these results.

After adjustment for stage, income, and WHR or BMI, no meaningful associations were observed for the remaining anthropometric variables, including elbow or wrist width, mid-upper arm circumference, sitting or standing height, triceps or subscapular skinfolds, or the ratio of the two skinfolds (data not shown).

Mortality by combined BMI and WHR status at interview is reported in Table 3. Compared with women with low WHR and BMI, mortality was elevated for women with either a high WHR (≥0.80) alone (HR, 1.42; 95% CI, 0.99-2.04) or high BMI (≥25) alone (HR, 1.61; 95% CI, 1.10-2.34). The highest mortality was observed for women with both high WHR and high BMI (HR, 1.92; 95% CI, 1.38-2.68). Results were similar when replacing WHR with waist circumference; results for the former are reported here because BMI and waist circumference were highly correlated.

Shown in Table 4 are results for the relationship between WHR or BMI and mortality stratified by the only effect measure modifiers in this study, recreational physical activity. Physical activity produced similar modifying effects for BMI and WHR. Increased mortality was associated with larger body size among those with low activity (WHR: HR, 1.41; 95% CI, 1.00-1.98; BMI: HR, 1.53; 95% CI, 1.09-2.14) but not for women with high activity (WHR: HR, 1.05; 95% CI, 0.72-1.54; BMI: HR, 1.23; 95% CI, 0.83-1.83).

Discussion

In this population-based follow-up study of young women, we found that both elevated BMI (≥25) and a high WHR (≥0.80) near the time of diagnosis were related to increased mortality following a diagnosis of breast cancer. We also found that having both an elevated BMI greater and a high WHR was more detrimental than either one alone. Results for waist circumference were similar to those for WHR, but there was no association between hip circumference and mortality. We conclude from our results that the absolute amount of

abdominal fat may be equally as important in relation to survival as the ratio of waist and hip circumferences. Our findings that the strongest associations were seen for women who were either obese at age 20 or overweight or obese throughout adulthood suggest that a poorer prognosis may be related to high exposure to circulating estrogens or insulin associated with a long history of being overweight or obese. It is also possible that long-term obesity status is an indicator of other chronic health problems linked to obesity or unhealthy lifestyle choices.

In addition to finding larger body size associated with increased mortality, we also found that women who were underweight (BMI, <18.5) at diagnosis were at greater risk for mortality compared with those of ideal weight. Similarly, women who lost weight between age 20 and the interview or during the interval between diagnosis and interview had poorer survival than those who either maintained or gained weight, regardless of how much was gained. It is possible that underweight women or those who lost weight in the two time periods were the most sick or had other preexisting comorbidities because breast cancer patients often gain weight with receipt of chemotherapy or hormonal therapy (39).

Our results are consistent with the majority of previous observational studies of premenopausal or younger women, which have observed poorer survival with increased weight or BMI (16, 40-46). A few studies have reported no association (47-50). The inverse relationship frequently noted between BMI and incidence of breast cancer among premenopausal women (51) does not seem to hold in the context of survival.

The relationship between abdominal obesity and the prognosis for women with breast cancer has not been frequently studied for patients of any age. One study exclusively of postmenopausal women reported no association with WHR (24). A recent study by Borugian et al. (25) of WHR and survival among 586 breast cancer patients (39% premenopausal) found a strong positive association for postmenopausal women only. Our study was similar with regard to length of follow-up and timing of the WHR measurement near diagnosis. However, the Borugian study included fewer premenopausal women and relied on self-reported waist and hip measurements, which may account, in part, for some of the difference in results. Further, the previous study found no association for BMI in either menopausal group, which is not consistent with most prior research, suggesting that there may be something different about that study population.

Two other studies that investigated how the distribution of body fat affects prognosis used skinfold thickness measurements. The first study, of 363 postmenopausal women, devised an algorithm using triceps and subscapular skinfolds to categorize participants as having either peripheral or abdominal fat patterning (52), but they found no difference in survival by these two types. The other study used the suprailiac/thigh ratio as a proxy for the distribution of abdominal fat to study its relation to survival among 166 breast cancer patients (53) and reported an increased mortality for high suprailiac/thigh ratio but little association between mortality and either weight or BMI. In our population-based sample of young women, we observed little or no association between skinfolds and survival.

That both WHR and BMI in the present study had independent effects on mortality suggests that more than one biological pathway may play a role in the relationship between obesity and tumor progression. High BMI is generally believed to increase circulating estrogens (54), and higher WHR is thought to have that effect and has been linked to a greater likelihood of insulin resistance and hyperinsulinemia independent of BMI (23). The relationship between larger body size and poorer survival may also reflect other nonhormonal factors not controlled for in this study, such as incorrect dosing of chemotherapy or incomplete surgical removal of the primary tumor, or it may be more difficult to detect recurrences in larger women (55, 56). We do know that our findings of poorer survival for women of larger body size do not seem to be a function of such women being diagnosed at a later stage

Table 1. Selected characteristics of 1,254 invasive breast cancer cases at diagnosis by baseline BMI and WHR

Characteristic	All cases, *n* (%)	BMI (*n* = 1,254)			WHR (*n* = 1248)		
		<25, *n* (%)	≥25, *n* (%)	*P**	≤0.80, *n* (%)	>0.80, *n* (%)	*P**
Age at diagnosis (y)							
<40	412 (32)	233 (34)	176 (31)	0.10	222 (36)	186 (30)	0.11
40-44	447 (36)	241 (36)	202 (35)		206 (33)	233 (37)	
45-54	405 (32)	206 (30)	196 (34)		196 (31)	205 (33)	
Race							
White	950 (75)	570 (85)	365 (65)	<0.0001	507 (81)	434 (70)	<0.0001
Non-White	314 (25)	103 (15)	199 (35)		117 (19)	190 (30)	
Stage of disease							
Local	721 (57)	420 (62)	297 (52)	0.0003	380 (61)	332 (53)	0.003
Regional	510 (40)	247 (36)	259 (45)		231 (37)	273 (44)	
Distant	31 (3)	12 (2)	17 (3)		11 (2)	19 (3)	
Unknown	2 (<1)	1 (<1)	1 (<1)		2 (<1)	0 (0)	
Menopausal status							
Pre	985 (78)	555 (82)	421 (74)	0.0005	501 (80)	472 (76)	0.04
Post	276 (22)	124 (18)	151 (26)		122 (20)	151 (24)	
Unknown	3 (<1)	1 (<1)	2 (<1)		1 (<1)	1 (<1)	
Estrogen receptor							
Positive	706 (56)	419 (62)	286 (50)	0.005	356 (57)	345 (55)	0.70
Negative	446 (35)	203 (30)	235 (41)		204 (33)	232 (37)	
Borderline	31 (3)	16 (2)	14 (2)		21 (3)	9 (2)	
Unknown	81 (6)	42 (6)	39 (7)		43 (7)	38 (6)	
Education							
High school or less	351 (28)	157 (23)	192 (33)	<0.0001	148 (24)	202 (32)	0.0007
Some college or more	913 (72)	523 (77)	382 (67)		476 (76)	422 (68)	
Household yearly income							
<$24,000	257 (20)	90 (13)	163 (28)	<0.0001	81 (13)	171 (27)	<0.0001
$24,000-$49,000	323 (26)	166 (24)	154 (27)		164 (26)	156 (25)	
≥$50,000	652 (52)	404 (59)	246 (43)		368 (59)	279 (45)	
Unknown	32 (2)	20 (3)	11 (2)		11 (2)	18 (3)	

*Mantel-Haenszel test of association, excludes ''unknown'' values.

Table 2. HR and 95% CI by selected anthropometrics for all-cause mortality among 1,217 women with breast cancer

Anthropometric factor	Overall mortality			
	No. alive	No. dead (%)	Stage, income adjusted HR (95% CI)	WHR/BMI, stage, income adjusted HR (95% CI)
BMI at age 20*				
<18.5	193	38 (16)	0.73 (0.52-1.04)	0.74 (0.53-1.05)
18.5-24.9	691	210 (23)	Reference	Reference
25-29.9	41	25 (38)	1.47 (0.96-2.24)	1.41 (0.93-2.16)
≥30	8	7 (47)	2.93 (1.37-6.29)	2.49 (1.15-5.37)
P for linear trend			0.0004	0.001
BMI at interview*				
<18.5	23	8 (26)	1.82 (0.89-3.72)	1.91 (0.93-3.93)
18.5-24.9	519	107 (17)	Reference	Reference
25-29.9	224	85 (28)	1.38 (1.04-1.83)	1.34 (1.01-1.79)
≥30	169	81 (32)	1.65 (1.23-2.21)	1.48 (1.09-2.01)
P for linear trend			0.001	0.002
Quartile of weight (kg) at interview*				
1 (<58.2)	243	59 (19)	Reference	Reference
2 (58.2-65.9)	249	51 (17)	0.86 (0.59-1.25)	0.85 (0.58-1.23)
3 (66.0-76.9)	234	66 (22)	1.02 (0.71-1.45)	0.97 (0.68-1.39)
4 (≥77.0)	203	100 (33)	1.49 (1.07-2.08)	1.34 (0.95-1.89)
P for linear trend			0.006	0.05
BMI at age 20, BMI at interview*				
<25, <25	541	115 (18)	Reference	Reference
<25, ≥25	350	134 (28)	1.40 (1.09-1.81)	1.35 (1.04-1.75)
≥25, ≥25	42	31 (42)	2.44 (1.61-3.71)	2.22 (1.45-3.40)
Percent change in body weight from age 20 to interview†				
Lost, >3%	57	18 (24)	1.44 (0.78-2.67)	1.95 (1.01-3.77)
Maintained, ±3%	80	13 (14)	Reference	Reference
Gained, 3.1-25%	428	103 (19)	1.03 (0.66-1.62)	1.21 (0.74-1.98)
Gained, >25%	358	141 (28)	1.36 (0.88-2.12)	1.27 (0.78-2.07)
P for linear trend			0.16	0.47
Quartile of WHR at interview†				
1 (<0.76)	257	50 (16)	Reference	Reference
2 (0.76-0.80)	242	62 (20)	1.09 (0.75-1.58)	1.05 (0.72-1.53)
3 (0.81-0.86)	229	72 (24)	1.17 (0.82-1.69)	1.12 (0.78-1.61)
4 (>0.86)	207	97 (32)	1.74 (1.23-2.46)	1.52 (1.05-2.19)
P for linear trend			0.0009	0.02
Waist circumference (cm)†				
<79	438	85 (16)	Reference	Reference
80-87	217	64 (23)	1.14 (0.83-1.59)	1.13 (0.81-1.58)
≥88	134	79 (32)	1.86 (1.40-2.46)	1.75 (1.20-2.55)
P for linear trend			<0.0001	0.03
Quartile of hip circumference (cm)†				
1 (50.7-96.0)	246	67 (21)	Reference	Reference
2 (96.1-101.6)	248	45 (15)	0.61 (0.42-0.89)	0.57 (0.39-0.84)
3 (101.7-109.8)	234	73 (24)	0.99 (0.42-1.38)	0.84 (0.58-1.20)
4 (109.9-223.0)	209	96 (32)	1.21 (0.88-1.66)	0.80 (0.49-1.30)
P for linear trend			0.04	0.54
Percentage change in body weight from diagnosis to interview †				
Lost, >3%	182	70 (28)	1.20 (0.88-1.63)	1.27 (0.93-1.74)
Maintained, ±3%	298	89 (23)	Reference	Reference
Gained, 3.1-8.0%	230	50 (18)	0.77 (0.55-1.08)	0.81 (0.57-1.14)
Gained, >8.0%	216	67 (24)	0.92 (0.67-1.26)	0.86 (0.63-1.18)
P for linear trend			0.07	0.007

NOTE: Excludes women who were missing data for BMI, WHR, stage, or income.
*Full adjustment (right-hand column) included WHR as well as stage and income.
†Full adjustment (right-hand column) included BMI as well as stage and income.

of disease, as we did not find mortality to vary when stratifying by stage, and the associations persisted after controlling for stage.

Physical activity was the only factor that interacted with BMI or WHR, although the heterogeneity in the HRs was somewhat more pronounced for WHR. The detrimental effects of larger body size on survival were restricted to women with low recreational activity levels. It is hopeful that exercise may counter the negative effect of overweight or obesity among this subpopulation possibly by lowering their serum insulin and estrogen concentrations (57, 58).

Table 3. HR and 95% CI for the relationship between WHR, BMI, and all-cause mortality

WHR and BMI at interview	No. women	No. deaths (%)	HR (95% CI)
BMI, <25; WHR, <0.80	407	56 (14)	Reference
BMI, <25; WHR, ≥0.80	250	21 (23)	1.42 (0.99-2.04)
BMI, ≥25; WHR, <0.80	204	56 (27)	1.61 (1.10-2.34)
BMI, ≥25; WHR, ≥0.80	355	39 (31)	1.92 (1.38-2.68)

NOTE: Adjusted for stage and income.

Exposure misclassification is potentially an issue for recall of weight at age 20. Given the relatively young age of the participants, however, we expect fewer problems with recall for this time period than would be seen in older women. Weight and waist circumference measured at the time of the interview may not reflect usual adult size if women gained a substantial amount of weight because they underwent systemic therapy (39) or other factors (59) or if they lost weight because of unmeasured comorbidities.

The inclusion of women who experienced weight loss due to other diseases before the baseline period for this study (time of

Table 4. HRs and 95% CIs for the relationship between WHR or BMI and all-cause mortality stratified by physical activity

	WHR				BMI			
	≤0.80		>0.80		<25		≥25	
	n	HR	*n*	HR (95% CI)*	*n*	HR	*n*	HR (95% CI)†
Unstratified	611	1.0	605	1.26 (0.98-1.62)	657	1.0	559	1.41 (1.09-1.81)
Physical activity								
High	321	1.0	250	1.05 (0.72-1.54)	359	1.0	212	1.23 (0.83-1.83)
Low	290	1.0	355	1.41 (1.00-1.98)	298	1.0	347	1.53 (1.09-2.14)

*Adjusted for income, stage, and BMI.
†Adjusted for income, stage, and WHR.

breast cancer diagnosis) could have attenuated the observed obesity-mortality association by increasing mortality for lower-weight women. The likelihood of comorbidities is low in this population, however, given the young age. In addition, bias could have been introduced through weight change that followed diagnosis, but measurements were taken close to the time of diagnosis to minimize that possibility. Furthermore, adjusting for the number of months between diagnosis and interview or for treatment initiated before the interview did not materially alter our results, suggesting a minimal presence of misclassification bias from these measurements as a result of treatment-related weight gain.

We were unable to assess changes in body size or any of the covariates in the later years of the postdiagnosis period. Therefore, it is unclear from this study whether fluctuations in weight over these time periods may have affected prognosis. Despite the fact that the majority of women gain weight while on treatment (39), many breast cancer patients adopt healthier behaviors following completion of treatment (60), which could affect their body size or distribution of fat.

This study has several strengths. First, loss to follow-up with regard to vital status was very low (<2%). Second, the cases were selected from a population-based sample and followed for a relatively long period. In addition, we expect a high degree of accuracy with respect to the outcome, all-cause mortality, as a study testing the effectiveness of the National Death Index found the service to correctly identify the vital status for 98% of a large cohort of women (61). Furthermore, the fact that restricting our analyses to mortality attributable to breast cancer (rather than all-cause mortality) or adjusting for the potential confounding effects of comorbidity did not change the association found between increased body size and lower survival underscores the likelihood that being overweight or obese indeed heightens risk of mortality. Finally, the present study had the benefit of using trained interviewers to do the anthropometric measures rather than relying on self-report or self-measure by the participant, which is deemed less reliable.

In summary, this large, population-based follow-up study of breast cancer patients provides evidence of a poorer prognosis for women with either high BMI or WHR near the time of diagnosis. This is one of just a few studies that have investigated the role of abdominal fat in survival among women with breast cancer, particularly among younger women. Future studies of the relationship of obesity to the survival of women with breast cancer are warranted given the sparse literature focused on the role of abdominal obesity.

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