Obesity and Survival Among Black Women and White Women 35 to 64 Years of Age at Diagnosis With Invasive Breast Cancer

Yani Lu, Huiyan Ma, Kathleen E. Malone, Sandra A. Norman, Jane Sullivan-Halley, Brian L. Strom, Polly A. Marchbanks, Robert Spirtas, Ronald T. Burkman, Dennis Deapen, Suzanne G. Folger, Michael S. Simon, Michael F. Press, Jill A. McDonald, and Leslie Bernstein

Yani Lu, Huiyan Ma, Jane Sullivan-Halley, and Leslie Bernstein, Beckman Research Institute, City of Hope, Duarte; Dennis Deapen and Michael F. Press, University of Southern California, Los Angeles, CA; Kathleen E. Malone, Fred Hutchinson Cancer Research Center, Seattle, WA; Sandra A. Norman and Brian L. Strom, University of Pennsylvania, Philadelphia, PA; Polly A. Marchbanks, Suzanne G. Folger, and Jill A. McDonald, Centers for Disease Control and Prevention, Atlanta, GA; Robert Spirtas, National Institute of Child Health and Development, National Institutes of Health, Bethesda, MD; Ronald T. Burkman, Tufts University School of Medicine and Baystate Medical Center, Springfield, MA; and Michael S. Simon, Wayne State University, Detroit, MI.

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Corresponding author: Yani Lu, PhD, Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, 1500 East Duarte Rd, Duarte, CA 91010; e-mail: yalu@coh.org.

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ABSTRACT

Purpose

To evaluate the effect of obesity on survival among black women and white women with invasive breast cancer and to determine whether obesity explains the poorer survival of black women relative to white women.

Patients and Methods

We observed 4,538 (1,604 black, 2,934 white) women who were 35 to 64 years of age when diagnosed with incident invasive breast cancer between 1994 and 1998. Multivariate Cox regression models were used to examine the effect of body mass index (BMI, in kilograms per square meter) 5 years before diagnosis on risk of death from any cause and from breast cancer.

Results

During a median of 8.6 years of follow-up, 1,053 women died (519 black, 534 white), 828 as a result of breast cancer (412 black, 416 white). Black women were more likely to die than white women (multivariate-adjusted relative risk [RR], 1.33; 95% CI, 1.16 to 1.53). Compared with women with BMI of 20 to 24.9 kg/m², those who were obese (BMI ≥ 30 kg/m²) had a greater risk of all-cause mortality (RR, 1.23; 95% CI, 1.04 to 1.47) and breast cancer-specific mortality (RR, 1.20; 95% CI, 0.99 to 1.46). These associations were observed among white women (all-cause RR, 1.54; 95% CI, 1.21 to 1.96; breast cancer RR, 1.46; 95% CI, 1.11 to 1.92), but not among black women (all-cause RR, 1.03; 95% CI, 0.81 to 1.29; breast cancer RR, 1.02; 95% CI, 0.79 to 1.33).

Conclusion

Obesity may play an important role in mortality among white but not black patients with breast cancer. It is unlikely that differences in obesity distributions between black women and white women account for the poorer survival of black women.

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INTRODUCTION

Although breast cancer-specific mortality rates have decreased for both black women and white women,¹ rates have decreased less among black women, and sizable survival disparity remains.^{2,3} The 5-year US relative breast cancer survival rates for women diagnosed between 1999 and 2006 were 78% for blacks and 90% for whites.³ Epidemiologic studies have suggested that obesity or high body mass index (BMI, measured in kilograms per square meter) before breast cancer diagnosis is associated with increased mortality risk.⁴⁻¹³ It has been well documented that black women have higher prevalence of obesity and are more likely to be diagnosed at more advanced stages of breast cancer than white women.¹⁴⁻¹⁶ However,

whether obesity explains the racial disparity in survival is largely unknown.

To explore whether obesity accounts for the black-white disparity in breast cancer survival, we examined whether BMI before diagnosis affects risk of all-cause and breast cancer-specific mortality among black women and white women with invasive breast cancer who participated in a large multicenter, population-based, case-control study.

PATIENTS AND METHODS

Study Design

Participants were breast cancer patients enrolled in the Women's Contraceptive and Reproductive Experiences (CARE) Study, a population-based, multicenter, case-control study designed to examine risk factors for

invasive breast cancer among black women and white women.¹⁷ Women 35 to 64 years of age diagnosed with histologically confirmed incident invasive breast cancer (International Classification of Diseases for Oncology codes C50.0–C50.9) from July 1994 through April 1998 were randomly sampled from five field sites: Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle. Black women were oversampled to maximize their numbers in the study, and white women were sampled to provide approximately equal numbers of women in each 5-year age category (35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, and 60 to 64 years). Among 5,982 eligible patients with breast cancer, 4,575 (76.5%) participated in this study, including 1,622 black women (72.2% of

eligible patients) and 2,953 white women (79.1% of eligible patients). The Women's CARE Study protocol was approved by the institutional review boards at participating institutions.

We abstracted stage of tumor at diagnosis, estrogen receptor (ER) status, and progesterone receptor (PR) status from Surveillance, Epidemiology, and End Results (SEER) registry records at the four SEER sites (Atlanta, Detroit, Los Angeles, and Seattle) and directly from medical records in Philadelphia.

Shortly after breast cancer diagnosis, trained staff administered standardized in-person interviews to collect detailed information on exposures before breast cancer diagnosis, including demographic characteristics, tallest

Table 1. Distribution of Selected Characteristics at Diagnosis of Patients With Breast Cancer According to BMI 5 Years Before Diagnosis and Race

Characteristic	All Women (%) (N = 4,538)	BMI 5 Years Before Diagnosis (%)				Race (%)	
		< 20 kg/m ² (n = 486)	20-24.9 kg/m ² (n = 2,074)	25-29.9 kg/m ² (n = 1,192)	≥ 30 kg/m ² (n = 786)	White (n = 2,934)	Black (n = 1,604)
Race							
White	64.7	73.6	85.4	53.5	45.0		
Black	35.4	26.4	14.6	46.5	55.0		
Age at diagnosis, years							
35-39	15.0	17.7	24.1	11.0	8.3	15.7	13.7
40-44	16.6	17.6	23.3	14.6	12.9	15.9	17.8
45-49	17.1	18.5	15.8	14.9	17.4	16.3	18.5
50-54	18.5	17.7	15.8	20.0	20.0	18.3	18.8
55-59	16.9	14.5	9.1	20.6	22.3	16.9	16.9
60-64	16.0	14.0	11.9	19.0	19.5	16.9	14.4
Study site							
Atlanta	19.4	20.1	24.1	19.1	14.9	19.0	20.0
Seattle	23.3	26.4	26.5	20.2	17.8	33.9	3.9
Detroit	14.8	13.6	13.6	15.3	18.2	13.6	17.0
Philadelphia	15.4	13.5	11.1	18.0	19.0	10.7	23.9
Los Angeles	27.2	26.5	24.7	27.4	30.2	22.8	35.3
Education							
College graduate	29.7	35.4	39.9	24.8	15.8	35.5	19.1
Some college or technical school	32.4	32.1	36.8	31.7	31.6	32.2	32.9
High school graduate	29.2	27.2	18.7	32.1	36.3	26.8	33.6
Not a high school graduate	8.7	5.2	4.5	11.4	16.4	5.6	14.4
Family history of breast cancer (first degree)							
No	79.0	79.1	83.5	79.4	75.6	77.9	81.2
Yes	17.1	17.8	13.8	17.0	17.3	18.5	14.5
Adopted/not known	3.9	3.0	2.7	3.7	7.1	3.7	4.2
Menopausal status							
Premenopausal	46.2	50.5	60.1	39.6	36.4	46.4	45.8
Postmenopausal	42.2	38.0	27.8	48.9	51.8	43.1	40.4
Not known	11.6	11.5	12.1	11.5	11.8	10.5	13.8
No. of comorbidities							
0	62.8	73.2	81.9	55.6	34.6	70.8	48.3
1	29.7	24.1	16.9	35.1	44.4	24.9	38.5
≥ 2	7.5	2.8	1.2	9.3	21.0	4.4	13.2
Stage							
Localized tumor	60.3	61.6	66.7	59.8	53.9	63.6	54.4
Nonlocalized tumor	38.5	37.2	31.7	39.0	45.1	35.7	43.6
Not known	1.2	1.2	1.7	1.2	1.0	0.8	2.0
ER status							
Positive	58.8	60.8	64.6	54.0	57.0	65.6	46.1
Negative	28.8	27.8	26.5	31.6	28.4	24.9	35.9
Not known	12.5	11.5	8.9	14.4	14.6	9.5	18.0
BMI 5 years before diagnosis, kg/m²							
< 20	10.7					14.1	4.4
20-24.9	45.7					52.0	34.1
25-29.9	26.3					21.8	34.5
≥ 30	17.3					12.1	26.9

Abbreviations: BMI, body mass index; ER, estrogen receptor.

height without shoes (in feet and inches), weight (in pounds) 5 years before breast cancer diagnosis, disease history and medical conditions, reproductive history, exogenous hormone use, mammography use, and histories of recreational physical activity, smoking, and alcohol consumption. Women were interviewed, on average, 5.1 months after diagnosis.

All interviewed patients from the Women's CARE Study were followed up annually for vital status, date of death, and cause of death. The four SEER-based field sites used standard SEER follow-up procedures. The Philadelphia field site used state death records to track vital status. Patients from the Atlanta, Detroit, and Seattle study sites were followed up through December 31, 2004; follow-up extended through December 2005 in Philadelphia and through December 2007 in Los Angeles.

We excluded 37 women who died as a result of injury, poisoning, and certain other consequences of external cause ($n = 9$), were immediately lost to follow-up ($n = 2$), or had missing information on education or BMI 5 years before diagnosis ($n = 26$). Thus our analytic cohort consisted of 1,604 black women and 2,934 white women.

Statistical Analysis

Our end points were death resulting from any cause and death resulting from breast cancer (International Classification of Diseases codes ICD9-174, ICD10-C50). Kaplan-Meier curves were constructed to describe the survival experience of the study population stratified by race (black ν white) and BMI 5 years before diagnosis (obese [BMI ≥ 30 kg/m²] ν nonobese [BMI < 30 kg/m²]). To compare survival across the four subgroups, we performed pairwise comparisons using the log-rank test, and we imposed a Bonferroni correction to the P value, restricting the overall type I error rate to 5% by considering only two-sided P values less than .008 as statistically significant for each pairwise comparison of obesity across the two race groups.¹⁸

Self-reported height and weight 5 years before diagnosis were used to calculate BMI, which was categorized into thin (< 20 kg/m²), normal weight (20 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), or obese (≥ 30 kg/m²).¹⁹

Multivariate Cox proportional hazards regression models provided estimates of the hazard rate ratio of death, a measure of relative risk (RR), and 95%

Table 2. Selected Characteristics at Diagnosis of Patients With Breast Cancer, Race, and RRs of Mortality

Characteristic	Total (N = 4,538)	All-Cause Mortality						Breast Cancer-Specific Mortality					
		No.	%	RR	95% CI	Black v White		No.	%	RR	95% CI	Black v White	
						RR	95% CI					RR	95% CI
Race*													
White	2,934	534	18.2	1.00	Ref			416	14.2	1.00	Ref		
Black	1,604	519	32.4	1.68	1.47 to 1.91			412	25.7	1.75	1.50 to 2.03		
Age at diagnosis, years†													
35-39	680	179	26.3	1.00	Ref	1.92	1.41 to 2.63	165	24.3	1.00	Ref	1.97	1.43 to 2.73
40-44	752	178	23.7	1.09	0.84 to 1.43	2.04	1.47 to 2.84	153	20.3	1.11	0.83 to 1.47	2.07	1.45 to 2.96
45-49	775	157	20.3	1.07	0.75 to 1.53	1.34	0.96 to 1.88	129	16.6	1.17	0.80 to 1.72	1.50	1.03 to 2.17
50-54	838	176	21.0	1.29	0.85 to 1.95	1.36	0.99 to 1.89	143	17.1	1.56	0.99 to 2.46	1.35	0.94 to 1.94
55-59	766	173	22.6	1.64	1.02 to 2.65	1.88	1.34 to 2.64	123	16.1	1.90	1.12 to 3.22	2.09	1.39 to 3.13
60-64	727	190	26.1	1.96	1.14 to 3.35	1.64	1.20 to 2.25	115	15.8	2.57	1.40 to 4.72	1.62	1.08 to 2.43
P trend				.01						< .01			
Education‡													
College graduate	1,348	219	16.3	1.00	Ref	1.90	1.42 to 2.55	178	13.2	1.00	Ref	2.21	1.60 to 3.06
Some college or technical school	1,471	349	23.7	1.38	1.17 to 1.64	1.67	1.32 to 2.10	283	19.2	1.39	1.15 to 1.68	1.67	1.29 to 2.15
High school graduate	1,324	340	25.7	1.51	1.27 to 1.80	1.59	1.27 to 2.01	274	20.7	1.56	1.28 to 1.89	1.57	1.22 to 2.03
Not a high school graduate	395	145	36.7	2.07	1.65 to 2.58	1.74	1.20 to 2.52	93	23.5	1.74	1.34 to 2.26	1.98	1.23 to 3.16
Family history of breast cancer (first degree)													
No	3,587	852	23.8	1.00	Ref	1.72	1.48 to 1.99	671	18.7	1.00	Ref	1.80	1.53 to 2.13
Yes	775	160	20.7	0.91	0.77 to 1.08	1.50	1.07 to 2.12	127	16.4	0.93	0.77 to 1.13	1.69	1.15 to 2.48
Adopted/not known	176	41	23.3	0.88	0.64 to 1.21			30	17.0	0.88	0.61 to 1.28		
Menopausal status													
Premenopausal	2,097	481	22.9	1.00	Ref	1.81	1.49 to 2.19	421	20.1	1.00	Ref	1.82	1.48 to 2.24
Postmenopausal	1,913	466	24.4	1.26	0.99 to 1.6	1.50	1.21 to 1.85	321	16.8	1.18	0.90 to 1.55	1.55	1.20 to 2.00
Not known	528	106	20.1	0.96	0.76 to 1.2			86	16.3	0.92	0.71 to 1.18		
No. of comorbidities													
0	2,851	580	20.3	1.00	Ref	1.89	1.58 to 2.26	487	17.1	1.00	Ref	1.91	1.57 to 2.33
1	1,348	352	26.1	1.17	1.02 to 1.35	1.45	1.16 to 1.83	278	20.6	1.16	0.99 to 1.36	1.53	1.18 to 1.99
≥ 2	339	121	35.7	1.44	1.16 to 1.79	0.98	0.65 to 1.49	63	18.6	1.00	0.75 to 1.32	1.38	0.75 to 2.54
P trend				< .01						.32			
SEER stage													
Localized	2,738	359	13.1	1.00	Ref	1.77	1.42 to 2.22	223	8.1	1.00	Ref	1.70	1.28 to 2.26
Nonlocalized	1,745	671	38.5	3.40	2.99 to 3.88	1.45	1.23 to 1.72	584	33.5	4.66	3.98 to 5.45	1.54	1.29 to 1.84
Not known	55	23	41.8	4.17	2.71 to 6.42			21	38.2	5.84	3.69 to 9.24		
ER status													
Positive	2,666	488	18.3	1.00	Ref	1.75	1.44 to 2.12	359	13.5	1.00	Ref	1.95	1.55 to 2.44
Negative	1,305	415	31.8	1.77	1.54 to 2.02	1.30	1.05 to 1.60	361	27.7	1.99	1.71 to 2.32	1.30	1.04 to 1.62
Not known	567	150	26.5	1.33	1.10 to 1.60			108	19.0	1.32	1.05 to 1.64		

NOTE. Cox proportional hazards models use age (days) as the time metric, are stratified by age at diagnosis in years, and include the following variables: race, study site, and education level, except where otherwise noted.

Abbreviations: ER, estrogen receptor; Ref, reference; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results.

*Models adjusted for study site and education level and are stratified by age at diagnosis.

†Models adjusted for race, study site, and education level.

‡Models adjusted for race and study site and are stratified by age at diagnosis.

CI. Age in days at diagnosis and age in days at death or end of follow-up defined the time scale for analysis. In the analyses of breast cancer–specific mortality, women who died from other causes were censored on their dates of death. All statistical multivariate models were stratified by age in years at diagnosis and adjusted for study site (Atlanta, Detroit, Los Angeles, Philadelphia, Seattle), race (black, white), education (less than high school, high school, some college, college graduate), tumor stage (localized, nonlocalized), ER status (positive, negative, unknown), and number of comorbidities before breast cancer diagnosis (zero, one, two or more). Comorbidities included hypertension, myocardial infarction, stroke, diabetes, and cancers other than nonmelanoma skin cancers. We also assessed the influence of additional potential confounders, including first-degree family history of breast cancer, alcohol consumption level, smoking history, average intensity-hours per week of physical activity, age at menarche, parity, number of full-term pregnancies, months of breastfeeding, lifetime total number of mammograms, months of oral contraceptive use, menopausal status, and months of postmenopausal hormonal use. As none of these factors substantially influenced the RR estimates, none were included in the final models.

We performed tests for trend for ordinal variables by fitting the median value for each category as a continuous variable. To test whether the association between BMI 5 years before diagnosis and mortality was modified by race, we constructed a likelihood ratio test comparing two multivariate Cox proportional hazards models (likelihood ratio test for heterogeneity of trends with 1 *df*).²⁰ We further examined the effect of BMI on mortality among black women and white women stratified by ER status, tumor stage, menopausal status, and education level. Results for models based on ER and PR status, although based on smaller numbers for ER-positive/PR-positive and ER-negative/PR-negative tumors, were consistent with those presented here stratified by ER status. The assumption of proportionality of hazards was assessed for each final model; no violation of the proportional hazards assumption was observed. Two-sided *P* values are reported. We did not adjust *P* values for multiple comparisons. All statistical analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC).

RESULTS

The mean age at breast cancer diagnosis was 49.7 years among these women who were, by design, sampled from women diagnosed at ages 35 to 64 years. During a median follow-up of 8.6 years, 1,053 women died (519 black, 534 white), 828 as a result of breast cancer (412 black, 416 white). Overall, 786 women (17.3%) were obese (BMI ≥ 30 kg/m²) 5 years before breast cancer diagnosis (26.9% of black women; 12.1% of white women; Table 1). Obese women were more likely to be older, have low education levels, be postmenopausal, have more comorbidities, and be diagnosed with nonlocalized tumors. Black women were more likely to have low education levels, have more comorbidities, and be diagnosed with nonlocalized tumors or ER-negative tumors.

The RRs for mortality associated with the demographic and tumor characteristics are shown in Table 2. Older women and women with lower levels of education, more comorbidities, ER-negative tumors, or nonlocalized tumors had higher risks of mortality. Within each demographic and tumor characteristics stratum, black women had a higher risk of mortality than white women, except for women who had two or more comorbidities.

The mortality risk for black women was nearly twice that of white women (RR = 1.90; 95% CI, 1.68 to 2.14). The RR decreased to 1.68 (95% CI, 1.47 to 1.91) when education and study site were included in the Cox model and decreased further when tumor characteristics (tumor stage, ER status) and comorbidities were added to this model (RR = 1.36; 95% CI, 1.19 to 1.57). Adjusting this latter model for BMI 5 years before diagnosis did not fundamentally change the RR from

this latter model (RR = 1.33; 95% CI, 1.16 to 1.53). Considering that BMI is associated with tumor characteristics and comorbidities, we also conducted analyses that adjusted for BMI before adding tumor characteristics and comorbidities into the model. Nevertheless, the RR risk only changed from 1.68 to 1.57 (95% CI, 1.37 to 1.80) when adding BMI to a model that included only education level and study site. Similar risk patterns were observed when using breast cancer–specific mortality as the outcome of interest.

Figures 1A and 1B show Kaplan-Meier survival curves for black women and white women stratified by obesity status 5 years before diagnosis. A survival difference was observed between nonobese and obese white women (log-rank *P* < .001 for all-cause and for breast cancer–specific mortality), but not between nonobese and obese black women. In fact, curves for black women (obese and nonobese) did not differ from those of obese white women.

Obese women overall had a 20% greater risk of dying as a result of any cause (*P* trend = .01; RR, 1.23; 95% CI, 1.04 to 1.47) or breast cancer (*P* trend = .03; RR, 1.20; 95% CI, 0.99 to 1.46) than women with BMI in the normal range (Table 3). Obese white women had a 54% greater risk of all-cause mortality than the reference group (*P* trend < .01; RR, 1.54; 95% CI, 1.21 to 1.96); however, no such association was observed for black women. The trends for black women and white women were statistically significantly different (*P* for homogeneity of trends = .03). Similar risk patterns were observed for breast cancer–specific mortality.

Fig 1. (A) Kaplan-Meier all-cause survival of black and white women diagnosed with invasive breast cancer stratified by obesity status 5 years before breast cancer diagnosis. (B) Kaplan-Meier breast cancer–specific survival of black and white women diagnosed with invasive breast cancer stratified by obesity status 5 years before breast cancer diagnosis.

Table 3. RR Estimates and 95% CIs for the Association Between BMI 5 Years Before Diagnosis and Risk of Mortality in the Women's CARE Study

Variable and BMI (kg/m ²)	Person-Years	All-Cause Mortality			Breast Cancer–Specific Mortality		
		No.	RR	95% CI	No.	RR	95% CI
Overall							
< 20	4134	82	0.89	0.70 to 1.14	65	0.86	0.65 to 1.12
20-24.9	17,336	423	1.00	Ref	348	1.00	Ref
25-29.9	9,700	287	0.99	0.84 to 1.15	226	0.99	0.83 to 1.18
≥ 30	6,142	261	1.23	1.04 to 1.47	189	1.20	0.99 to 1.46
<i>P</i> trend			.01			.03	
White women							
< 20	3,557	61	0.92	0.69 to 1.22	47	0.88	0.64 to 1.21
20-24.9	12,979	257	1.00	Ref	207	1.00	Ref
25-29.9	5,267	115	1.03	0.82 to 1.29	90	1.04	0.81 to 1.34
≥ 30	2,764	101	1.54	1.21 to 1.96	72	1.46	1.11 to 1.92
<i>P</i> trend			.001			.005	
Black women							
< 20	577	21	0.87	0.55 to 1.38	18	0.84	0.51 to 1.39
20-24.9	4,357	166	1.00	Ref	141	1.00	Ref
25-29.9	4,433	172	0.91	0.73 to 1.13	136	0.91	0.72 to 1.16
≥ 30	3,378	160	1.03	0.81 to 1.29	117	1.02	0.79 to 1.33
<i>P</i> trend			.63			.66	
White v black <i>P</i> for homogeneity of trend			.03			.08	

NOTE. Cox proportional hazards models use age (days) as the time metric, are stratified by age at diagnosis in years, and include the following variables: education, study site, tumor stage, estrogen receptor status, and number of comorbidities and race as necessary.

Abbreviations: BMI, body mass index; CARE, Contraceptive and Reproductive Experiences; Ref, reference; RR, relative risk.

When we examined the association between BMI 5 years before diagnosis, race, and mortality stratified by ER status, tumor stage, menopausal status, and education level, we observed risk patterns similar to those presented overall; that is, within these strata we observed the positive association among white women and the null results among black women across all strata except that of black women with nonlocalized tumors and of white women with low education (no more than high school education; Table 4). Among black women with nonlocalized tumors, obese women had slightly increased mortality risk associated with BMI 5 years before diagnosis (all-cause *P* trend = .07; RR for obese women, 1.25; 95% CI, 0.93 to 1.66; breast cancer *P* trend = .04; RR for obese women, 1.31; 95% CI, 0.97 to 1.78). Similar to the results for black women, among white women with no more than a high school education, obesity was not associated with all cause (*P* trend = .66) or breast cancer mortality (*P* trend = .60).

DISCUSSION

In this large, population-based study of black women and white women diagnosed with invasive breast cancer between ages 35 and 64 years, black women had greater risk of mortality than white women overall. High BMI 5 years before diagnosis was associated with increased risk of all-cause and breast cancer–specific mortality among white women, but not among black women.

Because black women generally have a higher prevalence of obesity than white women at the time of breast cancer diagnosis, several authors have postulated that obesity could explain some of the observed racial differences in mortality.²¹⁻²⁴ However, our data do not support this hypothesis. Black women were more likely than white women to have lower education levels, ER-negative tumors, nonlocalized tumors, and comorbidities. All of these factors were associated

with increased risk of mortality. After considering age, education, study site, tumor stage, ER status, and comorbidities, obesity did not further explain any differences in mortality risk between black women and white women. The study by Chlebowski et al²⁵ showed a continuing racial difference in mortality after adjusting for BMI. However, the number of deaths among black women was small (*n* = 21), and the median follow-up was only 3.1 years. Further, this study did not address the extent to which inclusion of BMI in the model affected the risk estimates, nor were they able to look separately for black and white women at how BMI affected risk.²⁵

Our results showing increased risk of mortality for obese white women compared with normal-weight white women are consistent with those of most previous studies,⁴⁻¹³ although results stratified by tumor characteristics are not totally consistent with previous studies. Our data and others^{4,5,10} show that obese women were more likely to be diagnosed with later-stage tumors. We, and one other study,⁴ observed similar obesity-survival risk patterns among women with different tumor stages. In contrast, another study reported a stronger association among women with early-stage tumors.⁶ However, the number of women with later-stage tumors was relatively small in the latter study (*n* = 192).⁶ Previous studies have demonstrated that obesity is more strongly associated with developing ER-positive tumors than ER-negative tumors.²⁵ For survival, our study and others have suggested that no differences exist in the obesity-survival association by ER status.^{4,6,8} However, a recent study with a small number of deaths (*n* = 87) reported that obesity was not associated with overall survival among women with triple-negative breast cancer.²⁶ These results suggest that mechanisms involved in the obesity-incidence association may differ from those involved in the obesity-survival association.

It has been hypothesized that adiposity affects breast cancer prognosis by elevating circulating levels of endogenous estrogen that result

Table 4. RR Estimates and 95% CIs for the Association Between BMI 5 Years Before Diagnosis and Risk of Mortality in Black and White Women in the Women's CARE Study

Variable and BMI (kg/m ²)	All-Cause Mortality						Breast Cancer–Specific Mortality					
	Death (No.)	White Women		Death (No.)	Black Women		Death (No.)	White Women		Death (No.)	Black Women	
		RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI
ER positive												
< 20	32	1.01	0.68 to 1.48	12	1.15	0.51 to 2.15	21	0.86	0.53 to 1.38	11	1.23	0.63 to 2.41
20-24.9	133	1.00	Ref	63	1.00	Ref	101	1.00	Ref	52	1.00	Ref
25-29.9	61	1.15	0.84 to 1.57	62	0.99	0.69 to 1.42	41	1.08	0.75 to 1.57	47	0.97	0.65 to 1.45
≥ 30	53	1.53	1.10 to 2.15	72	1.18	0.83 to 1.69	35	1.54	1.03 to 2.31	51	1.14	0.76 to 1.72
<i>P</i> trend		.02			.43			.02			.69	
<i>P</i> for homogeneity of trend				.27						.19		
ER negative												
< 20	24	0.89	0.56 to 1.40	5	0.48	0.19 to 1.19	22	0.93	0.58 to 1.51	4	0.40	0.15 to 1.12
20-24.9	97	1.00	Ref	76	1.00	Ref	85	1.00	Ref	70	1.00	Ref
25-29.9	43	0.95	0.66 to 1.38	74	0.85	0.61 to 1.19	41	1.05	0.72 to 1.55	65	0.86	0.60 to 1.22
≥ 30	40	1.57	1.06 to 2.32	56	0.94	0.65 to 1.37	32	1.38	0.90 to 2.11	42	0.82	0.54 to 1.24
<i>P</i> trend		.03			.81			.13			.74	
<i>P</i> for homogeneity of trend				.16						.19		
Localized tumor												
< 20	20	0.78	0.48 to 1.27	6	0.92	0.39 to 2.15	11	0.58	0.30 to 1.10	4	0.76	0.27 to 2.14
20-24.9	89	1.00	Ref	59	1.00	Ref	63	1.00	Ref	44	1.00	Ref
25-29.9	40	0.91	0.63 to 1.34	61	0.85	0.59 to 1.23	27	0.95	0.60 to 1.50	38	0.80	0.51 to 1.25
≥ 30	35	1.50	1.00 to 2.26	49	0.80	0.54 to 1.20	17	1.23	0.70 to 2.14	19	0.49	0.28 to 0.87
<i>P</i> trend		.03			.32			.16			.02	
<i>P</i> for homogeneity of trend				.02						.01		
Nonlocalized tumor												
< 20	40	1.06	0.75 to 1.51	12	0.79	0.43 to 1.45	35	1.07	0.74 to 1.56	11	0.79	0.42 to 1.49
20-24.9	164	1.00	Ref	102	1.00	Ref	140	1.00	Ref	92	1.00	Ref
25-29.9	73	1.12	0.84 to 1.49	108	0.95	0.72 to 1.26	61	1.11	0.81 to 1.50	95	0.96	0.71 to 1.29
≥ 30	64	1.54	1.14 to 2.07	108	1.25	0.93 to 1.66	54	1.55	1.12 to 2.15	96	1.31	0.97 to 1.78
<i>P</i> trend		.01			.07			.02			.04	
<i>P</i> for homogeneity of trend				.62						.83		
No more than high school education												
< 20	22	1.58	0.98 to 2.53	10	1.03	0.52 to 2.04	17	1.45	0.85 to 2.49	8	0.92	0.43 to 1.99
20-24.9	94	1.00	Ref	69	1.00	Ref	80	1.00	Ref	57	1.00	Ref
25-29.9	46	0.83	0.58 to 1.19	97	1.05	0.76 to 1.45	32	0.69	0.45 to 1.05	72	1.03	0.71 to 1.48
≥ 30	48	1.32	0.92 to 1.90	99	1.17	0.84 to 1.63	31	1.10	0.71 to 1.70	70	1.21	0.83 to 1.76
<i>P</i> trend		.66			.32			.60			.27	
<i>P</i> for homogeneity of trend				.75						.25		
College or higher level of education												
< 20	39	0.76	0.54 to 1.09	11	0.78	0.41 to 1.46	30	0.76	0.51 to 1.13	10	0.75	0.38 to 1.46
20-24.9	163	1.00	Ref	97	1.00	Ref	127	1.00	Ref	84	1.00	Ref
25-29.9	69	1.23	0.92 to 1.64	75	0.78	0.57 to 1.07	58	1.38	1.01 to 1.90	64	0.81	0.58 to 1.13
≥ 30	53	1.82	1.32 to 2.51	61	0.98	0.70 to 1.37	41	1.86	1.29 to 2.68	47	0.91	0.63 to 1.33
<i>P</i> trend		.01			.97			.01			.77	
<i>P</i> for homogeneity of trend				.004						.002		
Premenopausal women												
< 20	31	0.77	0.52 to 1.15	13	0.85	0.47 to 1.53	27	0.76	0.50 to 1.16	13	0.93	0.51 to 1.68
20-24.9	128	1.00	Ref	97	1.00	Ref	114	1.00	Ref	87	1.00	Ref
25-29.9	44	0.98	0.69 to 1.38	71	0.93	0.68 to 1.27	41	1.00	0.69 to 1.44	60	0.88	0.63 to 1.23
≥ 30	39	1.68	1.16 to 2.44	58	0.99	0.70 to 1.40	30	1.43	0.95 to 2.17	49	0.95	0.66 to 1.38
<i>P</i> trend		.003			.91			.04			.79	
<i>P</i> for homogeneity of trend				.04						.08		
Postmenopausal women												
< 20	23	1.17	0.74 to 1.84	4	0.63	0.22 to 1.79	16	1.13	0.66 to 1.96	2	0.38	0.09 to 1.62
20-24.9	109	1.00	Ref	51	1.00	Ref	78	1.00	Ref	38	1.00	Ref
25-29.9	65	1.03	0.75 to 1.42	79	0.86	0.60 to 1.24	43	1.04	0.71 to 1.53	57	0.90	0.58 to 1.38
≥ 30	53	1.46	1.04 to 2.07	82	0.91	0.62 to 1.32	34	1.53	1.00 to 2.34	53	0.90	0.57 to 1.40
<i>P</i> trend		.08			.94			.10			.94	
<i>P</i> for homogeneity of trend				.20						.26		

NOTE. Total number of deaths may vary due to missing values in corresponding variables. Cox proportional hazards models use age (days) as the time metric, are stratified by age at diagnosis in years, and include the following variables: education, study site, tumor stage, estrogen receptor status, and number of comorbidities in corresponding models.

Abbreviations: BMI, body mass index; CARE, Contraceptive and Reproductive Experiences; ER, estrogen receptor; Ref, reference; RR, relative risk.

from the conversion of adrenal androgens to estrogen in peripheral adipose tissue,²⁷ lowering circulating levels of sex hormone-binding globulin,²⁸ increasing insulin resistance,²⁹ and increasing insulin-like growth factor-1 levels.³⁰ Furthermore, adipose tissue produces leptin and a group of other growth factors (eg, interleukin-6, tumor necrosis factor- α , vascular endothelial growth factor) that may stimulate angiogenesis, lead to more rapid growth of malignant cells, and promote metastasis.³¹⁻³³

Another possible explanation for the adverse effect of obesity on mortality is attributed to the more advanced tumor stage associated with obesity.³³⁻³⁵ Among women with nonlocalized tumors, but not among women with localized tumors, we observed increased risk of mortality with obesity, especially breast cancer-specific mortality, for both black women and white women. Thus the obesity-mortality association may reflect the more advanced stage at cancer diagnosis.

It is not clear why obesity-associated mortality risk patterns differ between black women and white women with breast cancer. The Cancer Prevention Study II with a cohort of participants free of cancer at baseline examined the effect of BMI on the risk of fatal breast cancer.²² Of interest, the authors found that higher BMI at baseline was positively associated with fatal breast cancer among white women, but not among black women.²² Furthermore, increasing evidence suggests a stronger association between BMI and coronary heart disease, stroke, and cardiovascular disease mortality among white than among black individuals.³⁶ In our study, normal-weight black women had 53% (95% CI, 24% to 88%) greater risk of all-cause mortality than normal-weight white women, but obese black women did not have greater risk of all-cause mortality than obese white women (RR, 1.02; 95% CI, 0.78 to 1.32); these risk patterns were consistent across all strata examined. Thus other factors such as different cultural, social environmental, psychological, and behavioral factors; health care quality and access; and biologic characteristics that are associated with both obesity and survival may be a partial explanation for black women's higher mortality.

A major strength of our study is the large, population-based sampling of black women and white women. To our knowledge, our study is the first to examine the association of mortality with BMI between black women and white women with invasive breast cancer living in the same geographical regions. The detailed information on a large number of potential risk factors for breast cancer incidence and mortality enabled us to assess many potential confounders, build appropriate multivariate models, and evaluate possible effect modifiers. Finally, our high rate and long duration of follow-up (median, 8.6 years; 25th to 75th percentiles, 7.1 to 10.1 years) enabled us to have large numbers of events.

A limitation is that our results are not generalizable to all patients with breast cancer. In the United States, 57% of women diagnosed with invasive breast cancer are between the ages of 35 and 64 years.³ Our results apply only to women in this age range. Further, self-reported measures of body size may be inaccurate, with heavier women more likely to underreport their weights.^{14,37} Such measurement error would be expected to be nondifferential with respect to mortality, resulting in attenuation of the true underlying associations. Importantly, the validity of self-reported data on weight among black women is similar to that of white women.³⁸ We were unable to assess BMI at diagnosis or weight change after diagnosis, which were of prognostic value in some studies.^{39,40} Prior studies show no evidence to suggest that women's weight in the few years before cancer diagnosis

differs much from their weight at diagnosis.^{41,42} Further, prediagnosis body weight may be a stronger predictor of mortality than weight gain after diagnosis.^{9,12}

Although we lacked information on the breast cancer therapies, we have presumed that controlling for age, stage of disease, and hormone receptor status has provided some control for treatment. Nevertheless, previous studies have suggested that black women may have less optimal treatment than white women. They are more likely to delay the initiation of treatment,⁴³ less likely to receive radiation therapy or appropriate dose-intensities of adjuvant chemotherapy,^{44,45} more likely to terminate treatment prematurely,⁴⁶ and less likely to adhere to recommended treatment regimens^{44,45} than white women. However, we found no data regarding whether obese black women's treatment differs from that of normal weight black women. Further, the lack of data on human epidermal growth factor receptor 2 expression prevented informative analyses of the obesity-survival association for women with triple-negative subtype.

Because we did not adjust for multiple testing in our assessment of main effects and stratified analyses, some results (eg, that for the inverse BMI association with decreasing breast cancer mortality among black women) may be false positives and due to few deaths in some strata. Additionally, the results for thin women (BMI < 20 kg/m²) may not be as informative as those for heavier women given the small number of thin women.

In summary, we find that obesity 5 years before breast cancer diagnosis is an independent predictor of survival among white women ages 35 to 64 years, but not among black women in this age group. These findings suggest that differences in the distribution of obesity among black women and white women diagnosed with breast cancer are unlikely to account for the poorer survival of black women.

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AUTHOR CONTRIBUTIONS

Conception and design: Yani Lu, Kathleen E. Malone, Polly A. Marchbanks, Robert Spirtas, Dennis Deapen, Jill A. McDonald, Leslie Bernstein **Financial support:** Robert Spirtas, Leslie Bernstein **Administrative support:** Yani Lu, Leslie Bernstein **Provision of study materials or patients:** Kathleen E. Malone, Sandra A. Norman, Brian L. Strom, Dennis Deapen, Michael F. Press, Leslie Bernstein **Collection and assembly of data:** Yani Lu, Kathleen E. Malone, Sandra A. Norman, Jane Sullivan-Halley, Brian L. Strom, Polly A. Marchbanks, Dennis

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