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Overall and central adiposity and risk of contralateral breast cancer: The California Breast Cancer Survivorship Consortium

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Abstract

Data on associations between overall adiposity measured by body mass index (BMI) and risk of contralateral second primary breast cancer (CBC) are inconsistent and associations with central adiposity have not been investigated. We analyzed harmonized data from six studies for 9,479 women with a first primary invasive stage I-III breast cancer (FBC) diagnosed from 1993 through 2009. Linkage of this cohort with the California Cancer Registry identified 610 CBC, diagnosed

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Conflicts of interest

The authors declare no conflict of interest.

Ethics statement

The Institutional Review Boards of the collaborating institutions approved the studies, and study participants provided written informed consent or provided consent by completing the mailed questionnaire.

more than 180 days after FBC. Multivariable Fine and Gray regression models accounting for competing risks were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) associated with BMI, waist circumference (WC), waist-to-height ratio, and body roundness index. In postmenopausal women without use of menopausal hormone therapy (HT) before FBC diagnosis, obesity (vs. normal weight BMI) was associated with a nearly two-fold higher risk of CBC (HR=1.89, CI=1.10–3.24, per 5 kg/m² HR=1.22, CI=1.07–1.40). No associations with BMI were observed for survivors overall, premenopausal survivors, or postmenopausal survivors with a history of HT use. When stratified by FBC hormone receptor status, a higher risk was limited to postmenopausal women with hormone receptor-negative FBC without pre-diagnosis HT use (HR=2.55, CI=1.07–6.09, per 5 kg/m² HR=1.36, CI=1.12–1.65). In survivors overall, larger WC was associated with higher risk of CBC (tertile 3 vs. 1: HR=1.59, CI=1.05–2.39, p-trend=.02) in models adjusted for BMI. Breast cancer survivors with overall or central adiposity may benefit from risk-reducing weight loss strategies and more frequent surveillance screening after FBC diagnosis.

Keywords

Contralateral breast cancer; epidemiology; hormone receptor status; body mass index; waist circumference

INTRODUCTION

In survivors of a first primary invasive breast cancer (FBC), the risk of developing a contralateral second primary breast cancer (CBC) is at least two-fold higher compared with the risk of developing a FBC in women from the general population.¹ Risk factors for CBC include younger age at FBC diagnosis, FBC with negative hormone receptor and other tumor characteristics, radiation therapy, family history of breast cancer, and genetic susceptibility (e.g., *BRCA1* or *BRCA2* germline pathogenic variants).^{1–4} Furthermore, CBC risk is higher in African American, Asian American, and Hispanic survivors compared with non-Hispanic White survivors,^{5–11} particularly those first diagnosed at younger ages.^{8, 9, 12} Finally, given the increasing incidence of early-onset FBC and hormone receptor-positive FBC in the population,¹³ CBC is a growing concern. Little is known about the prevention of CBC and the role of potentially modifiable risk factors.¹⁴ Given advances in treatment and early detection, a better understanding of CBC prevention is essential for the growing number of FBC survivors.

Obesity is a well-established, potentially modifiable risk factor for FBC in postmenopausal women¹⁵ and is associated with higher breast cancer-specific and all-cause mortality.¹⁶ For other outcomes such as breast cancer recurrence and CBC, data on associations with obesity are limited, with suggestive, but not consistent, evidence for higher CBC risk¹⁶ (Supplementary Table 1). In premenopausal women, obesity was associated with higher CBC risk in one small study,¹⁷ but not in another study.¹⁸ Findings are also inconsistent in studies that included FBC survivors across a broad age range and did not stratify the analyses by age or menopausal status, with higher risks with obesity observed in some studies,^{19–21} but not others.^{22, 23} In three meta-analyses of BMI and CBC risk that included

up to nine partly overlapping studies, between-study heterogeneity was high.^{16, 24, 25} For FBC, BMI associations are modified by menopausal status and hormone receptor status. Higher risks associated with higher BMI are limited to postmenopausal women who never used menopausal hormonal therapy (HT) and those with hormone receptor-positive FBC.¹⁵

For CBC, potentially modifying factors have not been adequately investigated. It remains uncertain whether BMI associations with CBC differ by menopausal status or FBC hormone receptor status^{18, 26, 27} and the potentially modifying effect of HT use has not been examined. Central adiposity, which reflects visceral fat stores and is a strong predictor of health outcomes,²⁸ also has not been evaluated in relation to CBC risk. Furthermore, prior studies included primarily non-Hispanic White women, thus it is not known whether associations with obesity differ across racial and ethnic groups. To address these knowledge gaps, we evaluated associations of overall and central adiposity with risk of CBC, by menopausal status, HT use, FBC hormone receptor status, and race and ethnicity in a large, racially and ethnically diverse cohort of women diagnosed with FBC and followed for CBC.¹²

MATERIALS AND METHODS

Study sample and outcomes

The present study was conducted using data from the California Breast Cancer Survivorship Consortium (CBCSC)²⁹ that has been updated with second primary cancer diagnoses and vital status through 2020.¹² We analyzed harmonized data on clinical, personal, and lifestyle characteristics collected in six studies, including three case-control studies, a family-based study of breast cancer, a breast cancer survivor cohort, and a prospective general population cohort (see details and references in Supplementary Table 2). Women with FBC were diagnosed at age 18–79 years from 1993 through 2009 in Northern or Southern California and ascertained through regional cancer registries that are part of the California Cancer Registry and the Surveillance, Epidemiology, and End Results (SEER) program. For women with FBC who participated in more than one study, the data were retained from one study only. The remaining cohort (N=11,269) was linked with the California Cancer Registry, with follow-up through December 31, 2020 (n=8,045 FBC) or through December 31, 2019 for the Multiethnic Cohort (MEC, n=1,594 FBC). After exclusions (Supplementary Figure 1), analyses for CBC were based on 9,479 FBC survivors without a bilateral mastectomy at FBC diagnosis. As in other studies,^{7, 30} we limited the analysis to invasive CBC diagnosed more than 180 days after FBC diagnosis to minimize the inclusion of metastases that are misclassified as CBC.

Data collection

Variables obtained from the California Cancer Registry included tumor characteristics for FBC [histology, American Joint Committee on Cancer stage, grade, estrogen receptor (ER) status, progesterone receptor (PR) status, lymph node involvement, tumor size], initial treatment (surgery type, radiation therapy, chemotherapy), age and year of diagnosis, and marital status. Personal and lifestyle factors from questionnaires included self-reported race and ethnicity (categorized as non-Hispanic African American, non-Hispanic Asian

American, Hispanic (Black or White), or non-Hispanic White) and education level. Data on height, weight, and other risk factors were collected retrospectively after FBC diagnosis in the case-control studies [Asian American Breast Cancer Study (AABCS), Women's Contraceptive and Reproductive Experiences Study (CARE), San Francisco Bay Area Breast Cancer Study (SFBCS)] and family-based study [Northern California Breast Cancer Family Registry (NC-BCFR)] and assessed up to the year before FBC diagnosis. In the survivor cohort [Life After Cancer Epidemiology Study (LACE)], data were collected after FBC diagnosis and assessed up to the time of questionnaire completion (on average 1.8 years after FBC diagnosis); additionally, information was collected on weight in the year before FBC diagnosis. In MEC, the questionnaire data used in this analysis were collected at study enrollment (on average 6.7 years before FBC diagnosis). Data on HT use before FBC diagnosis were available for a subset of 5,587 FBC survivors from three studies for this specific analysis (AABCS, SFBCS, and NC-BCFR).

Pre-diagnosis BMI, a measure of overall adiposity, was calculated as self-reported weight (kg) divided by self-reported height (m) squared. In AABCS and SFBCS, missing self-reported height was replaced with measured height. BMI (kg/m^2) was categorized as normal weight (<25), overweight ($25\text{--}<30$), or obesity (≥ 30) for all women except Asian American survivors for whom BMI was categorized as normal weight (<23), overweight ($23\text{--}<27.5$), or obesity (≥ 27.5) according to cut-points suggested for Asian populations.³¹ Underweight (BMI $<18.5 \text{ kg/m}^2$, $n=177$) was combined with the normal BMI category. Waist circumference (WC) and height measurements were available for a subset of 2,760 FBC survivors from two studies (AABCS and SFBCS). We analyzed two measures of central adiposity at FBC diagnosis: WC, categorized according to the tertile distribution in our study sample and clinical cut-points of <80 , $80\text{--}<88$, and $\geq 88 \text{ cm}$.³² The second measure, waist-to-height ratio (WHtR), was calculated as measured waist (cm) divided by measured height (cm) and classified according to clinical cut-points of ≤ 0.5 , $>0.5\text{--}0.6$, and >0.60 .³³ We also calculated the body roundness index, a newer measure of visceral body fat distribution³⁴ which has been associated with risk of colorectal cancer,³⁵ other outcomes and all-cause mortality.³⁶ The body roundness index was calculated as $364.2 - 365.5 \times \text{the square root of } [1 - (\text{WC in centimeters} / 2\pi)^2 / (\text{height in centimeters} / 2)^2]$,³⁴ and categorized according to the tertile distribution in our study sample. Lastly, we examined the association with a composite measure of the joint classification by BMI (overweight or obesity vs. normal weight) and WC (tertiles 2 and 3 vs. tertile 1).

Statistical analysis

For the FBC cohort and CBC, we present distributions of clinical, personal, and lifestyle characteristics. For categorical body size variables, we assessed differences in distributions across racial and ethnic groups using chi square tests. Differences in mean BMI, WC, WHtR, and body roundness index across racial and ethnic groups were assessed using Student's t-distribution with Bonferroni's adjustment for multiple pairwise comparisons (critical p value 0.008, based on a significance level of 0.05 for six pairwise comparisons). We calculated the proportion of overweight or obesity by year of diagnosis and age categories and used Mantel-Haenszel chi-square to test for linear trend across the years of diagnosis within each age category. We assessed changes in BMI over time using linear

regression models and calculated means for BMI by year of FBC diagnosis (1993–1997, 1998–2002, 2003–2009), stratified by age at FBC diagnosis (<40, 40–49, 50–59, 60–69, ≥70 years), adjusted for age (continuous) and race and ethnicity. We used Fine and Gray competing risk regression models, with death and diagnosis of other primary cancers as competing events, and estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association of BMI, WC, WHtR, and body roundness index with risk of CBC. Follow-up extended until diagnosis of CBC, diagnosis of another primary cancer (n=577, comprising 291 ipsilateral breast cancers, 5 breast cancers with unknown laterality, and 281 other cancers), death (n=3,559), date of last contact, or study end, whichever was earliest. Deaths and other primary cancers were considered competing events. Models were adjusted for study (stratification variable), age at FBC diagnosis, and race and ethnicity, and for potentially confounding factors previously identified, including FBC hormone receptor status and first-degree family history of breast cancer.¹² We performed BMI analyses for all FBC survivors, and stratified by menopausal status, HT use in postmenopausal survivors, FBC hormone receptor status, and race and ethnicity. For WC, WHtR, and body roundness index, we fit competing risk regression models for all survivors combined and stratified the analyses by menopausal status, FBC hormone receptor status, and race and ethnicity. Heterogeneity in associations were assessed by including interaction terms in the models and using the Wald test to assess statistical significance. None of the variables included in the multivariable models violated the proportional hazards assumption. Two-sided p-values <0.05 were considered statistically significant. Analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

During follow-up of FBC survivors of up to 26.7 years (mean: 15.5 years, median: 16.9 years) 610 CBC were diagnosed, an incidence rate of 0.4% CBC cases per person-year. Mean time between FBC and CBC diagnosis was 9.7 years. In the five studies that administered questionnaires after FBC diagnosis, median time from FBC to questionnaire completion was 2.0 years with an interquartile range of 1.5–2.7 years. Of 9,479 FBC survivors, 2,110 (22%) were African American, 1,865 (20%) were Asian American, 2,330 (25%) were Hispanic, and 3,174 (33%) were non-Hispanic White (Table 1). Distributions of clinical, personal, and lifestyle factors are presented for FBC and CBC. High proportions of survivors had pre-diagnosis overweight or obesity (59%) or large (>0.5) WHtR (66%), and distributions varied by race and ethnicity (Supplementary Table 3). In age groups 40–49, 50–59, and 60–69 years, both mean BMI and proportion of overweight or obesity increased over time (Supplementary Figure 2).

In the analysis of the pooled dataset from six studies that did not consider HT use, BMI was not associated with risk of CBC, neither overall nor in premenopausal or postmenopausal survivors (Table 2). In the dataset from three studies with available data on HT use (5,287 FBC survivors, 342 CBC), a nearly two-fold higher risk of CBC was associated with obesity (vs. normal weight) in postmenopausal survivors without pre-diagnosis HT use (HR=1.89, CI=1.10–3.24, per 5 kg/m² increase HR=1.22, CI=1.07–1.40). Analyses stratified by FBC hormone receptor status showed more than two-fold higher risk of CBC only in postmenopausal survivors of hormone receptor-negative FBC without pre-diagnosis

HT use (HR=2.55, CI=1.07–6.09, per 5 kg/m² increase HR=1.36, CI=1.12–1.65) (Table 3). Heterogeneity by hormone receptor status, however, was not statistically significant (p-het=.66).

In analyses of six studies stratified by race and ethnicity, no associations between risk of CBC and BMI were observed in any group, neither overall, nor in survivors with hormone receptor-positive or hormone receptor-negative FBC (Supplementary Table 4). Positive associations per 5 kg/m² increase in BMI were observed in postmenopausal African American (HR=1.17, CI=0.999–1.37) and Asian American (HR=1.26, CI=1.001–1.59) survivors, but not in Hispanic (HR=0.86, CI=0.71–1.05) and non-Hispanic White (HR=1.01, CI=0.88–1.16) survivors. Sample sizes were too small to consider HT use in analyses stratified by race and ethnicity.

In the subset of survivors from two studies with available data on WC (2,760 FBC survivors, 192 CBC), a higher risk of CBC was associated with larger WC (tertile 1 vs. tertile 3: HR=1.59, CI=1.05–2.39, p-trend=.02), which was driven by two-fold higher risk observed in postmenopausal survivors (p-trend=.07) (Table 4). Sample size was too small to further stratify the analysis in postmenopausal survivors by HT use. No dose response trends were observed for WHtR or body roundness index. For the composite measure of BMI and WC, in survivors overall and postmenopausal survivors, risk was higher in those with larger WC, regardless of BMI, when compared to survivors with normal weight and smaller WC, with HRs ranging from 1.75 to 2.37. In premenopausal survivors, a higher risk of CBC (HR=1.68, 1.003–2.80) was also observed in survivors with overweight or obesity and larger WC compared with survivors with normal BMI and smaller WC. In survivors of hormone receptor-positive FBC, larger WC in postmenopausal survivors was the only central adiposity measure associated with higher risk of CBC (tertile 2 or 3 vs. tertile 1: HR=2.15, 1.03–4.49). In survivors of hormone receptor-negative FBC, two-fold higher risks were associated with larger WC (tertile 2 or 3 vs. tertile 1: HR=2.21, 1.02–4.81) or larger body roundness index (tertile 2 or 3 vs. tertile 1: HR=2.53, 1.17–5.46) (Supplementary Table 5).

Higher risk of CBC was associated with larger WC (tertile 2 or 3 vs. tertile 1: HR=1.71, CI=1.08–2.72) and larger body roundness index (tertile 2 or 3 vs. tertile 1: HR=1.75, CI=1.08–2.84) in Asian American women, whereas no associations were observed in Hispanic women (Supplementary Table 6). In survivors of hormone receptor-positive FBC, no statistically significant associations with any central adiposity measure were observed, with HR estimates that were somewhat lower than those observed overall. Sample sizes were too small for separate analyses in survivors of hormone receptor-negative FBC.

DISCUSSION

In this pooled cohort of California FBC survivors, a higher risk of CBC was associated with obesity in postmenopausal survivors who had never used HT before FBC diagnosis. To our knowledge, our study is the first to assess BMI associations with CBC risk in the context of HT use in postmenopausal survivors. Leveraging multiple measures of body size, our study is also the first to consider central adiposity, identifying that larger WC was

associated with higher risk of CBC. Importantly, the association with WC was independent of BMI. More than half of women diagnosed with FBC in our study had overweight or obesity and a large WC (≥ 78.8 cm), suggesting that a large proportion of FBC is at higher risk (estimated at 78%) of developing CBC compared with survivors with normal weight and lower WC. Given the continued rise of overall and central obesity seen in the U.S.^{37–39} and in our survivor cohort, the prevalence is likely higher in more recently diagnosed patients, highlighting the importance of considering enhanced surveillance and risk-reduction strategies in this population.

We observed an association between CBC risk and BMI only in postmenopausal survivors without pre-diagnosis HT use, although heterogeneity by menopausal status was not statistically significant. This result parallels findings on the BMI association with risk of FBC in postmenopausal women, where BMI associations are limited to or stronger in women who never used HT.^{15, 40} For FBC, the higher risk associated with BMI in postmenopausal women has been linked to hormone-related mechanisms,¹⁵ such as conversion of androgens to estrogens in peripheral adipose tissue, which is the major source of estrogen in postmenopausal women.⁴¹ Higher estrogen concentrations are associated with higher risk of FBC.⁴² The modifying effect of HT use has been attributed to the higher hormone concentrations in HT users which override the effects of endogenous estrogens derived from adipose tissue, thereby masking BMI associations in HT users.⁴⁰ Our findings suggest that HT use also may mask BMI associations with CBC in current or former HT users, and may contribute to the inconsistent findings for postmenopausal survivors in the current literature (Supplementary Table 1). Depending on the prevalence of HT use in different study populations, risk estimates associated with BMI in postmenopausal women vary accordingly. When we did not consider HT use, no BMI association in postmenopausal women was observed.

The epidemiological evidence on the BMI association with risk of CBC is sparse and inconsistent for younger women. In agreement with another study,¹⁸ we found no association of BMI with risk of CBC in premenopausal women. In a third study in survivors diagnosed with FBC at age <45 years, higher BMI (≥ 30 vs. ≤ 19.9 kg/m²) was associated with a two-fold higher risk of CBC.¹⁷ That study, however, included only 77 CBC. Several studies in survivors of FBC across a broad age range also produced mixed results, with reports of higher risk of CBC in survivors of FBC overall,¹⁹ ER-positive FBC,²⁰ and *in situ* FBC,²¹ and higher risk of ipsilateral and contralateral SBC combined.⁴³ Other studies found no association with BMI.^{22, 23} The summary estimates from three meta-analyses are difficult to interpret, as the data were combined across studies despite numerous differences in study design.^{16, 24, 25} Potentially modifying factors, including HT use, were not investigated, and some recent studies^{22, 43, 44} were not included in the meta-analyses.

We found that the association of WC with risk of CBC remained after adjustment for BMI. Our finding of higher CBC risk associated with larger WC regardless of BMI suggests that central adiposity may be a stronger risk factor for CBC than overall adiposity. Larger studies need to confirm this finding. Visceral fat is associated with insulin resistance and chronic inflammation,²⁸ which are risk factors for the development and progression of FBC.⁴⁵ These pathways and related biomarkers, however, have not been evaluated for CBC. Interestingly,

the association with WC was stronger for WC categorized by tertiles (p-trend=.02) than for WC categorized by clinical cut-points (p-trend=.05). The clinical cut-points have been primarily used for non-cancer outcomes such as hypertension, diabetes, dyslipidemia, and metabolic syndrome.³² The optimal cut-points for CBC remain to be determined. Our findings suggest that the higher cut-points by tertiles yield associations of larger magnitude. Although we found no statistically significant heterogeneity by menopausal status, associations with WC were limited to postmenopausal survivors.

We are not aware of any studies that examined BMI associations with CBC risk across racial and ethnic groups. Although the prevalence of overweight and obesity varied widely across the four racial and ethnic groups, we found no evidence of statistically significant heterogeneity in associations with BMI, likely because of limited sample size. As has been observed for FBC,⁴⁶ it is possible that the impact of BMI and WC on risk of CBC varies across racial and ethnic groups, given observations of borderline positive associations per 5 kg/m² increase in BMI in postmenopausal African American and Asian American survivors, but not in Hispanic and non-Hispanic White survivors, and a positive association with larger WC in Asian American survivors, but not in Hispanic survivors. Compared with non-Hispanic White women, Asian women have a higher prevalence of central adiposity at every level of BMI^{47, 48} and a higher proportion of visceral than subcutaneous adipose tissue,⁴⁹ whereas African American women have less visceral adipose tissue,^{50, 51} and Hispanic women have more subcutaneous adipose tissue than non-Hispanic White women.⁵¹ Given evidence that Asian populations have different health risks associated with obesity, we used BMI cut-points that have been recommended for Asian populations.³¹

Few studies have examined whether BMI associations with CBC differ by FBC hormone receptor status.^{18, 20, 26, 27, 43, 44} Risk estimates were of similar magnitude for ER-positive FBC and FBC overall in some studies,^{20, 43, 44} whereas other studies,^{26, 27} including ours, suggest that the BMI association may differ by FBC hormone receptor status, with a higher obesity-associated risk in postmenopausal survivors with ER-negative FBC than those with ER-positive FBC. Similarly, we found that WC was associated with higher risk only in survivors with hormone receptor-negative FBC. It is possible that treatment with endocrine therapy reduced CBC risk in postmenopausal women with hormone receptor-positive FBC,⁵² even in the presence of obesity. We did not have information available on endocrine therapy use. Other potential mechanisms that are independent of estrogen, such as inflammatory pathways, may also play a role. The sample size of hormone receptor-negative FBC was small in our pooled dataset, warranting confirmation in larger studies of CBC. Interestingly, some studies of FBC also observed BMI associations in postmenopausal women for hormone receptor-negative tumors,^{15, 53} although in most studies, the BMI associations were limited to hormone receptor-positive tumors.^{15, 40, 53}

Our study has some limitations. Foremost, despite a large cohort and long follow-up, the sample sizes for CBC in subgroup analyses tended to be small and rendered some HR estimates that were marginally statistically significant, although in the expected direction. BMI was based on self-reported height and weight and may therefore be underestimated.⁵⁴ The analysis by HT use was limited to data from three studies, and data on central adiposity measures were available only for two studies. Like most prior studies, we had no data

available on weight change after FBC diagnosis. Unlike some other risk factors, weight is a time-dependent variable, and weight or BMI at FBC diagnosis alone is likely not an optimal body size measure. We did not have information available on adjuvant endocrine therapy for FBC which has been associated with lower CBC risk in women with a hormone receptor-positive FBC.⁵² Lastly, we performed a large number of statistical comparisons. We can therefore not rule out the possibility that some associations may be due to chance.

Despite these limitations, our study has several strengths, including predominantly population-based studies with uniform ascertainment of CBC through the California Cancer Registry and a racially and ethnically diverse study population. Unlike most previous studies that evaluated associations with BMI, we also examined associations with three measures of central adiposity (WC, WHtR, body roundness index). The availability of both clinical and harmonized epidemiologic characteristics allowed us to adjust the multivariable models for potential confounding factors.

Our findings underline the importance of considering HT use in the assessment of BMI associations in postmenopausal women. We found that obesity was associated with a nearly two-fold higher risk of CBC in survivors who never used HT, with an even higher risk for survivors of hormone receptor-negative FBC. Thus, obesity may be a more important risk factor for CBC than gleaned from the current epidemiologic literature that did not consider HT use in the analysis. Higher risk also was associated with larger WC which needs to be confirmed in larger studies. Our findings suggest that weight and waist circumference in patients newly diagnosed with FBC should be considered in prevention strategies for CBC. Among patients newly diagnosed with FBC, those with overweight or obesity and with central adiposity may benefit from more frequent surveillance screening after FBC diagnosis and communications about potential risk-reducing strategies, such as weight loss through lifestyle modifications and/or use of weight loss medications such as GLP-1. Few modifiable risk factors have been identified for CBC, thus more research efforts should be directed towards investigating the role of overall and central adiposity and weight gain in CBC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data availability

A de-identified dataset with the data used in this publication will be archived at Stanford University. De-identified data will be shared at the request of qualified investigators for the purpose of replicating study findings. Data requests should be addressed to the corresponding author Esther M. John at emjohn@stanford.edu and will be dependent on an approved data sharing agreement with Stanford University and agreements with the institutions that provided the data for the data pooling project. Further information is available from the corresponding author upon request.

Abbreviations

AABCS

Los Angeles County Asian American Breast Cancer Study

BMI	Body mass index
CARE	Women's Contraceptive and Reproductive Experiences Study
CBC	Contralateral second primary breast cancer
CBCSC	California Breast Cancer Survivorship Consortium
CI	Confidence interval
ER	Estrogen receptor
FBC	First primary invasive breast cancer
HR	Hazard ratio
LACE	Life After Cancer Epidemiology Study
MEC	Multiethnic Cohort
NC-BCFR	Northern California Breast Cancer Family Registry
PR	Progesterone receptor
SEER	Surveillance, Epidemiology, and End Results
SFBCS	San Francisco Bay Area Breast Cancer Study
U.S.	United States
WC	Waist circumference
WHtR	Waist-to-height ratio

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Novelty and Impact

It remains unclear whether a large body size increases the risk of developing a contralateral second primary breast cancer (CBC). In a pooled cohort of breast cancer survivors, obesity in postmenopausal women who never used hormone therapy before their first diagnosis was associated with higher risk of CBC. Higher risk was also observed in survivors with a larger waist circumference. Breast cancer survivors with higher adiposity may benefit from more frequent surveillance screening and weight loss.

Table 1

Characteristics of women with a first primary invasive breast cancer and women with contralateral breast cancer: The California Breast Cancer Survivorship Consortium.

	FBC		CBC	
	N	% ^a	N	% ^a
	9,479	100	610	100
Study				
AABCS	1,001	11	72	12
CARE	1,062	11	93	15
LACE	1,556	16	90	15
MEC	1,574	17	85	14
NC-BCFR	2,405	25	149	24
SFBCS	1,881	20	121	20
Race and ethnicity				
African American	2,110	22	142	23
Asian American	1,865	20	130	21
Hispanic	2,330	25	134	22
Non-Hispanic White	3,174	33	204	33
Age at diagnosis (years)				
<40	922	10	90	15
40–49	2,289	24	157	26
50–59	2,746	29	182	30
60–69	2,146	23	119	20
≥70	1,376	15	62	10
Year of diagnosis				
1993–1999	5,944	63	274	45
2000–2004	2,496	26	264	43
2005–2009	1,039	11	72	12
Histology				
Ductal	7,312	77	467	77
Lobular	1,381	15	95	16
Other	786	8	48	8
AJCC stage				
Stage I	4,458	47	284	47
Stage II	4,384	46	281	46
Stage III	637	7	45	7
Grade				
I	1,511	18	85	15
II	3,490	40	226	40
III or IV	3,633	42	250	45
Unknown	845		49	
Hormone receptor status				
ER-positive and/or PR-positive	6,390	77	363	70

	FBC		CBC	
	N	% ^a	N	% ^a
ER-negative and PR-negative	1,906	23	155	30
Unknown	1,183		92	
Lymph node involvement				
No	5,999	64	387	65
Yes	3,304	36	212	35
Unknown	176		11	
Tumor size (cm)				
≤2.0	5,807	62	353	59
>2.0 – 5.0	3,025	32	208	35
>5.0	504	5	37	6
Unknown	143		12	
Surgery type				
Breast conserving surgery	5,293	56	343	56
Mastectomy	4,093	43	264	43
Other or no surgery	93	1	3	<1
Radiation therapy				
No	4,310	45	274	45
Yes	5,169	55	336	55
Chemotherapy				
No	4,630	50	274	45
Yes	4,720	50	336	55
Unknown	129		58	
Education				
Some high school or less	1,410	15	82	13
High school graduate	1,919	20	124	20
Some college or technical school	3,084	33	190	31
College or higher degree	3,039	32	213	35
Unknown	27		1	
Marital status ^{b,c}				
Married	5,681	61	380	64
Separated, divorced, widowed	2,122	23	109	18
Single, never married	1,476	16	103	17
Unknown	200		18	
Family history of breast cancer in first-degree relatives ^d				
No	7,543	80	443	73
Yes	1,890	20	163	27
Unknown	46		4	
Parity ^d				
Nulliparous	1,784	19	138	23
1	1,439	15	79	13

	FBC		CBC	
	N	% ^a	N	% ^a
2	2,722	29	184	30
3	1,759	19	119	20
≥4	1,747	18	90	15
Unknown	28		0	
Menopausal status ^{d,e}				
Premenopausal	2,701	30	230	40
Postmenopausal	6,390	70	350	60
Unknown	388		30	
Hormone therapy use (postmenopausal women) ^f				
Never	1,810	54	90	50
Former	660	20	31	17
Current	868	26	58	32
Cigarette smoking history ^d				
Never	4,913	61	326	63
Past	2,245	28	134	26
Current	930	11	58	11
Unknown ^g	1,391		92	
Alcohol consumption (drinks per week) ^d				
0	5,494	60	352	59
≤2	1,439	16	87	15
>2	2,205	24	156	26
Unknown	341		15	

Abbreviations: AABCS, Asian American Breast Cancer Study; AJCC, American Joint Committee on Cancer; CARE, Women's Contraceptive and Reproductive Experiences Study; CBC, contralateral second primary invasive breast cancer; ER, estrogen receptor; FBC, first primary invasive breast cancer; HR, hormone receptor; HT, hormone therapy; LACE, Life After Cancer Epidemiology Study; MEC, Multiethnic Cohort; NC-BCFR, Northern California Breast Cancer Family Registry; PR, progesterone receptor; SFBCS, San Francisco Bay Area Breast Cancer Study.

^aPercentage was calculated without unknowns.

^bAt FBC diagnosis.

^cFrom California Cancer Registry records.

^dIn the reference year, defined as the year before FBC diagnosis (AABCS, CARE, NC-BCFR, SFBCS), at questionnaire completion (LACE, on average 1.8 years after FBC diagnosis), or at study enrollment (MEC).

^eMenopausal status at FBC diagnosis was classified as premenopausal (menstruating, pregnant, breast-feeding, perimenopausal, or aged <55 years), postmenopausal (menstrual periods stopped naturally or due to surgery, medical treatment, or other reasons; menstruating at start of menopausal HT use and aged ≥55 years), or unknown.

^fWomen who were postmenopausal at FBC diagnosis from AABCS, NC-BCFR, and SFBCS.

^gCigarette smoking history was not collected in an early component of SFBCS.

Table 2

Associations of body mass index^{a,b} with risk of contralateral breast cancer, by menopausal status and hormone therapy use: The California Breast Cancer Survivorship Consortium.

	Analysis based on six studies ^c			Analysis based on three studies with data on hormone therapy use ^d		
	FBC	CBC	HR (95% CI) ^e	FBC	CBC	HR (95% CI) ^e
	N	N		N	N	
All survivors						
Normal weight	3,881	240	1.0	2,128	132	1.0
Overweight	3,101	214	1.22 (1.01–1.47)	1,744	122	1.23 (0.95–1.59)
Obesity	2,497	156	1.14 (0.93–1.41)	1,415	88	1.18 (0.89–1.57)
P-trend			0.14			0.18
Per 5 kg/m ² increase			1.05 (0.99–1.12)			1.09 (1.00–1.19)
P-het menopausal status ^f			0.89			0.26
Premenopausal survivors^g						
Normal weight	1,574	121	1.0	909	70	1.0
Overweight	885	83	1.22 (0.92–1.63)	569	52	1.14 (0.79–1.65)
Obesity	630	56	1.17 (0.84–1.62)	385	34	1.14 (0.75–1.74)
P-trend			0.24			0.47
Per 5 kg/m ² increase			1.06 (0.96–1.17)			1.08 (0.95–1.24)
Postmenopausal survivors						
Normal weight	2,307	119	1.0	1,219	62	1.0
Overweight	2,216	131	1.23 (0.95–1.58)	1,175	70	1.32 (0.93–1.89)
Obesity	1,867	100	1.15 (0.87–1.51)	1,030	54	1.24 (0.85–1.82)
P-trend			0.28			0.23
Per 5 kg/m ² increase			1.06 (0.97–1.15)			1.10 (0.98–1.23)
Postmenopausal survivors, ever HT use						
Normal weight				568	36	1.0
Overweight				517	34	1.10 (0.68–1.78)
Obesity				443	19	0.77 (0.43–1.38)
P-trend						0.45
Per 5 kg/m ² increase						0.94 (0.78–1.13)
Postmenopausal survivors, never HT use						
Normal weight				622	25	1.0
Overweight				619	32	1.57 (0.91–2.71)
Obesity				569	33	1.89 (1.10–3.24)
P-trend						0.02
Per 5 kg/m ² increase						1.22 (1.07–1.40)

Abbreviations. AABCS, Asian American Breast Cancer Study; BMI, body mass index; CARE, Women's Contraceptive and Reproductive Experiences Study; CBC, contralateral second primary invasive breast cancer; CI, confidence interval; ER, estrogen receptor status; FBC, first primary invasive breast cancer; HR, hazard ratio; HT, hormone therapy; LACE, Life After Cancer Epidemiology Study; MEC, Multiethnic Cohort; NC-BCFR, Northern California Breast Cancer Family Registry; PR, progesterone receptor status; SFBCS, San Francisco Bay Area Breast Cancer Study.

^aBody mass index (BMI) in the year before FBC diagnosis (AABCS, CARE, LACE, NC-BCFR, SFBCS) or at study enrollment in MEC was based on self-reported weight and height and calculated as weight (kg) divided by height (m) squared. Missing self-reported height in AABCS and SFBCS was supplemented with measured height.

^bFor African American, Hispanic, and non-Hispanic White women, BMI (kg/m²) was categorized as normal weight (<25), overweight (25 - <30), or obesity (≥30). For Asian American women, BMI (kg/m²) was categorized as normal weight (<23), overweight (23 - <27.5), or obesity (≥27.5), according to cut-points for Asian populations. Underweight (BMI <18.5 kg/m²) was combined with the normal weight category.

^cAnalysis based on AABCS, CARE, LACE, MEC, NC-BCFR, and SFBCS.

^dAnalysis based on AABCS, NC-BCFR, and SFBCS with available data on HT use.

^eFine and Gray competing risk models adjusted for study (stratification variable), age at FBC diagnosis (continuous), race and ethnicity (African American, Asian American, Hispanic, non-Hispanic White), FBC hormone receptor status (ER-positive and/or PR-positive, ER-negative and PR-negative, unknown), and first-degree family history of breast cancer (yes, no, unknown).

^fFor the analysis based on six studies, we tested for interaction between BMI (normal, overweight, obesity) and menopausal status (premenopausal, postmenopausal). For the analysis based on three studies, we tested for interaction between BMI (normal, overweight, obesity) and menopausal status and HT use (premenopausal, postmenopausal ever HT use, postmenopausal never HT use).

^gIncludes women with unknown menopausal status at the time of FBC diagnosis (aged <55 years who still had menstrual periods when they started using HT).

Table 3

Associations of body mass index^{a,b} with risk of contralateral breast cancer, by hormone receptor status of first breast cancer, menopausal status, and hormone therapy use: The California Breast Cancer Survivorship Consortium.

	Analysis based on six studies ^c			Analysis based on three studies with data on hormone therapy use ^d		
	FBC	CBC	HR (95% CI) ^e	FBC	CBC	HR (95% CI) ^e
	N	N		N	N	
Survivors of hormone receptor-positive FBC ^f						
Normal weight	2,679	152	1.0	1,453	82	1.0
Overweight	2,051	116	1.12 (0.88–1.44)	1,145	68	1.18 (0.85–1.65)
Obesity	1,660	95	1.19 (0.91–1.55)	930	48	1.10 (0.76–1.59)
P-trend			0.20			0.54
Per 5 kg/m ² increase			1.06 (0.99–1.14)			1.04 (0.92–1.17)
P-het hormone receptor status			0.43			0.49
Survivors of hormone receptor-negative FBC ^g						
Normal weight	742	55	1.0	448	32	1.0
Overweight	632	61	1.49 (1.03–2.15)	390	41	1.71 (1.06–2.78)
Obesity	532	39	1.16 (0.75–1.78)	336	30	1.62 (0.94–2.78)
P-trend			0.34			0.05
Per 5 kg/m ² increase			1.05 (0.96–1.14)			1.24 (1.08–1.43)
Premenopausal survivors of hormone receptor-positive FBC ^{f,h}						
Normal weight	1,081	76	1.0	639	45	1.0
Overweight	522	42	1.18 (0.80–1.73)	344	30	1.22 (0.76–1.95)
Obesity	383	33	1.33 (0.87–2.02)	239	19	1.14 (0.66–1.97)
P-trend			0.16			0.52
Per 5 kg/m ² increase			1.05 (0.92–1.20)			1.03 (0.86–1.24)
p-het menopausal status			0.70			0.83
p-het hormone receptor status ⁱ			0.60			0.89
Postmenopausal survivors of hormone receptor-positive FBC ^f						
Normal weight	1,598	76	1.0	814	37	1.0
Overweight	1,529	74	1.09 (0.78–1.51)	801	38	1.15 (0.72–1.84)
Obesity	1,277	62	1.13 (0.80–1.59)	691	29	1.06 (0.64–1.76)
P-trend			0.49			0.78

	Analysis based on six studies ^c			Analysis based on three studies with data on hormone therapy use ^d		
	FBC	CBC	HR (95% CI) ^e	FBC	CBC	HR (95% CI) ^e
	N	N		N	N	
Per 5 kg/m ² increase			1.05 (0.94–1.18)			1.04 (0.89–1.23)
p-het hormone receptor status ^j			0.76			0.60
Premenopausal survivors of hormone receptor-negative FBC^{g,h}						
Normal weight	298	26	1.0	177	15	1.0
Overweight	221	27	1.52 (0.89–2.60)	145	17	1.59 (0.77–3.30)
Obesity	162	15	1.05 (0.54–2.04)	104	11	1.32 (0.57–3.05)
P-trend			0.68			0.41
Per 5 kg/m ² increase			1.08 (0.89–1.31)			1.26 (0.97–1.62)
P-het menopausal status			0.96			0.99
Postmenopausal survivors of hormone receptor-negative FBC^g						
Normal weight	444	29	1.0	271	17	1.0
Overweight	411	34	1.43 (0.85–2.41)	245	24	1.86 (0.95–3.61)
Obesity	370	24	1.25 (0.71–2.20)	232	19	1.83 (0.89–3.77)
P-trend			0.38			0.08
Per 5 kg/m ² increase			1.09 (0.92–1.29)			1.23 (1.03–1.47)
Postmenopausal survivors of hormone receptor-positive FBC, ever HT use^f						
Normal weight				400	24	1.0
Overweight				366	19	0.84 (0.45–1.58)
Obesity				309	13	0.75 (0.37–1.53)
P-trend						0.42
Per 5 kg/m ² increase						0.92 (0.70–1.20)
p-het hormone receptor status ^k						0.32
Postmenopausal survivors of hormone receptor-positive FBC, never HT use^f						
Normal weight				397	13	1.0
Overweight				420	17	1.52 (0.74–3.12)
Obesity				371	14	1.44 (0.68–3.06)
P-trend						0.32
Per 5 kg/m ² increase						1.12 (0.90–1.40)
p-het hormone receptor status ^l						0.66
Postmenopausal survivors of hormone receptor-negative FBC, ever HT use^g						
Normal weight				106	7	1.0

	Analysis based on six studies ^c			Analysis based on three studies with data on hormone therapy use ^d		
	FBC	CBC	HR (95% CI) ^e	FBC	CBC	HR (95% CI) ^e
	N	N		N	N	
Overweight				91	11	1.97 (0.71–5.46)
Obesity				90	4	0.82 (0.22–3.02)
P-trend						0.96
Per 5 kg/m ² increase						0.94 (0.78–1.14)
Postmenopausal survivors of hormone receptor-negative FBC, never HT use^g						
Normal weight				156	10	1.0
Overweight				137	12	1.78 (0.70–4.50)
Obesity				138	15	2.55 (1.07–6.09)
P-trend						0.03
Per 5 kg/m ² increase						1.36 (1.12–1.65)

Abbreviations. AABCS, Asian American Breast Cancer Study; BMI, body mass index; CARE, Women's Contraceptive and Reproductive Experiences Study; CBC, contralateral second primary invasive breast cancer; CI, confidence interval; ER, estrogen receptor status; FBC, first primary invasive breast cancer; HR, hazard ratio; HT, hormone therapy; LACE, Life After Cancer Epidemiology Study; MEC, Multiethnic Cohort; NC-BCFR, Northern California Breast Cancer Family Registry; PR, progesterone receptor status; SFBCS, San Francisco Bay Area Breast Cancer Study.

^aBody mass index (BMI) in the year before FBC diagnosis (AABCS, CARE, LACE, NC-BCFR, SFBCS) or at study enrollment in MEC was based on self-reported weight and height and calculated as weight (kg) divided by height (m) squared. Missing self-reported height in AABCS and SFBCS was supplemented with measured height.

^bFor African American, Hispanic, and non-Hispanic White women, BMI (kg/m²) was categorized as normal weight (<25), overweight (25 - <30), or obesity (≥30). For Asian American women, BMI (kg/m²) was categorized as normal weight (<23), overweight (23 - <27.5), or obesity (≥27.5), according to cut-points for Asian populations. Underweight (BMI <18.5 kg/m²) was combined with the normal weight category.

^cAnalysis based on AABCS, CARE, LACE, MEC, NC-BCFR, and SFBCS.

^dAnalysis based on AABCS, NC-BCFR, and SFBCS with available data on HT use.

^eFine and Gray competing risk models adjusted for study (stratification variable), age at FBC diagnosis (continuous), race and ethnicity (African American, Asian American, Hispanic, non-Hispanic White), FBC hormone receptor status (ER-positive and/or PR-positive, ER-negative and PR-negative, unknown), and first-degree family history of breast cancer (yes, no, unknown).

^fER-positive and/or PR-positive FBC.

^gER-negative and PR-negative FBC.

^hIncludes women with unknown menopausal status at the time of FBC diagnosis (aged <55 years who still had menstrual periods when they started using HT).

ⁱFor premenopausal survivors, heterogeneity of BMI (normal, overweight, obesity) by hormone receptor status of FBC.

^jFor postmenopausal survivors, heterogeneity of BMI (normal, overweight, obesity) by hormone receptor status of FBC.

^kFor postmenopausal survivors who ever used HT, heterogeneity of BMI (normal, overweight, obesity) by hormone receptor status of FBC.

^lFor postmenopausal survivors who never used HT, heterogeneity of BMI (normal, overweight, obesity) by hormone receptor status of FBC.

Table 4

Associations of central adiposity with risk of contralateral breast cancer, by menopausal status and hormone receptor status of first breast cancer: The California Breast Cancer Survivorship Consortium.

Analysis based on two studies ^a	All survivors			Premenopausal survivors ^b			Postmenopausal survivors		
	FBC	CBC	HR (95% CI) ^c	FBC	CBC	HR (95% CI) ^c	FBC	CBC	HR (95% CI) ^c
All survivors									
WC (cm, tertiles)									
<78.8	915	51	1.0	492	35	1.0	423	16	1.0
78.8-91.6	923	74	1.65 (1.15-2.36)	364	32	1.21 (0.74-2.00)	559	42	2.27 (1.28-4.02)
≥91.6	922	67	1.59 (1.05-2.39)	310	32	1.42 (0.83-2.42)	612	35	1.90 (0.99-3.66)
P-trend			0.02			0.20			0.07
Per 10 cm increase			1.09 (0.98-1.21)			1.10 (0.94-1.28)			1.09 (0.94-1.26)
P-het menopause = 0.28									
WC (cm, clinical cut-points)									
<80	975	60	1.0	524	40	1.0	451	20	1.0
80-<88	607	44	1.30 (0.88-1.93)	246	17	0.89 (0.50-1.58)	361	27	1.81 (1.02-3.23)
≥88	1,178	88	1.45 (0.99-2.12)	396	42	1.35 (0.82-2.23)	782	46	1.62 (0.89-2.93)
P-trend			0.05			0.26			0.14
Per 10 cm increase			1.09 (0.98-1.21)			1.10 (0.94-1.28)			1.09 (0.94-1.26)
P-het menopause = 0.19									
WHtR									
≤0.5	942	57	1.0	514	36	1.0	428	21	1.0
>0.5 - 0.6	1,093	87	1.50 (1.06-2.14)	420	42	1.38 (0.86-2.21)	673	45	1.57 (0.93-2.67)
>0.6	725	48	1.31 (0.84-2.03)	232	21	1.20 (0.66-2.17)	493	27	1.43 (0.75-2.74)
P-trend			0.17			0.43			0.26
Per 0.1 unit increase			1.16 (0.995-1.36)			1.19 (0.95-1.48)			1.12 (0.90-1.40)
P-het menopause = 0.97									
Body roundness index (tertiles)									
<3.35	909	56	1.0	499	36	1.0	410	20	1.0
3.35-<4.98	927	69	1.36 (0.94-1.96)	364	29	1.05 (0.63-1.75)	563	40	1.65 (0.96-2.83)
≥4.98	924	67	1.42 (0.95-2.13)	303	34	1.48 (0.88-2.50)	621	33	1.37 (0.73-2.54)
P-trend			0.09			0.16			0.37
Per 1 unit increase			1.06 (0.99-1.13)			1.07 (0.98-1.18)			1.03 (0.94-1.14)

Analysis based on two studies ^a	All survivors			Premenopausal survivors ^b			Postmenopausal survivors		
	FBC	CBC	HR (95% CI) ^c	FBC	CBC	HR (95% CI) ^c	FBC	CBC	HR (95% CI) ^c
P-het menopause = 0.20									
Composite of BMI and WC									
Normal weight, WC T1	685	35	1.0	377	22	1.0	308	13	1.0
Normal weight, WC T2/T3	353	28	1.75 (1.05–2.91)	166	12	1.19 (0.58–2.43)	187	16	2.37 (1.12–5.03)
Overweight/obesity, WC T1	216	15	1.33 (0.72–2.47)	108	12	1.75 (0.85–3.62)	108	3	0.63 (0.18–2.19)
Overweight/obesity, WC T2/T3	1,423	109	1.78 (1.20–2.65)	484	51	1.68 (1.003–2.80)	939	58	1.81 (0.97–3.36)
P-het menopause = 0.14									
Survivors of hormone receptor-positive FBC^d									
WC (cm, T1 vs. T2/3)									
<78.8	623	34	1.0	333	25	1.0	290	9	1.0
≥78.8	1,280	82	1.39 (0.91–2.13)	433	33	0.98 (0.55–1.73)	847	49	2.15 (1.03–4.49)
Per 10 cm increase			1.01 (0.88–1.17)			0.93 (0.75–1.15)			1.08 (0.88–1.32)
P-het menopause = 0.18									
P-het hormone receptor status			0.38						
WC (cm, clinical cut-points)									
<80	671	42	1.0	356	29	1.0	315	13	1.0
≥80	1,232	74	1.09 (0.71–1.67)	410	29	0.81 (0.45–1.47)	822	45	1.47 (0.74–2.92)
P-het menopause = 0.33									
P-het hormone receptor status			0.17						
WHtR									
≤0.5	654	41	1.0	351	26	1.0	303	15	1.0
>0.5	1,249	75	1.10 (0.71–1.72)	415	32	1.00 (0.55–1.81)	834	43	1.19 (0.62–2.28)
Per 0.1 unit increase			1.03 (0.84–1.28)			0.98 (0.72–1.33)			1.06 (0.78–1.45)
P-het menopause = 0.96									
P-het hormone receptor status			0.08						
Body roundness index (T1 vs. T2/3)									
<3.35	629	40	1.0	342	26	1.0	287	14	1.0
≥3.35	1,274	76	1.08 (0.69–1.67)	424	32	0.94 (0.52–1.68)	850	44	1.23 (0.63–2.39)
Per 1 unit increase			1.00 (0.91–1.10)			0.99 (0.86–1.13)			1.01 (0.88–1.16)
P-het menopause = 0.90									

Analysis based on two studies ^a	All survivors			Premenopausal survivors ^b			Postmenopausal survivors		
	FBC	CBC	HR (95% CI) ^c	FBC	CBC	HR (95% CI) ^c	FBC	CBC	HR (95% CI) ^c
P-her hormone receptor status			0.08						
Abbreviations. AABCS, Asian American Breast Cancer Study; CBC, contralateral second primary invasive breast cancer; CI, confidence interval; ER, estrogen receptor status; FBC, first primary invasive breast cancer; HR, hazard ratio; HT, hormone use; PR, progesterone receptor status; SFBCS, San Francisco Bay Area Breast Cancer Study; T, tertile; WC, waist circumference; WHtR, waist-to-height ratio.									
^a Analysis based on AABCS and SFBCS with available measurements of waist circumference.									
^b Includes women with unknown menopausal status at the time of FBC diagnosis (aged <55 years who still had menstrual periods when they started using HT).									
^c Fine and Gray competing risk models adjusted for study (stratification variable), age at FBC diagnosis (continuous), race and ethnicity (African American, Asian American, Hispanic, non-Hispanic White), FBC hormone receptor status (ER-positive and/or PR-positive, ER-negative and PR-negative, unknown), and first-degree family history of breast cancer (yes, no, unknown). Analyses of WC, WHtR, and body roundness index were additionally adjusted for BMI (continuous).									
^d ER-positive and/or PR-positive FBC									