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Obesity and mortality after locoregional breast cancer diagnosis

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Abstract

Purpose—Higher mortality after a breast cancer diagnosis has been observed among women who are obese. We investigated the relationships between body mass index (BMI) and all-cause or breast cancer-specific mortality after a diagnosis of locoregional breast cancer.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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Methods—Women diagnosed in 2004 with AJCC Stage I, II, or III breast cancer (n = 5394) were identified from a population-based National Program of Cancer Registries (NPCR) patterns of care study (POC-BP) drawing from registries in seven U.S. states. Differences in overall and breast cancer-specific mortality were investigated using Cox proportional hazards regression models adjusting for demographic and clinical covariates, including age- and stage-based subgroup analyses.

Results—In women 70 or older, higher BMI was associated with lower overall mortality (HR for a 5 kg/m^2 difference in BMI = 0.85, 95% CI 0.75–0.95). There was no significant association between BMI and overall mortality for women under 70. BMI was not associated with breast cancer death in the full sample, but among women with Stage I disease; those in the highest BMI category had significantly higher breast cancer mortality (HR for BMI ≥ 35 kg/m^2 vs. 18.5–24.9 kg/m^2 = 4.74, 95% CI 1.78–12.59).

Conclusions—Contrary to our hypothesis, greater BMI was not associated with higher overall mortality. Among older women, BMI was inversely related to overall mortality, with a null association among younger women. Higher BMI was associated with breast cancer mortality among women with Stage I disease, but not among women with more advanced disease.

Keywords

Breast cancer; Obesity; Breast cancer mortality; All-cause mortality

Introduction

Although breast cancer treatment advances have substantially reduced mortality among the population of affected women, research suggests that disparities in relative mortality between obese and non-obese patients persist. A substantial amount of evidence suggests not only that obesity is associated with risk of developing breast cancer among post-menopausal women [1], but that women of all ages who have developed breast cancer are likely to have higher mortality if they are obese [2–26]. Given the increasing proportion of breast cancer patients who are obese, characterizing these disparities and exploring potential mechanisms behind them is important.

Existing literature suggests that higher body mass index (BMI) at diagnosis is associated with greater risk of death from any cause following a breast cancer diagnosis [3–5, 7, 9, 16, 27, 28]. Some studies indicate that this association may differ according to patient characteristics, and may not be present in all subgroups [3, 14, 28–31]. Many studies reported a U-shaped curve, with underweight patients also at higher risk of death from any cause [7]. However, taken as a whole, the existing literature strongly indicates that, with the potential exception of underweight individuals, women with higher BMI are at higher risk of all-cause mortality following a breast cancer diagnosis.

In addition to the observed relationship between higher BMI and overall mortality, a substantial amount of literature suggests that higher BMI is related specifically to death from breast cancer [7, 13, 14, 25, 26, 28]. A smaller number of studies indicate, in contrast, that

obesity is not associated with breast cancer-specific mortality [9, 32], or that the association may be present only among women in certain age-related subgroups [33, 34].

The observed pattern of higher breast cancer-specific mortality in obese patients likely reflects multiple factors. Obesity is associated with multiple physiological risk factors for breast cancer mortality, including chronic inflammation [35]; higher levels of endocrine factors, such as insulin, insulin-like growth factor, and estrogen, which are thought to promote tumor progression [35–37]; and altered production of the adipokines leptin and adiponectin (increased leptin and decreased adiponectin have been found to contribute to tumor growth) [35, 37]. Obese patients frequently have larger tumors at treatment onset due in part to delayed diagnosis, perhaps due to differences in screening patterns [35, 38–40]. Additionally, systematic differences in the postsurgical treatment received by patients with higher and lower BMI—such as appropriate dosing of chemotherapy, as well as other potential differences—may exist [25, 41–44]. Some of these differences may also be related to sociodemographic and clinical factors closely correlated with BMI. It is therefore important to examine the relationship between BMI and breast cancer mortality over an extended time period, in a diverse population, accounting for potentially influential sociodemographic and clinical characteristics, in order to attempt to isolate the independent effect of adiposity on breast cancer mortality.

We compared overall mortality and breast cancer-specific mortality according to BMI using data on female breast cancer patients identified from population-based cancer registries in seven states, hypothesizing that breast cancer-specific mortality would be higher among women with higher BMI and that overall mortality would be higher among both underweight and obese women.

Data and methods

Data sources

This study used data from the National Program of Cancer Registries (NPCR) Breast and Prostate Cancer Data Quality and Patterns of Care Study (POC-BP) to examine the relationships between patient BMI and mortality after breast cancer diagnosis. POC-BP data comprised breast and prostate cancer cases diagnosed in 2004 identified from population-based cancer registries in California, Georgia, Kentucky, Louisiana, Minnesota, North Carolina, and Wisconsin. Registry information was supplemented with data abstracted from medical records in hospitals and physicians' offices. Follow-up data on women's vital status were collected through the routine linkage of cancer registry data with death certificate data from state vital statistics departments, and through the use of the National Death Index (NDI) [45].

Eligibility criteria

Women aged 20 or older diagnosed with primary breast cancer in 2004 (other than by autopsy or death certificate) were included in the POC-BP if they had no previous diagnoses of in situ or invasive breast cancer, other reportable cancers, Paget's disease, Kaposi's sarcoma, or lymphoma. Cases were selected from registries using random sampling

stratified by race/ethnicity, as well as Appalachian/non-Appalachian region in North Carolina and Kentucky, facility type and volume in Wisconsin, and urban-rural status in Georgia.

This analysis focused on locoregional disease. A total of 6967 patients with Stage I, II, or III disease were identified. Women who did not receive any surgery for their breast cancer (n = 105), women with no vital status follow-up data (n = 6), and women with unknown BMI (n = 1462) were excluded, leaving 5394 cases.

Explanatory variables

Body mass index (kg/m^2) was calculated based on weight and height, measured at the time of diagnosis, abstracted from physicians' records.

Outcomes

Time to death (all-cause or overall mortality) was defined as days between diagnosis and death from any cause. Time to death from breast cancer was defined as days between diagnosis and breast cancer-specific death, as determined from ICD-10 codes in registry databases; we identified breast cancer deaths based on the presence of a primary cause-of-death code of C509. As a comparison, time to death from a cause other than breast cancer, as determined from the ICD-10 codes, was also examined. Survival analyses included data on women's vital status through 8 years after the date of diagnosis (2004–2012). All registries contributed at least 5 years' worth of vital status data, with some contributing up to 8 years.

Clinical and demographic covariates

Patient age was determined at time of diagnosis. Race/ethnicity information was obtained from patients' medical records, and from information found in Indian Health Services patient registration. When Hispanic origin was unclear, a North American Association of Central Cancer Registries identification algorithm was used [45].

Insurance status was categorized as private, Medicare or other public insurance only, Medicaid, uninsured, or unknown. The "private" category included patients with Medicare plus private supplemental insurance. Women who were dual-eligible for Medicare and Medicaid were grouped in the Medicaid category.

Education and socioeconomic status were based on census-tract information. Patients were categorized as living in a higher poverty (≥ 20% of residents below the federal poverty level) or lower-poverty area, and as living in a lower-education (≥ 25% of adults age 25 or older with less than high-school education) or higher-education area. Residential areas were described as 100% urban, mixed, or 100% rural, using the 2000 U.S. Census Bureau's urban and rural criteria [46].

Tumor pathologic stage was categorized as I, II, or III, as defined by American Joint Committee on Cancer (AJCC) staging criteria. Tumor grade was characterized by a I–IV score based on degree of cell differentiation, or as unknown. Estrogen receptor (ER) and progesterone receptor (PR) status were classified as positive (borderline was counted as positive), negative, or unknown.

A modification of the Piccirillo, or Adult Comorbidity Evaluation (ACE-27), comorbidity index [47] considered each of the 25 conditions (26 from the Piccirillo index, minus obesity, and not including the index breast cancer) and assigned a 1–3 score for "level of decompensation," with 1 being "mild," 2 "moderate," and 3 "severe." The overall comorbidity score was either based on the single highest ranking condition or assigned a value of 3 if the highest ranking ailments were grade 2 but occurred in different organ systems.

Statistical analysis

Age-adjusted, survey-weighted linear regression analyses were conducted to examine associations between BMI and other demographic and clinical variables. Next, overall mortality and breast cancer-specific mortality were compared across BMI categories, based on cutoffs defined by the World Health Organization ("underweight" if BMI < 18.5 kg/m^2, "normal" if BMI was 18.5–24.9 kg/m^2, "overweight" if BMI was 25.0–29.9 kg/m^2, "obese" if BMI was 30.0–34.9 kg/m^2, and "very obese" if BMI ≥ 35 kg/m^2). Hazard ratios (HR) and 95% confidence intervals (CI) for each outcome were estimated using Cox proportional hazards models with survey weights and stratification to account for POC-BP sampling. Covariates were chosen a priori because of a known or potential relationship with BMI, and included race/ethnicity, health insurance, education, socioeconomic status, tumor registry, urban/rural residence, tumor size, tumor grade, hormone receptor status, and comorbidity. As a comparison, non-breast cancer mortality was examined in the same fashion. We calculated p values for linear trend by running a second version of each model, in which BMI was represented by a continuous variable.

Results

Table 1 shows BMI according to demographic and clinical characteristics. The mean BMI was 29.1 kg/m^2 and the median, 28.0 kg/m^2. Age at diagnosis ranged from 20 to 98 years. Age and BMI at time of diagnosis were associated ($p < 0.001$); mean BMI was greater in higher age categories, except among women aged 70–79 and women aged 80 or older.

Race/ethnicity was associated with BMI ($p < 0.001$), with black women having the highest mean BMI (31.0 kg/m^2) and Asian/Pacific Islander women having the lowest (24.4). Insurance type was also associated with BMI ($p < 0.001$); women with private insurance had the lowest mean BMI (27.9 kg/m^2), while women insured through Medicaid had the highest (29.8 kg/m^2). Women in higher-education census tracts and in lower-poverty census tracts tended to have lower BMI ($p < 0.001$ for both). Women in urban areas had the lowest mean BMI, and women in rural areas, the highest ($p = 0.01$). State of residence was also associated with BMI ($p < 0.001$).

Most women had AJCC stage I (48.4%) or stage II (37.6%) disease. A more detailed description of AJCC stage at diagnosis according to BMI category is available as Supplement 1. Higher AJCC stage and larger tumor size were associated with higher BMI ($p < 0.001$ for both).

Most patients (90%) had either no comorbid conditions or mild comorbidity. Comorbidity burden was associated with BMI, although not linearly. The lowest mean BMI was among women with a comorbidity score of 0 (26.4 kg/m^2), and the highest among women with a score of 1 (30.0 kg/m^2).

Five-year all-cause mortality was 14% and five-year breast cancer-specific mortality was 9.5%. All registries provided vital status data through the five-year post-diagnosis time point, with some providing vital status data for longer, up to eight years. At eight years after diagnosis, 19.2% of women were known to be deceased (1,033 deaths), with half of these deaths from breast cancer (514 breast cancer deaths, 49.8%), and the remainder (all but five) had been censored because vital status data were no longer being collected (Supplement Table 2).

Table 2 shows results of proportional hazards regression models investigating the relationship between BMI and all-cause, breast cancer-specific, or non-breast cancer mortality. Estrogen receptor status was not found to be strongly associated with mortality (Supplement Table 5).

All-cause mortality

After adjusting for clinical and demographic characteristics, obese women with a BMI of 30–34.9 kg/m^2 appeared to have a lower hazard for all-cause mortality (HR for a 5 kg/ m^2 difference in BMI = 0.93, 95% CI, 0.87–0.95; p value for trend = 0.02). However, the association between BMI and all-cause mortality was found to vary according to age at diagnosis (Table 3); p value for interaction = 0.01). Among women in the under-50 and 50–69 age groups, there was no significant association between BMI and overall mortality, but among women 70 and older, BMI was inversely related to overall mortality (p value for trend = 0.01). In particular, among those 70 or older, women with BMI < 18.5 kg/m^2 had a significantly elevated mortality hazard compared to women with a BMI of 18.5–24.9 kg/m^2 (HR = 1.92, 95% CI 1.11–3.34) and there was a suggestion that women in higher BMI categories had a lower mortality hazard (HR for BMI of 25–29.9 kg/m^2, 30–34.9 kg/m^2, and ≥ 35 kg/m^2 compared to women with a BMI of 18.5–24.9 kg/m^2 = 0.84, 0.73, and 0.78, respectively; 95% CIs 0.63–1.14, 0.51–1.05, and 0.52–1.17, respectively). In an analysis (not shown) in which women over 70 were examined after excluding underweight women, the association between higher BMI and lower overall mortality hazard remained significant as gaged by the p value for linear trend (p = 0.02), with hazard ratios for the overweight, obese, and very obese categories similar to those found in all women over 70 (0.84, 0.77, and 0.84, respectively).

In models stratified according to AJCC stage (Table 4), no significant differences were observed in the HR estimates for each stage, and indeed within each stage-specific model, the BMI-overall mortality relationship was not significant. There was no significant interaction between BMI and AJCC stage with regard to all-cause mortality (p = 0.83). In models stratified according to estrogen receptor status (Supplement Table 6), there was a suggestion that higher BMI might be inversely associated with lower all-cause mortality among women with ER-positive tumors (p value for trend = 0.03). Among women with ER-negative tumors, no significant overall association was found (p value for trend = 0.22).

There was no significant interaction between ER status and BMI with regard to all-cause mortality ($p = 0.29$).

We explored whether the association between BMI and all-cause mortality might vary according to race/ethnicity or tumor registry. No significant interactions were observed.

Breast cancer mortality

BMI was not found to be associated with breast cancer-specific mortality in the overall model (Table 2). However, in models stratified according to AJCC stage (Table 5), specifically among patients with Stage I tumors, higher BMI was associated with greater breast cancer mortality hazard—in particular, women with BMI ≥ 35 kg/m^2 were found to have over four times the breast cancer mortality hazard (HR = 4.74, 95% CI 1.78–12.59) of women with a BMI of 18.5–24.9 kg/m^2. Among women with Stage II or III tumors, no relationship between BMI and breast cancer mortality was observed.

The association between BMI and breast cancer mortality was not found to differ according to age, estrogen receptor status (Supplement Table 7), race/ethnicity, or tumor registry.

Non-breast cancer mortality

Results for models of non-breast cancer mortality were generally similar to those for all-cause mortality (Table 2, Supplement Table 3, Supplement Table 4), including a significant inverse association between BMI and non-breast cancer mortality among women 70 or older (Supplement Table 3). The association between BMI and non-breast cancer mortality was not found to differ according to estrogen receptor status (Supplement Table 8; $p = 0.35$ for interaction).

Discussion

In this study, we examined all-cause mortality and breast cancer mortality according to BMI among women with locoregional disease followed for five to eight years after diagnosis. Our findings largely differed from the hypotheses we had laid out, in that higher BMI was not consistently associated with higher overall mortality hazard, and was associated with higher breast cancer mortality hazard among only those women with AJCC Stage I disease. We discuss these findings in greater detail below.

Contrary to our hypotheses, higher BMI was not associated with higher overall mortality, and was actually associated with lower overall mortality hazard among women age 70 or older. Among women in this age category, all-cause mortality hazard was substantially higher among underweight women, but the association between BMI and mortality remained in an analysis excluding women who were underweight. It is possible that our method of adjusting for comorbidities did not completely capture comorbidity burden; older women with lower BMI, particularly women who were underweight, may have been more likely to have had undiagnosed comorbid conditions not accounted for in the Piccirillo index framework, or to be smokers. However, poorer outcomes related to being underweight do not entirely explain the observed association—that is, having higher BMI, rather than simply not being underweight, may have a protective effect. This finding is in line with previous

research documenting an inverse relationship between BMI and mortality among older individuals in the general population, a pattern referred to as an “obesity paradox” or “reverse epidemiology” [48].

It is nevertheless surprising, given previous findings, that there was a null relationship between BMI and all-cause mortality among women under age 70. Where differences in the BMI-mortality relationship according to age have been examined, some other researchers have found the relationship between BMI and mortality to differ according to age [3, 23]; however, among these studies, a null BMI-mortality association among younger women and inverse association among older women was not observed. Rather, higher BMI was found to be associated with poorer outcomes among younger women, with no significant relationship among older women.

Our findings regarding breast cancer-specific mortality were, as mentioned earlier, also surprising. In the full analytic sample and in most subsamples, higher BMI was not associated with higher mortality from breast cancer. We observed an exception to this finding in women with AJCC Stage I cancer; those in the highest BMI category (BMI of 35 kg/m^2 or greater) had a substantially greater hazard for breast cancer mortality. Notably, we did not observe a difference in the BMI-breast cancer mortality relationship according to age, in contrast to our findings regarding overall mortality.

The finding that BMI was associated with breast cancer mortality only among women with lower-stage disease contrasts with some previous findings [5, 7, 9, 11, 13, 21], but is also consistent with a number of previous reports finding, for example, that BMI was significantly associated with breast cancer death only among women with less advanced disease [15, 49] or with no positive lymph nodes [50]. Some of the earliest studies reported a similar pattern [51, 52], prompting authors to suggest that effects of BMI are more apparent among women with generally better prognostic features. This is perhaps the most likely explanation, but further research could address whether other factors contribute. Women with higher BMI and less advanced disease may be less likely to receive adjuvant chemotherapy or hormonal therapy in line with recommendations. Alternatively or in addition to this potential contributor, women with higher BMI may be more likely to erroneously have their disease characterized as less advanced, due to technical challenges with staging procedures [49]. The possibility of statistical artifacts related to this issue needs to be considered in future study designs. As technologies make accurate staging easier, and as research continues to identify prognostic features beyond TNM stage, it will also be important to consider whether an apparent association remains between BMI and disease-specific mortality among women with an earlier assigned tumor stage, or in otherwise-defined favorable prognostic categories.

Strengths and limitations

In our analyses, we made use of a large sample of patients all diagnosed in the same year with locoregional disease, representing diverse geographic areas, racial/ethnic categories, and socioeconomic characteristics. The POC-BP data set was more complete than some registry-based studies due to additional resources made available to the investigators to verify data and collect more detailed information; thus, the study benefited from

meticulously collected comorbidity and staging data. The study benefited from a relatively long follow-up period, with up to eight years of data from most of the tumor registries represented.

This study's findings need to be considered in light of some limitations. Not all registries collected and provided data for the same length of time. Follow-up data for the full 8 years for all women would have improved statistical power, but we do not consider it likely that differences in follow-up duration by registry biased our results, because our statistical models accounted for tumor registry. Additionally, despite POC-BP study oversampling, there were low numbers of women in some racial/ethnic subgroups. We also could not investigate potential interactions according to menopausal status because data on menopausal status were not available. Additional data that were not available as part of the data set include information on women's smoking status and concomitant medication use.

BMI is not a precise or consistent means of characterizing adiposity [53, 54]; it is problematic at the extremes of height, and may exhibit systematically larger inaccuracies among older women [53]. Some researchers have therefore leaned away from BMI in favor of measures such as waist-to-hip ratio. However, BMI is still frequently used, as in this retrospective analysis, in the absence of other available measures.

Missing data on height and/or weight pose a potential threat to the validity of our findings because they are unlikely to be missing at random. 21.3% of the women in the parent data set who were eligible to be included in the analytic data set were excluded due to missing information on weight, height, or both. We conducted a sensitivity analysis in which missing weight or height was imputed among women whose records showed one but not the other. Findings (not shown) were very similar to those from our main analyses reported here.

Implications

Although our investigation did not replicate some previous findings linking greater BMI to higher breast cancer mortality in the general female breast cancer population, we did identify women with Stage I disease as a group in which obesity, particularly greater than moderate obesity, was strongly linked to poorer outcomes with regard to breast cancer death. With continued improvement in diagnostic techniques and screening practices, more women will likely be diagnosed with early-stage disease, making it even more important to understand and address the disparities in outcomes within this subgroup. Another notable finding was the inverse relationship between BMI and all-cause mortality among women above age 70. The average life span of women is now well above 70, and many women are diagnosed at a later age. It is therefore of critical importance to determine whether, perhaps due to differences in tumor characteristics, comorbidities, or other factors, body weight and adiposity may have differing effects on outcomes in this subgroup.

Conclusion

This study examined overall mortality and breast cancer mortality among women with locoregional breast cancer. It adds to existing evidence by drawing on a population-based sample of women diagnosed with Stage I, II, or III disease in seven different geographic

regions and followed for five to eight years. Continued research examining the multifactorial relationships linking obesity and breast cancer outcomes, including factors that may modify these relationships, will be important in the ongoing effort to reduce the burden of disease from breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledegements

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Table 1

Breast cancer cases according to body mass index and other demographic and clinical characteristics; stages I, II, and III breast cancer patients from the POC-BP study (2004)

Patient characteristic	No.[a] (*N* = 5394)	Weighted %	BMI (kg/m^2)		
			Mean	SE	*p* value[b]
BMI category (kg/m^2)					
< 18.5	78	1.5			
18.5–24.9	1614	32.5			
25–29.9	1589	30.3			
30–34.9	1120	19.8			
≥ 35	960	15.8			
Demographic characteristics					
Age					
20–40	398	6.3	27.9	0.4	< 0.001
40–49	1241	21.4	28.5	0.2	
50–59	1427	26.7	29.2	0.2	
60–69	1119	21.5	29.5	0.2	
70–79	823	16.3	28.0	0.2	
≥ 80	386	7.9	26.5	0.3	
Race					
White, non-Hispanic	3045	75.6	27.9	0.1	< 0.001
Black, non-Hispanic	1486	13.9	31.0	0.2	
AI/AN, non-Hispanic	43	0.3	29.4	1.7	
API, non-Hispanic	315	3.6	24.4	0.5	
Hispanic	502	6.6	28.6	0.3	
Insurance					
Private	3238	62.9	27.9	0.1	< 0.001
Medicare/other public	1083	21.2	28.3	0.2	
Medicaid	757	10.3	29.8	0.3	
None	158	2.0	28.4	0.6	
Unknown	158	3.7	28.7	0.5	
Census-tract education					
Higher	3286	69.2	27.8	0.1	< 0.001

Patient characteristic	No.[a] (*N* = 5394)	Weighted %	BMI (kg/m^2)		
			Mean	SE	*p* value[b]
Lower	2093	30.8	29.2	0.2	
Census-tract poverty					
Higher	4065	82.8	29.1	0.2	< 0.001
Lower	1314	17.2	28.1	0.1	
Urbanicity					
Urban	2773	52.5	28.0	0.1	0.01
Urban/rural mixed	1856	34.9	28.4	0.2	
Rural	751	12.7	28.9	0.3	
Registry (State)					
1	600	17.2	28.7	0.2	< 0.001
2	490	9.2	28.2	0.3	
3	577	11.2	28.5	0.3	
4	321	9.2	27.7	0.3	
5	983	8.7	29.2	0.3	
6	1298	18.6	28.7	0.2	
7	1125	25.9	27.5	0.2	
Clinical characteristics Tumor stage (AJCC)					
I	2509	48.4	27.6	0.1	< 0.001
II	2067	37.6	28.5	0.2	
III	818	14.0	29.4	0.2	
Lymph nodes					
Any positive	1920	33.9	28.9	0.2	< 0.001
All negative	3234	61.6	28.0	0.1	
Unknown	240	4.5	27.2	0.4	
Tumor size (cm)					
≤ 0.5	451	8.8	27.7	0.3	< 0.001
0.51–1	847	16.2	27.3	0.2	
1.01–2	1616	30.5	28.0	0.2	
2.01–5	2011	37.1	28.6	0.2	

Patient characteristic	No.[a] (*N* = 5394)	Weighted %	BMI (kg/m^2)		
			Mean	SE	*p* value[b]
> 5	410	6.3	29.5	0.4	
Unknown	59	1.2	31.1	0.8	
Histologic type					
Ductal	3978	73.2	28.3	0.1	0.02
Lobular	373	7.3	28.4	0.3	
Mixed ductal/lobular	348	7.3	27.1	0.3	
Other	695	12.3	28.3	0.3	
Grade					
Well differentiated	943	19.0	27.6	0.2	0.07
Moderately differentiated	2051	39.0	28.2	0.2	
Poorly differentiated	2036	35.8	28.5	0.2	
Undifferentiated	62	1.0	28.6	0.9	
Unknown/other	302	5.1	28.6	0.4	
Hormone receptor status					
ER+ and/or PR+	3846	73.0	28.4	0.1	0.13
ER– and PR–	1316	22.5	27.9	0.2	
Unknown	232	4.5	27.7	0.4	
HER2 receptor status					
HER2+	1907	34.4	28.2	0.2	0.93
HER2–	2647	49.7	28.3	0.1	
Unknown	840	15.9	28.3	0.2	
Comorbidity					
None	2420	45.5	26.4	0.1	< 0.001
Mild	2440	44.0	30.0	0.1	
Moderate	373	7.4	29.3	0.3	
Severe	161	3.1	28.9	0.5	

AI/AN American Indian/Alaska Native, *API* Asian/Pacific Islander, *ER+* estrogen receptor-positive, ER- estrogen receptor-negative, *PR+* progesterone receptor-positive, *PR-* progesterone receptor-negative, *HER2+* human epidermal growth factor 2 receptor-positive, *HER2-*human epidermal growth factor 2 receptor-negative

[a]Totals may not add up to 5394 due to missing values for some variables

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[b] p values from general linear models comparing means between categories adjusted for age

Table 2

Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality, breast cancer-specific mortality, and non-breast cancer mortality according to body mass index

	All-cause mortality			Breast cancer-specific mortality			Non-breast cancer mortality		
	HR	**95% CI**	***p* value**[a]	**HR**	**95% CI**	***p* value**[a]	**HR**	**95% CI**	***p* value**[a]
Body mass index (kg/m^2)									
< 18.5	1.31	0.80–2.15		**0.33**	0.12–0.93		**1.78**	1.09–2.95	
18.5–24.9	1 (ref)			1 (ref)			1 (ref)		
25–29.9	0.82	0.67–1.01		0.87	0.40–1.19		0.82	0.63–1.06	
30–34.9	**0.75**	0.59–0.95		0.94	0.68–1.30		**0.67**	0.47–0.93	
≥35	0.85	0.67–1.08		0.93	0.64–1.35		0.88	0.64–1.21	
Per 5 kg/m^2 Δ	**0.93** (0.87–0.95)		**0.02**	0.98 (0.94–1.02)		0.42	**0.90** (0.82–0.99)		**0.04**

Model adjusted for age, American Joint Commission on Cancer (AJCC) stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity

[a] *p* value for trend, calculated from model using BMI as a continuous measure

Table 3

Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality according to body mass index, stratified by age at time of diagnosis

	N	All-cause mortality[a]		
		HR	**95% CI**	***p* value for trend**
Under 50 years of age (*N*= 1637)				
Body mass index (kg/m^2)				
< 18.5	26	**0.10**	0.01–0.85	
18.5–24.9	585	1 (ref)		
25–29.9	408	0.94	0.59–1.51	
30–34.9	306	0.89	0.54–1.46	
≥ 35	312	1.04	0.63–1.73	
per 5 kg/m^2 Δ		1.01	0.91–1.13	0.79
50–69 years of age (*N* = 2541)				
Body mass index (kg/m^2)				
< 18.5	26	1.05	0.36–3.04	
18.5–24.9	651	1 (ref)		
25–29.9	773	0.82	0.57–1.19	
30–34.9	581	0.77	0.52–1.13	
≥ 35	510	0.84	0.56–1.28	
Per 5 kg/m^2 Δ		0.95	0.86–1.05	0.30
70 years of age or older (*N* = 1201)				
Body mass index (kg/m^2)				
< 18.5	25	**1.92**	1.11–3.34	
18.5–24.9	381	1 (ref)		
25–29.9	414	0.84	0.63–1.14	
30–34.9	239	0.73	0.51–1.05	
≥ 35	142	0.78	0.52–1.17	
per 5 kg/m^2 Δ		**0.85**	0.75–0.95	**0.01**

p value for interaction term (age*BMI) = 0.01

[a]Models adjusted for AJCC stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity

Table 4

Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality according to body mass index, stratified by AJCC stage at diagnosis

	N	All-cause mortality[a]		
		HR	**95% CI**	***p* value for trend**
Stage I (*N* = 2504)				
Body mass index (kg/m^2)				
< 18.5	40	**1.95**	1.03–3.69	
18.5–24.9	807	1 (ref)		
25–29.9	780	0.85	0.60–1.21	
30–34.9	495	0.71	0.48–1.06	
≥ 35	382	1.16	0.74–1.83	
Per 5 kg/m^2 Δ		0.94	0.82–1.08	0.40
Stage II (*N* = 2060)				
Body mass index (kg/m^2)				
< 18.5	27	0.90	0.35–2.29	
18.5–24.9	594	1 (ref)		
25–29.9	584	0.77	0.55–1.08	
30–34.9	448	**0.66**	0.45–0.96	
≥ 35	407	0.84	0.58–1.23	
Per 5 kg/m^2 Δ		0.93		0.17
Stage III (*N* = 815)				
Body mass index (kg/m^2)				
< 18.5	10	0.63	0.24–1.70	
18.5–24.9	216	1 (ref)		
25–29.9	231	0.73	0.49–1.08	
30–34.9	183	0.86	0.56–1.30	
≥35	175	0.70	0.44–1.11	
Per 5 kg/m^2 Δ		0.92	0.83–1.02	0.11

A significant interaction between BMI and AJCC stage was not found ($p = 0.83$); stratified analysis was conducted descriptively

[a] All models adjusted for age, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity

Table 5

Hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer-specific mortality according to body mass index, strati-fied by AJCC stage at diagnosis

	N	Breast cancer-specific mortality[a]		
		HR	**95% CI**	***p* value for trend**
Stage I (*N* = 2414)				
Body mass index (kg/m^2)				
< 18.5	39	2.33	0.54–10.08	
18.5–24.9	788		1 (ref)	
25–29.9	739	1.47	0.67–3.20	
30–34.9	475	1.06	0.45–2.52	
≥ 35	373	**4.74**	1.78–12.59	
Per 5 kg/m^2 Δ		**1.38** (1.22–1.55)		**0.004**
Stage II (*N* = 2060)				
Body mass index (kg/m^2)				
< 18.5	27	Not estimable		0.51
18.5–24.9	594	1 (ref)		
25–29.9	584	0.88	0.53–1.47	
30–34.9	448	0.80	0.47–1.35	
≥ 35	407	0.87	0.48–1.58	
Stage III (*N* = 815)				
Body mass index (kg/m^2)				
< 18.5	10	0.32	0.06–1.84	0.20
18.5–24.9	216	1 (ref)		
25–29.9	231	0.74	0.47–1.17	
30–34.9	183	0.97	0.62–1.54	
≥35	175	0.69	0.41–1.17	

p value for interaction term (stage*BMI) = 0.04

[a]All models adjusted for age, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comor-bidity level. Survey sampling was stratified by tumor registry and by race/ethnicity