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The effect of body mass index on breast cancer stage and breast cancer specific survival

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Abstract

Purpose: Underweight women and those with obesity, defined as having a body mass index (BMI) ≥ 30 kg/m², diagnosed with breast cancer (BC) are known to have worse prognosis. Whether BMI impacts BC stage at diagnosis and BC specific survival (BCSS) is not understood. We aim to better understand the relationship between BMI with stage at BC diagnosis and BCSS.

Methods: Women age ≥ 15 years old diagnosed with BC between 2014 and 2019 were identified from the California Cancer Registry. BMI at diagnosis was classified as underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obesity class 1–2 (30–39.9 kg/m²), and obesity class 3 (≥ 40 kg/m²). BC late stage of diagnosis was defined as American Joint Committee on Cancer stage 3 and 4. Multivariate logistic regression was performed to compare sociodemographic and clinical factors associated with late stage. Multivariable cox proportional hazards regression models assessed association of BMI and BCSS.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was approved by the California Committee for the Protection of Human Subjects. Patient consent for publication is not applicable.

Results: Of 159,248 patients: 2.2% were underweight, 34.6% normal weight, 30.5% overweight, 26.7% obesity class 1–2, and 6.0% obesity class 3. Compared to normal weight, patients who were underweight [Hazard Ratio (HR) 1.54, 95% Confidence Interval (CI) 1.51–1.57], obesity class 1–2 [HR 1.06, 1.05–1.07], and obesity class 3 [HR 1.14, 1.12–1.16] were more likely to be diagnosed with late-stage BC. In models stratified by age, patients ≥ 40 years who were underweight had worse BCSS, while patients ≥ 51 years with obesity class 1–2 had better BCSS.

Conclusion: Patients with obesity class 1–2 were more likely to be diagnosed with a later stage, but had improved BCSS, supporting an “obesity paradox” in BC and suggesting that other measures are needed to better assess body composition, adipose distribution, and metabolic health of patients. Patients who were underweight had worse survival, suggesting this high-risk group may benefit from being assessed and treated for possible sarcopenia and malnourishment.

Keywords

Obesity; Body mass index; Underweight; Breast cancer stage at diagnosis; Breast cancer specific survival

Introduction

Breast cancer (BC) is the most common cancer for women worldwide [1]. In the United States in 2018, there were an estimated 268,670 new BC cases and 40,920 deaths from BC causes [2]. BC prognosis is dependent on multiple factors including tumor stage, hormone receptor status, lymph node involvement, but also patient factors, like obesity, may also influence prognosis. Obesity has been on the rise globally [3], contributing to significant patient morbidity and increased risk of premature death in patients in the highest and lowest body mass index (BMI) categories [4]. Obesity increases the risk of developing multiple cancers, especially sex-hormone related cancers like BC. Obesity has been studied as a risk factor and poor prognosis indicator for BC. In multiple meta-analyses, patients with obesity had worse disease-free survival, overall survival [6, 7] and this persisted across all subtypes [8]. Higher BMI has also been associated with larger tumor size, greater regional/distant stage [5], more lymph node metastases [9] and increased risk of recurrence [10].

However, the relationship between BMI and BC remains complex, particularly with respect to menopausal status. In premenopausal women, an inverse relationship has been found between weight and BC development [11]. In postmenopausal women, women who were obese had over two-fold increased risk of BC development [12, 13]. Regardless, once diagnosed, women of all ages with obesity have been found to have worse BC specific and overall survival [14, 15]. The association between BMI with BC stage at diagnosis at all ages and subsequent survival has not been studied.

Therefore, in this study, we aimed to investigate how differences in BMI impact breast cancer stage at diagnosis and survival. Using a large population database, the California Cancer Registry (CCR), we analyzed associations between BMI at breast cancer diagnosis, stage of diagnosis and survival among women with breast cancer. The purpose of this study was to better understand the relationship of BMI with stage of breast cancer diagnosis and survival to identify high risk groups and improve care.

Methods

Data source and study population

Data for this analysis was provided by the CCR. The CCR is one of the country's largest and most diverse registries by race/ethnicity and socioeconomic status (SES), capturing more than 99% of all invasive cancers diagnosed in California. Patients eligible for the study were women age ≥ 15 years who resided in California when diagnosed with primary breast cancer during 2014–2019 and reported to the CCR. The final study population included 159,248 BC patients after exclusion of patients with invalid followup time and non-adenocarcinoma BC histology.

Sociodemographic and clinical variables

For each patient, we obtained CCR information routinely recorded in the medical record at diagnosis including age at diagnosis, race/ethnicity, neighborhood SES based on patients' residential census-block group and categorized in tertiles [16–18], health insurance, American Joint Committee on Cancer (AJCC) stage, tumor grade, histology, tumor size, lymph node involvement, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) tumor-expression status, and initial treatment (chemotherapy, radiation, and primary surgery details). In addition, BMI at diagnosis was collected and classified as underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obesity class 1–2 (30–39.9 kg/m²), and obesity class 3 (≥ 40 kg/m²). Late stage at BC diagnosis was defined as AJCC stage 3 and 4.

Statistical analyses

Due to the high proportion of missing BMI (36.5%), a multivariate imputation by fully conditional specification methods was performed [19]. We assessed missingness by BMI status and found some differences by race/ethnicity, age at cancer diagnosis, neighborhood SES, health insurance, stage at diagnosis, tumor marker, but an overall missing at random pattern (Supplemental Table 1). We performed 20 imputations using demographic variables (age at diagnosis, race/ethnicity, neighborhood SES, marital status, year of diagnosis, stage at diagnosis, health insurance type, rural or urban residence, geographic area of the state, and Charlson comorbidity index score) as auxiliary variables in our imputation models. We conducted sensitivity analyses excluding patients with missing BMI information to compare with the imputed results (Supplemental Tables 2 and 3). Multivariate logistic regression compared sociodemographic and clinical factors associated with late stage at diagnosis. Results are presented as odds ratio (OR) and corresponding 95% confidence intervals (CI).

We estimated unadjusted, 5-year BC-specific survival (BCSS) using the Kaplan–Meier method. Multivariable Cox proportional hazards regression models assessed associations of BMI with BCSS while controlling for sociodemographic and clinical factors. Effect modification was assessed between BMI with age group (15–39, 40–50, ≥ 51) and stage at diagnosis by including interaction terms in the multivariable models. An interaction was observed by age group ($p < 0.001$), so Cox proportional hazards regression models are presented by age group. For deceased patients, survival time was measured from diagnosis date of BC to the date of death from BC. Deaths from other causes were

considered as competing risks. Patients alive at the study end date (31 December 2022) were censored at this date or at last known contact. In all survival models, the proportional hazards assumption was assessed numerically based on cumulative sums of Martingale residuals and visually based on inspection of the survival curves [log (– log) of the survival distribution function by log (months)]; variables that violated this assumption were included as stratifying variables to allow for differing baseline hazards associated with these variables (chemotherapy, radiation, surgery, AJCC stage). Results are presented as hazard ratios (HR) and 95% CI. Statistical analyses were performed using SAS statistical software (version 9.4), and a 2-sided P value of less than 0.05 was considered statistically significant.

Results

Our study consisted of 159,248 female patients diagnosed with a primary invasive BC. Selected characteristics are shown in Table 1. Among patients in our study, 2.2% were underweight, 34.6% normal weight, 30.5% overweight, 26.7% obesity class 1–2, and 6.0% obesity class 3. The distribution of BMI categories pre-and post-imputation were equivalent (Supplemental Table 1). In the cohort, 75.3% of women were age ≥ 51 years old, 39.8% lived in a high SES neighborhood and 56.6% had private insurance. 53.3% were non-Hispanic (nH) white, 22.1% Hispanic, 16.4% Asian/Pacific Islander, and 6.2% nH Black. 12.3% had a late stage BC diagnosis (AJCC stage III and IV). Most were treated surgically (89.9%), 31.9% received chemotherapy, and 48.3% radiation therapy. In total, 6.9% had died from BC and 5.6% from other causes.

Patients who were underweight (vs normal weight) had the highest risk of late stage at diagnosis [Odds Ratio (OR) 1.54, 95% CI 1.51–1.57] (Table 2). Obesity class 1–2 and class 3 were also associated with late stage at diagnosis [OR 1.06, 1.05–1.07 and OR 1.14, 1.12–1.16], but these associations were not observed among patients who were overweight ($p = 0.11$). These results were similar when looking at the pre-and post-imputation data (Supplemental Table 2).

In models stratified by age (Table 4), underweight (vs normal weight) patients had worse BCSS in the 40–50 age group (Hazard Ratio (HR) 1.43, 1.01–2.03) and ≥ 51 age group (HR 1.18, 1.03–1.36), but not the < 40 age group ($p = 0.91$). Overweight or class 3 obesity were not associated with worse BCSS in any of the age groups. Patients who were categorized as obesity class 1–2 had a better BCSS in the ≥ 51 age group [HR 0.93, 0.87–0.99], but not in the younger age categories. Results for BCSS prior to imputation were similar (Supplemental Table 3).

Unadjusted 5-year BCSS rates stratified by age identified that patients in the age group 40–50 are estimated to have better survival across all weight categories compared to ages 15–39 and ≥ 51 year-olds (Table 3; Fig. 1). Patients in the age group 15–39 were estimated to have worse survival if overweight, with obesity class 1–2, or class 3 compared to normal weight or underweight (Fig. 1). Patients with normal weight were shown to have better survival across all age groups, especially in the age group 40–50. Underweight patients were shown to have decreased 5-year BCSS in both the 40–50 [90.4% (CI 89.9%, 90.9%)] and the ≥ 51 [71.8% (CI 71.3%, 72.2%)] age groups. Patients with obesity class 3 were also estimated to

have worse 5-year survival across all age groups, but for age ≥ 51 , underweight patients had worse survival than patients with obesity class 3.

Discussion

In this large population-based study, we observed that patients with obesity, who comprised 33% of our cohort, were more likely to be diagnosed with a later stage of BC, adding to a growing literature that obesity is a risk factor for advanced BC. However, patients who were overweight or obesity class 3 did not have worse BCSS than normal weight women. Instead, patients 51 years of age or older with obesity class 1–2 had improved BCSS, supporting an “obesity paradox” in BC. Our study also identified a high-risk population of BC patients, approximately 2% of our cohort, who were underweight and more likely as well to be diagnosed at a late stage. In addition, underweight women over 40 years of age at diagnosis experienced worse BCSS, highlighting the need for interventions to improve outcomes in this population.

Our findings align with prior work showing women with obesity are more likely to be diagnosed with BC and have more advanced BC [5, 9, 10, 15]. The reasons for this are multifactorial. First, women with obesity have excessive adipose tissue. Adipose tissue contains aromatase, which converts androstenediol into estradiol and produces estrogen. High levels of estrogen stimulate the growth of breast tumor cells [20]. Also, individuals with obesity produce more leptin than those of normal weight. Leptin induces expression of aromatase in breast cancer cells, leading to more estrogen and proliferation [21]. In addition, obese adipose tissue over-expresses inflammatory mediators like interleukin-6, tumor necrosis factor, and intercellular adhesion molecule 1 [22], a pro-inflammatory state that stimulates tissue growth [23]. Patients with obesity frequently have imbalances in insulin and insulin-like growth factor, which also stimulate tumor growth and inhibit apoptosis [24]. Finally, patients with obesity typically have larger breast size, which can reduce the accuracy and sensitivity of ultrasound or other examinations, potentially leading to missed BC diagnoses [25]. Overall, our finding of women with obesity being diagnosed with a later stage of BC [26] adds to the growing body of literature that being obese is a risk factor for the development of advanced BC.

However, unlike prior studies, [5–8] we found that patients with obesity class 1–2 had better BCSS in patients over 50 years of age. One reason for this could be the “obesity paradox” seen in other cancers, including gynecological and colorectal cancers [27], but previously not seen with BC [28]. This paradox refers to patients who are over-weight or obese being more likely to develop a disease, but also more likely to have better survival than their normal counterparts [28]. The mechanisms underlying these associations are still unknown, but potential theories have been explored. Lee and Giovannucci touch on the theory of “cancer cachexia,” which describes an inaccurate categorization of patients into a normal or underweight BMI category based on the observation that cancer patients with advanced disease have often already lost a lot of weight prior to diagnosis. While these patients might have been overweight or obese before, due to this cachectic state, they are now labeled as normal or even underweight and have a higher risk of mortality. This supports the paradox that obese patients are more likely to have a better survival, even though this

may not be true [29]. Also, patients with a high BMI have an increased metabolic buffer that can protect them from this catabolic state [28] and provide supportive nutrients during cancer treatments leading to a better tolerance of cancer cachexia and subsequent treatments [30]. Prior literature has shown that the “obesity paradox” is a more beneficial in older individuals [31]. That is, older individuals who have obesity may have survival benefits due to protection against protein-energy wasting and the nutritional insult of a cancer diagnosis [31].

Another consideration is the use of BMI. BMI is the most widely used tool to assess adiposity in obesity with clinical outcomes [32]; however, it is limited by its inability to discriminate body composition, adipose distribution, and cardiovascular health [33, 34]. Prior work has shown that people with the same BMI measurement can have vastly different body compositions which leads to different metabolic profiles and the negative health associations commonly attributed to BMI and weight [35]. The different distributions of adipose tissue are variably tied to adverse effects due to differences in adipokine synthesis [36]. Additionally, being cardiovascular unfit, regardless of one’s BMI, is associated with twice the risk of death compared to normal weight patients [37, 38]. Using solely BMI, and not considering leanness and adipose distribution, likely contributes to less accurate results and contributing to an “obesity paradox” [29]. Future studies should incorporate other methods to assess body composition, adipose distribution and metabolic health, like waist-to-height ratio or waist circumference [39].

Patients who were underweight had the highest risk of late-stage disease. Prior work has shown that underweight women have lower odds of complying with regular screening mammograms [40, 41], potentially contributing to this finding. We also found underweight women had worse BCSS, consistent with prior studies [42, 43]. Underweight may be associated with sarcopenia, cancer cachexia, or undernourishment, which are conditions that decrease the efficacy and potency of chemotherapy [44, 45]. Sarcopenia also carries a high risk of morbidity and mortality in a variety of health conditions [35], potentially contributing to the worse survival observed in our study. We found for patients over the age of 39 years, being underweight is associated with worse survival, indicating that this high-risk group may benefit from screening for sarcopenia and malnourishment for early physical therapy or registered dietician interventions to improve outcomes.

This study has some important limitations. We had a high percentage of missing BMI data (36.5%) but were able to impute the missing information using a validated method [19]. In addition, BMI data was only recorded at BC diagnosis, which does not account for BMI changes in the time prior to cancer diagnosis or during treatment, an important consideration for future studies. With the increased use of glucagon-like peptide-1 (GLP-1) receptor agonists to treat obesity, their effects on BC stage and BCSS remain unknown. While our dataset did not include the use of GLP-1 receptor agonists, further exploration into the potential association of weight loss via the use of GLP-1 receptor agonists or bariatric surgery in BC outcomes may be useful. Despite these limitations, our large population-based study has added to the complex picture concerning BMI, stage of BC diagnosis, and BCSS.

Conclusion

Patients with obesity class 1–2 were more likely to be diagnosed with a later stage of diagnosis but had improved BCSS, potential evidence of an “obesity paradox” in BC. Other measures besides BMI are needed to better assess body composition, adipose distribution and metabolic health of patients. Patients who were underweight were more likely to be diagnosed late stage BC and have worse survival, indicating a high-risk group that should be assessed for early interventions to improve outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data that support the findings of this study are available from the California Cancer Registry and the California Department of Health Care Access and Innovation. Access to these data sources is granted through an application process by the management or data custodians. The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Sect. 103,885; Centers for Disease Control (CDC) and Prevention’s National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the NCI’s Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the State of California, Department of Public Health, the NCI, and the CDC or their Contractors and Subcontractors.

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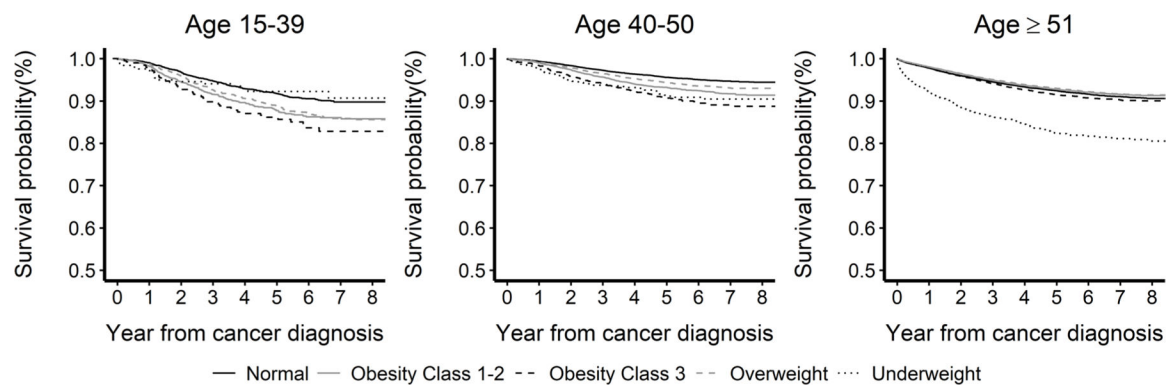


Fig. 1.
Kaplan Meier breast cancer survival estimates by body mass index (BMI) stratified by age group

Table 1

Selected characteristics among breast cancer survivors (N = 159,248), California, 2014–2019

	Total
Characteristics	N = 159,248 N (%)
Body mass index (kg/m ²)	
Underweight (< 18.5)	3568 (2.2)
Normal weight (18.5–24.9)	54,992 (34.6)
Overweight (25–29.9)	48,524 (30.5)
Obesity class 1–2 (30–39.9)	42,519 (26.7)
Obesity class 3 (≥ 40)	9556 (6.0)
Race/ethnicity	
NH White	84,924 (53.3)
NH Black	9918 (6.2)
Hispanic	35,235 (22.1)
Asian/Pacific Islander	26,149 (16.4)
Other/unknown	3,122 (2.0)
Age (years)	
15–39	8,248 (5.2)
40–50	31,035 (19.5)
≥ 51	119,965 (75.3)
Year of diagnosis	
2014–2016	77,981 (49.0)
2017–2019	81,267 (51.0)
Neighborhood socioeconomic status	
Low SES	38,203 (24.0)
Middle SES	57,651 (36.2)
High SES	63,394 (39.8)
Payment	
Private/military	90,117 (56.6)
Public/medicaid/medicare	63,910 (40.1)
Uninsured/self-pay	975 (0.6)
Unknown	4246 (2.7)
AJCC Stage	
Stage I	68,180 (42.8)
Stage II	35,701 (22.4)
Stage III	12,546 (7.9)
Stage IV	7053 (4.4)
Unstaged/unknown	7479 (4.7)
Grade	
Grade I	33,483 (21.0)
Grade II	65,051 (40.8)
Grade III	44,258 (27.8)
Undifferentiated	828 (0.5)

	Total
Histology	
Ductal	115,498 (72.5)
Lobular	32,056 (20.1)
Other	11,694 (7.3)
T category	
T1a: ≤ 0.5 cm	14,479 (9.1)
T1b: > 0.5–1 cm	23,831 (15.0)
T1c: > 1–2 cm	48,032 (30.2)
T2: > 2–5 cm	49,304 (31.0)
T3: ≥ 5 cm	12,956 (8.1)
Diffuse	190 (0.1)
No mass/tumor found/unknown/missing	10,456 (6.6)
Lymph node involvement	
Regional lymph node involvement	34,595 (21.7)
No lymph node involvement	92,297 (58.0)
Unknown	32,356 (20.3)
Chemotherapy	
No/unknown	108,395 (68.1)
Yes	50,853 (31.9)
Radiation	
No/unknown	82,319 (51.7)
Yes	76,929 (48.3)
Surgery	
Lumpectomy	91,190 (57.3)
Mastectomy	51,922 (32.6)
None	15,434 (9.7)
Regional nodes examined	
Sentinel lymph node biopsy	94,415 (59.3)
Axillary lymph node dissection	30,633 (19.2)
No nodes examined/unknown	34,200 (21.5)
Tumor marker	
Hormone receptor positive	91,673 (57.6)
Her-2 positive	6197 (3.9)
Triple negative	12,530 (7.9)
Triple positive	16,242 (10.2)
Unknown	32,606 (20.5)

nH non-Hispanic, *SES* socioeconomic status, *AJCC* American Joint Committee on Cancer

Table 2

Multivariable adjusted odds ratio (OR) and associated 95% confidence interval (CI) estimates for the association between patient characteristics and late stage of breast cancer diagnosis

Characteristics	OR (95% CI)
Body mass index	
Underweight	1.54 (1.51, 1.57)
Normal weight	Reference
Overweight	0.99 (0.98, 1.00)
Obesity class 1–2	1.06 (1.05, 1.07)
Obesity class 3	1.14 (1.12, 1.16)
Race/ethnicity	
NH white	Reference
NH black	1.39 (1.37, 1.41)
Hispanic	1.08 (1.07, 1.09)
Asian/Pacific Islander	0.97 (0.96, 0.98)
American Indian	0.99 (0.95, 1.04)
Other/unknown	0.58 (0.56, 0.60)
Age (years)	
15–39	Reference
40–50	0.55 (0.54, 0.55)
≥ 51	0.41 (0.41, 0.42)
Year of diagnosis	
2014–2016	Reference
2010–2012	0.82 (0.82, 0.83)
Neighborhood socioeconomic status	
Low SES	Reference
Middle SES	0.87 (0.86, 0.87)
High SES	0.71 (0.70, 0.71)
Payment	
Private/military	Reference
Public/medicaid/medicare	1.46 (1.45, 1.47)
Uninsured/self-pay	2.23 (2.16, 2.31)
Unknown	1.57 (1.54, 1.61)
Charlson comorbidity index	
0	Reference
1	1.06 (1.05, 1.07)
2 +	1.55 (1.54, 1.57)
Unknown	1.28 (1.27, 1.29)

nH non-Hispanic, *SES* socioeconomic status

Adjusted for race/ethnicity, age at diagnosis, year of diagnosis, neighborhood socioeconomic status, health insurance, Charlson co-morbidity index, and treatment location

Table 3

Unadjusted 5-year breast cancer specific survival (BCSS) rates and associated 95% confidence interval (CI) estimates stratified by age group

Body mass index	Age 15–39	Age 40–50	Age ≥ 51
	% (CI)	% (CI)	% (CI)
Underweight	90.4 (89.5, 91.3)	90.4 (89.9, 90.9)	71.8 (71.3, 72.2)
Normal	90.4 (90.2, 90.6)	94.5 (94.4, 94.6)	86.2 (86.1, 86.3)
Overweight	87.5 (87.1, 87.8)	93.0 (92.9, 93.1)	86.9 (86.9, 87.0)
Obesity class 1–2	85.4 (85.0, 85.8)	91.6 (91.5, 91.8)	86.4 (86.3, 86.5)
Obesity class 3	85.1 (84.3, 86.0)	89.2 (88.8, 89.5)	82.6 (82.4, 82.8)

Table 4

Multivariable adjusted hazard ratio (HR) and associated 95% confidence interval (CI) estimates for the association between body mass index and breast cancer specific death stratified by age group

	Age 15–39	Age 40–50	Age ≥ 51
Body Mass Index	HR (CI)	HR (CI)	HR (CI)
Underweight	0.97 (0.56, 1.68)	1.43 (1.01, 2.03)	1.18 (1.03, 1.36)
Overweight	1.14 (0.92, 1.41)	1.03 (0.88, 1.21)	0.95 (0.89, 1.01)
Obesity class 1–2	1.11 (0.88, 1.38)	1.05 (0.89, 1.24)	0.93 (0.87, 0.99)
Obesity class 3	1.09 (0.74, 1.6)	1.17 (0.92, 1.5)	0.92 (0.82, 1.02)

Referenced to normal weight

Adjusted for race/ethnicity, neighborhood socioeconomic status, health insurance, tumor marker status and stratified by stage at diagnosis (AJCC stage), receipt of chemotherapy, radiation and surgery