original report

Adipose Tissue Distribution and Cardiovascular Disease Risk Among Breast Cancer Survivors

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abstract

PURPOSE Cardiovascular disease (CVD) is a major source of morbidity and mortality among breast cancer survivors. Although body mass index (BMI) is associated with CVD risk, adipose tissue distribution may better identify patients with a high risk of CVD after breast cancer.

METHODS Among 2,943 patients with nonmetastatic breast cancer without prior CVD, we used International Classification of Diseases (9th and 10th revisions) codes to identify incidence of nonfatal stroke, myocardial infarction, heart failure, or CVD death. From clinically acquired computed tomography scans obtained near diagnosis, we measured visceral adiposity (centimeters squared), subcutaneous adiposity (centimeters squared), and intramuscular adiposity (fatty infiltration into muscle [Hounsfield Units, scored inversely]). We estimated hazard ratios (HRs) and 95% CIs per SD increase in adiposity accounting for competing risks and adjusting for demographics, smoking, cancer treatment, and pre-existing CVD risk factors.

RESULTS Mean (SD) age was 56 (12) years. Over a median follow-up of 6 years, 328 CVD events occurred. Each SD increase in visceral or intramuscular adiposity was associated with an increase in CVD risk (HR, 1.15 [95% CI, 1.03 to 1.29] and HR, 1.21 [95% CI, 1.06 to 1.37]), respectively). Excess visceral and intramuscular adiposity occurred across all BMI categories. Among normal-weight patients, each SD greater visceral adiposity increased CVD risk by 70% (HR, 1.70 [95% CI, 1.10 to 2.62]).

CONCLUSION Visceral and intramuscular adiposity were associated with increased CVD incidence after breast cancer diagnosis, independent of pre-existing CVD risk factors and cancer treatments. The increased CVD incidence among normal-weight patients with greater visceral adiposity would go undetected with BMI alone. Measures of adipose tissue distribution may help identify high-risk patients and tailor CVD prevention strategies.

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INTRODUCTION

Improvements in early detection and treatment have improved prognosis for the more than 3.4 million women in the United States who are living with breast cancer.[1] For older patients with early-stage disease, the risk of death from cardiovascular disease (CVD) is now higher than the risk of cancer recurrence.[2,3] Breast cancer survivors may be at increased risk of CVD relative to women without a cancer history because of their high burden of pre-existing CVD risk factors combined with the direct (eg, radiation-induced cardiovascular injury and the cardiotoxic effects of systemic therapies) and the indirect (eg, deconditioning and physical inactivity) effects of cancer treatment.[4,5]

It is well known that higher body mass index (BMI) is associated with CVD mortality in the general population. However, BMI is not always an accurate proxy for individual level adiposity and does not describe adipose tissue distribution. In populations without cancer, visceral (intra-abdominal) and intramuscular (triglyceride accumulation within skeletal muscle cells) adiposity have the strongest associations with CVD,[6-11] hypertension, diabetes, and metabolic syndrome.[12-16] Prior research among breast cancer survivors has examined only CVD mortality and BMI or waist circumference, surrogate measures of overall and central adiposity, without measuring body composition, nonfatal CVD events, or CVD subtypes with differing etiology.[17,18] Furthermore, in addition to overall adiposity, the location of the adipose tissue (eg, visceral, subcutaneous, or intramuscular) may be crucial to identifying patients with high CVD risk.

In the current study of 2,943 patients with nonmetastatic breast cancer without prior CVD, we quantified visceral, subcutaneous, and intramuscular adiposity from clinically acquired computed tomography (CT) images and examined associations with incident CVD, adjusting for pre-existing risk factors (diabetes, dyslipidemia, and hypertension) and receipt

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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of chemotherapy or radiation. Second, we examined whether cancer treatment type (eg, anthracycline-containing chemotherapy, which has known cardiotoxic effects) modified these associations.

METHODS

The Breast, Sarcopenia, Cancer and Near-Term Survival study's population included all Kaiser Permanente Northern California (KPNC) members diagnosed from 2005 to 2013 with nonmetastatic stage I to III invasive breast cancer who had an abdominal CT scan at diagnosis and no cancer history. For all women, prospectively collected electronic medical record (EMR) data were available.[19] We excluded women with any EMR-recorded International Classification of Diseases (ICD) code or history of myocardial infarction, stroke, heart failure, intracranial hemorrhage, or coronary artery revascularization before breast cancer diagnosis (n = 194) and missing smoking exposure (n = 2). The KPNC institutional review board approved the study.

CT Image Analysis

We quantified adiposity from CT scans taken within 6 months of diagnosis before chemotherapy or radiation (the median time from diagnosis to scan was 1.2 months). Two centrally trained researchers (blinded to clinical outcomes, including CVD) using SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada)[9] contoured the cross-sectional area of each tissue in centimeters squared (cm^2) at the third lumbar vertebra (L3), distinguishing muscle from visceral and subcutaneous adipose tissue using anatomic knowledge and tissue-specific Hounsfield unit ranges. The coefficients of variation (%) for muscle, subcutaneous adipose, and visceral adipose tissue quantifications between raters were 0.66%, 0.79%, and 6.72%, respectively. Single-slice L3 areas are well correlated with whole-body tissue volumes from magnetic resonance imaging.[10] To quantify intramuscular adiposity, we computed the average radiation attenuation of skeletal muscle tissue in Hounsfield units, scaled inversely because lower muscle radiodensity indicates higher intramyocellular triglyceride.[20]

Covariate and Death Assessment

From KPNC's comprehensive EMR and cancer registry, we obtained information on tumor characteristics (American Joint Committee on Cancer stage and estrogen, progesterone receptor, and human epidermal growth factor receptor 2 [HER2] status) and cancer treatment (radiation, anthracycline-containing *v* nonanthracycline chemotherapy, HER2-directed, and/or endocrine therapy). The KPNC EMR began in 1996 and encapsulates all care within KPNC, including diagnostic, procedural, laboratory, and radiographic data from various sources, including, but not limited to, inpatient, outpatient, claims, and referrals. We obtained information on pre-existing cardiovascular risk factors (diabetes, hypertension, and dyslipidemia) through the KPNC diabetes registry and the ICD 9th and 10th revision codes shown in the Data Supplement. The EMR also captured age, race/ethnicity (non-Hispanic white, black, Hispanic/Latino, Asian/Pacific Islander, or other) and smoking history (current, former, or never). Medical assistants measured height and weight at clinical visits. We calculated BMI from the measurements closest to the CT scan, categorized as underweight (less than 18.5 kg/m^2), normal weight (18.5 to less than 25 kg/m^2), overweight (25 to less than 30 kg/m^2), class I obesity (30 to less than 35 kg/m^2), and class II obesity (35 kg/m^2 or greater). We combined mortality data from KPNC, California death records, and the Social Security Administration to determine patients' vital status and cause of death.

CVD Outcomes

Events of interest included acute myocardial infarction, ischemic stroke, heart failure, and a composite end point that included any of these events in addition to intracranial hemorrhage, coronary artery revascularization, and deaths for which CVD was listed as a primary cause (Data Supplement).

Statistical Analysis

To facilitate comparison among exposures with different ranges and units, we treated each continuously in SD units. To create more easily interpretable risks groups, we also categorized adipose depots into tertiles.[21,22] Follow-up began at breast cancer diagnosis and continued until the first date of occurrence of any event of interest (acute myocardial infarction, ischemic stroke, heart failure, intracranial hemorrhage, coronary artery revascularization, or death from CVD), disenrollment from the health plan, death from non-CVD causes, or June 30, 2018.

To account for competing risks, we used Fine and Gray's[23] extension of Cox regression that models (the hazards of) the cumulative incidence function, herein referred to as the subdistribution hazard ratio (HR) and its corresponding 95% CIs.[24] The subdistribution HRs are reported in the text. The cause-specific HRs, wherein individuals who experienced competing events were censored, were similar and are reported in the Data Supplement. We assessed proportional hazards through product terms between exposures and logged follow-up time; we detected no violations. We calculated *P* for trend by treating adipose tissue tertiles as ordinal variables.

We examined each adipose depot in separate multivariable models adjusted for a priori covariates, including diagnosis age, height, race/ethnicity, smoking, diabetes, hypertension, dyslipidemia, and tumor and treatment characteristics. In addition to evaluating overall associations, we stratified by BMI category. To evaluate possible effect modification, we used likelihood ratio tests for the inclusion of cross-product terms of adiposity measures with radiation

therapy (received or not), age at diagnosis (younger than 55 years or 55 years and older, as a proxy for menopausal status) and chemotherapy type (none, anthracycline containing, or nonanthracycline containing).

In sensitivity analyses, we examined whether results changed with adjustment for additional treatment variables (aromatase inhibitors, radiation, and HER2-directed therapy, which can increase CVD risk through altering blood lipids or direct cardiotoxic effects).

All statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC). A P value of $< .05$ for a two-tailed test was considered statistically significant.

RESULTS

Table 1 lists sample characteristics. At breast cancer diagnosis, mean (SD) age was 56 (12) years, and mean (SD) BMI was 28 (6) kg/m^2. Pre-existing CVD risk factors were common at diagnosis, with more than a third of women having hypertension and/or dyslipidemia, and a quarter having diabetes.

Figure 1 illustrates the distributions of visceral (Fig 1A), subcutaneous (Fig 1B), and intramuscular (Fig 1C) adiposity across BMI categories. All types of adiposity increase with BMI, but this is most pronounced for subcutaneous and least pronounced for intramuscular adiposity. For example, most patients with normal BMI have visceral and subcutaneous adiposity in the lowest tertile (83% and 84%, respectively), whereas most patients with class II obesity have visceral and subcutaneous adiposity in the highest tertile (69% and 90%, respectively). By contrast, intramuscular adiposity occurs across BMI categories, with less than one half of patients with class II obesity and more than 10% of normal-weight patients in the highest tertile.

Over a median follow-up of 6 years (maximum, 13 years), 328 CVD events occurred. Four hundred sixty-six women died as a result of competing events before developing CVD, including 361 deaths as a result of breast cancer. The cumulative incidence of CVD reached 15% by year 10 of follow-up (Fig 2A; cumulative incidence, 0.15 [95% CI, 0.14 to 0.17]). Women in the highest tertiles of adiposity had the highest cumulative incidence of CVD (Figs 2B-2D).

The association of BMI with CVD risk was nonlinear. Compared with normal-weight women, those who were underweight or who had class II obesity had an increased CVD risk after breast cancer diagnosis (HR, 2.16 [95% CI, 1.06 to 4.43] and HR, 1.70 [95% CI, 1.20 to 2.42], respectively; Table 2). Meanwhile, women with overweight BMI or class I obesity had no statistically significant increased risk of CVD (HR, 1.01 [95% CI, 0.75 to 1.37] and HR, 1.32 [95% CI, 0.95 to 1.83], respectively; Table 2).

TABLE 1. Characteristics of Patients Diagnosed With Nonmetastatic Breast Cancer at Kaiser Permanente Northern California (2006-2011)

Characteristic	Overall (N = 2,943)
Age at diagnosis, years, mean (SD)	55.5 (11.6)
BMI closest to scan, kg/m^2, mean (SD)	28.2 (6.4)
Muscle radiodensity, HU, mean (SD)	40.8 (9.8)
Visceral adiposity, cm^2, mean (SD)	102.5 (77.6)
Subcutaneous adiposity, cm^2, mean (SD)	251.1 (126.7)
Race/ethnicity	
Non-Hispanic white	1,860 (63.2)
Black/African American	219 (7.4)
Hispanic/Latina	342 (11.6)
Asian/Pacific Islander	500 (17.0)
Other/mixed race	22 (0.7)
AJCC stage	
I	619 (21.0)
II	1,337 (45.4)
III	987 (33.5)
Any adjuvant chemotherapy	2,220 (75.4)
Anthracycline chemotherapy	1,423 (48.4)
Herceptin	539 (18.3)
Radiation	
Left sided	374 (12.7)
Right sided	368 (12.5)
History of smoking	
Never	1,839 (62.5)
Former	808 (27.5)
Current	296 (10.1)
Dyslipidemia	1,055 (35.8)
Hypertension	1,169 (39.7)
Type 2 diabetes	737 (25.0)
ER positive	2,225 (75.6)
PR positive	1,602 (54.4)
HER2 positive	623 (21.2)

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HU, Hounsfield units; PR, progesterone receptor.

Examining specific adipose tissue depots (Table 3), we observed an increased CVD risk in the highest (v lowest) tertiles of visceral (HR, 1.42 [95% CI, 1.05 to 1.91]; P-trend = .03) and intramuscular (HR, 1.39 [95% CI, 1.01 to 1.91]; P-trend = .04) adiposity. Modeling associations continuously (linear in the log-hazard) yielded consistent results, with increases of 15% (95% CI, 1.03% to 1.29%) and 21% (95% CI, 1.06% to 1.37%) per SD increase in visceral and intramuscular adiposity, respectively. Associations were slightly weaker when comparing the highest

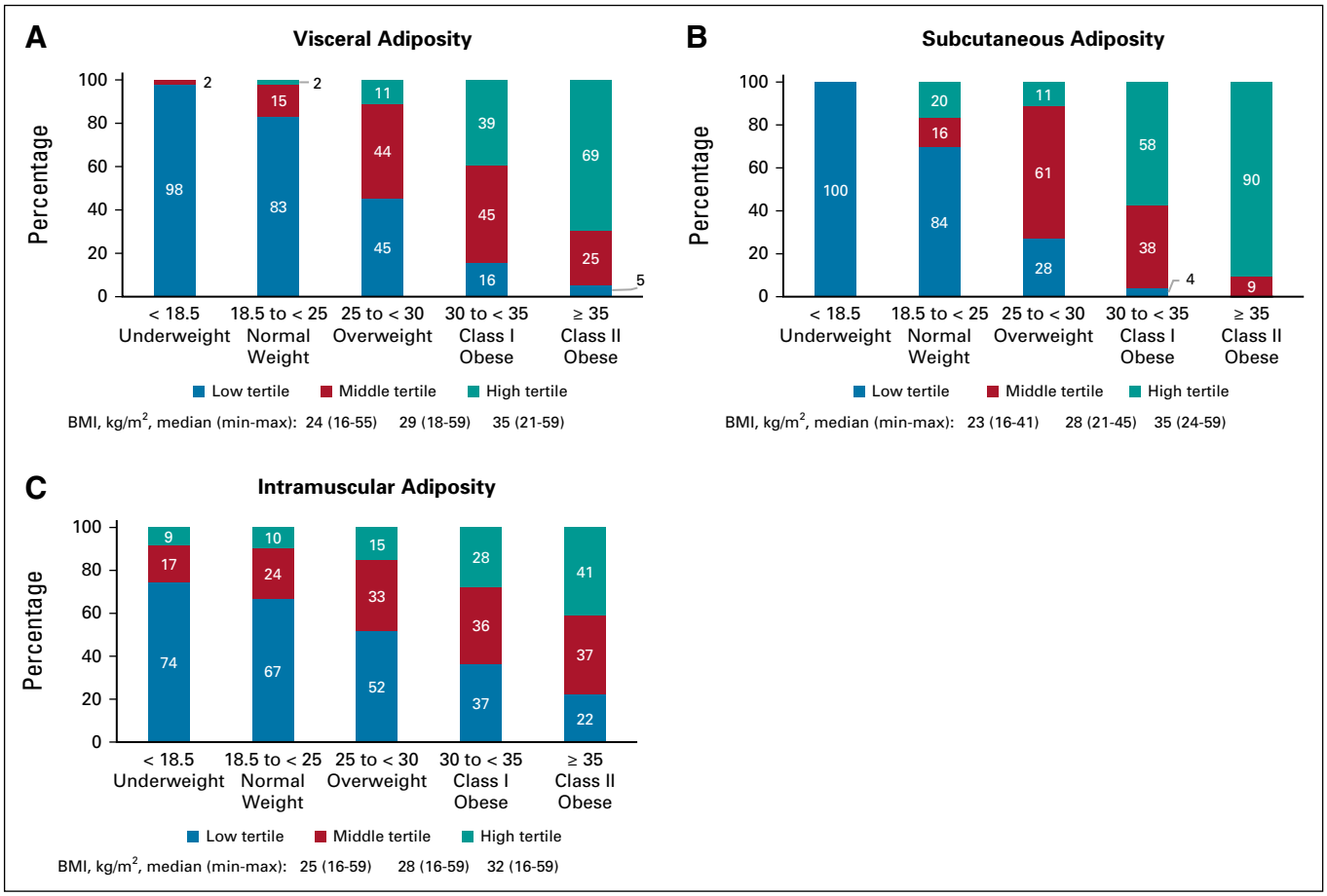

FIG 1. Specific adipose tissue depots within body mass index (BMI, kg/m^2) categories. Both visceral (A) and subcutaneous (B) adiposity increase with BMI. However, visceral adiposity in particular occurs across the BMI spectrum (eg, 2% of normal-weight and 11% of overweight patients in the highest tertile of visceral adiposity). Meanwhile, (C) intramuscular adiposity occurs in substantial numbers of patients in every BMI group (low muscle radiodensity). This novel cardiovascular disease risk factor is occult unless imaging methods such as computed tomography are used.

(*v* lowest) tertile of subcutaneous adiposity (HR, 1.31 [95% CI, 1.00 to 1.73]), and the continuous association per SD increase (HR, 1.11 [95% CI, 0.99 to 1.25]) was statistically nonsignificant. Associations with CVD subtypes followed a similar pattern, although estimates were imprecise given the smaller numbers of events (Data Supplement).

When we stratified analyses by BMI category (Table 4), we found that increasing visceral adiposity was most strongly associated with CVD risk among normal-weight women (HR, 1.70 [95% CI, 1.10 to 2.62] per SD). Effect estimates per SD subcutaneous and intramuscular adiposity among normal-weight women were similar to those in the overall sample, although CIs were wider (HR, 1.14 [95% CI, 0.66 to 1.95] per SD increase in subcutaneous adiposity and HR, 1.22 [95% CI, 0.89 to 1.67] per SD increase in intramuscular adiposity).

The association of adiposity with CVD risk did not vary by age, radiation, or chemotherapy type (Data Supplement). Additional adjustment for other treatment variables (endocrine and HER2-directed therapies) did not alter the association of adiposity with CVD (data not shown).

DISCUSSION

Among 2,943 survivors, we observed for the first time that visceral and intramuscular adiposity are associated with an increased CVD incidence after breast cancer. Furthermore, our data highlight visceral adiposity as an occult risk factor among normal-weight patients with breast cancer, who are not typically considered to have a high CVD risk: greater visceral adiposity was associated with a 70% increased CVD risk among normal-weight women independent of cancer treatments and preexisting risk factors such as diabetes, hypertension, or dyslipidemia.

BMI was also associated with an increased risk of CVD, but this became apparent only with class II obesity. The lack of association of overweight BMI with CVD risk is likely because BMI scales weight to height without distinguishing muscle from adipose tissue or describing adipose tissue distribution.[25-32] High BMI levels (eg, class II obesity) are a reasonable proxy for total adiposity. However, we found that, at lower BMI levels, body composition and therefore CVD risk is more heterogeneous. For example, 11% of

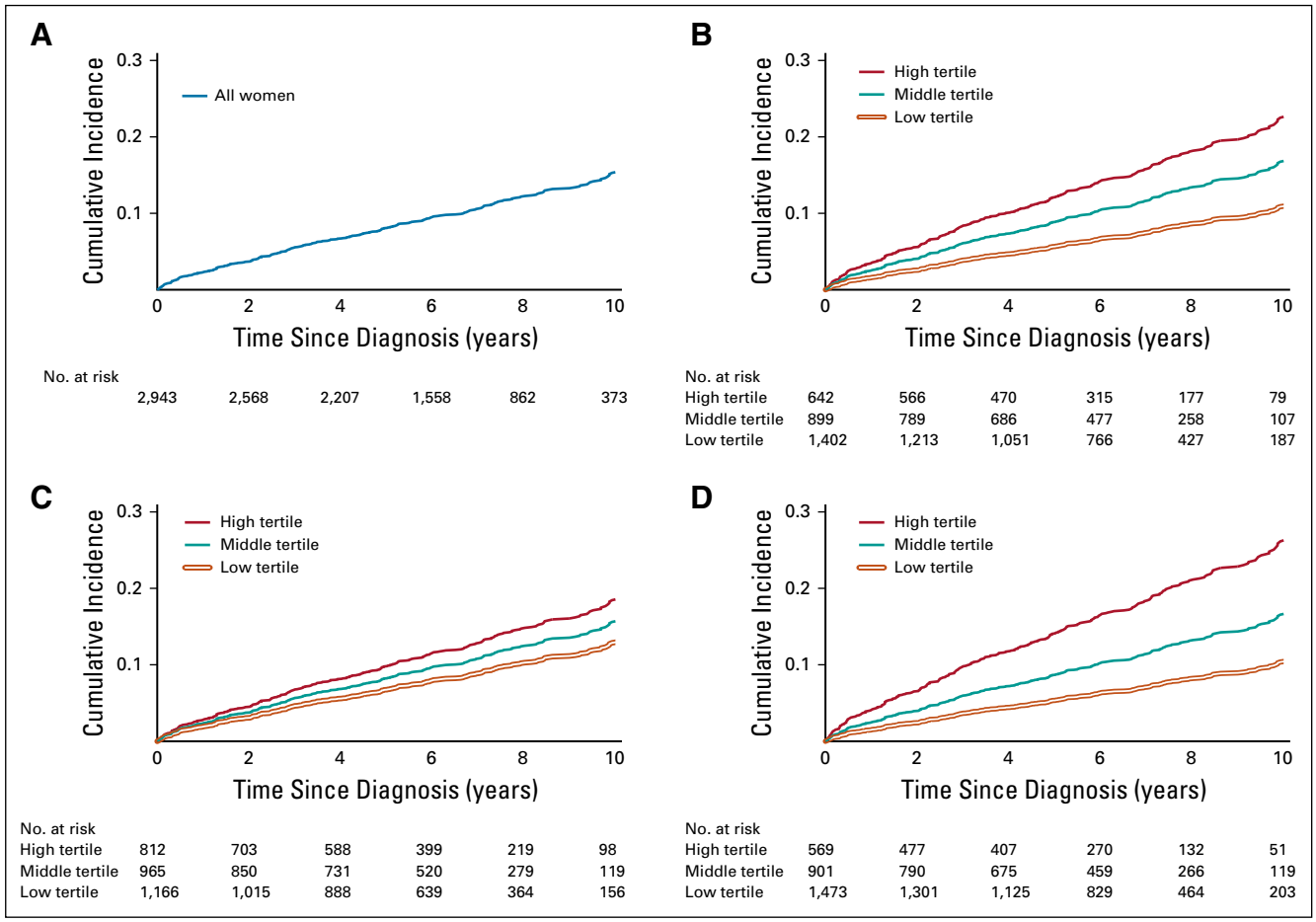

FIG 2. Incidence of cardiovascular events in the decade after a diagnosis of nonmetastatic breast cancer. Results from the Breast, Sarcopenia, Cancer and Near-Term Survival study (n = 2, 943). Overall, the cumulative incidence of cardiovascular disease increased steadily, exceeding 15% by year 10 of follow-up (A; cumulative incidence at year 10 = 0.15 [95% CI, 0.14 to 0.17]). Cardiovascular disease incidence was highest for women in the highest tertile of visceral (B; Gray's test $P = .01$), subcutaneous (C; Gray's test $P = .01$), and intramuscular (D; Gray's test $P \leq .001$) adiposity.

normal-weight women would be reclassified as high risk after consideration of their intramuscular and/or visceral adiposity. Thus, measures of adipose tissue distribution may be necessary to identify patients with breast cancer with high CVD risk.

Studies in patients without cancer have also shown that adipose tissue distribution outperforms BMI in identifying patients with cardiometabolic dysfunction. In addition, many patients with normal BMI have excess adiposity.[33-36] For example, using data from the National Health and

TABLE 2. Association of Body Mass Index Categories With Incident Cardiovascular Events

Body Mass Index	Underweight (< 18.5 kg/m^2)	Normal weight (18.5 to < 25 kg/m^2)	Overweight (25 to < 30 kg/m^2)	Obese Class I (30 to < 35 kg/m^2)	Obese Class II (≥ 35 kg/m^2)
kg/m^2, mean ± SD	17.68 ± 0.64	22.42 ± 1.71	27.35 ± 1.39	32.18 ± 1.40	39.78 ± 4.45
No. events/No. at risk	8/47	83/1,006	89/898	76/563	72/429
Hazard ratio (95% CI)	2.16 (1.06 to 4.43)	Reference	1.01 (0.75 to 1.37)	1.32 (0.95 to 1.83)	1.70 (1.20 to 2.42)

NOTE. Subdistribution hazard ratios are reported from models accounting for competing risks and are adjusted for age, race/ethnicity, cancer stage, estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 status, type of chemotherapy (none, anthracycline containing, or other), smoking history, diabetes, hypertension, and dyslipidemia. Test for trend across body mass index categories excludes underweight; *P*-trend = .001. Continuous, per SD association of body mass index with cardiovascular disease: subdistribution hazard ratio = 1.19 (95% CI, 1.06 to 1.34). Patients were considered to have experienced an incident cardiovascular event on the first date of the occurrence of any of the events of interest; first events included 36 acute myocardial infarctions, 95 ischemic strokes, 153 cases of heart failure, 33 intracranial hemorrhages, four coronary artery revascularizations, and seven deaths as a result of other cardiovascular disease–related causes.

TABLE 3. Association of Adiposity at Diagnosis With Incident Cardiovascular Events Accounting for Competing Risks

Body Composition	Tertile 1*	Tertile 2*	Tertile 3*	*P*-Trend†	Continuous per SD
Visceral adiposity					
Mean ± SD, cm^2	38 ± 24	118 ± 22	219 ± 53		103 ± 78
No. of events/No. at risk	109/1,402	110/899	109/642		328/2,943
Hazard ratio (95% CI)‡	Reference	1.22 (0.92 to 1.61)	1.42 (1.05 to 1.91)	.03	1.15 (1.03 to 1.29)
Subcutaneous adiposity					
Mean ± SD, cm^2	137 ± 43	250 ± 30	416 ± 93		251 ± 127
No. of events/No. at risk	109/1,166	110/965	109/812		328/2,943
Hazard ratio (95% CI)‡	Reference	1.15 (0.88 to 1.51)	1.31 (1.00 to 1.73)	.05	1.11 (0.99 to 1.25)
Intramuscular adiposity					
Mean ± SD, HU§	49 ± 6	37 ± 3	26 ± 5		41 ± 10
No. of events/No. at risk	110/1,473	109/901	109/569		328/2,943
Hazard ratio (95% CI)‡	Reference	1.17 (0.89 to 1.54)	1.39 (1.01 to 1.91)	.04	1.21 (1.06 to 1.37)

NOTE. Patients were considered to have experienced an incident cardiovascular event on the first date of the occurrence of any of the events of interest; first events included 36 acute myocardial infarctions, 95 ischemic strokes, 153 cases of heart failure, 33 intracranial hemorrhages, four coronary artery revascularizations, and seven deaths as a result of other cardiovascular disease–related causes

Abbreviation: HU, Hounsfield units.

*To maximize statistical efficiency, tertiles are derived according to the distribution among those who experienced an event.

†*P*-trend treats adiposity variables as continuous in their native units (cm^2 for visceral and subcutaneous adiposity and HU, scaled inversely, for intramuscular adiposity).

‡Subdistribution hazard ratios are reported from models accounting for competing risks and adjusted for age, race/ethnicity, height, estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 status, type of chemotherapy (none, anthracycline containing, or other), smoking history, diabetes, hypertension, and dyslipidemia.

§Lower muscle radiodensity in HU indicates greater intramuscular adiposity (more intramyocellular triglyceride). To report results in terms of greater adiposity, HU are scaled inversely in all multivariable models.

Nutrition Examination Survey, Sahakyan et al[37] reported that normal-weight central obesity was the body composition phenotype that carried the highest CVD risk: normal-weight women with a high waist-to-hip ratio (a proxy for visceral adiposity) had a higher risk of cardiovascular death than did normal-weight women without central obesity, and also a higher risk than obese women, according to BMI only. The need for precise measures of adipose tissue distribution is potentially greater among patients with breast cancer than among the general population because of aging and the high prevalence of comorbidities and deconditioning, known to influence adipose tissue distribution and to decrease BMI's sensitivity as a measure of total adiposity.[38,39] CT scans, already collected at diagnosis in many patients with breast cancer, can be used opportunistically to measure adipose tissue distribution and thereby improve the identification of those with high CVD risk. Although our analyses used trained research assistants, automated methods to measure body composition using CT scans are increasingly available and have excellent correlation and similarity metrics relative to manual analysis by a trained rater.[40-42]

In patients without cancer, a limited number of prospective studies have examined adipose tissue depots and incident CVD; consistent with our findings, associations with CVD were typically stronger for visceral and intramuscular adiposity than for subcutaneous adiposity.[6-11] This is likely because visceral and intramuscular adiposity directly promote metabolic dysfunction and inflammation and are reflective of anatomic and functional disturbances in adipose tissue.[43] Subcutaneous adipose tissue is the body's primary energy store. In the obese state, excess energy overloads subcutaneous adipose tissue stores. Once no additional lipid can be accommodated in subcutaneous adipose tissue, excess lipid and adipose tissue accumulates in abnormal depots, such as intramuscular and visceral adipose depots.[43] Intramuscular and visceral adiposity help promote a cascade of changes that increase CVD risk: lipotoxic free fatty acid delivery to nonadipose organs (eg, muscle, liver, and pancreas), insulin resistance,[20] type 2 diabetes,[12] and inflammation.[44]

Examining whether adiposity increases CVD incidence after breast cancer is clinically important because CVD is an important source of morbidity and mortality after a breast cancer diagnosis.[45] Breast cancer therapies have direct and indirect effects that may promote heart failure, arrhythmias, valvular heart disease, and accelerated atherosclerosis.[46] Anthracycline-containing regimens are associated with acute and long-term cardiac toxicity.[47] Aromatase inhibitors can result in weight gain and altered lipid profiles,[48] and there are documented declines in physical activity after breast cancer diagnosis.[49] The association of adiposity with CVD risk did not vary by chemotherapy type in this study, possibly because clinicians

TABLE 4. Association of Adiposity at Diagnosis Within Body Mass Index Categories With Incident Cardiovascular Events Accounting for Competing Risks

	Normal Weight (18.5 to < 25 kg/m^2)	Overweight (25 to < 30 kg/m^2)	Obese Class I (30 to < 35 kg/m^2)	Obese Class II (≥ 35 kg/m^2)
No. of events/No. at risk*	83/1,006	89/898	76/563	72/429
Hazard ratio per continuous SD				
Visceral adiposity				
Mean ± SD, cm^2	46 ± 40	96 ± 51	147 ± 61	201 ± 78
Hazard ratio (95% CI)†	1.70 (1.10 to 2.62)	0.91 (0.65 to 1.26)	0.89 (0.63 to 1.26)	1.12 (0.82 to 1.52)
Subcutaneous adiposity				
Mean ± SD, cm^2	148 ± 54	237 ± 60	326 ± 79	445 ± 116
Hazard ratio (95% CI)†	1.14 (0.66 to 1.95)	0.85 (0.55 to 1.32)	0.92 (0.62 to 1.35)	0.94 (0.66 to 1.34)
Intramuscular adiposity				
Mean ± SD, HU ‡	45 ± 9	41 ± 9	38 ± 9	34 ± 9
Hazard ratio (95% CI)†	1.22 (0.89 to 1.67)	1.12 (0.84 to 1.50)	1.20 (0.90 to 1.61)	1.00 (0.72 to 1.39)

NOTE. Patients were considered to have experienced an incident cardiovascular event on the first date of the occurrence of any of the events of interest.

Abbreviation: HU, Hounsfield units.

*Underweight patients are excluded from this analysis because of small numbers (eight events and 47 patients), precluding multivariable adjustment.

†Subdistribution hazard ratios are reported from models accounting for competing risks and adjusted for age, race/ethnicity, height, estrogen receptor/progesterone receptor/human epidermal growth factor receptor 2 status, type of chemotherapy (none, anthracycline containing, or other), smoking history, diabetes, hypertension, and dyslipidemia.

‡Lower muscle radiodensity in HU indicates greater intramuscular adiposity (more intramyocellular triglyceride). To report results in terms of greater adiposity, HU are scaled inversely in all multivariable models.

already consider patients' cardiovascular history when prescribing chemotherapy. Furthermore, our study was limited to women with CT scans without a history of CVD at diagnosis to avoid the influence of pre-existing CVD before diagnosis. Therefore, most women received chemotherapy (62% of these regimens contained anthracyclines). With most patients receiving chemotherapy, we may have been underpowered to detect whether the associations differed by the type of chemotherapy received.

Importantly, adipose tissue distribution is modifiable among patients with breast cancer and should be a priority target for preventive interventions regardless of weight loss. Interventions such as aerobic exercise and resistance training are effective for reducing overall, visceral, and intramuscular adiposity,[50] are safe in patients with breast cancer (including those on active treatment),[51] and have beneficial effects on CVD risk factors.[52] For some patients, pharmacologic management of CVD risk factors should also be considered.

Our study was enabled by the comprehensive EMR, but there are also important limitations that result from our use of EMR data. For example, physical activity information was not collected routinely at clinical visits until 2006 and thus is not included as a covariate. Furthermore, we did not confirm CVD outcomes via medical record review in the current study but instead defined CVD conservatively from ICD codes and death certificates validated in prior studies.[53] In addition, CT scans were not available for all women. Among otherwise eligible women diagnosed with invasive breast cancer at KPNC, 36% of stage II and 77% of stage III women had scans. However, this is unlikely to have induced substantial bias because women with (*v* without) scans were slightly younger (mean age, 55 years *v* 58 years at diagnosis), the 10-year cumulative incidence of the CVD events examined was similar, and there were no differences in BMI or race/ethnicity.

To our knowledge, this is the first study to demonstrate that adipose tissue distribution is associated with incidence of new CVD events after a breast cancer diagnosis, including among patients with a normal BMI. Body composition may be useful in identifying CVD risk in these women, who may be sedentary or have metabolic disturbances that have not yet reached clinical thresholds for dyslipidemia, hypertension, or diabetes. Prior research among breast cancer survivors has examined only CVD mortality and BMI or waist circumference, surrogate measures of overall and central adiposity, without including nonfatal CVD events or body composition data.[54,55] Our study provides new evidence to help identify patients with breast cancer at high CVD risk during and after treatment and suggests that adipose tissue distribution may improve on BMI for risk stratification.

Although it has been assumed that excess adiposity increases the risk of CVD after breast cancer, this first-of-its-kind study demonstrates that adipose tissue distribution

best identifies patients with breast cancer with higher CVD risk after diagnosis, including those with normal BMI. Specifically, visceral and intramuscular adiposity were associated most strongly with CVD risk. Software is now available that automatically measures body composition from clinically acquired CT scans, facilitating clinical integration. Measures of adipose tissue distribution from CT or anthropometry (eg, waist circumference) may help identify individuals with high CVD risk and tailor prevention efforts to patients' body composition.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adipose Tissue Distribution and Cardiovascular Disease Risk Among Breast Cancer Survivors

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