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Article

Abdominal visceral and subcutaneous adipose tissue associations with postmenopausal breast cancer incidence

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Abstract

Background: Obesity, classified by body mass index (BMI), is associated with higher postmenopausal breast cancer (BCa) risk. Yet, the associations between abdominal visceral (VAT) and subcutaneous adipose tissue (SAT) with BCa are unclear.

Methods: We assessed BCa associations with abdominal VAT and SAT in a prospective cohort of postmenopausal women without a history of cancer and with 27 years follow-up (N = 9950), during which all new cancers were adjudicated. Dual-energy x-ray absorptiometry scans assessed adiposity at baseline, year 3, and year 6. Competing-risks multivariable sub-hazard ratios (SHR), with adjustments for sociodemographic, behavioral, reproductive, and anthropometric characteristics, were estimated for baseline and time-dependent associations between VAT, SAT, and incident BCa.

Results: Participants averaged 63.3 ± 7.4 years of age and a BMI of 28.20 ± 5.72 kg/m^2 at baseline. The models included 738 incident BCa case patients (N = 593 invasive; N = 145 in situ). Baseline VAT and SAT area were associated with statistically significantly increased BCa risk, by 36% and 19%, respectively. Increasing VAT/SAT ratio was associated with an 8% increase in incident BCa. Time-dependent models produced similar results. VAT and VAT/SAT associated BCa risk was highest for African American/Black women, although not statistically significantly different from other groups. Quartiles (Q) of VAT/SAT were also explored; the SHR for Q4 compared with Q1 was 1.49 (95% CI = 1.18 to 1.87).

Conclusion: Higher abdominal VAT and SAT are associated with an increased risk of postmenopausal BCa, and VAT/SAT may provide a distinctive risk estimate. Potential racial and ethnic differences require replication in a larger sample (Women's Health Initiative; NCT00000611; https://clinicaltrials.gov/study/NCT00000611).

Introduction

Obesity is associated with increased risk of postmenopausal breast cancer (BCa), the leading cancer among women in the United States.[1] Forty percent of the US adult population is categorized as obese by body mass index (BMI),[2-4] and yet BMI may not characterize the degree or type of adipose tissue well in postmenopausal women.[5-8] Even postmenopausal women classified as "normal weight" have wide-ranging total body fat.[9] Further, normal-weight women of the Women's Health Initiative (WHI) who were assessed by dual-energy x-ray absorptiometry (DXA)

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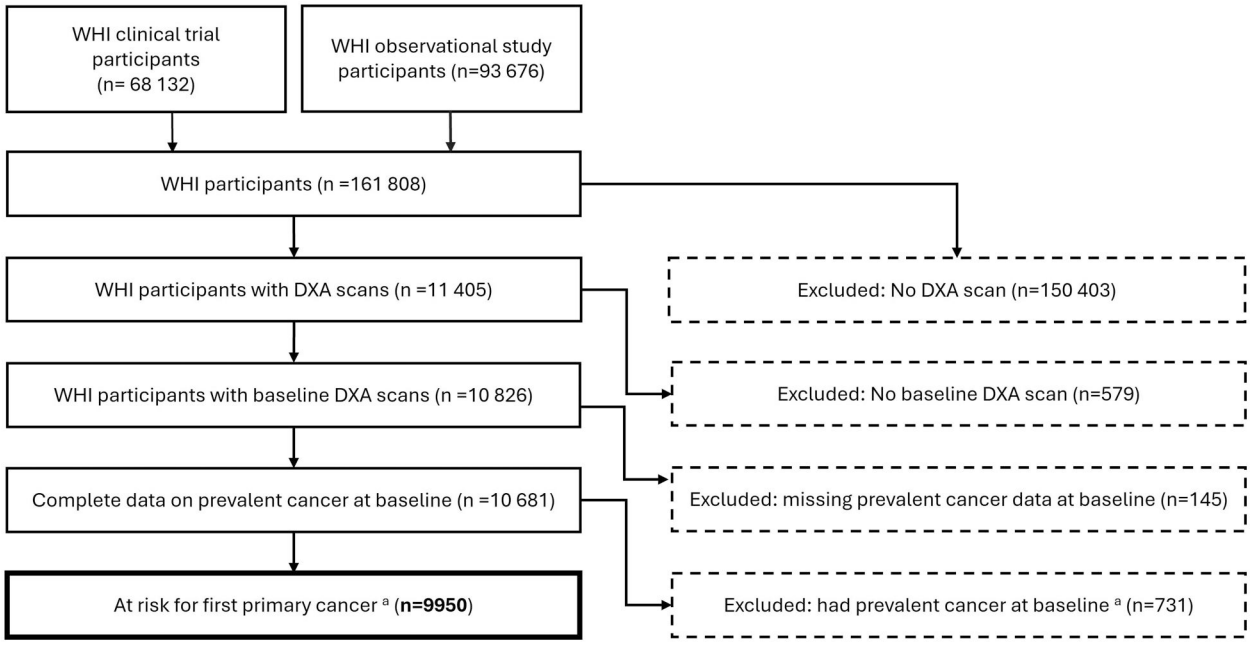

Figure 1. CONSORT diagram of postmenopausal women in the Women's Health Initiative (WHI) included in the analyses of first incidence of breast cancer related to body composition. [a]Cancer includes all types of cancer reported in WHI except nonmelanoma skin cancer. Abbreviation: DXA = dual-energy X-ray absorptiometry.

had an increased hazard ratio (HR) for BCa incidence in the highest quartile of total body fat, at 1.89 (95% CI = 1.21 to 2.95).[10] This exceeds the previously published HR for BMI defined obesity (≥30kg/m^2).[11] Therefore, understanding the relationship between BCa and directly measured adipose tissue is paramount.

Elevated adipose tissue is particularly problematic postmenopause, due to its role in estrogen production and the influence of estrogen on breast tumor development and progression.[12] Abdominal visceral adipose tissue (VAT) deposition accelerates with menopause[12,13] and is increasingly characterized as more deleterious compared with subcutaneous adipose tissue (SAT) due to its influence on metabolic, immune, and inflammatory biomarkers,[14-18] all of which are hallmarks of cancer.[19] Systematic reviews on obesity and cancer risk have emphasized the need for repeat measures of adipose tissue depots over time to advance etiological understanding.[12,20] Recently generated VAT and SAT values derived from historical WHI DXA scans have the potential to further elucidate the importance of adipose tissue type in relation to BCa risk.

Associations between anthropometric, total body, trunk, and predicted VAT (eVAT) measures of adiposity and risk of breast cancer have been examined.[21-23] Still, direct measures of abdominal VAT and SAT have been unavailable in a large prospective sample of usual-risk women. Further, studies that have examined measured VAT and SAT related to BCa have been in cancer survivorship, not the prevention setting.[21,22] The WHI provided a unique opportunity to examine repeat measures of DXA-derived VAT and SAT over 6 years of follow-up, with adjudicated BCa incidence data over 27 years. We sought to determine if these abdominal sub-compartment measures were associated with BCa incidence among postmenopausal women. We hypothesized that VAT was a key determinant of BCa risk.

Methods

Sample

The WHI (N = 161 808) enrolled postmenopausal women into 4 clinical trials and an observational study (OS) at 40 clinics across the United States between 1993 and 1998 (NCT00000611).[24] Participants at sites in Tucson/Phoenix, AZ, Pittsburgh, PA, and Birmingham, AL, received DXA scans in addition to other study measures, regardless of clinical trial or OS enrollment (N = 11 405). Women missing valid baseline DXA scans (N = 579), data on prevalent cancers (N = 145), or those who had a prestudy history of cancer at baseline (except nonmelanoma skin cancer; N = 731) were excluded from the final sample of N = 9950 (Figure 1).

Outcomes

Cancer outcomes and deaths were identified annually by self-report via telephone, questionnaire, or in-person using standard procedures. Participants reporting BCa were asked to provide consent for medical record review, and breast events were classified as ductal carcinoma in situ (DCIS) or invasive BCa if a pathology report substantiated a malignant primary invasive cancer.[25] Pathology reports from diagnostic aspirations, biopsies, surgeries, and the discharge summary were used to further characterize BCa. The local adjudicator coded the primary cancer site based on ICD-O-2 codes, BCa subtype, and tumor behavior (eg, invasive, in situ). Tumor size, lymph node involvement, and local vs regional/distant disease were considered markers of severity in the analyses.

Primary exposure: Body composition

Whole-body DXA scans were completed at baseline, year 3, and year 6 to assess total and regional body composition at the time of visit (QDR2000, 2000+, 4500 W models and software v12.1, Hologic, Inc, Bedford, MA).[9,26] Scans were reanalyzed using new software (APEX 4.0) to quantify abdominal depots, which was not originally available at time of visits.[27] The software selected a 5 cm high, torso-wide region of interest at approximately the fourth lumbar vertebra, and then a trained technician manually adjusted lines of demarcation, as needed, to distinguish lateral subcutaneous adipose and abdominal muscle as well as the visceral cavity areas. Proprietary Hologic algorithms then quantified

abdominal VAT, SAT, and total adipose tissue (TAT) (cm^2).[27] Correlations between criterion magnetic resonance imaging (MRI) and DXA measured VAT and SAT were 0.90 and 0.92, respectively ($P \leq .001$).[27] Continuous model results are reported per 100 cm^2 (10 cm by 10 cm square) to roughly align with quartiles of VAT and SAT and to provide units large enough to be clinically meaningful.

Covariates

Sociodemographic characteristics, including age, race and ethnicity, education, and income, were self-reported at baseline. A validated, self-administered questionnaire was used to assess physical activity and compute metabolic equivalents (MET-h/wk)[28-30]; time points aligned with DXA scans were used. Diet quality was assessed using a validated food frequency questionnaire and subsequent computation of the Healthy Eating Index (HEI-2015)[31-33] at baseline and additionally in year 3 for OS participants. Baseline self-reported alcohol intake was used to create categories of never, past, minimal (<1 drink/week), moderate (1 to <7 drinks/week), and heavy (7+ drinks/week) intake. Smoking status was classified as never, former, and current. Updated smoking information was obtained at years 1, 3, and 6. Reproductive factors, including oral contraceptive (OCP), hormone therapy (HT) use, family history of BCa, age at menarche, age at first birth, and breastfeeding history, were collected by self-report at baseline. OCP was categorized as use (ever) vs no use at baseline. Women were classified as current, past, and never users of HT.[9,34] Randomization to HT, calcium and vitamin D, and dietary modification clinical trial arms was recorded. Other medications, such as metformin and history of diabetes, were assessed by self-report. Surgical menopause was defined by self-reported hysterectomy. Mammographic screening compliance was calculated from self-reported mammograms from baseline and questionnaires from ages 50 to 75. Anthropometric covariates included clinic-measured weight, height, and waist circumference (WC). Body mass index was calculated as weight (kg)/height(m)^2, and skeletal muscle index (SMI) was calculated at DXA-derived appendicular lean soft tissue (kg)/height(m)^2.

Data analysis

Descriptive statistics were calculated and compared by VAT quartiles using t tests for continuous and χ^2 tests for categorical variables (or nonparametric tests as appropriate). Spearman rank correlations for VAT and SAT were computed within BMI category.

To evaluate the association between first incident BCa and baseline VAT and SAT, we used competing-risks regression (based on Fine and Gray's proportional sub-hazards model).[35] The competing-risk regression accounts for the risk of the event being influenced by the presence of other events.[35] Thus, we created a 3-level outcome variable: (1) survived cancer-free to last contact (censored), (2) developed BCa as the first incident cancer type observed (event), (3) developed another type of cancer first or died before developing cancer (competing risks). Time since WHI baseline was the underlying time metric. The outcome of first incident BCa was selected because cancer and cancer treatment are associated with both changes in body composition and risk of second cancers. In exploratory analyses, we also examined severity and tumor characteristic outcomes (see Supplementary Methods definitions).

We fit a series of 3 models for each primary exposure, with the primary model being multivariable-adjusted (Model 1). Two sensitivity models were fitted, including the multivariable-adjusted model plus either body mass index (BMI; Model 2) or skeletal muscle index (SMI; Model 3) due to prevalence in the literature, although not featured due to potential confounding (Spearman rank correlations: BMI and VAT = 0.82, SAT = 0.89; SMI and VAT = 0.52, SAT = 0.54, $P_{all} < .00001$). Waist was not included in models (Spearman rank correlation VAT 0.66; SAT 0.72). The following sensitivity analyses did not affect the results, so were not presented: inclusion of diabetes or mammography compliance, exclusion of DCIS, incident BCa within the first 2 years of follow-up, or when using age at last follow-up instead of age at baseline. There was no statistically significant interaction between age, HT use, race and ethnicity, or BMI and VAT or SAT; thus, interaction terms were not included. However, to enhance clinical relevance, stratified analyses by age, race and ethnicity, and BMI category were conducted. Age, race and ethnicity, and BMI were removed as covariates in respective stratified models. For BCa subtype analyses, the primary subtype in a given model was the outcome and the other subtypes were considered competing risks. The severity of BCa at the time of diagnosis was examined.

Time-varying body composition models were similarly constructed with body composition measurements at baseline, Y3, and Y6 used, and covariates were used as available by the time points described above.

Multiple imputation using chained equations (MICE—also known as sequential generalized regression) with predictive mean matching was used to impute missing variables. In baseline analyses 3664 participants had missing data; therefore, the covariates education (n = 64), income (n = 734), race and ethnicity (n = 374), height at baseline (n = 22), alcohol intake (n = 82), smoking status (n = 132), physical activity (MET-h/wk; n = 964), physical function (RAND-36 instrument; n = 218), total energy intake (kcal/day; n = 22), HEI-2015 score (n = 22), HT use at baseline (n = 5), first degree female relative with breast cancer (n = 444), age at first birth (n = 960), age at menarche (n = 38), total number of months of breastfeeding (n = 134), age at menopause (n = 991), and surgical menopause (n = 991) were imputed when missing. In time-varying analyses, abdominal adipose variables were additionally imputed for years 3 (n = 2456) and 6 (n = 3057), when missing.

Data were analyzed using Stata 18 (StataCorp, College Station, TX) and SAS 9.4 (SAS Institute, Inc, Cary, NC). A type I error rate of 0.05 and 2-sided tests were used for all analyses.

Results

A total of 738 women developed BCa (invasive [N = 593] and in situ BCa [N = 145]) as the first primary cancer during 177 295 years of total follow-up time. A total of 1280 women developed another type of first primary cancer, 3384 women died without a cancer diagnosis, and 4548 were alive without cancer at last follow-up (n = 9950).

At enrollment, women with lower VAT, by quartile, were more likely to be younger, non-Hispanic, highly educated, with higher income, physically active, have greater physical function, and have lower total energy intake (Table 1). Women with lower VAT were also younger at age of menarche, older at age of first birth and menopause, more likely to be current HT users, and did not use OCP. Women with higher VAT had higher BMI, WC, total body fat, SAT, TAT, the ratio of VAT to SAT, total-body lean soft tissue mass, and appendicular lean soft tissue mass. Women who developed BCa had higher BMI, total body fat, android fat,

Table 1. Baseline demographic characteristics of DXA cohort participants, stratified by VAT quartiles (mean ± SD or N [column %], as appropriate).

	VAT Quartile				
Variable	**Q1 (n = 2487)**	**Q2 (n = 2488)**	**Q3 (n = 2488)**	**Q4 (n = 2487)**	***P***
Breast Cancer case patients (n = 738)	139 (18.83%)	199 (26.96%)	170 (23.04%)	230 (31.17%)	<.0001
Age at baseline, years	62.70 ± 7.63	63.23 ± 7.37	63.65 ± 7.26	63.41 ± 7.20	<.0001
Ethnicity: Hispanic or Latina	100 (4.02%)	161 (6.47%)	201 (8.08%)	212 (8.52%)	<.0001
Race					
American Indian or Alaska Native	19 (0.76%)	19 (0.76%)	40 (1.61%)	77 (3.10%)	<.0001
Asian or Pacific Islander[a]	[a]	[a]	[a]	[a]	<.0001
African American/Black	224 (9.01%)	362 (14.55%)	429 (17.24%)	429 (17.24%)	<.0001
White	2194 (88.22%)	2024 (81.35%)	1913 (76.89%)	1922 (77.28%)	<.0001
Education					<.0001
Less than high school (includes no education)	99 (3.98%)	190 (7.64%)	263 (10.57%)	334 (13.43%)	
High school or GED completed	495 (19.90%)	581 (23.35%)	601 (24.16%)	597 (24.00%)	
Vocational training, technical school, or some college	874 (35.14%)	931 (37.42%)	955 (38.38%)	958 (38.52%)	
College degree	290 (11.66%)	215 (8.64%)	169 (6.79%)	149 (5.99%)	
Some postgraduate or professional school	269 (10.82%)	209 (8.40%)	182 (7.32%)	174 (7.00%)	
Graduate degree	452 (18.17%)	342 (13.75%)	299 (12.02%)	258 (10.37%)	
Income					<.0001
Less than $20 000	422 (16.97%)	536 (21.54%)	719 (28.90%)	792 (31.85%)	
$20 000 to $34 999	624 (25.09%)	625 (25.12%)	639 (25.68%)	712 (28.63%)	
$35 000 to $49 999	451 (18.13%)	487 (19.57%)	422 (16.96%)	381 (15.32%)	
$50 000 to $74 999	425 (17.09%)	405 (16.28%)	312 (12.54%)	263 (10.57%)	
$75 000 and greater	384 (15.44%)	276 (11.09%)	193 (7.76%)	148 (5.95%)	
Anthropometry					
BMI category					<.0001
Underweight (<18.5)[b]	[b]	[b]	[b]	[b]	
Normal (18.5-24.9)	1970 (79.21%)	967 (38.87%)	208 (8.36%)	22 (0.88%)	
Overweight (25.0-29.9)	424 (17.05%)	1248 (50.16%)	1332 (53.54%)	494 (19.86%)	
Obesity I (30.0-34.9)	12 (0.48%)	222 (8.92%)	734 (29.50%)	1008 (40.53%)	
Obesity II (35.0-39.9)	[c]	27 (1.09%)	154 (6.19%)	627 (25.21%)	
Extreme obesity III (≥40)	[c]	13 (0.52%)	54 (2.17%)	331 (13.31%)	
BMI, kg/m^2	22.81 ± 2.53	26.24 ± 3.27	29.51 ± 3.98	34.26 ± 5.14	<.0001
Waist circumference, cm	72.19 ± 5.98	80.90 ± 6.72	89.28 ± 7.62	101.04 ± 9.94	<.0001
DXA body composition					
VAT, cm^2	70.30 ± 24.98	132.50 ± 15.04	186.37 ± 16.49	276.89 ± 52.01	<.0001
SAT, cm^2	233.92 ± 74.28	349.13 ± 85.30	427.37 ± 99.74	512.77 ± 107.30	<.0001
TAT, cm^2	304.21 ± 93.61	481.62 ± 90.83	613.73 ± 104.10	789.66 ± 130.48	<.0001
VAT to SAT ratio	0.30 ± 0.08	0.40 ± 0.08	0.46 ± 0.11	0.56 ± 0.12	<.0001
Total body fat, %	35.95 ± 6.12	43.00 ± 4.77	46.49 ± 4.63	50.08 ± 4.71	<.0001
Total body fat, kg	21.30 ± 5.60	29.08 ± 6.46	35.42 ± 7.78	44.66 ± 10.15	<.0001
Android fat, kg	1.19 ± 0.46	2.08 ± 0.49	2.84 ± 0.63	4.02 ± 0.97	<.0001
Gynoid fat, kg	4.25 ± 1.12	5.20 ± 1.32	5.95 ± 1.53	7.06 ± 1.85	<.0001
Trunk fat, kg	8.30 ± 2.64	13.05 ± 2.64	16.82 ± 3.24	22.39 ± 4.84	<.0001
Total body lean, kg	35.29 ± 3.92	36.07 ± 4.43	38.17 ± 4.97	41.60 ± 5.71	<.0001
Appendicular lean, kg	13.37 ± 1.93	13.92 ± 2.29	15.07 ± 2.62	16.79 ± 3.00	<.0001
Skeletal muscle index, kg/m^2	5.10 ± 0.62	5.34 ± 0.77	5.77 ± 0.90	6.41 ± 1.03	<.0001
Physical activity, MET-hours/week	15.89 ± 16.18	12.12 ± 13.86	9.62 ± 12.00	7.87 ± 10.91	<.0001
Physical function (RAND 36 score)	86.41 ± 16.16	82.15 ± 18.97	76.42 ± 21.65	69.28 ± 23.56	<.0001
Total energy intake, kcal/day	1548.64 ± 698.58	1589.45 ± 725.67	1685.86 ± 830.22	1797.42 ± 904.39	<.0001
HEI-2015 score	66.94 ± 10.27	64.39 ± 10.41	62.30 ± 10.63	60.29 ± 10.22	<.0001
Smoking status					0.0004
Never	1343 (54.00%)	1363 (54.78%)	1388 (55.79%)	1304 (52.43%)	
Former	879 (35.34%)	918 (36.90%)	862 (34.65%)	977 (39.28%)	
Current	235 (9.45%)	180 (7.23%)	201 (8.08%)	168 (6.76%)	
Alcohol intake					<.0001
Nondrinker	344 (13.83%)	393 (15.80%)	435 (17.48%)	507 (20.39%)	
Past drinker	425 (17.09%)	497 (19.98%)	572 (22.99%)	667 (26.82%)	
Minimal, <1 drink per week	766 (30.80%)	832 (33.44%)	840 (33.76%)	770 (30.96%)	
Moderate, 1 to <7 drinks per week	678 (27.26%)	537 (21.58%)	439 (17.64%)	384 (15.44%)	
Heavy, 7+ drinks per week	255 (10.25%)	216 (8.68%)	175 (7.03%)	136 (5.47%)	
Age at menarche					<.0001
10 or less	112 (4.50%)	128 (5.14%)	158 (6.35%)	187 (7.52%)	
11-12	923 (37.11%)	988 (39.71%)	981 (39.43%)	1076 (43.26%)	
13-14	1134 (45.60%)	1091 (43.85%)	1042 (41.88%)	942 (37.88%)	
15+	306 (12.30%)	272 (10.93%)	300 (12.06%)	272 (10.94%)	
Age at first birth					<.0001
<20	279 (11.22%)	409 (16.44%)	447 (17.97%)	529 (21.27%)	
20-29	1528 (61.44%)	1408 (56.59%)	1388 (55.79%)	1332 (53.56%)	
30+	154 (6.19%)	149 (5.99%)	139 (5.59%)	156 (6.27%)	

(continued)

Table 1. (continued)

Variable	VAT Quartile Q1 (n = 2487)	Q2 (n = 2488)	Q3 (n = 2488)	Q4 (n = 2487)	P
Number of live births					<.0001
Never pregnant	246 (9.89%)	226 (9.08%)	192 (7.72%)	185 (7.44%)	
None	66 (2.65%)	60 (2.41%)	66 (2.65%)	53 (2.13%)	
1	257 (10.33%)	242 (9.73%)	191 (7.68%)	205 (8.24%)	
2-4	1627 (65.42%)	1628 (65.43%)	1567 (62.98%)	1499 (60.27%)	
5+	274 (11.02%)	319 (12.82%)	463 (18.61%)	524 (21.07%)	
Breastfed any children					.009
Yes	1324 (53.24%)	1325 (53.26%)	1409 (56.63%)	1404 (56.45%)	
No	1137 (45.72%)	1133 (45.54%)	1053 (42.32%)	1046 (42.06%)	
Total number of months of breastfeeding					0003
Never breastfed	1138 (45.76%)	1137 (45.70%)	1059 (42.56%)	1051 (42.26%)	
1-6 months	653 (26.26%)	679 (27.29%)	701 (28.18%)	705 (28.35%)	
7-12 months	297 (11.94%)	299 (12.02%)	298 (11.98%)	282 (11.34%)	
13-23 months	230 (9.25%)	206 (8.28%)	227 (9.12%)	210 (8.44%)	
24+ months	138 (5.55%)	133 (5.35%)	173 (6.95%)	200 (8.04%)	
Age at menopause	48.35 ± 6.12	47.51 ± 6.78	47.40 ± 6.89	46.87 ± 7.33	<.0001
Menopause category					<.0001
Unknown: missing menopause age, no hysterectomy	111 (4.46%)	121 (4.86%)	145 (5.83%)	171 (6.88%)	
Natural menopause, age <50 years	638 (25.65%)	580 (23.31%)	588 (23.63%)	549 (22.07%)	
Natural menopause, age 50+ years	924 (37.15%)	798 (32.07%)	772 (31.03%)	691 (27.78%)	
Surgical menopause, age <50 years	478 (19.22%)	601 (24.16%)	582 (23.39%)	646 (25.98%)	
Surgical menopause, age 50+ years	258 (10.37%)	295 (11.86%)	294 (11.82%)	265 (10.66%)	
Menopause age unknown, hysterectomy age <50 years	78 (3.14%) [c]	92 (3.70%) [c]	107 (4.30%) [c]	165 (6.63%) [c]	
Menopause age unknown, hysterectomy age 50+ years					
Hormone therapy use					<.0001
Never	1010 (40.61%)	1057 (42.48%)	1238 (49.76%)	1416 (56.94%)	
Former	354 (14.23%)	393 (15.80%)	413 (16.60%)	411 (16.53%)	
Current	1122 (45.11%)	1037 (41.68%)	834 (33.52%)	660 (26.54%)	
Oral contraceptive use					<.0001
Yes	1008 (40.53%)	953 (38.30%)	932 (37.46%)	816 (32.81%)	
No	1479 (59.47%)	1535 (61.70%)	1556 (62.54%)	1671 (67.19%)	
Family history of cancer					.90
Female relative with any cancer	1104 (44.39%)	1133 (45.54%)	1101 (44.25%)	1134 (45.60%)	
Female relative with breast cancer	390 (15.68%)	402 (16.16%)	397 (15.96%)	405 (16.28%)	
Male relative with any cancer	848 (34.10%)	826 (33.20%)	813 (32.68%)	829 (33.33%)	

[a] Asian and Pacific Islander group is not reported in detail by case status due to small cell sizes. In the total sample there were 2 Asian Indian, 11 Chinese, 4 Filipino, 6 Japanese, 1 Korean, and 13 Other Asian women. There were 83 women who identified as more than one race; totals for all race categories will exceed 100% because participants reported all races they identified as.
[b] There were 75 women in the underweight BMI group, and due to small sizes the number per group are redacted.
[c] Cell sizes not reported due to small sizes.
Abbreviations: DXA = dual energy X-ray absorptiometry; GED = general education development; HEI = Healthy Eating Index; MET-h = metabolic equivalent task hours; SAT = subcutaneous adipose tissue; TAT = total adipose tissue (in the abdominal region of interest); VAT = visceral adipose tissue.

gynoid fat, trunk fat, VAT, SAT, total body lean soft tissue mass, and appendicular lean soft tissue mass at baseline (Table S1).

VAT and SAT were strongly, positively correlated in underweight (0.94) and normal weight classes (0.80), whereas overweight, Obesity Class I, II, and III correlations were 0.47, 0.11, −0.09, and −0.33, respectively ($P_{all} \leq .01$). Non-Hispanic African American/Black women had a lower mean VAT/SAT (0.39 ± 0.11) than non-Hispanic White women (0.43 ± 0.14) and Hispanic women (0.45 ± 0.12) (not presented).

Overall and stratified models are presented in Figure 2. Higher VAT and SAT were each statistically significantly associated with higher BCa risk in multivariable-adjusted models. Per 100 cm^2 increase, VAT was associated with 36% and SAT with a 19% increased risk of BCa (Model 1). The TAT estimates were similar to those for SAT (not presented). Higher VAT/SAT was associated with an 8% higher risk for BCa in the continuous model (per one-tenth increase in VAT/SAT ratio). A stepwise pattern for VAT/SAT quartile associations with BCa risk emerged; that was not true of VAT and SAT separately. However, quartile 4 of VAT was associated with the greatest increase in BCa risk overall (SHR = 2.21, 95% CI = 1.69 to 2.65).

Confidence intervals overlapped in the stratified analyses, indicating no statistically significant differences between demographic, tumor subtype, and cancer severity strata. However, VAT-associated BCa risk was highest for African American/Black women (65% higher risk per 100 cm^2 increase in VAT), whereas SAT associated risk was highest for Hispanic/Latina women (55% higher risk per 100 cm^2 increase in SAT); these differences persisted in VAT/SAT models. Importantly, in BMI stratified models, there was a statistically significantly increased risk of incident BCa with higher VAT (48%) and SAT (32%) among normal-weight women (BMI 18.5 to <25 kg/m^2). Power was limited, and confidence intervals widened for stratified models using quartiles of body composition. The lack of statistically significant differences between demographic, tumor subtype, and cancer severity strata persisted in quartile models (not presented). Stratified time-varying models using repeat body composition measures demonstrated similar results, although not all remained statistically significant (Table 2).

Results from multivariable models were slightly attenuated but remained statistically significant for the continuous models of VAT when additionally adjusted by BMI (SHR 1.31 instead of 1.36, so −0.05) or SMI (-0.09) in sensitivity analyses, and similarly SAT (BMIadj: −0.04; SMIadj: −0.01; Table S2). VAT and SAT quartile models remained statistically significant across analyses, although some VAT/SAT quartile associations with BCa

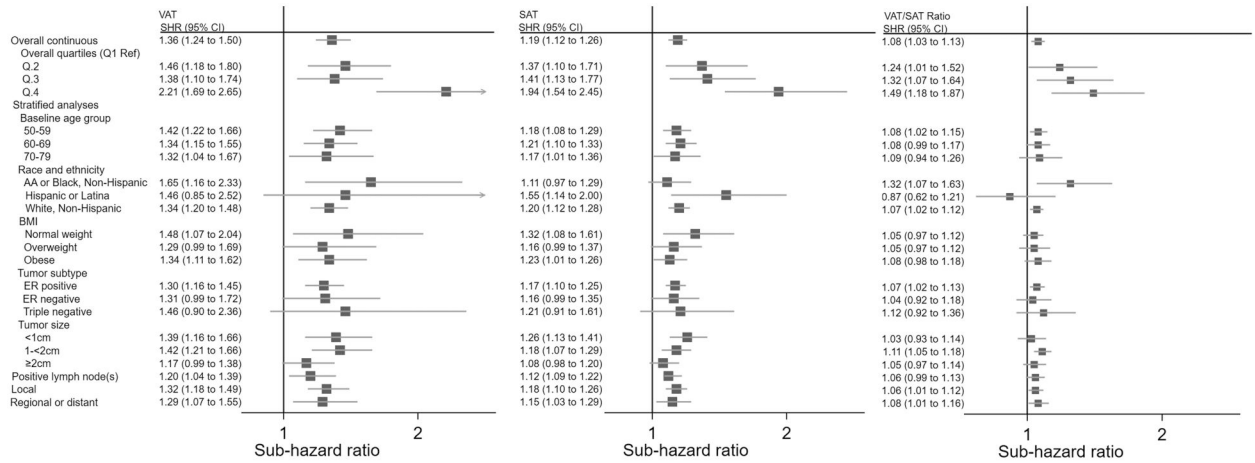

Figure 2. Baseline abdominal adipose tissue variables (continuous per 100 cm^2) and incident breast cancer overall and stratified by age, race/ethnicity, BMI category, and tumor characteristics (multivariable-adjusted models). Multivariable-adjusted models presented were adjusted for height at baseline, age at baseline, region, education, income, race and ethnicity, trial arm, alcohol intake, smoking status, physical activity (MET-h/wk), physical function (RAND 36 score), total energy intake (kcal/day), HEI-2015 score, menopausal hormone therapy use at baseline, aspirin use at baseline, metformin use at baseline, female relative with breast cancer, age at first birth, total number of months of breastfeeding, age at menopause, age at menarche, and surgical menopause. Adjusted models for American Indian/Alaska Native women did not converge. n = 9950 women observed for 177 294.53 person-years total. Competing risks are death without developing any type of cancer and developing a first primary cancer other than breast cancer. Multivariable-adjusted models used MICE to address missing covariates. Abbreviations: AA = African American; BMI = body mass index; ER = estrogen receptor; MET-h/wk = metabolic equivalent task hours per week; MICE = multiple imputation by chained equations; SAT = subcutaneous adipose tissue; SHR = sub-hazard ratio; VAT = visceral adipose tissue; CI = confidence interval.

Table 2. Competing risks time to event multivariable models: association of time-dependent abdominal adipose tissue over 6 years with incident breast cancer over 27 years of follow-up in postmenopausal women (SHR and 95% CI).

Category	Strata		
Age	50-59 years (n=3341)	60-69 years (n=4363)	70+ years (n=2246)
VAT, 100 cm^2	1.42 (1.22 to 1.66)	1.34 (1.15 to 1.55)	1.32 (1.04 to 1.67)
SAT, 100 cm^2	1.18 (1.08 to 1.29)	1.21 (1.10 to 1.33)	1.17 (1.01 to 1.36)
VAT/SAT ratio	1.08 (1.02 to 1.15)	1.08 (0.99 to 1.17)	1.09 (0.94 to 1.26)
Race/Ethnicity	AA/Black, non-Hispanic (n=1390)	Hispanic or Latina (n=674)	NHW (n=7745)
VAT, 100 cm^2	1.65 (1.16 to 2.33)	1.46 (0.85 to 2.52)	1.34 (1.20 to 1.48)
SAT, 100 cm^2	1.11 (0.97 to 1.29)	1.55 (1.14 to 2.11)	1.20 (1.12 to 1.28)
VAT/SAT ratio	1.32 (1.07 to 1.63)	0.87 (0.62 to 1.21)	1.07 (1.02 to 1.12)
BMI category	Normal weight (n=3167)	Overweight (n=3498)	Obese (n=3184)
VAT, 100 cm^2	1.48 (1.07 to 2.04)	1.29 (0.99 to 1.69)	1.34 (1.11 to 1.62)
SAT, 100 cm^2	1.32 (1.08 to 1.61)	1.16 (0.99 to 1.37)	1.13 (1.01 to 1.26)
VAT/SAT ratio	1.05 (0.97 to 1.12)	1.05 (0.94 to 1.17)	1.08 (0.98 to 1.18)
Tumor subtype	ER+ (n case patients=515)	ER− (n case patients =115)	Triple negative (n case patients=36)
VAT, 100 cm^2	1.30 (1.16 to 1.45)	1.31 (0.99 to 1.72)	1.46 (0.90 to 2.36)
SAT, 100 cm^2	1.17 (1.02 to 1.13)	1.16 (0.99 to 1.35)	1.21 (0.91 to 1.61)
VAT/SAT ratio	1.07 (1.02 to 1.13)	1.04 (0.92 to 1.18)	1.12 (0.92 to 1.36)

Multivariable-adjusted model presented: adjusted for height at baseline, age at baseline, region, education, income, race and ethnicity, trial arm, alcohol intake, smoking status, physical activity (MET-hrs/wk), physical function (RAND 36 score), total energy intake (kcal/day), HEI-2015 score, menopausal hormone therapy use at baseline, aspirin use at baseline, metformin use at baseline, female relative with breast cancer, age at first birth, total number of months of breastfeeding, age at menopause, age at menarche, and surgical menopause. Adjusted models for American Indian/Alaska Native women did not converge. Body composition was measured at baseline, 3 and 6 years.
Abbreviations: AA = African American; ER = estrogen receptor; HEI-2015 score = Healthy eating index 2015 score; MET = Metabolic equivalents; NHW = non-Hispanic or Latina White; SAT = subcutaneous adipose tissue; SHR = sub-hazard ratio; VAT = visceral adipose tissue.

incidence were no longer statistically significant upon adjustment for BMI or SMI. Sensitivity analysis examining HT use (Table S3) showed similar results when using the full cohort. However, confidence intervals widened among the HT never users (N = 3173), and the VAT/SAT relationship with breast cancer incidence was no longer statistically significant.

Discussion

Overall, the most impressive increase in BCa risk was seen for the fourth quartile of VAT (>2 fold). However, we found a statistically significantly higher risk of BCa with both higher continuous VAT (36%) and SAT (19%), although VAT was a smaller proportion of total abdominal fat. The VAT/SAT ratio was also associated with higher risk of BCa, but to a lesser degree (8%). We examined the VAT/SAT ratio to account for adipose distribution in the region, and its findings indicate the potential need to consider the balance of the two abdominal depots for a better understanding of individual risk. Importantly, the increased risk of BCa with elevated abdominal VAT and SAT was independent of BMI and remained detectable among stratified analyses of normal-weight women, suggesting a role for abdominal adiposity specifically.

Analyses by race and ethnicity strata, although not statistically significantly different from one another, elucidated potential heterogeneity in BCa risk related to the abdominal adipose

depots. Although non-Hispanic African American/Black women tended to have lower VAT and VAT/SAT, they were at greater risk of BCa as VAT/SAT increased compared with non-Hispanic White women. Thus, the lower BCa incidence rate but higher prevalence of "obesity" (by BMI) in African American women[36] may not be the paradox it seems to be, but rather attributable to how obesity is measured. VAT reducing interventions, specifically, could be meaningfully prioritized among African American women. Conversely, results suggested that SAT may be a more valuable risk biomarker among Hispanic women. The potential race and ethnic differences herein are worthy of replication in a sample with greater diversity, particularly given the racial and ethnic differences in VAT accumulation,[37,38] correlations between VAT and anthropometric measures of adiposity (BMI and WC),[38,39] and proposed BMI and WC cut-points for risk of other chronic conditions.[40-42]

Clinically relevant applications of the overall results may also be pursued. For example, although limited by smaller sample size and wider confidence intervals, quartile analyses allowed for a glimpse of potential cutoff values in future studies. Additionally, the consistency between baseline and time-dependent models lends confidence to using abdominal body composition measures in a single postmenopausal clinic visit to predict future BCa risk.

Despite a paucity of abdominal adipose studies in the breast cancer prevention setting for comparison, two were identified. Results from a case-control study using computed tomography, CT (middle-aged women, n = 234 case patients; 211 control individuals)[43] showed an increased risk of postmenopausal breast cancer with higher VAT, but not SAT, whereas a prospective cohort using MRI (middle-aged)[44] did not find statistically significant associations between VAT or SAT and postmenopausal breast cancer (women only, N = 1418).[44] Power appeared to be an issue in both studies. Differing imaging technologies hampered direct comparison across studies.

Better-powered studies examining adiposity and BCa associations were limited to measured total body fat and trunk fat or eVAT. However, the VAT and SAT associations presented herein were consistent with the previous findings in the WHI and other studies (eg, statistically significant, positive association between higher adiposity and BCa risk),[45] independent of BMI.[10,46,47] Most of these prior studies assessed adipose via bioelectrical impedance,[45] with only the WHI and UK Biobank (UKB)[48] studies using the more precise DXA and MRI imaging technology in subsets.[10,46-48] The UKB Study found a 62% increase in BCa risk in the highest quartile of total body fat (32.6-108.4 kg),[48] whereas the WHI demonstrated up to 2-fold increased risk in the top quantile of total body fat, compared with the lowest.[46,47] In the present sample of 9950 WHI women, the total body fat range in the upper quartile is less than in the UKB Study (38.99-83.6 kg), and follow-up was shorter in UKB (8.8 years)[49] than in WHI (up to 15 years in these prior publications).[46,47] Unfortunately, due to the differing units of measurement, the effect sizes from total body fat models cannot be directly compared with the VAT and SAT results herein. Studies that used anthropometric measures to predict eVAT showed both similar BCa risk[23] and higher risk of BCa, particularly in tertile 3 of eVAT.[50] Due to the predicted vs measured aspect of VAT, the models should not be directly compared.

The present study has several strengths and limitations. The robust characterization of the WHI cohort was a major strength and enabled adjustment for potential confounders in competing-risks models. The repeated measures allowed for examination of time-dependent abdominal body composition and incident BCa in a large cohort of postmenopausal women. Results were independent of BMI and SMI. Therefore, all available total and regional body composition variables may be standardized and directly compared for optimal inclusion in existing risk prediction models in the future. Nevertheless, there were limitations. The 2-dimensional nature of DXA limits VAT and SAT measures vs 3-dimensional CT or MRI, although we have validated WHI VAT and SAT against MRI.[27] Further DXA may be more practical, due to limited access to CT and MRI, related to higher costs, more extensive technician training, and greater radiation exposure (CT only). The lack of access to a measure of breast adiposity specifically, a potentially important consideration in risk prediction, particularly related to the tumor microenvironment,[18] is another limitation. Lastly, increased racial and ethnic diversity is needed in future studies to better understand potential differences in the association between BCa incidence and VAT and/or SAT among under-represented women.

In conclusion, this study demonstrates the important contribution of abdominal adiposity to BCa risk, independent of BMI category classification, in the prevention setting for the first time, and has generated critical hypotheses related to racial and ethnic heterogeneity that require further exploration. Future studies may explore serum biomarkers, as mediators of the relation between abdominal body composition and BCa, and test cut-points of measures of abdominal adipose sub-compartments for targeted interventions.

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For a list of all the investigators who have contributed to WHI science, please visit: https://s3- us-west-2.amazonaws.com/www-whi-org/wp-content/uploads/WHI-Investigator-Long-List.pdf
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Author contributions

Jennifer W. Bea, PhD (Conceptualization; Methodology; Supervision; Writing—original draft; Writing—review & editing), Heather M. Ochs-Balcom, PhD (Writing—review & editing), Celina I. Valencia, DrPH (Methodology; Writing—review & editing), Zhao Chen, PhD (Conceptualization; Methodology; Writing—review & editing), Robert Blew, MS (Data curation; Methodology; Writing—original draft), Kimberly E. Lind, PhD (Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing), Bette J. Caan, DrPH (Data curation; Methodology; Writing—review & editing), Denise J. Roe, DrPH (Conceptualization; Data curation; Formal analysis; Methodology; Writing—review & editing), Thomas E. Rohan, MBBS, PhD, DHSc (Writing—review & editing), Katherine W. Reeves, PhD, MPH (Writing—review & editing), JoAnn E. Manson, MD, DrPH (Writing—review & editing), Tarah Ballinger, MD (Writing—review & editing), Kerryn W. Reding, PhD, MPH, BSN (Writing—review & editing), Shawna Follis, PhD (Data curation; Formal analysis; Methodology; Writing—review & editing), Shelby G. Ziller, MPH (Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing), and Andrew O. Odegaard, PhD (Conceptualization; Formal analysis; Methodology; Writing—review & editing).

Supplementary material

Supplementary material is available at *JNCI Cancer Spectrum* online.

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Conflicts of interest

Jennifer W. Bea discloses board membership with the Global Health and Body Composition Institute and a contract with Disarm Therapeutics for an investigator-initiated trial among chemotherapy treated breast cancer patients within the last 3 years. Dr Bea is also a consultant for the Women's Health Initiative Western Region. Dr Rohan is supported in part by the Breast Cancer Research Foundation (BCRF-22-140). The remaining authors have no disclosures to report.

Data availability

This research uses pre-existing data and DXA images from the Women's Health Initiative study. Persons interested in obtaining Women's Health Initiative data can follow the formal procedures for manuscript proposals and ancillary study proposal codified on the WHI website; data use agreements and instructions for researchers are also available (www.whi.org).

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