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# Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index
## A Secondary Analysis of a Randomized Clinical Trial and Observational Study

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**IMPORTANCE** Obesity is associated with an increased risk of breast cancer, including the estrogen receptor (ER)–positive subtype in postmenopausal women. Whether excess adiposity is associated with increased risk in women with a normal body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) is unknown.

**OBJECTIVE** To investigate the association between body fat and breast cancer risk in women with normal BMI.

**DESIGN, SETTING, AND PARTICIPANTS** This ad hoc secondary analysis of the Women's Health Initiative (WHI) clinical trial and observational study cohorts was restricted to postmenopausal participants with a BMI ranging from 18.5 to 24.9. Women aged 50 to 79 years were enrolled from October 1, 1993, through December 31, 1998. Of these, 3460 participants underwent body fat measurement with dual-energy x-ray absorptiometry (DXA) at 3 US designated centers with follow-up. At a median follow-up of 16 years (range, 9-20 years), 182 incident breast cancers had been ascertained, and 146 were ER positive. Follow-up was complete on September 30, 2016, and data from October 1, 1993, through September 30, 2016, was analyzed August 2, 2017, through August 21, 2018.

**MAIN OUTCOMES AND MEASURES** Body fat levels were measured at baseline and years 1, 3, 6, and 9 using DXA. Information on demographic data, medical history, and lifestyle factors was collected at baseline. Invasive breast cancers were confirmed via central review of medical records by physician adjudicators. Blood analyte levels were measured in subsets of participants.

**RESULTS** Among the 3460 women included in the analysis (mean [SD] age, 63.6 [7.6] years), multivariable-adjusted hazard ratios for the risk of invasive breast cancer were 1.89 (95% CI, 1.21-2.95) for the highest quartile of whole-body fat and 1.88 (95% CI, 1.18-2.98) for the highest quartile of trunk fat mass. The corresponding adjusted hazard ratios for ER-positive breast cancer were 2.21 (95% CI, 1.23-3.67) and 1.98 (95% CI, 1.18-3.31), respectively. Similar positive associations were observed for serial DXA measurements in time-dependent covariate analyses. Circulating levels of insulin, C-reactive protein, interleukin 6, leptin, and triglycerides were higher, whereas levels of high-density lipoprotein cholesterol and sex hormone–binding globulin were lower in those in the uppermost vs lowest quartiles of trunk fat mass.

**CONCLUSIONS AND RELEVANCE** In postmenopausal women with normal BMI, relatively high body fat levels were associated with an elevated risk of invasive breast cancer and altered levels of circulating metabolic and inflammatory factors. Normal BMI categorization may be an inadequate proxy for the risk of breast cancer in postmenopausal women.

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The recognition of obesity as a risk factor for several cancers is largely based on the use of anthropometric indices, such as body mass index (BMI).[1,2] However, BMI is a crude measure of body size that does not discriminate between adiposity and muscle.[3,4] Some individuals thought to be healthy by virtue of a normal BMI may in fact have cardiometabolic disorders, collectively termed *metabolic obesity in normal weight*.[5,6]

Recent evidence suggests that a subset of women with normal BMI and excess body fat may be at increased risk for breast cancer. Specifically, excess body fat is associated with adipocyte hypertrophy. In women with normal BMI, breast adipocyte hypertrophy correlates with white adipose tissue inflammation, elevated levels of aromatase (the rate-limiting enzyme for estrogen biosynthesis), and increased circulating levels of leptin.[7] In addition, insulin resistance is a well-known consequence of excess body fat.[8] In postmenopausal women with normal BMI, elevated insulin levels have been associated with an increased risk of breast cancer.[9] Importantly, insulin resistance, breast adipose inflammation, elevated aromatase expression, and increased levels of leptin have all been suggested to play a role in the pathogenesis of obesity-related breast cancer.[10-14] Collectively, these prior findings raise the possibility that excess body fat may be associated with an increased risk of postmenopausal breast cancer in women with normal BMI, a group in which the etiology of breast cancer is poorly understood.[15]

Direct measurement of body fat can be precisely obtained using dual-energy x-ray absorptiometry (DXA).[16] Body mass index and DXA-derived measures of body fat are associated with breast cancer risk in overweight and obese postmenopausal women.[17] Currently, women with normal BMI are not thought to harbor an increased breast cancer risk apart from those with familial and/or genetic syndromes. To determine whether body fat contributes to postmenopausal breast cancer risk in women with normal BMI, we used DXA-derived measures obtained in a subset of participants in the Women's Health Initiative (WHI).[18] In addition, we examined the associations between body fat levels in women with normal BMI and circulating metabolic and inflammatory factors that have been linked to the pathogenesis of breast cancer.

### Key Points

**Question** Are increased levels of body fat in women with normal body mass index associated with an elevated risk of breast cancer?

**Findings** In a cohort of 3460 postmenopausal women with normal body mass index enrolled in the Women's Health Initiative randomized clinical trial and observational study, higher body fat levels measured by dual-energy x-ray absorptiometry were associated with increased risk of invasive breast cancer at a median follow-up of 16 years.

**Meaning** Postmenopausal women with higher body fat levels are at elevated risk for breast cancer despite having a normal body mass index.

## Methods

### Study Population and Design

A detailed description of the WHI design and study population was presented elsewhere.[19] The trial protocol is available in Supplement 1. Briefly, the study included 161 808 postmenopausal women aged 50 to 79 years, from major racial/ethnic groups, who were enrolled at 40 clinical centers throughout the United States from October 1, 1993, through December 31, 1998. Women were included in the randomized clinical trial, which has 3 overlapping components (hormone therapy [2 trials], low-fat diet modification, and calcium and vitamin D supplementation [n = 68 132]), or the observational study (n = 93 676).[19] Women included in the WHI had normal mammogram findings at baseline or mammogram findings not suggestive of cancer within 2 years before enrollment. The study was approved by the institutional review boards of all participating institutions, and all participants provided written informed consent.

### Data Collection and Variable Definition

At baseline, self-administered questionnaires were used to collect information on demographic characteristics, menstrual history, reproductive history, exogenous hormone use, family history, medical history, and diet and lifestyle factors, and a fasting blood sample was obtained. Anthropometric measurements were also taken by trained staff at baseline. Weight and height were measured to calculate BMI as weight in kilograms divided by height in meters squared.[2] Based on responses to questions regarding physical activity level, metabolic equivalent task (MET) in hours per week was computed.[20]

### Body Fat Measurements

For 11 393 WHI participants in 3 designated centers (Birmingham, Alabama; Tucson and Phoenix, Arizona; and Pittsburgh, Pennsylvania), body fat was measured at baseline and 4 follow-up visits (years 1, 3, 6, and 9) by DXA performed in fan-beam mode and obtained from multidetector scanners (QDR 2000, 2000+, or 4500; Hologic, Inc). Scanner performance was monitored longitudinally using spine and whole-body phantom scans.[21] Quality control measures included review of unacceptable scans, outliers, and a random sample of all scans. When 2 QDR 2000 scanners were retired, in vivo cross-calibration was performed at 2 sites to convert QDR 4500 values to QDR 2000–equivalent values.[21] These correction factors and adjustments for longitudinal changes in scanner performance were applied to participant scan results.

Of the total DXA study population, 3464 women had BMIs ranging from 18.5 to 24.9, consistent with the World Health Organization criterion for normal BMI. Four women without information on follow-up time were excluded, leaving 3460 women for this ad hoc analysis (**Figure**). Body fat measures included whole-body fat (in kilograms), percentage of whole-body fat, trunk fat (defined by the fat contained in the torso apart from head and limbs), and fat mass of the legs. The ratio of trunk to leg fat mass was also calculated; a relatively high ratio is associated with an increased risk of diabetes and mortality.[22]

## Analytes

Detailed descriptions of the procedures used to measure analytes in fasting blood specimens have been reported previously.[9,23-26] Briefly, serum insulin and C-reactive protein (high sensitivity) concentrations were measured by immunoassay, whereas serum glucose level was measured using an enzymatic method. For white blood cell count, blood samples were analyzed at certified laboratories across the 40 clinical centers. Triglyceride (GB Reagent; Roche Diagnostics) and high-density lipoprotein cholesterol (HDL-C Plus 3rd Generation Direct; Roche Diagnostics) levels were quantified using commercially available methods. Serum estradiol levels were determined using radioimmunoassays after organic solvent extraction.[25] Sex hormone–binding globulin levels were determined by use of a direct chemiluminescent immunoassay (Immulite Analyzer; Siemens Medical Solutions Diagnostics).[27] Adiponectin was quantified using a commercially available panel (Panel A; Millipore).[28] A summary of the methods used to quantify interleukin 6 and leptin can be found in eTable 1 in Supplement 2. To account for systematic differences in location and/or scale of measurements between laboratories, these measurements were standardized.[29] Insulin and glucose measurements were used to calculate the homeostatic assessment model algorithm for insulin resistance using the following formula: [fasting insulin level in international units per milliliter × fasting glucose level in milligrams per deciliter]/405.

## Outcome Ascertainment

Participants were followed up semiannually in the clinical trial group and annually in the observational study group using in-person, mailed, or telephone questionnaires to collect information on clinical outcomes. Breast cancer cases were confirmed via central review of medical records and pathology reports by trained physician adjudicators. Breast tumor hormone receptor status was coded using the National Cancer Institute's Surveillance Epidemiology and End Results coding system.[30] As of September 2016, a total of 182 primary invasive breast cancer cases had been ascertained in the cohort of women with normal weight and DXA measurements; 146 of these cancer cases were estrogen receptor (ER) positive. Vital status was collected through follow-up of participants and proxies and periodic searches of the National Death Index.

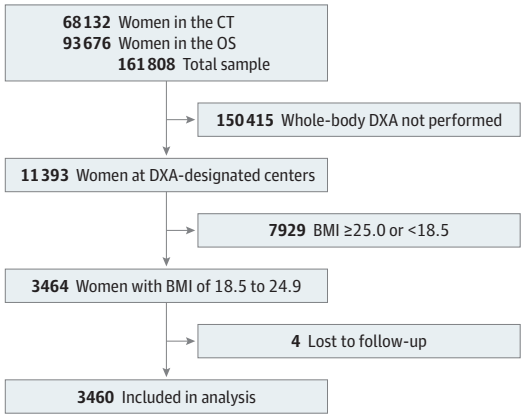
## Statistical Analysis

Data from October 1, 1993, through September 30, 2016, was analyzed August 2, 2017, through August 21, 2017. Means and frequencies were used to summarize the study cohort characteristics. The correlation between measures of adiposity was assessed using the Spearman rank correlation. Age- and multivariable-adjusted hazard ratios (HRs) and 95% CIs for the associations between the body fat measures and risk of invasive breast cancer were estimated using Cox proportional hazards regression. The underlying time scale was time to diagnosis of invasive breast cancer. Cases contributed person-time to the study from their date of enrollment until the date of diagnosis of breast cancer, and noncases contributed person-time from their date of enrollment until the date of death, date of withdrawal from the study, or the end of follow-up (September 30, 2016), whichever came first. Covariates were selected a priori or if their inclusion in the models resulted in a 10% change in the estimates. The models were internally validated using 10-fold cross-validation to assess performance and minimize overfitting.[31] The multivariable model with the smallest mean of the minimum square error was selected as the model with the best fit. The regression models were adjusted for age at enrollment, educational level, race/ethnicity, age at menarche, age at first full-term birth, parity, age at menopause, oral contraceptive use, use of combined estrogen and progesterone therapy, use of unopposed estrogen therapy, physical activity (MET in hours per week), alcohol intake, and smoking. Tests for trend were performed by assigning the median value to each of the quartiles of the body fat measures, which were then modeled as continuous variables; Wald tests were used to assess statistical significance. The proportional hazards assumption was tested using Schoenfeld residuals, and the assumption was not violated. For variables with missing data, we included a missing value indicator. We used C statistics to evaluate the discriminatory ability of the multivariable models.[32]

To assess the association of changes in DXA measurements over time with breast cancer risk, we also conducted time-dependent covariate analysis using available DXA measures from all time points (≤5). Because some women may have crossed into the overweight or obese BMI category during follow-up, we reran these models in sensitivity analyses restricted to women whose BMI remained within the normal category during follow-up visits. Median cut points were used to categorize the DXA measures.

We fitted restricted cubic splines with 3 knots at the 25th, 50th, and 75th percentiles in Cox proportional hazards regression models to evaluate the potential nonlinear dose-response association between the continuous body fat measures and ER-positive breast cancer.[33] A *P* value for nonlinearity was calculated by testing whether the coefficient of the second spline transformation was equal to zero ($P < .05$).[33]

Figure. CONSORT Diagram of Participants Included in the Analysis




BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); CT, clinical trial; DXA, dual-energy x-ray absorptiometry; and OS, observational study.

Table 1. Association of Baseline Body Fat and Incident, Invasive Breast Cancer in Postmenopausal Women With Normal BMI[a]

| DXA Measurement | No. of Cases/ Person-Years | HR (95% CI) | |
|---|---|---|---|
| | | Age Adjusted | Multivariable Adjusted[b] |
| Whole-body fat mass, kg | | | |
| ≤18.7 | 31/12 384.9 | 1 [Reference] | 1 [Reference] |
| 18.8-22.0 | 44/12 733.4 | 1.40 (0.88-2.21) | 1.45 (0.91-2.30) |
| 22.1-25.1 | 50/12 657.1 | 1.59 (1.02-2.49) | 1.68 (1.06-2.64) |
| >25.1 | 57/12 816.8 | 1.80 (1.16-2.80) | 1.89 (1.21-2.95) |
| *P* value for trend | NA | .01 | .004 |
| C statistic (95% CI) | NA | NA | 0.662 (0.622-0.703) |
| Continuous per 5-unit increase | NA | 1.26 (1.09-1.45) | 1.28 (1.10-1.49) |
| Whole-body fat, % | | | |
| ≤33.7 | 32/12 716.2 | 1 [Reference] | 1 [Reference] |
| 33.8-37.9 | 54/13 237.4 | 1.61 (1.04-2.50) | 1.67 (1.08-2.61) |
| 38.0-41.3 | 44/12 600.9 | 1.37 (0.87-2.16) | 1.45 (0.91-2.30) |
| >41.3 | 52/12 037.7 | 1.69 (1.08-2.62) | 1.79 (1.14-2.83) |
| *P* value for trend | NA | .04 | .03 |
| C statistic (95% CI) | NA | NA | 0.653 (0.611-0.694) |
| Continuous per 5-unit increase | NA | 1.16 (1.01-1.32) | 1.19 (1.03-1.37) |
| Fat mass of trunk, kg | | | |
| ≤7.3 | 30/12 720.9 | 1 [Reference] | 1 [Reference] |
| 7.4-9.3 | 41/12 858.8 | 1.35 (0.84-2.16) | 1.45 (0.90-2.32) |
| 9.4-11.4 | 61/12 686.7 | 2.02 (1.30-3.12) | 2.16 (1.39-3.37) |
| >11.4 | 50/12 325.9 | 1.71 (1.08-2.68) | 1.88 (1.18-2.98) |
| *P* value for trend | NA | .01 | .002 |
| C statistic (95% CI) | NA | NA | 0.665 (0.624-0.705) |
| Continuous per 5-unit increase | NA | 1.38 (1.09-1.75) | 1.46 (1.14-1.87) |
| Fat mass of right leg, kg | | | |
| ≤3.8 | 32/12 045.5 | 1 [Reference] | 1 [Reference] |
| 3.9-4.5 | 50/12 462.0 | 1.54 (0.99-2.40) | 1.45 (0.93-2.26) |
| 4.6-5.3 | 47/12 847.8 | 1.42 (0.90-2.22) | 1.32 (0.84-2.08) |
| >5.3 | 53/13 237.0 | 1.58 (1.01-2.45) | 1.50 (0.96-2.34) |
| *P* value for trend | NA | .08 | .12 |
| C statistic (95% CI) | NA | NA | 0.654 (0.613-0.695) |
| Continuous per 5-unit increase | NA | 2.06 (1.07-3.98) | 1.94 (0.99-3.80) |
| Fat mass of left leg, kg | | | |
| ≤3.7 | 32/12 054.5 | 1 [Reference] | 1 [Reference] |
| 3.8-4.4 | 48/12 437.5 | 1.48 (0.94-2.31) | 1.40 (0.90-2.19) |
| 4.5-5.1 | 48/12 918.7 | 1.44 (0.92-2.26) | 1.37 (0.88-2.14) |
| >5.1 | 54/13 181.6 | 1.60 (1.03-2.49) | 1.49 (0.96-2.32) |
| *P* value for trend | NA | .006 | .11 |
| C statistic (95% CI) | NA | NA | 0.653 (0.612-0.693) |
| Continuous per 5-unit increase | NA | 2.07 (1.06-4.08) | 1.95 (0.96-3.90) |
| Ratio of trunk fat mass to mean of right and left leg fat mass | | | |
| ≤1.6 | 40/13 051.2 | 1 [Reference] | 1 [Reference] |
| 1.7-2.0 | 40/13 044.6 | 0.98 (0.63-1.52) | 1.05 (0.68-1.63) |
| 2.1-2.6 | 59/12 658.7 | 1.49 (1.00-2.23) | 1.57 (1.05-2.36) |
| >2.6 | 43/11 837.8 | 1.14 (0.74-1.76) | 1.30 (0.83-2.02) |
| *P* value for trend | NA | .28 | .10 |
| C statistic (95% CI) | NA | NA | 0.651 (0.610-0.692) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DXA, dual-energy x-ray absorptiometry; HR, hazard ratio; NA, not applicable.

[a] Indicates BMI of 18.5 to 24.9.

[b] Adjusted for age at enrollment, educational attainment, race/ethnicity, age at menarche, age at first full-term birth, parity, age at menopause, oral contraceptive use, use of combined estrogen and progesterone therapy, use of unopposed estrogen therapy, physical activity, alcohol intake, and smoking.

The associations between geometric mean concentrations of selected analytes and fat mass of the trunk were assessed by linear regression after natural logarithm transformation of the analyte values. Models were adjusted for age and race/ethnicity.

*P* values were 2 sided. All statistical analyses were performed using Stata (version 14.1; StataCorp) and SAS (release 9.4; SAS Institute Inc). Stata and SAS codes are provided in eMethods in Supplement 2.

## Results

The 3460 women included in the analysis (mean [SD] age, 63.6 [7.6] years) were followed up for a median of 16.4 years (range, 9-20 years). The distribution of the study population characteristics by quartiles of trunk fat mass is provided in eTable 2 in Supplement 2. Compared with those in the lowest quartile, mean (SD) physical activity levels were lower among

Table 2. Association of Baseline Body Fat and Incident, Invasive, ER-Positive Breast Cancer in Postmenopausal Women With Normal BMI[a]

| Body Fat Measurement | No. of Cases/ Person-Years | HR (95% CI) | |
|---|---|---|---|
| | | Age Adjusted | Multivariable Adjusted[b] |
| Whole-body fat mass, kg | | | |
| ≤18.7 | 23/12 384.9 | 1 [Reference] | 1 [Reference] |
| 18.8-22.0 | 36/12 733.4 | 1.55 (0.92-2.62) | 1.61 (0.95-2.73) |
| 22.1-25.1 | 39/12 657.1 | 1.68 (1.00-2.81) | 1.80 (1.07-3.03) |
| >25.1 | 48/12 816.8 | 2.06 (1.25-3.39) | 2.21 (1.23-3.67) |
| *P* value for trend | NA | .004 | .002 |
| C statistic (95% CI) | NA | NA | 0.671 (0.625-0.716) |
| Continuous per 5-unit increase | NA | 1.31 (1.12-1.54) | 1.35 (1.14-1.60) |
| Whole-body fat, % | | | |
| ≤33.7 | 23/12 716.2 | 1 [Reference] | 1 [Reference] |
| 33.8-37.9 | 43/13 237.4 | 1.78 (1.07-2.96) | 1.87 (1.12-3.12) |
| 38.0-41.3 | 36/12 600.9 | 1.56 (0.92-2.63) | 1.69 (1.00-2.88) |
| >41.3 | 44/12 037.7 | 1.98 (1.20-3.28) | 2.17 (1.29-3.66) |
| *P* value for trend | NA | .02 | .01 |
| C statistic (95% CI) | NA | NA | 0.665 (0.619-0.711) |
| Continuous per 5-unit increase | NA | 1.22 (1.05-1.42) | 1.27 (1.08-1.48) |
| Fat mass of trunk, kg | | | |
| ≤7.3 | 24/12 720.9 | 1 [Reference] | 1 [Reference] |
| 7.4-9.3 | 31/12 858.8 | 1.27 (0.75-2.17) | 1.40 (0.82-2.39) |
| 9.4-11.4 | 50/12 686.7 | 2.07 (1.27-3.36) | 2.27 (1.38-3.72) |
| >11.4 | 41/12 325.9 | 1.75 (1.06-1.90) | 1.98 (1.18-3.31) |
| *P* value for trend | NA | .01 | .003 |
| C statistic (95% CI) | NA | NA | 0.671 (0.625-0.717) |
| Continuous per 5-unit increase | NA | 1.44 (1.11-1.88) | 1.56 (1.18-2.06) |
| Fat mass of right leg, kg | | | |
| ≤3.8 | 23/12 045.5 | 1 [Reference] | 1 [Reference] |
| 3.9-4.5 | 42/12 462.0 | 1.80 (1.08-3.00) | 1.74 (1.04-2.90) |
| 4.6-5.3 | 34/12 847.8 | 1.44 (0.85-2.44) | 1.34 (0.79-2.30) |
| >5.3 | 47/13 237.0 | 1.97 (1.19-3.25) | 1.90 (1.40-3.16) |
| *P* value for trend | NA | .02 | .04 |
| C statistic (95% CI) | NA | NA | 0.668 (0.623-0.712) |
| Continuous per 5-unit increase | NA | 2.63 (1.27-5.46) | 2.52 (1.18-5.35) |
| Fat mass of left leg, kg | | | |
| ≤3.7 | 24/12 054.5 | 1 [Reference] | 1 [Reference] |
| 3.8-4.4 | 40/12 437.5 | 1.64 (0.99-2.73) | 1.60 (0.96-2.66) |
| 4.5-5.1 | 35/12 918.7 | 1.41 (0.84-2.37) | 1.33 (0.78-2.24) |
| >5.1 | 47/13 181.6 | 1.88 (1.15-3.08) | 1.82 (1.10-3.01) |
| *P* value for trend | NA | .03 | .04 |
| C statistic (95% CI) | NA | NA | 0.664 (0.619-0.709) |
| Continuous per 5-unit increase | NA | 2.58 (1.22-5.44) | 2.49 (1.15-5.40) |
| Ratio of trunk fat mass to mean of right and left leg fat mass | | | |
| ≤1.6 | 32/13 051.2 | 1 [Reference] | 1 [Reference] |
| 1.7-2.0 | 31/13 044.6 | 0.94 (0.58-1.55) | 1.00 (0.61-1.65) |
| 2.1-2.6 | 49/12 658.7 | 1.54 (0.99-2.41) | 1.67 (1.06-2.62) |
| >2.6 | 34/11 837.8 | 1.11 (0.69-1.81) | 1.28 (0.78-2.10) |
| *P* value for trend | NA | .33 | .13 |
| C statistic (95% CI) | NA | NA | 0.663 (0.619-0.708) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ER, estrogen receptor; HR, hazard ratio; NA, not applicable.

[a] Indicates BMI of 18.5 to 24.9.

[b] Adjusted for age at enrollment, educational attainment, race/ethnicity, age at menarche, age at first full-term birth, parity, age at menopause, oral contraceptive use, use of combined estrogen and progesterone therapy, use of unopposed estrogen therapy, physical activity, alcohol intake, and smoking.

cases (11.4 [13.2] MET h/wk) and noncases (10.1 [13.0] MET h/wk) with relatively high trunk fat mass (quartile 4), whereas mean (SD) BMI (24.1 [0.9] for cases and 23.8 [1.0] for noncases) and waist circumference (80.9 [5.9] cm for cases and 79.5 [6.0] cm for noncases) were highest among those with high trunk fat mass. Moderately strong positive correlations were observed between BMI and DXA measures; for example, the correlation coefficient between BMI and whole-body fat mass was 0.67 (eTable 3 in Supplement 2). However, nearly half of the participants in the highest quartile of trunk fat were distributed among the lowest 3 quartiles of BMI (420 of 870 [48.3%]) (eTable 4 in Supplement 2).

**Table 1** provides the HRs and 95% CIs for the associations of the body fat measures with the risk of invasive breast cancer. In multivariable analyses, a 5-unit increase in whole-body fat mass was associated with a statistically significant 28% increase in the risk of invasive breast cancer; a 5-unit increase in percentage of whole-body fat, a 19% increase in the risk of

Table 3. Time-Dependent Covariate Analysis for the Association of Body Fat With Risk of Incident, Invasive Breast Cancer Among Postmenopausal Women With Normal BMI[a]

| DXA Measurement | Multivariable-Adjusted HR (95% CI)[b] |
|---|---|
| Whole-body fat mass, kg | |
| <22.1 | 1 [Reference] |
| ≥22.1 | 1.43 (1.06-1.93) |
| Whole-body fat, % | |
| <38.0 | 1 [Reference] |
| ≥38.0 | 1.45 (1.07-1.95) |
| Fat mass of trunk, kg | |
| <9.4 | 1 [Reference] |
| ≥9.4 | 1.50 (1.12-2.03) |
| Fat mass of right leg, kg | |
| <4.6 | 1 [Reference] |
| ≥4.6 | 1.34 (0.99-1.80) |
| Fat mass of left leg, kg | |
| <4.5 | 1 [Reference] |
| ≥4.5 | 1.36 (1.01-1.83) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DXA, dual-energy x-ray absorptiometry; HR, hazard ratio.

[a] Indicates BMI of 18.5 to 24.9.

[b] Adjusted for age at enrollment, educational attainment, race/ethnicity, age at menarche, age at first full-term birth, parity, age at menopause, oral contraceptive use, use of combined estrogen and progesterone therapy, use of unopposed estrogen therapy, physical activity, alcohol intake, and smoking.

Table 4. Time-Dependent Covariate Analysis for the Association of Body Fat With Risk of Incident, ER-Positive Breast Cancer Among Postmenopausal Women With Normal BMI[a]

| DXA Measurement | Multivariable-Adjusted HR (95% CI)[b] |
|---|---|
| Whole-body fat mass, kg | |
| <22.1 | 1 [Reference] |
| ≥22.1 | 1.41 (1.01-1.97) |
| Whole-body fat, % | |
| <38.0 | 1 [Reference] |
| ≥38.0 | 1.50 (1.07-2.10) |
| Fat mass of trunk, kg | |
| <9.4 | 1 [Reference] |
| ≥9.4 | 1.46 (1.05-2.04) |
| Fat mass of right leg, kg | |
| <4.6 | 1 [Reference] |
| ≥4.6 | 1.32 (0.95-1.83) |
| Fat mass of left leg, kg | |
| <4.5 | 1 [Reference] |
| ≥4.5 | 1.31 (0.94-1.82) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DXA, dual-energy x-ray absorptiometry; ER, estrogen receptor; HR, hazard ratio.

[a] Indicates BMI of 18.5 to 24.9.

[b] Adjusted for age at enrollment, educational attainment, race/ethnicity, age at menarche, age at first full-term birth, parity, age at menopause, oral contraceptive use, use of combined estrogen and progesterone therapy, use of unopposed estrogen therapy, physical activity, alcohol intake, and smoking.

invasive breast cancer; and a 5-unit increase in trunk fat, a 46% increased risk of invasive breast cancer. Positive associations were also observed when risk was examined by quartiles (multivariable-adjusted HR for highest quartile of whole-body fat, 1.89 [95% CI, 1.21-2.95]; multivariable-adjusted HR for the highest quartile of trunk fat mass, 1.88 [95% CI, 1.18-2.98]).

The associations of the body fat measures with the risk of ER-positive breast cancer are shown in **Table 2**. After adjusting for potential confounders, a 5-unit increase in whole-body fat mass was associated with a statistically significant increased risk of 35%; a 5-unit increase in percentage of whole-body fat, 27%; a 5-unit increase in fat mass of the trunk, 56%; a 5-unit increase in fat mass of the right leg, 152%; and a 5-unit increase in fat mass of the left leg, 149%. Positive associations were also observed when the body fat measures were categorized by quartiles. The C-statistic estimates ranged from 0.651 (95% CI, 0.610-0.692) to 0.671 (95% CI, 0.625-0.716) (Tables 1 and 2). After further adjustment for BMI, positive associations persisted for whole-body fat mass and fat mass of the trunk with risk of overall and ER-positive breast cancer. In time-dependent covariate analyses of serial DXA measurements, serial body fat measures were positively associated with the risk of invasive breast cancer (**Table 3**). Similar positive associations were observed for risk of ER-positive breast cancer (**Table 4**). Positive associations of whole-body fat mass and fat mass of the trunk with breast cancer risk were observed in sensitivity analyses restricted to women whose BMI remained within the normal BMI category during follow-up visits (eTables 5 and 6 in Supplement 2). Tests for nonlinear associations between the body fat measures and risk of ER-positive breast cancer were not statistically significant (eFigure in Supplement 2).

The results were essentially unchanged when women in the intervention arms of the estrogen alone (n = 79) and estrogen plus progestin (n = 163) trials were excluded. Waist circumference was also positively associated with overall and ER-positive breast cancer risk, although the association was not significant in the final multivariable model (eTable 7 in Supplement 2).

After adjusting for age and race/ethnicity, we observed positive associations between baseline levels of insulin, homeostatic model assessment of insulin resistance, C-reactive protein, white blood cells, interleukin 6, leptin, and triglycerides and fat mass of the trunk, whereas inverse associations were seen for levels of high-density lipoprotein cholesterol, adiponectin, and sex hormone–binding globulin (eTable 8 in Supplement 2). These associations remained after adjustment for BMI.

## Discussion

In this long-term prospective study of postmenopausal women with normal BMI, relatively high body fat levels were associated with an elevated risk of invasive breast cancer. Specifically, we found a 56% increase in the risk of developing ER-positive breast cancer per 5-kg increase in trunk fat, despite a normal BMI. This association could not be explained by a rise in BMI into the overweight or obese range. We observed a persistent association between higher trunk fat and increased risk of ER-positive breast cancer in women who remained in the normal BMI range during

the follow-up period. Elevated trunk fat levels were also associated with metabolic dysregulation and inflammation characterized by increased blood levels of insulin, triglycerides, leptin, C-reactive protein, and interleukin 6. Collectively, these findings indicate the inadequacy of normal BMI categorization for determining the association of breast cancer risk with body fat.

Findings in this study may be explained in part by the recent observation that enlarged adipocytes and inflammation are found in the breast tissue of some women with normal BMI.[7] Excess adiposity is associated with adipocyte hypertrophy and cell death leading to chronic, subclinical inflammation of adipose tissue.[12] Inflammation of breast white adipose tissue is observed consistently in women with elevated levels of total body fat.[34] Inflamed breast white adipose tissue is associated with activation of nuclear factor-κB, a transcription factor that induces expression of proinflammatory mediators, elevated levels of aromatase, and an increased ratio of estrogens to androgens.[10,11,13,35] Locally enhanced production of estrogens in the setting of white adipose inflammation would be expected to drive the development of estrogen-dependent tumors. Consistent with these observations, Carter et al[36] recently reported that high levels of breast white adipose inflammation were associated with increased breast cancer risk.

Systemic metabolic alterations in individuals with normal BMI and excess adiposity may also contribute to the increased risk of breast cancer. Dysregulation of insulin signaling can activate the PI3K/Akt/mTOR and Ras/Raf/MAPK pathways that may enhance cell proliferation and increase the risk of neoplasia in the breast.[37,38] Insulin also induces insulinlike growth factor-1, which can activate ERα.[37] Insulin resistance leads to reduced levels of sex hormone-binding globulin, which, in turn, results in elevated levels of free estradiol.[39] Finally, leptin can induce aromatase, directly stimulate cancer cell proliferation and survival, and activate ERα via ligand-independent mechanisms.[40-42] Thus, a combination of increased levels of aromatase in the breast, ligand-independent activation of ERα, and elevated circulating levels of free estradiol are likely to contribute to the increased risk of ER-positive breast cancer in women with normal BMI and excess adiposity.

Few studies have examined cancer risk in metabolically obese normal-weight individuals. In a case-cohort study within the WHI, Gunter and colleagues[9] reported increased risk of breast cancer in women with elevated fasting insulin levels regardless of whether they were normal weight or overweight. Similarly, in the Sister Study,[43] normal-weight women with at least 1 metabolic abnormality and women with BMI of at least 25.0 had a nearly equivalent increase in the risk of postmenopausal breast cancer compared with normal-weight women with no metabolic abnormalities. Other studies, however, have yielded different results. Women in the Framingham Heart Study[44] with BMI of at least 25.0 and elevated glucose levels had an increased risk of postmenopausal breast cancer, whereas normal-weight women with elevated glucose levels were not at increased risk. Kabat and colleagues[45] found no difference in breast cancer risk between metabolically healthy vs metabolically unhealthy normal-weight participants in the WHI when using multiple criteria to define metabolic health. The use of varying criteria to classify metabolic status apart from BMI may contribute to these conflicting findings.

To our knowledge, this is the first study of body fat and risk of invasive breast cancer in a cohort of women with exclusively normal BMI. The use of DXA provides highly accurate measurements of adiposity.[16] Anthropometric approaches, such as measurement of waist circumference have variable sensitivity for diagnosing excess body fat.[46,47] When considering an individual's health, physicians generally assess BMI by absolute categorical levels (ie, normal, overweight, or obese). As such, increased adiposity in an individual categorized as having normal BMI is likely to remain clinically unrecognized. Indeed, nearly half of individuals in this study who had the highest amounts of trunk fat had BMIs within the lower quartiles. Future studies are needed to determine whether interventions that reduce fat mass, such as diet and exercise programs or medications including aromatase inhibitors,[48] might lower the elevated risk of breast cancer in this population with normal BMI.

### Strengths and Limitations

Strengths of this study include the prospective design, long-term follow-up, central adjudication of breast cancer diagnoses, availability of fasting blood samples, and use of standardized procedures administered by trained personnel for measurement of anthropometric variables and body fat using DXA. Furthermore, stringent multivariate models were used to control for multiple potential confounders. Limitations include the nongeneralizability of the findings beyond postmenopausal women, the relatively small number of incident invasive breast cancers, and the small sample size for some blood factors, which limited the number of covariates that could be adjusted for in the multivariate model. Despite the small number of events, we were able to detect an association between body fat levels and breast cancer risk. Furthermore, the effect sizes were of similar magnitude to those reported in previous studies that examined associations between body fat and risk of breast cancer across the full range of BMI.[49]

## Conclusions

The results of this study indicate that postmenopausal women with increased levels of body fat are at elevated risk of breast cancer despite having a normal BMI. These findings support the need for clinical trials evaluating the role of fat loss interventions and antiestrogen therapy for breast cancer risk reduction in postmenopausal women with normal BMI and high body fat levels.

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