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The association between metabolic health, obesity phenotype and the risk of breast cancer

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Abstract

Beyond the current emphasis on body mass index (BMI), it is unknown whether breast cancer risk differs between metabolically healthy and unhealthy normal weight or overweight/obese women. The Sister Study is a nationwide prospective cohort study. Data came from 50,884 cohort participants aged 35 to 74 years enrolled from 2003 through 2009. Cox proportional hazards models were used to estimate multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for breast cancer risk. Metabolic abnormalities considered included: high waist circumference (≥88 cm); elevated blood pressure (≥130/85 mm Hg or antihypertensive medication); previously diagnosed diabetes or antidiabetic drug treatment; and cholesterol-lowering medication use. During follow-up (mean, 6.4 years), 1,388 invasive breast cancers were diagnosed at least 1 year after enrollment. Compared to women with BMI <25 kg/m^2 with no metabolic abnormalities (metabolically healthy normal weight phenotype), women with a BMI <25 kg/m^2 and ≥1 metabolic abnormality (metabolically unhealthy, normal weight phenotype) had increased risk of postmenopausal breast cancer (HR=1.26, 95% CI:1.01–1.56), as did women with a BMI ≥25 kg/m^2 and no metabolic abnormalities (metabolically healthy overweight/obese phenotype) (HR=1.24, 95% CI:0.99–1.55). Furthermore, risk of postmenopausal breast cancer was consistently elevated in women with normal BMI and central obesity (normal weight central obesity phenotype) regardless of the criterion used to define central obesity, with HR for waist circumference ≥88 cm, waist circumference ≥80 cm, and waist-hip ratio ≥0.85 of 1.58, 95% CI: 1.02–2.46; 1.38, 95% CI:1.09–1.75; and 1.38, 95% CI:1.02–1.85, respectively. There was an inverse association between premenopausal breast cancer and metabolically healthy overweight/obese phenotype (HR=0.71, 95% CI:0.52–0.97). Our findings suggest that postmenopausal

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DISCLOSURE

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women who are metabolically unhealthy or have central adiposity may be at increased risk for breast cancer despite normal BMI.

Keywords

metabolic health; obesity; postmenopausal breast cancer; metabolically unhealthy normal weight; normal weight central obesity; metabolically healthy obese

Introduction

Obesity, a persistent public health problem in the United States, is a major risk factor for type 2 diabetes and cardiovascular disease,[1,2] as well as for certain types of cancer.[3] Epidemiological studies have demonstrated that excess adiposity represented by higher body mass index (BMI) is associated with increased risk of breast cancer after menopause.[4,5] There is some evidence that central obesity, represented by waist circumference (WC) or waist-hip ratio (WHR), is associated with increased risk of both pre- and postmenopausal breast cancer.[6] Proposed mechanisms for the association between obesity and breast cancer include insulin resistance,[7] inflammation,[8] and unfavorable adipocytokines.[9]

Normal weight individuals with certain abnormal metabolic characteristics such as central obesity, glucose intolerance, increased blood pressure (BP), or dyslipidemia (traits identifying them as “metabolically unhealthy”) are at higher risk for cardiovascular morbidity and mortality, compared with metabolically healthy normal weight (MHNW) individuals.[10,11] Another form of metabolically unhealthy phenotype represented by normal BMI with central obesity is also associated with cardiometabolic morbidity and mortality.[12, 13,14] Underlying mechanisms for these associations could include impaired insulin sensitivity, pro-inflammatory markers, and oxidative stress.[15, 16] In contrast, obese individuals who are within normal limits for metabolic characteristics (“metabolically healthy”) are at lower risk for cardiovascular morbidity and mortality compared with metabolically unhealthy obese individuals.[17,18] This may be because metabolically healthy obese individuals have less visceral fat mass, lower ectopic fat deposition, and more favorable inflammatory and hormonal profiles than their metabolically unhealthy counterparts.[19,20] However, previous studies comparing metabolically health obese individuals with MHNW individuals have not clarified the role of these factors.[21,22]

Abnormal metabolic status is also associated with increased risk of breast cancer.[23] We sought to determine whether the risk of breast cancer differs by metabolic status even among those in the same category of BMI. A few studies have explored the association between metabolic health, as defined by elevated glucose levels, and the risk for obesity-related cancers[24] and cancer mortality.[25] However, there is little information available on the potential differential association between metabolic dysfunction including central obesity, diabetes, hypertension and dyslipidemia, and breast cancer among normal BMI or overweight/obese women. Assessment of effects of metabolic phenotypes within categories of normal weight and overweight/obese women will allow us to better identify women at high risk of breast cancer. In the present study, we examined the association between

metabolic health, obesity, and the risk of invasive breast cancer, using data from the nationwide prospective Sister Study cohort.

MATERIALS AND METHODS

Study population

Study participants came from the Sister Study, a nationwide prospective cohort study investigating environmental and genetic risk factors for breast cancer. During 2003 to 2009, 50,884 women whose sister had been diagnosed with breast cancer were enrolled. Participants were ages 35–74 at enrollment and had never been diagnosed with breast cancer. Details of study design, data collection, and outcome measurements have been published.[26, 27] The Sister Study was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences/NIH and the Copernicus Group. All participants provided written informed consent. The data presented in the current analyses were obtained from Sister Study data release 4.1 (October, 2015) in which incident breast cases were diagnosed as of July 1, 2014.

Ascertainment of metabolic health and obesity phenotype

We categorized participants according to metabolic health using the cardiometabolic abnormalities associated with metabolic syndrome (MetS): central obesity, elevated BP, type 2 diabetes, and dyslipidemia.[28]

WC, hip circumference, and BP were measured by trained personnel during a home visit at enrollment. WC was measured at the midpoint between the lowest rib and the top of the iliac crest. Hip circumference was measured around the hips at their maximum. The average of the second and third measurements of systolic and diastolic BP was used when three BP readings were available. When there were only two BP measurements, the two were averaged.

Blood glucose and lipids were not measured. As an approximation, women were considered to have type 2 diabetes if they used antidiabetic medication or if they had self-reported diagnosis of diabetes at age 30 years or older. Women who both self-reported high cholesterol and reported using cholesterol-lowering medication for specific treatment of lipid abnormalities at enrollment, including fibrates, niacin, long-chain omega-3 fatty acids, and statins, were considered to have dyslipidemia representing elevated triglycerides and reduced high-density lipoprotein (HDL) cholesterol.[28, 29] We defined elevated BP as either measured systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or use of antihypertensive medication for self-reported hypertension currently or in the past year. Central obesity was defined as WC ≥88 cm.[28] WC ≥80 cm has been suggested to increase the risk of metabolic complications[30] and was also considered in some analyses.

The metabolically healthy phenotype was defined as having no evidence of cardiometabolic abnormalities. This phenotype was further categorized as MHNW phenotype (18.5≤ BMI <25 kg/m^2) and metabolically healthy overweight/obese (MHO) phenotype (BMI ≥25 kg/m^2). The metabolically unhealthy phenotype was defined within each BMI group as women who had at least one cardiometabolic abnormality and subcategorized as either metabolically

unhealthy normal weight (MUNW) phenotype or metabolically unhealthy overweight/obese (MUO) phenotype).

The obesity phenotype was further investigated by combining general obesity (BMI) and central obesity measures (WC and WHR). There are different approaches to define central obesity.[13, 2814] Thus, we classified and explored central obesity using two established WC cutoffs known to increase or substantially increase risk of metabolic complications in women (80 cm and 88 cm); 0.85 was used as a cutoff for WHR[30]. Normal weight, central obesity was defined in three ways: BMI <25 kg/m^2 and either 1) WC ≥80 cm, 2) WC ≥88 cm, or 3) WHR ≥0.85. BMI-defined general overweight and obesity with and without central obesity were also defined using the same cutoffs. Other covariates were obtained from computer-assisted baseline telephone interviews.

Ascertainment of breast cancer

Participants were queried at least annually about new medical events with follow-up questionnaires. Response rates were >92% for all follow-ups.[31] Self-reported incident breast cancers and tumor characteristics were verified by medical records, which had been obtained for 82% of the 1,388 cases at time of this data release. Agreement was high between self-reported breast cancer diagnosis and medical records (99.4%). Classification of an invasive cancer (98.5 %), and estrogen receptor (ER)-positive status (99 %) were also in high agreement. Therefore, self-reported tumor characteristics were included in the analyses when medical records were not available.

We excluded women who had incomplete information for BMI (n=19), WC (n=189), WHR (n=218), metabolic abnormalities (elevated BP, type 2 diabetes, or dyslipidemia) (n=364), or unclear menopausal status, i.e. retention of an ovary despite hysterectomy, ablation, or embolization before age 55 (n=2,886). To reduce bias from reverse-causal effects of tumors prior to diagnosis, we also excluded person-time within 12 months after enrollment (758 incident breast cancers). In addition, we excluded women who were pregnant (n=20) or breast feeding (n=38) at baseline, who were underweight (BMI <18.5 kg/m^2) (n=563), or who had a history of any cancer except non-melanoma skin cancer (n=2,681). A total of 43,599 women were included, contributing 240,863 person-years of follow-up.

Statistical Analysis

We used Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between metabolic phenotype, obesity phenotype and breast cancer risk. Proportional hazards assumptions were evaluated by Schoenfeld residuals with the logarithm of the cumulative hazards function based on Kaplan-Meier estimates for metabolic phenotype and obesity phenotype. There was no significant departure from proportionality in hazards over time. Since age was used as the primary time scale, study subjects were entered into the risk set at one year after the age when they finished baseline evaluations (left truncation). Person-time was accrued from then until the age of breast cancer diagnosis or last follow-up. We focused on invasive breast cancer in the present analysis, because those with metabolic abnormalities may differ in cancer screening behaviors leading to higher chance of detecting *in situ* breast cancer. Thus,

in situ tumors were censored at the age of diagnosis. Time-varying menopausal status was considered for both incident cases and non-cases. For follow up time at risk, post-menopausal time was considered to begin at the age of the last menstrual period prior to a 12 month interval with no menses. In addition, estrogen receptor (ER) expression in the tumor was determined with opposing or undefined ER expression censored at the age of diagnosis.[32]

Potential confounders were identified *a priori* based on literature review. The following covariates were included in multivariable adjusted models: age at baseline, race (non-Hispanic white, non-Hispanic black, Hispanic, or other), education (<high school, high school equivalent, some college, or ≥4-year degree), age at menarche, breastfeeding history (total number of weeks), age at first live birth (nulliparous, <21 years, 21 to <25 years, 25 to <29 years, 29 to <32 years, or ≥32 years), and the following variables as assessed at baseline: parity (nulliparous or 1, 2–3, ≥4), hormone replacement therapy (none, estrogen only, estrogen and progesterone, or both estrogen alone and estrogen and progesterone), oral contraceptive use (ever or never), menopausal status at baseline, sister age at diagnosis of breast cancer, smoking history (total pack-years), alcohol consumption (never-drinker, former drinker, currently drink <1 drink/day, currently drink 1 drink/day, currently drink 1.1–1.9 drinks/day, or currently drink ≥2 drinks/day), and physical activity (metabolic equivalent hours/week).

A likelihood ratio test was used to investigate which component(s) of metabolic phenotype contributed significantly to the association between metabolic phenotype and breast cancer risk. Case-only analysis was applied to evaluate whether the association between metabolic phenotype and breast cancer differed according to ER expression. We also assessed whether the joint effect of high BMI and metabolic abnormalities was multiplicative by carrying out goodness of fit tests for including an interaction term for metabolic abnormalities × BMI in the models. Potential effect modification by time varying menopausal status, postmenopausal hormone use, strong family history (i.e. >1 versus 1 first-degree relative with breast cancer), and race/ethnicity was evaluated through stratified analysis and interaction testing using a likelihood ratio test. In addition, we performed several sensitivity analyses: (1) re-analysis with exclusion of subjects who had a history of cardiovascular disease (angina, myocardial infarction, congestive heart failure, transient ischemic attack and stroke) or polycystic ovary syndrome at baseline, which may affect metabolic status; (2) exploring the association separately for overweight (25≤ BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2) status; (3) investigation of the association between number of metabolic abnormalities and BMI classification and risk of invasive breast cancer; (4) investigation of the association between each metabolic abnormality and BMI classification and risk of invasive breast cancer. Statistical significance was evaluated with two-sided tests, with the level of significance at 0.05. SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

RESULTS

10.3% and 13.8% of participants were categorized as MUNW and MHO, respectively (Table 1). Compared to metabolically healthy women in each obesity-status category, metabolically

unhealthy women were older and less likely to be non-Hispanic white. They also had younger age at first live birth and shorter lifetime duration of breastfeeding and were less likely to use birth control pills and alcohol, but more likely to be physically inactive and to smoke. Descriptive characteristics of study participants according to the number of metabolic abnormalities in each normal and overweight/obese BMI category are also shown in Supplemental Table 1.

The associations between metabolic phenotypes and invasive breast cancer are shown in Table 2. During follow-up (mean, 6.4 years) from one year after enrollment, 1,388 invasive breast cancers were diagnosed. Overall, MUO phenotype was associated with higher risk of invasive breast cancer compared with MHNW phenotype. After menopause, women with either the MUNW or the MHO phenotype at enrollment had similarly increased risk of breast cancer (HR=1.26, 95% CI:1.01–1.56; HR=1.24, 95% CI:0.99–1.55, respectively) relative to MHNW phenotype. The estimate was larger for women with the MUO phenotype (HR=1.51, 95% CI:1.28–1.78). Overall, the HR tended to be greater for postmenopausal versus premenopausal breast cancer, especially for the MUO phenotypes. There was a significant inverse association between premenopausal breast cancer and MUO phenotype (HR=0.71, 95% CI:0.52–0.97). The overall associations between metabolic health and risk of breast cancer in overweight/obese women were similar for women categorized as overweight (25≤ BMI <30 kg/m^2) or obese (BMI ≥30 kg/m^2), although the estimates for some phenotypes were unreliable due to small numbers of cases (Supplemental Table 2).

Evidence related to the role of central obesity in the association between metabolic phenotypes and invasive breast cancer is shown in Table 3 and Supplemental Table 3. Compared to MHNW women, women with normal BMI, high WC, and no other metabolic abnormality had the highest estimated HR for postmenopausal breast cancer among all combinations of metabolic abnormalities and central obesity (HR=2.12, 95% CI:1.19–3.80). Similar associations were observed in ER-positive postmenopausal breast cancer (data not shown). As shown in the Supplemental Table 3, there was a relatively large difference of the effect size between the model with and without central obesity as a covariate, especially for the MHO and MUO phenotypes, compared to the other models with and without another metabolic parameter as a covariate. In addition, the inclusion of central obesity significantly improved the fit of the model. There were no significant differences in model fit when other metabolic parameters such as type 2 diabetes, dyslipidemia, and elevated BP were left out of the model.

The association between obesity phenotypes and invasive breast cancer with and without elevated WC or WHR is shown in Table 4. The correlation between BMI and WC was 0.87. The proportions of women who had central obesity within the category of normal weight, overweight, and obesity were 1.4%, 12.3%, and 27.2% for WC ≥88 cm, and 7.8%, 25.0%, and 29.4% for WC ≥80 cm, and 4.1%, 9.4%, and 14.1% for WHR ≥0.85, respectively (Supplemental Table 4). Normal weight central obesity phenotype was associated with a 38% increase in risk of postmenopausal breast cancer (HR=1.38, 95% CI:1.09–1.75; HR=1.38, 95% CI:1.02–1.85) using cutoffs of WC ≥80 cm and WHR ≥0.85, respectively. The highest relative risk of postmenopausal breast cancer was noted in the normal weight central obesity phenotype using a cutoff of WC ≥88 cm (HR=1.58, 95% CI:1.02–2.46).

Similar associations were observed in ER-positive postmenopausal breast cancer (data not shown). Normal weight central obesity phenotype also tended to have high risk of premenopausal breast cancer using WHR ≥0.85, but the number of cases was small.

There were no significant interactions between metabolic abnormalities and BMI, and central obesity and BMI, based on a multiplicative model for joint effects. For the association between metabolic phenotype, obesity phenotype, and invasive postmenopausal breast cancer, there was also no effect modification by strong family history of breast cancer or hormone replacement therapy use. Sensitivity analyses that excluded women with cardiovascular disease or polycystic ovary syndrome did not materially change the overall results. There was no significant interaction between number of metabolic abnormalities and BMI classification and risk of invasive breast cancer. There was no significant trend of breast cancer risk with increasing numbers of metabolic abnormalities in each BMI category (Supplemental Table 5). When we further investigated the association between each metabolic abnormality and BMI classification and risk of invasive breast cancer, overweight/obese women had higher risk of postmenopausal breast cancer regardless of presence or absence of type 2 diabetes, high blood pressure, or dyslipidemia (data not shown).

DISCUSSION

In this nationwide large prospective cohort study, we found that women who had the MUNW phenotype at enrollment, defined as normal weight with one or more metabolic abnormalities, including central obesity, type 2 diabetes, dyslipidemia, and elevated BP had increased risk of postmenopausal breast cancer. Overweight or obese women had increased risk for postmenopausal breast cancer regardless of accompanying metabolic abnormalities.

There is consistent evidence that both the MUNW phenotype and the normal weight central obesity phenotype are associated with cardiometabolic dysregulation,[13] inflammation,[16] and increased cardiovascular mortality[14]. Whether these phenotypes increase cancer risk or breast cancer risk, specifically, has not been clarified. Metabolic dysfunction is one of the potential mechanisms purported to underlie breast cancer pathogenesis.[23] MUNW women have higher levels of proinflammatory cytokines such as interleukin (IL)-1alpha, IL-1beta, IL-6, IL-8, and tumor necrosis factor-alpha[16] as well as lower insulin sensitivity and adverse metabolic profiles related to poor dietary habits[33] or sedentary behavior.[34, 35] All of these may increase the risk of postmenopausal breast cancer.[36]

Our study identified elevated breast cancer risk among metabolically healthy and metabolically unhealthy overweight/obese women. Whether the MHO phenotype is benign has been controversial.[21, 37] A meta-analysis showed that the MHO phenotype was not associated with a higher risk of all-cause mortality, but it was associated with increased risk of cardiovascular events compared with MHNW phenotype.[38] In contrast, another meta-analysis showed that the MHO phenotype was associated with lower risk of cardiovascular events compared with MUNW or MUO phenotypes.[22] The MHO phenotype has been reported to be a condition lacking long-term stability.[39] Thus, frequent progression to the MUO phenotype may explain inconsistent results. Based on our results, overall adiposity

might contribute to increasing the risk of postmenopausal breast cancer in ways that are not mediated by obesity-induced metabolic abnormalities in overweight/obese women.

In the present study, central obesity was the driver for the association between metabolic phenotype and the risk of breast cancer. Excess central adiposity, a crucial correlate of insulin resistance, has been regarded as a key component of MetS[40, 41] as well as a risk factor for breast cancer beyond BMI.[32] It has been suggested that increased abdominal fat may increase the risk of breast cancer through elevated levels of estrogen, testosterone, and insulin-like growth factor-1.[6] In our results, the normal weight central obesity phenotype, regardless of the criterion used to define central obesity, was associated with increased risk of postmenopausal breast cancer, although the number of women who had this phenotype was small. Furthermore, postmenopausal breast cancer risk was increased among normal weight women with central obesity who did not have evidence of other metabolic abnormalities such as diabetes, dyslipidemia, or elevated blood pressure. Much evidence shows that the normal weight central obesity phenotype is associated with cardiometabolic morbidity and mortality[424314], but less is known about this phenotype and breast cancer risk.

Metabolic abnormalities other than central obesity did not contribute much to the risk of postmenopausal breast cancer. Although imprecise estimates make it difficult to draw clear inferences from these findings, it is possible that the use of medications such as metformin[44, 45] and statins,[46] which may be used to treat type 2 diabetes and dyslipidemia, might play a protective role against breast cancer. This would mask or attenuate any risk associated with these metabolic abnormalities. In the absence of laboratory measures, we inferred several MetS components from use of specific medications. It is also likely that there is some misclassification due to clinically undetected or misreported metabolic abnormalities. It has been suggested that MetS as a whole increases the risk of breast cancer rather than a specific component of MetS.[47] Based on our results, however, central obesity may play a primary role.

There was suggestion of decreasing risk for premenopausal breast cancer among overweight/obese women with metabolic abnormalities. Overweight/obese premenopausal women may have reduced risk of breast cancer because of decreased estrogen and progesterone exposure related to increased anovulatory menstrual cycles.[3] Previous studies showed little association between MetS and breast cancer in premenopausal women.[48, 49] Considering that BMI increases with increasing number of metabolic abnormalities in overweight/obese women in our data (Table 1 and Supplemental Table 1), our findings suggest that BMI may dominantly contribute to decreasing the risk of premenopausal breast cancer regardless of accompanying metabolic abnormalities.

In the present study, the association between metabolic status and risk of breast cancer was evaluated separately within BMI strata to especially focus on normal weight women who are metabolically unhealthy, and overweight/obese women who are metabolically healthy. Our interest was motivated by well-established evidence of a differential association between these phenotypes and cardiometabolic morbidity and mortality.[1011–131415–1718, 1920, 4243] However, women with high BMI at baseline are at risk for future metabolic abnormalities and thus may not represent a distinct risk group, as supported by a recent Mendelian

randomization study.[50] Non-significant interaction between metabolic abnormalities and BMI status on risk of breast cancer might support that both obesity and metabolic abnormality contribute independently and multiplicatively to increase the risk of breast cancer.

We were unable to address the possibility that women who were normal weight but metabolically unhealthy at baseline had recently lost weight and thus were misclassified. We did not collect self-reported weights in the years immediately preceding study enrollment. Furthermore, sustained weight loss is known to be difficult to achieve, and we would expect weight loss to have been accompanied by reductions in other metabolic abnormalities, making misclassification an unlikely explanation.

Strengths of the present study include the large sample size, standardized data collection, examiner-measured height, weight, and BP, and comprehensive information on potential risk factors for breast cancer. Additionally, the Sister Study cohort study has a prospective design, highly motivated participants and high retention.

One potential limitation is that we have grouped women treated for an abnormality with women having the abnormality. If for example actual hypertension is related to risk, but medication-induced normal BP is not, this mixing of phenotypes will complicate the inference. Another limitation is that the definition of some metabolic abnormalities such as type 2 diabetes and cholesterol was based on self-reported information instead of direct measurement of fasting glucose, triglycerides, and HDL cholesterol. In this way, we could not capture women with subclinical metabolic risk factors, which may lead to misclassification of metabolic health status and reduced comparability of the study results. Such misclassification could be systematic if, for example, obese women tend to get less regular preventive care and screening. However, medication use is considered a reasonable alternative indicator for metabolic abnormalities.[28] We limited use of cholesterol-lowering medication to fibrates, niacin, long-chain omega-3 fatty acids, and statins to represent elevated triglycerides and reduced HDL cholesterol to improve the sensitivity of our measure.[29] In addition, previous studies using self-reported information for defining MetS showed consistent results with those using direct measurements in the association between MetS and breast cancer.[48, 51] Study participants have a first-degree family history of breast cancer and have, on average, two times the risk of getting breast cancer as women without a first-degree family history.[52] However, women in our study are similar to the general population in terms of non-familial breast cancer risk factors.[27] Furthermore, we did not find any interactions between the presence of strong family history of breast cancer and the association between obesity-metabolic phenotypes and breast cancer risk. Also, despite exclusion of person-time within 12 months after enrollment, reverse causality cannot be entirely ruled out. However, weight loss due to undiagnosed breast cancer seems unlikely as most cases were diagnosed in early stages. In addition, there might be residual confounding or bias that we could not control.

In conclusion, our findings suggest that normal weight postmenopausal women who are metabolically unhealthy or have central obesity may be at increased risk of post-menopausal breast cancer despite normal BMI. Also, overweight/obese postmenopausal women who are

metabolically healthy, regardless of central obesity may also be at increased risk of breast cancer. However, obese women may be at decreased risk of premenopausal breast cancer even with metabolic abnormalities. Future studies should focus on elucidating the mechanisms underlying the relationship of these phenotypes to breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BP	blood pressure
BMI	body mass index
CI	confidence interval
ER	estrogen receptor
HR	hazard ratio
MetS	metabolic syndrome
MHNW	metabolically healthy normal weight
MHO	metabolically healthy overweight/obese
MUNW	metabolically unhealthy normal weight
MUO	metabolically unhealthy overweight/obese
WC	waist circumference
WHR	waist-hip ratio

References

1. Sowers JR. Obesity as a cardiovascular risk factor. The American Journal of Medicine. 2003; 115:37–41.
2. Ota T. Chemokine systems link obesity to insulin resistance. Diabetes Metab J. 2013; 37:165–72. [PubMed: 23807918]
3. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004; 4:579–91. [PubMed: 15286738]
4. Amadou A, Ferrari P, Muwonge R, Moskal A, Biessy C, Romieu I, Hainaut P. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. Obes Rev. 2013; 14:665–78. [PubMed: 23615120]

5. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, Ochs-Balcom HM, Thomson CA, Caan BJ, Tinker LF, Urrutia RP, Knudtson J, et al. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. JAMA Oncol. 2015; 1:611–21. [PubMed: 26182172]
6. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. Obes Rev. 2003; 4:157–73. [PubMed: 12916817]
7. Ferroni P, Riondino S, Buonomo O, Palmirotta R, Guadagni F, Roselli M. Type 2 Diabetes and Breast Cancer: The Interplay between Impaired Glucose Metabolism and Oxidant Stress. Oxid Med Cell Longev. 2015; 2015:183928. [PubMed: 26171112]
8. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer. 2011; 11:886–95. [PubMed: 22113164]
9. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev. 2004; 5:153–65. [PubMed: 15245384]
10. Conus F, Rabasa-Lhoret R, Peronnet F. Characteristics of metabolically obese normal-weight (MONW) subjects. Appl Physiol Nutr Metab. 2007; 32:4–12. [PubMed: 17332780]
11. Park YM, Fung TT, Steck SE, Zhang J, Hazlett LJ, Han K, Lee SH, Merchant AT. Diet Quality and Mortality Risk in Metabolically Obese Normal-Weight Adults. Mayo Clin Proc. 2016; 91:1372–83. [PubMed: 27712636]
12. Kim MK, Han K, Kwon HS, Song KH, Yim HW, Lee WC, Park YM. Normal weight obesity in Korean adults. Clin Endocrinol (Oxf). 2014; 80:214–20. [PubMed: 23362933]
13. Romero-Corral A, Somers VK, Sierra-Johnson J, Korenfeld Y, Boarin S, Korinek J, Jensen MD, Parati G, Lopez-Jimenez F. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. Eur Heart J. 2010; 31:737–46. [PubMed: 19933515]
14. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T, Jensen MD, Roger VL, Singh P, Lopez-Jimenez F. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. Ann Intern Med. 2015; 163:827–35. [PubMed: 26551006]
15. Di Renzo L, Galvano F, Orlandi C, Bianchi A, Di Giacomo C, La Fauci L, Acquaviva R, De Lorenzo A. Oxidative stress in normal-weight obese syndrome. Obesity (Silver Spring). 2010; 18:2125–30. [PubMed: 20339360]
16. De Lorenzo A, Del Gobbo V, Premrov MG, Bigioni M, Galvano F, Di Renzo L. Normal-weight obese syndrome: early inflammation? Am J Clin Nutr. 2007; 85:40–5. [PubMed: 17209175]
17. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, Sladek R, Rabasa-Lhoret R. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond). 2011; 35:971–81. [PubMed: 20975726]
18. Park YM, Steck SE, Fung TT, Zhang J, Hazlett LJ, Han K, Merchant AT. Mediterranean diet and mortality risk in metabolically healthy obese and metabolically unhealthy obese phenotypes. Int J Obes (Lond). 2016; 40:1541–9. [PubMed: 27339604]
19. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. The lancet Diabetes & endocrinology. 2013; 1:152–62. [PubMed: 24622321]
20. Goncalves CG, Glade MJ, Meguid MM. Metabolically healthy obese individuals: Key protective factors. Nutrition. 2016; 32:14–20. [PubMed: 26440861]
21. Kramer CK, Zinman B, Retnakaran R. Are Metabolically Healthy Overweight and Obesity Benign Conditions? A Systematic Review and Meta-analysis. Ann Intern Med. 2013; 159:758–69. [PubMed: 24297192]
22. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: A systematic review and meta-analysis. European journal of preventive cardiology. 2016; 23:956–66. [PubMed: 26701871]
23. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2007; 8:395–408. [PubMed: 17716297]
24. Moore LL, Chadid S, Singer MR, Kreger BE, Denis GV. Metabolic health reduces risk of obesity-related cancer in framingham study adults. Cancer Epidemiol Biomarkers Prev. 2014; 23:2057–65. [PubMed: 25012997]

25. Oh CM, Jun JK, Suh M. Risk of cancer mortality according to the metabolic health status and degree of obesity. Asian Pacific journal of cancer prevention : APJCP. 2014; 15:10027–31. [PubMed: 25520064]
26. Nichols HB, DeRoo LA, Scharf DR, Sandler DP. Risk-benefit profiles of women using tamoxifen for chemoprevention. Journal of the National Cancer Institute. 2015; 107:354. [PubMed: 25475563]
27. Weinberg CR, Shore DL, Umbach DM, Sandler DP. Using risk-based sampling to enrich cohorts for endpoints, genes, and exposures. Am J Epidemiol. 2007; 166:447–55. [PubMed: 17556763]
28. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120:1640–5. [PubMed: 19805654]
29. Ito MK. Long-chain omega-3 fatty acids, fibrates and niacin as therapeutic options in the treatment of hypertriglyceridemia: A review of the literature. Atherosclerosis. 2015; 242:647–56. [PubMed: 26296750]
30. Consultation, WE. Waist circumference and waist-hip ratio. 2011.
31. Ekenga CC, Parks CG, Sandler DP. A prospective study of occupational physical activity and breast cancer risk. Cancer causes & control : CCC. 2015
32. White AJ, Nichols HB, Bradshaw PT, Sandler DP. Overall and central adiposity and breast cancer risk in the sister study. Cancer. 2015; 121:3700–8. [PubMed: 26193782]
33. Park YM, Steck SE, Fung TT, Zhang J, Hazlett LJ, Han K, Lee SH, Kwon HS, Merchant AT. Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) style diet, and metabolic health in U.S. adults. Clin Nutr. 2016
34. Conus F, Allison DB, Rabasa-Lhoret R, St-Onge M, St-Pierre DH, Tremblay-Lebeau A, Poehlman ET. Metabolic and behavioral characteristics of metabolically obese but normal-weight women. J Clin Endocrinol Metab. 2004; 89:5013–20. [PubMed: 15472199]
35. Lee DH, Kim YM, Jekal Y, Park S, Kim KC, Naruse M, Kim SH, Kim SH, Park JH, Lee MK, Chu SH, Jeon JY. Low levels of physical activity are associated with increased metabolic syndrome risk factors in korean adults. Diabetes Metab J. 2013; 37:132–9. [PubMed: 23641354]
36. Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, Foti D, Chiefari E, Brunetti A. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res. 2012; 2012:789174. [PubMed: 22701472]
37. Bradshaw PT, Stevens J. Invited Commentary: Limitations and Usefulness of the Metabolically Healthy Obesity Phenotype. Am J Epidemiol. 2015; 182:742–4. [PubMed: 26363515]
38. Zheng R, Zhou D, Zhu Y. The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis. J Epidemiol Community Health. 2016; 70:1024–31. [PubMed: 27126492]
39. Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M. The natural course of healthy obesity over 20 years. J Am Coll Cardiol. 2015; 65:101–2. [PubMed: 25572516]
40. Lim JS, Choi YJ, Kim SK, Huh BW, Lee EJ, Huh KB. Optimal Waist Circumference Cutoff Value Based on Insulin Resistance and Visceral Obesity in Koreans with Type 2 Diabetes. Diabetes Metab J. 2015; 39:253–63. [PubMed: 26124996]
41. Park YM, Kwon HS, Lim SY, Lee JH, Yoon KH, Son HY, Yim HW, Lee WC. Optimal waist circumference cutoff value reflecting insulin resistance as a diagnostic criterion of metabolic syndrome in a nondiabetic Korean population aged 40 years and over: the Chungju Metabolic Disease Cohort (CMC) study. Yonsei Med J. 2010; 51:511–8. [PubMed: 20499415]
42. Coutinho T, Goel K, Correa de Sa D, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee SH, et al. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. J Am Coll Cardiol. 2011; 57:1877–86. [PubMed: 21545944]
43. Coutinho T, Goel K, Corrêa de Sá D, Carter RE, Hodge DO, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, et al. Combining Body Mass Index With Measures

of Central Obesity in the Assessment of Mortality in Subjects With Coronary Disease: Role of "Normal Weight Central Obesity". J Am Coll Cardiol. 2013; 61:553–60. [PubMed: 23369419]

44. Col NF, Ochs L, Springmann V, Aragaki AK, Chlebowski RT. Metformin and breast cancer risk: a meta-analysis and critical literature review. Breast cancer research and treatment. 2012; 135:639–46. [PubMed: 22847511]
45. Park HK. Metformin and cancer in type 2 diabetes. Diabetes Metab J. 2013; 37:113–6. [PubMed: 23641351]
46. McDougall JA, Malone KE, Daling JR, Cushing-Haugen KL, Porter PL, Li CI. Long-term statin use and risk of ductal and lobular breast cancer among women 55 to 74 years of age. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013; 22:1529–37.
47. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, Giugliano D. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. Menopause (New York, NY). 2013; 20:1301–9.
48. Bosco JL, Palmer JR, Boggs DA, Hatch EE, Rosenberg L. Cardiometabolic factors and breast cancer risk in U.S. black women. Breast cancer research and treatment. 2012; 134:1247–56. [PubMed: 22710709]
49. Agnoli C, Grioni S, Sieri S, Sacerdote C, Ricceri F, Tumino R, Frasca G, Pala V, Mattiello A, Chiodini P, Iacoviello L, De Curtis A, et al. Metabolic syndrome and breast cancer risk: a case-cohort study nested in a multicentre italian cohort. PloS one. 2015; 10:e0128891. [PubMed: 26030767]
50. Wurtz P, Wang Q, Kangas AJ, Richmond RC, Skarp J, Tiainen M, Tynkkynen T, Soininen P, Havulinna AS, Kaakinen M, Viikari JS, Savolainen MJ, et al. Metabolic signatures of adiposity in young adults: Mendelian randomization analysis and effects of weight change. PLoS medicine. 2014; 11:e1001765. [PubMed: 25490400]
51. Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A, Negri E, La Vecchia C. Metabolic syndrome and the risk of breast cancer in postmenopausal women. Annals of oncology : official journal of the European Society for Medical Oncology/ESMO. 2011; 22:2687–92.
52. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. International journal of cancer Journal international du cancer. 1997; 71:800–9. [PubMed: 9180149]

Novelty and Impact

It is unknown whether breast cancer risk differs between metabolically healthy and unhealthy normal weight or overweight/obese women. The present study shows that normal weight postmenopausal women who are metabolically unhealthy or have central obesity may be at increased risk of breast cancer despite normal body mass index; overweight/obese postmenopausal women who are metabolically healthy, regardless of central obesity may also be at increased risk of breast cancer. The findings suggest that additional consideration of metabolic abnormalities could provide important targets for prevention strategies to reduce breast cancer risk.

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Table 1

Descriptive characteristics of study participants according to metabolic phenotypes

	Metabolically Healthy Normal Weight (MHNW)		Metabolically Unhealthy Normal Weight (MUNW)		Metabolically Healthy Overweight/Obese (MHO)		Metabolically Unhealthy Overweight/Obese (MUO)	
Characteristic	**0**		**≥ 1**		**0**		**≥ 1**	
No. of participants, n %	12,150	(27.9)	4,469	(10.3)	6,014	(13.8)	20,966	(48.1)
Mean (SD)								
Age at baseline, yr	53.0	(8.8)	60.2	(8.2)	53.4	(8.6)	57.3	(8.7)
BMI, kg/m^2	22.2	(1.6)	22.8	(1.6)	27.3	(2.0)	32.2	(5.6)
Waist circumference, cm	73.1	(6.1)	77.9	(9.0)	81.1	(4.7)	97.5	(12.2)
Waist-hip ratio	0.76	(0.06)	0.80	(0.08)	0.77	(0.05)	0.85	(0.07)
Age at menarche, yr	12.9	(1.5)	12.9	(1.5)	12.6	(1.4)	12.5	(1.5)
Age at first live birth, yr[†]	26.3	(5.4)	24.5	(4.8)	25.1	(5.4)	23.9	(5.1)
Total MET-hours of physical activity, wk	57.2	(33.5)	54.3	(32.2)	52.3	(31.1)	45.8	(28.9)
Lifetime duration of breastfeeding, wk[‡]	73.7	(76.2)	59.8	(64.0)	71.0	(75.5)	60.5	(70.9)
Proportion (%)								
Non-Hispanic white		90.6		87.7		84.1		79.5
Postmenopausal at enrollment		57.4		85.3		59.8		77.1
Parous at enrollment		79.5		83.1		80.9		83.3
Ever used birth control pill		86.4		81.3		85.6		82.7
Ever hormone replacement therapy		34.3		59.1		35.0		40.3
Ever smoker		39.8		47.6		40.9		45.7
Current drinker		86.7		82.4		84.6		76.9
Abdominal obesity[§]				13.9				82.0
Elevated blood pressure[‖]				62.4				53.9
Type 2 diabetes[¶]				5.4				10.8
Dyslipidemia[**]				45.7				32.0

Data are presented as mean (standard deviation), or percentage (% column, except that of the participants).

Abbreviations: BMI, body mass index; MET, metabolic equivalent.

[*] Metabolic abnormalities include central obesity (waist circumference ≥ 88 cm), elevated blood pressure, type 2 diabetes, and dyslipidemia.

† Among women who had live births

‡ Among women who ever breastfed.

§ Defined as waist-circumference≥88 cm

‖ Systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥85 mm Hg or antihypertensive medication use for self-reported hypertension taken currently or in the past year

¶ Antidiabetic medication use and self-reported diagnosis of diabetes at age 30 years or older

** Self-reported hypercholesterolemia and on cholesterol-lowering medication use, including fibrates, niacin, long-chain omega-3 fatty acids, and statins as a proxy variable for elevated triglycerides and reduced high-density lipoprotein cholesterol.

Table 2

Hazard ratios (HRs) and 95% CIs for the association between metabolic phenotypes and invasive breast cancer

	Metabolic phenotype	BMI (kg/m^2)	No. of metabolic abnormalities*	No. of participants at baseline	Person-years†	Total invasive breast cancer		ER+ breast cancer		ER− breast cancer	
						No. of cases	Multivariable-adjusted HR (95% CI)‡	No. of cases	Multivariable-adjusted HR (95% CI)‡	No. of cases	Multivariable-adjusted HR (95% CI)‡
Overall	MHNW	< 25	0	12,150	70,151	337	1 (reference)	264	1 (reference)	49	1 (reference)
	MUNW		≥ 1	4,469	24,591	149	1.12 (0.92–1.37)	118	1.13 (0.90–1.42)	18	1.01 (0.58–1.76)
	MHO	≥ 25	0	6,014	33,622	181	1.14 (0.95–1.37)	144	1.18 (0.96–1.46)	19	0.79 (0.47–1.35)
	MUO		≥ 1	20,966	112,499	721	1.28 (1.12–1.48)	547	1.28 (1.09–1.50)	98	1.13 (0.78–1.63)
Post-menopause	MHNW	< 25	0	6,968	48,955	218	1 (reference)	169	1 (reference)	35	1 (reference)
	MUNW		≥ 1	3,814	22,460	138	1.26 (1.01–1.56)	107	1.23 (0.96–1.58)	18	1.19 (0.67–2.13)
	MHO	≥ 25	0	3,595	24,115	127	1.24 (0.99–1.55)	99	1.28 (0.99–1.64)	15	0.88 (0.48–1.61)
	MUO		≥ 1	16,155	95,254	648	1.51 (1.28–1.78)§	490	1.50 (1.25–1.81)§	89	1.26 (0.83–1.92)
Pre-menopause	MHNW	< 25	0	5,182	21,183	117	1 (reference)	94	1 (reference)	13	N/A
	MUNW		≥ 1	655	2,132	11	0.89 (0.48–1.65)	11	1.12 (0.60–2.10)	0	N/A
	MHO	≥ 25	0	2,419	9,504	53	0.94 (0.67–1.32)	44	0.98 (0.67–1.42)	4	N/A
	MUO		≥ 1	4,811	17,239	72	0.71 (0.52–0.97)	56	0.71 (0.50–1.02)	9	N/A

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy overweight/obese; MUO, metabolically unhealthy overweight/obese; BMI, body mass index; HR, hazard ratio; 95% CI, 95% confidence interval; ER, estrogen receptor; +, positive; −, negative.

*Metabolic abnormalities include central obesity (waist circumference ≥ 88 cm), elevated blood pressure, type 2 diabetes, and dyslipidemia.

†For this analysis, postmenopausal person-years begin to accrue one year after enrollment and include person-years from both women who were post-menopausal at enrollment and those who were pre-menopausal at baseline but experienced menopause during follow-up.

‡Adjusted for age at baseline, race (non-Hispanic white, non-Hispanic black, Hispanic, or other), education (<high school, high school equivalent, some college, or ≥4-year degree), age at menarche, breastfeeding history (total number of weeks), age at first live birth (nulliparous, <21 years, 21 to <25 years, 25 to <29 years, 29 to <32 years, or ≥32 years), parity (nulliparous or 1, 2–3, ≥4), hormone replacement therapy (none, estrogen only, estrogen and progesterone, or both estrogen alone and estrogen and progesterone), oral contraceptive use (ever or never), menopausal status at baseline, sister age at diagnosis of breast cancer, smoking history (total pack-years), alcohol consumption (never-drinker, former drinker, currently drink <1 drink/day, currently drink 1 drink/day, currently drink 1.1–1.9 drinks/day, or currently drink ≥2 drinks/day), and physical activity (metabolic equivalent hours/week).

§HR was significantly different from pre-menopausal breast cancer.

Table 3

Hazard ratios and 95% confidence intervals for the combined effects of metabolic abnormalities and central obesity on risk of invasive breast cancer by time-varying menopausal status

	Metabolic phenotype	BMI (kg/m^2)	Metabolic abnormalities*	Central obesity†	No. of participants at baseline‡	Person-years	No. of cases	Multivariable-adjusted HR (95% CI)§
Post-menopause	MHNW	< 25	No	No	6,968	48,955	218	1 (reference)
	MUNW	< 25	No	Yes	214	1,304	12	2.12 (1.19–3.80)
			Yes	No	3,344	19,743	117	1.20 (0.95–1.50)
			Yes	Yes	256	1,413	9	1.32 (0.67–2.57)
	MHO	≥ 25	No	No	3,595	24,115	127	1.24 (0.99–1.55)
	MUO	≥ 25	No	Yes	4,034	25,878	174	1.59 (1.30–1.96)**
			Yes	No	3,257	19,165	135	1.46 (1.17–1.82)**
			Yes	Yes	8,864	50,211	339	1.48 (1.24–1.78)**
Pre-menopause	MHNW	< 25	No	No	5,182	21,183	117	1 (reference)
	MUNW	< 25	No	Yes	121	454	1	NA
			Yes	No	505	1,584	9	0.96 (0.48–1.90)
			Yes	Yes	29	93	1	NA
	MHO	≥ 25	No	No	2,419	9,504	53	0.94 (0.67–1.31)
	MUO	≥ 25	No	Yes	2,612	10,150	46	0.78 (0.55–1.12)
			Yes	No	523	1,645	5	0.49 (0.20–1.21)
			Yes	Yes	1,676	5,444	21	0.63 (0.38–1.02)

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy overweight/obese; MUO, metabolically unhealthy overweight/obese; BMI, body mass index; HR, hazard ratio; 95% CI, 95% confidence interval; ER, estrogen receptor; +, positive.

*Metabolic abnormalities were here defined by only using elevated blood pressure, type 2 diabetes, and dyslipidemia, and excluding central obesity.

†Waist circumference ≥ 88 cm.

‡For this analysis, postmenopausal person-years begin to accrue one year after enrollment and include person-years from both women who were post-menopausal at enrollment and those who were pre-menopausal at baseline but experienced menopause during follow-up.

§Adjusted for the same covariates used in Table 2.

**HR was significantly different from pre-menopausal breast cancer.

Table 4

Hazard ratios (HRs) and 95% CIs for the association between different obese phenotypes and invasive breast cancer by time-varying menopausal status

		Post-menopause				Pre-menopause			
		No. of participants at baseline*	Person-years	No. of cases	Multivariable-adjusted HR (95% CI)†	No. of participants at baseline*	Person-years	No. of cases	Multivariable-adjusted HR (95% CI)†
BMI (kg/m^2)	Waist circumference (cm)								
18.5–24.9	< 88	10,312	68,698	335	1 (reference)	5,687	22,767	126	1 (reference)
	≥ 88	470	2,716	21	1.58 (1.02–2.46)	150	547	2	NA
≥ 25	< 88	6,852	43,280	262	1.26 (1.07–1.49)	2,942	11,149	58	0.88 (0.63–1.21)
	≥ 88	12,898	76,089	513	1.43 (1.24–1.66) ‡	4,288	15,594	67	0.74 (0.54–1.01)
BMI (kg/m^2)	Waist circumference (cm)								
18.5–24.9	< 80	8,290	56,200	259	1 (reference)	4,933	19,906	106	1 (reference)
	≥ 80	2,492	15,214	97	1.38 (1.09–1.75)	904	3,409	22	1.24 (0.78–1.97)
≥ 25	< 80	2,152	13,985	79	1.22 (0.94–1.59)	1,093	4,144	15	0.67 (0.39–1.15)
	≥ 80	17,598	105,384	696	1.48 (1.27–1.72) ‡	6,137	22,600	110	0.87 (0.65–1.16)
BMI (kg/m^2)	Waist-hip ratio								
18.5–24.9	< 0.85	9,484	63,826	305	1 (reference)	5,335	21,372	113	1 (reference)
	≥ 0.85	1,298	7,589	51	1.38 (1.02–1.85)	502	1,943	15	1.52 (0.89–2.61)
≥ 25	< 0.85	11,816	73,841	458	1.34 (1.15–1.55)≠	4,953	18,869	86	0.81 (0.61–1.09)
	≥ 0.85	7,934	45,528	317	1.49 (1.26–1.76)≠	2,277	7,874	39	0.91 (0.62–1.33)

Abbreviations: BMI, body mass index; HR, hazard ratio; 95% CI, 95% confidence interval; ER, estrogen receptor; +, positive.

*For this analysis, postmenopausal person-years begin to accrue one year after enrollment and include person-years from both women who were post-menopausal at enrollment and those who were pre-menopausal at baseline but experienced menopause during follow-up.

†Adjusted for the same covariates used in Table 2.

≠HR was significantly different from pre-menopausal breast cancer.