Research Article

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Metabolic Obesity Phenotypes and Risk of Breast Cancer in Postmenopausal Women

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Abstract

Background: Obesity and the metabolic syndrome (MetS) have both been linked to increased risk of postmenopausal breast cancer; however, their relative contributions are poorly understood.

Methods: We examined the association of metabolic phenotypes of obesity defined by presence of the MetS (yes and no) and body mass index (BMI; normal, overweight, obese) with risk of postmenopausal breast cancer in a prospective analysis of a cohort of postmenopausal women ($n \sim 21{,}000$) with baseline measurements of blood glucose, triglycerides, HDL-cholesterol, blood pressure, waist circumference, and BMI. Women were classified into 6 metabolic obesity phenotypes according to their BMI (18.5–<25.0, 25.0–<30.0, ≥30.0 kg/m^2) and presence of the MetS (≥3 of the following: waist circumference ≥88 cm, triglycerides ≥150 mg/dL, HDL-C <50 mg/dL, glucose ≥100 mg/dL, and systolic/diastolic blood pressure ≥130/85 mmHg or treatment for hypertension). HRs for incident breast cancer and 95% confidence intervals (95% CI) were estimated using Cox proportional hazards models.

Results: Over 15 years of follow-up, 1,176 cases of invasive breast cancer were diagnosed. Obesity, regardless of metabolic health, was associated with increased risk of breast cancer. Being obese and metabolically unhealthy was associated with the highest risk: HR, 1.62; 95% CI, 1.33–1.96. These associations were stronger in women who had never used hormone therapy.

Conclusions: Our findings suggest that both obesity and metabolic dysregulation are associated with breast cancer risk.

Impact: Beyond BMI, metabolic health should be considered a clinically relevant and modifiable risk factor for breast cancer. *Cancer Epidemiol Biomarkers Prev; 26(12); 1730–5. ©2017 AACR.*

Introduction

The prevalence of obesity has been increasing in the United States over the past three decades (1). At present, roughly one-third of U.S. adults are overweight [body mass index (BMI) of 25.0–<30.0 kg/m^2], and one-third are obese (BMI ≥ 30 kg/m^2; ref. 1). In addition, there has been an increase in the prevalence of diabetes and of the metabolic syndrome (MetS; 2–4). The utility of the MetS is subject to controversy (5), and definitions of the syndrome vary widely and, depending on the definition used and the population studied, the prevalence of the MetS ranges from 10% to 34% (6). Both obesity and the MetS are associated with increased risks of cardiovascular disease, diabetes, and mortality, but there is disagreement as to their relative contributions (7–10).

Obesity is an established risk factor for postmenopausal breast cancer (11), and, in addition, there is limited evidence that both the MetS and diabetes are associated with increased risk of the disease (12–15). However, to date, only three studies have examined the relative contributions of BMI, or waist circumference, and the MetS (or insulin resistance syndrome) to breast cancer risk (16–18). Two of these had relatively small sample size, and all three dichotomized BMI into normal weight and overweight/obese.

To address this question, considering the full range of BMI, we examined the contributions of BMI and the MetS to risk of breast cancer in a subset of nearly 21,000 participants in the Women's Health Initiative cohort with measurements of BMI and components of the MetS.

Materials and Methods

The Women's Health Initiative (WHI) is a large, multicenter study designed to improve our understanding of the determinants of major chronic diseases in postmenopausal women. It is composed of a clinical trial component (CT, $n = 68{,}132$) and an observational study component (OS, $n = 93{,}676$; ref. 19). The CT component included four randomized controlled intervention studies: hormone therapy (two trials), low-fat dietary modification, and calcium + vitamin D supplementation. Women between the ages of 50 and 79 and representing the

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major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998. Details of the study design and reliability of the baseline measures have been published (19, 20). Written informed consent was obtained from participants at all WHI centers in accordance with recognized ethical guidelines, and the study was approved by the institutional review board of each center, as well as by that of the Coordinating Center at the Fred Hutchinson Cancer Research Center.

At study entry, self-administered questionnaires were used to collect information on demographics, medical, reproductive, family history of cancer, and lifestyle factors, including smoking history, alcohol consumption, dietary habits, and recreational physical activity. All participants had their weight and height measured by trained staff at baseline. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. BMI was computed as weight in kilograms divided by the square of height in meters. Two blood pressure measurements were obtained $\geq$30 seconds apart, and the average of the 2 measurements was used in the analysis. Questions about physical activity at baseline referred to a woman's usual pattern of activity, including walking and recreational physical activity. A variable "current total leisure-time physical activity" (MET-h/wk) was computed by multiplying the number of hours per week of leisure-time physical activity by the metabolic equivalent (MET) value of the activity and summing over all types of activities (21).

Follow-up and ascertainment of outcomes

Clinical outcomes (including new cancer diagnoses) were updated semiannually in the CT and annually in the OS using in-person, mailed, or telephone questionnaires. Self-reports of malignancy were verified by central review of medical records and pathology reports by trained physician adjudicators (22).

The CVD biomarkers subsample

Individuals who had baseline measurements of fasting serum glucose and insulin and other clinical parameters that were made in various substudies within WHI were assembled into the CVD Biomarkers Subsample ($n = 25,446$). Some substudies entailed selecting a random sample; others selected participants based on specific age and ethnicity/race criteria within the hormone therapy trials; another substudy was a nested case–control study within the hormone therapy trials with random sampling of controls.

Assays for glucose, HDL-C, and triglycerides

Blood was obtained after at least 8 hours of fasting for 99.8% of participants in the Subsample. The specimens were centrifuged, and serum and plasma were frozen at −70°C and shipped on dry ice to a central processing facility. HDL-C was measured in serum using the HDLC Plus 3rd Generation Direct Method (Roche) on the Roche Modular P Chemistry Analyzer. Triglycerides were measured in serum using Triglyceride GB reagent (Roche) on the Roche Modular P Chemistry Analyzer. In the vast majority of women ($n = 22,314,88\%$), glucose was measured in serum using the Gluco-quant Glucose/hexokinase reagent (Roche Diagnostics) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation). In the remainder of the women, serum glucose was determined by the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics).

Definition of the MetS

We used the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition of the MetS (4): having $\geq$3 of the 5 following criteria: waist circumference $\geq$88 cm, triglycerides $\geq$150 mg/dL, HDL-C <50 mg/dL, glucose $\geq$100 mg/dL, and systolic/diastolic blood pressure $\geq$130/85 mmHg or treatment for hypertension. In addition to the MetS, we computed homeostasis model assessment-insulin resistance (HOMA-IR), a measure of insulin resistance, using the formula [fasting glucose (mg/dL) $\times$ fasting insulin (mg/dL)]/405 (23), which was used in the study by Gunter and colleagues (17) as an index of metabolic health.

Exclusions

For the purposes of the present analysis, baseline BMI and components of the MetS were available for 23,900 (99%) of 24,210 women in the subsample. We excluded women with diabetes reported at baseline ($n = 2,440$), women missing waist circumference measurements ($n = 53$), and women with a history of breast cancer ($n = 557$). After exclusions, 20,944 women were available for analysis (88% of women with information on MetS and BMI), among whom, as of September 20, 2015, 1,176 incident invasive breast cancer cases had occurred.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations of interest. The outcome was time to diagnosis of breast cancer. Participants who had not developed breast cancer by the end of follow-up, who had died, or who withdrew from the study before the end of follow-up were censored. Cases contributed person-time to the study from their date of enrollment until the date of diagnosis, and noncases (participants who were censored) contributed person-time from their date of enrollment until the end of follow-up (September 20, 2015), date of death, or date of withdrawal from the study, whichever came first. We examined both age-adjusted and fully adjusted models, which included breast cancer risk factors as well as other potential confounding variables. Because the results differed little, we present the fully adjusted results.

We examined the association of categories of BMI (18.5–<25.0 – normal weight, 25.0–<30.0 - overweight, and $\geq$30.0 kg/m^2 - obese) and of presence of the MetS, separately and with mutual adjustment, with risk of breast cancer. We then estimated risk after cross-classifying women by categories of BMI and presence of the MetS simultaneously, yielding six groups: metabolically healthy/normal weight (MHNW); metabolically unhealthy/normal weight (MUNW); metabolically healthy/overweight (MHOW); metabolically unhealthy/overweight (MUOW); metabolically healthy/obese (MHO); and metabolically unhealthy/obese (MUO).

Because the MetS is a composite of different clinical factors, we further examined the association of each component with breast cancer risk. In addition, we examined the association of combinations of metabolic health defined by HOMA-IR ("low" = lowest quartile/"high" = quartiles 3 and 4) and BMI (normal, overweight, obese) with breast cancer risk.

Tests for linear trend were performed by assigning the median value to each category and modeling the variable as a continuous variable.

We conducted two sensitivity analyses: we excluded the first 3 years of follow-up to address the possibility of reverse causation (effects of subclinical cancer on body weight and metabolic status); also, because waist circumference is strongly correlated with BMI, we repeated the analyses after excluding waist circumference from the definition of the MetS and defining presence of the syndrome as $\geq$2 of the four remaining components.

We tested the proportional hazards assumption using PROC LIFETEST (SAS Institute). None of the formal tests for nonproportional hazards and the log-log survival plots indicated any marked deviation from nonproportionality.

All analyses were performed in SAS 9.4 (SAS Institute). All *P* values are two-sided.

Results

The metabolic obesity phenotypes showed differences by demographic and behavioral characteristics (Table 1). Within BMI categories, compared with metabolically healthy women, metabolically unhealthy women tended to be older and to have fewer years of education, and were more likely to be white. Both alcohol intake and MET-h/wk of physical activity showed decreasing trends from MHNW to MUO; frequency of mammographic screening (ever and in the past 5 years) varied little across obesity phenotypes. As expected, serum glucose, triglycerides, HDL-C, and hypertension differed mainly by presence of the MetS (higher in those with the MetS), whereas serum insulin and waist circumference were positively associated both with BMI and with poor metabolic status.

Both BMI and the MetS, considered individually, were positively associated with breast cancer: HRs for overweight and obese women were 1.12 (95% CI, 0.95–1.33) and 1.51 (95% CI, 1.28–1.78), p for trend <0.0001, respectively; women with the MetS had a HR of 1.28 (95% CI, 1.13–1.44; Table 2). After mutual adjustment, the HRs for BMI and metabolic status were somewhat attenuated; however, the HR for obese women and the trend with BMI as well as the HR for the MetS remained statistically significant. A similar pattern was seen when MetS and tertiles of waist circumference were considered separately and together in the same model.

The association of metabolic obesity phenotypes with breast cancer is presented in Table 3. Relative to women who were MHNW, risk of breast cancer was unchanged in women who were MUNW or MHOW; however, the number of MUNW women was small. Metabolically unhealthy overweight women had a nonsignificantly increased risk.

Women who were MHO and MUO were at increased risk, with the highest risk evident among MUO women: HR 1.61 (95% CI, 1.34–1.94). When the analysis was restricted to never users of hormone therapy and to women who were not in the treatment arms of the hormone therapy clinical trials, the associations with MHO and MUO were strengthened. In addition, when the first 3 years of follow-up were excluded to address possible reverse causality, the associations were slightly strengthened compared with those for all subjects.

In the sensitivity analysis in which waist circumference was excluded from the definition of the MetS [due to its strong correlation with BMI ($r = 0.8$)], the HRs for metabolic obesity phenotypes relative to metabolically healthy normal weight women were virtually unchanged.

We examined the association of each individual component of the MetS with breast cancer, with all covariates including BMI in the model. Blood glucose, triglycerides, HDL-C were not associated with breast cancer (HR for highest vs. lowest quartile: 1.07 (95% CI, 0.90–1.29), p for trend 0.43; 1.16 (95% CI, 0.97–1.39), P_{trend} 0.09, and 0.88 (95% CI, 0.74–1.05, p for trend 0.10, respectively). Hypertension was also not associated with risk: HR for presence versus absence of hypertension at baseline 1.02, 95% CI, 0.89–1.16. Waist circumference showed a positive association with breast cancer risk when BMI was not included in the model: HR for middle and upper tertiles: 1.20 (95% CI, 1.03–1.39) and 1.47 (95% CI, 1.27–1.72), P_{trend} <0.0001.

Table 1. Baseline characteristics by metabolic obesity phenotypes ($n = 20,944$)

Characteristics	MHNW *N* = 4,570	MUNW *N* = 560	MHOW *N* = 5,156	MUOW *N* = 2,431	MHO *N* = 3,335	MUO *N* = 4,892
Mean (SD)						
Age	64.8 (7.5)	66.9 (6.5)	63.8 (7.4)	65.5 (6.9)	62.3 (7.2)	63.4 (7.0)
BMI (kg/m^2)	22.7 (1.6)	23.3 (1.4)	27.3 (1.4)	27.9 (1.4)	34.7 (5.0)	35.6 (4.9)
Waist circumf (cm)	75.0 (6.7)	81.0 (10.4)	83.7 (6.7)	90.2 (7.0)	96.6 (11.2)	103.1 (10.4)
Alcohol intake (drinks/wk)	2.7 (5.4)	2.4 (5.1)	2.1 (4.8)	2.0 (4.7)	1.5 (4.5)	1.4 (4.7)
Pack-years of smoking	8.6 (16.5)	12.3 (21.3)	7.6 (15.7)	10.9 (19.1)	7.6 (15.5)	9.8 (18.7)
MET-h/wk	13.9 (15.3)	11.0 (13.0)	11.7 (13.7)	9.2 (11.6)	8.8 (12.3)	7.1 (10.4)
Parity	2.5 (1.7)	2.9 (1.7)	2.7 (1.7)	2.9 (1.7)	2.7 (1.8)	2.9 (1.7)
Serum glucose (mg/dL)	89.8 (10.0)	103.4 (26.6)	91.6 (12.7)	103.4 (24.0)	92.2 (12.1)	108.2 (29.3)
Serum insulin (mIU/L)	33.1 (18.6)	52.8 (28.7)	47.1 (44.4)	69.2 (35.3)	63.6 (34.6)	96.1 (85.5)
Serum triglycerides (mg/dL)	103.1 (53.0)	205.7 (125.3)	110.7 (51.4)	196.2 (97.1)	101.5 (37.9)	174.0 (88.5)
Serum HDL-C (mg/dL)	61.9 (13.7)	44.6 (9.5)	58.4 (12.4)	45.5 (9.9)	58.3 (11.3)	46.0 (9.7)
Proportions						
Education (% postgraduate)	29.5	20.0	27.1	19.4	24.3	18.4
Ethnicity (% white)	57.1	66.8	45.5	57.0	33.1	50.6
% current smokers	12.2	16.3	7.3	11.8	6.1	8.5
Oral contraceptives (% ever used)	37.0	32.9	38.1	34.3	38.1	37.4
Hormone therapy (% ever used)	43.1	37.9	42.9	39.0	40.9	34.9
Hypertension (%)	43.9	87.8	48.5	82.8	52.0	83.2

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOW, metabolically healthy overweight; MUOW, metabolically unhealthy overweight; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

Table 2. Separate and mutually adjusted associations of BMI and presence of the MetS with breast cancer, Women's Health Initiative CVD Biomarkers Sub-Cohort

A. Separate			
BMI (kg/m^2)	**Cases (n = 1,176)**	**Noncases (n = 19,768)**	**HR[a] (95% CI)**
18.5–<25.0	240	4,890	1.00 (Ref.)
25.0–<30.0	389	7,198	1.12 (0.95–1.33)
≥30.0	547	7,680	1.51 (1.28–1.78)
P_{trend}			<0.0001
MetS			
No	682	12,379	1.00 (Ref.)
Yes	494	7,389	1.28 (1.13–1.44)
B. Mutually adjusted			
BMI (kg/m^2)	**Cases (n)**	**Noncases (n)**	**HR[a] (95% CI)**
18.5–<25.0	240	4,890	1.00 (Ref.)
25.0–<30.0	389	7,1981	1.09 (0.92–1.30)
≥30.0	547	7,680	1.42 (1.18–1.70)
P_{trend}			<0.0001
MetS			
No	682	12,379	1.00 (Ref.)
Yes	494	7,389	1.18 (1.04–1.34)

[a]Adjusted for age (continuous), smoking status (never, former, current), pack-years of smoking (continuous), alcohol intake (drinks/week – continuous), physical activity (MET-h/wk), age at first birth (<20, 20–29, ≥30, missing), age at menarche (<12, 12, 13, ≥14), age at menopause (<45, 45–54, ≥55, missing), oral contraceptives (never, ever), hormone therapy (never, ever), parous/nulliparous, family history of breast cancer in first-degree relative (no, yes), history of breast biopsy (no, yes), breastfed for more than 6 months (no, yes), education (less than high school grad, high school grad/some college, college grad, post-college), ethnicity (white, black, other), allocation to the OS or specific arm of clinical trials.

Table 3. Metabolic obesity phenotypes defined by presence of the MetS and BMI in relation to risk of breast cancer, in the Women's Health Initiative CVD Biomarkers Sub-Cohort

Metabolic phenotypes	**Cases, *N***	**Noncases, *N***	**HR[a] (95% CI)**
Total population (n cases 1,176; n noncases 19,819)			
MHNW	219	4,366	1.00 (Ref.)
MUNW	28	647	0.86 (0.51–1.38)
MHOW	261	4,904	1.08 (0.90–1.31)
MUOW	128	2,307	1.17 (0.93–1.47)
MHO	202	3,145	1.31 (1.07–1.61)
MUO	345	4557	1.61 (1.34–1.94)
Never used hormone therapy (n cases 714; n noncases 11,855)			
MHNW	121	2,486	1.00 (Ref.)
MUNW	12	337	0.76 (0.40–1.45)
MHOW	148	2,800	1.14 (0.88–1.46)
MUOW	75	1,411	1.18 (0.87–1.60)
MHO	125	1,855	1.45 (1.11–1.90)
MUO	233	2,966	1.81 (1.42–2.29)
Never used hormone therapy and not in treatment arms of the HT clinical trials (n cases 458; n noncases 7,827)			
MHNW	70	1,584	1.00 (Ref.)
MUNW	9	196	1.15 (0.55–2.40)
MHOW	95	1,902	1.18 (0.85–1.63)
MUOW	48	891	1.27 (0.86–1.88)
MHO	83	1,319	1.45 (1.03–2.04)
MUO	153	1,935	2.01 (1.48–2.73)
First 3 years of follow-up excluded (n cases 983; n noncases 19,410)			
MHNW	176	4,281	1.00 (Ref.)
MUNW	17	517	0.90 (0.54–1.51)
MHOW	214	4,830	1.11 (0.90–1.37)
MUOW	111	2,244	1.23 (0.96–1.58)
MHO	174	3,087	1.38 (1.10–1.73)
MUO	291	4,451	1.65 (1.35–2.02)

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOW, metabolically healthy overweight; MUOW, metabolically unhealthy overweight; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

[a]Adjusted for age (continuous), smoking status (never, former, current), pack-years of smoking (continuous), alcohol intake (drinks/week – continuous), physical activity (MET-h/wk), age at first birth (<20, 20–29, ≥30, missing), age at menarche (<12, 12, 13, ≥14), age at menopause (<45, 45–54, ≥55, missing), oral contraceptives (never, ever), hormone therapy (never, ever), parous/nulliparous, family history of breast cancer in first-degree relative (no, yes), history of breast biopsy (no, yes), breastfed for more than 6 months (no, yes), education (less than high school grad, high school grad/some college, college grad, post-college), ethnicity (white, black, other), allocation to the OS or specific arm of clinical trials.

Combinations of HOMA-IR (lowest quartile vs. 2 highest quartiles) and BMI (18.5–<25.0, 25.0–<30.0, ≥30.0 kg/m^2) were examined to isolate insulin resistance instead of the MetS (Table 4). Only women who were obese and had high HOMA-IR had significantly elevated risk of breast cancer. The HR for obese women with low HOMA-IR was elevated but not statistically significant.

Discussion

In the present study, both obesity and being metabolically unhealthy were each individually associated with increased risk of breast cancer. After mutual adjustment, both associations remained significant. Relative to MHNW women, only MHO and MUO women were at increased risk, whereas HRs for MUNW, MHOW, and MUOW were close to unity. Exclusion of waist circumference from the definition of metabolic health did not alter the associations. When women were cross-classified by HOMA-IR and BMI, only women who were both obese and had high HOMA-IR were at increased risk; however, the number of cases in some subgroups was small.

The three previous studies that have examined metabolic obesity phenotypes in relation to breast cancer all used different markers of metabolic status: glucose levels (16), HOMA-IR (17), and an approximation of the MetS, based on central obesity, elevated blood pressure, type 2 diabetes, and dyslipidemia (18). All three studies contrasted overweight and obese women combined to normal weight women. Using data from the Framingham Heart Study, Moore and colleagues (16) found that overweight/obese women with elevated glucose levels had a 2.6-fold increased risk (95% CI, 1.4–4.9) of female reproductive cancers and postmenopausal breast cancer (n = 171), whereas normal weight women with elevated glucose had no excess risk. Overweight/obese women with normal glucose levels had a 1.7-fold (95% CI, 1.1–2.5) increased risk.

In an analysis of a case-cohort study within the Women's Health Initiative, Gunter and colleagues (17) reported that metabolically healthy overweight/obese women, with metabolic health defined using HOMA-IR, were not at elevated risk of breast cancer compared with metabolically healthy normal weight women (HR 0.96, 95% CI, 0.64–1.42), whereas women with elevated HOMA-IR (>median) had elevated risk when they were either overweight/obese or normal weight, compared to normal weight women with normal HOMA-IR; however, the latter HR was not significant (HRs 1.76, 95% CI, 1.19–2.60 and 1.80, 95% CI, 0.88–3.70, respectively). The authors concluded that metabolic health may be more biologically relevant and more useful for breast cancer risk stratification than adiposity per se.

Table 4. Association of combinations of metabolic health defined by HOMA-IR and BMI (normal, overweight, obese) with risk of postmenopausal breast cancer, Women's Health Initiative CVD Biomarkers Sub-Cohort ($n = 20{,}569$)

(*n* cases 829; *n* noncases 13,955)				
Low HOMA-IR[a]/normal weight	134	2,680	1.00	Ref.
High HOMA-IR[b]/normal weight	91	1,919	0.95	0.72–1.25
Low HOMA-IR/overweight	32	650	0.97	0.64–1.46
High HOMA-IR/overweight	26	650	0.85	0.55–1.34
Low HOMA-IR/obese	152	2,796	1.17	0.91–1.49
High HOMA-IR/obese	394	5,260	1.57	1.26–1.95

NOTE: 41 cases and 385 noncases were missing HOMA-IR. Total n is reduced because the 2nd quartile was excluded in the analysis. Adjusted for age (continuous), smoking status (never, former, current), pack-years of smoking (continuous), alcohol intake (drinks/week – continuous), physical activity (MET-h/wk), age at first birth (<20, 20–29, ≥30, missing), age at menarche (<12, 12, 13, ≥14), age at menopause (<45, 45–54, ≥55, missing), oral contraceptives (never, ever), hormone therapy (never, ever), parous/nulliparous, family history of breast cancer in first-degree relative (no, yes), history of breast biopsy (no, yes), breastfed for more than 6 months (no, yes), education (less than high school grad, high school grad/some college, college grad, post-college), ethnicity (white, black, other), allocation to the OS or specific arm of clinical trials.
[a]Low HOMA-IR defined as lowest quartile.
[b]High HOMA-IR defined as quartiles 3 and 4.

Using data from the Sister Study, Park and colleagues (18) observed that, compared with normal weight women with no metabolic abnormalities, normal weight women with ≥1 metabolic abnormality and overweight/obese women with no metabolic abnormalities had similarly increased risk of postmenopausal breast cancer: HR, 1.26; 95% CI, 1.01–1.56 and 1.24; 95% CI, 0.99–1.55, respectively. Park and colleagues (18) did not have blood glucose, insulin, or lipid measurements, and used a diagnosis of diabetes or use of diabetes medication and cholesterol-lowering medications to assess metabolic health. In addition, the authors defined metabolic health as having none of 4 factors, whereas most definitions of metabolic health allow for 1 or 2 factors.

Our results underscore the importance of examining the full range of BMI when investigating the relative contributions of obesity and metabolic dysregulation to the risk of breast cancer. Combining overweight and obese subjects, as has been done in previous studies, dilutes the trend toward increasing risk with increasing levels of BMI in combination with metabolic status. Our findings suggest that both increasing adiposity (whether measured by BMI or waist circumference) and metabolic status make independent and joint contributions to the risk of breast cancer. Both presence of the MetS and its individual components (other than waist circumference) showed weak or nonsignificant associations with breast cancer. In contrast, HOMA-IR was significantly associated with risk, and the association of the MetS with breast cancer appears to reflect this, because HOMA-IR is robustly associated with the MetS (41% of women with the MetS were in the highest quartile of HOMA-IR compared with 7.5% of women without the MetS ($P < 0.0001$). Our analysis indicated that waist circumference did not did not show a stronger association with breast cancer compared to BMI and that removing waist circumference from the definition of the MetS did not affect the association of metabolic obesity phenotypes with breast cancer.

Consistent with the analysis of Gunter and colleagues (17), in our analysis, obese women with high HOMA-IR were at increased risk of breast cancer. Normal weight women with high HOMA-IR were not at increased risk in our study, and the HR for normal-weight women with high HOMA-IR was not statistically significant in Gunter and colleagues. The numbers of cases among overweight women with either high or low HOMA-IR in our study were small. The total number of cases in our analysis was 1,176 compared with 497 in Gunter and colleagues (17), permitting us to subdivide the ≥25 kg/m^2 group into 25.0–<30 and ≥30.0 kg/m^2. Overlap between the present study population and that of Gunter and colleagues (17) is minimal (on the order of 20%). It should be noted that in both analyses the numbers of cases among women with normal weight who were metabolically unhealthy (Gunter and colleagues; ref. 17), and among women with the MUNW and MUOW phenotypes in the present study were small, so that it is not possible to rule out an elevated risk of breast cancer in these groups. The findings from the present analysis regarding the associations of BMI and HOMA-IR with breast cancer are consistent with those concerning the association of insulin and glucose with risk of breast cancer in this same cohort (24).

Obesity and the MetS are overlapping in their biological pathways influencing risk of postmenopausal breast cancer. Insulin resistance can be a consequence of obesity but can have genetic determinants as well (4). Increased estrogen levels resulting from the aromatization of androgens in adipose tissue may promote cell proliferation in breast tissue (25). Second, elevated insulin concentrations resulting from insulin resistance may exert promitotic and anti-apoptotic effects (26, 27) and stimulate cell-cycle progression in breast cancer cells (28). Prolonged hyperinsulinemia may additionally result in increased levels of free or bioactive IGF-1, which also promotes signaling pathways favoring tumor development (25). Finally, inflammatory cytokines, including tumor necrosis factor-α, interleukin 6, and prostaglandin E2, may contribute to breast carcinogenesis by promoting cell proliferation and cell-cycle progression (25, 29, 30). These molecular factors interfere with cell signaling in the PI3K-AKT-mTOR pathway, which regulates cell-cycle progression, apoptosis, and protein synthesis (29–31).

Strengths of the present study include its large sample size, the central adjudication of all breast cancer diagnoses, the availability of fasting blood samples on all participants, and measured anthropometric variables, including all components of the MetS. Limitations include: small numbers of cases in some subgroups defined by BMI and metabolic health, the lack of information on change in metabolic phenotype and adiposity over time, and the lack of assessment of medications, including statins and metformin. Although we excluded women with prevalent diabetes at enrollment, we did not exclude women with blood glucose >100 mg/dL treated with metformin. However, only a small percentage (∼2%) of women in this category have received treatment with metformin in recent years, and this would not pertain to women enrolled in the WHI in the 1990s. Finally, the WHI is not a representative sample and, therefore, our results are not generalizable to all postmenopausal women.

In conclusion, in this study, regardless of metabolic health, obesity was associated with increased risk of breast cancer. However, being obese and metabolically unhealthy is associated with the highest risk. Our analysis suggests that, in addition to adiposity, high levels of HOMA-IR may be an independent risk factor for breast cancer. Insulin sensitivity showed a clearer association with risk than the MetS or its individual components.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G.C. Kabat, M.Y. Kim, J.S. Lee, G.Y. Ho, R.T. Chlebowski, T.E. Rohan
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