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A Longitudinal Study of the Metabolic Syndrome and Risk of Postmenopausal Breast Cancer

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Abstract

The metabolic syndrome, characterized by abdominal obesity, high blood glucose levels, impaired glucose tolerance, dyslipidemia, and hypertension, is associated with increased risk of type 2 diabetes and coronary heart disease. Several studies have examined the association of individual components of the metabolic syndrome with breast cancer; however, to date, no study has assessed the metabolic syndrome per se in relation to breast cancer risk. Furthermore, previous studies have relied only on baseline assessment of components of the syndrome. Therefore, we assessed the association of the metabolic syndrome with risk of postmenopausal breast cancer among women in the 6% sample of subjects in the Women's Health Initiative clinical trial who had repeated measurements of the components of the syndrome during follow up. We used Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for the association of breast cancer risk with presence of the metabolic syndrome, as well as its components, at baseline and in time-dependent analyses. After exclusion of women with diabetes, among 4,888 women with baseline measurements, 165 incident cases of breast cancer were ascertained over a median of 8.0 years of follow-up. Presence of the metabolic syndrome at baseline was not associated with altered risk. Of the individual components measured at baseline, diastolic blood pressure showed a

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borderline positive association with breast cancer. In time-dependent covariate analyses, however, certain scenarios indicated a positive association between the metabolic syndrome and breast cancer, due primarily to positive associations with serum glucose, serum triglycerides, and diastolic blood pressure.

Keywords

metabolic syndrome; repeated measures; breast cancer; Women's Health Initiative

Introduction

The metabolic syndrome, or insulin resistance syndrome, which is associated with increased risk of diabetes and heart disease (1–3), has recently been suggested to play a role in breast carcinogenesis (4–6). This syndrome is characterized by abdominal obesity, high blood glucose levels, impaired glucose tolerance, dyslipidemia, and hypertension -- conditions often associated with obesity, a poor diet, and lack of physical activity (4). The prevalence of the metabolic syndrome has increased in the United States in recent years (7, 8), and one estimate indicates that roughly 47 million Americans currently have the syndrome (7). The metabolic syndrome could influence the risk of breast cancer through changes in a number of interrelated hormonal pathways, including those involving insulin, estrogen, cytokines, and growth factors (4, 6).

Numerous studies have examined the association of individual components of the metabolic syndrome with breast cancer risk, but their results have been inconclusive (9–41). To date, however, no study has assessed the metabolic syndrome per se in relation to breast cancer risk, and it is conceivable that the syndrome may show a stronger association with risk than its individual components. Furthermore, previous studies have had only baseline measurements of specific components of the syndrome. We therefore evaluated the association of the metabolic syndrome with risk of postmenopausal breast cancer among women in the 6% sample of subjects in the Women's Health Initiative (WHI) Clinical Trial (CT) who had repeated measurements of the components of the syndrome during follow-up, thereby allowing assessment of the association longitudinally.

Materials and Methods

Study Subjects

The WHI CT is a large (N=68,132), multi-institutional study designed to assess the health effects of hormone therapy, dietary modification, and calcium plus vitamin D supplementation (42). Details of the study have been reported previously (42). Briefly, postmenopausal women 50–79 years of age were enrolled at 40 centers throughout the United States between October 1, 1993 and December 31, 1998. The present analysis is based on a 6% random sample of women (n=5,459) in the CT whose fasting blood samples, collected at baseline and in years 1, 3, and 6, were analyzed for glucose, triglycerides, and HDL-cholesterol (43). In addition, waist circumference, and systolic and diastolic blood pressure were measured by study staff using a standardized protocol at these clinical visits.

The 6% random sample was stratified by age, clinical center, and hysterectomy status, with over-sampling of minority groups to increase the numbers of Black, Hispanic, and Asian-Pacific women.

Case Ascertainment

Cancer outcomes were ascertained through self-administered questionnaires completed every six months, and then confirmed by centralized review of pathology reports, discharge summaries, operative and radiology reports, and tumor registry abstracts.

Laboratory Methods

Fasting bloods were collected with minimal stasis and maintained at 4^0 C until plasma/serum was separated. Plasma/serum aliquots were then frozen at -70^0 C and sent on dry ice to the central repository (Fisher BioServices, Rockville, MD), where storage at -70^0 C was maintained. Glucose was measured using the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics, Indianapolis, Indiana) (44, 45). An ongoing monthly quality assurance program is maintained with the Diabetes Diagnostic Laboratory (DDL) at the University of Missouri. Monthly inter-assay coefficients of variation (CV) were <2% for mean concentrations of 84 and 301 mg/dL. Total cholesterol and triglycerides were analyzed by enzymatic methods on the Hitachi 747 analyzer (46). High-density lipoprotein (HDL-C) was isolated using heparin manganese chloride (47). CVs for total cholesterol, triglycerides, and HDL-C were all $\leq$2.0.

Anthropometric Measures and Blood Pressure

Waist circumference at the natural waist or narrowest part of the torso was measured to the nearest 0.1 cm. On each visit, two blood pressure measurements were obtained $\geq$30 seconds apart, and the average of the two measurements was used in the analysis. Values for waist circumference and blood pressure in the years corresponding to the blood analytes were used in the analysis.

Definition of the Metabolic Syndrome.

We used the definition of the metabolic syndrome proposed by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) (48, 49). An indicator variable was created for presence of the metabolic syndrome (yes/no), defined as having 3 or more of the following characteristics: waist circumference $\geq$88 cm, fasting glucose $\geq$100 mg/dL, fasting HDL-C <50 mg/dL, fasting triglycerides $\geq$150 mg/dL, and blood pressure $\geq$130/85 mmHg.

Exclusion of Women with Diabetes.

Diabetes has been studied as a risk factor for breast cancer (4). We were interested in whether the criteria for the metabolic syndrome, including insulin resistance, predict breast cancer risk before a clinical diagnosis of diabetes. Therefore, women reporting taking diabetes medication at baseline or having a baseline fasting serum glucose level of $\geq$126 mg/dL were excluded from the analysis (26 breast cancer cases and 548 non-cases). The results were not changed when women with diabetes were included in the analysis.

Statistical Analysis.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the associations between presence of the metabolic syndrome and its components and risk of breast cancer, with duration of follow-up (days) as the time scale. For these analyses, study participants were considered to be at risk from their date of enrollment until the date of diagnosis of their breast cancer, termination of follow-up (September 12, 2005), loss to follow-up, withdrawal from the study, or death, whichever occurred first. Event times of 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.

In the first stage of the analysis we estimated the risk of breast cancer in association with presence of the metabolic syndrome or its individual components at baseline. Presence of the metabolic syndrome was defined as having 3 or more of the individual components relative to having 2 or fewer. In addition, individual components of the metabolic syndrome were divided into three groups, using the ATP III cutoffs for the highest category (lowest for HDL-C), and the median for the remainder of the distribution. We also examined the association of “degree of metabolic syndrome” with risk, using each individual’s score, ranging from 0 (reference group) to 5 and obtained by summing scores (1=present, 0=absent) for each of the individual components. Tests for trend were performed by assigning the median value to each category and modeling this variable as a continuous variable. Established breast cancer risk factors and potential confounding variables, obtained at baseline, were included in multivariable models as follows: age (continuous), education (less than high school, high school grad/some college, college graduate, post-college), ethnicity (white, black, other), body mass index (continuous), oral contraceptive use (ever/never), postmenopausal hormone therapy (ever/never), age at menarche (continuous), age at first birth (<20, 20–29, ≥30, missing)), age at menopause (<50, ≥50, missing), alcohol (servings per week – continuous), family history of breast cancer (yes/no), history of breast biopsy (ever, never), physical activity (METs per week - continuous), energy intake (continuous), smoking status (never, former, current smoker), and randomization status in the hormone therapy, calcium plus vitamin D, and dietary modification trials. All *P*-values were two-sided.

Analyses were performed on all breast cancers (invasive and in situ) and on invasive cancers only. In addition, two sensitivity analyses were carried out: restricting the analysis to women who did not participate in any WHI-CT intervention; and excluding cases diagnosed during the first two years of follow-up. The results were not altered in either analysis, and we present the results for the total study population.

In the second stage of the analysis, the repeated measurements of the different components of the metabolic syndrome were analyzed by modeling them as time-dependent covariates in the Cox proportional hazards model (50). With this approach, we evaluated the predictive value of the most recent measurement, measurements obtained in the intervals 1–3 years, 2–4 years, and 3–5 years before the date of diagnosis of breast cancer, and the average of all available measurements. In all time-dependent analyses, measurements which were obtained

within 1 year of diagnosis were excluded from all analyses, since these values may have been influenced by the presence of sub-clinical disease.

Results

During a median follow-up of 8.0 years, a total of 165 breast cancer cases (131 invasive and 34 *in situ*) were ascertained. Of the total breast cancer cases, 81 were not randomized to any of the CT intervention groups, while the remaining 84 were randomized to at least one intervention group. The corresponding numbers for non-cases were 2324 and 2399.

At baseline, cases and non-cases were similar with respect to age and anthropometric and reproductive variables (Table 1). Cases had significantly lower levels of physical activity and were more likely to be non-Hispanic white compared to non-cases.

Presence of the metabolic syndrome at baseline was not associated with altered risk of total breast cancer (invasive + in situ) or of invasive breast cancer alone: multivariable HR 1.12 (95% CI 0.78–1.62) and 1.19 (95% CI 0.79–1.79), respectively (Table 2). Of the individual components of the metabolic syndrome measured at baseline, diastolic blood pressure was associated with increased risk of total breast cancer (multivariable HR for highest versus lowest tertile 1.55, 95% CI 1.02–2.36) but not of invasive breast cancer (HR 1.43, 95% CI 0.90–2.29). None of the other components was associated with altered risk of the endpoints of interest. When the number of components of the syndrome was treated as an ordinal variable (relative to a reference group of 0), women with 4 or more components had an HR of 1.56 (95% CI 0.86–2.85). These results were not affected by restriction of the sample to women who were not randomized to any of the clinical trial intervention groups or by exclusion of cases diagnosed within the first two years of follow-up (data not shown).

In the time-dependent covariate analyses, presence of the metabolic syndrome 3–5 years prior to diagnosis was associated with increased risk of total breast cancer and of invasive breast cancer: HR 1.84 (95% CI 1.12–3.01) and 1.77 (95% CI 1.01–3.12), respectively (Table 3). A borderline positive association was also seen for metabolic syndrome 2–4 years prior to diagnosis but not for presence of the syndrome 1–3 years prior to diagnosis. When presence of the metabolic syndrome (3 or more components satisfying the ATP III cutoff values) was based on the average of all individual components, the HR for all breast cancer was 1.57 (95% CI 1.09–2.26), and that for invasive breast cancer was 1.59 (95% CI 1.06–2.41).

Because the time-dependent analysis suggested that metabolic syndrome status measured earlier in time is more predictive of breast cancer than more recent measurements, we also evaluated the association of cumulative exposure to the metabolic syndrome with breast cancer. For a subject at risk at time t, cumulative exposure was estimated as the number of visits up to time t at which the subject was determined to have syndrome and was analyzed as a time-dependent covariate. The hazard ratio associated with 2 or more prior diagnoses of the syndrome versus fewer than 2 diagnoses was 1.59 (95% CI: 1.05–2.41) for total breast cancer and 1.68 (95% CI: 1.05–2.71) for invasive breast cancer only.

Of the individual components of the metabolic syndrome, positive associations were seen for serum glucose (average and 1–3 years prior to diagnosis) with all breast cancer, serum triglycerides (3–5 years prior to diagnosis) with total breast cancer and invasive breast cancer, and average diastolic blood pressure with total breast cancer and invasive breast cancer (Table 3).

Discussion

In this longitudinal study, presence of the metabolic syndrome at baseline was not associated with breast cancer risk. Furthermore, of the individual components of the syndrome, only baseline diastolic blood pressure showed any suggestion of an association. However, in some time-dependent analyses (particularly, presence of the syndrome 3–5 prior to diagnosis and presence of the syndrome based on the average value of its components), use of repeated measures was suggestive of a positive association of the metabolic syndrome with breast cancer. In addition, after adjustment for other components of the metabolic syndrome, serum glucose and triglycerides and diastolic blood pressure were associated with increased risk in the time-dependent analyses. While numerous studies have examined individual components of the metabolic syndrome in relation to breast cancer risk (9–41), no study to date has assessed the association of the metabolic syndrome per se with breast cancer.

The results of previous studies which reported on individual components of the metabolic syndrome have been inconsistent. Increased central adiposity (as measured by waist circumference and waist-hip-ratio) has been associated with increased risk of postmenopausal breast cancer in some (9–13) but not all cohort studies (23–26; see ref. 27 for review). An inverse association between HDL cholesterol and breast cancer risk has been reported in several case-control studies (19, 20, 23, 24) and in two cohort studies (25, 26), but not in other studies (27, 28). A nested case-control study (30) found that HDL cholesterol was inversely associated with breast cancer among pre-menopausal women but positively associated with disease in postmenopausal women. A number of studies have found that serum triglyceride levels were positively associated with breast cancer risk (19–22, 24, 28, 29), whereas other studies have found no association (26, 27). In several studies, hypertension has been linked to higher breast cancer risk (31–33); however, two of these studies (32, 33) were case-control studies which relied on self-reports of history of hypertension or treatment for hypertension. Among cohort studies that measured blood pressure at baseline (31, 34–36), only one study (31) reported a positive association with systolic blood pressure. Finally, of six studies (34, 37–41) that have examined the association of fasting blood glucose level with breast cancer risk, three studies (37, 39, 41) showed evidence of a positive association with breast cancer, while the results of the remaining studies were null. Among the two cohort studies indicating a positive association, one (37) showed a significant association in pre-menopausal women, whereas the other (41) reported a significant association in all women, the largest increase in risk being among women of age 65+.

Hyperinsulinemia may provide the unifying mechanism by which the metabolic syndrome might be associated with increased breast cancer risk (4, 16, 51). Insulin has mitogenic activity in addition to metabolic effects and can promote cell proliferation in normal

mammary epithelial cells and breast cancer cell lines (52, 53). Insulin may also contribute to tumor promotion by up-regulating the secretion of ovarian hormones (54, 55). In theory, high glucose levels could additionally increase the risk of postmenopausal breast cancer by conferring a selective growth advantage to malignant cells (56), as high rates of glucose uptake and glycolysis are a common feature of malignant growth (57). In addition to its association with insulin resistance and the metabolic syndrome, abdominal obesity is associated with the release of non-esterified fatty acids from adipose tissue and their accumulation in muscle and liver, leading to dyslipidemia (16). Furthermore, adipose tissue in obese individuals exhibits abnormalities in the production of several adipokines, including increased production of inflammatory cytokines and plasminogen activator inhibitor-1 and reduced production of adiponectin, that may affect insulin resistance (16). Thus, in addition to the effects of insulin and glucose, low-grade chronic inflammatory effects associated with the metabolic syndrome may be relevant to breast carcinogenesis (58). While hypertension associated with the metabolic syndrome appears to be secondary to the effects of insulin resistance and compensatory hyperinsulinemia on the sympathoadrenal system (59), breast cancer and hypertension may share common pathways involving inflammation and hormone synthesis and metabolism (4, 60, 61).

Our results provide some support for an association between the metabolic syndrome and breast cancer risk, but need to be interpreted with caution. Certain time-dependent analyses showed significant associations of both the metabolic syndrome per se and of glucose, triglycerides, and diastolic blood pressure with breast cancer risk. However, only baseline diastolic blood pressure showed any association with risk. The time-dependent measures provide a more reliable estimate of exposure over the time period relevant to the development of breast cancer and, therefore, perhaps should carry greater weight than those derived from the baseline measures alone. However, given the many comparisons performed and the limited sample size, some of these differences could also be due to chance. In addition, waist circumference ≥88 cm relative to waist circumference <79 cm was not associated with breast cancer risk in any of the analyses, whereas excess abdominal adiposity is an important determinant of insulin resistance (22) and is thought to play a key role in the metabolic syndrome (22). Our findings of positive associations of breast cancer with diastolic blood pressure (in both the baseline and the repeated measures analyses) and of serum glucose and serum triglycerides (in the time-dependent analyses) have some support in the literature but require further elucidation.

Given the limited number of cases in this study, it would be premature to draw definitive conclusions about whether the associations with individual components or with the composite metabolic syndrome are more informative in our data or how convincing a biological rationale exists for the observed associations with individual components. Larger studies with repeated measurements are needed to determine whether the metabolic syndrome per and/or particular components show a consistent association with breast cancer risk.

Strengths of the present study include its prospective nature, the availability of detailed information on breast cancer risk factors and other potential confounders, and availability of

repeated measurements of components of the metabolic syndrome. Limitations include the relatively small sample size and the lack of information on circulating estrogen levels.

In conclusion, the present study, which is the first to assess the association of the metabolic syndrome per se with breast cancer risk, provides some evidence of a modest positive association of postmenopausal breast cancer with the metabolic syndrome per se (in repeated measures analyses), diastolic blood pressure (baseline and repeated measures analyses), and serum glucose and triglycerides (repeated measures analyses).

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Table 1.

Baseline characteristics of breast cancer cases and non-cases in the Women's Health Initiative clinical trial

	Cases (n = 165)	Non-cases (n = 4,723)	P-value
Age *	62.9 ± 6.6	62.5 ± 7.2	0.45
Body mass index (kg/m^2) *	28.8 ± 5.6	28.6 ± 5.9	0.72
Height (cm) *	160.4 ± 6.2	160.8 ± 6.8	0.83
Waist circumference (cm) *	87.3 ± 12.6	87.4 ± 13.5	0.94
Parity *	2.5 ± 1.7	2.6 ± 1.7	0.21
Age at menopause *	47.6 ± 6.6	46.8 ± 6.8	0.19
Alcohol (servings/week) *	1.8 ± 3.1	1.7 ± 4.1	0.79
Physical activity (METs/week †) *	7.3 ± 10.0	10.3 ± 13.2	0.002
Oral contraceptive use (% ever)	36.4	42.4	0.12
Hormone therapy use (% current)	36.4	28.8	0.11
Age at menarche (% ≤12 yrs)	48.8	46.4	0.29
Age at first birth (% ≥30 yrs)	11.2	9.0	0.16
Breast cancer in a first-degree family member (% yes)	16.4	15.4	0.73
Education (% some post-college)	27.3	24.9	0.50
Ethnicity (% non-Hispanic white)	66.1	53.8	0.004
Smoking (% current smokers)	5.5	8.3	0.29

* Mean (SD)

† METs, metabolic equivalent tasks (defined as caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour at rest) per hour per week.

Table 2.

Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of presence at baseline of the metabolic syndrome, and of individual components of the metabolic syndrome, with risk of breast cancer in the Women's Health Initiative clinical trial

Variables	All cases (N = 165)	All cases (N = 162*)	Invasive cases (N = 128*)
	Age-adjusted HR (95% CI)	MV-adjusted† HR (95% CI)	MV-adjusted† HR (95% CI)
Metabolic syndrome			
No (N_{cases} = 111)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes (N_{cases} = 54)	1.16 (0.84–1.61)	1.12 (0.78–1.62)	1.19 (0.79–1.79)
Individual components of the metabolic syndrome‡			
Waist circumference (cm)			
<79 (N_{cases} = 55)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
79 –<88 (N_{cases} = 62)	1.05 (0.72–1.54)	0.98 (0.64–1.50)	0.94 (0.58–1.52)
≥88 (N_{cases} = 48)	1.00 (0.69–1.45)	0.78 (0.46–1.31)	0.73 (0.41–1.32)
P_{trend}	*0.97*	*0.34*	*0.30*
Glucose (mg/dL)			
<90 (N_{cases} = 49)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
90–<100 (N_{cases} = 74)	1.39 (0.97–2.00)	1.36 (0.94–1.97)	1.32 (0.87–1.47)
>100 (N_{cases} = 42)	1.24 (0.82–1.87)	1.25 (0.81–1.93)	1.22 (0.75–2.00)
P_{trend}	*0.26*	*0.27*	*0.38*
HDL-cholesterol (mg/dL)			
>63 (N_{cases} = 54)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
50–<=63 (N_{cases} = 54)	1.05 (0.75–1.48)	1.06 (0.72–1.54)	0.93 (0.61–1.43)
<50 (N_{cases} = 57)	1.13 (0.79–1.61)	1.25 (0.83–1.89)	1.13 (0.71–1.78)
P_{trend}	*0.40*	*0.32*	*0.67*
Triglycerides (mg/dL)			
<104 (N_{cases} = 51)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
104–<150 (N_{cases} = 49)	0.98 (0.65–1.47)	0.91 (0.60–1.39)	0.84 (0.53–1.35)
≥150 (N_{cases} = 65)	1.37 (0.95–1.97)	1.22 (0.82–1.80)	1.14 (0.74–1.77)
P_{trend}	*0.08*	*0.27*	*0.47*
Systolic blood pressure (mm Hg)			
<118 ((N_{cases} = 46)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
118–<130 (N_{cases} = 59)	1.29 (0.84–1.97)	1.36 (0.88–2.10)	1.31 (0.81–2.12)

Variables	All cases (N = 165)	All cases (N = 162*)	Invasive cases (N = 128*)
	Age-adjusted HR (95% CI)	MV-adjusted† HR (95% CI)	MV-adjusted† HR (95% CI)
≥130 (N_{cases} = 60)	1.33 (0.89–1.97)	1.39 (0.92–2.09)	1.25 (0.79–1.98)
P_{trend}	*0.18*	*0.13*	*0.39*
Diastolic blood pressure (mm Hg)			
<74 (N_{cases} = 54)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
74–<85 (N_{cases} = 58)	1.05 (0.74–1.49)	1.15 (0.81–1.65)	1.04 (0.70–1.56)
≥85 (N_{cases} = 53)	1.43 (0.95–2.15)	1.55 (1.02–2.36)	1.43 (0.90–2.29)
P_{trend}	*0.12*	*0.05*	*0.17*

*Reduced numbers are due to 3 cases missing information energy intake, alcohol intake, and age at menarche, respectively.

†Multivariable adjusted HR -- adjusted for the following variables: age (continuous), education (less than high school, high school grad/some college, college graduate, post-college), ethnicity (white, black, other), body mass index (continuous), oral contraceptive use (ever/never), hormone therapy (ever/never), age at menarche (continuous), age at first birth (<20, 20–29, ≥30, missing)), age at menopause (<50, ≥50, missing), alcohol (servings per week – continuous), family history of breast cancer (yes/no), history of breast biopsy (ever, never), physical activity (METs per week - continuous), energy intake (continuous), smoking status (never, former, current smoker), and randomization status in hormone therapy, calcium plus vitamin D, and dietary modification trials.

‡Mutually adjusted for all other components of the metabolic syndrome in addition to covariates listed above.

Table 3.

Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of the metabolic syndrome (MS) and its individual components with breast cancer in time-dependent covariates analyses in the Women's Health Initiative clinical trial

MS Components	All Cases HR (95% CI)*	Invasive Cases HR (95% CI)*
Metabolic Syndrome		
1–3 years**		
No (N_{cases} = 71)	1.00 (ref.)	1.00 (ref.)
Yes (N_{cases} = 29)	1.15 (0.71–1.85)	1.01 (0.59–1.74)
2–4 years**		
No (N_{cases} = 59)	1.00 (ref.)	1.00 (ref.)
Yes (N_{cases} = 34)	1.57 (0.98–2.51)	1.48 (0.87–2.52)
3–5 years**		
No (N_{cases} = 52)	1.00 (ref.)	1.00 (ref.)
Yes (N_{cases} = 33)	1.84 (1.12–3.01)	1.77 (1.01 – 3.12)
Individual components of the metabolic syndrome†		
Waist circumference (cm)		
Average‡		
< 79	1.00 (ref.)	1.00 (ref.)
79–88	0.81 (0.52–1.25)	0.86 (0.53–1.39)
≥ 88	0.69 (0.40–1.18)	0.65 (0.35–1.18)
P_{trend}	0.17	0.16
1–3 years		
< 79	1.00 (ref.)	1.00 (ref.)
79–88	0.99 (0.55–1.76)	0.86 (0.46–1.62)
≥ 88	1.31 (0.67–2.59)	1.06 (0.51–2.23)
P_{trend}	0.44	0.89
2–4 years		
< 79	1.00 (ref.)	1.00 (ref.)
79–88	0.73 (0.39–1.34)	0.70 (0.34–1.40)
≥ 88	1.08 (0.55–2.11)	1.08 (0.51–2.31)
P_{trend}	0.84	0.85
3–5 years		
< 79	1.00 (ref.)	1.00 (ref.)
79–88	0.92 (0.50–1.70)	1.01 (0.50–2.07)
≥ 88	1.17 (0.57–2.38)	1.32 (0.58–3.01)

MS Components	All Cases HR (95% CI)*	Invasive Cases HR (95% CI)*
P_{trend}	0.68	0.51
Glucose (mg/dL)		
Average		
< 90	1.00 (ref.)	1.00 (ref.)
90–<100	1.43 (0.98–2.09)	1.32 (0.86–2.01)
≥ 100	1.57 (1.01–2.46)	1.42 (0.86–2.36)
P_{trend}	0.04	0.15
1–3 years		
< 90	1.00 (ref.)	1.00 (ref.)
90–<100	1.90 (1.20–3.02)	1.79 (1.08–2.95)
≥ 100	1.67 (0.95–2.94)	1.35 (0.71–2.56)
P_{trend}	0.04	0.20
2–4 years		
< 90	1.00 (ref.)	1.00 (ref.)
90–<100	1.42 (0.89–2.27)	1.25 (0.74–2.11)
≥ 100	1.30 (0.74–2.29)	1.02 (0.53–1.96)
P_{trend}	0.27	0.82
3–5 years		
< 90	1.00 (ref.)	1.00 (ref.)
90–100	1.60 (0.98–2.62)	1.35 (0.78–2.35)
≥ 100	1.63 (0.92–2.91)	1.26 (0.65–2.44)
P_{trend}	0.07	0.42
HDL-C (mg/dL)		
Average < 50	1.00 (ref.)	1.00 (ref.)
50– 63	0.70 (0.47–1.05)	0.65 (0.41–1.03)
≥ 63	0.81 (0.54–1.21)	0.79 (0.50–1.25)
P_{trend}	0.34	0.37
1–3 years		
< 50	1.00 (ref.)	1.00 (ref.)
50– 63	0.74 (0.46–1.21)	0.79 (0.46–1.38)
≥ 63	0.72 (0.44–1.17)	0.83 (0.48–1.44)
P_{trend}	0.19	0.54
2–4 years		
< 50	1.00 (ref.)	1.00 (ref.)
50– 63	0.64 (0.38–1.07)	0.56 (0.30–1.03)
≥ 63	0.80 (0.49–1.32)	0.88 (0.51–1.54)
P_{trend}	0.42	0.73
3–5 years		

MS Components	All Cases HR (95% CI)*	Invasive Cases HR (95% CI)*
< 50	1.00 (ref.)	1.00 (ref.)
50– 63	0.63 (0.36–1.10)	0.57 (0.30–1.08)
≥ 63	0.96 (0.57–1.60)	0.90 (0.50–1.61)
P_{trend}	0.94	0.77
Triglycerides (mg/dL)		
Average		
< 104	1.00 (ref.)	1.00 (ref.)
104–150	0.91 (0.58–1.43)	0.86 (0.52–1.43)
≥150	1.44 (0.95–2.20)	1.43 (0.89–2.28)
P_{trend}	0.049	0.08
1–3 years		
< 104	1.00 (ref.)	1.00 (ref.)
104–150	1.66 (0.96–2.87)	1.68 (0.92–3.07)
≥150	1.67 (0.97–2.88)	1.58 (0.86–2.90)
P_{trend}	0.09	0.18
2–4 years		
< 104	1.00 (ref.)	1.00 (ref.)
104–150	0.93 (0.53–1.64)	0.75 (0.39–1.44)
≥150	1.41 (0.84–2.37)	1.22 (0.69–2.15)
P_{trend}	0.15	0.40
3–5 years		
< 104	1.00 (ref.)	1.00 (ref.)
104–150	0.99 (0.54–1.83)	0.67 (0.32–1.42)
≥150	1.76 (1.02–3.04)	1.72 (0.94–3.15)
P_{trend}	0.03	0.03
Systolic Blood Pressure (mm Hg)		
Average		
<118	1.00 (ref.)	1.00 (ref.)
118–130	1.01 (0.66–1.55)	0.98 (0.61–1.58)
≥130	1.16 (0.77–1.76)	1.04 (0.65–1.66)
P_{trend}	0.45	0.86
1–3 years		
<118	1.00 (ref.)	1.00 (ref.)
118–130	1.26 (0.75–2.12)	1.50 (0.84–2.71)
≥130	1.45 (0.88–2.40)	1.64 (0.92–2.91)
P_{trend}	0.14	0.10
2–4 years		
<118	1.00 (ref.)	1.00 (ref.)

MS Components	All Cases HR (95% CI)*	Invasive Cases HR (95% CI)*
118–130	0.68 (0.39–1.19)	0.74 (0.39–1.38)
≥130	1.10 (0.68–1.78)	1.14 (0.65–1.98)
P_{trend}	0.64	0.58
3–5 years		
<118	1.00 (ref.)	1.00 (ref.)
118–130	0.94 (0.55–1.59)	0.76 (0.41–1.40)
≥130	0.94 (0.56–1.59)	0.83 (0.46–1.49)
P_{trend}	0.83	0.54
Diastolic Blood Pressure (mm Hg)		
Average		
<74	1.00 (ref.)	1.00 (ref.)
74–<85	1.21 (0.86–1.72)	1.20 (0.81–1.77)
≥85	2.40 (1.49–3.87)	2.22 (1.28–3.86)
P_{trend}	0.002	0.01
1–3 years		
<74	1.00 (ref.)	1.00 (ref.)
74–<85	1.56 (1.02–2.37)	1.54 (0.97–2.46)
≥85	1.33 (0.69–2.55)	1.37 (0.67–2.79)
P_{trend}	0.12	0.14
2–4 years		
<74	1.00 (ref.)	1.00 (ref.)
74–<85	1.34 (0.87–2.07)	1.36 (0.82–2.24)
≥85	1.15 (0.58–2.26)	1.41 (0.69–2.91)
P_{trend}	0.37	0.22
3–5 years		
<74	1.00 (ref.)	1.00 (ref.)
74–<85	1.06 (0.67–1.68)	1.00 (0.59–1.70)
≥85	1.32 (0.70–2.49)	1.36 (0.66–2.79)
P_{trend}	0.44	0.52

*Adjusted for the following variables: age (continuous), education (less than high school, high school grad/some college, college graduate, post-college), ethnicity (white, black, other), body mass index (continuous), oral contraceptive use (ever/never), hormone therapy (ever/never), age at menarche (continuous), age at first birth (<20, 20–29, ≥30, missing)), age at menopause (<50, ≥50, missing), alcohol (servings per week – continuous), family history of breast cancer (yes/no), history of breast biopsy (ever, never), physical activity (METs per week - continuous), energy intake (continuous), smoking status (never, former, current smoker), and randomization status in hormone therapy, calcium plus vitamin D, and dietary modification trials.

**Most recent measurement within the time interval was used to predict presence of the metabolic syndrome.

†Mutually adjusted for all other components of the metabolic syndrome in addition to covariates listed above.

‡Average of all measurements taken up to one year prior to diagnosis of breast cancer.