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 the individual components of the metabolic syndrome with breast cancer; to date, however, 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 the risk of postmenopausal breast cancer among women in the 6% sample of subjects in the Women’s Health Initiative clinical trial and the 1% sample of women in the observational study 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 the 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 years of follow-up. The 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 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.

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, 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 the risk of postmenopausal breast cancer among women in the 6% sample of subjects in the Women’s Health Initiative clinical trial and the 1% sample of women in the observational study 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 Women’s Health Initiative is a large, prospective, multicenter study of factors affecting the health of postmenopausal women. It includes an

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observational study (N = 93,676) and three clinical trials
(N = 68,132) of hormone therapy, dietary modification,
and calcium plus vitamin D supplementation (42). Women were recruited at 40 clinical centers throughout
the United States, largely via direct mailings, and were
eligible to participate if they were postmenopausal, ages
50 to 79, likely to reside in their current residence for at
least 3 y, and had provided written informed consent.
Enrollment took place from October 1, 1993 to December
31, 1998. The clinical trials had a number of additional
eligibility requirements. In general, eligible women were
enrolled in the clinical trial component. Women who did
not wish to be randomly assigned to an intervention or
who were ineligible for the clinical trial component were
invited to participate in the observational study.

The present analysis is based on a 6% random sample
of women in the clinical trials (n = 4,396) who provided
fasting blood samples at baseline and at years 1, 3, and
6 of follow-up, and a 1% sample of women in the
observational study (n = 1,054) who provided fasting
blood samples at baseline and in year 3 (43). Blood
samples were analyzed for glucose, triglycerides, and
high-density lipoprotein cholesterol (HDL-C; ref. 43). In
addition, waist circumference, and systolic and diastolic
blood pressure were measured by study staff using a
standardized protocol at clinical visits. The 6% random
sample was stratified by age, clinical center, and
hysterectomy status, with oversampling of minority
groups to increase the numbers of Black, Hispanic, and
Asian-Pacific women.

Case Ascertainment. In the clinical trial cancer
outcomes were ascertained through self-administered ques-
tionnaires completed every 6 mo, and then confirmed by
a centralized review of pathology reports, discharge
summaries, operative and radiology reports, and tumor
registry abstracts. In the observational study cancer
outcomes were ascertained annually.

Laboratory Methods. Fasting blood samples were
collected with minimal stasis and maintained at 4°C
until plasma/serum was separated. Plasma/serum
aliquots were then frozen at −70°C and sent on dry
ice to the central repository (Fisher BioServices), where
storage at −70°C was maintained. Glucose was
measured using the hexokinase method on the Hitachi
747 (Boehringer Mannheim Diagnostics; refs. 44, 45).
An ongoing monthly quality assurance program is
maintained with the Diabetes Diagnostic Laboratory at
the University of Missouri. Monthly interassay coeffi-
cients of variation (CV) were <2% for mean concen-
trations of 84 and 301 mg/dL. Total cholesterol and
triglycerides were analyzed by enzymatic methods on
the Hitachi 747 analyzer (46). HDL-C was isolated
using heparin manganese chloride (47). CVs for total
cholesterol, triglycerides, and HDL-C were all ≤2%.

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. Oneach
circumference at the natural waist or narrowest part of
the torso was measured to the nearest 0.1 cm. Oneach
circumference at the natural waist or narrowest part of

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 (48, 49). An indicator
variable was created for the presence of the metabolic
syndrome (yes/never), defined as having ≥3 of the
following characteristics: waist circumference ≥88 cm,
fasting glucose ≥100 mg/dL, fasting HDL-C <50 mg/dL,
fasting triglycerides ≥150 mg/dL, and blood pressure
≥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 who reported taking diabetes medica-
tion at baseline or having a baseline fasting serum
glucose level of ≥126 mg/dL were excluded from the
analysis (25 breast cancer cases and 537 noncases). The
results were not changed when women with diabetes
were included in the analysis.

Statistical Analysis. Cox proportional hazards mod-
els were used to estimate hazard ratios (HR) and 95%
confidence intervals (95% CI) for the associations
between the presence of the metabolic syndrome and
its components and the 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 the presence of the
metabolic syndrome or its individual components at
baseline. Presence of the metabolic syndrome was
defined as having ≥3 of the individual components
relative to having ≤2. In addition, the 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 perform by assign-
ing 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, postcollege), 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 (metabolic equivalent tasks per week - continuous), energy intake (continuous), smoking status (never, former, current smoker), and randomization status (for women in the clinical trial) 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 Women’s Health Initiative clinical trial 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 to 3 y, 2 to 4 y, and 3 to 5 y before the date of diagnosis of breast cancer; and the average of all available measurements. In all time-dependent analyses, measurements that were obtained within 1 y of diagnosis were excluded from all analyses, because these values may have been influenced by the presence of subclinical disease.

Results

During a median follow-up of 8 years, a total of 165 breast cancer cases (131 invasive and 34 in situ) were ascertained. Of the total breast cancer cases, 99 were not randomized to any of the clinical trial intervention groups or were in the observational study, whereas the remaining 66 were randomized to at least one intervention group. The corresponding numbers for noncases were 2,620 and 2,103.

At baseline, cases and noncases 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 with noncases.

The presence of the metabolic syndrome at baseline was not associated with altered risk of total breast cancer (invasive plus in situ) or of invasive breast cancer alone, with multivariable HR of 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 end points 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 components had a 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 were in the observational study, 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 to 5 years prior to diagnosis was associated with increased risk of total breast cancer and of invasive breast cancer, with HR of 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 to 4 years prior to diagnosis but not for presence of the syndrome 1 to 3 years prior to diagnosis. When presence of the metabolic syndrome (≥3 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

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**Table 1. Baseline characteristics of breast cancer cases and noncases in the Women’s Health Initiative**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 165)</th>
<th>Noncases (n = 4,723)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>62.9 ± 6.6</td>
<td>62.5 ± 7.2</td>
<td>0.45</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>28.8 ± 5.6</td>
<td>28.6 ± 5.9</td>
<td>0.72</td>
</tr>
<tr>
<td>Height (cm)*</td>
<td>160.4 ± 6.2</td>
<td>160.8 ± 6.8</td>
<td>0.83</td>
</tr>
<tr>
<td>Waist circumference (cm) *</td>
<td>87.3 ± 12.6</td>
<td>87.4 ± 13.5</td>
<td>0.94</td>
</tr>
<tr>
<td>Parity*</td>
<td>2.5 ± 1.7</td>
<td>2.6 ± 1.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Age at menopause (y)*</td>
<td>47.6 ± 6.6</td>
<td>46.8 ± 6.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Alcohol (servings/wk) *</td>
<td>1.8 ± 3.1</td>
<td>1.7 ± 4.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Physical activity (MET/wk)*</td>
<td>7.3 ± 10.0</td>
<td>10.3 ± 13.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Oral contraceptive use (% ever)</td>
<td>36.4</td>
<td>42.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Hormone therapy use (% current)</td>
<td>36.4</td>
<td>28.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Age at menarche (% ≤12 y)</td>
<td>48.8</td>
<td>46.4</td>
<td>0.29</td>
</tr>
<tr>
<td>Age at first birth (% ≥30 y)</td>
<td>11.2</td>
<td>9.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Breast cancer in a first-degree family member (% yes)</td>
<td>16.4</td>
<td>15.4</td>
<td>0.73</td>
</tr>
<tr>
<td>Education (% some postcollege)</td>
<td>66.1</td>
<td>53.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Ethnicity (% non-Hispanic white)</td>
<td>5.5</td>
<td>8.3</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Abbreviation: MET, 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.

*Mean (SD).
Table 2. Adjusted hazard ratios and 95% confidence intervals 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>All cases (n = 165)</th>
<th>All cases (n = 162*)</th>
<th>Invasive cases (n = 128*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-adjusted HR (95% CI)</td>
<td>MV-adjusted HR (95% CI)</td>
<td>MV-adjusted HR (95% CI)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n_cases = 111)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Yes (n_cases = 54)</td>
<td>1.16 (0.84-1.61)</td>
<td>1.12 (0.78-1.62)</td>
<td>1.19 (0.79-1.79)</td>
</tr>
<tr>
<td>Individual components of the metabolic syndrome*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;79 (n_cases = 55)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>79-&lt;88 (n_cases = 62)</td>
<td>1.05 (0.72-1.54)</td>
<td>0.98 (0.64-1.50)</td>
<td>0.94 (0.58-1.52)</td>
</tr>
<tr>
<td>≥88 (n_cases = 48)</td>
<td>1.00 (0.69-1.45)</td>
<td>0.78 (0.46-1.31)</td>
<td>0.73 (0.41-1.32)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.34</td>
<td>0.34</td>
<td>0.30</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90 (n_cases = 49)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>90-&lt;118 (n_cases = 74)</td>
<td>1.39 (0.97-2.00)</td>
<td>1.36 (0.94-1.97)</td>
<td>1.32 (0.87-1.47)</td>
</tr>
<tr>
<td>≥118 (n_cases = 42)</td>
<td>1.24 (0.82-1.87)</td>
<td>1.25 (0.81-1.93)</td>
<td>1.22 (0.75-2.00)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.26</td>
<td>0.27</td>
<td>0.38</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;63 (n_cases = 54)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>50-&lt;63 (n_cases = 54)</td>
<td>1.05 (0.75-1.48)</td>
<td>1.06 (0.72-1.54)</td>
<td>0.93 (0.61-1.43)</td>
</tr>
<tr>
<td>&lt;50 (n_cases = 57)</td>
<td>1.13 (0.79-1.61)</td>
<td>1.25 (0.83-1.89)</td>
<td>1.13 (0.71-1.78)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.40</td>
<td>0.32</td>
<td>0.67</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;104 (n_cases = 51)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>104-&lt;150 (n_cases = 49)</td>
<td>0.98 (0.65-1.47)</td>
<td>0.91 (0.60-1.39)</td>
<td>0.84 (0.53-1.35)</td>
</tr>
<tr>
<td>≥150 (n_cases = 65)</td>
<td>1.37 (0.95-1.97)</td>
<td>1.22 (0.82-1.80)</td>
<td>1.14 (0.74-1.77)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.08</td>
<td>0.27</td>
<td>0.47</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;118 (n_cases = 46)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>118-&lt;130 (n_cases = 59)</td>
<td>1.29 (0.84-1.97)</td>
<td>1.36 (0.88-2.10)</td>
<td>1.31 (0.81-2.12)</td>
</tr>
<tr>
<td>≥130 (n_cases = 60)</td>
<td>1.33 (0.89-1.97)</td>
<td>1.39 (0.92-2.09)</td>
<td>1.25 (0.79-1.98)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.18</td>
<td>0.13</td>
<td>0.39</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;74 (n_cases = 54)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>74-&lt;85 (n_cases = 58)</td>
<td>1.05 (0.74-1.49)</td>
<td>1.15 (0.81-1.65)</td>
<td>1.04 (0.70-1.56)</td>
</tr>
<tr>
<td>≥85 (n_cases = 53)</td>
<td>1.43 (0.95-2.15)</td>
<td>1.55 (1.02-2.36)</td>
<td>1.43 (0.90-2.29)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.12</td>
<td>0.05</td>
<td>0.17</td>
</tr>
</tbody>
</table>

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

†Multivariable (MV)-adjusted HR is adjusted for the following variables: age (continuous), education (less than high school, high school grad/some college, college graduate, postcollege), 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), 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.

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 years prior to diagnosis and presence of the syndrome based on the average value of its components), presence of the metabolic syndrome showed a positive association 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. Although numerous studies have examined individual components of the metabolic syndrome in relation to breast cancer risk, 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 the syndrome and was analyzed as a time-dependent covariate. The HR associated with ≥2 prior diagnoses of the syndrome versus ≤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).
Table 3. Adjusted hazard ratios and 95% confidence intervals for the association of the metabolic syndrome and its individual components with breast cancer in time-dependent covariates analyses in the Women’s Health Initiative

<table>
<thead>
<tr>
<th>Metabolic syndrome components</th>
<th>All cases HR (95% CI)*</th>
<th>Invasive cases HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n cases = 71)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Yes (n cases = 29)</td>
<td>1.15 (0.71-1.85)</td>
<td>1.01 (0.59-1.74)</td>
</tr>
<tr>
<td>2-4 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n cases = 59)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Yes (n cases = 34)</td>
<td>1.57 (0.98-2.51)</td>
<td>1.48 (0.87-2.52)</td>
</tr>
<tr>
<td>3-5 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n cases = 52)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Yes (n cases = 33)</td>
<td>1.84 (1.12-3.01)</td>
<td>1.77 (1.01-3.12)</td>
</tr>
</tbody>
</table>

Individual components of the metabolic syndrome

- Waist circumference (cm)
  - Average
  - 1-3 y
    - <79 1.00 (ref.)
    - 79-<88 0.81 (0.52-1.39)
    - ≥88 0.69 (0.40-1.18)
    - Ptrend 0.17
  - 2-4 y
    - <79 1.00 (ref.)
    - 79-<88 0.99 (0.55-1.76)
    - ≥88 1.31 (0.67-2.59)
    - Ptrend 0.44
  - 3-5 y
    - <79 1.00 (ref.)
    - 79-<88 0.73 (0.39-1.34)
    - ≥88 1.08 (0.55-2.21)
    - Ptrend 0.84

- Glucose (mg/dL)
  - Average
    - <90 1.00 (ref.)
    - 90-<100 1.43 (0.98-2.09)
    - ≥100 1.57 (1.01-2.64)
    - Ptrend 0.04
    - 1-3 y
      - <90 1.00 (ref.)
      - 90-<100 1.90 (1.20-3.02)
      - ≥100 1.67 (0.95-2.94)
      - Ptrend 0.04
    - 2-4 y
      - <90 1.00 (ref.)
      - 90-<100 1.42 (0.89-2.27)
      - ≥100 1.30 (0.74-2.29)
      - Ptrend 0.27
    - 3-5 y
      - <90 1.00 (ref.)
      - 90-<100 1.60 (0.98-2.62)
      - ≥100 1.63 (0.92-2.91)
      - Ptrend 0.07

- HDL-C (mg/dL)
  - Average
    - <50 1.00 (ref.)
    - 50-<63 0.70 (0.47-1.05)
    - ≥63 0.81 (0.54-1.21)
    - Ptrend 0.34
    - 1-3 y
      - <50 1.00 (ref.)
      - 50-<63 0.74 (0.46-1.21)
      - ≥63 0.72 (0.44-1.17)
      - Ptrend 0.19
    - 2-4 y
      - <50 1.00 (ref.)
      - 50-<63 0.74 (0.46-1.21)
      - ≥63 0.72 (0.44-1.17)
      - Ptrend 0.19
    - 3-5 y
      - <50 1.00 (ref.)
      - 50-<63 0.74 (0.46-1.21)
      - ≥63 0.72 (0.44-1.17)
      - Ptrend 0.19

(Continued on the following page)
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 that reported on the 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 (15-17; see ref. 18 for review). An inverse association between HDL-C 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-C was inversely associated with breast cancer among premenopausal 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), 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 that 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 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, whereas the results of the remaining studies were null. Of the two cohort studies indicating a positive association, one (37) showed a significant association in premenopausal 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 on 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 nonesterified 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, which 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). Although hypertension associated with the metabolic syndrome seems 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 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 of ≥88 cm relative to waist circumference of <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 with 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

<table>
<thead>
<tr>
<th>Metabolic syndrome components</th>
<th>All cases HR (95% CI)*</th>
<th>Invasive cases HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥85</td>
<td>1.15 (0.58-2.26)</td>
<td>1.41 (0.69-2.91)</td>
</tr>
<tr>
<td>P&lt;sub&gt;rend&lt;/sub&gt;</td>
<td>0.37</td>
<td>0.27</td>
</tr>
<tr>
<td>Age &lt;74</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>≥75</td>
<td>1.06 (0.67-1.68)</td>
<td>1.00 (0.59-1.70)</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>1.32 (0.70-2.49)</td>
<td>1.36 (0.66-2.79)</td>
</tr>
</tbody>
</table>

*Adjusted for the following variables: age (continuous), education (less than high school, high school grad/some college, college graduate, postcollege), 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 cancer (ever/never), hormone therapy (ever/never), oral contraceptive use (ever/never), age at menopause (<50, ≥50, missing), alcohol (servings per week - continuous), physical activity (METs per week - continuous), fasting blood glucose level (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.

Table 3. Adjusted hazard ratios and 95% confidence intervals for the association of the metabolic syndrome and its individual components with breast cancer in time-dependent covariates analyses in the Women’s Health Initiative (Cont’d)
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 se and/or particular components show a consistent association with breast cancer risk.

The 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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References

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