Research Article

Cancer Epidemiology, Biomarkers & Prevention

Metabolic Syndrome and Breast Cancer in the Me-Can (Metabolic Syndrome and Cancer) Project

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Abstract

Background: Few studies have assessed the metabolic syndrome (MetS) as an entity in relation to breast cancer risk, and results have been inconsistent. We aimed to examine the association between MetS factors (individually and combined) and risk of breast cancer incidence and mortality.

Methods: Two hundred ninety thousand women from Austria, Norway, and Sweden were enrolled during 1974-2005, with measurements of height, weight, blood pressure, and levels of glucose, cholesterol, and triglycerides. Relative risks (RR) of breast cancer were estimated using Cox proportional hazards regression for each MetS factor in quintiles and for standardized levels (*z*-scores) and for a composite *z*-score for the MetS.

Results: There were 4,862 incident cases of breast cancer and 633 deaths from breast cancer identified. In women below age 50, there was a decreased risk of incident cancer for the MetS (per 1-unit increment of *z*-score; RR, 0.83; 95% confidence interval, 0.76-0.90) as well as for the individual factors (except for glucose). The lowest risks were seen among the heaviest women. In women above age 60, there was an increased risk of breast cancer mortality for the MetS (RR, 1.23; 95% confidence interval, 1.04-1.45) and for blood pressure and glucose. The strongest association with mortality was seen for increased glucose concentrations.

Conclusions: The MetS was associated with a decreased risk of incident breast cancer in women below age 50 with high body mass index, and with an increased risk of breast cancer mortality in women above 60.

Impact: Lifestyle interventions as recommended for cardiovascular disease prevention may be of value to prevent breast cancer mortality in postmenopausal women. *Cancer Epidemiol Biomarkers Prev; 19(7); 1737–45.* ©2010 AACR.

Introduction

Breast cancer is the most common cancer in women worldwide, accounting for about 23% of all cancers in women, and age-adjusted incidence rates are increasing in most countries (1). This increase parallels the increase in lifestyle-related diseases, such as type 2 diabetes and the metabolic syndrome (MetS; ref. 2). The MetS is a cluster of risk factors associated with increased risk of cardiovascular diseases, which also embraces several components individually related to breast cancer etiology: postmenopausal obesity, hypertension, hyperglycemia, and low high-density lipoprotein cholesterol (1, 3-5).

To date, few studies have assessed the MetS as an entity in relation to breast cancer risk, and the results have been inconsistent (6-8). Breast cancer is hormone related, and consequently, the effects of established risk factors for the disease, including obesity, a key component of the MetS, differ before and after menopause (1, 9). In addition to effects on incidence, metabolic factors have been suggested to affect breast cancer progression and prognosis (10).

In 2006, we initiated the MEtabolic syndrome and CANcer (Me-Can) project to investigate the effects of MetS factors and the MetS as an entity on cancer risk (11). Existing long-standing cohorts in Austria, Norway, and Sweden were included in the project. The aim of this study was to examine the association between MetS factors (both individually and combined) and the risk of breast cancer incidence and mortality.

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Materials and Methods

Study population

The Me-Can study design, participating cohorts, and data collection procedures have been described previously (11). Briefly, for studies on female cancers, six cohorts from Austria (the Vorarlberg Health Monitoring and Prevention Programme), Norway (the Norwegian Counties study, the Cohort of Norway, and the Age 40 Programme), and Sweden (the Västerbotten Intervention Project and the Malmö Preventive Project) were pooled in 2006. All women in the cohorts had undergone one or more health examination(s). In Norway and Sweden, participants were asked to fill in questionnaires covering lifestyle (including smoking) and various topics of specific interest for the recruiting centers. In Austria, specific questions about lifestyle (including smoking) were asked and recorded by the physician performing the examination.

Data on 288,834 women, collected during 1974-2005, were used in the Me-Can studies on female cancers (12). In all Me-Can cohorts, measurements of height, weight, and systolic and diastolic blood pressure had been done, and blood/plasma/serum levels of glucose, total cholesterol, and triglycerides were analyzed. Anthropometric measurements were conducted in a similar way in all individual cohorts, with participants wearing light indoor clothes and no shoes. Different resting time before measurements, body positions, and equipment were used in the cohorts for measurement of blood pressure. Also, various fasting times before blood draw were used in the different cohorts (11).

Detailed and complete information on known confounders of breast cancer risk such as reproductive history and exogenous hormone use (oral contraceptives and use/type/duration of hormone replacement therapy) was not available in all the individual Me-Can cohorts. In the Norwegian cohorts, however, data on parity, year of childbirth(s), and physical activity were available.

In all three countries, incident cases of breast cancer (International Classification of Diseases, seventh revision: 170) were identified through linkages with national cancer registries. The cohorts have also been linked to the respective National Cause of Death Register and, in Norway and Sweden, to the Register of the Total Population and Population Changes, for vital status. Causes of death were coded according to the Eurostat European shortlist for cause of death (13).

To reduce the possibility of reverse causation, follow-up started 1 year after the baseline examination. While exploring the breast cancer incidence, the follow-up ended at the date of the first cancer diagnosis, emigration, death, or December 31, 2003 (Austria), 2005 (Norway), and 2006 (Sweden). While exploring the breast cancer mortality, the follow-up ended at the date of death or emigration or December 31, 2003 (Austria) and 2004 (Norway and Sweden).

Statistical analysis

Cox proportional hazards regression models with age as the time variable were fitted to obtain hazard ratios, in this article denoted as relative risks (RR), of breast cancer incidence and mortality with 95% confidence intervals (95% CI; ref. 14). Quintile cutoff points for the exposure variables were determined within the six subcohorts, and for glucose, cholesterol, and triglycerides, also in categories of fasting time (fasting, >8 hours; nonfasting, ≤8 hours). The models were stratified for cohort (six subcohorts) and adjusted for year of birth (five categories: ≤1929, 1930-1939, 1940-1949, 1950-1959, and ≥1960), age at measurement (as a continuous variable), and smoking status (three categories: never, former, and current smokers). Blood pressure, glucose, cholesterol, and triglycerides were further adjusted for quintile levels of body mass index [BMI; (weight in kilograms)/(height in meters)^2], a known risk factor for breast cancer.

Tests for trend across quintiles were calculated using the mean levels of cohort-specific quintiles, and for glucose, cholesterol, and triglycerides, also in fasting time categories.

The variables BMI, blood pressure [(systolic blood pressure + diastolic blood pressure)/2], glucose, cholesterol, and triglycerides were standardized to *z*-score variables with mean = 0 and SD = 1. The variables were standardized separately for the six subcohorts, and for glucose, cholesterol, and triglycerides, also for fasting time. As glucose and triglycerides were skewed and had outliers, they were log transformed before standardization. A score for the MetS, constructed by adding the individual *z*-scores, was also standardized to a *z*-score variable with mean = 0 and SD = 1. This variable was standardized separately for the six subcohorts and for fasting time.

We examined the possibility of effect modification by BMI status. Analyses were stratified on BMI at measurement (three lowest and two highest quintiles), and we tested for interactions of each of the *z*-scores for blood pressure, glucose, cholesterol, triglycerides, and MetS with the two BMI groups.

As information on age at menopause was unavailable for most of the study subjects, we used age 50 years as a proxy for age at menopause, and stratified some analyses according to attained age <50, 50-59, and ≥60 years. In some analyses of breast cancer mortality, stratification was done according to attained age <50 and ≥50 years due to small numbers.

In the Norwegian cohorts, potential confounders such as parity, maternal age at childbirth(s), and physical activity were also adjusted for. However, the inclusion of these variables in the regression models did not appreciably change the risk estimates, and thus were not included in the final models.

Risk estimates were adjusted for random error in exposure assessment based on observations from subjects in which two or more observations with the same fasting time before measurements were available. Data from 71,789 women with 232,152 observations were used for

Table 1. Characteristics of the study population in the Me-Can project

	Breast cancer incidence		Breast cancer mortality	
	No. of cases	Person-years	No. of cases	Person-years
Cohort				
Norway				
NCS	932	653,973	257	658,099
CONOR	573	352,278	32	302,828
40-y	794	502,531	50	441,452
Austria				
VHM&PP	1,239	837,945	177	855,768
Sweden				
VIP	709	345,418	49	278,578
MPP	615	200,320	68	194,342
Year of birth				
-1919	149	52,349	44	54,486
1920-1929	681	302,846	159	305,690
1930-1939	1,499	715,936	209	704,342
1940-1949	1,077	482,972	135	458,495
1950-1959	1,329	934,835	79	835,668
1960-	127	403,528	7	372,386
Age at measurement (y)				
-29	148	357,594	14	349,101
30-39	730	613,892	97	586,549
40-49	2,165	1,254,546	303	1,162,839
50-59	1,106	406,757	106	382,415
60-69	499	180,352	63	171,941
≥70	214	79,324	50	78,222
Attained age (y)				
<50	1,466	1,486,602	111	1,408,584
50-59	1,302	644,415	183	597,668
≥60	2,094	761,448	339	724,817
Smoking status				
Never smoker	2,500	1,464,075	339	1,401,562
Ex-smoker	1,186	653,749	110	593,354
Smoker	1,162	766,426	181	728,899
Missing	14	8,215	3	7,253
BMI (kg/m^2)				
<18.5	81	74,083	10	72,245
18.5-24.9	2,701	1,697,802	339	1,606,994
25.0-29.9	1,483	800,883	201	751,817
≥30	597	319,697	83	300,011
Fasting time (h)				
≤8	2,394	1,511,269	350	1,404,782
>8	2,468	1,381,196	283	1,326,286
Follow-up (y)				
0-9	3,372	2,188,364	322	2,053,309
10-19	987	505,895	211	493,763
≥20	503	198,206	100	183,996
Total	4,862	2,892,465	633	2,731,068

Abbreviations: NCS, Norwegian Counties study; CONOR, Cohort of Norway; 40-y, Age 40 Programme; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; VIP, Västerbotten Intervention Project; MPP, Malmö Preventive Project.

analyses of random error. Mean time between the baseline measurement and repeated measurements was 6.9 years (SD = 3.9). RRs in quintiles were corrected directly by dividing the regression coefficient in the Cox model by the estimated regression dilution ratio (RDR) of exposure (15). RRs of *z*-scores were corrected indirectly by replacing each original *z*-score in the Cox model with its conditional expected value (i.e., regression calibration; ref. 16). RRs of *z*-scores were adjusted for all metabolic factors, which all, except BMI, have substantial random error (17-19). Therefore, the regression calibration method that allows for correction for random error also for covariates in the model was used in these analyses. Analyses of RDR and regression calibration were based on linear mixed-effect models, similar to those described by Woods et al. (15, 16).

The statistical package SPSS (version 14.0.2) was used for risk estimation, and R (version 2.7.2) for random error calculation.

Ethics

The Me-Can project has been approved by ethical committees in the respective countries.

Results

Incidence

The 287,320 women in this study were followed for an average of 11 years (range, 0-32 years) after measurement, constituting 2.9 million person-years when excluding the first year after measurements (Table 1). The mean age at measurement was 44 years. During follow-up, 4,862 breast cancers were diagnosed. The mean age at diagnosis was 58 years, and the breast cancer cases had their measurements taken, on average, 11 years before diagnosis.

The risk of breast cancer was first examined in quintile levels of the individual MetS factors (Table 2). When the analyses were stratified on attained age, there was a decreasing risk with increasing BMI (RR for the top versus bottom quintile was 0.70; 95% CI, 0.57-0.85) and levels of cholesterol and triglycerides in women below

Table 2. Relative risks of incident breast cancer with 95% CIs obtained in Cox regression analyses

Exposure	Cohort-specific quintiles	Mean (SD)	Total no. of cases	RR (95% CI)*	Attained age (y)		
					<50	50-59	≥60
					RR (95% CI)*	RR (95% CI)*	RR (95% CI)*
BMI	1	20.0 (1.2)	833	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	22.3 (0.8)	939	1.01 (0.91-1.12)	1.04 (0.89-1.23)	0.94 (0.78-1.15)	1.01 (0.84-1.22)
	3	24.1 (0.8)	976	0.95 (0.86-1.06)	0.92 (0.78-1.10)	0.91 (0.75-1.11)	1.01 (0.84-1.21)
	4	26.4 (1.0)	1,049	0.96 (0.86-1.06)	0.90 (0.75-1.08)	0.89 (0.73-1.09)	1.04 (0.87-1.25)
	5	31.7 (3.6)	1,065	0.98 (0.88-1.09)	0.70 (0.57-0.85)	0.87 (0.71-1.07)	1.21 (1.01-1.43)
	P_{trend}			0.7	<0.001	0.2	0.003
Systolic BP	1	104.5 (5.9)	761	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	114.4 (3.3)	748	0.99 (0.82-1.19)	0.84 (0.63-1.12)	1.02 (0.72-1.45)	1.24 (0.86-1.77)
	3	122.7 (3.0)	967	0.96 (0.80-1.14)	1.11 (0.84-1.47)	0.82 (0.59-1.15)	0.98 (0.71-1.36)
	4	133.6 (4.8)	1,142	1.00 (0.84-1.20)	0.97 (0.71-1.31)	1.07 (0.76-1.49)	1.05 (0.76-1.43)
	5	156.3 (16.1)	1,228	0.96 (0.79-1.15)	0.84 (0.59-1.20)	1.03 (0.72-1.47)	1.08 (0.79-1.47)
	P_{trend}			0.8	0.5	0.6	0.8
Diastolic BP	1	63.5 (5.5)	814	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	70.3 (3.5)	697	1.02 (0.84-1.25)	0.86 (0.63-1.18)	0.86 (0.58-1.25)	1.37 (0.96-1.95)
	3	76.9 (3.6)	1,203	1.08 (0.91-1.29)	1.08 (0.81-1.44)	0.97 (0.70-1.36)	1.21 (0.89-1.65)
	4	81.0 (3.5)	905	1.06 (0.87-1.28)	1.17 (0.85-1.60)	0.95 (0.66-1.37)	1.10 (0.79-1.54)
	5	92.6 (7.6)	1,227	1.02 (0.84-1.22)	0.68 (0.48-0.97)	1.02 (0.72-1.44)	1.22 (0.90-1.66)
	P_{trend}			1.0	0.2	0.7	0.6
Glucose	1	4.1 (0.5)	878	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	4.6 (0.3)	887	1.01 (0.71-1.43)	0.97 (0.53-1.75)	0.74 (0.39-1.42)	1.32 (0.75-2.33)
	3	5.0 (0.3)	1,005	1.07 (0.76-1.50)	1.23 (0.69-2.20)	0.87 (0.47-1.63)	1.15 (0.67-1.99)
	4	5.4 (0.3)	1,041	1.44 (1.03-2.01)	1.40 (0.78-2.52)	0.95 (0.50-1.79)	1.97 (1.15-3.35)
	5	6.6 (1.7)	1,042	1.30 (0.93-1.83)	1.28 (0.69-2.38)	0.98 (0.51-1.88)	1.61 (0.95-2.72)
	P_{trend}			0.08	0.3	0.9	0.09
Cholesterol	1	4.2 (0.4)	823	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	4.9 (0.2)	905	0.97 (0.84-1.13)	1.06 (0.85-1.32)	0.99 (0.76-1.30)	0.80 (0.61-1.05)
	3	5.5 (0.3)	990	0.95 (0.82-1.09)	0.86 (0.68-1.09)	1.13 (0.87-1.48)	0.81 (0.63-1.04)
	4	6.1 (0.3)	1,046	0.87 (0.76-1.01)	0.93 (0.73-1.19)	0.84 (0.63-1.11)	0.78 (0.61-1.00)
	5	7.3 (0.9)	1,077	0.74 (0.64-0.86)	0.67 (0.50-0.89)	0.93 (0.70-1.24)	0.64 (0.50-0.81)
	P_{trend}			<0.001	0.002	0.4	<0.001
Triglycerides	1	0.6 (0.1)	884	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	0.9 (0.1)	916	1.10 (0.91-1.32)	1.02 (0.75-1.37)	1.01 (0.71-1.42)	1.36 (0.98-1.89)
	3	1.1 (0.1)	919	0.92 (0.76-1.10)	0.96 (0.70-1.30)	0.91 (0.64-1.29)	1.02 (0.74-1.41)
	4	1.5 (0.2)	960	0.89 (0.73-1.07)	0.87 (0.63-1.21)	0.87 (0.61-1.25)	1.07 (0.78-1.47)
	5	2.5 (1.1)	1,044	0.92 (0.76-1.11)	0.65 (0.45-0.93)	0.91 (0.63-1.31)	1.26 (0.92-1.73)
	P_{trend}			0.1	0.002	0.6	0.3

*Stratified for cohort and adjusted for year of birth, age at measurement, smoking, and quintile levels of BMI (except BMI). RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; systolic BP, 0.54; diastolic BP, 0.51; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.

age 50. In women above age 60, there was an increasing risk with increasing BMI (RR for the top versus bottom quintile was 1.21; 95% CI, 1.01-1.43) and a decreasing risk with increasing cholesterol level.

Then we examined the individual factors and the combined MetS score as continuous *z*-scores in relation to incident breast cancer (Table 3). In women below age 50, there was a decreased risk for the MetS (per 1-unit increment of *z*-score; RR, 0.83; 95% CI, 0.76-0.90) as well as for the individual factors, except for glucose. In women above age 60, there was an increased risk for BMI and glucose and a decreased risk for cholesterol. In analyses adjusted for the other individual *z*-scores, there was a decreased risk for BMI and triglycerides in women below age 50, whereas there was an increased risk for glucose. In women above age 60, there was a decreased risk for cholesterol and an increased risk for glucose, although not significant.

When the analyses were stratified on baseline BMI (three lowest and two highest quintiles; Table 4), the lowest estimates were seen among the heaviest women with attained age below 50 years; the RR for the MetS was 0.67 (95% CI, 0.57-0.78) per 1-unit increment of *z*-score. Statistically significant interactions were observed for blood pressure ($P = 0.04$), glucose ($P = 0.006$), and the MetS ($P = 0.004$) in this age group.

Mortality

During follow-up, 633 deaths from breast cancer were identified. Of these cases, 92% had a prior diagnosis of incident breast cancer.

In analyses of quintile levels for the individual MetS factors (Table 5), there was an increased risk of breast cancer mortality with increasing diastolic blood pressure. The strongest association, however, was seen in the third, fourth, and fifth quintiles of glucose versus the bottom quintile in women above 50 years, but without a significant trend.

Of the continuous *z*-score factors, increasing levels of blood pressure, glucose, and the MetS conferred an increased risk on women above age 60 (Table 3). The RR for the MetS was 1.23 (95% CI, 1.04-1.45) per 1-unit increment of *z*-score. The association for blood pressure and glucose remained also after adjustment for the other individual *z*-scores. The highest RR was observed for glucose (RR, 1.50; 95% CI, 1.05-2.14).

Discussion

Analyses of risk of breast cancer incidence and mortality in relation to the MetS within this large, prospective cohort study showed that there was a decreased risk of incident breast cancer in women below age 50 with high BMI, but an increased risk of breast cancer mortality in women above age 60. Despite the inverse association of most MetS components with breast cancer before age 50, glucose was positively associated with risk. In women above age 60, blood pressure and glucose were associated with increased risk of breast cancer mortality.

Strengths and limitations

The main strengths of our study are its large size, including almost 5,000 breast cancer cases, and its prospective design. Evaluation of the association between the MetS and breast cancer incidence and mortality within the same cohort is another major strength. We used data from population-based surveys in three countries, with almost complete coverage of data for measured exposure factors (11). The large number of repeated measurements within the cohort allowed us to adjust for random error in the individual MetS factors (20). We also used high-quality national registers in Austria, Norway, and Sweden for follow-up of subjects. Reporting of cancer cases to the national cancer

Table 3. Relative risks of breast cancer incidence and mortality for continuous *z*-scores with 95% CIs obtained in Cox regression analyses, stratified by attained age

Exposure	RR (95% CI)*	RR (95% CI)†	RR (95% CI)*	RR (95% CI)†	RR (95% CI)*	RR (95% CI)†
	Attained age <50 y		Attained age 50-59 y		Attained age ≥60 y	
Breast cancer incidence						
BMI	0.86 (0.80-0.92)	0.87 (0.80-0.95)	0.96 (0.90-1.02)	0.96 (0.88-1.05)	1.07 (1.02-1.13)	1.03 (0.97-1.10)
Blood pressure	0.89 (0.80-0.99)	0.94 (0.83-1.07)	1.02 (0.92-1.13)	1.06 (0.94-1.19)	1.03 (0.95-1.11)	0.97 (0.89-1.05)
Glucose	1.13 (0.93-1.38)	1.30 (1.05-1.61)	0.96 (0.78-1.19)	1.03 (0.82-1.30)	1.20 (1.04-1.38)	1.16 (0.99-1.36)
Cholesterol	0.86 (0.79-0.94)	0.92 (0.83-1.02)	0.94 (0.85-1.03)	0.98 (0.88-1.08)	0.87 (0.81-0.93)	0.87 (0.80-0.93)
Triglycerides	0.80 (0.72-0.90)	0.85 (0.74-0.97)	0.93 (0.83-1.04)	0.94 (0.81-1.08)	1.05 (0.96-1.15)	1.06 (0.95-1.18)
MetS‡	0.83 (0.76-0.90)		0.95 (0.87-1.04)		1.04 (0.97-1.12)	
Breast cancer mortality						
BMI	1.06 (0.86-1.32)	0.88 (0.66-1.17)	1.05 (0.89-1.25)	0.99 (0.79-1.23)	1.00 (0.89-1.14)	0.87 (0.75-1.02)
Blood pressure	1.35 (0.94-1.93)	1.22 (0.78-1.89)	1.17 (0.89-1.54)	1.12 (0.82-1.52)	1.29 (1.07-1.56)	1.24 (1.02-1.52)
Glucose	1.47 (0.74-2.92)	1.26 (0.59-2.70)	1.14 (0.66-1.96)	1.24 (0.70-2.22)	1.57 (1.13-2.18)	1.50 (1.05-2.14)
Cholesterol	0.80 (0.58-1.10)	0.63 (0.42-0.92)	0.94 (0.74-1.20)	0.96 (0.73-1.27)	1.00 (0.84-1.18)	0.97 (0.81-1.17)
Triglycerides	1.38 (0.95-2.01)	1.58 (0.99-2.54)	0.97 (0.71-1.32)	0.90 (0.62-1.31)	1.14 (0.91-1.42)	1.00 (0.76-1.31)
MetS‡	1.21 (0.91-1.62)		1.07 (0.84-1.35)		1.23 (1.04-1.45)	

*Stratified for cohort and adjusted for year of birth, age at measurement, and smoking. RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; systolic BP, 0.54; diastolic BP, 0.51; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.

†Stratified for cohort and adjusted for year of birth, smoking, and the other individual *z*-scores. *z*-scores, derived from original values, were calibrated.

‡Standardized sum of the *z*-scores for BMI, blood pressure, glucose, cholesterol, and triglycerides.

Table 4. Relative risks of incident breast cancer for continuous *z*-scores with 95% CIs obtained in Cox regression analyses, stratified by attained age and BMI at measurement

Exposure	RR (95% CI)*	RR (95% CI)†	RR (95% CI)*	RR (95% CI)†	RR (95% CI)*	RR (95% CI)†
	Attained age <50 y		Attained age 50-59 y		Attained age ≥60 y	
Three lowest BMI quintiles (combined)						
Blood pressure	1.03 (0.90-1.19)	0.99 (0.85-1.16)	1.12 (0.97-1.30)	1.14 (0.97-1.33)	0.95 (0.84-1.08)	0.92 (0.81-1.05)
Glucose	1.38 (1.08-1.75)	1.51 (1.16-1.96)	0.88 (0.66-1.17)	0.92 (0.67-1.26)	1.15 (0.90-1.46)	1.19 (0.92-1.54)
Cholesterol	0.94 (0.84-1.06)	0.95 (0.83-1.08)	0.97 (0.86-1.09)	1.01 (0.88-1.16)	0.88 (0.79-0.98)	0.89 (0.79-1.00)
Triglycerides	0.92 (0.80-1.07)	0.86 (0.73-1.02)	0.91 (0.77-1.07)	0.90 (0.75-1.09)	1.01 (0.87-1.17)	1.05 (0.88-1.25)
MetS‡	1.02 (0.89-1.16)		0.95 (0.82-1.11)		0.96 (0.84-1.09)	
Two highest BMI quintiles (combined)						
Blood pressure	0.79 (0.65-0.95)	0.82 (0.66-1.02)	0.94 (0.79-1.12)	0.96 (0.80-1.14)	1.04 (0.94-1.16)	1.01 (0.90-1.12)
Glucose	0.86 (0.60-1.24)	0.91 (0.62-1.34)	1.11 (0.81-1.52)	1.14 (0.83-1.58)	1.16 (0.97-1.40)	1.11 (0.92-1.34)
Cholesterol	0.78 (0.67-0.90)	0.87 (0.72-1.04)	0.91 (0.79-1.05)	0.93 (0.79-1.09)	0.86 (0.78-0.94)	0.85 (0.77-0.94)
Triglycerides	0.74 (0.61-0.89)	0.83 (0.66-1.04)	0.97 (0.82-1.16)	0.97 (0.79-1.20)	1.02 (0.90-1.15)	1.06 (0.92-1.22)
MetS‡	0.67 (0.57-0.78)		0.96 (0.83-1.12)		1.03 (0.93-1.13)	

*Stratified for cohort and adjusted for year of birth, smoking and quintile levels of BMI (except MetS). RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; systolic BP, 0.54; diastolic BP, 0.51; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.

†Stratified for cohort and adjusted for year of birth, smoking, quintile levels of BMI, and the other individual *z*-scores. *z*-scores, derived from original values, were calibrated.

‡Standardized sum of the *z*-scores for BMI, blood pressure, glucose, cholesterol, and triglycerides.

registries in Norway and Sweden has been compulsory since the 1950s, and the reporting has been almost complete and of high quality (21, 22). Also, the cancer register in Austria has shown a high coverage (23).

There is no single universally accepted definition of the MetS. Nevertheless, all existing definitions (24-27) include indicators of insulin resistance, lipid abnormalities, blood pressure, and obesity. Because high-density lipoprotein cholesterol was not available in all Me-Can cohorts, we included total cholesterol in our analyses.

We lack complete information on reproductive history and exogenous hormone use, in particular hormone replacement therapy use in postmenopausal women, which may act as confounders. However, data on parity, year of childbirth(s), and physical activity were available in the Norwegian cohorts, but adjusting for these variables did not appreciably change the risk estimates.

We did not have data on estrogen and progesterone receptor status of the tumors. A recent meta-analysis indicated that the association between body weight and breast cancer risk varied by estrogen receptor/progesterone receptor status and by menopausal status (28). On the other hand, a nested case-control study from Sweden, evaluating the influence of overweight and insulin resistance on breast cancer risk and tumor stage at diagnosis, found only minor differences overall in the exposure-risk associations according to receptor status (29).

Different measurement methods were used in the individual Me-Can cohorts (11). Anthropometric measurements were conducted similarly in all cohorts, but there were differences with regard to blood pressure measurements and analyses of blood samples. To account for these differences, cohort-specific cutoff points were used in the analyses.

Comparisons with the literature

Incidence. Very few studies have assessed the MetS as an entity to breast cancer risk, and the studies have focused on postmenopausal breast cancer. In a longitudinal study of the MetS and postmenopausal breast cancer risk in the United States (7), the presence of the MetS at baseline was not associated with risk. In time-dependent analyses, however, the MetS showed a positive association with breast cancer. In an Italian nested case-control study, the MetS was significantly associated with postmenopausal breast cancer risk, with a significant risk increase for increasing number of factors present (6). In our study, we found no increased risk of incident breast cancer for the MetS in women above 60 years.

In this large cohort study, approximately 1,500 breast cancer cases were diagnosed before age 50. Among these, there was a decreased risk of breast cancer for the MetS, mostly confined to the heaviest women (in the two highest BMI quintiles), and also a decreased risk for the individual factors, except for glucose. Interestingly, glucose concentrations were positively associated with risk, particularly in women with BMI in the three lowest BMI quintiles. At present, the mechanisms underlying the inverse association of the MetS and of its individual factors (except for glucose) with premenopausal

breast cancer remain speculative (30), and further research is of interest.

The association between individual components of the MetS and risk of breast cancer has been investigated in numerous epidemiologic studies (31). Obesity, the most extensively explored factor, has opposite associations with breast cancer risk before and after menopause (32, 33). Also in our study, there was an increased breast cancer risk in women above age 60 with high BMI (both in analyses of quintile levels and in analyses of continuous *z*-scores) and a reduced risk in women below age 50.

It has been suggested that type 2 diabetes may be associated with a 10% to 20% excess RR of breast cancer (34). Also, high levels of fasting plasma glucose and hyperinsulinemia have been associated with an increased breast cancer risk, both in premenopausal and in postmenopausal women (4, 35). Our data are in line with these observations.

Table 5. Relative risks of breast cancer mortality with 95% CIs obtained in Cox regression analyses

Exposure	Cohort-specific quintiles	Mean (SD)	Total no. of cases	RR (95% CI)*	Attained age (y)	
					<50 RR (95% CI)*	≥50 RR (95% CI)*
BMI	1	20.0 (1.2)	104	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	22.2 (0.8)	102	0.86 (0.63-1.16)	0.73 (0.38-1.40)	0.87 (0.61-1.23)
	3	24.1 (0.8)	132	0.99 (0.74-1.32)	0.85 (0.45-1.63)	0.98 (0.70-1.37)
	4	26.4 (1.0)	147	0.99 (0.74-1.32)	1.11 (0.59-2.09)	0.93 (0.67-1.29)
	5	31.7 (3.6)	148	0.99 (0.74-1.32)	1.22 (0.64-2.31)	0.92 (0.66-1.27)
	P_{trend}			0.7	0.3	0.8
Systolic BP	1	105.4 (5.8)	94	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	115.4 (2.9)	70	1.07 (0.60-1.92)	1.25 (0.38-4.17)	0.99 (0.51-1.93)
	3	122.7 (3.0)	110	1.03 (0.61-1.72)	1.80 (0.60-5.39)	0.84 (0.46-1.51)
	4	133.6 (4.8)	163	1.64 (1.00-2.69)	2.52 (0.83-7.63)	1.38 (0.79-2.39)
	5	156.3 (16.1)	196	1.54 (0.93-2.56)	2.49 (0.73-8.50)	1.33 (0.76-2.33)
	P_{trend}			0.06	0.06	0.2
Diastolic BP	1	63.5 (5.5)	86	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	70.4 (3.4)	79	1.08 (0.59-1.98)	0.79 (0.21-2.99)	1.12 (0.57-2.20)
	3	77.0 (3.6)	158	1.40 (0.83-2.36)	2.20 (0.74-6.59)	1.20 (0.67-2.17)
	4	81.0 (3.5)	110	1.54 (0.87-2.71)	1.60 (0.46-5.56)	1.45 (0.77-2.74)
	5	92.6 (7.7)	200	2.10 (1.24-3.54)	2.93 (0.90-9.58)	1.88 (1.05-3.38)
	P_{trend}			0.002	0.05	0.01
Glucose	1	4.1 (0.5)	96	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	4.7 (0.3)	112	1.64 (0.60-4.49)	0.48 (0.05-4.45)	2.26 (0.72-7.07)
	3	5.0 (0.3)	138	2.48 (0.94-6.54)	0.67 (0.08-5.88)	3.44 (1.15-10.26)
	4	5.4 (0.3)	145	3.27 (1.25-8.57)	2.36 (0.31-17.83)	3.68 (1.23-11.01)
	5	6.6 (1.7)	142	2.41 (0.91-6.36)	0.85 (0.09-8.01)	3.13 (1.05-9.32)
	P_{trend}			0.1	0.8	0.1
Cholesterol	1	4.2 (0.4)	105	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	4.9 (0.2)	108	0.84 (0.56-1.27)	0.89 (0.39-2.01)	0.79 (0.49-1.28)
	3	5.5 (0.3)	108	0.67 (0.44-1.02)	0.84 (0.36-1.94)	0.60 (0.37-0.97)
	4	6.1 (0.3)	135	0.77 (0.52-1.15)	0.79 (0.33-1.91)	0.72 (0.46-1.14)
	5	7.3 (0.9)	171	0.81 (0.55-1.21)	0.46 (0.16-1.31)	0.82 (0.53-1.28)
	P_{trend}			0.5	0.08	0.8
Triglycerides	1	0.6 (0.1)	88	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2	0.9 (0.1)	114	1.37 (0.78-2.39)	1.13 (0.31-4.08)	1.39 (0.75-2.60)
	3	1.1 (0.1)	127	1.46 (0.85-2.53)	2.35 (0.71-7.77)	1.30 (0.70-2.41)
	4	1.5 (0.2)	125	1.17 (0.67-2.04)	2.10 (0.61-7.21)	1.03 (0.55-1.92)
	5	2.5 (1.1)	162	1.62 (0.93-2.80)	2.11 (0.58-7.65)	1.53 (0.83-2.82)
	P_{trend}			0.2	0.3	0.3

*Stratified for cohort and adjusted for year of birth, age at measurement, smoking, and quintile levels of BMI (except BMI). RRs are corrected for RDR; conversion into uncorrected RR = exp[log(RR)*RDR]. RDR: BMI, 0.90; systolic BP, 0.54; diastolic BP, 0.51; glucose, 0.27; cholesterol, 0.66; triglycerides, 0.50.

The lipoprotein pattern in relation to breast cancer risk has received substantial attention as well. In a previous Norwegian study, Furberg et al. (3) reported that low high-density lipoprotein cholesterol was associated with increased postmenopausal breast cancer risk among overweight women. Several epidemiologic studies have reported an association between low cholesterol levels and higher cancer incidence and mortality, and this association has mostly been attributed to reverse causation (36, 37). In our study, we also found a decreased breast cancer risk with increasing levels of cholesterol, and we excluded cases diagnosed within the first year after blood draw. Some studies have also indicated that hypertension is associated with a slight increase in risk of breast cancer (38).

Mortality. Metabolic factors have been suggested to affect breast cancer prognosis as well. In an Italian study on the risk of breast cancer recurrence in postmenopausal women (10), the presence of the MetS at baseline was an important adverse factor for breast cancer recurrence, in particular in women with high serum levels of testosterone. When considered alone, none of the individual MetS factors was significantly associated with prognosis. Also, a recent Norwegian study supported a relationship between mortality among breast cancer patients and BMI, blood pressure, lipids, and physical activity (39). In our study, there was an increased risk of breast cancer mortality for the MetS as well as for blood pressure and glucose in women above age 60. In particular, a strong association was seen in the third, fourth, and fifth quintiles of glucose in women above 50 years, although the trend was insignificant.

Among individual risk factors, obesity has been shown to increase the risk of breast cancer recurrence, contralateral breast cancer, wound complications after breast surgery, lymphedema, and possibly mortality (40). It has been suggested that less active participation in mammography screening of obese in comparison with normal-weight women can account for some of these differences, although a recent meta-analysis of studies from the United States indicated that the differences in the breast cancer screening participation rates may be evident only when morbidly obese women (BMI >40 kg/m^2) are compared with normal-weight women. In our study, we did not observe a positive association between BMI and breast cancer mortality.

Conclusion

The MetS was associated with a decreased risk of incident breast cancer in women below age 50 with high BMI, and with an increased risk of breast cancer mortality in women above age 60. The strongest association with breast cancer mortality was seen for increased glucose concentrations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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