



Original Contribution

Metabolic Syndrome and Endometrial Carcinoma

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The authors examined the association between the metabolic syndrome and risk of incident endometrial and fatal uterine corpus cancer within a large prospective cohort study. Approximately 290,000 women from Austria, Norway, and Sweden were enrolled during 1974–2005, with measurements of height, weight, systolic and diastolic blood pressure, and circulating levels of glucose, total cholesterol, and triglycerides. Relative risks were estimated using Cox proportional hazards regression. The metabolic syndrome was assessed as a composite z score, as the standardized sum of z scores for body mass index, blood pressure, glucose, cholesterol, and triglycerides. A total of 917 endometrial carcinomas and 129 fatal cancers were identified. Increased risks of incident endometrial carcinoma and fatal uterine corpus cancer were seen for the metabolic syndrome factors combined, as well as for individual factors (except for cholesterol). The relative risk of endometrial carcinoma for the metabolic syndrome was 1.37 (95% confidence interval: 1.28, 1.46) per 1-unit increment of z score. The positive associations between metabolic syndrome factors (both individually and combined) and endometrial carcinoma were confined to the heaviest women. The association between the metabolic syndrome and endometrial carcinoma risk seems to go beyond the risk conferred by obesity alone, particularly in women with a high body mass index.

cohort studies; endometrial neoplasms; metabolic syndrome X

Abbreviations: BMI, body mass index; CI, confidence interval; Me-Can, Metabolic Syndrome and Cancer Project; SD, standard deviation.

The metabolic syndrome is a cluster of risk factors including obesity, hypertension, insulin resistance, and dyslipidemia and is associated with an increased risk of cardiovascular disease (1). The prevalence of the metabolic syndrome (according to a modified World Health Organization definition) in European nondiabetic adults has been estimated at 15% (2). In the United States, higher prevalence rates (according to National Cholesterol Education Program/Adult Treatment Panel III criteria) have been reported, reaching 23% among nondiabetics in the Third National Health and Nutrition Examination Survey (3).

Although the term “metabolic syndrome” has been useful in denoting this cluster of risk factors, there is some controversy regarding the existence of this syndrome (4), and different definitions are in use (5). Furthermore, it might be useful to have a combined risk score for the metabolic

syndrome (6, 7) that could address small increases in risk for multiple components even if none of the individual risk factors were particularly high.

Individual components of the metabolic syndrome have previously been linked to the development of various types of cancer. Evidence has begun to emerge linking the metabolic syndrome as an entity to certain types of cancer (8), but data are still sparse (9, 10).

Adult overweight/obesity is one of the strongest risk factors for endometrial cancer (11, 12), accounting for approximately 40% of endometrial cancer incidence in affluent societies (13). Other factors suggestive of metabolic abnormalities, such as hypertension and hyperglycemia, have also been associated with increased risk, especially among overweight/obese women (14, 15). Diabetes (both type 1 and type 2) has been related to an increased risk of endometrial

Table 1. Cohorts Included and Measurement Methods Used in the Metabolic Syndrome and Cancer Project^a

Variable	Norway				Austria	Sweden	
	Oslo Study I	Norwegian Counties Study	Cohort of Norway	Age 40 Programme	Vorarlberg Health Monitoring and Prevention Programme	Västerbotten Intervention Project	Malmö Preventive Project
Purpose	To study risk factors for CVD and to prevent CVD	To prevent CVD	To collect data for research on the etiology of various diseases	To study risk factors for CVD and to prevent CVD	To prevent chronic diseases, particularly CVD and cancer	To prevent diabetes and CVD	To prevent CVD and alcohol abuse
Participants	Men in Oslo, Norway, aged 40–49 years and a subset of men aged 20–39 years	Men and women in Finnmark, Sogn og Fjordane, and Oppland counties aged 35–49 years and, in 1974–1978, a subset of inhabitants aged 20–34 years	Men and women in different regions of Norway within different age groups	Men and women aged 40–42 years in all Norwegian counties	Men and women aged ≥19 years in the province of Vorarlberg	Men and women aged 30 (before 1996), 40, 50, and 60 years in Västerbotten County	Men and women in Malmö, Sweden, born in 1921–1949; mean age at first screening: men, 44 years; women, 50 years
Year(s)	1972–1973	1974–1978, 1977–1983, and 1985–1988	1994–2003	1985–1999	1985–2005	1985–ongoing	1974–1992 and subset in 1981–1989
Attendance rate	60%	78%–90%	Average = 56%; range, 30%–76% in surveys	69%	66%	60%	71% at first screening
Measurement methods							
Height	No shoes	No shoes	No shoes	No shoes	No shoes	No shoes	No shoes
Weight	Light clothes	Light clothes	Light clothes	Light clothes	Light clothes	Light clothes	Light clothes
Blood pressure							
No. of measurements	2 ^b	2 ^{b,c}	3 ^b	3 ^b	1	1	1–2 (mean value was recorded)
Rest time before measurement	4 minutes; 1 minute between measurements	4 minutes; 1 minute between measurements ^c	2 minutes; 1 minute between measurements	2 minutes; 1 minute between measurements	5 minutes	5 minutes	10 minutes
Position	Sitting	Sitting	Sitting	Sitting	Sitting	Supine	Supine
Instrument	Mercury sphygmomanometer	Mercury sphygmomanometer	Automatic device	Automatic device	Mercury sphygmomanometer	Mercury sphygmomanometer	Mercury sphygmomanometer
Fasting status before measurement	Nonfasting	Nonfasting	Nonfasting	Nonfasting	Fasting from 1988 onwards	Fasting from 1992 onwards	Fasting
Glucose							
Substance	Serum	Serum	Serum	Serum	Plasma	Plasma	Whole blood
Method	Nonenzymatic ^d	Nonenzymatic ^d	Enzymatic ^d	Enzymatic ^d	Enzymatic	Enzymatic	Enzymatic
Cholesterol and triglycerides							
Substance	Serum	Serum	Serum	Serum	Serum	Serum	Serum
Method	Nonenzymatic ^e	Nonenzymatic; enzymatic from 1980 onwards ^e	Enzymatic ^e	Enzymatic ^e	Enzymatic	Enzymatic	Enzymatic

Abbreviation: CVD, cardiovascular disease.

^a Cohorts and measurement methods outlined by Stocks et al. (18, 19).

^b In accordance with previous studies carried out in Norway (20, 21), the second of 2 blood pressure measurements is used in the Metabolic Syndrome and Cancer Project, and if 3 measurements were recorded, the mean value of the second and third measurements is used.

^c From 1985 onward—that is, the third screening in the Norwegian Counties Study—blood pressure was measured as described for the Cohort of Norway and the Age 40 Programme cohort.

^d Measurements taken by means of the nonenzymatic method yielded levels 0.8–1.1 mmol/L higher than those obtained by the enzymatic method.

^e Levels obtained by means of the nonenzymatic method were compared with those obtained by the enzymatic method (22, 23); accordingly, levels measured with the nonenzymatic method were transformed according to the formulas $0.92 \times \text{cholesterol level} + 0.03$ and $0.90 \times \text{triglyceride level} - 0.11$.

Table 2. Characteristics of the Study Population, Metabolic Syndrome and Cancer Project

	Incident Endometrial Carcinoma		Fatal Uterine Corpus Cancer	
	No. of Cases	Person-Years	No. of Cases	Person-Years
Country and cohort				
Norway				
Norwegian Counties Study	272	653,973	51	658,099
Cohort of Norway	97	352,278	16	302,828
Age 40 Programme	56	502,531	4	441,452
Austria				
Vorarlberg Health Monitoring and Prevention Programme	217	837,945	39	855,768
Sweden				
Västerbotten Intervention Project	161	345,418	9	278,578
Malmö Preventive Project	114	200,320	10	194,342
Year of birth				
≤1919	29	52,349	11	54,486
1920–1929	212	302,846	38	305,690
1930–1939	383	715,936	55	704,342
1940–1949	199	482,972	17	458,495
1950–1959	93	934,835	8	835,668
≥1960	1	403,528	0	372,386
Age at measurement, years				
≤29	10	357,594	1	349,101
30–39	118	613,892	15	586,549
40–49	352	1,254,546	48	1,162,839
50–59	240	406,757	28	382,415
60–69	138	180,352	19	171,941
≥70	59	79,324	18	78,222
Smoking status				
Never smoker	592	1,464,075	86	1,401,562
Ex-smoker	146	653,749	14	593,354
Current smoker	175	766,426	28	728,899
Missing data	4	8,215	1	7,253
Body mass index ^a				
<18.5	7	74,083	1	72,245
18.5–24.9	377	1,697,802	41	1,606,994
25.0–29.9	291	800,883	44	751,817
≥30	242	319,697	43	300,011
Fasting time, hours				
<4	366	1,218,658	61	1,131,207
4–8	88	292,610	13	273,574
>8	463	1,381,196	55	1,326,286
Duration of follow-up, years				
0–9	552	2,188,364	63	2,053,309
10–19	223	505,895	42	493,763
≥20	142	198,206	24	183,996
Total	917	2,892,465	129	2,731,068

^a Weight (kg)/height (m)².

cancer as well (15, 16). Cust et al. (17) recently reported on the metabolic syndrome and the risk of endometrial cancer in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition. The metabolic syndrome was directly associated with endometrial cancer, and the risk increased with the number of metabolic syndrome factors present.

In 2006, we initiated the Metabolic Syndrome and Cancer Project (Me-Can) to investigate the associations between metabolic syndrome factors and the metabolic syndrome as an entity and cancer risk (18). Existing long-standing cohorts in Austria, Norway, and Sweden were included in the project. Our aim in the current study was to examine the association between metabolic syndrome factors (both individually and combined) and risk of incident endometrial and fatal uterine corpus cancer in this large pooled data set.

MATERIALS AND METHODS

Study population

The Me-Can study design, cohorts included, and data collection have previously been described (18). In brief, data collected from cohorts in Austria (the Vorarlberg Health Monitoring and Prevention Programme), Norway (in females: 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 (Table 1). All persons in the cohorts had undergone 1 or more health examination(s) and had been asked to fill in questionnaires (except for the Austrian cohort) covering lifestyle factors and various topics of specific interest for the program, in connection with the examination. In Austria, however, specific questions about lifestyle were asked, and responses were recorded by the physician performing the examination.

Data on 288,834 women, collected during 1974–2005, were used in the Me-Can study in females. In all Me-Can cohorts, measurements of height, weight, and systolic and diastolic blood pressure were performed, and blood/plasma/serum levels of glucose, total cholesterol, and triglycerides were analyzed. Data on smoking status were available as well. We lacked detailed and complete information on known confounders of endometrial cancer risk, such as reproductive history and exogenous hormone use (oral contraceptives and hormone replacement therapy) for all of the individual Me-Can cohorts. For the Norwegian cohorts, however, data on parity, year(s) of childbirth(s), and physical activity were available. Data on hysterectomy status in the cohorts were not available.

In all 3 countries, incident cases of cancer of the uterine corpus (*International Classification of Diseases*, Seventh Revision, code 172) were identified through linkage with national cancer registries. When analyzing incident cancer, only histologically verified endometrial carcinomas were included (24), and some analyses were restricted to type I tumors (12). Type I tumors, mostly endometrioid adenocarcinomas, have been described as estrogen-dependent. The cohorts were also linked to the respective national cause-of-death registers and, in Norway and Sweden, to the central

population registries for ascertainment of vital status. When analyzing fatal cancer, we included all cases of uterine corpus cancer. Causes of death were coded according to the Eurostat “European shortlist” for causes of death (25).

To reduce the possibility of reverse causation, we started follow-up 1 year after the baseline examination ($n = 1,514$ women excluded). While exploring the incidence of endometrial carcinoma, we ended follow-up at the date of the first cancer diagnosis, emigration, death, or December 31, 2003 (Austria), 2005 (Norway), or 2006 (Sweden). While exploring mortality from uterine corpus cancer, we ended follow-up at the date of death or emigration or December 31, 2003 (Austria) or 2004 (Norway and Sweden).

Statistical analysis

We fitted Cox proportional hazards regression models with age as the time variable to obtain hazard ratios (denoted relative risks in this paper) and 95% confidence intervals for endometrial carcinoma incidence and mortality (26). Quintile cutpoints were determined for the exposure variables within the 6 subcohorts and, for glucose, cholesterol, and triglycerides, in categories of fasting time as well (fasting; >8 hours, nonfasting; ≤ 8 hours). The models were stratified for cohort (6 subcohorts) and adjusted for year of birth (5 categories: ≤ 1929 , 1930–1939, 1940–1949, 1950–1959, and ≥ 1960) and smoking status (3 categories: never, former, and current smokers). Blood pressure, glucose, cholesterol, and triglycerides were further adjusted for quintile of body mass index (BMI; weight (kg)/height (m)²), which is known to be a strong risk factor for endometrial cancer.

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

To test for trend across quintiles, we used mean levels within cohort-specific quintiles and, for glucose, cholesterol, and triglycerides, in fasting time categories as well.

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 standard deviation (SD) = 1. The variables were standardized separately for the 6 subcohorts and, for glucose, cholesterol, and triglycerides, also for fasting time. Since data for glucose and triglycerides were skewed and had outliers, they were log-transformed before standardization. A score for the metabolic syndrome, 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 6 subcohorts and for fasting time.

We examined the possibility of effect modification by BMI status. Analyses were stratified on BMI at measurement (3 lowest quintiles and 2 highest quintiles), and we tested for interactions between the z scores for blood pressure, glucose, cholesterol, and triglycerides and BMI group.

Table 3. Relative Risks of Incident Endometrial Carcinoma and Fatal Uterine Corpus Cancer Obtained in Cox Regression Analyses, Metabolic Syndrome and Cancer Project

Exposure and Cohort-specific Quintile	Incident Endometrial Carcinoma						Fatal Uterine Corpus Cancer					
	Mean (SD)	No. of Cases	RR ^a	95% CI	RR ^b	95% CI	Mean (SD)	No. of Cases	RR ^a	95% CI	RR ^b	95% CI
BMI^c												
1	20 (1.2)	79	1.00	Referent			20 (1.2)	7	1.00	Referent		
2	22 (0.8)	130	1.37	1.04, 1.82			22 (0.8)	15	1.73	0.71, 4.26		
3	24 (0.8)	159	1.45	1.11, 1.91			24 (0.8)	16	1.45	0.59, 3.57		
4	26 (1.0)	213	1.73	1.33, 2.25			26 (1.0)	24	1.99	0.85, 4.67		
5	32 (3.6)	336	2.68	2.09, 3.45			32 (3.6)	67	5.35	2.43, 11.80		
<i>P</i> _{trend}				<0.001						<0.001		
Systolic blood pressure, mm Hg												
1	104 (5.9)	94	1.00	Referent	1.00	Referent	105 (5.8)	7	1.00	Referent	1.00	Referent
2	114 (3.3)	103	1.17	0.88, 1.55	1.11	0.83, 1.47	115 (2.9)	13	2.27	0.89, 5.79	2.05	0.80, 5.24
3	123 (3.0)	159	1.23	0.95, 1.59	1.11	0.86, 1.44	123 (3.0)	18	2.04	0.85, 4.89	1.72	0.71, 4.13
4	134 (4.8)	223	1.39	1.08, 1.78	1.18	0.92, 1.52	134 (4.8)	38	3.38	1.49, 7.67	2.55	1.12, 5.84
5	156 (16.1)	337	1.73	1.36, 2.22	1.38	1.07, 1.77	156 (16.1)	53	3.36	1.48, 7.63	2.22	0.97, 5.12
<i>P</i> _{trend}				<0.001		0.003				0.004		0.1
Diastolic blood pressure, mm Hg												
1	63 (5.5)	115	1.00	Referent	1.00	Referent	64 (5.5)	11	1.00	Referent	1.00	Referent
2	70 (3.5)	121	1.10	0.85, 1.42	1.05	0.81, 1.36	70 (3.4)	6	0.58	0.21, 1.57	0.54	0.20, 1.46
3	77 (3.5)	176	0.92	0.72, 1.17	0.84	0.66, 1.06	77 (3.6)	26	1.32	0.64, 2.69	1.13	0.55, 2.31
4	81 (3.5)	191	1.24	0.98, 1.57	1.07	0.84, 1.36	81 (3.5)	26	1.96	0.96, 4.00	1.52	0.74, 3.14
5	93 (7.6)	313	1.38	1.11, 1.72	1.11	0.88, 1.39	93 (7.7)	60	2.71	1.41, 5.24	1.86	0.95, 3.65
<i>P</i> _{trend}				<0.001		0.2				<0.001		0.002
Glucose, mmol/L												
1	4.1 (0.5)	128	1.00	Referent	1.00	Referent	4.1 (0.5)	17	1.00	Referent	1.00	Referent
2	4.6 (0.3)	136	1.01	0.79, 1.28	0.98	0.77, 1.25	4.7 (0.3)	19	1.05	0.54, 2.02	0.99	0.52, 1.91
3	5.0 (0.3)	200	1.27	1.02, 1.59	1.21	0.97, 1.51	5.0 (0.3)	29	1.33	0.73, 2.43	1.20	0.66, 2.20
4	5.4 (0.3)	196	1.32	1.05, 1.65	1.23	0.99, 1.54	5.4 (0.3)	26	1.26	0.68, 2.33	1.11	0.60, 2.06
5	6.6 (1.7)	253	1.57	1.27, 1.95	1.41	1.13, 1.75	6.6 (1.7)	38	1.60	0.90, 2.85	1.32	0.74, 2.36
<i>P</i> _{trend}				<0.001		0.001				0.05		0.2
Cholesterol, mmol/L												
1	4.2 (0.4)	126	1.00	Referent	1.00	Referent	4.2 (0.4)	16	1.00	Referent	1.00	Referent
2	4.9 (0.2)	142	0.94	0.74, 1.20	0.91	0.71, 1.16	4.9 (0.2)	20	1.00	0.51, 1.92	0.94	0.49, 1.83
3	5.5 (0.3)	191	1.06	0.84, 1.33	0.99	0.79, 1.25	5.5 (0.3)	26	0.99	0.53, 1.88	0.89	0.47, 1.68
4	6.1 (0.3)	191	0.88	0.70, 1.11	0.80	0.64, 1.01	6.1 (0.3)	26	0.82	0.43, 1.56	0.71	0.38, 1.35
5	7.3 (0.9)	262	0.97	0.78, 1.22	0.87	0.70, 1.10	7.3 (0.9)	41	0.98	0.53, 1.81	0.82	0.45, 1.51
<i>P</i> _{trend}				0.7		0.2				0.8		0.4

Triglycerides, mmol/L	0.6 (0.1)	116	1.00	Referent	1.00	Referent	0.6 (0.1)	12	1.00	Referent	1.00	Referent
1	0.6 (0.1)	116	1.00	Referent	1.00	Referent	0.6 (0.1)	12	1.00	Referent	1.00	Referent
2	0.9 (0.08)	157	1.30	1.02, 1.66	1.24	0.97, 1.58	0.9 (0.08)	27	1.87	0.95, 3.70	1.69	0.85, 3.35
3	1.1 (0.1)	163	1.19	0.93, 1.51	1.08	0.85, 1.38	1.1 (0.1)	18	1.11	0.53, 2.33	0.93	0.44, 1.95
4	1.5 (0.2)	190	1.28	1.01, 1.61	1.10	0.86, 1.39	1.5 (0.2)	25	1.36	0.68, 2.74	1.01	0.50, 2.06
5	2.5 (1.1)	263	1.61	1.29, 2.02	1.26	1.00, 1.59	2.5 (1.1)	45	2.14	1.11, 4.13	1.36	0.69, 2.66
P_{trend}				<0.001		0.05				0.01		0.4

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk; SD, standard deviation.

^a Stratified by cohort and adjusted for year of birth and smoking.

^b Further adjusted for quintile of BMI (except BMI).

^c Weight (kg)/height (m)².

Since we had no information on age at menopause for most of the study subjects, we used age 50 years as a proxy for age at menopause and stratified some analyses according to age <50 years and ≥ 50 years at measurement and attained age.

Absolute risks of incident endometrial carcinoma between ages 50 and 70 years were calculated for women with metabolic z scores less than or equal to 1 SD and above 1 SD, using the age groups 50–54, 55–59, 60–64, and 65–69 years.

The statistical package SPSS was used for risk estimation (27).

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 10 years (range, 0–31 years), constituting 2.9 million person-years (Table 2). The mean age at measurement was 44 years. During follow-up, 917 endometrial carcinomas were diagnosed. The mean age at diagnosis was 62 years, and the cases had their measurements taken on average 11 years prior to diagnosis.

In analyses stratified for cohort and adjusted for year of birth and smoking, the relative risk of endometrial carcinoma increased with increasing BMI, systolic and diastolic blood pressure, glucose level, and triglyceride level (Table 3). When the analyses were further adjusted for quintile of BMI, the risk was still present for systolic blood pressure and glucose level.

There was an increased risk of endometrial carcinoma for the metabolic syndrome (per 1-unit increment of z score, relative risk = 1.37, 95% confidence interval (CI): 1.28, 1.46) (Table 4). The association was not affected by exclusion of any of the subcohorts from the analysis, and relative risks for endometrial carcinoma after exclusion of 1 cohort at a time ranged between 1.34 (95% CI: 1.24, 1.44) and 1.40 (95% CI: 1.31, 1.50), indicating that the association between the metabolic syndrome and the risk of endometrial carcinoma was not driven by a single cohort.

There were also increased risks for all of the individual z scores except for cholesterol when stratifying for cohort and adjusting for year of birth and smoking, and there was increased risk for blood pressure and glucose after further adjustment for quintile of BMI. Restricting the analyses to type I tumors yielded results very similar to those obtained in analyses of all tumors (data not shown).

When the analyses were stratified on baseline BMI (3 lowest quintiles and 2 highest quintiles), statistically significant heterogeneity was observed for blood pressure ($P < 0.001$), glucose ($P = 0.02$), cholesterol ($P = 0.01$), and triglycerides ($P = 0.004$), with stronger associations among the heaviest women (Table 5). For BMI, the association was somewhat stronger among older women when the analyses were

Table 4. Relative Risks of Incident Endometrial Carcinoma and Fatal Uterine Corpus Cancer for Continuous Z Scores Obtained in Cox Regression Analyses, Metabolic Syndrome and Cancer Project

Exposure	RR ^a	95% CI	RR ^b	95% CI	RR ^c	95% CI
<i>Incident endometrial carcinoma</i>						
BMI ^d	1.46	1.38, 1.53			1.39	1.31, 1.47
Blood pressure	1.20	1.13, 1.28	1.12	1.05, 1.20	1.06	0.99, 1.14
Glucose	1.16	1.10, 1.23	1.13	1.07, 1.19	1.09	1.02, 1.15
Cholesterol	0.98	0.91, 1.05	0.94	0.88, 1.01	0.93	0.86, 1.00
Triglycerides	1.17	1.09, 1.24	1.07	1.00, 1.15	1.03	0.96, 1.11
Metabolic syndrome ^e	1.37	1.28, 1.46				
<i>Fatal uterine corpus cancer</i>						
BMI	1.68	1.48, 1.90			1.60	1.39, 1.85
Blood pressure	1.37	1.17, 1.60	1.21	1.02, 1.43	1.17	0.98, 1.39
Glucose	1.16	1.01, 1.34	1.10	0.95, 1.28	1.06	0.91, 1.23
Cholesterol	0.96	0.80, 1.15	0.91	0.76, 1.09	0.92	0.76, 1.12
Triglycerides	1.19	1.00, 1.42	1.02	0.85, 1.22	0.99	0.81, 1.21
Metabolic syndrome ^e	1.56	1.32, 1.84				

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

^a Stratified by cohort and adjusted for year of birth and smoking.

^b Further adjusted for quintile of BMI (except BMI).

^c Stratified by cohort and adjusted for year of birth, smoking, and the other individual z scores.

^d Weight (kg)/height (m)².

^e Standardized sum of the z scores for BMI, blood pressure, glucose, cholesterol, and triglycerides.

stratified on attained age (<50 years and ≥50 years). No major differences were seen in the estimates when the analyses were stratified on age at measurement (<50 years and ≥50 years).

Analyses focusing on more extreme values of the metabolic syndrome factors, as defined by >1 SD, showed similar tendencies. However, the estimates were somewhat higher; the relative risk for the metabolic syndrome was 1.85 (95% CI: 1.60, 2.15). Further, the risk increased with increasing number of factors with high levels present, reaching 2.09 (95% CI: 1.65, 2.64) with 3 factors present at high levels and 3.39 (95% CI: 1.64, 6.61) with all 5 factors present (Table 6).

The absolute risks of developing endometrial carcinoma over a 20-year period for 50-year-old women with metabolic z scores less than or equal to 1 SD and greater than 1 SD were 1% and 1.7%, respectively.

Fatal cancer

During follow-up, 129 fatal uterine corpus cancers were identified. Of these cases, 58% had a prior diagnosis of incident endometrial carcinoma. In analyses stratified for cohort and adjusted for year of birth and smoking, the relative risk of fatal cancer increased with increasing BMI, systolic and diastolic blood pressure, and triglyceride level (Table 3). When the analyses were further adjusted for quintile of BMI, the risk was still present for diastolic blood pressure. There was an increased risk of fatal cancer for the metabolic syndrome (relative risk = 1.56, 95% CI: 1.32, 1.84) as well (Table 4). There were also increased risks for all of the individual z scores except for cholesterol when

stratifying for cohort and adjusting for year of birth and smoking, and there was increased risk for blood pressure after further adjustment for quintile of BMI.

DISCUSSION

The results of this large, prospective study strongly suggest that the metabolic syndrome and most of its individual components (BMI, glucose and triglyceride concentrations, and hypertension) are important contributors in the development of endometrial carcinoma. More importantly, the risk increased with the number of metabolic alterations present. The positive associations between glucose, triglycerides, and hypertension and endometrial carcinoma were confined to the heaviest women. These observations are strikingly reminiscent of the results of 2 recent well-designed prospective studies (14, 17), and they add further evidence that the influence of the metabolic syndrome on endometrial carcinoma risk goes beyond the risk conferred by obesity alone, particularly in women with a high BMI. Similar results were seen for fatal uterine corpus cancer.

Strengths and limitations

Major strengths of our study were its large size and the prospective design. Evaluation of the association between the metabolic syndrome and both incident and fatal cancer within the same cohort is another major strength, as the metabolic syndrome may affect not only the development of endometrial carcinoma but also the subsequent risk of death from the disease. We used data from population-based surveys carried out in 3 countries, with almost complete

Table 5. Relative Risk of Incident Endometrial Carcinoma for Continuous Z Scores Obtained in Cox Regression Analyses, According to Body Mass Index at Measurement, Metabolic Syndrome and Cancer Project

Exposure	RR ^a	95% CI	RR ^b	95% CI	RR ^c	95% CI
<i>3 Lowest BMI^d Quintiles (Combined)</i>						
Blood pressure	1.01	0.90, 1.14	1.00	0.89, 1.12	0.99	0.88, 1.11
Glucose	1.09	0.98, 1.21	1.08	0.98, 1.20	1.08	0.97, 1.20
Cholesterol	0.93	0.83, 1.04	0.91	0.82, 1.03	0.92	0.81, 1.03
Triglycerides	1.02	0.90, 1.14	1.00	0.89, 1.12	1.02	0.90, 1.15
Metabolic syndrome ^e	1.07	0.93, 1.24				
<i>2 Highest BMI Quintiles (Combined)</i>						
Blood pressure	1.22	1.13, 1.32	1.19	1.09, 1.29	1.16	1.07, 1.26
Glucose	1.17	1.09, 1.25	1.15	1.08, 1.23	1.12	1.04, 1.20
Cholesterol	0.97	0.89, 1.06	0.96	0.88, 1.05	0.92	0.84, 1.01
Triglycerides	1.15	1.06, 1.25	1.11	1.02, 1.21	1.10	1.00, 1.20
Metabolic syndrome ^e	1.40	1.28, 1.53				

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

^a Stratified by cohort and adjusted for year of birth and smoking.

^b Further adjusted for quintile of BMI.

^c Stratified by cohort and adjusted for year of birth, smoking, quintile of BMI, and the other individual z scores.

^d Weight (kg)/height (m)².

^e Standardized sum of the z scores for BMI, blood pressure, glucose, cholesterol, and triglycerides.

coverage of data for measured exposure factors (18). We also used high-quality national registers in Austria, Norway, and Sweden for follow-up of subjects, and during follow-up more than 900 cases of endometrial carcinoma were identified. Reporting of cancer cases to the national cancer registries in Norway and Sweden has been compulsory since the 1950s, and the reporting has been almost complete and of high quality (28, 29). In addition, the cancer register in Austria has shown high coverage (30); only 7% of cancers in males and 9% of cancers in females were discovered by death certificate alone in 1993–1997 and only 5% in both sexes in 1998–2002.

There is no single, universally accepted definition of the metabolic syndrome. Several definitions are used (5, 31–33), and all of them include indicators of insulin resistance, lipid abnormalities, blood pressure, and obesity.

Table 6. Relative Risk of Incident Endometrial Carcinoma Obtained in Cox Regression Analyses, According to Number of Metabolic Syndrome Exposure Variables Present at High Levels, Metabolic Syndrome and Cancer Project

No. of Metabolic Syndrome Factors With High Levels ^a	No. of Cases	Relative Risk ^b	95% Confidence Interval
0	330	1.00	Referent
1	251	1.21	1.02, 1.43
2	156	1.46	1.20, 1.78
3	102	2.09	1.65, 2.64
4	40	2.61	1.86, 3.66
5	9	3.39	1.64, 6.61

^a The metabolic syndrome factors included body mass index, blood pressure, glucose, cholesterol, and triglycerides. High levels were defined as greater than 1 standard deviation.

^b Stratified by cohort and adjusted for year of birth and smoking.

Since data on high density lipoprotein cholesterol were not available in all Me-Can cohorts, we included total cholesterol in our analyses instead.

To adjust for different methods and distributions of the individual risk factors in the different cohorts, we chose to use standardized z scores, standardized separately for the 6 subcohorts and for fasting time. Because risk increases gradually over standardized metabolic syndrome values, a cut-off for high risk will be more or less arbitrary, and the use of a continuous variable also has the advantage of increased power. We defined a high level of each individual risk factor as >1 SD. This is relevant, since risk increases by the number of risk factors with moderate-to-high levels. Finally, the baseline observation for each individual was selected for use in studies of the association between metabolic syndrome and cancer risk, and it may not fully reflect long-term variations.

We lacked complete information on reproductive history and exogenous hormone use, which may have acted as confounders. However, for the Norwegian cohorts, data on parity, year(s) of childbirth(s), and physical activity were available, and adjusting for these variables did not appreciably change the risk estimates. Further, stratifying some analyses according to age at measurement and attained age (<50 years and ≥50 years), as a proxy for age at menopause, had only a weak impact on the associations. Additionally, some studies have shown a weaker association connected to elevated insulin concentrations in women using exogenous estrogens (34, 35), and the lack of information on hormone replacement therapy may have resulted in underestimation of the true magnitude of the association.

Data on hysterectomy status in the cohorts were not available. Approximately 70% of the person-years in this study came from the Scandinavian cohorts. Although hysterectomy rates have been increasing in Norway and

Sweden (to 209 per 100,000 women in 2000 in Norway (36) and 232 per 100,000 in 1999 in Sweden (37)), the overall hysterectomy rate in the United States is considerably higher (approximately 538 per 100,000 women-years in 2003) (38).

Comparisons with the literature

Among the individual metabolic syndrome components, obesity is the most powerful correlate of cancer risk (14, 17). In our data, BMI was the strongest single predictor of risk. In addition, glucose concentration and hypertension were significantly associated with risk (after accounting for BMI)—observations consistent with the reports from most large epidemiologic investigations (14, 15, 17, 39, 40). The direct association of triglycerides with risk in our data was abolished after we accounted for BMI, while total cholesterol was not related to risk in any model. Similarly, most studies on the association of dyslipidemia, as reflected by the association of various cholesterol fractions and/or triglyceride concentrations, with risk of endometrial or other cancers have yielded inconsistent results, and for total cholesterol results appear to depend on time to cancer diagnosis (41).

Mechanisms that could contribute to the adverse impact of metabolic syndrome and its components on risk of endometrial carcinoma include insulin resistance (34, 42–44), a proinflammatory milieu favoring the development of neoplastic transformation (44), and mechanisms related to sex steroid metabolism (30, 36–38).

Elevated availability of glucose may offer a selective advantage to malignant cells, which have an increased glucose requirement because of their accelerated metabolic rate (45, 46). Other links between elevated glucose concentrations and endometrial carcinoma risk may involve up-regulation of glucose transporter proteins (e.g., glucose transporters 1, 4, and 8) (47, 48), formation of reactive oxygen species (49), and increased endogenous synthesis of advanced glycation end products (45, 50–52).

The putative biologic mechanisms that underlie the association of hypertension or elevated triglycerides with endometrial carcinoma risk are unclear at present. It has been speculated that long-term exposure to hypertension may lead to inhibition of apoptosis (53), while hypertriglyceridemia could contribute to the oxidative stress and formation of reactive oxygen species by excessive cytosolic tryglyceride concentration in nonadipose tissue (8).

Investigations have shown that the influence of metabolic syndrome components is stronger or confined to overweight or obese women (14, 15, 17, 40). The exact biologic mechanisms that may account for such interaction have not yet been elucidated.

Conclusion

The results of this large prospective study show direct associations between the metabolic syndrome, as well as individual metabolic syndrome factors (except for cholesterol), and the risk of endometrial carcinoma. The study offers further evidence that the influence of the metabolic

syndrome on risk of endometrial carcinoma goes beyond the risk conferred by obesity alone, particularly in women with a high BMI.

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