Metabolic Syndrome and Risks of Colon and Rectal Cancer: The European Prospective Investigation into Cancer and Nutrition Study

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Abstract

Metabolic syndrome (MetS) is purportedly related to risk of developing colorectal cancer; however, the association of MetS, as defined according to recent international criteria, and colorectal cancer has not been yet evaluated. In particular, it remains unclear to what extent the MetS components individually account for such an association. We addressed these issues in a nested case–control study that included 1,093 incident cases matched (1:1) to controls by using incidence density sampling. Conditional logistic regression was used to estimate relative risks (RR) and 95% CIs. MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the International Diabetes Federation (IDF), and the 2009 harmonized definition. Among individual components, abdominal obesity (RR = 1.51; 95% CI: 1.16–1.96) was associated with colon cancer, whereas abnormal glucose metabolism was associated with both colon (RR = 2.05; 95% CI: 1.57–2.68) and rectal cancer (RR = 2.07; 95% CI: 1.45–2.96). MetS, as defined by each of the definitions, was similarly associated with colon cancer (e.g., RR = 1.91; 95% CI: 1.47–2.42 for MetS by NCEP/ATPIII), whereas MetS by NCEP/ATPIII, but not IDF or harmonized definition, was associated with rectal cancer (RR = 1.45; 95% CI: 1.02–2.06). Overall, these associations were stronger in women than in men. However, the association between MetS and colorectal cancer was accounted for by abdominal obesity and abnormal glucose metabolism such that MetS did not provide risk information beyond these components (likelihood ratio test $P = 0.10$ for MetS by NCEP/ATPIII). These data suggest that simple assessment of abnormal glucose metabolism and/or abdominal obesity to identify individuals at colorectal cancer risk may have higher clinical utility than applying more complex MetS definitions. *Cancer Prev Res; 4(11); 1873–83. ©2011 AACR.*

Introduction

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including abdominal obesity, elevated blood pressure (BP), abnormal glucose metabolism, and dyslipidemia, suggested to play a major role in the development of cardiovascular diseases and diabetes mellitus (1). Recent evidence shows that components of MetS may also be associated with risk of developing colorectal cancer (2, 3). In particular, high waist circumference (WC, a marker

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for abdominal obesity; ref. 4), elevated levels of hemoglobin A1c (HbA$_{1c}$, a marker for abnormal glucose metabolism; ref. 5), and reduced levels of high-density lipoprotein cholesterol (HDL-C, a marker for dyslipidemia; ref. 6) were shown to be independently associated with risk of developing colorectal cancer. In line with these observations, a number of studies have reported that MetS may be associated with risk of developing colorectal cancer (7–12); however, a number of questions remain. First, studies defined MetS according to different criteria, mainly other than those originally proposed by a number of expert groups. Second, metabolic abnormalities, such as WC, may be more strongly related to risk of developing colon cancer than that of rectal cancer, and results may differ between men and women (4); however, most studies on MetS published thus far have been relatively small and have incompletely defined results by sex (8, 11) or by colon/rectal cancer site (11–13).

Finally, MetS is a heterogeneous condition that may reflect various combinations of metabolic abnormalities, and it is not clear to what extent the components individually account for the potential association between MetS and colorectal cancer (14, 15). The answer to this question is crucial for understanding whether complex assessment of MetS may be more useful for identifying subjects at risk of developing colorectal cancer than assessing certain MetS components.

We conducted a nested case–control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort with the aim to examine the association of components and definitions of MetS with risks of developing colon and rectal cancer. In particular, we aimed to examine to what extent the components individually account for the potential association between MetS and colorectal cancer.

Participants and Methods

Data collection and follow-up

EPIC is a large prospective study with 519,978 participants, aged 25 to 70 years at period of enrollment (1992–2000), and recruited predominantly from the general population in 23 centers from 10 European countries. Participants gave written informed consent, underwent anthropometric measurements, and completed questionnaires on sociodemographic and lifestyle characteristics.

Blood samples were collected according to a standardized protocol (16). Approval was obtained from ethics review board of the International Agency for Research on Cancer and local review boards. The present study includes subjects from Denmark, France, Germany, Greece, Italy, Spain, the Netherlands, and the United Kingdom. Excluded from the analysis were the subjects from Norway, where blood samples were only recently collected and few cases have a diagnosis after blood donation, and the Malmö center of Sweden, which did not provide blood samples.

Incident cancer cases were identified through record linkage with regional cancer registries or based on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next of kin. Closure dates for the present study were defined as the latest date of complete follow-up for both cancer incidence and vital status and ranged from December 1999 to June 2003 for centers using registry data and from June 2000 to December 2002 for centers using active follow-up procedures. Colon and rectal cancers were defined according to the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10), proximal colon tumors include tumors in the cecal appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (ICD-10 codes C18.0–18.5); distal colon tumors include those in the descending colon (ICD-10 code C18.6) and sigmoid colon (ICD-10 code C18.7); and rectal tumors are those occurring at the rectosigmoid junction (ICD-10 code C19) or in the rectum (ICD-10 code C20). A total of 1,093 incident cancer cases (689 colon, 404 rectum) with available baseline information for each of the MetS components were included in the analysis and were matched to same number of controls, selected with incidence density sampling procedure, such that controls could include subjects who became a case later in time; also, each control subject could be sampled more than once. Matching characteristics were the study center, sex, age at blood collection, follow-up time since blood collection, time of the day at blood collection, and fasting status, and among women, menopausal status. Premenopausal women were matched on phase of menstrual cycle at blood collection, and postmenopausal women were matched on hormonal replacement therapy (HRT) use.

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MetS definitions

We defined MetS using the 2005 revised criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), the 2005 International Diabetes Federation (IDF) criteria, and the latest harmonized definition published in 2009 (Table 1). In contrast to the other 2 definitions, the IDF definition requires abdominal obesity as an essential component of MetS. Furthermore, the IDF and the harmonized criteria, but not the NCEP/ATPIII criteria, use population specific cutoffs to define abdominal obesity. We slightly modified these definitions, using baseline HbA_{1c} instead of blood glucose as a surrogate marker for abnormal glucose metabolism (see the following text).

MetS components

WC was measured either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest (4). Abdominal obesity was defined as WC 102 cm or more in men or 88 cm or more in women for the NCEP/ATPIII definition (17), or as WC 94 cm or more in men or 80 cm or more in women for the IDF and the harmonized definitions (18, 19).

Systolic BP and diastolic BP were measured at baseline by trained personnel. Two readings were performed on the right arm in a sitting position (spaced by 1–5 minutes) after an initial resting time of at least 5 minutes by use of a standard mercury manometer or oscillometric device. To avoid any possible white-coat effect, for the present analysis, we primarily used the second reading (567 cases; 549 controls) and, where unavailable, the first reading (379 cases; 375 controls). Elevated BP was defined as systolic BP 130 mm/Hg or more, diastolic BP 85 mm/Hg or more, self-reported physician diagnosed hypertension, or self-reported treatment of hypertension (17–19).

Serum HDL-C and triglyceride (TG) concentrations were quantitatively determined by a colorimetric method, using a Synchron LX-20 Pro autoanalyzer (Beckman-Coulter; ref. 6). Reduced HDL-C concentrations were defined as less than 40 mg/dL (1.03 mmol/L) in men and less than 50 mg/dL (1.29 mmol/L) in women. Because 76% of the study participants provided nonfasting blood samples (time since last meal <6 hours), for the TG concentrations, we subtracted the sex-specific geometric mean difference between nonfasting and fasting subjects from the individual levels of nonfasting subjects. Elevated TG levels were defined as 150 mg/dL or more (1.7 mmol/L; refs. 17–19).

Subjects were determined as having abnormal glucose metabolism on the basis of self-reported diabetes (57 cases, 42 controls) or HbA_{1c} 5.7% or more (572 cases; 433 controls), which corresponds to fasting plasma glucose levels of 100 mg/dL, as proposed by the American Diabetes Association. Measurements of HbA_{1c} in erythrocyte hemolysate were done using high-performance liquid chromatography with a Bio-Rad Variant IITM instrument (5).

Table 1. Definitions of MetS

Definition	NCEP/ATPIII (2005 revision)	IDF (2005)	Harmonized definition (2009)[a]
Components: AO (high WC)	Three or more of the following: ≥102 cm in men, 　≥88 cm in women	≥94 cm in men, ≥80 cm in women (for European population) plus any 2 of the following:	Any three of the following: ≥94 cm in men, ≥80 cm in women (for European population)
Elevated TG	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism	150 mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men 　<50 mg/dL (1·29 mmol/L) in women	<40 mg/dL (1.03 mmol/L) in men 　<50 mg/dL (1.29 mmol/L) in women	<40 mg/dL (1.03 mmol/L) in men 　<50 mg/dL (1.29 mmol/L) in women or specific treatment for lipid metabolism
Elevated BP	systolic ≥130, diastolic ≥85 mmHg or treatment of previously diagnosed hypertension	systolic ≥130, diastolic ≥85 mmHg or treatment of previously diagnosed hypertension	systolic ≥130, diastolic ≥85 mmHg or treatment of previously diagnosed hypertension
AGM[b]	fasting glucose levels ≥100 mg/dl (≥5.6 mmol/l) or previously diagnosed type 2 diabetes	fasting glucose levels ≥100 mg/dl (≥5.6 mmol/l) or previously diagnosed type 2 diabetes	fasting glucose levels ≥100 mg/dl (≥5.6 mmol/l) or drug treatment for elevated glucose

Abbreviations: AO, abdominal obesity; AGM, abnormal glucose metabolism; WC, waist circumference; TG, tryglicerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.
[a]Based on a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.
[b]In this analysis, HbA1c 5.7% or more was used instead of fasting glucose for defining abnormal glucose metabolism, according to the American Diabetes Association recommendations (2010).

Statistical analyses

Case–control differences were assessed using Student's paired *t* test or Wilcoxon's signed-rank test for continuous variables and by McNemar's test or Bowker's test of symmetry for categorical variables. The association of MetS and its components, as defined on the basis of NCEP/ATPIII, IDF, and the harmonized criteria, with risk of developing colorectal cancer was analyzed using multivariable-adjusted conditional logistic regression, adjusted for confounders other than those controlled for by matching, including smoking status (never, former, current, or missing), education (no school degree/primary school, technical/professional school, secondary school, university degree, or missing), physical activity (inactive, moderately inactive, moderately active, active, or missing), alcohol (g/d), fiber (g/d), red and processed meat (g/d), fruits and vegetables (g/d), fish (g/d), and shellfish (g/d). In the same model, we estimated the relative risks (RRs) for the mutually adjusted components of MetS. We present the results in terms of estimated RRs, under the assumption that with risk-set sampling, the odds ratio derived from the conditional logistic regression directly estimates the hazard ratio as a measure of the RR (20). We conducted the main multivariable-adjusted analysis separately for men and women and for colon (proximal/distal) and rectal cancer. We examined whether the associations differ by sex and cancer site (colon/rectum; proximal/distal colon) by using interaction terms of MetS definitions and components (both dichotomous), respectively, multiplied by the stratum variable in the main multivariable-adjusted model. To study the potential effect of various combinations of MetS components, we estimated the multivariable-adjusted risk of developing colon cancer associated with combinations of MetS components, relative to the absence of the respective combinations. To examine to what extent the association between MetS and colorectal cancer is statistically explained by single components, we added those components that were significantly associated with risk (abdominal obesity, abnormal glucose metabolism, and reduced HDL-C) individually and in combinations to the multivariable-adjusted model for each MetS definition. To explore whether MetS may be more useful to assess colon cancer risk than its individual components, we used likelihood ratio test (LRT), a standard statistical test for comparing nested models, and compared the fit of a multivariable-adjusted model, including only abnormal glucose metabolism and abdominal obesity, with a model also including the MetS variable (21).

To distinguish any potential effect of diagnosed diabetes, we repeated the analyses by using a cutoff point for HbA1c of 6.5% or more (95 cases; 47 controls) and excluding people with reported diabetes at baseline (35 cases; 18 controls). To account for the high proportion of nonfasting participants, we repeated the multivariable-adjusted analyses after excluding nonfasting cases and their corresponding controls (830 case–control sets). To test the possibility of reverse causation, we repeated the main multivariable-adjusted analyses after exclusion of cases with a diagnosis within the first 2 years of recruitment (284 cases). All *P* values were 2-tailed, and *P* values below 0.05 were considered to indicate statistical significance. Data were analyzed using the Statistical Analysis System (SAS) software package, version 9·2 (SAS Institute Inc.).

Results

The median time between study recruitment and cancer diagnosis among cases was 3.7 years; the average follow-up time among controls was 9.3 years. Colon cancer cases had a higher number of metabolic abnormalities and a higher prevalence of MetS by any of the 3 definitions at baseline than controls, whereas rectal cancer cases had a higher prevalence for MetS as defined by NCEP/ATPIII but not for the other 2 definitions (Table 2).

In multivariable-adjusted conditional logistic regression, abdominal obesity, reduced HDL-C, and abnormal glucose metabolism, but not elevated TG or BP, were each associated with colon cancer risk whereas abnormal glucose metabolism was the only component associated with risk of developing rectal cancer (Table 3). When the components were mutually adjusted, abdominal obesity by IDF (RR = 1.51; 95% CI: 1.16–1.96) and abnormal glucose metabolism (RR = 2.05; 95% CI = 1.57–2.68), but not abdominal obesity by NCEP/ATPIII and reduced HDL-C, remained statistically significantly related to risk of developing colon cancer (Fig. 1A). For rectal cancer, abnormal glucose metabolism remained strongly associated with risk after adjustment for all other components (Fig. 1B).

The analysis on the association of different combinations of the MetS components with colon cancer risk showed that the strength of the association of a certain combination was highly reflecting the strength of the association of the components included in that combination (Table 4). For example, a combination of abdominal obesity and abnormal glucose metabolism, each of which was significantly associated with colon cancer risk, resulted in a RR of 2.29 (95% CI: 1.72–3.03) whereas the combination of elevated BP and elevated TG levels, both of which were not associated with risk, expectedly produced nonsignificant risk estimates (RR = 1.33; 95% CI: 0.97–1.84).

MetS as determined on the basis of each of the 3 original definitions was statistically significantly associated with colon cancer risk. The multivariable-adjusted RRs were as follows: 1.91 (95% CI: 1.47–2.42) for the NCEP/ATPIII definition, 1.91 (95% CI: 1.48–2.46) for the IDF definition, and 2.00 (95% CI: 1.56–2.56) for the harmonized definition, with no statistically significant differences between sexes (*P* = 0.49, *P* = 0.84, *P* = 0.73 for difference between sexes for each respective definition). For rectal cancer, there was an association with MetS by NCEP/ATPIII (RR = 1.45; 95% CI: 1.02–2.06) but not with the other 2 definitions (Table 3). When stratified by sex, this association was statistically present in women (RR = 2.03; 95% CI: 1.14–3.62) but not in men (RR = 1.35; 95% CI: 0.83–2.21, *P* = 0.80 for difference between sexes; Table 3). The differences between colon and rectal cancer were statistically

Table 2. Baseline characteristics and baseline prevalence of MetS and individual components in colon and rectal cancer cases and matched controls, EPIC, 1992–2003

	Colon cancer			Rectal cancer		
	Cases (N = 689)	Controls (N = 689)	P^a	Cases (N = 404)	Controls (N = 404)	P^a
Sociodemographic and lifestyle characteristics						
Women, %	54.7	54.7		45.8	45.8	
Age, mean (SD), y	58.8 (7.3)	58.8 (7.3)	0.97	58.1 (7.0)	58.1 (7.0)	0.74
University degree, %	16.7	18.4	0.31	20.0	20.0	0.23
Postmenopausal women, %	72.2	70.8	0.70	69.2	69.7	0.98
Ever use of HRT, %	11.5	10.6	0.79	8.7	7.8	0.32
Not fasting overnight, %	48.2	48.7	0.57	57.5	57.8	0.54
Smokers, %	23.7	20.8	0.42	27.7	28.2	0.87
Physically inactive, %	15.5	12.8	0.13	15.8	14.9	0.007
Alcohol intake, median (IQR), g/d	7.9 (2.3–17.9)	7.5 (2.7–17.4)	0.20	11.9 (3.5–27.2)	10.6 (3.5–22.4)	0.009
Fruits and vegetables intake, median (IQR), g/d	381.3 (244.1–549.7)	412.3 (259.7–564.2)	0.08	355.7 (247.8–522.6)	372.7 (256.9–541.9)	0.43
Metabolic abnormalities						
WC, mean (SD)	90.5 (13.1)	88.0 (12.1)	<0.001	90.5 (13.1)	89.9 (13.1)	0.58
BMI, mean (SD)	26.9 (4.4)	26.3 (3.8)	0.02	26.6 (4.1)	26.5 (3.9)	0.55
TG, median (IQR), mmol/L	1.13 (0.77–1.61)	1.05 (0.76–1.50)	0.02	1.14 (0.79–1.62)	1.14 (0.79–1.63)	0.99
HDL-C, median (IQR), mmol/L	1.37 (1.12–1.66)	1.44 (1.19–1.75)	<0.001	1.44 (1.16–1.71)	1.40 (1.14–1.70)	0.94
Systolic BP, mean (SD), mmHg	137.1 (22.3)	135.3 (19.3)	0.11	136.6 (20.7)	137.9 (21.6)	0.17
Diastolic BP, mean (SD), mmHg	83.0 (12.5)	81.8 (10.9)	0.22	82.9 (10.9)	83.0 (11.2)	0.46
HbA_{1c}, median (IQR), %	5.8 (5.5–6.1)	5.7 (5.5–6.0)	0.02	5.7 (5.5–6.0)	5.7 (5.5–6.0)	0.93
Components of the definitions of MetS						
AO by NCEP/ATPIII definition, %	33.5	25.4	<0.001	31.4	25.9	0.08
AO by IDF definition, %	63.6	52.8	<0.001	59.2	57.2	0.56
Elevated TG, %	21.9	17.7	0.04	23.3	21.5	0.54
Reduced HDL-C, %	25.5	19.7	0.009	19.3	21.5	0.42
Elevated BP, %	64.2	59.9	0.08	64.6	62.1	0.43
AGM, %	51.7	38.3	<0.001	50.7	39.9	0.003
Number of MetS components,[b] %						
0	12.2	18.3	<0.001	11.9	16.3	0.05
1 or 2	54.6	60.8	0.02	58.2	60.4	0.51
3 or more	33.2	20.9	<0.001	30.0	23.3	0.02
Definitions of MetS						
MetS by NCEP/ATPIII definition, %	33.2	20.9	<0.001	30.0	23.3	0.02
MetS by IDF definition, %	40.6	27.3	<0.001	35.6	30.7	0.13
MetS by the harmonized definition, %	44.4	29.8	<0.001	38.4	32.9	0.09

NOTE: Sex, age, menopausal status, fasting status, and HRT use were among the matching criteria.

Abbreviations: AO, abdominal obesity; AGM, abnormal glucose metabolism; BMI, body mass index; WC, waist circumference; TG, tryglicerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; HRT, hormonal replacement therapy; HbA1c, glycated hemoglobin; MetS, metabolic syndrome; IQR, interquartile range; SD, standard deviation.

[a]P values for the difference between cases and controls were determined by Student's paired t test for variables expressed as means, by Wilcoxon's signed-rank test for variables expressed as medians, and by Mc Nemar's test and Bowker's test of symmetry for variables expressed as percentages.

[b]MetS components as defined according to the NCEP/ATPIII definition.

significant for MetS by IDF ($P = 0.04$) and harmonized definition ($P = 0.03$) but not for MetS by NCEP/ATPIII ($P = 0.17$). The association with MetS was somewhat stronger for distal colon cancer (e.g., RR = 2.27; 95% CI: 1.51–3.41 for MetS by NCEP/ATPIII) than for proximal colon cancer (RR = 1.83; 95% C: 1.21–2.75; $P = 0.21$ for

Table 3. Multivariable-adjusted[a] estimated RRs of colon and rectal cancer according to MetS definitions and individual MetS components, follow-up 1992–2003

RR (95% CI)	Colon cancer				Rectal cancer			
	All	Men	Women	P[b]	All	Men	Women	P[b]
Components of MetS								
AO (high WC) by NCEP/ATPIII	1.55 (1.19–2.02)	2.07 (1.36–3.14)	1.32 (0.93–1.87)	0.06	1.34 (0.96–1.87)	1.21 (0.75–1.97)	1.68 (0.97–2.92)	0.67
N, cases/controls	231/175	106/67	125/108		127/105	73/61	54/44	
	438/364	208/165	230/199		239/231	141/131	98/100	
AO (high WC) by IDF	1.68 (1.31–2.15)	1.78 (1.22–2.60)	1.63 (1.15–2.31)	0.53	1.07 (0.79–1.45)	1.16 (0.75–1.80)	1.09 (0.67–1.79)	0.64
N, cases/controls	151/122	81/69	70/53		94/87	72/61	22/26	
Elevated TG	1.36 (0.95–1.68)	1.11 (0.73–1.67)	1.44 (0.95–2.18)	0.53	1.00 (0.70–1.44)	0.98 (0.61–1.59)	1.02 (0.52–1.98)	0.54
N, cases/controls	176/136	72/48	104/88		78/87	43/43	35/44	
Reduced HDL-C	1.36 (1.04–1.77)	1.60 (1.02–2.49)	1.21 (0.86–1.70)	0.37	0.91 (0.63–1.32)	1.21 (0.70–2.12)	0.83 (0.48–1.44)	0.27
N, cases/controls	442/413	218/208	224/205		261/251	152/147	109/104	
Elevated BP	1.26 (0.98–1.61)	1.25 (0.86–1.83)	1.40 (0.98–1.98)	0.92	1.07 (0.77–1.50)	1.02 (0.61–1.70)	1.25 (0.77–2.03)	0.99
N, cases/controls	356/264	178/139	178/125		205/161	116/102	89/59	
AGM	2.14 (1.64–2.77)	1.85 (1.28–2.66)	2.80 (1.86–4.22)	0.16	2.07 (1.45–2.96)	1.66 (1.00–2.73)	3.20 (1.78–5.77)	0.12
Definitions of MetS								
MetS by NCEP/ATPIII	1.91 (1.47–2.42)	1.70 (1.15–2.50)	2.25 (1.55–3.26)	0.49	1.45 (1.02–2.06)	1.35 (0.83–2.21)	2.03 (1.14–3.62)	0.80
N, cases/controls	229/144	108/74	121/70		121/94	75/60	46/34	
	280/188	140/94	140/94		144/124	87/77	57/47	
MetS by IDF	1.91 (1.48–2.46)	1.97 (1.35–2.88)	2.02 (1.41–2.88)	0.84	1.28 (0.93–1.76)	1.16 (0.75–1.78)	1.83 (1.05–3.18)	0.66
N, cases/controls	306/205	150/107	156/98		155/133	97/84	58/49	
MetS by harmonized criteria	2.00 (1.56–2.56)	1.84 (1.28–2.66)	2.33 (1.63–3.33)	0.73	1.31 (0.95–1.79)	1.24 (0.80–1.90)	1.70 (0.98–2.93)	0.82

NOTE: For all RRs, reference category was no presence of the characteristic. The presented RR estimates refer to dichotomized variables. The numbers for the cases and controls refer to the presence of MetS components or definitions.

Abbreviations: AO, abdominal obesity; AGM, abnormal glucose metabolism; WC, waist circumference; TG, tryglicerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; MetS, metabolic syndrome.

[a]Results based on conditional logistic regression (matching factors: age, sex, study center, follow-up time since blood collection, time of the day at blood collection and fasting status; women were further matched by menopausal status and phase of menstrual cycle at blood collection; and postmenopausal women were matched by HRT use) with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish, and shellfish.

[b]P for difference by sex calculated by using interaction terms of MetS definitions and components (categorical), multiplied by the stratum variable in the multivariable-adjusted model.
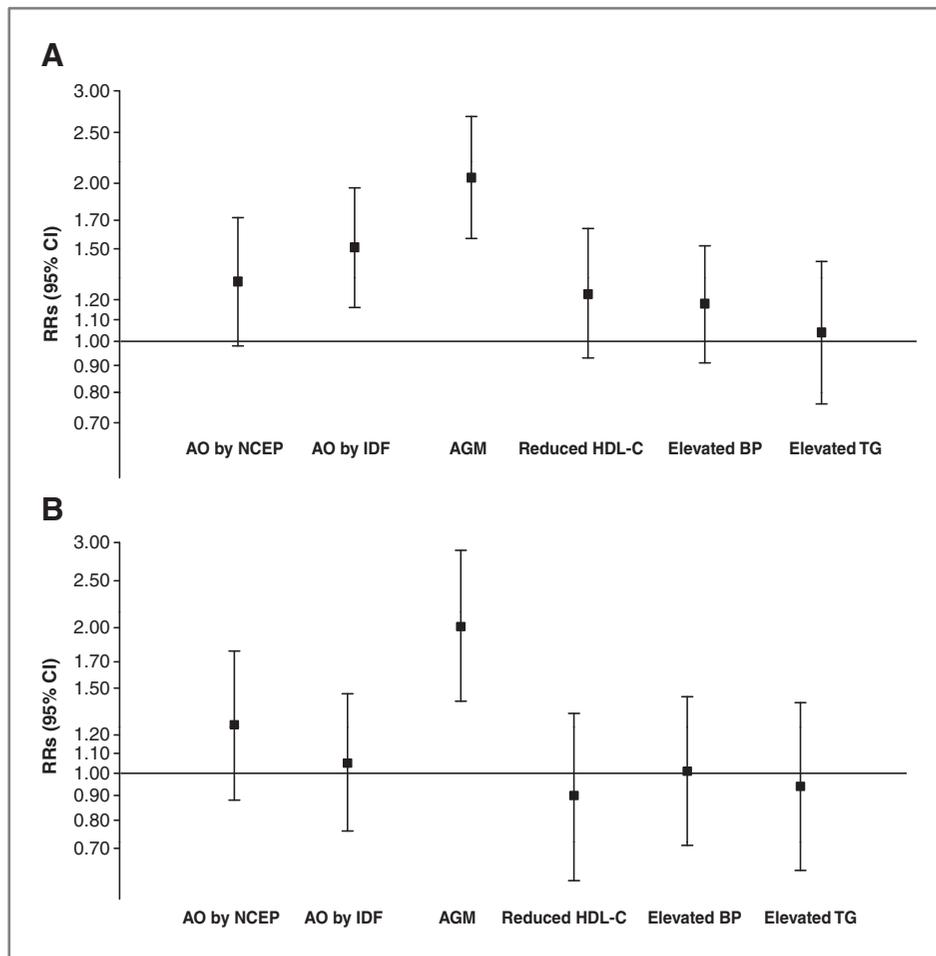
Figure 1. Multivariable-adjusted RRs (95% CI) of colon (A) and rectal (B) cancers for the MetS components mutually adjusted for the other components. AO, abdominal obesity; AGM, abnormal glucose metabolism; TG, tryglicerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure. Results based on conditional logistic regression (matching factors: age, sex, study center, follow-up time since blood collection, time of the day at blood collection and fasting status; women were further matched by menopausal status and phase of menstrual cycle at blood collection; postmenopausal women were matched by HRT use) with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish, and shellfish. Note: AO as defined on the basis of NCEP/ATPIII definition was used in the mutually adjusted models presented in the figure. The RRs (95% CI) when the IDF criteria to define AO was used instead of NCEP/ATPIII criteria were as follows: for colon cancer: AGM 2.05 (1.57–2.68), reduced HDL-C 1.24 (0.93–1.65), elevated BP 1.15 (0.91–1.52), and elevated TG 1.04 (0.76–1.42); for rectal cancer: AGM 2.07 (1.45–2.95), reduced HDL-C 0.91 (0.61–1.35), elevated BP 1.04 (0.73–1.48), and elevated TG 0.97 (0.66–1.44). RRs are plotted on a logarithmic scale.

difference by cancer subsite; Supplementary Table S1, Appendix). However, the interpretation of these findings is hampered by the small number of cases in these analyses (281 proximal colon cases and 314 distal colon cases), which may have lowered the precision of the risk estimates.

To examine to what extent the components may explain the association between MetS and colorectal cancer, we next adjusted the multivariable-adjusted model containing the MetS variable with each of the single components, individually and in combinations. In this analysis, abdominal obesity and abnormal glucose metabolism most strongly attenuated the association toward unity for both colon and rectal cancer. For example, when MetS was defined by the NCEP/ATPIII criteria, the RR was 1.44 (95% CI: 0.94–2.20) for colon cancer and 1.02 (95% CI: 0.65–1.60) for rectal cancer.

Thereafter, we tested whether MetS variable improves colorectal cancer risk assessment beyond abdominal obesity and abnormal glucose metabolism by comparing models containing only abdominal obesity and abnormal glucose metabolism with models also including the MetS variable. In this analysis, addition of the MetS did not statistically significantly improve the multivariable-adjusted model (LRT; colorectal cancer, $P = 0.10$, colon cancer; $P = 0.18$; rectal cancer, $P = 0.22$ for MetS by NCEP/ATPIII).

When the main analyses was repeated using a cutoff point for HbA_{1c} of 6.5% or more and excluding people with reported diabetes, MetS by any of the 3 definitions was similarly associated with colon cancer risk (e.g., RR = 1.69; 95% CI: 1.23–2.31 for MetS by NCEP/ATPIII) but not with risk of rectal cancer (RR = 1.26; 95% CI: 0.85–1.85). In this analysis, none of the components were associated with risk

Table 4. Multivariable-adjusted[a] estimated RRs of colon cancer associated with specific combinations of MetS[b] components, follow-up 1992–2003

Model	MetS components					% of all subjects (% of subjects among those with MetS by IDF)	RR	95% CI
	AGM	Elevated TG	AO by IDF[c]	Elevated BP	Reduced HDL			
1 MetS component								
1.1	X					45.0 (72.4)	2.14	1.64–2.77
1.2		X				19.8 (41.9)	1.36	0.95–1.68
1.3			X			58.2 (100.0)	1.68	1.31–2.15
1.4				X		62.1 (87.6)	1.26	0.98–1.61
1.5					X	22.6 (43.0)	1.36	1.04–1.77
2 MetS components								
2.1	X	X				9.7 (22.7)	1.93	1.30–2.87
2.2	X				X	10.5 (23.5)	2.45	1.66–3.62
2.3	X		X			29.8 (72.4)	2.29	1.72–3.03
2.4	X			X		30.6 (63.0)	1.99	1.51–2.62
2.5		X			X	8.3 (21.6)	1.58	1.05–2.37
2.6		X	X			15.4 (41.9)	1.47	1.06–2.03
2.7		X		X		14.4 (34.0)	1.33	0.97–1.84
2.8			X		X	16.7 (43.0)	1.48	1.10–1.98
2.9				X	X	14.2 (32.7)	1.48	1.07–2.04
2.10			X	X		40.1 (87.6)	1.67	1.31–2.12
3 MetS components								
3.1	X	X	X			7.7 (22.7)	1.92	1.23–2.99
3.2	X		X		X	8.0 (23.5)	2.57	1.64–4.01
3.3	X		X	X		21.4 (63.0)	2.45	1.80–3.35
3.4	X	X			X	4.0 (10.5)	2.46	1.32–4.58
3.5	X	X		X		7.3 (17.7)	2.06	1.31–3.23
3.6	X			X	X	7.3 (21.6)	1.66	1.07–2.57
3.7		X	X	X		11.5 (34.0)	1.69	1.17–2.43
3.8			X	X	X	7.6 (22.2)	1.47	0.96–2.26
3.9		X	X		X	4.9 (14.3)	1.65	0.99–2.76
3.10		X		X	X	0.0 (0.0)	–	–

NOTE: RRs are shown for persons with the MetS combination specified compared with persons without that combination. Consequently, models 1.1–1.5, 2.1–2.10, and 3.10 do not define mutually exclusive groups, and the prevalence of trait combinations do not sum to 100%.

Abbreviations: AO, abdominal obesity; AGM, abnormal glucose metabolism; TG, tryglicerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; MetS, metabolic syndrome.

[a]Results based on conditional logistic regression (matching factors: age, sex, study center, follow-up time since blood collection, time of the day at blood collection, and fasting status; women were further matched by menopausal status and phase of menstrual cycle at blood collection; postmenopausal women were matched by HRT use) with adjustment for smoking status, education, alcohol consumption, physical activity, fiber intake, consumption of fruits and vegetables, red and processed meat, fish, and shellfish.

[b]MetS is defined here according to the criteria of the IDF.

[c]Results are shown for AO by IDF as this is the factor that showed to be independently associated with risk of developing colon cancer in a model mutually adjusted for the other components.

of rectal cancer (data not shown). After excluding non-fasting subjects, the risk estimates did not substantially change (e.g., RR = 2.25; 95% CI: 1.26–4.00 for MetS by NCEP/ATPIII). After exclusion of cases that occurred during the first 2 years of the follow-up, the studied associations remained unaltered (e.g., RR = 1.77; 95% CI: 1.29–2.40 for the association of MetS by NCEP/ATPIII and colon cancer).

Discussion

In this large population-based study, abdominal obesity, reduced HDL-C concentrations, and abnormal glucose metabolism, but not elevated TG concentrations or BP, were each associated with colon cancer risk whereas abnormal glucose metabolism was associated with risks

of developing both colon and rectal cancer. However, abdominal obesity and abnormal glucose metabolism, but not reduced HDL-C concentrations, remained associated with colorectal cancer risk independently from the other components. Furthermore, the association of MetS as defined here and colorectal cancer risk was largely accounted for by abdominal obesity and abnormal glucose metabolism. To our knowledge, this is the first study documenting that MetS did not add information for the assessment of colorectal cancer risk beyond these 2 metabolic abnormalities.

To date, several prospective studies investigated the association of MetS with risk of developing colorectal cancer, predominantly reporting positive associations (7–12). However, the comparison of the results from these prior studies is hampered by the fact that each of them defined MetS according to different criteria and that most studies did not distinguish between colon and rectal cancer (7, 11, 12) or between men and women (8, 11). To address these gaps in the previous research, for defining MetS, we applied 3 different definitions recently proposed by international expert groups and studied the association separately for colon and rectal cancer. MetS, as defined according to the NCEP/ATPIII, IDF, or the harmonized criteria, was similarly associated with colon cancer risk and, when based on the NCEP/ATPIII criteria, was also associated with risk of developing rectal cancer. Overall, the results showing stronger associations of MetS components and definitions for colon than for rectal cancer in our study are consistent with previous studies on other metabolic factors (4, 22), suggesting that colon and rectum may differ in their susceptibility to risks associated with the metabolic abnormalities and justify the need to distinguish between these cancer sites in future epidemiologic research.

Our findings that MetS is somewhat more strongly related to risk of developing colorectal cancer in women than in men are in contradiction to some prior studies (7, 9, 12). However, our data provide much higher number of cases than these studies. Furthermore, previous reports had higher proportion of men than women, which may have led to a higher power to detect associations in men, whereas our study population was equally distributed by sex. Although in our study, the differences by sex were not statistically significant, the question whether men and women may potentially have different susceptibility to metabolic abnormalities in terms of colorectal cancer risk warrant further investigation.

Interestingly, we observed an association for MetS by NCEP/ATPIII definition and rectal cancer risk that was no longer statistically significant when abnormal glucose metabolism was defined using a cutoff point for HbA$_{1c}$ of 6.5% instead of 5.7%. These differences in the associations by using different cutoff point levels may be explained by that applying a lower cutoff point increased the number of exposed individuals and thus also increased the power to detect statistically significant associations. Nevertheless, previous evidence suggests hyperglycemia to be associated with colorectal cancer incidence and mortality (5, 12) and plausible biological mechanisms to explain its role in colorectal

cancer risk include direct involvement of insulin resistance, as well as acting as an energy depot for cancer cell growth (12).

We studied the association between abdominal obesity and colorectal cancer according to cutoff points defined specifically for European populations (IDF definition) and were able to judge upon its relative performance compared with the cutoff points suggested for the American populations (NCEP/ATPIII definition). The prevalence of abdominal obesity when defined according to the IDF criteria was approximately 2 times higher than that by the NCEP/ATPIII criteria. In parallel, abdominal obesity by IDF, but not abdominal obesity by NCEP/ATP III, was independently associated with colon cancer, suggesting that the lower cutoff point of the IDF definition might be more appropriate to assess the risk in European population than the cutoff point of the NCEP/ATPIII definition. These results, however, should be confirmed by other studies and additional reclassification analyses are needed to draw meaningful recommendations.

It should be noted that the detection of an association with risk of developing colorectal cancer in our study might depend on the categorization of the metabolic markers according to the different set of cutoff points. Thus, any insignificant associations may not necessarily imply the absence of a true biological relationship. For example, in our analysis, reduced HDL-C level as defined according to the MetS criteria was not associated with colon cancer independently from the other components. However, a previous report on same data showed that high concentrations of serum HDL-C (continuously) were associated with a decreased risk of developing colon cancer independently from markers of systemic inflammation, insulin resistance, and oxidative stress, as well as from the other MetS components (6). To overcome the limitations of using arbitrary cutoff points, other analytic approaches might be further explored such as development of risk scores composed by metabolic markers.

Over the recent years, there has been controversy surrounding the concept of MetS and its clinical usefulness for assessing the risk of developing cardiovascular diseases and diabetes mellitus has been questioned. Thus, it was discussed that the "cardiovascular risk associated with the syndrome may be no greater than the sum of its parts" (23) and that "a simple fasting plasma glucose measurement may serve as a much better predictor of future diabetes than the expense and inconvenience necessary to diagnose the syndrome" (24). Recently, the World Health Organization expert consultation concluded that the MetS has little utility as a diagnostic or management tool (25). Our results suggest that abdominal obesity and abnormal glucose metabolism may have an independent effect on colorectal cancer risk. Furthermore, these 2 factors statistically explained to the highest extent the observed association between MetS definitions and colon cancer. In fact, MetS did not did not provide risk information beyond its individual components. Thus, our data highlight the role of abdominal fatness and the subsequent hyperinsulinemia among the rest of the metabolic consequences of the insulin

resistance state in the etiology of colorectal cancer. Hyper-insulinemia is suggested to stimulate proliferation and promote metastasis of malignant colonic epithelial cells by elevating the bioactivity of insulin-like growth factor (IGF) I and reducing IGF-binding protein-3 (26). Although future research to shed light on the underlying pathophysiology that links metabolic factors with colorectal cancer risk is still warranted, the clinical and cancer-preventive implications of assessing abnormal glucose metabolism and abdominal obesity might be timely considered.

Among the main strengths of our study are the prospective design and the largest number of cases to date, which allowed analysis by cancer subsite and sex. Availability of detailed information about dietary and lifestyle factors allowed sufficient control for potential residual confounding. To be more objective and complete, we defined MetS according to 3 different international criteria, including the most recent definitions, which were not studied before in the same context. Finally, we addressed a question that has not been answered so far, but being of both clinical and public health importance, namely, whether MetS improves colorectal cancer risk assessment beyond its components.

Some limitations need to be taken into account when interpreting the results. More than 70% of the study participants provided nonfasting blood samples, which may have affected the TG levels; however, we accounted for fasting status and found essentially the same results after excluding nonfasting participants. A single assessment of metabolic indicators may be susceptible to short-term variation, which would bias the results toward the null; however, the parameters assessed in our study were shown to be relatively stable over time (27). Use of nonsteroidal anti-inflammatory drugs (NSAID) may be inversely related to MetS components and may reduce colorectal cancer risk; however, information about NSAID use is not available in EPIC. Similarly, information about family history of colorectal cancer is not recorded in EPIC. However prior studies do not suggest that NSAID use and family history are strong confounders of the association of metabolic markers with colorectal cancer risk (7).

Despite excluding participants with cancer at baseline, we cannot exclude the possibility that some individuals had, yet, undiagnosed cancer, although results were similar when cancer cases diagnosed during the first 2 years of follow-up were excluded from our analysis.

In conclusion, our findings illustrate the heterogeneity of MetS, reflecting various combinations of metabolic abnormalities, and expand the previous literature showing that the association of MetS and colorectal cancer is largely accounted for by abdominal obesity and abnormal glucose metabolism but not by the rest of the MetS components. In terms of primary prevention, these results suggest that

simple assessment of these factors to identify individuals at risk of developing colorectal cancer may have higher clinical utility than the complex assessment of MetS. From a public health perspective, prevention strategies through nutritional and lifestyle modifications aiming to alleviate the metabolic abnormalities may have profound cancer-protective effects and should be further prioritized.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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