available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Metabolic syndrome is associated with colorectal cancer in men

Claudio Pelucchi [a,*], *Eva Negri* [a], *Renato Talamini* [b], *Fabio Levi* [c], *Attilio Giacosa* [d], *Anna Crispo* [e], *Ettore Bidoli* [b], *Maurizio Montella* [e], *Silvia Franceschi* [f], *Carlo La Vecchia* [a,g]

[a] *Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy*
[b] *S.O.C. di Epidemiologia e Biostatistica, Centro di Riferimento Oncologico, Aviano (PN), Italy*
[c] *Unité d'épidémiologie du cancer et Registre vaudois des tumeurs, Institut de medicine sociale et preventive (IUMSP), Centre Hospitalier Universitaire Vaudois et Université de Lausanne, Lausanne, Switzerland*
[d] *Dipartimento di Gastroenterologia e Nutrizione Clinica, Policlinico di Monza, Monza, Italy*
[e] *Dipartimento di Epidemiologia, 'Fondazione G. Pascale', Istituto Nazionale Tumori, Naples, Italy*
[f] *International Agency for Research on Cancer, Lyon Cedex, France*
[g] *Istituto di Statistica Medica e Biometria "G.A. Maccacaro", Università degli Studi di Milano, Milan, Italy*

ARTICLE INFO

Article history:
Received 29 December 2009
Received in revised form 10 March 2010
Accepted 15 March 2010
Available online 13 April 2010

Keywords:
Case–control studies
Colorectal neoplasms
Diabetes
Epidemiology
Metabolic syndrome X
Risk factors

ABSTRACT

Aim of the study: We assessed the relation between metabolic syndrome (MetS) and its components and colorectal cancer.

Methods: We analysed data from a multicentre case–control study conducted in Italy and Switzerland, including 1378 cases of colon cancer, 878 cases of rectal cancer and 4661 controls. All cases were incident and histologically confirmed. Controls were subjects admitted to the same hospitals as cases with acute non-malignant conditions. MetS was defined according to the International Diabetes Federation criteria. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated by multiple logistic regression models, including terms for major identified confounding factors for colorectal cancer.

Results: With reference to each component of the MetS, the ORs of colorectal cancer in men were 1.27 (95% CI, 0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). Colorectal cancer risk was increased in men (OR = 1.86; 95% CI, 1.21–2.86), but not in women (OR = 1.13; 95% CI, 0.66–1.93), with MetS. The ORs were 2.09 (95% CI, 1.38–3.18) in men and 1.15 (95% CI, 0.68–1.94) in women with $\geqslant$3 components of the MetS, as compared to no component. Results were similar for colon and rectal cancers.

Conclusion: This study supports a direct association between MetS and both colon and rectal cancers in men, but not in women.

* *Corresponding author:* Address: Istituto di Ricerche Farmacologiche "Mario Negri", Via Giuseppe La Masa 19, 20156 Milan, Italy. Tel.: +39 02 39014 577; fax: +39 02 33200231.
E-mail address: claudio.pelucchi@marionegri.it (C. Pelucchi).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.03.010

1. Introduction

The metabolic syndrome (MetS) is characterised by a clustering of components associated with cardiovascular diseases (i.e. hyperglycaemia, obesity, hypertension and dyslipidaemia). Several definitions of the MetS have been proposed during the last decade,[1–3] and experts of major organisations have recently agreed a joint scientific statement trying to unify its diagnostic criteria.[4]

Besides cardiovascular conditions, the MetS has more recently been associated to the risk of various cancers, including those of the colon and rectum, in a number of epidemiological studies.[5–14] The MetS might increase colorectal cancer risk through various biological mechanisms, particularly those related to insulin resistance.[15] However, not all findings supported a relation between MetS and colorectal cancer,[11,12] and the results between studies were often inconsistent when the associations were examined by site (i.e. colon or rectum) and sex.

With reference to the components of the MetS, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report concluded that there is convincing evidence that greater body fat causes colorectal cancer.[16] Further, increasing evidence shows that abdominal fat, and particularly visceral adiposity, is associated with increased risk of colorectal adenoma and cancer, independently of overall body mass index (BMI).[16,17] Several epidemiological studies conducted in different populations indicated diabetes as a risk factor for colorectal cancer.[18–21] On the other hand, most findings suggest that the association between hypertension and dyslipidaemia and colorectal cancer risk is – if any – modest.[9,12]

To provide further information on the relation between MetS and its components and colorectal cancer, we analysed data from a case–control study conducted in Italy and Switzerland.

2. Patients and methods

Data were derived from a multicentre case–control study of colorectal cancer conducted in six Italian areas (the provinces of Pordenone and Gorizia in the north-east; the urban areas of Milan and Genoa and the province of Forlì in the North; Latina in the centre; and the urban area of Naples in the South) and in Canton Vaud, Switzerland, between 1992 and 2001. The general design of the investigation has already been described.[22,23] The study included 1378 cases of colon cancer (International Classification of Diseases, ICD-9, 153.0–153.9), 1209 from Italy and 169 from Switzerland, 780 men and 598 women, aged 31–79 years (median age, 61 years); 878 cases of rectal cancer (ICD-9, 154.0–154.1), 723 from Italy and 155 from Switzerland, 530 men and 348 women, aged 31–75 years (median age, 61 years); and 4661 controls, 4055 from Italy and 606 from Switzerland, 2364 men and 2297 women, aged 31–79 years (median age, 57 years). Subjects aged $\leqslant$30 and $\geqslant$80 years were excluded. All cancer cases were incident and histologically confirmed.

Controls were patients admitted to the same network of hospitals of cases for acute, non-neoplastic conditions unrelated to digestive tract diseases (23% had traumatic conditions, mostly fractures and sprains; 26% non-traumatic orthopaedic disorders; 25% acute surgical conditions and 26% miscellaneous other illnesses such as eye, ear and skin diseases). The proportion of refusals was <5% for both cases and controls in all Italian centres and about 15% in Switzerland. The design was the same for the Italian and Swiss studies.

Centrally trained interviewers used a structured questionnaire to collect data during the hospital stay on socio-demographic characteristics, smoking, alcohol drinking, dietary habits, physical activity, family history of cancer, self-reported height and weight at various ages, and personal history of selected medical conditions. BMI was computed according to Quetelet's index (weight/height^2, kg/m^2). Since in this study the most consistent association between measures of body size and colorectal cancer was that with BMI at age 30,[23] the presence of central obesity was defined as a BMI value $\geqslant$25 kg/m^2 at age 30. Information on medical conditions, including history of clinical obesity, history of drug-treated hypertension, history of clinical diagnosis of hypercholesterolaemia and type-2 diabetes, was self-reported and included age at diagnosis.

The indicator of MetS was defined according to the International Diabetes Federation (IDF) criteria,[2] adapted to our data, as the simultaneous presence of central obesity plus at least two other components of the following: history of a clinical diagnosis of hypercholesterolaemia (as a proxy of raised triglycerides and reduced HDL–cholesterol levels), history of drug-treated hypertension and diabetes. We also considered various components of the MetS separately. When the information on BMI at age 30 was missing (i.e. 107 cases [4.7%] and 139 controls [3.0%]), the subjects were excluded from the analyses on MetS.

2.1. Statistical analysis

Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were derived from unconditional multiple logistic regression models, including terms for age, study centre, sex (when appropriate), education (<7, 7 to <12 and $\geqslant$12 years), tobacco smoking (never, ex, current smokers of <15, 15 to <25 and $\geqslant$25 cigarettes per day), alcohol drinking (never, ex, current drinkers of <1, $\geqslant$1 to <3 and $\geqslant$3 glasses per day), occupational physical activity at age 30–39 (low, intermediate and high) and non-alcohol energy intake (in continuous).

3. Results

Table 1 gives the distribution of cases and controls by age, study centre, education and occupational physical activity, separately for men and women. In men only, cases had more frequently than controls a high level of education and a low level of occupational physical activity.

Table 2 shows the distribution of colon and rectal cancer cases and controls according to the components of the MetS, separately by gender, and the corresponding ORs and 95% CIs. For colorectal cancer, the ORs in men were 1.27 (95% CI,

Table 1 – Distribution of colorectal cancer cases and controls[a] by age and selected characteristics, separately for men and women. Italy and Switzerland, 1992–2001.

	Men		Women	
	Cases (%)	Controls (%)	Cases (%)	Controls (%)
Age (years)				
<40	32 (2.4)	130 (5.5)	33 (3.5)	154 (6.7)
40–49	107 (8.2)	370 (15.6)	108 (11.4)	461 (20.1)
50–59	330 (25.2)	720 (30.5)	247 (26.1)	699 (30.4)
60–69	600 (45.8)	836 (35.4)	357 (37.7)	712 (31.0)
⩾70	241 (18.4)	308 (13.0)	201 (21.2)	271 (11.8)
Study centre				
Pordenone/Gorizia	351 (26.8)	765 (32.4)	260 (27.5)	571 (24.9)
Milan	269 (20.5)	306 (12.9)	214 (22.6)	751 (32.7)
Genoa	141 (10.8)	295 (12.5)	82 (8.7)	199 (8.7)
Forlì	58 (4.4)	119 (5.0)	36 (3.8)	127 (5.5)
Naples	113 (8.6)	164 (6.9)	76 (8.0)	194 (8.4)
Rome/Latina	186 (14.2)	385 (16.3)	146 (15.4)	179 (7.8)
Canton Vaud	192 (14.7)	330 (14.0)	132 (13.9)	276 (12.0)
Education (years)				
<7	549 (41.9)	1065 (45.0)	512 (54.1)	1248 (54.3)
7–11	383 (29.2)	739 (31.3)	257 (27.2)	663 (28.9)
⩾12	378 (28.8)	560 (23.7)	177 (18.7)	386 (16.8)
Occupational physical activity				
Low	518 (39.6)	757 (32.0)	331 (35.0)	786 (34.3)
Medium	335 (25.6)	645 (27.3)	464 (49.1)	1143 (49.8)
High	456 (34.8)	961 (40.7)	150 (15.9)	365 (15.9)

[a] The sum of subjects might not add up to the total because of a few missing values.

0.95–1.69) for diabetes, 1.24 (95% CI, 1.03–1.48) for hypertension, 1.14 (95% CI, 0.93–1.40) for hypercholesterolaemia and 1.26 (95% CI, 1.08–1.48) for overweight at age 30. The corresponding ORs in women were 1.20 (95% CI, 0.82–1.75), 0.87 (95% CI, 0.71–1.06), 0.83 (95% CI, 0.66–1.03) and 1.06 (95% CI, 0.86–1.30). The association with diabetes was somewhat stronger for rectal (OR = 1.48, 95% CI, 1.02–2.15, in men and 1.40, 95% CI, 0.82–2.37, in women) than for colon cancer (OR = 1.15, 95% CI, 0.82–1.64, in men and 1.13, 95% CI, 0.72–1.77, in women), whereas hypertension and hypercholesterolaemia were associated with male colon cancer (OR = 1.36, 95% CI, 1.10–1.68, and 1.27, 95% CI, 1.00–1.61, respectively) but not with male rectal cancer (OR = 1.08, 95% CI, 0.84–1.40, and 0.97, 95% CI, 0.72–1.31, respectively).

Table 3 gives the distribution of colorectal cancer cases and controls according to an indicator of MetS and number of its components, separately by gender and overall, and the corresponding ORs and 95% CIs. The risk of colorectal cancer was increased in men (OR = 1.86, 95% CI, 1.21–2.86), but not in women (OR = 1.13, 95% CI, 0.66–1.93), with MetS (p-value for heterogeneity, 0.22). In men, the ORs of colorectal cancer were 1.04 (95% CI, 0.88–1.22) for subjects with 1 component of the MetS, 1.44 (95% CI, 1.16–1.80) for those with 2 components and 2.09 (95% CI, 1.38–3.18) for those with 3 or more components (p-value for trend <0.001). The corresponding ORs were 0.84 (95% CI, 0.70–1.02), 0.82 (95% CI, 0.62–1.09) and 1.15 (95% CI, 0.68–1.94) in women (p-value for heterogeneity, 0.02), and 0.95 (95% CI, 0.84–1.06), 1.15 (95% CI, 0.98–1.37) and 1.69 (95% CI, 1.23–2.33) in all subjects. Results were similar when colon and rectal cancers were considered separately. In men, the ORs of colon and rectal cancers for the indicator of MetS were 1.88 (95% CI, 1.13–3.13) and 1.96 (95% CI, 1.13–3.40), respectively. Men with 3 as compared to no components of the MetS had ORs of 2.15 (95% CI, 1.31–3.53) for colon and 2.19 (95% CI, 1.29–3.73) for rectal cancer, while women had ORs of 1.17 (95% CI, 0.64–2.14) and 1.14 (95% CI, 0.53–2.46), respectively.

4. Discussion

The MetS, and particularly its underlying component hyperinsulinaemia, might influence colorectal cancer risk through several plausible biological mechanisms. By suppression of hepatic secretion of insulin-like growth factors (IGF)-binding protein-1, insulin enhances the levels of bioavailable IGF-1.[24] IGF-1 stimulates cell proliferation and differentiation, inhibits apoptosis[25] and increases production of vascular endothelial growth factors, important in tumour angiogenesis. Further, insulin stimulated cell growth in a human colon cancer cell line in a dose-dependent manner.[26]

The association between obesity and both colon and rectal cancers varies according to gender. A meta-analysis of prospective studies[27] found that the risk of colon and rectal cancers is higher in men (relative risk, RR = 1.30 for colon, RR = 1.12 for rectal cancer, for a 5-unit increase in BMI) than in women (RRs = 1.12 and 1.03, respectively). Our results are consistent with those findings. Since central obesity has a key role in the MetS and is more common in men than in women – the IDF included central obesity as essential in its definition of the MetS[2] – this component might explain the

Table 2 – Distribution of colorectal cancer cases and controls, with odds ratios (ORs) and corresponding 95% confidence intervals (CIs), according to selected components of the metabolic syndrome, separately for men and women. Italy and Switzerland, 1992–2001.

	Men			Women		
	Cases (%)	Controls (%)	OR[a] (95% CI)	Cases (%)	Controls (%)	OR[a] (95% CI)
Colorectal cancer						
Diabetes						
No	1212 (92.5)	2241 (94.8)	1[b]	893 (94.4)	2210 (96.2)	1[b]
Yes	98 (7.5)	123 (5.2)	1.27 (0.95–1.69)	53 (5.6)	87 (3.8)	1.20 (0.82–1.75)
Hypertension						
No	1011 (77.2)	1975 (83.5)	1[b]	743 (78.5)	1833 (79.8)	1[b]
Yes	299 (22.8)	389 (16.5)	1.24 (1.03–1.48)	203 (21.5)	464 (20.2)	0.87 (0.71–1.06)
Hypercholesterolaemia						
No	1122 (85.6)	2070 (87.6)	1[b]	800 (84.6)	1948 (84.8)	1[b]
Yes	188 (14.4)	294 (12.4)	1.14 (0.93–1.40)	146 (15.4)	349 (15.2)	0.83 (0.66–1.03)
Overweight at age 30[c,d]						
No	864 (68.6)	1644 (71.3)	1[b]	705 (79.2)	1786 (80.5)	1[b]
Yes	395 (31.4)	660 (28.6)	1.26 (1.08–1.48)	185 (20.8)	432 (19.5)	1.06 (0.86–1.30)
Colon cancer						
Diabetes						
No	727 (93.2)	2241 (94.8)	1[b]	566 (94.6)	2210 (96.2)	1[n]
Yes	53 (6.8)	123 (5.2)	1.15 (0.82–1.64)	32 (5.4)	87 (3.8)	1.13 (0.72–1.77)
Hypertension						
No	588 (75.4)	1975 (83.5)	1[b]	465 (77.8)	1833 (79.8)	1[b]
Yes	192 (24.6)	389 (16.5)	1.36 (1.10–1.68)	133 (22.2)	464 (20.2)	0.92 (0.73–1.16)
Hypercholesterolaemia						
No	658 (84.4)	2070 (87.6)	1[b]	498 (83.3)	1948 (84.8)	1[b]
Yes	122 (15.6)	294 (12.4)	1.27 (1.00–1.61)	100 (16.7)	349 (15.2)	0.91 (0.70–1.18)
Overweight at age 30[c,d]						
No	512 (68.2)	1644 (71.3)	1[b]	454 (80.1)	1786 (80.5)	1[b]
Yes	239 (31.8)	660 (28.6)	1.29 (1.07–1.56)	113 (19.9)	432 (19.5)	1.02 (0.79–1.30)
Rectal cancer						
Diabetes						
No	485 (91.5)	2241 (94.8)	1[b]	327 (94.0)	2210 (96.2)	1[b]
Yes	45 (8.5)	123 (5.2)	1.48 (1.02–2.15)	21 (6.0)	87 (3.8)	1.40 (0.82–2.37)
Hypertension						
No	423 (79.8)	1975 (83.5)	1[b]	278 (79.9)	1833 (79.8)	1[b]
Yes	107 (20.2)	389 (16.5)	1.08 (0.84–1.40)	70 (20.1)	464 (20.2)	0.80 (0.59–1.07)
Hypercholesterolaemia						
No	464 (87.5)	2070 (87.6)	1[b]	302 (86.8)	1948 (84.8)	1[b]
Yes	66 (12.5)	294 (12.4)	0.97 (0.72–1.31)	46 (13.2)	349 (15.2)	0.69 (0.49–0.98)
Overweight at age 30[c,d]						
No	352 (69.3)	1644 (71.3)	1[b]	251 (77.7)	1786 (80.5)	1[b]
Yes	156 (30.7)	660 (28.6)	1.26 (1.01–1.58)	72 (22.3)	432 (19.5)	1.12 (0.83–1.52)

[a] ORs adjusted for age, study centre, education, smoking habit, alcohol drinking, occupational physical activity and non-alcohol energy intake.
[b] Reference category.
[c] Body mass index $\geqslant 25\ kg/m^2$ at age 30.
[d] The sum of subjects does not add up to the total because of 246 missing values.

different findings for MetS according to gender. Among other possible mechanisms related to obesity that might explain the different results in men and women are a role of total IGF-1, i.e. a major determinant of free IGF-1 levels, as men have higher circulating concentration levels than women,[28] and of adiponectin, a hormone secreted by the adipose tissue, whose serum levels are inversely related to both BMI and colorectal cancer risk[29] and that is present at higher concentrations in women than in men.[30]

Our findings on MetS are in broad agreement with those of other studies. An US prospective study,[10] based on 14,109 subjects, found a direct association with colorectal cancer in men (RR = 1.78) but not in women (RR = 1.16). Similarly, the Aerobics Centre Longitudinal Study,[8] based on 33,230 men,

Table 3 – Distribution of colorectal cancer cases and controls,[a] with odds ratios (ORs) and corresponding 95% confidence intervals (CIs), according to the indicator of metabolic syndrome (MetS) and the number of its components. Italy and Switzerland, 1992–2001.

	Men			Women			All subjects
	Cases (%)	Controls (%)	OR[c] (95% CI)	Cases (%)	Controls (%)	OR[c] (95% CI)	OR[c] (95% CI)
Colorectal cancer							
Number of components of the MetS							
None	595 (47.3)	1208 (52.4)	1[d]	498 (56.0)	1253 (56.5)	1[d]	1[d]
1	418 (33.2)	803 (34.8)	1.04 (0.88–1.22)	269 (30.2)	692 (31.2)	0.84 (0.70–1.02)	0.95 (0.84–1.06)
2	193 (15.3)	243 (10.5)	1.44 (1.16–1.80)	96 (10.8)	231 (10.4)	0.82 (0.62–1.09)	1.15 (0.98–1.37)
⩾3	53 (4.2)	50 (2.2)	2.09 (1.38–3.18)	27 (3.0)	42 (1.9)	1.15 (0.68–1.94)	1.69 (1.23–2.33)
p for trend			16.2 ($p < 0.001$)			1.5 ($p = 0.22$)	5.8 ($p = 0.02$)
Indicator of MetS[b]							
No	1212 (96.3)	2257 (98.0)	1[d]	866 (97.3)	2177 (98.2)	1[d]	1[d]
Yes	47 (3.7)	47 (2.0)	1.86 (1.21–2.86)	24 (2.7)	41 (1.8)	1.13 (0.66–1.93)	1.58 (1.14–2.19)
Colon cancer							
Number of components of the MetS							
None	344 (45.8)	1208 (52.4)	1[d]	312 (55.0)	1253 (56.5)	1[d]	1[d]
1	246 (32.8)	803 (34.8)	1.04 (0.86–1.26)	175 (30.9)	692 (31.2)	0.87 (0.70–1.08)	0.96 (0.83–1.10)
2	132 (17.6)	243 (10.5)	1.69 (1.31–2.18)	62 (10.9)	231 (10.4)	0.87 (0.63–1.20)	1.31 (1.08–1.59)
⩾3	29 (3.9)	50 (2.2)	2.15 (1.31–3.53)	18 (3.2)	42 (1.9)	1.17 (0.64–2.14)	1.71 (1.17–2.50)
p for trend			18.3 ($p < 0.001$)			0.5 ($p = 0.48$)	8.7 ($p = 0.003$)
Indicator of MetS[b]							
No	725 (96.5)	2257 (98.0)	1[d]	552 (97.4)	2177 (98.2)	1[d]	1[d]
Yes	26 (3.5)	47 (2.0)	1.88 (1.13–3.13)	15 (2.6)	41 (1.8)	1.06 (0.56–1.99)	1.52 (1.03–2.25)
Rectal cancer							
Number of components of the MetS							
None	251 (49.4)	1208 (52.4)	1[d]	186 (57.6)	1253 (56.5)	1[d]	1[d]
1	172 (33.9)	803 (34.8)	1.06 (0.85–1.33)	94 (29.1)	692 (31.2)	0.80 (0.60–1.05)	0.94 (0.79–1.11)
2	61 (12.0)	243 (10.5)	1.14 (0.82–1.57)	34 (10.5)	231 (10.4)	0.75 (0.49–1.14)	0.97 (0.75–1.24)
⩾3	24 (4.7)	50 (2.2)	2.19 (1.29–3.73)	9 (2.8)	42 (1.9)	1.14 (0.53–2.46)	1.82 (1.19–2.79)
p for trend			4.6 ($p = 0.03$)			1.6 ($p = 0.20$)	0.9 ($p = 0.34$)
Indicator of MetS[d]							
No	487 (95.9)	2257 (98.0)	1[d]	314 (97.2)	2177 (98.2)	1[d]	1[d]
Yes	21 (4.1)	47 (2.0)	1.96 (1.13–3.40)	9 (2.8)	41 (1.8)	1.30 (0.61–2.78)	1.79 (1.16–2.77)

[a] Two hundred and forty-six subjects were excluded because of missing values in one of the components of the MetS.
[b] Derived from the definition given by the International Diabetes Federation,[2] adapted to our data.
[c] ORs adjusted for age, sex (when appropriate), study centre, education, smoking habit, alcohol drinking, occupational physical activity and non-alcohol energy intake.
[d] Reference category.

reported a 71% increased mortality from colorectal cancer in subjects with MetS, as defined by the Adult Treatment Panel (ATP) III.[1] In the Northern Sweden Health and Disease Cohort study,[7] including 306 cases of colorectal cancer, a case–control approach was used to analyse the issue, and the OR was 2.57 for combined presence of obesity, hypertension and hyperglycaemia as compared to the absence of any component. Other studies on MetS and colorectal cancer have however reported contrasting results, with elevated risks among women but not among men.[6,9] In an Italian study using data from archives of pharmaceutical prescriptions and from the local Cancer Registry,[6] increased incidence of colorectal cancer (RR = 1.32) was found in women, while no association emerged in men (RR = 0.91). Another recent investigation on metachronous colorectal neoplasia, considering a subset of 2392 subjects from the Wheat Bran Fibre and Ursodeoxycholic Acid trials,[9] reported ORs of 1.37 in women and 0.99 in men with MetS, defined according to the ATP III. Therefore, the issue of possible risk variation according to gender is still open to discussion.

Our information on MetS is based on a questionnaire collecting details on history of selected diseases (i.e. age at first diagnosis of treated hypertension, hypercholesterolaemia, diabetes) rather than from direct measurements of blood pressure, triglycerides, HDL–cholesterol and fasting plasma glucose. Thus, the prevalence of MetS in our data is likely to be underestimated. This was confirmed when comparison was made to another Italian study that however used a different criterion (ATP III)[1] to define the MetS.[31] Cases may be more sensitised to report history of disease more frequently than controls. However, the hospital-based design should represent an optimal framework for investigating medical histories, since cases and controls are interviewed under similar conditions and are therefore equally sensitised towards

recalling past diseases,[32] and medical history in our studies has proven satisfactorily reproducible.[33]

Colorectal cancer causes weight loss and is therefore likely to interfere with various body measures,[23] including waist circumference. Thus, we used BMI at age 30 as an indicator for central obesity. Though subjects might have experienced important changes in BMI during their life, overweight in youth was equally or even more important than recent overweight to address the association with colorectal cancer, notably in this and other case–control and cohort analyses.[23,34,35]

These limitations suggest caution in the interpretation of the results. Among the strengths of this study, were its large database, the high proportion of respondents, and the availability of a large questionnaire that allowed to adjust in the regression models for several covariates, including energy intake and physical inactivity, i.e. possible underlying factors in the development of MetS.[5]

In conclusion, this study supports a direct association between MetS and both colon and rectal cancers in men, but not in women. The risk increased with the number of components of the MetS, up to a more than doubled risk for men with three or more components. The most important components to explain the association were hypertension and overweight, though none of the factors increased the risk by more than 30% when considered individually. This weighs in favour of a combined role of factors involved in the MetS in the aetiology of male colorectal cancer.

Financial support

This work was conducted with the contribution of the Italian Association for Cancer Research and the Italian League against Cancer.

Conflict of interest statement

None declared.

Acknowledgement

The authors thank Mrs. I. Garimoldi for editorial assistance.

REFERENCES

1. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–97.
2. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. *Lancet* 2005;**366**:1059–62.
3. World Health Organization (WHO). *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation*. Geneva: WHO; 1999.
4. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: 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. *Circulation* 2009;**120**:1640–5.
5. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr* 2007;**86**:s836–42.
6. Russo A, Autelitano M, Bisanti L. Metabolic syndrome and cancer risk. *Eur J Cancer* 2008;**44**:293–7.
7. Stocks T, Lukanova A, Johansson M, et al. Components of the metabolic syndrome and colorectal cancer risk; a prospective study. *Int J Obes (Lond)* 2008;**32**:304–14.
8. Jaggers JR, Sui X, Hooker SP, et al. Metabolic syndrome and risk of cancer mortality in men. *Eur J Cancer* 2009;**45**:1831–8.
9. Ashbeck EL, Jacobs ET, Martinez ME, et al. Components of metabolic syndrome and metachronous colorectal neoplasia. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:1134–43.
10. Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. *Cancer* 2006;**107**:28–36.
11. Inoue M, Noda M, Kurahashi N, et al. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. *Eur J Cancer Prev* 2009;**18**:240–7.
12. Sturmer T, Buring JE, Lee IM, Gaziano JM, Glynn RJ. Metabolic abnormalities and risk for colorectal cancer in the physicians' health study. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:2391–7.
13. Colangelo LA, Gapstur SM, Gann PH, Dyer AR, Liu K. Colorectal cancer mortality and factors related to the insulin resistance syndrome. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:385–91.
14. Ma J, Giovannucci E, Pollak M, et al. A prospective study of plasma C-peptide and colorectal cancer risk in men. *J Natl Cancer Inst* 2004;**96**:546–53.
15. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev* 1994;**3**:687–95.
16. World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR). Cancers. Colon and rectum. In: *Food, nutrition, physical activity and the prevention of cancer: a global perspective*. World Cancer Research Fund International; 2007. p. 280–8.
17. Yamaji T, Iwasaki M, Sasazuki S, et al. Visceral fat volume and the prevalence of colorectal adenoma. *Am J Epidemiol* 2009;**170**:1502–11.
18. La Vecchia C, D'Avanzo B, Negri E, Franceschi S. History of selected diseases and the risk of colorectal cancer. *Eur J Cancer* 1991;**27**:582–6.
19. La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 1997;**6**:1007–10.
20. Vinikoor LC, Long MD, Keku TO, et al. The association between diabetes, insulin use, and colorectal cancer among Whites and African Americans. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:1239–42.
21. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005;**97**:1679–87.
22. Levi F, Pasche C, La Vecchia C, Lucchini F, Franceschi S. Food groups and colorectal cancer risk. *Br J Cancer* 1999;**79**:1283–7.
23. Russo A, Franceschi S, La Vecchia C, et al. Body size and colorectal-cancer risk. *Int J Cancer* 1998;**78**:161–5.
24. Macaulay VM. Insulin-like growth factors and cancer. *Br J Cancer* 1992;**65**:311–20.
25. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc Nutr Soc* 2001;**60**:91–106.

26. Bjork J, Nilsson J, Hultcrantz R, Johansson C. Growth-regulatory effects of sensory neuropeptides, epidermal growth factor, insulin, and somatostatin on the non-transformed intestinal epithelial cell line IEC-6 and the colon cancer cell line HT 29. *Scand J Gastroenterol* 1993;**28**:879–84.
27. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr* 2007;**86**:556–65.
28. Juul A, Bang P, Hertel NT, et al. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab* 1994;**78**:744–52.
29. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. *J Natl Cancer Inst* 2005;**97**:1688–94.
30. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;**371**:569–78.
31. Miccoli R, Bianchi C, Odoguardi L, et al. Prevalence of the metabolic syndrome among Italian adults according to ATP III definition. *Nutr Metab Cardiovasc Dis* 2005;**15**:250–4.
32. Breslow NE, Day NE. *Statistical methods in cancer research. The analysis of case–control studies*, vol. 1. Geneva: IARC Science Publication 32; 1980.
33. Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. *J Clin Epidemiol* 2001;**54**:902–6.
34. Le Marchand L, Wilkens LR, Mi MP. Obesity in youth and middle age and risk of colorectal cancer in men. *Cancer Causes Control* 1992;**3**:349–54.
35. Engeland A, Tretli S, Austad G, Bjorge T. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. *Cancer Causes Control* 2005;**16**:987–96.