RESEARCH COMMUNICATION

The Metabolic Syndrome is Associated with Increased Risk of Colorectal Adenoma Development: The Self-Defense Forces Health Study

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Abstract

The metabolic syndrome, a cluster of metabolic abnormalities linked to insulin resistance, has attracted much interest as a risk factor for cardiovascular disease and type 2 diabetes. Hyperinsulinemia is also a postulated biological risk factor for colorectal carcinogenesis. We therefore here examined the relation between the metabolic syndrome and colorectal adenoma development. The study subjects were 756 cases of colorectal adenoma and 1751 controls with no polyps who underwent total colonoscopy during the period January 1995 to March 2002 at two Self Defense Forces (SDF) hospitals in Japan. The metabolic syndrome was defined with reference to abdominal obesity in combination with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg); and raised fasting glucose (≥110 mg/dL). Abdominal obesity was defined as a waist circumference of 85cm or more(Japanese criterion) or ≥ 90cm (Asian criterion). Statistical adjustment was made for age, hospital, and rank in the SDF. The metabolic syndrome was found to be associated with a moderately increased risk of colorectal adenomas whether either of the Japanese and Asian criteria was used; adjusted odds ratios with the Japanese and Asian criteria were 1.38 (95% confidence interval [CI] 1.13-1.69) and 1.48 (95% CI 1.13-1.93), respectively. Increased risk was more evident for proximal than distal colon or rectal adenomas, and was almost exclusively observed for large lesions (≥ 5mm in diameter). Thus the metabolic syndrome appears to be an important entity with regard to the prevention of colorectal cancer, as well as cardiovascular disease and type 2 diabetes.

Key Words: Abdominal obesity – metabolic syndrome – colorectal adenoma – Japanese men

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Introduction

The metabolic syndrome has recently drawn much attention in connection with the emerging global epidemic of obesity and type 2 diabetes mellitus (Haslam and James, 2005; King et al., 1998). The syndrome is a constellation of metabolic abnormalities including glucose intolerance, hypertriglyceridemia, and hypertension which increases the risk of cardiovascular disease as well as type 2 diabetes mellitus (Eckel et al., 2005). The pathophysiology of the metabolic syndrome is considered to be primarily attributable to insulin resistance associated with obesity and physical inactivity. In this context, abdominal rather than subcutaneous fat appears of particular concern because visceral fat leads to high influx of abundant free fatty acids and proinflammatory cytokines into the liver, thereby accentuating insulin resistance and a local and systematic proinflammatory state (Eckel et al., 2005; Haslam and James, 2005). Thus abdominal obesity is currently considered as a core component of metabolic syndrome, with two or more comorbid conditions of abnormalities of serum triglycerides, serum HDL cholesterol, fasting blood glucose, and blood pressure as criteria for diagnosis (Alberti et al., 2005).

Obesity and physical inactivity are also consistently related to an increased risk of colon cancer (IARC, 2002), with hyperinsulinemia associated with insulin resistance as one of the postulated underlying mechanisms (McKeown-Eyssen, 1994; Giovannucci, 1995; Moore et al., 1998a).

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Insulin has been shown to promote colorectal carcinogenesis (Corpet et al., 1997; Tran et al., 1996) and several studies have shown an increased risk of colon or colorectal cancer with diabetes (Weiderpass et al., 1997; Wideroff et al., 1997; Hu et al., 1999). Diabetes mellitus has also been shown to be associated with an increased risk of colon adenoma development (Kono et al., 1998; Nishii et al., 2001; Marugame et al., 2002). It is thus naturally of interest whether the metabolic syndrome is related to colorectal carcinogenesis. In this paper, we therefore examined links between the metabolic syndrome and colorectal adenoma, a well-established precursor lesion for colorectal cancer (O'Brien et al., 1990), in a population of middle-aged Japanese men.

Materials and Methods

Subjects

Study subjects were male officials in the Self-Defense Forces (SDF) who received a preretirement health examination at the SDF Fukuoka Hospital from January 1995 to March 2002 or at the SDF Kumamoto Hospital from May 1996 to March 2002. The preretirement health examination is a nationwide program offering a comprehensive medical examination to those retiring from the SDF, details of which have been described elsewhere (Kono et al., 1999; Toyomura et al., 2004). Colonoscopy was a routine procedure among others during a 5-day admission. The study was approved by the ethical committee of Kyushu University.

The present investigation included 756 cases of histologically confirmed colorectal adenomas and 1751 controls with no polyps among 3552 men who underwent total colonoscopy successfully. In a consecutive series of 4219 men during the above-mentioned period, 8 refused to participate in the survey, and 659 did not undergo successful total colonoscopy (no colonoscopy, 126; poor results, 11; and partial colonoscopy, 522). Of the 3552 undergoing total colonoscopy, 324 were excluded because of a history of colectomy (n = 20), colorectal polypectomy (n = 283), malignant neoplasms (n = 36), or inflammatory bowel disease (n = 3). In the remaining 3228 men, colonoscopic findings were classified as colorectal cancer (n = 2), polyp (n = 1471), non-polyp benign lesions such as diverticula (n = 207), and normal (n = 1548). Of the 1755 controls with normal or non-polyp benign lesions, 1751 were used as controls after exclusion of 4 men for whom the waist was not measured. Of the 1471 men with colorectal polyps, 756 were found to have adenomas without in situ or invasive carcinoma, and they were used as cases for the present study.

Numbers of cases having adenomas of the proximal colon alone, distal colon alone, and rectum alone were 258, 294, and 79, respectively. Proximal colon included cecum, ascending colon and transverse colon. A total of 125 cases had adenomas at multiple sites. Cases with adenomas sized of <5, 5–9, and ≥10 mm (the largest size for multiple adenomas) numbered 460, 243, and 49, respectively. Size of adenoma was not recorded with 4 cases. In the present study, adenomas of 5 mm or greater diameter was classified as large, while lesions measuring less than 5 mm in diameter were defined as small adenomas.

Clinical and Laboratory Data

Venous blood was drawn after an overnight fast for the determination of serum lipids and other biochemical measurements. Serum triglycerides and HDL-cholesterol were assayed enzymatically at each hospital laboratory using reagents from different sources. Plasma glucose levels were assayed by the glucose oxidase method using a commercial kit (Shino Test, Co. Ltd., Tokyo) at each hospital laboratory. A single blood pressure reading on the first day of admission was used for the present study. Waist and hip circumferences were measured in the horizontal plane at the level of the umbilicus and at the largest circumference around the buttocks, respectively. Medical history and current medication were ascertained by ward nurses and physicians.

Definition of the Metabolic Syndrome

In accordance with the diagnostic criteria proposed by the Japanese Committee of the Metabolic Syndrome Diagnostic Criteria (2005) and the International Diabetes Federation (Alberti et al., 2005), the metabolic syndrome was defined as the combination of abdominal obesity with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg); and raised fasting glucose (≥110 mg/dL). Medication for hypertension and treatment for diabetes mellitus were taken as evidence of raised blood pressure and fasting glucose, respectively. Of the cases and controls combined, 300 (12.0%) were under antihypertensive medication, 109 (4.3%) were under dietary or drug treatment for diabetes mellitus. It has been recommended by the International Diabetes Federation (Alberti et al., 2005) that cutoff points for abdominal obesity take account of the ethnicity and sex, and a waist circumference of ≥ 85cm has been adopted as the definition for abdominal obesity for Japanese men (≥ 90cm for Japanese women). However, cutoffs of 90 cm for men and 80 cm for women have already been specified for Chinese and South Asians (Alberti et al., 2005). The clinical significance of the different cutoffs remains uncertain at the present, and therefore we applied both 85 cm and 90 cm (for men), as the Japanese and Asian definitions, respectively, for the present analysis.

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by logistic regression analysis; the 95% CI was derived from the standard error for the logistic regression coefficient. Statistical adjustment was made for age (continuous variable), hospital, and rank in the SDF. Two-sided P values less than 0.05 were regarded as statistically significant. All computations were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

Table 1. Relation of Each Component of the Metabolic Syndrome to Colorectal Adenomas

Variable/category	Number (%)		OR (95% CI) [a]
	Cases	Controls	
Waist circumference (cm)			
<85	377 (50)	1034 (59)	1.00 (referent)
85-89	199 (26)	417 (24)	1.31 (1.06-1.61)
≥90	180 (24)	300 (17)	1.66 (1.33-2.06)
Triglycerides (mg/dL)			
<150	491 (65)	1201 (69)	1.00 (referent)
≥150	265 (35)	550 (31)	1.18 (0.98-1.41)
HDL (mg/dL)			
≥40	702 (93)	1605 (92)	1.00 (referent)
<40	54 (7)	146 (8)	0.85 (0.61-1.18)
Elevated blood pressure [b]			
(–)	287 (38)	729 (42)	1.00 (referent)
(+)	469 (62)	1022 (58)	1.16 (0.98-1.39)
Raised fasting glucose [c]			
(–)	613 (81)	1435 (82)	1.00 (referent)
(+)	143 (19)	316 (18)	1.06 (0.85-1.32)

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, hospital, and rank in the Self Defense Forces.
[b] Either systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or medication for hypertension.
[c] Either fasting plasma glucose ≥110 mg/dL or treatment for diabetes mellitus.

Results

Ages ranged 49-57 years for the cases and 44-59 years for the controls, with 99% in the range of 50-55 years in both groups. Abdominal obesity defined by the Japanese criterion (≥85cm in waist circumference) was observed with 50% of of the cases and 41% of the controls. Abdominal obesity based on the Asian criterion (≥90 cm) was much less frequent, but was also more prevalent in the cases (Table 1). Prevalent odds of colorectal adenoma progressively increased with higher values for waist circumference. Adjusted ORs for colorectal adenoma with abdominal obesity as classified by the Japanese (≥85 cm versus <85 cm) and Asian (≥90 versus < 90 cm) criteria were 1.45 (95% CI 1.22-1.73) and 1.52 (95% CI 1.23-1.87), respectively. Hypertriglyceridemia, lowered HDL cholesterol, raised blood pressure, and raised fasting glucose were evident in 31%, 8%, 58%, and 18%, respectively, for the control group. None of these four components of the metabolic syndrome was measurably associated with colorectal adenoma.

Table 2. Risk of Colorectal Adenomas in Relation to the Metabolic Syndrome

Metabolic syndrome	Number (%)		OR (95% CI) [a]
	Cases	Controls	
Japanese criteria			
(–)	563 (74)	1403 (80)	1.00 (referent)
(+)	193 (26)	348 (20)	1.38 (1.13-1.69)
Asian criteria			
(–)	657 (87)	1588 (91)	1.00 (referent)
(+)	99 (13)	163 (9)	1.48 (1.13-1.93)

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, hospital, and rank in the Self Defense Forces.

The prevalence rates for the metabolic syndrome as defined by the Japanese criteria were 26% in the cases and 20% in the controls. The corresponding values on the basis of the Asian criteria were 13% and 9% (Table 2). The adjusted OR for colorectal adenomas was moderately but statistically significantly increased in individuals with the metabolic syndrome, independent of the criteria applied. When the analysis was conducted by tissue site (Table 3), the ORs associated with metabolic syndrome were consistently increased for proximal colon adenomas. A less evident increase in the OR of distal colon adenoma associated with metabolic syndrome was statistically significant only when the Japanese definition was used, while a statistically non-significant increase in the OR of rectal adenoma was more pronounced with the Asian definition.

A positive association with metabolic syndrome was observed almost exclusively for large adenomas (Table 4). Of the cases with proximal colon adenoma alone (n = 258), 85 cases were classified as having large adenomas, and adenomas of the remaining 173 cases were classified as small. Cases of large proximal colon adenoma with the metabolic syndrome defined by the Japanese and Asian criteria numbered 27 and 12, respectively, resulting in an OR of 1.90 (95% CI 1.18-3.04) for the Japanese definition and an OR of 1.70 (95% CI 0.90-3.20) for the Asian definition. The ORs for small proximal adenomas were 1.42 (95% CI 0.99-2.03) and 1.61 (95% CI 1.02-2.55), respectively.

Discussion

The present study revealed a statistically significant

Table 3. Risk of Adenomas of the Proximal Colon, Distal Colon and Rectum in Relation to the Metabolic Syndrome

Metabolic syndrome	Proximal colon		Distal colon		Rectum	
	No [a]	OR (95% CI) [b]	No [a]	OR (95% CI) [b]	No [a]	OR (95% CI) [b]
Japanese criteria						
(–)	186	1.00 (referent)	218	1.00 (referent)	60	1.00 (referent)
(+)	72	1.56 (1.16-2.10)	76	1.41 (1.06-1.88)	19	1.27 (0.75-2.16)
Asian criteria						
(–)	221	1.00 (referent)	259	1.00 (referent)	67	1.00 (referent)
(+)	37	1.64 (1.11-2.40)	35	1.33 (0.90-1.96)	12	1.75 (0.92-3.31)

OR, odds ratio; CI, confidence interval. [a] Number of adenoma cases. [b] Adjusted for age, hospital, and rank in the Self Defense Forces.

Table 4. Risks of Colorectal Adenoma in Relation to the Metabolic Syndrome by Size of Adenoma

Metabolic syndrome	Small adenomas		Large adenomas	
	No [a]	OR (95% CI) [b]	No [a]	OR (95% CI) [b]
Japanese criteria				
(–)	352	1.00 (referent)	209	1.00 (referent)
(+)	108	1.24 (0.97-1.59)	83	1.60 (1.21-2.12)
Asian criteria				
(–)	407	1.00 (referent)	247	1.00 (referent)
(+)	53	1.26 (0.90-1.75)	45	1.83 (1.28-2.62)

OR, odds ratio; CI, confidence interval.
[a] Number of adenoma cases.
[b] Adjusted for age, hospital, and rank in the Self Defense Forces.

increase in the risk of colorectal adenoma associated with the metabolic syndrome, most prevalent for the proximal colon rather than the distal colon or rectum, and particularly for large adenomas. We were unable to rule out a small increase in the risk of distal colon or rectal adenoma associated with metabolic syndrome, however. It should be noted that the findings were consistent with both the Japanese and Asian criteria for abdominal obesity.

Previously, to our knowledge, only one study has examined the relation between a cluster of metabolic abnormalities and colorectal cancer (Trevisan et al., 2001). The focus was on abnormal values for triglycerides, HDL cholesterol, and fasting glucose (each defined by the highest or lowest quartile) and hypertension (systolic pressure ≥140 mmHg and/or ≥90 mmHg). Abdominal obesity was not taken into account, but the cluster of metabolic abnormalities was associated with a statistically significant 3-fold increase in mortality from colorectal cancer (Trevisan et al., 2001).

The present findings are in agreement with the previous observations regarding diabetes mellitus and colon adenomas in the SDF Health Study. In earlier analyses (Nishii et al., 2001; Marugame et al., 2002), based on some of the subjects included in the present analysis, diabetes mellitus was associated with increased risks of both proximal and distal colon adenomas, but was more strongly associated with proximal colon adenoma and with large adenomas (≥5 mm in diameter). The finding that the metabolic syndrome might also be more strongly associated with large adenomas indicates that hyperinsulinemic status may be responsible for growth of adenomas. Insulin may exert a proliferative effect on colonic tumor cells directly (Corpet et al., 1997; Tran et al., 1996) or via the insulin-like growth factor pathway indirectly (Yu and Rohan, 2000). Furthermore, increased production of proinflammatory cytokines and decreased production of an anti-inflammatory adiponectin in adipocytes may be relevant to the growth of adenomas (Eckel et al., 2005). Recently, high plasma levels of adiponectin were shown to be inversely related to the risk of colon cancer (Wu et al., 2005). However, it is not clear why the metabolic syndrome or diabetes mellitus should be most strongly associated with proximal colon adenoma. Subsite differences in the association with diabetes mellitus has also been observed as regards colorectal cancer. At least three studies have examined the relation of diabetes mellitus to subsite-specific colorectal cancer risk. One of these studies showed an increased risk associated with diabetes mellitus for proximal colon cancer exclusively (Limburg et al., 2005), and the other two found a more evident increase in the risk of proximal colon cancer (Weiderpass et al., 1997; Hu et al., 1999). However, central obesity has been reported to increase the risk in both proximal and distal sites (Moore et al., 2004) and dietary zinc, protective against diabetes, has been linked with reduction in both sites (Lee et al., 2004).

The present study features methodological advantages in that total colonoscopy was performed almost non-selectively in a defined population and that the absence of polyp lesions could thereby be confirmed in the controls. However, the study subjects were not representative of Japanese men in the general population. Thus the present findings may not be generalized. Another important aspect is that a fairly large number of the subjects (n = 283) had previously undergone colorectal polypectomy, and consequently cases with small adenoma accounted for a large proportion of the total adenoma cases. If the metabolic syndrome is most relevant to the growth of adenomas, the observed association may have been underestimated.

In the present study, physical activity and other factors associated with colorectal adenoma and cancer were not taken into consideration. Physical inactivity is one of the most important lifestyle factors related to the metabolic syndrome, as well as to colon cancer development (Moore et al., 1998b). In addition, moderate alcohol use is related to increased insulin-sensitivity (Facchini et al., 1994; Davies et al., 2002) while smoking exerts an opposite effect (Facchini et al., 1992). Both alcohol use and cigarette smoking are associated with increased risk of colorectal adenoma (Giovannucci et al., 1993; Giovannucci and Martinez 1996; Toyomura et al., 2000). Adjustment for these factors (except alcohol) probably causes overadjustment which necessarily tends to mask any association between the metabolic syndrome and colorectal adenoma. In fact, analysis allowing for physical activity, alcohol use, and cigarette smoking only attenuated the association to a limited extent with our subjects; ORs for adenomas at the colorectum, proximal colon, distal colon, and rectum with the Japanese definition were thus 1.31 (95% CI 1.07-1.61), 1.47 (95% CI 1.09-1.99), 1.34 (95% CI 1.00-1.79), and 1.16 (0.68-1.99), respectively. It could be argued that controlling for such factors is not appropriate when the aim is to address the role of the metabolic syndrome per se in the occurrence of colorectal adenomad.

In summary, the present reasonably large cross-sectional study in a population of middle-aged Japanese men showed an increased risk of colorectal adenomas, particularly of proximal colon adenomas and of large adenomas, associated with the metabolic syndrome. Thus the metabolic syndrome can be considered an important entity with regard to prevention of colorectal cancer as well as circulatory disease and type 2 diabetes.

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