学位論文

Increased Homeostasis Model Assessment Insulin Resistance is a significant risk factor for colorectal adenoma in Japanese males

（日本人男性において HOMA-IR の上昇は

有意な大腸腺腫のリスク因子である）

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Abstract

Many previous reports have documented a relationship between metabolic syndrome, in terms of insulin resistance, and colorectal cancer. However, the association of insulin resistance with colorectal adenoma has not been investigated in detail. To elucidate the association of metabolic syndrome components and insulin resistance with adenoma, homeostasis model assessment insulin resistance (HOMA-IR) and metabolic syndrome were investigated in individuals with adenoma. A cross-sectional study was conducted involving individuals who underwent scheduled health examinations using total colonoscopy. Total 963 males and 306 females were investigated. Male and female subjects comprised controls 702 and 260, individuals with adenoma 261 and 46, respectively. HOMA-IR was categorized into three groups as follows; normal (<1.6), intermediate (>1.6 - <2.5), and insulin resistance (≥2.5). Metabolic syndrome was defined by a combination of any three of the following components: central obesity (waist circumference >90 cm in men, 80 cm in women); elevated blood pressure (systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg); elevated fasting plasma glucose (>100 mg/dL); reduced high-density lipoprotein-cholesterol (<40 mg/dL in men, <50 mg/dL in women); elevated triglyceride (>150 mg/dL). Only in male subjects, multivariate analysis of HOMA-IR showed that the intermediate and insulin resistance groups had a significantly increased risk for colorectal adenoma, even after adjustment for waist circumference (odds ratio, 1.62 and 2.23; 95% confidence interval, 1.07-2.45 and 1.31-3.79, respectively). Accumulation of any metabolic syndrome components increased the risk of colorectal adenoma (P-trend =0.001). However, none of the components alone demonstrated a significant risk for colorectal adenoma. In female, no any significant risk was detected except component of triglyceride under the condition that evaluated by multivariate analysis. Our data indicate that an increased level of HOMA-IR is a significant risk factor for colorectal adenoma in Japanese males, surpassing any individual component of metabolic syndrome.

Introduction

Colorectal cancer is one of the most common cancers worldwide. It has already been shown that obesity (Frezza et al. 2002; Moghaddam et al. 2007), abdominal obesity (Pischon et al. 2006), insulin resistance (Giovannucci 1995; Colangelo et al. 2002; Trevisan et al. 2001) and metabolic syndrome (Cowey and Hardy 2006; Ahmed et al. 2006) are associated with colorectal cancer.

In the late 1990s, colorectal cancer started to increase rapidly in Japan (Yui et al. 2004), and currently it is the third leading cause of cancer death in Japanese males and the leading cause in Japanese females (Center for Control and Information Services, National Cancer Center, Japan). To reduce the incidence and mortality of colorectal cancer, it is necessary to prevent, find, and treat colorectal adenomas, which are the established precursor lesions of colorectal cancer. Therefore, it is important to elucidate the risk factors for colorectal adenoma. Recently, the reported relationship between colorectal cancer and metabolic syndrome has drawn considerable attention (Stocks et al. 2008; Omata et al. 2009). Moreover, some studies have shown that metabolic syndrome is a risk factor for colorectal adenoma (Morita et al. 2005; Kim et al. 2007). Among the components of metabolic syndrome, waist circumference was shown to be that most strongly associated with colorectal adenoma (Kim et al. 2007; Lee et al. 2008), whereas the influences of plasma glucose, lipids and blood pressure appear to vary (Ashbeck et al. 2009; Lui et al. 2010).

Previously, in a study involving a small population, we demonstrated that homeostasis model assessment insulin resistance (HOMA-IR) had a positive association with the incidence of colorectal adenoma (Otake et al. 2005). HOMA-IR has been suggested that it's a method to estimate insulin resistance from the fasting glucose and insulin concentrations. HOMA-IR is a useful model to give us the information about degree of insulin resistance only from fasting blood samples, so this index thought to be valid in epidemiological studies (Haffner et al. 1997). Unfortunately, only a few subsequent studies have addressed the significance of HOMA-IR as a risk factor for colorectal adenoma (Kang et al. 2010; Yamamoto et al. 2010). Therefore, in the present study, we evaluated the significance of HOMA-IR as a risk factor for colorectal adenoma in a large population representing that of Japan as a whole. In addition to HOMA-IR, we investigated the relationship of metabolic syndrome and its individual components with colorectal adenoma, to determine which factors are significant.

Methods and procedures

Study population

We studied a consecutive series of subjects who underwent a health examination, including colonoscopy, for school teachers and staff at the

Tohoku Central Hospital for Public School Teachers, Yamagata, Japan, between June 2008 and January 2010. This study was approved by the ethics committee of Tohoku Central Hospital. Among the individuals examined during this period, 1,667 agreed to participate in our study. Because 15 participants canceled their colonoscopy, we enrolled 1,652 participants. We then excluded patients for whom any of the following criteria applied: a) a history of colorectal polypectomy (n=298), b) incomplete colonoscopy (n=31), c) history or presence of malignant neoplasms (n=50), d) chronic inflammatory diseases such as collagen disease (n=6), c) inflammatory bowel disease (n=2), e) history of proctocolectomy (n=14), and f) treatment with insulin (n=1). After the subjects had undergone colonoscopy, the colonoscopists reported the features observed, including the location, size, and number of adenomas, hyperplastic polyps, and other benign lesions. Adenomas were diagnosed by endoscopical observation with white light and dye method. The final diagnosis was checked by another colonoscopist at Tohoku Central Hospital. In this health examination program, endoscopic treatment for colorectal adenoma was not allowed, so we were unable to collect any pathological information about the polyps observed. We assessed only adenomas in this study, because they are well known to be precursors of colorectal cancer. Two were excluded because of incomplete data collection with regard to blood samples and the characteristics of adenomas, respectively. Therefore, a total of 383 participants were excluded. Finally, 963 males and 306 females remained. Male and female subjects comprised controls 702 and 260, cases with adenoma 261 and 46, respectively.

Covariate assessment

Participants were encouraged to answer a self-administered questionnaire about alcohol intake, smoking habits, family medical history, past disease, current disease, medication, and history of colorectal polyps or colorectal polypectomy. In this health examination, participants were questioned about smoking status (never, past, current) and daily number of cigarettes consumed, and the interval since cessation of smoking among ever-smokers. Questions about medical history were also asked, including both use of therapeutic and recreational drugs, and previous surgery. Consumption of alcoholic beverages was converted to the amount of ethanol with reference to a previous study (Okamura et al. 2004). The amount of alcohol consumed (g/day) was estimated, and pack-year values calculated for cigarette consumption. One pack-year was defined as the smoking of 20 cigarettes daily for 1 year. We also asked whether participants had a first-degree family history of colorectal cancer. Menopause was asked to female subjects, additionally.

Anthropometric measurements

Anthropometric variables were measured by well-trained examiners. Before colonoscopy, body weight and height were measured, and body mass index

(BMI) was calculated as the weight in kilograms divided by the height in meters squared. Waist circumference was measured in the horizontal plane at the level of the umbilicus. Sitting blood pressure was also measured.

Clinical and laboratory data

Venous blood samples were drawn after an overnight fast to determine the levels of serum lipids and other biochemical parameters. Serum fasting plasma glucose, hemoglobin A1c (HbA1c), fasting insulin, high-density lipoprotein-cholesterol (HDL-cholesterol), low-density lipoprotein-cholesterol (LDL-cholesterol), triglycerides and uric acid were assayed in the hospital laboratory. HOMA-IR was calculated as the fasting glucose (mg/dL) × fasting insulin (μU/mL) / 405 (Matthews et al. 1985).

In the classification study, HOMA-IR was used to categorize patients into three groups: a normal group (<1.6), an intermediate group (>1.6 - <2.5), and a true insulin resistance group (≥2.5), according to the criteria proposed by the Japan Diabetes Society (The Japan Diabetes Society 2010).

Diagnostic criteria for metabolic syndrome

To evaluate the association of metabolic syndrome with adenoma, we used the classification of metabolic syndrome established in 2009 as a result of harmonization of the two common definitions proposed by the American Heart Association/National Heart, Lung and Blood Institute and the

International Diabetes Federation (Alberti et al. 2009). This harmonized definition of metabolic syndrome includes a combination of any three of the following components: central obesity (waist circumference >90 cm in men, 80 cm in women); elevated blood pressure (systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg or treatment for previously diagnosed hypertension); an elevated fasting plasma glucose level (>100 mg/dL) or receiving drug treatment for elevated glucose; a reduced HDL cholesterol level (<40 mg/dL in men, <50mg/dL in women) or receiving specific treatment for this disorder; an elevated triglyceride level (>150 mg/dL) or receiving specific treatment for this disorder. Central obesity was defined on the basis of population- and country-specific criteria, and the cut-off point for central obesity was that for Asians proposed by the International Diabetes Federation Task Force Metabolic Syndrome Criteria 2005 (Alberti et al. 2005).

Statistical analysis

All statistical analyses were performed using the SPSS version 11.0J software package (SPSS Inc. Tokyo, Japan). Chi-squared test was used for comparison of discrete variables, and the Mann-Whitney U-test for comparison of continuous variables. A two-tailed P value of <0.05 was considered statistically significant. The continuous variables measured in this study were expressed as the means ± standard deviation, and categorical variables were expressed as the number (%). Multivariate analysis was performed using logistic regression and adjusted by age, pack-year value, mean daily alcohol consumption, first-degree familial history of colorectal cancer, and use of therapeutic drugs. At multivariate analysis in female, menopause was also added. For each variable, the odds ratio (OR), 95% confidence interval (95% CI), and P-value were calculated.

Results

Background characteristics, anthropometric index and biochemical markers

Table 1 shows the characteristics of adenoma cases and controls in male subjects. Individuals with adenoma were significantly older than the controls. However, familial history of colorectal cancer, pack-year value, and mean daily alcohol consumption did not differ significantly between the groups. The rate of drug use also showed no significant inter-group difference. Individuals with adenoma had a significantly higher body mass index, waist circumference, systolic blood pressure, fasting plasma glucose level, HbA1c, insulin, HOMA-IR, and triglycerides. Table 2 shows the characteristics of adenoma cases and controls in female subjects. Individuals with adenoma had significant higher menopause rate and uric acid.

Odds ratios for the three categories of HOMA-IR

Table 3 and 4 show division of the patients into three categories based on

HOMA-IR to evaluate the risk of colorectal adenoma. In male, the >1.6-<2.5 (intermediate) and ≥2.5 (true resistance) categories of HOMA-IR were associated with a significant risk even after adjustment for age, familial history of colorectal adenoma, pack-year value, mean daily ethanol consumption, treatment for diabetes mellitus, use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), and waist circumference (OR, 1.61; 95% CI, 1.06-2.44; P-value, 0.024 and OR, 2.22; 95% CI, 1.30-3.77; P-value, 0.003, respectively). On the other hand, all HOMA-IR categories indicated no any significant risk in female (Table 4).

HOMA-IR, glucose, and insulin characteristics of individuals with adenoma in male subjects

We evaluated HOMA-IR, glucose, and insulin in relation to characteristics of adenoma in male and female subjects (Table 5 & Table 6). HOMA-IR was slightly higher in individuals with adenoma in both the right and left sides of the colon than in either side of the colon alone, and with an adenoma size exceeding 10 mm, but the differences were not significant. The number of adenomas was not related to HOMA-IR. The fasting plasma glucose level was not associated with adenoma location, size or number. However, the fasting insulin level was significantly higher in individuals with large adenomas. Adenoma cases of female subjects showed inverse association the size of adenoma. HOMA-IR and Insulin were smaller revel in >10 mm group compared with small adenoma group.

Metabolic syndrome-associated colorectal adenoma

Table 7 shows the various components of the harmonized metabolic syndrome criteria for colorectal adenoma in male. When the individual components were analyzed separately, none of component demonstrated a significant association with colorectal adenoma risk in male. Table 8 also showed analysis of individual components of metabolic syndrome in female. The component of elevated triglyceride had significant risk for colorectal adenoma only by multivariate analysis (OR, 3.19; 95% CI, 1.19-8.51; P-value, 0.021).

The male subjects with metabolic syndrome had a significantly higher risk for colorectal adenoma, as shown in Table 9 (OR, 1.67; 95% CI, 1.19-2.36; P-value, 0.003). Subjects who had more than three or four components of metabolic syndrome had a higher risk, and the risk was increased in patients with three or four compared with those who had none (OR, 1.69; 95% CI, 1.03 -2.77; P-value, 0.036 and OR 2.23; 95% CI 1.28-3.88; P-value, 0.005, respectively, P-trend =0.001). On the other hand female had none of the association with colorectal adenoma and metabolic syndrome diagnosis and the number of components (Table 10).

Discussion

The HOMA-IR was proposed on the basis of the results of the normal glucose clump test, the product of the fasting plasma glucose level and the insulin level being inversely associated with glucose intake (Matthews et al. 1985). This index is generally used to reflect insulin resistance, and is thought to be the most useful index for health assessment in a large number of subjects. Previously, many studies have evaluated the relationship between colorectal adenoma and glucose metabolism-related factors such as hyperglycemia, hyperinsulinemia, increased levels of insulin-like growth factor (IGF)-1, and decreased levels of IGF binding protein-3 (Giovannucci et al. 2000; Renehan et al. 2001; Marugame et al. 2002). However, only a few studies applying HOMA-IR have been reported. In the present study, we revealed that HOMA-IR was a significant risk factor for colorectal adenoma, and moreover this represented the first application of HOMA-IR categorized according to the Japanese insulin resistance classification. The OR of the true resistance group relative to the normal group was 2.23. Previous study indicated high level of IGF-1 and low levels of IGFBP-3 were associated with an elevated risk of adenoma (Giovannucci et al. 2000). Kang et al. reported that the OR of the highest HOMA-IR group relative to the lowest group in five categories was increased significantly to 1.99 (Kang et al. 2010). In contrast, Yamamoto et al. reported that the mean value of HOMR-IR in patients with adenoma was not different from that in controls, and that HOMA-IR was not a risk factor for colorectal adenoma (Yamamoto et al.

2010). They described that highly rate of smoker might ascribed no association of visceral adiposity area and colorectal adenoma. Cigarette is well known having strong effect for decrease body weight (Mizoue et al. 1998 0) and also association for colorectal adenoma. In fact Adenoma cases indicated lower level in factors of abdominal obesity and also of insulin resistance. We indicated that association of 8-hydroxy-2'-deoxyguanosine (8-OHdG) which is the marker of systematic oxidative stress and colorectal adenoma (Sato, et al. 2010). Smoking is one of the causes of oxidative stress, and increases 8-OHdG level (Campos et al. 2011; Morita et al. 2005). Oxidative stress might more affect for incidence of colorectal adenoma than abdominal obesity and insulin resistance in their study.

We also evaluated the relationship of HOMA-IR to the location, size and number of colorectal adenomas. Individuals with adenomas over 10 mm in size showed a significantly higher insulin level, but not a higher HOMA-IR. Adenomas learned toward <10mm, >10mm group was so small. This might have accounted for the large difference in the insulin level between the two groups. However, it is known that an increased insulin level prevents apoptosis of colorectal tumors (Keku et al. 2005). As the present study did not involve a pathological assessment of colorectal adenomas, we were unable to investigate the relationship between HOMA-IR and advanced adenomas, which have been described as colorectal polyps >10 mm in diameter and/or villous components and/or severe dysplasia, which have high malignant potential (Winawer et al. 1993; Zarchy and Ershoff 1994). Therefore our evaluation was limited to only the size of advanced adenomas. On the other hand women indicated inverse association advanced adenoma with HOMA-IR and insulin compared with male cases. Large adenoma cases were just only two cases. So father investigation with more cases of large adenoma is needed to evaluate the certain relation in females.

The present study also revealed that metabolic syndrome is a risk factor for colorectal adenoma. The OR for patients with metabolic syndrome relative to controls was 1.67, which was similar to the values reported in other studies (Morita et al. 2005; Kim et al. 2007; Lui et al. 2010). In addition to metabolic syndrome itself, Wang et al. reported that accumulation of a number of components of metabolic syndrome led to an increasing risk of colorectal adenoma, according to the NCEP-ATPIII diagnostic criteria (Wang et al. 2005). Their evaluation was conducted using rectosigmoidscopy. However, Lee et al. obtained similar results using total colonoscopy in male subjects (Lee et al. 2008). In contrast, Tsilidis et al. did not find any relationship between an accumulated number of metabolic syndrome components and an increased risk of adenoma (Tsilidis et al. 2010). However, their evaluation was a cohort study, and the population was relatively small, including 132 controls and 260 individuals with adenoma. In the present study we clearly revealed that an accumulated number of components of metabolic syndrome were associated with an increased risk of colorectal adenoma.

We were also interested in which component(s) of metabolic syndrome most strongly influenced the risk of colorectal adenoma. Most studies have reported that waist circumference is a significant risk factor in itself (Martikainen and Marmot 1999; Kim et al. 2007; Ashbeck et al. 2009; Nam et al. 2010; Yamamoto et al. 2010). However, we did not find any significant relationship with waist circumference in males. Although we applied the Asian criteria for waist circumference (>90 cm) (Alberti et al. 2005), we also applied the Japanese criteria (>85 cm) (Japanese Committee of the Metabolic Syndrome Diagnostic Criteria 2005) and obtained similar results (data not shown). Kang and Sass investigated visceral fat area as a significant risk factor for colorectal adenoma, and also reported that waist circumference and subcutaneous fat did not show a constant relationship (Kang et al. 2010; Sass et al. 2004). Tsilidis also reported that there was no relationship between BMI and adenoma in their cohort study (Tsilidis et al. 2010). Although the relationship between visceral fat area and colorectal adenoma appears to be undeniable, any association with waist circumference, subcutaneous fat or BMI remains to be clarified.

In this current study, female was indicated to have no association for colorectal adenoma in both highly HOMA-IR and metabolic syndrome diagnosis. Previous studies showed that female had less age-adjusted incidence for colorectal cancer than male (Tamura, et al 1996; Ji et al. 1998; Sung 2005). Huang also reported female reduce the risk for colorectal adenoma compared with male (Huang et al. 2010). This reduction has interpreted by the protection effects of sex hormones. Certain mechanism has not been clear yet, but several studies indicate that reproductive agents such age of menarche, age of menopause and estrogen replacement therapy associated with colorectal cancer (Crandall 1999; Grodstein, et al. 1998). Protective effects for colorectal adenoma also reported but not consistently than for colorectal cancer. Consequently the association with colorectal adenoma and HOMA-IR or metabolic syndrome might hardly reveal. Further study is needed for evaluate association of colorectal adenoma and several factors of reproductive agents.

Only component of elevated triglyceride assessed by multivariate analysis was a significant risk for colorectal adenoma in female. But the t-test and univariat analysis had not demonstrated any significance of triglycerides. Only few previous studies indicated the association of hyper triglyceride and colorectal adenoma (Kang et al. 2010; Liu et al. 2010). If this result doesn't contradict previous report, triglycerides is thought to have a limited association from our study. Additionally Lui evaluated elevated triglyceride component of metabolic syndrome in men and women respectively, no significant association of elevated triglyceride and colorectal adenoma in women.

Almost all of the subjects evaluated in this study were teachers working in public schools. Some previous studies have demonstrated an inverse association of obesity with education status (Kahn and Williamson 1990; Lee et al. 2005). Therefore, the high education status of the present population might have affected their waist circumference. Other than waist circumference, none of the other components of metabolic syndrome was extracted as a significant risk factor by logistic regression analysis. These results indicate that each of the components of metabolic syndrome had a weak association with colorectal adenoma. However, the risk for colorectal adenoma increased as more of these components accumulated.

Conclusion

In conclusion, although our study was restricted to males, we confirmed that metabolic syndrome is a significant risk factor for colorectal adenoma. Moreover, we revealed that an increased HOMA-IR value was also a significant risk factor for colorectal adenoma, surpassing any of the components of metabolic syndrome. The OR for HOMA-IR was comparable to that for metabolic syndrome. Hereafter, HOMA-IR should be considered for large-scale screening for colorectal adenoma risk, as well as metabolic syndrome. HOMA-IR witch calculated from only a fasting blood sample, potentially assist to narrow down high risk group of colorectal adenoma. If screening colonoscopy intensively performed to highly HOMA-IR group, it will grow up cost-effectiveness for colorectal cancer prevention.

Conflict of interest

All authors have no conflict of interest.

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Table 1. Characteristics of cases with adenoma and controls in male subjects

Characteristics	Control (n=702)	Adenoma (n=261)	P-value
Age (years)	48.8 ± 7.1	52.1 ± 6.0	<0.001※
Familial history of CRC (%)	42 (6.4)	15 (6.3)	1.000
Cigarette smoking status			
Never (%)	287 (40.9)	106 (40.6)	0.125
Former (%)	243 (34.6)	76 (29.1)	
Current (%)	172 (24.5)	79 (30.3)	
Smoking (pack-years)	10.9 ± 13.0	12.2 ± 14.4	0.209
Daily alcohol consumption (g/day)	22.5 ± 29.6	22.0 ± 27.5	0.805
Use of anti-hypertensive drugs (%)	83 (12.1)	39 (15.8)	0.153
Use of anti-diabetic drugs (%)	22 (3.1)	11 (4.2)	0.426
Use of lipid disorder treatment (%)	56 (8.0)	28 (11.1)	0.155
Use of Aspirin/NSAIDs (%)	18 (2.6)	6 (2.3)	1.000
BMI (kg/m^2)	24.5 ± 3.0	25.1 ± 3.5	0.017※
WC (cm)	86.8 ± 7.9	88.6 ± 9.5	0.012
SBP (mmHg)	121.6 ± 15.3	124.0 ± 15.1	0.020※
DBP (mmHg)	77.2 ± 9.7	78.5 ± 9.8	0.059
FPG (mg/dl)	93.1 ± 31.8	97.8 ± 26.8	<0.001※
HbA1c (%)	5.3 ± 0.6	5.5 ± 0.9	<0.001※
Insulin (μU/ml)	5.9 ± 4.3	7.2 ± 6.1	<0.001※
HOMA-IR	1.4 ± 1.1	1.8 ± 2.1	<0.001※
HDL-c (mg/dl)	59.0 ± 14.9	57.4 ± 14.1	0.167
LDL-c (mg/dl)	130.2 ± 31.8	130.3 ± 32.3	0.835
Triglycerides (mg/dl)	162.9 ± 106.1	173.5 ± 96.8	0.020※
Uric acid (mg/dl)	6.2 ± 1.2	6.2 ± 1.3	0.912

CRC; colorectal cancer, NSAIDs; non-steroidal anti-inflammatory drugs, BMI; body mass index, WC; waist circumference, SBP; systolic blood pressure, DBP; diastolic blood pressure, FPG; fasting plasma glucose, HOMA-IR; homeostasis model assessment-insulin resistance, HDL-c; high-density lipoprotein-cholesterol, LDL-c; low-density lipoprotein-cholesterol. The P-value was given by the chi-square test or the Mann-Whitney U-test. ※ $P<0.05$.

Table 2. Characteristics of cases with adenoma and controls in female subjects

Characteristics	Control (n=260)			Adenoma (n=46)			P-value
Age (years)	51.3	±	6.9	53.2	±	5.6	0.099
Menopause (%)	129	(54.2)		31	(73.8)		0.018※
Familial history of CRC (%)	19	(7.6)		3	(13.6)		1.000
Cigarette smoking status							
Never (%)	241	(92.7)		41	(89.1)		0.286
Former (%)	16	(6.2)		3	(6.5)		
Current (%)	3	(1.1)		2	(4.4)		
Smoking (pack-years)	1.1	±	13.0	12.3	±	14.7	0.331
Daily alcohol consumption (g/day)	17.6	±	27.0	19.9	±	26.7	0.591
Use of anti-hypertensive drugs (%)	6	(2.3)		1	(14.3)		1.000
Use of anti-diabetic drugs (%)	18	(7.0)		5	(11.6)		0.347
Use of lipid disorder treatment (%)	6	(2.3)		1	(14.3)		1.000
Use of Aspirin/NSAIDs (%)	18	(7.0)		2	(4.4)		0.749
BMI (kg/m^2)	23.1	±	3.7	23.3	±	3.4	0.490
WC (cm)	82.2	±	10.5	84.0	±	8.7	0.157
SBP (mmHg)	113.7	±	14.5	115.4	±	18.4	0.886
DBP (mmHg)	70.9	±	9.3	72.1	±	10.6	0.482
FPG (mg/dl)	88.7	±	12.5	90.3	±	1.0	0.110
HbA1c (%)	5.2	±	0.5	5.2	±	0.4	0.558
Insulin (μU/ml)	4.9	±	3.3	5.9	±	4.4	0.267
HOMA-IR	1.1	±	0.9	1.4	±	1.2	0.228
HDL-c (mg/dl)	72.1	±	16.4	72.9	±	17.4	0.658
LDL-c (mg/dl)	128.6	±	31.0	135.1	±	31.9	0.217
Triglycerides (mg/dl)	103.1	±	57.7	112.9	±	68.4	0.396
Uric acid (mg/dl)	4.7	±	1.0	5.1	±	0.9	0.005※

CRC; colorectal cancer, NSAIDs; non-steroidal anti-inflammatory drugs, BMI; body mass index, WC; waist circumference, SBP; systolic blood pressure, DBP; diastolic blood pressure, FPG; fasting plasma glucose, HOMA-IR; homeostasis model assessment-insulin resistance, HDL-c; high-density lipoprotein-cholesterol, LDL-c; low-density lipoprotein-cholesterol. The P-value was given by the chi-square test or the Mann-Whitney U-test. ※ $P<0.05$.

Table 3. The association of the three categories of HOMA-IR with colorectal adenoma in male subjects

HOMA-IR	Control	Adenoma	Univariate			Multivariate[†]		
	(N=702)	(N=261)	OR	95% C.I.	P-value	OR	95% C.I.	P-value
Normal (<1.6)	502 (71.5)	151 (57.8)	1.00	ref		1.00	ref	
Intermediate (>1.6-<2.5)	128 (18.2)	66 (25.3)	1.71	(1.21-2.43)	0.002[※]	1.62	(1.07-2.45)	0.003[※]
Insulin resistance (≥2.5)	72 (10.3)	44 (16.9)	2.03	(1.34-3.08)	0.001[※]	2.23	(1.31-3.79)	<0.001[※]
P_{trend}			<0.001[※]			0.001[※]		

HOMA-IR; homeostasis model assessment-insulin resistance. † adjusted for age, pack-years, daily alcohol consumption, familial history of colorectal cancer, use of anti-diabetic drugs, use of aspirin/NSAIDs, and waist circumference. The *P*-trend was evaluated by entering it into the model as a single variable. ※ P<0.05.

Table 4. The association of the three categories of HOMA-IR with colorectal adenoma in female subjects

HOMA-IR	Control (N=260)	Adenoma (N=46)	Univariate OR	Univariate 95% C.I.	Univariate P-value	Multivariate ‡ OR	Multivariate ‡ 95% C.I.	Multivariate ‡ P-value
Normal (<1.6)	211 (81.2)	35 (76.1)	1.00	ref		1.00	ref	
Intermediate (≥1.6-<2.5)	33 (12.7)	5 (10.9)	0.91	(0.33-2.50)	0.860	0.89	(2.4-3.29)	0.865
Insulin resistance (≥2.5)	16 (6.1)	6 (13.0)	2.26	(0.83-6.17)	0.111	2.20	(4.9-9.85)	0.304
P_{trend}			<0.204			0.458		

HOMA-IR; homeostasis model assessment-insulin resistance. ‡ adjusted for age, menopause, pack-years, daily alcohol consumption, familial history of colorectal cancer, use of anti-diabetic drugs, use of aspirin/NSAIDs, and waist circumference. The *P*-trend was evaluated by entering it into the model as a single variable.

Table 5. The association of the HOMA-IR, fasting plasma glucose, and insulin levels with the characteristics of adenoma in male subjects

Character	N	HOMA-IR				Fasting Plasma Glucose				Insulin			
		mean	±	S.D.	P-value	mean	±	S.D.	P-value	mean	±	S.D.	P-value
Location													
Each side	224	1.8	±	1.8	0.642	97.8	±	27.8	0.966	7.0	±	5.4	0.632
Both side	37	2.3	±	3.0		97.7	±	19.8		8.7	±	9.1	
Size													
<10mm	247	1.7	±	1.7	0.098	97.9	±	27.0	0.874	6.9	±	5.3	0.031※
≥10mm	14	3.4	±	5.5		95.6	±	23.0		12.2	±	13.8	
Number													
1	161	1.7	±	1.9	0.071	96.5	±	22.3	0.957	6.6	±	5.5	0.054
≥2	101	2.1	±	2.2		99.8	±	32.6		8.1	±	6.8	

The P-value was provided by the Mann-Whitney U test. ※P<0.05

Table 6. The association of the HOMA-IR, fasting plasma glucose, and insulin levels with the characteristics of adenoma in female

Character	N	HOMA-IR				Fasting Plasma Glucose				Insulin			
		mean	±	S.D.	P-value	mean	±	S.D.	P-value	mean	±	S.D.	P-value
Location													
Each side	41	1.4	±	1.3	0.459	90.8	±	10.6	0.243	6.0	±	5.4	0.514
Both side	5	0.9	±	0.6		86.0	±	3.7		4.3	±	9.1	
Size													
<10mm	44	1.4	±	1.2	0.024※	97.9	±	10.3	0.402	6.1	±	4.3	0.022※
≥10mm	2	0.3	±	0.0		95.6	±	3.5		1.2	±	0.3	
Number													
1	34	1.3	±	1.2	0.271	90.3	±	8.7	0.310	5.4	±	4.3	0.169
≥2	12	1.7	±	1.2		90.3	±	14.0		7.1	±	4.5	

The P-value was provided by the Mann-Whitney U test. ※P<0.05

Table 7. The association of the components of harmonized metabolic syndrome criteria (2009) with the risk for colorectal adenoma in male subjects

Variables	Control	Adenoma	Univariate			Multivariate ¶		
	(N=702)	(N=261)	OR	95% C.I.	P-value	OR	95% C.I.	P-value
Central obesity	272 (38.8)	101 (38.7)	1.00	(0.74-1.33)	0.976	0.97	(0.70-1.35)	0.861
Elevated BP	256 (36.5)	80 (30.7)	0.77	(0.57-1.04)	0.090	0.72	(0.51-1.02)	0.065
Elevated FPG	125 (17.8)	43 (16.5)	0.91	(0.62-1.33)	0.622	0.95	(0.62-1.45)	0.815
Reduced HDL-c	282 (40.2)	107 (41.0)	1.03	(0.77-1.38)	0.829	1.12	(0.80-1.58)	0.518
Elevated TG	91 (13.0)	31 (11.9)	0.90	(0.59-1.40)	0.647	0.95	(0.57-1.57)	0.836

BP; blood pressure, FPG; fasting plasma glucose, HDL-c; high-density lipoprotein-cholesterol, TG; triglyceride.
¶analyzed with all components and adjusted for age, smoking status, daily alcohol consumption, and familial history of colorectal cancer.

Table 8. The association of the components of harmonized metabolic syndrome criteria (2009) with the risk for colorectal adenoma in female subjects

Variables	Control	Adenoma	Univariate			Multivariate§		
	(N=260)	(N=46)	OR	95% C.I.	P-value	OR	95% C.I.	P-value
Central obesity	106(40.8)	15(32.6)	0.30	(0.36-1.37)	0.976	0.94	(0.41-2.11)	0.876
Elevated BP	85(32.7)	19(41.3)	1.45	(0.76-2.76)	0.257	1.78	(0.77-4.14)	0.164
Elevated FPG	40(15.4)	5(10.9)	0.67	(0.25-1.80)	0.428	0.71	(0.22-2.33)	0.575
Reduced HDL-c	112(43.1)	20(43.5)	1.02	(0.54-1.91)	0.960	0.72	(0.29-1.78)	0.478
Elevated TG	41(15.8)	11(23.9)	1.68	(0.79-3.57)	0.179	3.19	(1.19-8.51)	0.021※

BP; blood pressure, FPG; fasting plasma glucose, HDL-c; high-density lipoprotein-cholesterol, TG; triglyceride.
§analyzed with all components and adjusted for age, menopause, smoking status, daily alcohol consumption, and familial history of colorectal cancer. ※ $P<0.05$.

Table 9. The association of the number of harmonized metabolic syndrome criteria (2009) with the risk for colorectal adenoma in male subjects

Variables	Control (N=702)	Adenoma (N=261)	Univariate OR	Univariate 95% C.I.	Univariate P-value	Multivariate¶ OR	Multivariate¶ 95% C.I.	Multivariate¶ P-value
MS diagnosis	145 (20.7)	86 (33.0)	1.89	(1.38-2.59)	<0.001※	1.67	(1.19-2.36)	0.003※
MS risk number								
0	211 (30.1)	56 (21.5)	1.00	ref		1.00	ref	
1	201 (28.6)	59 (22.6)	1.02	(0.73-1.67)	0.633	1.04	(0.67-1.61)	0.876
2	145 (20.7)	60 (23.0)	1.56	(1.02-2.38)	0.039※	1.45	(0.91-2.29)	0.115
3	93 (13.2)	50 (19.1)	2.04	(1.29-3.19)	0.002※	1.69	(1.03-2.77)	0.036※
≥4	52 (7.4)	36 (13.8)	2.61	(1.56-4.38)	<0.001※	2.23	(1.28-3.88)	0.005※
P_{trend}			<0.001※			0.001※		

¶adjusted for age, smoking status, alcohol intake, and familial history of colorectal cancer. The P trend was evaluated by entering it into the model as a single variable. ※ P<0.05.

Table 10. The association of the number of harmonized metabolic syndrome criteria (2009) with the risk for colorectal adenoma in female subjects

Variables	Control	Adenoma	Univariate			Multivariate§		
	(N=260)	(N=46)	OR	95% C.I.	P-value	OR	95% C.I.	P-value
MS diagnosis	39(15.0)	7(15.2)	1.02	(0.43-2.44)	0.970	0.62	(0.18-2.10)	0.441
MS risk number								
0	98(37.7)	10(21.7)	1.00	ref		1.00	ref	
1	81(31.2)	19(41.3)	2.30	(1.01-5.22)	0.047※	1.88	(0.70-4.84)	0.213
2	42(16.2)	10(21.7)	2.33	(0.90-6.02)	0.080	1.96	(0.66-5.84)	0.229
3	25(9.6)	5(10.9)	1.96	(0.62-6.25)	0.255	1.11	(0.26-4.86)	0.886
≥4	14(5.3)	2(4.4)	1.40	(0.28-7.06)	0.684	0.57	(0.04-8.74)	0.689
P_{trend}			0.263			0.827		

§adjusted for age, menopause, smoking status, alcohol intake, and familial history of colorectal cancer. The P trend was evaluated by entering it into the model as a single variable. ※ P<0.05.