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Gender difference in metabolic syndrome and incident colorectal adenoma

A prospective observational study (KCIS No.42)

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Abstract

This community-based study aimed to elucidate whether there is a gender difference in the effect of metabolic syndrome (MetS) and its individual components on an elevated risk for incident colorectal adenoma.

A prospective cohort study was conducted by enrolling 59,767 subjects aged 40 years or older between 2001 and 2009 in Keelung, Taiwan, to test this hypothesis, excluding those with a prior history of colorectal cancer and those with colorectal cancer diagnosed at the first screening. Cox proportional hazards regression models were used to assess the effect of MetS in terms of a dichotomous classification, each individual component and the number of components for males and females.

Colorectal adenoma was present in 2.7% (n = 652) of male participants and 1.1% (n = 403) of female participants. The prevalence rate of MetS was 26.7% and 23.3% for males and females, respectively. The effect of MetS on colorectal adenoma was statistically significant and similar for the 2 genders, with an adjusted hazard ratio (aHR) of 1.33 (95% CI: 1.13–1.58) in males and 1.33 (95% CI: 1.06–1.66) in females after adjustment for confounders. However, MetS led to higher risk of advanced colorectal adenoma in men than in women. Regarding the effect of each component of MetS on colorectal adenoma, abnormal waist circumference and hypertriglyceridemia led to an elevated risk of colorectal adenoma in both genders. A rising risk of colorectal adenoma among females was noted in those with a moderately higher level of glycemia (100–125 mg/dL, aHR = 1.44, 95% CI: 1.12–1.85). Hypertriglyceridemia and high blood pressure were associated with an increased risk of advance colorectal adenoma in males.

Both male and female subjects with MetS had a higher risk of colorectal adenoma. The contributions from individual components of MetS varied by gender. These findings suggest that the possible risk reduction of colorectal adenoma through metabolic syndrome-based lifestyle modifications may differ between genders.

Abbreviations: CRC = colorectal cancer, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome.

Keywords: cohort studies, colorectal adenoma, metabolic syndrome

1. Introduction

An emerging body of evidence on the association between metabolic syndrome (MetS) and the risk of colorectal adenoma has been demonstrated, particularly emphasizing obesity, diabetes and insulin resistance.[1–9] However, most studies were based on the assessment of the association with a cross-sectional design, which renders the temporal relationship between MetS and colorectal adenoma elusive. Recent studies from Korea have demonstrated the impact of fasting glucose on incident colorectal cancer (CRC) based on a prospective cohort study.[10,11] Several systematic reviews involving prospective cohort studies also demonstrated that obesity and waist circumference have

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independent and direct relationships with CRC,[12,13] especially for those with early-life obesity or younger populations.[14,15] A meta-analysis also emphasized that diabetes is associated with a greater risk for incident CRC.[16] It is therefore of great interest to further show whether MetS is the cause or the consequence of colorectal adenoma. To clarify the temporal relationship between MetS and colorectal cancer (CRC), a longitudinal prospective cohort study design excluding prevalent colorectal adenoma at the time of study entry, which has been rarely conducted before, is required.

In addition to the corroboration of a temporal relationship, there are 2 additional aspects that are worth investigating. First, gender differences in colorectal cancer and adenoma have long been noted, but the findings are still inconsistent. Men have been reported to have a higher risk of developing colorectal polyps and tumors,[17,18] and a meta-analysis also showed strong evidence that men have a higher risk of advanced colorectal cancer than women;[19] however, a national polyp study showed that gender was not associated with high-grade dysplasia.[20] A gender difference was also found in the prevalence of MetS, obesity, abnormal lipid profile and glucose intolerance.[21]

Second, as MetS is composed of 5 individual components (elevated blood pressure, cholesterol, triglycerides, hyperglycemia, and waist circumference) studies of gender differences in the effect of individual components of MetS on the risk of colorectal adenoma, a well-recognized premalignancy for CRC, are also lacking. We therefore tested the hypothesis that MetS, as defined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII: Asia modified diagnostic criteria), is caused by the epidemiological definition of a temporal relationship of the risk of colorectal adenoma and advanced colorectal adenoma, and we also examined whether the effect of MetS and its individual components on the risk of colorectal adenoma varied with gender using a large population-based prospective cohort study in Keelung, Taiwan.

2. Subjects and methods

2.1. Study population and design

A total of 59,767 subjects aged 40 years or older participating in the Keelung community-based integrated screening (hereafter abbreviated as KCIS) program between 2001 and 2009 in Keelung, Taiwan were recruited. Patients with CRC diagnosed prior to or at first screen were excluded. The KCIS used the existing pap smear screening program as the basis for integrating other disease screening activities to create a unified platform. Five neoplastic diseases (cervical neoplasia, breast cancer, colorectal neoplasia, liver cancer, and oral neoplasia) and 3 nonneoplastic chronic diseases (type 2 diabetes, hypertension, and hyperlipidemia) were screened for in this program. Due to the integration of health checkups for 3 chronic diseases, biochemical variables pertaining to the 3 nonneoplastic chronic diseases as well as blood pressure and anthropometric measures allowed us to define MetS in accordance with National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII: Asia modified diagnostic criteria) criteria.[22] Collecting both information on MetS and colorectal neoplasia offers an opportunity to evaluate the temporal relationship between MetS and colorectal adenoma by using a prospective cohort design to follow up a normal cohort by excluding prevalent cases of colorectal neoplasia (including adenoma and invasive carcinoma) at the time of study entry to ascertain incident colorectal adenoma over time. Ethics approval was obtained from the Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201112024). All participants provided written informed consent.

2.2. Ascertainment of colorectal adenoma

We used a two-stage screening design for CRC. Participants aged 40 years or older were provided with a fecal immunochemical test (FIT) kit (OC-Sensor). Those with a fecal hemoglobin concentration 100 ng/mL or above were referred for a colonoscopic examination. After completing the follow-up colonoscopies, pathologically confirmed colorectal adenomas were identified, including villous, tubular adenomas, and tubulovillous adenomas. Tubulovillous adenomas, villous adenomas, or those with size larger than 1 cm were defined as advanced adenomas. Details of the Keelung colorectal cancer screening program were given elsewhere.[23,24]

2.3. MetS and other characteristics

The information collected in the KCIS program included each diagnostic component of MetS. This enabled us to identify the criteria for MetS according to the following 5 items: central obesity (defined using the adjustment for Oriental countries as men with a waist circumference greater than 90 cm or women with a waist circumference greater than 80 cm), triglycerides $\geq$150 mg/dL, high-density lipoprotein (HDL) $<$40 mg/dL for men and HDL $<$50 mg/dL for women, systolic blood pressure $\geq$130 mm Hg or diastolic blood pressure $\geq$85 mm Hg, and fasting glucose $\geq$100 mg/dL. In the light of NCEP ATP III, the number of criteria in the abnormal range for each subject was defined as metabolic score. Those having a metabolic score larger than or equal to 3 were defined as having MetS. Note that information regarding fecal hemoglobin (f-Hb) concentration from FIT and medical treatment and metabolic control of preexisting cases of diabetes mellitus or hypertension obtained via self-administered questionnaires were taken into account for the criteria for impaired serum glucose and elevated blood pressure. Other characteristics such as cigarette smoking, alcohol consumption, physical activity, meat and vegetable intake, and family history of CRC were also inquired about in the questionnaire.

2.4. Statistical analyses

Cox proportional regression models were used to assess the effect size of the association between baseline MetS and the risks of colorectal adenoma and advanced adenoma with adjustment for age, gender, smoking habits, betel nut chewing, alcohol consumption, physical activity, vegetable intake, meat consumption, family history of CRC, and f-Hb concentration. The outcomes of interest included adenoma and advanced adenoma. Those in the absence of an event until the end of the follow-up period were considered censored cases. The date at the end of the follow-up period was December 31, 2009. In addition to MetS, the risk of developing adenoma and advanced adenoma according to each component of MetS as defined above was also examined. The statistically significant variables in the univariate analysis were selected for the multivariate analysis. The interaction effects between gender and MetS or its individual components were tested. A subgroup analysis by gender was

conducted to exam whether the effects of the components of MetS vary across gender. A *P* value less than .05 was considered statistically significant. All statistical analyses were performed with SAS version 9.4.

3. Results

In this study, 59,767 subjects (23,849 (39.9%) men aged 57.2 (±12.4) years and 35,918 (60.1%) women aged 54.2±11.2 years) were enrolled. The demographic characteristics and prevalence rate of an abnormal waist circumference, hypertriglyceridemia, low- and high-density lipoprotein cholesterol, high blood pressure, fasting hyperglycemia and a family history of CRC are shown in Table 1. The mean follow-up time for our study cohort was 5.8 (±2.4) years (5.7 (±2.5) years for men and 5.9 (±2.4) years for women). Colorectal adenoma was presented in 1055 (1.8%) subjects (652 (2.7%) men and 403 (1.1%) women). Among them, 342 (0.6%) cases were advanced adenoma (231 (1.0%) in males and 111 (0.3%) in females). MetS was present in 14,717 (24.6%) subjects (6362 (26.7%) males and 8355 (23.3%) females). Hypertriglyceridemia, elevated blood pressure, and higher glycemia were more frequent in men, while more women had an abnormal waist circumference and low HDL cholesterol.

The effect of MetS on colorectal adenoma was statistically significant, with a crude HR of 1.47 (95% CI: 1.29–1.68) (Table 2). MetS status elevated the risk of colorectal adenoma after considering other significant confounding factors, including age, sex, smoking status, betel quid chewing, alcohol consumption and f-Hb concentration, with an HR of 1.32

Table 1

Demographic characteristics of the study population by gender.

	Men (n=23849)		Women (n=35918)		Total (n=59767)	
	N	%	N	%	N	%
Age group						
40–49	8103	34.0	14676	40.9	22779	38.1
50–59	5929	24.9	10290	28.6	16219	27.1
60–69	4975	20.9	6938	19.3	11913	19.9
≥70	4842	20.3	4014	11.2	8856	14.8
Smoking						
Yes	13117	55.5	2441	6.9	15558	26.3
No	10498	44.5	33052	93.1	43550	73.7
Unknown	234		425		659	
Betel quid chewing						
Yes	2909	12.4	226	0.6	3135	5.3
No	20610	87.6	35215	99.4	55825	94.7
Unknown	330		477		807	
Drinking						
Yes	10720	45.7	2876	8.1	13596	23.1
No	12746	54.3	32450	91.9	45196	76.9
Unknown	383		592		975	
Physical activity						
Frequent	6794	29.2	12871	36.8	19665	33.7
Infrequent	16512	70.8	22090	63.2	38602	66.3
Unknown	543		957		1500	
Meat Intake						
Frequent	5274	22.9	5530	16.1	10804	18.8
Infrequent	17759	77.1	28848	83.9	46607	81.2
Unknown	816		1540		2356	
Vegetable Intake						
Frequent	5848	25.3	10106	29.2	15954	27.7
Infrequent	17260	74.7	24464	70.8	41724	72.3
Unknown	741		1348		2089	
Family history of CRC	564	2.36	822	2.29	1386	2.32
f-Hb concentration						
undetected	9772	41.0	14854	41.4	24626	41.2
1–19 ng/mL	7542	31.6	12048	33.5	19590	32.8
20–39 ng/mL	3077	12.9	4682	13.0	7759	13.0
40–59 ng/mL	1140	4.8	1543	4.3	2683	4.5
60–89 ng/mL	746	3.1	990	2.8	1736	2.9
99–100 ng/mL	135	0.6	182	0.5	317	0.5
≥100 ng/mL	1437	6.0	1619	4.5	3056	5.1
MetS						
Yes	6362	26.7	8355	23.3	14717	24.6
No	17483	73.3	27562	76.7	45045	75.4
Unknown	4		1		5	
Waist circumference †						

(*continued*)

Table 1

(continued).

	Men (n = 23849)		Women (n = 35918)		Total (n = 59767)	
	N	%	N	%	N	%
Normal	15677	66.4	22685	63.8	38362	64.8
Abnormal	7938	33.6	12895	36.2	20833	35.2
Unknown	234		338		572	
Triglyceride						
<150 mg/dL	15111	63.9	26839	75.1	41950	70.6
≥150 mg/dL	8555	36.1	8878	24.9	17433	29.4
Unknown	183		201		384	
HDL						
≥40 mg/dL (M); ≥50 mg/dL (F)	19549	82.6	27344	76.6	46893	79.0
<40 mg/dL (M); <50 mg/dL (F)	4117	17.4	8373	23.4	12490	21.0
Unknown	183		201		384	
Blood pressure						
<130/85 mm Hg	9746	41.1	20481	57.4	30227	50.9
≥130/85 mmHg	13961	58.9	15200	42.6	29161	49.1
Unknown	142		237		379	
Glycemia						
<100 mg/dL	17172	72.56	27287	76.40	44459	74.87
100–125 mg/dL	4342	18.35	5775	16.17	10117	17.04
≥126 mg/dL	2152	9.09	2656	7.44	4808	8.10
Unknown	183		200		383	
Adenoma	652	2.7	403	1.1	1055	1.8
Advanced adenoma	231	1.0	111	0.3	342	0.6
Follow-up time (Yr)*	5.7	2.5	5.9	2.4	5.8	2.4

* Data are presented as the mean and sd.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

f-Hb = fecal hemoglobin, HDL = high-density lipoprotein, MetS = metabolic syndrome.

(95% CI: 1.15–1.51). All individual components of MetS except for hyperglycemia were associated with an increased risk of colorectal adenoma (Table 2). The significant impacts of an abnormal waist circumference, hypertriglyceridemia and moderately higher level of glycemia (100–125 mg/dL) held after considering other significant confounders. There was no interaction between gender and MetS or its individual components, except for the HDL cholesterol component ($P = .035$).

Table 2

Hazard ratio (95% CI) of metabolic syndrome and other risk factors for colorectal adenoma.

	HR	95% CI	aHR*	95% CI
Age	1.03	(1.02, 1.03)	1.01	(1.00, 1.01)
Sex	2.46	(2.17, 2.80)	1.91	(1.64, 2.24)
Smoking	1.97	(1.74, 2.24)	1.17	(1.00, 1.37)
Betel quid chewing	1.53	(1.21, 1.93)	0.98	(0.76, 1.27)
Drinking	1.83	(1.60, 2.08)	1.19	(1.02, 1.39)
Physical activity	0.92	(0.80, 1.05)		
Meat intake	0.99	(0.85, 1.16)		
Vegetable intake	1.20	(0.89, 1.17)		
Family history of CRC	1.19	(0.81, 1.74)		
f-Hb concentration	1.80	(1,76, 1.85)	1.78	(1.73, 1.83)
MetS	1.47	(1.29, 1.68)	1.32	(1.15, 1.51)
Abnormal WC†	1.37	(1.09, 1.74)	1.28	(1.13, 1.46)
Hypertriglyceridemia‡	1.58	(1.24, 2.01)	1.34	(1.17, 1.52)
Low HDL§	0.90	(0.66, 1.23)	1.05	(0.89, 1.23)
High Blood Pressure‖	1.73	(1.36, 2.21)	1.12	(0.99, 1.28)
Glycemia				
100-125	1.39	(1.04, 1.85)	1.27	(1.08, 1.48)
≥126	1.00	(0.65, 1.56)	0.93	(0.75, 1.04)

f-Hb = fecal hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.

* The results of the individual components of MetS in the multivariable analysis are from another model in which MetS was not included.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

‡ Hypertriglyceridemia, ≥150 mg/dL.

§ Low HDL, <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.

‖ High blood pressure, ≥130/85 mmHg.

The effect of MetS on colorectal adenoma was statistically significant in both genders (Table 3). In males, the crude HR was 1.39 (95% CI: 1.17–1.64), and the adjusted hazard ratio (aHR) was 1.33 (95% CI: 1.13–1.58) after adjustment for age, smoking, alcohol consumption and f-Hb concentration. The corresponding figures for females were 1.50 (95% CI: 1.21–1.87) and 1.33 (95% CI: 1.06–1.66) after adjustment for age and f-Hb concentration.

The effect of each component of MetS on colorectal adenoma varied with gender (Table 3). For males, an abnormal waist circumference (aHR = 1.25 95% CI: 1.06–1.47) and hypertriglyceridemia (≥150 mg/dL; aHR = 1.36; 95% CI: 1.16–1.60) led to a significant increase in colorectal adenoma after adjustment for confounding factors. However, an abnormal waist circumference (aHR = 1.38 95% CI: 1.12–1.71), hypertriglyceridemia (≥150 mg/dL; aHR = 1.31; 95% CI: 1.05–1.62) and a moderately higher level of glycemia (100–125 mg/dL, aHR = 1.44, 95% CI: 1.12–1.85) contributed to a higher risk of colorectal adenoma in females.

Furthermore, we found that the effect of MetS on colorectal advanced adenoma was also statistically significant, with an increased risk of 50% (95% CI: 17%–92%), compared to those without MetS (Table 4). MetS status was associate with an elevated risk of advanced adenoma after considering other significant confounding factors, including age, sex, smoking status, alcohol consumption and f-Hb concentration, with an HR of 1.34 (95% CI: 1.04–1.72). All individual components of MetS except for low HDL cholesterol increased the risk of colorectal advanced adenoma. Hypertriglyceridemia (aHR = 1.32; 95% CI: 1.04–1.69) and high blood pressure (aHR = 1.35; 95% CI: 1.05–1.73) were associated with a risk of advanced adenoma.

Table 5 shows the impact of MetS on advanced adenoma by gender. The results show that MetS increased the risk of advanced adenoma in men in terms of dichotomous type (aHR =

Table 3

Hazard ratio (95% CI) of metabolic syndrome and other risk factors for colorectal adenoma by gender.

	HR	95% CI	aHR*	95% CI
Male				
Age	1.02	(1.02, 1.03)	1.01	(1.00, 1.02)
Smoking	1.33	(1.13, 1.56)	1.22	(1.03, 1.46)
Betel quid chewing	1.04	(0.82, 1.32)		
Drinking	1.32	(1.12, 1.54)	1.25	(1.06, 1.48)
Physical activity	0.89	(0.74, 1.06)		
Meat intake	0.89	(0.74, 1.08)		
Vegetable intake	1.01	(0.85, 1.20)		
Family history of CRC	1.17	(0.72, 1.89)		
f-Hb concentration	1.84	(1.78, 1.90)	1.82	(1.76, 1.89)
MetS	1.39	(1.17, 1.64)	1.33	(1.13, 1.58)
Abnormal WC†			1.25	(1.06, 1.47)
Hypertriglyceridemia‡			1.36	(1.16, 1.60)
Low HDL§			0.94	(0.75, 1.17)
High Blood Pressure‖			1.17	(0.99, 1.38)
Glycemia				
100–125			1.15	(0.95, 1.40)
≥126			0.87	(0.66, 1.16)
Female				
Age	1.02	(1.01, 1.03)	1.00	(0.99, 1.01)
Smoking	0.95	(0.63, 1.44)		
Drinking	0.88	(0.60, 1.31)		
Physical activity	1.15	(0.94, 1.41)		
Meat intake	0.92	(0.70, 1.20)		
Vegetable intake	0.94	(0.76, 1.16)		
Family history of CRC	1.18	(0.63, 2.21)		
f-Hb concentration	1.71	(1.64, 1.79)	1.71	(1.63, 1.78)
MetS	1.50	(1.21, 1.87)	1.33	(1.06, 1.66)
Abnormal WC†			1.38	(1.12, 1.71)
Hypertriglyceridemia‡			1.31	(1.05, 1.62)
Low HDL§			1.19	(0.95, 1.50)
High Blood Pressure			1.07	(0.87, 1.32)
Glycemia				
100–125			1.44	(1.12, 1.85)
≥126			1.05	(0.74, 1.51)

f-Hb = fecal hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.

* The results of individual components of MetS in the multivariable analysis are from another model in which MetS was not included.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

‡ Hypertriglyceridemia, ≥150 mg/dL.

§ Low HDL, <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.

‖ High blood pressure, ≥130/85 mmHg.

Table 4

Hazard ratio (95% CI) of metabolic syndrome and other risk factors for advanced colorectal adenoma.

	HR	95% CI	aHR*	95% CI
Age	1.03	(1.02, 1.04)	1.00	(0.99, 1.01)
Sex	3.08	(2.41, 3.95)	2.20	(1.63, 2.97)
Smoking	2.43	(1.92, 3.06)	1.28	(0.96, 1.70)
Betel quid chewing	1.26	(0.78, 2.03)		
Drinking	2.14	(1.68, 2.71)	1.22	(0.92, 1.61)
Physical activity	0.78	(0.60, 1.01)		
Meat intake	0.91	(0.68, 1.23)		
Vegetable intake	1.12	(0.87, 1.45)		
Family history of CRC	1.41	(0.73, 2.73)		
f-Hb concentration	1.88	(1.78, 1.98)	1.84	(1.75, 1.94)
MetS	1.50	(1.17, 1.92)	1.34	(1.04, 1.72)
Abnormal WC†	1.37	(1.09, 1.74)	1.26	(0.99, 1.61)
Hypertriglyceridemia‡	1.58	(1.24, 2.01)	1.32	(1.04, 1.69)
Low HDL§	0.90	(0.66, 1.23)	0.98	(0.72, 1.33)
High Blood Pressure‖	1.73	(1.36, 2.21)	1.35	(1.05, 1.73)
Glycemia				
100-125	1.39	(1.04, 1.85)	1.22	(0.91, 1.62)
≥126	1.00	(0.65, 1.56)	0.79	(0.51, 1.23)

f-Hb = fecal hemoglobin, HDL = high-density, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.

* The results of individual components of MetS in the multivariable analysis are from another model in which MetS was not included.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

‡ Hypertriglyceridemia, ≥150 mg/dL.

§ Low HDL, <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.

‖ High blood pressure, ≥130/85 mmHg.

1.36, 95% CI: 1.01–1.83). For females, the corresponding effect was marginally statistically significant for MetS (aHR = 1.20, 95% CI: 0.75–1.90). Hypertriglyceridemia remained statistically significantly associated with a higher risk of advanced adenoma in males (aHR = 1.42, 95% CI: 1.06–1.90). Nevertheless, high blood pressure was accompanied with elevated risk of advanced adenoma in males (aHR = 1.54, 95% CI: 1.12–2.11). None of the individual MetS components was associated with the risk of advanced adenoma in females.

4. Discussion

Although several studies have already shown an association between MetS and colorectal neoplasia,[1–9,18,25] few studies were proposed to corroborate the temporal relationship between MetS (cause) and colorectal adenoma (consequence). We conducted a large population-based cohort study to confirm the cause of MetS leading to the occurrence of colorectal adenoma to demonstrate that a temporal relationship plays an important role in the reduction of the risk of colorectal cancer with a potential lifestyle modification program for the improvement of the metabolic factor profiles composing MetS.

In addition to the clarifying the temporal relationship, the innovative part of the present study in contrast to previous studies[1–9,25] is that it showed that MetS is an independent risk factor after controlling for the most important risk factor, f-Hb concentration, for colorectal adenoma and advance adenoma,[24,26] and it identified the gender-specific relationship between incident colorectal adenoma and MetS. Our study found that the presence of MetS led to a 33% elevated risk of colorectal adenoma in both genders, but the contribution of individual components of MetS was different between males and females. Hypertriglyceridemia and an abnormal waist ratio relative to others played more important roles in males, whereas hyperglycemia seemed to be the most significant factor leading to colorectal adenoma in females.

4.1. MetS and colorectal adenoma

The finding that MetS is a risk factor for adenoma was consistent with the findings of previous studies.[1,2,18,25,27–30] In contrast to other studies that either considered only CRC or the prevalence of adenoma as the main outcome, our study first identified MetS as a risk factor for colorectal adenoma with a distinct temporal relationship. This effect was further intensified by the additional finding that a greater number of individual components led to an elevated risk of colorectal adenoma suggesting, a dose-response effect.

4.2. Individual components of MetS and colorectal adenoma

As far as the results regarding gender difference are concerned, previous studies found an association between obesity and CRC or adenoma both in men and women.[18,31,32] Abdominal obesity was also mentioned as positively associated with CRC.[33] Our results also showed a positive relationship between an abnormal waist circumference and adenoma in both genders (aOR = 1.25, 95% CI: 1.06–1.47 in men and aOR = 1.38, 95% CI: 1.12–1.71 in women). However, a higher level of glycemia as an additional risk factor associated with an increased risk of colorectal adenoma for females was noted in our study. Colorectal cancer and insulin resistance have common risk factors. By using a rat model, Koohestani [34] demonstrated the relationship between insulin resistance and colorectal cancer proposed by McKeown-Eyssen and Giovannucci,[31,35] demonstrating a biologically plausible mechanism for increased CRC risk among persons with type 2 DM.

Table 5

Hazard ratio (95% CI) of metabolic syndrome and other risk factors for advanced colorectal adenoma by gender.

	HR	95% CI	aHR*	95% CI
Male				
Age	1.02	(1.01, 1.03)	1.01	(1.00, 1.02)
Smoking	1.52	(1.13, 2.05)	1.30	(0.95, 1.79)
Betel quid chewing	0.77	(0.48, 1.26)		
Drinking	1.54	(1.15, 2.04)	1.39	(1.03, 1.89)
Physical activity	0.72	(0.51, 1.01)		
Meat intake	0.89	(0.63, 1.25)		
Vegetable intake	1.00	(0.73, 1.37)		
Family history of CRC	0.89	(0.33, 2.40)		
f-Hb concentration	1.95	(1.82, 2.08)	1.93	(1.81, 2.06)
MetS	1.49	(1.10, 2.00)	1.36	(1.01, 1.83)
Abnormal WC†			1.23	(0.92, 1.64)
Hypertriglyceridemia‡			1.42	(1.06, 1.90)
Low HDL§			0.71	(0.45, 1.10)
High Blood Pressure‖			1.54	(1.12, 2.11)
Glycemia				
100-125			1.17	(0.83, 1.66)
≥126			0.82	(0.49, 1.38)
Female				
Age	1.02	(1.00, 1.03)	1.00	(0.98, 1.02)
Smoking	0.98	(0.43, 2.24)		
Drinking	0.39	(0.12, 1.23)		
Physical activity	1.13	(0.75, 1.71)		
Meat intake	0.61	(0.33, 1.15)		
Vegetable intake	1.20	(0.77, 1.86)		
Family history of CRC	2.50	(1.01, 6.14)	2.70	(1.09, 6.70)
f-Hb concentration	1.69	(1.54, 1.84)	1.68	(1.54, 1.84)
MetS	1.34	(0.86, 2.09)	1.20	(0.75, 1.90)
Abnormal WC†			1.40	(0.91, 2.17)
Hypertriglyceridemia‡			1.15	(0.73, 1.82)
Low HDL§			1.54	(0.98, 2.41)
High Blood Pressure‖			1.05	(0.68, 1.61)
Glycemia				
100-125			1.30	(0.78, 2.19)
≥126			0.73	(0.31, 1.69)

f-Hb = fecal hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome, WC = waist circumference.

* The results of individual components of MetS in the multivariable analysis are from another model in which MetS was not included.

† Abnormal waist circumference, >90 cm in men and >80 cm in women.

‡ Hypertriglyceridmia, ≥150 mg/dL.

§ Low HDL, <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women.

‖ High blood pressure, ≥130/85 mmHg.

Some animal models have also shown that colonocytes under the circumstances of insulin resistance over prolonged periods lead to hyperinsulinemia, hyperglycemia, and elevated levels of triglycerides, nonesterified fatty acids, and insulin-like growth factor-1 (IGF-1). Thus, the positive association between hypertriglyceridemia and colorectal adenoma in both genders found in current study could also be explained. Such exposure could affect the growth, development, and homeostasis of colonic cells.[31,35] In this context, it is interesting to note that insulin promotes the growth of aberrant crypt foci (ACF) at 100 days after initiation in animals.[36,37] In an in vivo study,[38] intravenous infusion of insulin to rats further increased the proliferation of 5-bromo-2-deoxyuridine labeling of replicating DNA in colorectal epithelial cells. Many studies show that adult-onset DM is associated with a higher risk of CRC.[39–42] Some studies found that man with DM had a statistically increased risk of CRC after adjusting for potential confounders in a cohort of Swedish men.[41,43] For the premalignant state of CRC, the risk of a moderate level of blood glucose (prediabetes status, 100–126 mg/dL) was significant in women (OR = 1.78, 95% CI: 1.16–2.75).[44] The result may be due to an early promoting effect of abnormal glucose to the adenoma-adenocarcinoma sequence under the insulin resistance-colorectal cancer hypothesis. A prospective study found a cluster of 3 IRS-related conditions with a significantly increased risk of CRC (HR = 1.40, 95% CI: 1.12–1.74).[45] The IOWA Women's Health Study confirmed that type 2 DM leads to an elevated risk of CRC. However, we found a null association between DM and colorectal adenoma in both men and women, whereas a significant association of pre-DM in women was found. Menopause status may be linked to insulin-mediated growth regulation pathways and thus could have affected colorectal carcinogenesis.[46]

Hyperinsulinemia is a possible link between diabetes and CRC. Some studies have shown that insulin is an important growth factor for colonic mucosal cells and stimulates colonic tumor cells.[47,48] Plasma concentrations of insulin-like growth factor (IGF-I) and IGF binding protein-3 (IGFBP-3) have been shown to influence the risk of CRC in a prospective follow-up study.[47] In their study, they found that subjects with values of IGF-I in the highest quintile were 2.5-fold more likely to develop colorectal cancer (CRC) than those with values in the lowest quintile. In contrast, increased plasma concentrations of IGFBP-3 were protective.

4.3. Individual components of MetS and colorectal advance adenoma

We found that men with hypertriglyceridemia and high blood pressure were more likely to have advanced adenoma, but none of the individual components was associated with advanced adenoma in women. In addition to hypertriglyceridemia, whether high blood pressure is a possible risk factor for disease progression remains unclear. However, a cross-sectional study revealed the use of antihypertensive drugs was associated with the risk of colorectal polyps.[49] Men are known to have higher blood pressure than women.[50] The more frequent use of antihypertensive drugs in men could be one of the possible reasons for this.

The study limitations included that the results of our study were derived from Taiwanese individuals older than 40 years; thus, the generalization of our results to other populations should be limited, and other confounding factors, particularly individual gene information, were not collected and included in our analysis.

In conclusion, an effect of MetS on colorectal adenoma was observed in both genders in a community-based study, whereas the contribution of the individual components of MetS differed between men and women. These findings suggest that a possible risk reduction in colorectal adenoma occurs through metabolic-syndrome-based lifestyle modifications and may take sex differences into account.

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