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Association Between Metabolic Syndrome and the Risk of Colorectal Cancer Diagnosed Before Age 50 Years According to Tumor Location

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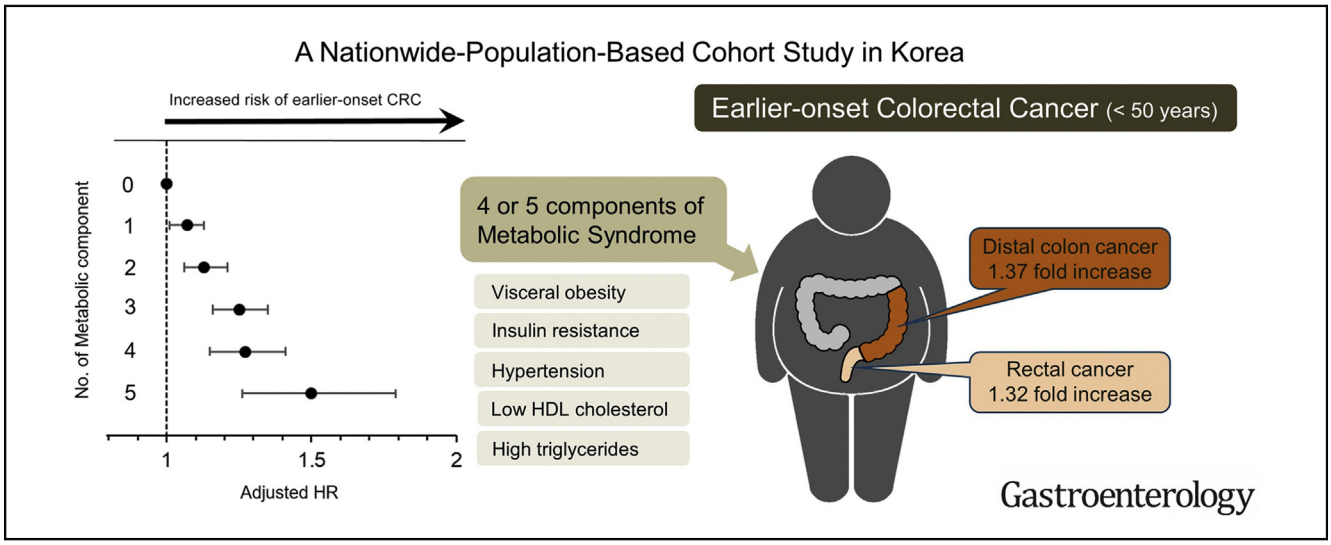

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BACKGROUND & AIMS: The increasing prevalence of obesity at younger ages is concurrent with an increased earlier-onset colorectal cancer (CRC) (before age 50 years) incidence, particularly left-sided colon cancer. We investigated whether obesity and metabolic syndrome (MetS) are associated with increased earlier-onset CRC risk according to tumor location. **METHODS:** Our nationwide population-based cohort study enrolled 9,774,081 individuals who underwent health checkups under the Korean National Health Insurance Service from 2009 to 2010, with follow-up until 2019. We collected data on age, sex, lifestyle factors, body mass index (BMI), waist circumference (WC), blood pressure, and laboratory findings. A multivariate Cox proportional hazards regression analysis was performed. **RESULTS:** A total of 8320 earlier-onset and 57,257 later-onset CRC cases developed during follow-up. MetS was associated with increased earlier-onset CRC (adjusted hazard ratio, 1.20; 95% CI, 1.14–1.27), similar to later-onset CRC (adjusted hazard ratio, 1.19; 95% CI, 1.17–1.21). The adjusted hazard ratios for earlier-onset CRC with 1, 2, 3, 4, and 5 MetS components were 1.07 (95% CI, 1.01–1.13), 1.13 (95% CI, 1.06–1.21), 1.25 (95% CI, 1.16–1.35), 1.27 (95% CI, 1.15–1.41), and 1.50 (95% CI, 1.26–1.79), respectively (P for trend $<$ .0001). We found that higher body mass index and larger waist circumference were significantly associated with increased earlier-onset CRC (P for trend $<$ .0001). These dose–response associations were significant in distal colon and rectal cancers, although not in proximal colon cancers. **CONCLUSIONS:** MetS and obesity are positively associated with CRC before age 50 years with a similar magnitude of association as people diagnosed after age 50 years. Thus, people younger than 50 years with MetS require effective preventive interventions to help reduce CRC risk.

Keywords: Earlier-Onset Colorectal Cancer; Metabolic Syndrome; Obesity; Waist Circumference; Epidemiology.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer deaths worldwide.[1] The overall CRC incidence and associated mortality have decreased gradually in patients 50 years and older, owing to the combination of screening uptake and favorable changes in modifiable risk factors and improvements in treatment.[2,3] Despite the decreasing CRC trend in adults after age 50 years, an increasing trend in earlier-onset CRC (before age 50 years) has been observed globally since the mid-1990s.[4,5] The cancer registration data of 42 countries from 2008–2012 indicate that the incidence of earlier-onset CRC was the highest in South Korea (12.9/100,000).[4] Furthermore, incidence of earlier-onset CRC in Korea increased more rapidly (average annual percentage change [AAPC], 4.2) than in the United States (AAPC, 2.2).[4] According to the Korean Central Cancer Registry (1999–2014), the incidence of earlier-onset CRC increased in both men (colon cancer: AAPC, 4.7; rectal cancer: AAPC, 6.0) and women (colon cancer: AAPC, 5.5; rectal cancer: 4.8).[6]

Compared with later-onset CRC (50 years and older), earlier-onset CRC is characterized by an advanced stage at diagnosis and displays unfavorable features, including poor cell differentiation, signet ring cell differentiation, and perineural invasion.[7] Earlier-onset CRC occurs mainly in the rectum or distal colon (left-sided colon) and, in older age groups (65 years and older), one-half of all CRC cases are in the proximal colon.[5] Owing to these distinct features of earlier-onset CRCs, many researchers have investigated the risk factors for CRC in young adults. Recent research has found that sedentary behaviors,[8] consumption of sugar-sweetened beverages,[9] obesity,[10] and metabolic syndrome (MetS)[11] may contribute to development of earlier-onset CRCs. Meanwhile, in recent decades, the global young obese population has increased concurrently with changes in lifestyle and dietary patterns.[12] The prevalence of MetS has also increased significantly among the younger age groups (younger than 40 years) from 16.2% in 2011 to 21.3% in 2016.[13] We note here that MetS is the key component linking obesity to CRC, which is mediated through insulin resistance and adipokines.[14]

Because earlier-onset CRC occurs mainly in the left colon, further investigations are needed to examine whether MetS and obesity in young populations act differently according to the tumor's anatomic location; however, no studies have been conducted on this topic. Against this backdrop, in this study, using the nationally representative data of 9.8 million Korean adults, we evaluated the association of MetS and obesity with earlier-onset CRC risk according to anatomic subsites.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Colorectal cancer is rapidly increasing in younger populations (earlier-onset colorectal cancer; younger than 50 years); however, differences in the tumor location–based effects of risk factors have not been examined thus far.

NEW FINDINGS

Among 8320 earlier-onset colorectal cancer cases, metabolic syndrome and obesity were positively associated with earlier-onset colorectal cancer, particularly in the distal colon and rectum, but not the proximal colon.

LIMITATIONS

This is a population-based study that covered Korea only. Larger studies involving various races are required to validate these findings.

IMPACT

Our findings suggest that the recent, rapid increase in the incidence of obesity and metabolic syndrome in young adults is probably associated with the increasing incidence of earlier-onset colorectal cancer.

Methods

Study Design

This retrospective, population-based cohort was conducted using the South Korean population database provided by the National Health Insurance Service (NHIS). We included those who underwent health checkups administered by the NHIS between January 1, 2009 and December 31, 2010 (index year). We tracked them until the end of 2019 to identify newly developed CRCs. Our study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB X-2007-627-905). All procedures involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Requirements for informed consent were waived because the data were publicly available and deidentified.

National Health Insurance Service Database and Health Checkup Program

As a nonprofit institution supervised by the Ministry of Health and Welfare, the NHIS is a single insurer providing health insurance to all resident Korean citizens (approximately 50 million).[15] The NHIS is responsible for implementing a health insurance program that manages the eligibility of the insured, collects insurance contributions, estimates medical-service fees, and provides health insurance benefits, including health checkups.[16] The NHIS provides a biannual free health checkup program for all insured Koreans. All Koreans are obliged to subscribe to compulsory health insurance and pay income-based insurance contributions. The NHIS database

Abbreviations used in this paper: **aHR, adjusted hazard ratio; AAPC, average annual percentage change; BMI, body mass index; CRC, colorectal cancer; DM, diabetes mellitus; HDL, high-density lipoprotein; ICD-10-CM, *International Classification of Disease, 10th Revision, Clinical Modification*; LDL, low-density lipoprotein; MetS, metabolic syndrome; NHIS, National Health Insurance Service; WC, waist circumference.**

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contains the health information of all insured individuals: demographic data (age, sex, and region), socioeconomic variables (income), and health checkup and claims data (diagnosis, prescription, and procedure records). All data are publicly available for researchers to use after study-protocol approval by the official review committee.[17] As this database represents the entire South Korean population, it can be used as the basis of a nationwide population-based study. Details on the NHIS have been reported previously.[18,19]

Study Population

The enrollment process of this cohort is presented in Figure 1. We initially considered 10,585,843 individuals who underwent health checkups between 2009 and 2010 (Figure 1). Overall, 623,112 individuals were excluded, owing to incomplete data. We excluded 155,071 individuals diagnosed with any malignancy before 2009 and 33,579 individuals diagnosed with CRC within 1 year of enrollment to avoid including patients with pre-existing CRC. We categorized the remaining patients into 2 age-specific groups at enrollment and tracked them until December 31, 2019. Eventually, 5,672,153 participants aged 20–49 years were enrolled, and participants were censored when they reached age 50 years. Among censored participants, 5536 individuals (50 years and older) were diagnosed with CRC. We included 4,101,928 participants 50 years and older.

Data Collection

The NHIS health checkup programs include anthropometric measurements, laboratory tests, health-behavior surveys (eg, smoking, alcohol consumption, and regular exercise), and medical and family history.[15,19] Height, weight, waist circumference (WC), and blood pressure are measured by trained examiners during the health checkup.[19] WC is measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.[20] After at least 5 minutes of rest in the sitting position, brachial blood pressure is measured by a trained clinician using a sphygmomanometer or oscillometer with an appropriately sized cuff.[21] Blood sampling is conducted after an overnight fast lasting at least 8 hours, and serum levels of glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol are measured. The laboratory test quality is certified by the Korean Association for Laboratory Medicine, and the NHIS certifies the hospitals participating in the health checkup programs. Health behaviors are assessed using a standardized self-reported questionnaire at enrollment. Smoking status is surveyed based on participant smoking status at the time of the study (ie, nonsmoker, past smoker, and current smoker) and pack-years are derived. Alcohol consumption is defined based on the frequency of intake per week and the amount consumed per drinking episode. Alcohol consumption is categorized as none, moderate (<30 g/d), or heavy (≥30 g/d). The questionnaire on exercise comprises items on the frequency (days per week) of light, moderate, and vigorous exercise in recent weeks.[22] Regular exercise is defined as vigorous-intensity exercise 3 or more times per week or moderate-intensity exercise 5 or more times per week.[23]

Colorectal Cancer Ascertainment

The primary outcome was newly diagnosed CRC before age 50 years (earlier-onset). CRC was coded as C18–20, based on the *International Classification of Disease, 10th Revision, Clinical Modification* (ICD-10-CM) codes (C18.0–18.4 for proximal colon cancer; C18.5–18.7, C19.0 for distal colon cancer; C20.0 for rectal cancer and the registration code for cancer [V193]). In the tumor subsite–based subgroup analysis, malignant neoplasms in overlapping sites in the colon (C18.8) and unspecified colon cancer (C18.9) were excluded because they were not single-location–specific.

Obesity and Abdominal Obesity Definitions

Body mass index (BMI) was calculated as the weight (kg) divided by height in meters squared (m^2). We defined obesity as a BMI of ≥25 kg/m^2 and categorized patients into underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), obese (25–29.9 kg/m^2), or severely obese (≥30 kg/m^2) groups based on World Health Organization recommendations for Asian people.[24] WC was categorized into 5 levels at 10-cm WC intervals: <70, 70–79.9 (reference category), 80–89.9, 90–99.9, and ≥100 cm in men and <65, 65–74.9 (reference category), 75–84.9, 85–94.9, and ≥95 cm in women. Abdominal obesity was defined as WC ≥90 cm in men and ≥85 cm in women, according to the definition of the Korean Society for the Study of Obesity.[25]

Metabolic Syndrome and Comorbidity Ascertainment

MetS was defined using the harmonized International Diabetes Federation criteria, and the Korean-specific WC cutoff was adopted for abdominal obesity.[25,26] To define each MetS component, anthropometric measurements and laboratory data of the NHIS health checkup and claim data for the definition of comorbid diseases were used. Individuals with at least 3 of the 5 following components were diagnosed with MetS: WC of ≥85 cm in women or ≥90 cm in men, fasting plasma glucose of ≥100 mg/dL or drug treatment for diabetes mellitus (DM), blood pressure of ≥130/85 mm Hg or drug treatment for hypertension, serum HDL-C of <50 mg/dL in women or <40 mg/dL in men, and serum triglyceride of ≥150 mg/dL.

Comorbidities related to MetS (eg, hypertension, DM, and dyslipidemia) were identified from NHIS health checkup and claims data. Hypertension was defined based on ICD-10-CM codes I10–I13 or I15, the presence of a claim for prescriptions of antihypertensive medications, or documented blood pressure of ≥140/90 mm Hg in the index year. DM was defined based on ICD-10 codes E11–E14, fasting glucose level of ≥126 mg/dL, or at least 1 annual claim for prescriptions of medications for diabetes. Dyslipidemia was defined based on ICD-10 code E78, serum total cholesterol level of ≥240 mg/dL, or at least 1 annual claim for prescriptions of lipid-lowering medications.

Statistical Analysis

We evaluated the association between MetS and earlier-onset CRC risk and examined the dose–response relationship between the prevalence of MetS and earlier-onset CRC risk. Secondarily, we investigated the association between obesity

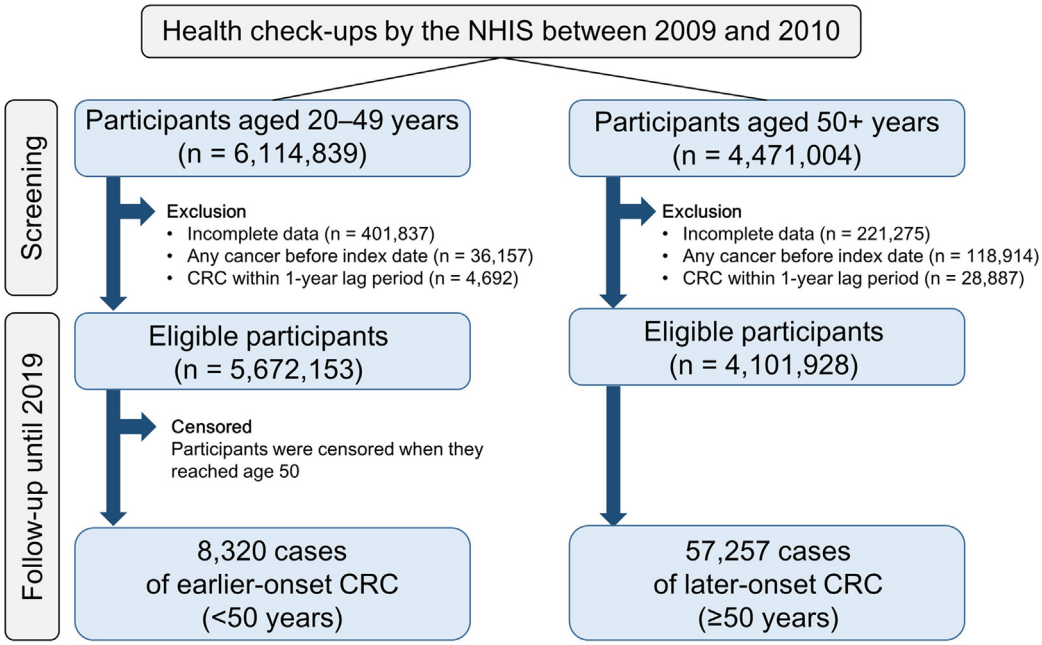

Figure 1. Flowchart showing the enrollment process for the study cohort.

and abdominal obesity and earlier-onset CRC risk using the BMI and WC classification. Subgroup analyses of the associations were performed according to the anatomic sites (ie, proximal colon, distal colon, and rectum).

We presented the baseline characteristics of this study population using descriptive statistics and compared them using independent t test and χ^2 test. The incidence rates of the outcomes were calculated by dividing the number of events by the total person-years of follow-up. Multivariable Cox proportional hazard regression analyses were performed to estimate hazard ratios and 95% CIs. Model 1 was unadjusted, model 2 was adjusted for age (year) and sex (male vs female), and model 3 was further adjusted for smoking status (never, former, or current), alcohol consumption (none, moderate, or heavy), regular exercise (yes vs no), and low income (based on the lowest quintile). Linear trend tests were tested on variables of interest defined on continuous scales. To examine whether the association between MetS and CRC risk differed by anatomic site, hazard ratios and 95% CIs were estimated using a multivariable Cox proportional hazard model, which accounted for tumors located at different anatomic sites as competing risks. We also performed a heterogeneity test within the main subsites (proximal colon, distal colon, and rectum). We performed an interaction analysis for age (20–29, 30–39, and 40–49 years) and sex (male, female) using the Wald test. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC), and results with 2-sided P-values $< .05$ were considered significant.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of the participants based on the presence or absence of MetS. Among the 5,672,153 enrolled individuals aged 20–49 years, 855,948 (15.1%) were diagnosed with MetS. Individuals with MetS aged 20–49 years were predominantly male (79.8%) and exhibited higher rates of current smoking (44.5%) and heavy alcohol drinking (15.7%) compared with the non-MetS group. Among 4,101,928 enrolled individuals 50 years and older, 1,589,581 (38.8%) were diagnosed with MetS.

Earlier-Onset Colorectal Cancer Risk According to the Presence of Metabolic Syndrome and its Components

Among the 5,672,153 enrolled individuals aged 20–49 years, 8320 cases of earlier-onset CRC were documented (median age at diagnosis, 46.0 years; interquartile range, 41.0–49.0 years) for a median of 9.1 years of follow-up. MetS (3 or more components) was associated with an increased risk of earlier-onset CRC development (adjusted hazard ratio [aHR], 1.20; 95% CI, 1.14–1.27) after adjusting for sex, age, smoking, alcohol consumption, regular exercise, and low-income status (Table 2). Apart from high HDL-C, all single MetS components were associated with an increased risk of earlier-onset CRC. In particular, increased WC was most significantly associated with earlier-onset CRC development (aHR 1.23; 95% CI, 1.16–1.30). The number of MetS components was positively associated with the risk of earlier-onset CRC. Compared with individuals without any metabolic component, those with 1, 2, 3, 4, or 5 metabolic components had a 7% (aHR, 1.07; 95% CI, 1.01–1.13), 13% (aHR, 1.13; 95% CI, 1.06–1.21), 25% (aHR, 1.25; 95% CI, 1.16–1.35), 27% (aHR, 1.27; 95% CI, 1.15–1.41), and 50% (aHR, 1.50; 95% CI, 1.26–1.79) higher risk of earlier-onset CRC (P for trend $< .0001$), respectively.

Table 1. Baseline Characteristics of Enrolled National Health Insurance Service Cohort, 2009–2010

Characteristic	Participants aged 20–49 y		Participants aged 50+ y	
	Non-MetS (n = 4,816,205)	MetS (n = 855,948)	Non-MetS (n = 2,512,347)	MetS (n = 1,589,581)
Sex (male), n (%)	2,684,271 (55.7)	683,169 (79.8)	1,232,930 (49.1)	747,819 (47.1)
Age at recruitment, n (%)				
20–29 y	1,118,514 (23.2)	69,201 (8.1)	—	—
30–39 y	1,606,636 (33.4)	279,466 (32.6)	—	—
40–49 y	2,091,055 (43.4)	507,281 (59.3)	—	—
50–59 y	—	—	1,413,571(56.3)	659,884 (41.5)
60–69 y	—	—	730,360 (29.1)	581,002 (36.6)
≥70 y	—	—	368,416 (14.7)	348,695 (21.9)
Current smoker, n (%)	1,465,519 (30.4)	381,048 (44.5)	460,693 (18.3)	263,194 (16.6)
Heavy alcohol drinker (≥30 g/d), n (%)	385,323 (8.0)	134,700 (15.7)	151,878 (6.1)	112,655 (7.1)
Regular exercise,[a] n (%)	742,736 (15.4)	136,986 (16.0)	536,420 (21.4)	328,491 (20.7)
Low income,[b] n (%)	690,340 (14.3)	104,246 (12.2)	442,257 (17.6)	274,455 (17.3)
BMI, kg/m^2, mean ± SD	22.8 ± 3.0	26.8 ± 3.4	23.3 ± 3.1	25.5 ± 3.8
WC, *cm*, mean ± SD	77.0 ± 8.7	88.6 ± 9.4	79.6 ± 7.6	86.5 ± 8.6
Systolic blood pressure, *mm Hg*, mean ± SD	117.4 ± 12.7	131.0 ± 13.5	123.1 ± 15.2	132.1 ± 15.4
Diastolic blood pressure, *mm Hg*, mean ± SD	73.8 ± 9.2	82.7 ± 10.0	76.3 ± 9.9	80.6 ± 10.1
Fasting glucose, *mg/dL*, mean ± SD	90.9 ± 15.1	109.8 ± 33.7	95.7 ± 20.2	112.3 ± 33.6
Total cholesterol, *mg/dL*, mean ± SD	188.0 ± 36.8	207.0 ± 47.5	200.2 ± 39.4	203.8 ± 49.5
Triglycerides, *mg/dL*, mean ± SD	111.3 ± 76.3	236.3 ± 138.6	114.7 ± 65.6	185.4 ± 109.8
HDL-C, *mg/dL*, mean ± SD	58.5 ± 30.9	47.8 ± 29.3	58.7 ± 36.0	51.3 ± 33.2
LDL-C, *mg/dL*, mean ± SD	122.1 ± 294.3	118.7 ± 164.3	122.4 ± 70.4	119.0 ± 91.1
Hypertension, n (%)	369,353 (7.7)	344,952 (40.3)	708,714 (28.2)	1,096,478 (69.0)
Diabetes mellitus, n (%)	83,104 (1.7)	140,454 (16.4)	156,846 (6.2)	470,073 (29.6)
Dyslipidemia, n (%)	343,381 (7.1)	264,281 (30.9)	351,417 (14.0)	809,804 (50.9)

LDL-C, low-density lipoprotein cholesterol.
[a]Regular exercise was defined as vigorous-intensity exercise 3 or more times per week or moderate-intensity exercise 5 or more times per week.
[b]Low income was defined as the lowest quintile.

Later-Onset Colorectal Cancer Risk According to the Presence of Metabolic Syndrome and its Components

Among 4,101,928 enrolled individuals 50 years and older, 57,257 cases of later-onset CRC were diagnosed for a median of 9.4 years of follow-up. Similar to earlier-onset CRC, MetS (3 or more components) was associated with an increased risk of later-onset CRC development (aHR, 1.19; 95% CI, 1.17–1.21) after adjusting for confounding factors (Table 3). All single MetS components were associated with an increased risk of later-onset CRC. Compared with individuals without any metabolic component, those with 1, 2, 3, 4, or 5 metabolic components had a 10% (aHR, 1.10; 95% CI, 1.06–1.13), 22% (aHR, 1.22; 95% CI, 1.18–1.26), 31% (aHR, 1.31; 95% CI, 1.27–1.35), 36% (aHR, 1.36; 95% CI, 1.32–1.41), and 49% (aHR, 1.49; 95% CI, 1.43–1.55) higher risk of later-onset CRC (P for trend $< .0001$), respectively.

Earlier-Onset Colorectal Cancer Risk According to Tumor Location

MetS (vs non-MetS) was significantly associated with increased risk of earlier-onset CRC across anatomic subsites (P for heterogeneity $=.222$) (Figure 2, Supplementary Table 1). The sum of the MetS components showed a positive association with a higher risk of earlier-onset distal colon and rectal cancer, although not for proximal colon

Table 2. Incidence and Risk of Earlier-Onset Colorectal Cancer According to the Components of Metabolic Syndrome Among Participants Aged 20–49 years (National Health Insurance Service 2009–2019)

Variable	Cases	Person-years	IR[a]	Model 1,[b] HR (95% CI)	Model 2,[c] HR (95% CI)	Model 3,[d] HR (95% CI)
WC						
Male < 90 cm, female < 85 cm	6748	35,924,166	0.19	1 (ref)	1 (ref)	1 (ref)
Male ≥ 90 cm, female ≥ 85 cm	1572	5,822,889	0.27	1.43 (1.35–1.51)	1.24 (1.17–1.31)	1.23 (1.16–1.30)
P value	—	—	—	<.0001	<.0001	<.0001
Fasting glucose						
Normal	5985	32,662,913	0.18	1 (ref)	1 (ref)	1 (ref)
High[e]	2335	9,084,142	0.26	1.39 (1.32–1.45)	1.09 (1.03–1.14)	1.08 (1.03–1.13)
P value	—	—	—	<.0001	.001	.003
Blood pressure						
Normal	5279	29,489,488	0.18	1 (ref)	1 (ref)	1 (ref)
High[f]	3041	12,257,567	0.25	1.38 (1.32–1.44)	1.13 (1.08–1.19)	1.13 (1.07–1.18)
P value	—	—	—	<.0001	<.0001	<.0001
HDL-C						
Male ≥40 mg/dL, female ≥50 mg/dL	6582	34,318,204	0.19	1 (ref)	1 (ref)	1 (ref)
Male <40 mg/dL, female <50 mg/dL	1738	7,428,852	0.23	1.21 (1.15–1.28)	1.04 (0.98–1.09)	1.04 (0.99–1.10)
P value	—	—	—	<.0001	.179	.149
Triglycerides						
<150 mg/dL	5392	30,302,362	0.18	1 (ref)	1 (ref)	1 (ref)
≥150 mg/dL	2928	11,444,694	0.26	1.43 (1.37–1.50)	1.14 (1.09–1.20)	1.13 (1.08–1.18)
P value	—	—	—	<.0001	<.0001	<.0001
MetS (≥3 components)[g]						
No	6651	36,156,598	0.18	1 (ref)	1 (ref)	1 (ref)
Yes	1669	5,590,457	0.30	1.60 (1.52–1.69)	1.21 (1.15–1.28)	1.20 (1.14–1.27)
P value	—	—	—	<.0001	<.0001	<.0001
No. of MetS components						
0	2500	16,381,098	0.15	1 (ref)	1 (ref)	1 (ref)
1	2423	12,449,785	0.19	1.27 (1.20–1.34)	1.07 (1.01–1.13)	1.07 (1.01–1.13)
2	1728	7,325,716	0.24	1.53 (1.44–1.63)	1.14 (1.07–1.22)	1.13 (1.06–1.21)
3	1073	3,760,970	0.29	1.84 (1.72–1.98)	1.27 (1.18–1.37)	1.25 (1.16–1.35)
4	464	1,493,416	0.31	2.00 (1.81–2.21)	1.29 (1.17–1.43)	1.27 (1.15–1.41)
5	132	336,071	0.39	2.52 (2.11–3.00)	1.53 (1.28–1.82)	1.50 (1.26,1.79)
P for trend	—	—	—	<.0001	<.0001	<.0001

IR, incidence rate.
[a]Per 1000 person-years.
[b]Model 1 was unadjusted.
[c]Model 2 was adjusted for age and sex.
[d]Model 3 was adjusted for age, sex, smoking status, alcohol consumption, regular exercise, and low-income status.
[e]Fasting plasma glucose ≥100 mg/dL or medications for diabetes.
[f]Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or medications for hypertension.
[g]MetS components were defined based on the harmonized International Diabetes Federation criteria, and the Korean-specific WC cutoff was adopted for abdominal obesity[25,26]: WC ≥85 cm in women or ≥90 cm in men; fasting plasma glucose ≥100 mg/dL or medications for diabetes mellitus; systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or medications for hypertension; serum HDL-C <50 mg/dL in women or <40 mg/dL in men; and serum triglyceride ≥150 mg/dL.

cancer. In particular, individuals with 4 or 5 metabolic components exhibited an increased risk of earlier-onset CRC compared with individuals without any metabolic component, as per the following figures: distal colon cancer (aHR, 1.37; 95% CI, 1.14–1.64) and rectal cancer (aHR, 1.32; 95% CI, 1.14–1.51). However, the association for proximal colon cancer (aHR, 1.10; 95% CI, 0.84–1.46) did not reach statistical significance.

Earlier-Onset Colorectal Cancer According to Body Mass Index and Waist Circumference Categories

Table 4 presents the association of the BMI and WC categories with the risk of earlier-onset CRC. When compared with individuals with a BMI of 18.5–22.9, the overweight group had an aHR of 1.10 (95% CI, 1.04–1.17), the obese group had an aHR of 1.19 (95% CI, 1.12–1.25),

Table 3. Incidence and Risk of Later-Onset Colorectal Cancer According to the Components of Metabolic Syndrome Among Participants Aged 50 Years and Older (National Health Insurance Service 2009–2019)

Variable	Cases	Person-years	IR[a]	Model 1,[b] HR (95% CI)	Model 2,[c] HR (95% CI)	Model 3,[d] HR (95% CI)
WC						
Male <90 cm, female <85 cm	38,911	26,960,425	1.44	1 (ref)	1 (ref)	1 (ref)
Male ≥90 cm, female ≥85 cm	18,346	9,805,652	1.87	1.30 (1.27–1.32)	1.21 (1.19–1.23)	1.21 (1.19–1.23)
P value	—	—	—	<.0001	<.0001	<.0001
Fasting glucose						
Normal	29,503	21,552,245	1.37	1 (ref)	1 (ref)	1 (ref)
High[e]	27,754	15,213,832	1.82	1.33 (1.31–1.35)	1.18 (1.16–1.20)	1.17 (1.16–1.19)
P value	—	—	—	<.0001	<.0001	<.0001
Blood pressure						
Normal	17,861	14,711,690	1.21	1 (ref)	1 (ref)	1 (ref)
High[f]	39,396	22,054,386	1.79	1.47 (1.44–1.49)	1.18 (1.16–1.20)	1.17 (1.15–1.20)
P value	—	—	—	<.0001	<.0001	<.0001
HDL-C						
Male ≥40 mg/dL, female ≥50 mg/dL	35,791	22,564,953	1.59	1 (ref)	1 (ref)	1 (ref)
Male <40 mg/dL, female <50 mg/dL	21,466	14,201,123	1.51	0.96 (0.94–0.97)	1.02 (1.00–1.03)	1.02 (1.01–1.04)
P value	—	—	—	<.0001	.1041	.0099
Triglycerides						
<150 mg/dL	29,974	20,661,752	1.45	1 (ref)	1 (ref)	1 (ref)
≥150 mg/dL	27,283	16,104,325	1.69	1.17 (1.15–1.19)	1.13 (1.11–1.15)	1.12 (1.10–1.14)
P value	—	—	—	<.0001	<.0001	<.0001
MetS (≥3 components)[g]						
No	31,479	22,624,340	1.39	1 (ref)	1 (ref)	1 (ref)
Yes	25,778	14,141,736	1.82	1.31 (1.29–1.33)	1.20 (1.18–1.22)	1.19 (1.17–1.21)
P value	—	—	—	<.0001	<.0001	<.0001
No. of MetS component						
0	5531	5,150,854	1.07	1 (ref)	1 (ref)	1 (ref)
1	11,721	8,587,465	1.37	1.27 (1.23–1.31)	1.10 (1.07–1.14)	1.10 (1.06–1.13)
2	14,227	8,886,020	1.60	1.49 (1.44–1.54)	1.23 (1.19–1.27)	1.22 (1.18–1.26)
3	12,866	7,397,420	1.74	1.62 (1.57–1.67)	1.32 (1.28–1.36)	1.31 (1.27–1.35)
4	9088	4,894,031	1.86	1.73 (1.67–1.78)	1.37 (1.33–1.42)	1.36 (1.32–1.41)
5	3824	1,850,286	2.07	1.92 (1.84–2.00)	1.50 (1.44–1.56)	1.49 (1.43–1.55)
P for trend	—	—	—	<.0001	<.0001	<.0001

IR, incidence rate.
[a]Per 1000 person-years.
[b]Model 1 was unadjusted.
[c]Model 2 was adjusted for age and sex.
[d]Model 3 was adjusted for age, sex, smoking status, alcohol consumption, regular exercise, and low-income status.
[e]Fasting plasma glucose ≥100 mg/dL or medications for diabetes.
[f]Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or medications for hypertension.
[g]MetS components were defined based on the harmonized International Diabetes Federation criteria, and the Korean-specific WC cutoff was adopted for abdominal obesity[25,26]: WC ≥85 cm in women or ≥90 cm in men; fasting plasma glucose ≥100 mg/dL or medications for diabetes mellitus; systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or medications for hypertension; serum HDL-C <50 mg/dL in women or <40 mg/dL in men, and serum triglyceride ≥150 mg/dL.

and the severely obese group had an aHR of 1.45 (95% CI, 1.31–1.61) for earlier-onset CRC (*P* for trend < .0001). After adjusting for selected confounding variables, individuals with a high waist circumference (≥100 cm in men or ≥95 cm in women) had a 53% increased risk of earlier-onset CRC (aHR, 1.53; 95% CI, 1.34–1.74) compared with the reference. According to tumor location, the association between each BMI and WC category and risk of earlier-onset CRC was significant for distal and rectal cancer, but not for proximal colon cancer ($P = .091$ for BMI, $P = .075$ for WC) (Figure 3).

Discussion

In this nationwide cohort study of 9,774,081 Korean people (2009–2019), 8320 were diagnosed with CRC between 20 and 49 years of age, and 57,257 were diagnosed with CRC at 50 years or older during follow-up. We found

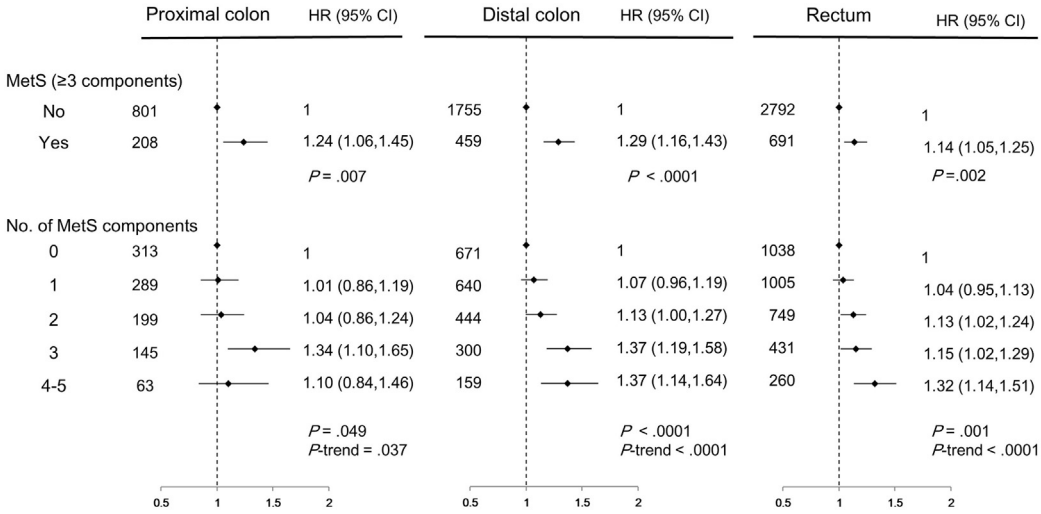

Figure 2. Multivariable-adjusted HRs (adjusted for age, sex, smoking status, alcohol consumption, physical activity, and low-income status) and 95% CIs for earlier-onset CRC incidence for MetS components by anatomic site.

that MetS and obesity were positively associated with earlier-onset CRC, similar to later-onset CRC. As the number of MetS components increased, the risk of earlier-onset CRC increased in a positive linear association of up to 50% among participants with 5 MetS components. This dose–response association was significant in the cases of distal colon and rectal cancers, although not for proximal colon cancer. We also found that a higher BMI and WC was significantly associated with increased incidence of earlier-onset CRC for distal and rectal cancers but not proximal colon cancers. Our findings suggest that the recent rapid increase in the incidence of MetS and obesity in younger adults is probably associated with the increasing incidence of earlier-onset CRC, which is prevalent in the distal colon and rectum.

Obesity-induced insulin resistance, chronic inflammation, and adipokines may play crucial roles in the complex metabolic pathways in colorectal carcinogenesis.[27–30] Increasing evidence suggests that obesity may influence CRC risk through microbial dysbiosis.[31] Obesity and MetS could be surrogate markers for other established lifestyle factors for CRC, such as sedentary behavior, Western diet,

Table 4. Association of Body Mass Index and Waist Circumference With Earlier-Onset Colorectal Cancer Risk (National Health Insurance Service 2009–2019)

Variable	Cases	Person-years	IR[a]	Model 1,[b] HR (95% CI)	Model 2,[c] HR (95% CI)	Model 3,[d] HR (95% CI)
BMI						
<18.5 kg/m^2	256	2,311,854	0.11	0.67 (0.59–0.76)	1.01 (0.88–1.14)	1.00 (0.88–1.14)
18.5–22.9 kg/m^2	3064	18,405,313	0.17	1 (ref)	1 (ref)	1 (ref)
23.0–24.9 kg/m^2	2011	9,002,741	0.22	1.33 (1.26–1.41)	1.10 (1.04–1.17)	1.10 (1.04–1.17)
25.0–29.9 kg/m^2	2569	10,420,498	0.25	1.47 (1.40–1.55)	1.19 (1.13–1.26)	1.19 (1.12–1.25)
≥30 kg/m^2	420	1,606,649	0.26	1.57 (1.42–1.74)	1.46 (1.32–1.62)	1.45 (1.31–1.61)
P value	—	—	—	<.0001	<.0001	<.0001
P value for trend	—	—	—	<.0001	<.0001	<.0001
WC						
Male <70 cm/female <65 cm	389	3,534,354	0.11	0.68 (0.61–0.75)	0.94 (0.85–1.05)	0.94 (0.85–1.05)
Male <80 cm /female <75 cm	2704	16,495,377	0.16	1 (ref)	1 (ref)	1 (ref)
Male <90 cm /female <85 cm	3655	15,894,435	0.23	1.39 (1.33–1.46)	1.14 (1.08–1.20)	1.13 (1.08–1.19)
Male <100 cm /female <95 cm	1317	4,910,123	0.27	1.62 (1.52–1.73)	1.29 (1.21–1.38)	1.28 (1.20–1.37)
Male ≥100 cm /female ≥95 cm	255	912,766	0.28	1.70 (1.49–1.93)	1.55 (1.36–1.76)	1.53 (1.34–1.74)
P value	—	—	—	<.0001	<.0001	<.0001
P for trend	—	—	—	<.0001	<.0001	<.0001

IR, incidence rate.
[a]Per 1000 person-years.
[b]Model 1 was unadjusted.
[c]Model 2 was adjusted for age and sex.
[d]Model 3 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, and low-income status.

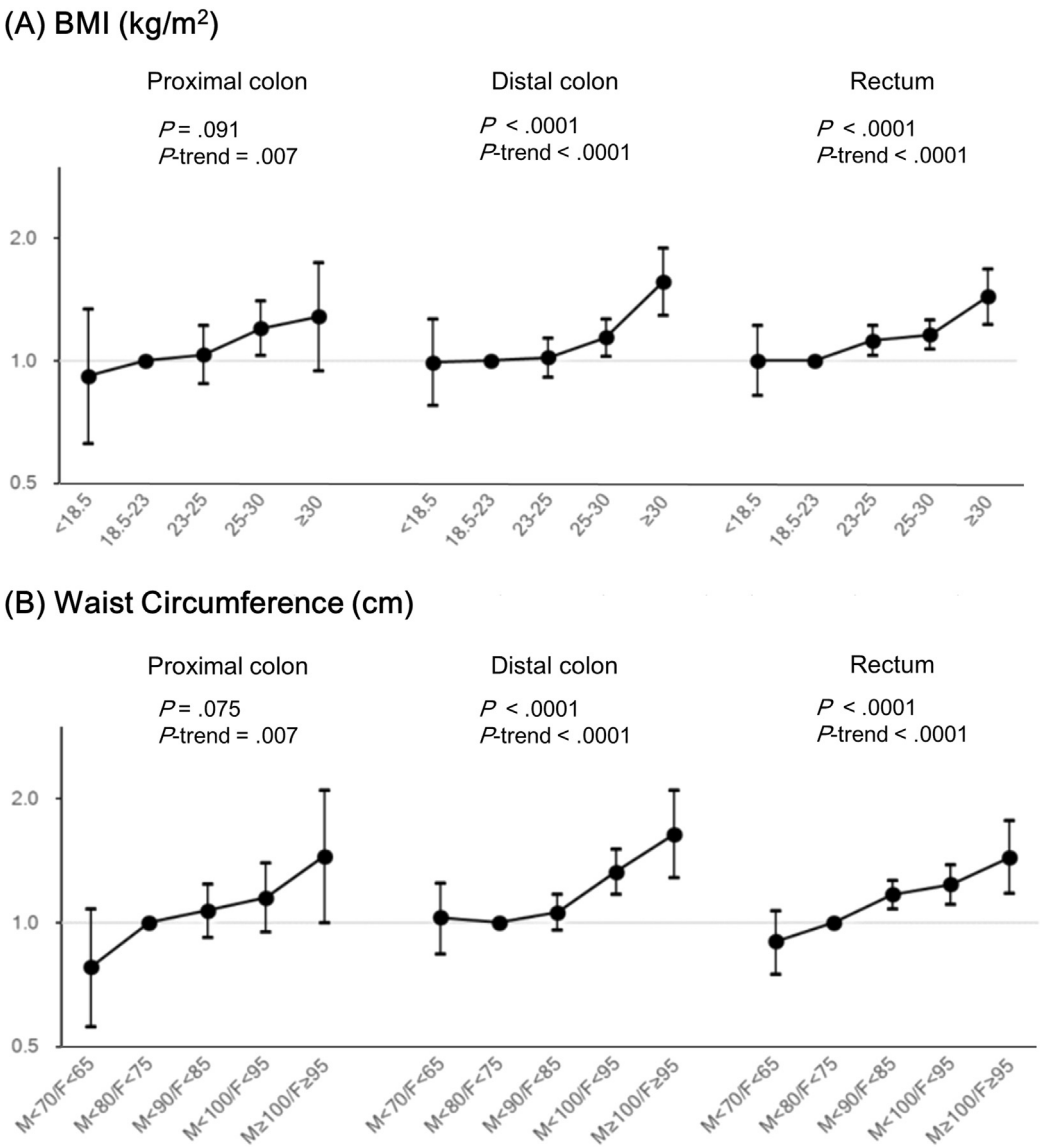

Figure 3. BMI- and WC-adjusted HRs (adjusted for age, sex, smoking status, alcohol consumption, physical activity, and low-income status) of earlier-onset CRC incidence by anatomic site. (*A*) BMI and earlier-onset CRC by anatomic site. (*B*) WC and earlier-onset CRC by anatomic site.

and alcohol use.[11] Recent studies have reported the association of earlier-onset CRC incidence with obesity and MetS.[10,11] We hypothesized that because obesity and MetS are associated with CRC in older adults, this association may also exist for earlier-onset CRC.[10] Modifiable factors, which afford different effects based on anatomic location, are of particular interest because earlier-onset CRC is predominant in the left colon.[5]

MetS comprises a cluster of heterogeneous conditions, including abdominal obesity, hyperglycemia, raised blood pressure, elevated triglycerides, and low HDL-C.[32] Abdominal obesity, glucose intolerance, and type 2 DM have been associated with an increased risk of CRC, whereas CRC association with other components, such as dyslipidemia, has yielded mixed results in prior studies.[32–34] Our study showed that of the MetS components, abdominal obesity was the strongest single risk factor associated with earlier-onset CRC (HR, 1.23; 95% CI, 1.16–1.30). Compared with individuals without MetS, those who met the definition of MetS (3 or more components) had an increased risk of earlier-onset CRC (aHR, 1.20; 95% CI, 1.14–1.27). The positive association between MetS and the risk of earlier-onset CRC was similar between the sexes and age groups (20–29, 30–39, and 40–49 years) across all subsites (all, *P* for interaction $>$ .05) (Supplementary Table 2). In this regard, Chen et al[11] showed that MetS is associated with an increased risk of earlier-onset CRC (odds ratio, 1.25; 95% CI, 1.09–1.43), and the risk is positively associated with the number of MetS components, which is in line with the results of our study. In this study, we investigated the association between MetS and the risk of later-onset CRC (aHR, 1.19; 95% CI, 1.17–1.21) and found that the strength of this association is similar to that for earlier-onset CRC (HR, 1.20; 95% CI, 1.14–1.27). We also found a dose–response

association between the number of MetS components and the risk of earlier-onset CRC and later-onset CRC. These results suggest that the effect of MetS on the development of earlier-onset CRC is not different from that for later-onset CRC.

Interestingly, the positive dose–response association between the number of MetS components and the risk of earlier-onset CRC was driven by the associations with distal colon and rectal cancers. The risk of earlier-onset CRC increased with increasing numbers of MetS components, which were pronounced with a linear trend in distal colon and rectal cancer cases, but not proximal colon cancers. Individuals aged 20–49 years with 4 or 5 MetS components had a markedly increased risk of earlier-onset CRC in the distal colon (1.37-fold) and rectum (1.32-fold) compared with individuals with no MetS components; however, this association was not observed for earlier-onset proximal colon cancer. In contrast to our results, Chen et al[11] reported that earlier-onset proximal and distal colon cancer (not rectal cancer) were associated with metabolic comorbidities. Prior studies defined MetS using claim data only and may have underestimated the prevalence of MetS. In our study, we used augmented claims data with clinical information on metabolic variables that were assessed during health checkups. Despite inconsistent results in the proximal colon and rectum cases, earlier-onset CRC was significantly associated with an increasing number of MetS components in both our study and that of Chen et al.[11]

Many epidemiologic datasets have indicated that higher BMI and WC levels are positively associated with CRC risk.[28,35,36] In addition, recent studies have investigated the association between BMI and earlier-onset CRC.[10,37] Although previous studies suggest that abdominal obesity (high WC) may be more predictive of CRC risk than general obesity (high BMI),[34] little is known about the association between WC and the risk of earlier-onset CRC. Ours is the first study to investigate the association between abdominal obesity and risk of earlier-onset CRC; the findings demonstrated a graded, increased risk of earlier-onset CRC associated with the WC and BMI categories. There was a positive dose–response association for distal colon cancers that was weaker for rectal cancer and not significant for proximal colon cancer. A similar pattern of relationship has been reported previously between obesity and CRCs across all anatomic subsites in people 50 years and older that was most pronounced for the distal colon.[38–40] In our study, we found that rectal cancer was also significantly associated with obesity. As per our findings, obesity and impaired metabolic regulation in adults 20–49 years old may be associated with development of left-sided colon cancer.

CRCs located at different anatomic subsites may have distinct clinical and molecular characteristics, suggesting differences in risk factors and carcinogenetic mechanisms by tumor location in the colon.[39,41,42] Although the underlying biological mechanism for the development of CRCs, depending on tumor location, remains poorly understood, a possible hypothesis is that the bile-acid concentration, metabolite presence, pH level, and microbial environment vary along the colon and rectum.[43] Molecular subtypes of CRC are also disproportionally distributed across the colon and rectum. The microsatellite instable–high, CpG island methylator phenotype–high, and *BRAF* mutation cancer subtypes are prevalent in proximal colon cancer, whereas the chromosomal instability–positive cancer subtype occurs predominantly in the distal colon.[42] Moreover, 60% of microsatellite- and chromosome-stable tumors are rectal cancers.[29] Findings of interest relating to earlier-onset CRCs include a relatively high rate of microsatellite- and chromosome-stable tumors and a lower prevalence of CpG island methylator phenotype–high and *BRAF* mutation tumors.[29,41,42] The distinct molecular features of earlier-onset CRC can account for the variations across locations and explain their unique pathogenesis mechanism.

The increasing trend of earlier-onset CRC incidence has been described for all racial groups, with differences in prevalence reported according to race and ethnicity.[4,6] A recent study reported that Asian and African-American people have higher rates of earlier-onset CRC than non-Hispanic, White people in the United States.[44] Similar to the growing trend of earlier-onset CRC in Western countries, 4 Asian regions (ie, Hong Kong, Korea, Japan, and Taiwan) have shown a considerable increase in earlier-onset CRC over the past 20 years.[6] The most prominent increase was observed in rectal cancer incidence among younger male individuals in Korea (1999–2014), followed by Taiwan.[6] As per multinational cancer registry data from 2008–2012, earlier-onset CRC incidence was highest and increasing most rapidly in Korea.[4] The reason for the high burden of this disease in Korea is unclear; however, it may be related to drastic lifestyle changes subsequent to Korea's remarkable economic recovery after the 1997 economic crisis.[45] The prevalence of obesity and MetS also increased rapidly in Korea from 1998–2007.[45,46] Therefore, Korea is an appropriate model to determine the association between metabolic abnormalities and incidence of earlier-onset CRC.

To the best of our knowledge, this study is the first to investigate the risk factors for earlier-onset CRC by anatomic subsites, namely, proximal, distal colon, and rectum. However, this study has several limitations. First, some data were not available, including those on potential confounding factors, such as a family history of CRC and inflammatory bowel disease, dietary intake, history of colonoscopy, medication use (eg, nonsteroidal anti-inflammatory drugs), and history of colectomy. In particular, hereditary cancer was not excluded in this study, about 30% of earlier-onset CRCs are due to familial history and hereditary conditions.[29] Inflammatory bowel disease is a risk factor for earlier-onset CRC; however, the incidence of inflammatory bowel disease in Asia remains low compared with the West.[44,47] Second, we could not determine the histologic and molecular types of cancers. Third, this work was a large population-based study that included ethnic Korean people only, and the findings may not be generalizable to other ethnic groups. Large-scale studies involving other races and ethnicities may be needed to confirm our findings.

In conclusion, in our large-cohort study, we found that MetS and obesity in the age range of 20–49 years are

associated with an increased risk of earlier-onset CRC, particularly in the left colon. The severity of obesity could be an independent risk factor for predicting earlier-onset CRC risk. Our study suggests that people younger than age 50 years with MetS require effective preventive interventions, including screening and lifestyle changes, to help reduce the risk and potentially stem the increasing rates of CRC at younger ages.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2022.05.032.

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Data Availability
Data are available at https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do. Researchers can access the data by requesting access from the Korean National Health Insurance Sharing Service.

Conflicts of interest
The authors disclose no conflicts.

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Supplementary Table 1. Incidence and Risk of Earlier-Onset Colorectal Cancer According to the Components of Metabolic Syndrome by Anatomic Subsites (National Health Insurance Service 2009–2019)

Variable	Colon, HR (95% CI)	Rectum, HR (95% CI)	Proximal colon, HR (95% CI)	Distal colon, HR (95% CI)	*P* for heterogeneity	
					Colon–rectum	Proximal–distal–rectum
WC					.100	.134
Male <90 cm, female <85 cm	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
Male ≥90 cm, female ≥85 cm	1.28 (1.19–1.37)	1.16 (1.06–1.27)	1.16 (0.99–1.37)	1.33 (1.19–1.48)		
P value	<.0001	.001	.068	<.0001		
Fasting glucose					.114	.198
Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
High	1.11 (1.04–1.18)	1.03 (0.95–1.11)	1.01 (0.87–1.16)	1.14 (1.03–1.25)		
P value	.001	.528	.921	.008		
Blood pressure					.051	.098
Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
High	1.16 (1.09–1.23)	1.06 (0.98–1.14)	1.13 (0.99–1.29)	1.20 (1.10–1.31)		
P value	<.0001	.127	.077	<.0001		
HDL-C					.508	.570
Male ≥40 mg/dL, female ≥50 mg/dL	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
Male <40 mg/dL, female <50 mg/dL	1.03 (0.96–1.10)	1.07 (0.98–1.16)	1.05 (0.90–1.23)	0.99 (0.90–1.10)		
P value	.425	.126	.521	.910		
Triglyceride					.193	.459
<150 mg/dL	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
≥150 mg/dL	1.10 (1.03–1.17)	1.18 (1.09–1.26)	1.10 (0.96–1.27)	1.10 (1.00–1.20)		
P value	.003	<.0001	.164	.055		
MetS (≥3 components)					.161	.222
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
Yes	1.24 (1.15,1.33)	1.14 (1.05,1.25)	1.24 (1.06–1.45)	1.29 (1.16,1.43)		
P value	<.0001	.002	.007	<.0001		
No. of MetS components	1 (ref)	1 (ref)	1 (ref)	1 (ref)	—	—
0	1.09 (1.01–1.17)	1.04 (0.95–1.14)	1.01 (0.86–1.19)	1.07 (0.96–1.19)		
1	1.13 (1.04–1.23)	1.13 (1.03–1.25)	1.04 (0.86–1.25)	1.13 (1.00–1.28)		
2	1.33 (1.21–1.47)	1.15 (1.02–1.29)	1.35 (1.10–1.65)	1.37 (1.19–1.58)		
3	1.20 (1.05–1.38)	1.36 (1.17–1.58)	1.08 (0.8–1.47)	1.31 (1.08–1.60)		
4	1.78 (1.43–2.21)	1.12 (0.82–1.53)	1.16 (0.67–2.04)	1.57 (1.12–2.21)		
5	<.0001	.001	.091	<.0001		
P for trend	<.0001	<.0001	.041	<.0001		

Supplementary Table 2. Stratified Analysis for Metabolic Syndrome and Risk of Earlier-Onset Colorectal Cancer

Outcomes	Subgroup	HR (95% CI)	*P* for interaction
CRC	Male	1.19 (1.11–1.26)	.280
	Female	1.27 (1.13–1.44)	
	Age 20–29 y	1.16 (0.87–1.55)	.861
	Age 30–39 y	1.21 (1.10–1.33)	
	Age 40–49 y	1.20 (1.12–1.29)	
Colon cancer	Male	1.22 (1.13–1.33)	.593
	Female	1.31 (1.13–1.52)	
	Age 20–29 y	1.18 (0.78–1.78)	.436
	Age 30–39 y	1.22 (1.07–1.40)	
	Age 40–49 y	1.26 (1.15–1.37)	
Rectal cancer	Male	1.14 (1.04–1.25)	.464
	Female	1.20 (0.97–1.49)	
	Age 20–29 y	1.14 (0.77–1.71)	.788
	Age 30–39 y	1.19 (1.04–1.37)	
	Age 40–49 y	1.12 (1.00–1.25)	
Proximal colon cancer	Male	1.26 (1.05–1.50)	.747
	Female	1.24 (0.88–1.75)	
	Age 20–29 y	0.68 (0.25–1.89)	.569
	Age 30–39 y	1.27 (0.97–1.66)	
	Age 40–49 y	1.27 (1.04–1.55)	
Distal colon cancer	Male	1.22 (1.08–1.38)	.186
	Female	1.50 (1.22–1.83)	
	Age 20–29 y	1.45 (0.79–2.67)	.143
	Age 30–39 y	1.17 (0.94–1.44)	
	Age 40–49 y	1.33 (1.17–1.51)	