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ORIGINAL ARTICLE—ALIMENTARY TRACT

Obesity-related parameters and colorectal adenoma development

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Abstract
Background Obesity increases the risk of colorectal adenoma and colorectal cancer. However, the obesity-related parameters that are best for assessing the risk of colorectal adenoma development remain unclear. We analyzed the parameters that may best describe the association between obesity and colorectal adenoma development.
Methods In this retrospective cohort study, 3405 individuals underwent screening colonoscopy during routine health examinations. We measured body mass index; waist circumference; and metabolic parameters such as high-density lipoprotein-cholesterol, glucose, triglyceride, and systolic blood pressure. We analyzed the risk of developing colorectal adenoma, relative to obesity-related parameters, over a mean interval of 5.8 years from baseline colonoscopy.
Results In a multivariate analysis, waist circumference was the only obesity-related marker associated with an increased risk of metachronous colorectal adenoma. Men with waist circumferences ≥85 cm and women with waist circumference ≥82 cm had a 31% increased risk of metachronous colorectal adenoma compared to those with smaller waist circumferences [odds ratio (OR) 1.31; 95% confidence interval (CI, 1.09–1.57)]. Other factors associated with metachronous colorectal adenoma were age (OR, 1.03; 95% CI 1.02–1.04), male sex (OR 1.49; 95% CI 1.17–1.88), alcohol consumption ≥3/week (OR 1.33; 95% CI 1.10–1.62), the number of adenoma at baseline (OR 1.21; 95% CI 1.10–1.33), and the presence of advanced adenoma at baseline (OR 1.60; 95% CI 1.24–2.06).
Conclusions Our findings suggest that central obesity, represented by waist circumference, is a significant predictor of metachronous colorectal adenoma, independent of body mass index and other metabolic variables.

Keywords Colorectal adenoma · Obesity · Epidemiology · Cohort study

Introduction

The obesity epidemic continues to grow and imposes a global health burden through chronic diseases and their morbidities. In addition to direct health consequences, obesity is a risk factor for various diseases, including some cancers such as colorectal cancer (CRC) [1]. According to the World Health Organization, the worldwide prevalence of obesity has more than doubled since 1980, with approximately 13% of the global adult population being considered obese in 2014 [2]. CRC is also a global concern as it is the fourth most frequently diagnosed malignancy and the second leading cause of cancer-related death overall [3]. The possible biological mechanisms linking obesity to CRC include high caloric intake, physical inactivity, insulin resistance/hyperinsulinemia, adipokine hypersecretion, chronic inflammation, and oxidative stress [4].

CRC develops through a stepwise series of neoplastic changes in the colonic epithelium associated with an

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accumulation of genetic and epigenetic alterations [5, 6]. There are at least three major pathways leading to the transformation of normal colonic mucosa into colorectal cancer. These are the chromosomal instability pathway, the microsatellite instability pathway, and the cytosine-phospho-guanine island methylator phenotype pathway [7]. Through these or other pathways, malignant transformation of normal mucosa is believed to occur over a period of several years; therefore, colonoscopic screening and surveillance have been effective tools in preventing CRC [8, 9]. In addition, modification of environmental and lifestyle risk factors is important in colorectal neoplasm prevention [10, 11]. Obesity has consistently been associated with an increased risk of developing CRC and colorectal adenoma [12, 13]. However, the studies that have evaluated obesity in relation to adenoma recurrence are both limited and inconsistent [1, 14]. Central obesity, expressed as waist circumference, might better correlate with the risk of colorectal neoplasms than general obesity, expressed as elevated body mass index (BMI) [15, 16]. However, previous studies did not provide results for either central and general obesity in relation to the risk of colorectal adenoma [11, 14, 15, 17, 18]. In addition to anthropometric factors, measures of metabolic parameters, such as hyperglycemia, dyslipidemia, and elevated blood pressure may be used to assess the risk of developing obesity-related colorectal neoplasms. However, the best obesity-related factors for evaluating the risk of colorectal adenomas remain unclear.

In this cohort study with repetitive measurement of anthropometric and metabolic parameters, we evaluated whether these parameters were associated with colorectal adenoma development and assessed which of these parameters best describe the association between obesity and the development of colorectal adenomas.

Methods

Study population

We conducted a cohort study of healthy individuals ≥30 years of age who underwent routine health check-ups, including endoscopy, at the Center for Health Promotion, Samsung Medical Center, South Korea [19]. Regular health check-ups are very common in South Korea because of the Industrial Safety and Health Law; the National Cancer Screening Program recommends biennial health examinations, including for several cancers [20]. Since our objective was to evaluate the association between obesity-related parameters and metachronous colorectal adenoma, we included participants who underwent both screening colonoscopy and surveillance colonoscopy ($n = 5890$). We excluded 343 participants who met any of the following exclusion criteria: poor bowel preparation ($n = 298$), incomplete colonoscopy ($n = 35$), history of previous colonoscopy or prior polypectomy ($n = 2142$), history of malignancy ($n = 60$), history of colorectal surgery ($n = 6$), or inflammatory bowel disease ($n = 3$). Finally, 3405 individuals who underwent screening colonoscopy with or without polypectomy and surveillance colonoscopy were included in this study (Fig. 1). This study used only de-identified data that were collected for clinical purposes as part of the health screening check-up. This study was approved by the Institutional Review Board of the Samsung Medical Center.

Data collection

The comprehensive health screening program included demographic characteristics, anthropometric measurements, endoscopy, serum biochemical measurements, and an epidemiological questionnaire assessing smoking, alcohol consumption, medication history (including currently used medicines), personal medical history, and family history of colorectal cancer [19]. The personal medical histories collected information regarding history of diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, colorectal polyps, colorectal cancer, and colorectal surgery. The medication history included current and regular use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Weight and height measurements were determined using an Inbody 720 machine (Biospace, Seoul, Korea), to the nearest 0.1 kg and 0.1 cm, respectively; measurements were taken with participants wearing light clothing and in bare feet. The BMI was calculated as weight in kilograms divided by height in square meters (kg/m^2), and waist circumference was measured in a horizontal plane at the midpoint between the inferior margin of the last rib and the superior iliac crest. Smoking status assessments were divided into three groups: never smoked, former smoker, or current smoker; alcohol consumption was also divided into three groups: never or occasionally consumed (once or twice per month), consumed once or twice per week, or consumed three or more times per week.

After a ≥12 h fast, fasting blood samples were obtained from the antecubital vein, and were used to determine the serum levels of glucose, total cholesterol, triglycerides, and high-density lipoprotein-cholesterol (HDL-C). Serum levels of total cholesterol, triglycerides, and high-density lipoprotein-cholesterol (HDL-C) were measured with a Hitachi 7600 (Hitachi, Tokyo, Japan) using enzymatic colorimetric and liquid-selective detergent methods. Serum levels of glucose were measured using the hexokinase/glucose-6-phosphate dehydrogenase method with a Hitachi 7600 Modular Dp-110 autoanalyzer (Hitachi, Tokyo,

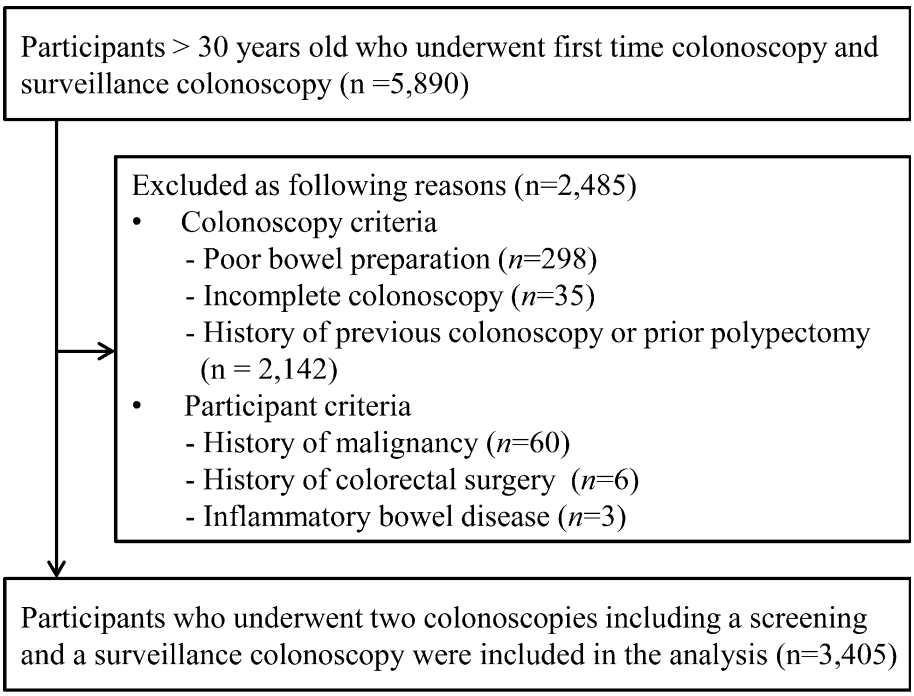

Fig. 1 Flow diagram of study participants

Japan). The inter- and intra-assay coefficients of variation for quality control specimens were <5% for all blood variables.

Colonoscopies

Experienced, board-certified gastroenterologists performed the colonoscopies using either a CF-Q260AI or CF-Q260AL endoscope (Olympus Medical Systems, Tokyo, Japan), after bowel preparation with a 4-L volume of polyethylene glycol solution (CoLyte and CoLyte-F; Taejun, Seoul, South Korea). The endoscopists routinely performed endoscopic resection of detected polyps including diminutive polyp during colonoscopy. The locations of colorectal neoplasms were assessed by the endoscopists, and the size of each lesion was estimated using open biopsy forceps. The gross appearance of each polyp was classified according to the Paris endoscopic classification [21]. The following information was recorded in the electronic medical record after the colonoscopy: number of polyps, polyp location and size, time and results of the last colonoscopy, family history of CRC, bowel preparation (excellent/good/fair/poor), cecal intubation time, withdrawal time, and colonoscopy completeness. Biopsy samples were sent to the pathology department, where qualified pathologists assessed the histopathology of the lesions. All colorectal neoplasms were histologically evaluated and classified according to the World Health Organization system. An advanced neoplasm was defined as any adenoma larger than 1 cm or any adenoma with a villous component or high-grade dysplasia. The proximal colon was defined as all colonic segments including and proximal to the splenic flexure. The distal colon was defined as the colonic portions distal to the splenic flexure.

Statistical analysis

Continuous variables were reported as mean ± standard deviation, whereas categorical variables were presented as percentages. Continuous variables were compared between groups using Student's *t* test or one-way ANOVA, whereas categorical variables were compared using the Chi squared test. The associations between developing colorectal adenoma and obesity-related parameters (waist circumference, BMI, fasting glucose, triglycerides, HDL-C, and systolic blood pressure) were assessed by odds ratios (ORs) with 95% confidence intervals (CIs) using the univariate and multivariate logistic regression models. Multivariate analyses were performed to assess the association of developing colorectal adenomas with each obesity-related parameter, adjusting for age, sex, smoking status, alcohol intake, physical activity, regular aspirin use, NSAID use, family history of CRC, number and pathologic characteristics of baseline adenomas, and follow-up interval. In addition, we selected significant risk factors for developing colorectal adenoma using multivariate logistic regression with stepwise variable selection. The candidate factors included age, sex, BMI, waist circumference, fasting glucose, triglyceride, HDL-C, and systolic blood pressure, smoking status, alcohol consumption, physical activity,

regular aspirin use, NSAID use, family history of CRC, number and characteristics of baseline adenomas, and follow-up interval.

A p value <0.05 was considered statistically significant; statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Among the 3405 participants enrolled in this study, the incidence of any metachronous colorectal adenomas was 38.7% (1317/3405) and that of metachronous advanced colorectal neoplasms was 1.2% (42/3405). Among the 42 participants who developed metachronous advanced neoplasm, six participants developed adenoma with high-grade dysplasia, four participants developed adenoma with a villous component, and 32 participants developed adenoma larger than 1 cm. Based on the presence of metachronous colorectal adenoma, the study population baseline characteristics are shown in Table 1. Participants who had metachronous colorectal adenoma were more likely to be older, men, current smokers, heavy alcohol consumers, those with lower HDL-C, higher triglycerides, higher systolic blood pressure levels, a large number of baseline colorectal adenomas, and those with higher average BMI and waist circumference measurements.

The baseline characteristics of the study population, by waist circumference quartiles, are shown in Table 2. The group with a higher waist circumference demonstrated higher values of BMI, fasting glucose, triglycerides, and systolic blood pressure and lower values of HDL-C. Additionally, they were more likely to be older, men, current smokers, heavy alcohol consumers, and aspirin users. Further, they were likely to not exercise regularly, have a history of diabetes, and have a larger number of colorectal adenomas at baseline.

Obesity-related parameters and colorectal adenoma development

In the univariate analysis, metachronous colorectal adenomas were positively associated with waist circumference, BMI, fasting glucose, HDL-C, triglycerides, systolic blood pressure, the number of baseline adenomas, and advanced adenomas at baseline (Table 3). After adjusting for age, sex, smoking status, alcohol intake, physical activity, regular aspirin use, NSAID use, family history of CRC, number and characteristics of baseline adenomas, and follow-up interval, metachronous colorectal adenoma was significantly associated with waist circumference (OR 1.02; 95% CI 1.01–1.03), number of baseline colorectal adenomas (OR 1.33; 95% CI 1.23–1.43), and advanced colorectal adenoma at baseline (OR 2.01; 95% CI 1.63–2.46).

We also examined the associations between obesity-related parameters and metachronous adenoma separately, based on location (Table 4). In multivariate analyses, metachronous proximal adenoma was associated with waist circumference, BMI, the number of baseline adenomas, and advanced colorectal adenomas at baseline. Waist circumference, systolic blood pressure, the number of baseline adenomas and advanced colorectal adenoma at baseline were significant risk factors for metachronous distal adenoma.

Obesity-related parameters and colorectal adenoma development in multivariate analyses with stepwise variable selection

Through a variable selection procedure, six variables were identified as significant risk factors for colorectal adenoma recurrence (Table 5). These factors other than obesity were age (OR 1.03; 95% CI 1.02–1.04), male sex (OR 1.49; 95% CI 1.17–1.88), alcohol consumption ≥3/week (OR 1.33; 95% CI 1.10–1.62), number of baseline adenomas (OR 1.21; 95% CI 1.10–1.33), and presence of advanced colorectal adenoma at baseline (OR 1.60; 95% CI 1.24–2.06). Among the obesity-related factors, waist circumference was the only risk factor for metachronous adenoma (OR 1.01; 95% CI 1.00–1.02). In addition, we dichotomized waist circumference, age, frequency of alcohol consumption, number of baseline adenomas, and characteristics of baseline adenomas to predict metachronous colorectal adenoma using all possible cutoff values, and we found a combination of cutoff values maximizing the area under curve of the receiver operating characteristic curves. The selected cutoff values were a waist circumference ≥85 cm in men and ≥82 cm in women, ≥50 years of age, ≥3/week alcohol consumption, ≥2 baseline adenomas, and presence of advanced adenoma at baseline. Men with waist circumferences ≥85 cm and women with waist circumference ≥82 cm had a 31% increased risk of metachronous adenomas, compared to those with smaller waist circumferences.

Discussion

In this large cohort study, we found that waist circumference was significantly associated with the development of colorectal adenoma. In contrast, other obesity-related parameters such as BMI, fasting glucose, HDL-C, triglycerides, and systolic blood pressure, were not related to adenoma development in multivariate analysis. Further,

Table 1 Baseline characteristics by colorectal adenoma development

	Total ($N = 3405$)	No adenoma ($N = 2088$)	Any adenomas ($N = 1317$)	p value[c]
Age (years)[a]	51.4 ± 7.3	50.5 ± 7.0	52.8 ± 7.4	**<0.001**
Sex				**<0.001**
Male[b]	2532 (74.4)	1458 (69.8)	1074 (81.6)	
Female[b]	873 (25.6)	630 (30.2)	243 (18.4)	
Waist circumference (cm)[a]	85.4 ± 8.5	84.5 ± 8.7	86.7 ± 7.9	**<0.001**
BMI (kg/m^2)[a]	24.4 ± 2.7	24.2 ± 2.8	24.7 ± 2.6	**<0.001**
Body fat rate (%)[a]	24.6 ± 6.1	24.7 ± 6.3	24.4 ± 5.8	0.219
Smoking status				**<0.001**
Never[b]	1202 (38.3)	821 (42.4)	381 (31.6)	
Former[b]	1161 (36.9)	647 (33.4)	514 (42.6)	
Current[b]	780 (24.8)	469 (24.2)	311 (25.8)	
Alcohol consumption				**<0.001**
Never or occasional[b]	1538 (48.8)	1031 (52.9)	507 (42.1)	
Once or twice a week[b]	886 (28.1)	535 (27.4)	351 (29.1)	
Three or more times a week[b]	731 (23.2)	384 (19.7)	347 (28.8)	
Physical activity				0.965
Two or less times a week[b]	1701 (53.6)	1048 (53.5)	653 (53.9)	
Three or four times a week[b]	948 (29.9)	588 (29.9)	360 (29.7)	
Five or more times a week[b]	523 (16.5)	325 (16.6)	198 (16.4)	
Regular aspirin use[b]	360 (12.2)	194 (10.7)	166 (14.8)	**0.001**
Regular NSAIDs use[b]	63 (2.1)	40 (2.2)	23 (2.1)	0.88
Regular calcium supplements use[b]	239 (8.1)	156 (8.6)	83 (7.4)	0.276
Diabetes[b]	223 (7.0)	132 (6.7)	91 (7.5)	0.402
Family history of CRC[b]	133 (8.9)	93 (9.7)	40 (7.3)	0.13
Fasting glucose (mg/dl)[1]	94.9 ± 18.3	94.3 ± 18.1	95.9 ± 18.6	0.545
HDL-C (mg/dl)	53.1 ± 13.5	53.7 ± 13.5	52.2 ± 13.4	**0.002**
Triglycerides (mg/dl)	135.9 ± 84.7	132.3 ± 83.2	141.9 ± 86.9	**0.002**
SBP (mmHg)	116.9 ± 15.9	116.2 ± 15.5	117.9 ± 16.3	**0.003**
Number of baseline adenoma[a]	0.8 ± 1.3	0.6 ± 1.0	1.2 ± 1.5	**<0.001**
Interval of follow-up (years)[a]	5.8 ± 0.8	5.8 ± 0.8	5.7 ± 0.8	

BMI body mass index, *NSAIDs* non-steroidal anti-inflammatory drugs, *CRC* colorectal cancer, *HDL-C* high-density lipoprotein-cholesterol, *SBP* systolic blood pressure

[a] Data are mean ± standard deviation

[b] Data are number (%)

[c] *P* value expressed in bold corresponds to a statistically significant value less than 0.05

waist circumference was statistically related to development of adenomas, even after adjustment for BMI and other metabolic abnormalities. That is, even in individuals with normal BMIs, central obesity is a significant risk factor for colorectal adenoma development. Thus, waist circumference conveyed significant information, beyond body weight or BMI, regarding the development of colorectal adenomas. These results support the hypothesis that central obesity is the most reliable risk factor for predicting colorectal adenoma development and suggest that fat distribution is a more important predictor of disease risk than is BMI or body weight.

The majority of previous studies reporting the association of obesity with colorectal neoplasm reported the incidence of CRC and the prevalence of colorectal adenomas [12, 13, 15, 17, 22–27]. There have been a few studies evaluating the association of obesity with adenoma recurrence [14, 18, 28, 29]. Yamaji et al. reported that the incidence of colorectal adenoma among 2568 patients increased according to the baseline BMI over a 1-year follow-up period [10]. Jacobs et al. also reported that obesity (BMI ≥30 kg/m^2) was associated with an increased risk of developing colorectal adenomas over a median follow-up of 3.1 years among 1304 participants [14].

Table 2 Baseline characteristics by quartiles of waist circumference

	Quartile 1 (<81 cm)	Quartile 2 (81–85 cm)	Quartile 3 (86–90 cm)	Quartile 4 (>90 cm)	*p* value[c]
Age (years)[a]	49.8 ± 6.5	51.7 ± 7.1	51.1 ± 6.8	51.8 ± 7.4	**<0.001**
Sex					**<0.001**
Male[b]	224 (35.6)	488 (81.2)	647 (91.1)	628 (94.4)	
Female[b]	405 (64.4)	113 (18.8)	63 (8.9)	37 (5.6)	
BMI (kg/m^2)[a]	21.6 ± 1.8	23.6 ± 1.6	24.9 ± 1.5	27.3 ± 2.2	**<0.001**
Body fat rate (%)[a]	24.2 ± 6.6	22.9 ± 6.1	23.8 ± 5.2	26.6 ± 5.2	**<0.001**
Smoking status					**<0.001**
Never[b]	407 (67.9)	195 (34.5)	186 (27.2)	131 (20.7)	
Former[b]	119 (19.9)	234 (41.4)	286 (41.9)	292 (46.2)	
Current[b]	73 (12.2)	136 (24.1)	211 (30.9)	209 (33.1)	
Alcohol consumption					**<0.001**
Never or occasional[b]	446 (73.7)	258 (45.7)	255 (37.3)	225 (35.1)	
Once or twice a week[b]	103 (17.0)	200 (35.4)	234 (34.3)	193 (30.2)	
Three or more times a week[b]	56 (9.3)	107 (18.9)	194 (28.4)	222 (34.7)	
Physical activity					**0.001**
Two or less times a week[b]	288 (47.8)	307 (53.2)	388 (56.6)	374 (58.9)	
Three or four times a week[b]	204 (33.8)	173 (29.9)	210 (30.6)	160 (25.2)	
Five or more times a week[b]	111 (18.4)	98 (16.9)	88 (12.8)	101 (15.9)	
Regular aspirin use[b]	39 (6.9)	60 (11.4)	78 (12.4)	100 (16.5)	**<0.001**
Regular NSAIDs use[b]	15 (2.7)	13 (2.5)	5 (0.8)	14 (2.3)	0.077
Regular calcium supplements use[b]	77 (13.8)	38 (7.2)	32 (5.1)	33 (5.5)	**<0.001**
Diabetes[b]	26 (4.3)	34 (5.9)	51 (7.4)	66 (10.3)	**<0.001**
Family history of CRC[b]	35 (11.1)	19 (7.8)	23 (7.9)	18 (6.2)	0.171
Fasting glucose (mg/dL)[a]	89.5 ± 14.2	94.5 ± 19.3	96.0 ± 17.6	99.2 ± 19.5	**<0.001**
HDL-C (mg/dL)	60.7 ± 14.2	52.6 ± 12.5	49.7 ± 11.3	48.7 ± 11.5	**<0.001**
Triglycerides (mg/dL)	99.2 ± 51.8	134.6 ± 90.5	147.6 ± 79.1	164.2 ± 98.8	**<0.001**
SBP (mmHg)	112.2 ± 15.1	116.6 ± 16.3	118.1 ± 15.5	120.4 ± 15.0	**<0.001**
Number of baseline adenoma[a]	0.5 ± 0.8	0.8 ± 1.1	0.9 ± 1.5	1.0 ± 1.3	**<0.001**
Interval of follow-up (years)[a]	5.8 ± 0.8	5.8 ± 0.8	5.7 ± 0.8	5.7 ± 0.9	

BMI body mass index, *NSAIDs* non-steroidal anti-inflammatory drugs, *CRC* colorectal cancer, *HDL-C* high-density lipoprotein-cholesterol, *SBP* systolic blood pressure

[a] Data are mean ± standard deviation

[b] Data are number (%)

[c] *P* value expressed in bold corresponds to a statistically significant value less than 0.05

Further, Laiyemo et al. reported an increased risk of developing adenoma associated with BMI over a 4-year period following 1826 patients [18]. In the present study, central obesity, as assessed by increased waist circumference, was associated with colorectal adenoma development over a mean follow-up period of 5.8 years among 3405 participants.

Epidemiological evidence suggests that abdominal obesity is more predictive of CRC than measures of general obesity, such as BMI [15, 30–32]. This positive association between central obesity, as measured by waist circumference or waist-hip ratio, and CRC remains even after adjusting for BMI. Unlike the association between central obesity and CRC risk, the studies that investigated both central and general obesity relative to the risk of colorectal adenoma showed that central and general obesity resulted in similar colorectal adenoma risks [11, 33–36]. A cross-sectional study from Korea reported that abdominal obesity was associated with an increased risk of colorectal adenoma, even after adjusting for BMI; however, BMI was not related to the risk of colorectal adenoma after adjusting for waist circumference [37]. Interestingly, several recent studies have used computed tomography measurements of visceral abdominal fat to show that visceral obesity is

Table 3 Association between obesity related parameters and the risk of colorectal adenoma development

	Univariate model			Multivariate model		
	OR	95% CI	*p* value[a]	OR	95% CI	*p* value[a]
Waist circumference	1.04	1.03–1.05	**<0.001**	1.02	1.01–1.03	**0.002**
BMI	1.06	1.03–1.09	**<0.001**	1.03	1.00–1.07	0.058
Fasting glucose	1.01	1.00–1.01	**0.002**	1.01	1.00–1.01	0.884
HDL-C	0.99	0.99–1.00	**0.002**	1.00	0.99–1.00	0.253
Triglycerides	1.01	1.00–1.02	**0.002**	1.01	1.00–1.02	0.167
SBP	1.01	1.00–1.02	**0.003**	1.00	1.00–1.01	0.548
Number of baseline adenomas	1.45	1.36–1.54	**<0.001**	1.33	1.23–1.43	**<0.001**
Characteristics of baseline adenomas						
None	1.00	Reference		1.00	Reference	
Non-advanced adenomas	2.29	1.67–3.14	**<0.001**	1.48	0.99–2.22	0.057
Advanced neoplasm	2.34	1.98–2.77	**<0.001**	2.01	1.63–2.46	**<0.001**

Multivariate logistic regression model adjusted for the variables and age, sex, smoking status, alcohol intake, physical activity, regular aspirin use, family history of colorectal cancer, and follow-up interval

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *HDL-C* high-density lipoprotein-cholesterol, *SBP* systolic blood pressure

[a] *P* value expressed in bold corresponds to a statistically significant value less than 0.05

Table 4 Association between obesity related parameters and the risk of colorectal adenoma development according to the location

	Univariate model			Multivariate Model		
	OR	95% CI	*p* value[a]	OR	95% CI	*p* value[a]
Proximal colon						
Waist circumference	1.03	1.02–1.04	**<0.001**	1.02	1.01–1.03	**0.007**
BMI	1.06	1.03–1.09	**<0.001**	1.04	1.01–1.08	**0.014**
Fasting glucose	1.01	1.00–1.01	**0.003**	1.00	1.00–1.01	0.488
HDL-C	0.99	0.98–1.00	**0.001**	0.99	0.99–1.00	0.154
Triglycerides	1.04	1.01–1.07	**0.014**	1.01	1.00–1.02	0.18
SBP	1.00	1.00–1.01	0.112	1.00	0.99–1.00	0.404
Number of baseline adenomas	1.39	1.31–1.48	**<0.001**	1.27	1.18–1.37	**<0.001**
Characteristics of baseline adenomas						
None	1.00	Reference		1.00	Reference	
Non-advanced adenomas	2.51	1.81–3.49	**<0.001**	1.51	0.98–2.31	0.061
Advanced neoplasm	2.20	1.83–2.64	**<0.001**	1.84	1.47–2.29	**<0.001**
Distal colon						
Waist circumference	1.04	1.02–1.05	**<0.001**	1.01	1.00–1.03	**0.018**
BMI	1.06	1.02–1.09	**0.003**	1.02	0.98–1.07	0.24
Fasting glucose	1.01	1.00–1.01	**0.024**	1.00	1.00–1.01	0.253
HDL-C	0.99	0.99–1.00	0.075	1.00	0.99–1.01	0.455
Triglycerides	1.01	1.00–1.02	**0.03**	1.01	1.00–1.02	0.206
SBP	1.01	1.01–1.02	**<0.001**	1.01	1.00–1.01	**0.024**
Number of baseline adenomas	1.30	1.22–1.38	**<0.001**	1.22	1.13–1.32	**<0.001**
Characteristics of baseline adenomas						
None	1.00	Reference		1.00	Reference	
Non-advanced adenomas	2.08	1.16–2.59	**<0.001**	1.83	1.41–2.37	**<0.001**
Advanced neoplasm	2.20	1.50–3.22	**<0.001**	1.90	1.18–3.07	**0.002**

Multivariate model adjusted for the variables and age, sex, smoking status, alcohol intake, physical activity, regular aspirin use, family history of colorectal cancer, and follow-up interval

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *HDL-C* high-density lipoprotein-cholesterol, *SBP* systolic blood pressure

[a] *P* value expressed in bold corresponds to a statistically significant value less than 0.05

Table 5 Association between obesity-related parameters and the risk of colorectal adenoma development in multivariate analysis

	Final model[a]		
	OR	95% CI	*p* value[b]
By continuous variables			
Waist circumference	1.01	1.00–1.02	**0.044**
Age	1.03	1.02–1.04	**<0.001**
Male sex	1.49	1.17–1.88	**0.001**
Alcohol consumption ≥3/week	1.33	1.10–1.62	**0.004**
Number of baseline adenomas	1.21	1.10–1.33	**<0.001**
Advanced neoplasm at baseline	1.60	1.24–2.06	**<0.001**
By binary variables			
Waist circumference			
≥85 cm in men	1.31	1.09–1.57	**0.004**
≥82 cm in women	1.31	1.09–1.56	**0.003**
Age ≥50	1.56	1.32–1.85	**<0.001**
Male sex	1.50	1.21–1.87	**<0.001**
Alcohol consumption ≥3/week	1.32	1.09–1.61	**0.005**
Number of baseline adenomas ≥2	1.60	1.28–2.00	**<0.001**
Advanced neoplasm at baseline	1.80	1.50–2.16	**<0.001**

OR odds ratio, *CI* confidence interval

[a] Final model is multivariate analysis using logistic regression with stepwise variable selection. The candidate risk factors included age, sex, body mass index, waist circumference, smoking status, alcohol intake, physical activity, regular aspirin use, NSAIDs use, family history of CRC, fasting glucose, high-density lipoprotein-cholesterol, triglycerides, systolic blood pressure, number of baseline adenomas, characteristics of baseline adenomas, and follow-up time interval

[b] *P* value expressed in bold corresponds to a statistically significant value less than 0.05

associated with an increased risk of colorectal adenoma [24, 38]. However, these studies were not adjusted for BMI.

Several mechanisms have been proposed to explain the association between central obesity and the risk of colorectal neoplasms. Visceral adipose tissue is now recognized as an endocrine organ rather than as simple fat storage. Multiple cytokines are released from adipose tissue, including leptin, adiponectin, tumor necrosis factor, and interleukin-6. Leptin stimulates the growth of colonic epithelial cells, and adiponectin is involved in colon carcinogenesis [39]. Tumor necrosis factor and interleukin-6 are also known to have direct tumorigenic effects on the gastrointestinal tract [40, 41]. In addition, insulin resistance and hyperinsulinemia, resulting from the accumulation of visceral fat, are related to increased levels of insulin-like growth factor 1, which stimulates cellular mitogenesis [42–44].

This study has several strengths. First, its cohort study design and large sample size allowed us to identify causal associations, unlike cross-sectional studies. From our results, we could determine that abdominal obesity is a significant factor associated with the development of colorectal adenoma. Second, we repetitively examined the obesity-related parameters at the same hospital for all participants and used high-quality, standardized clinical and laboratory methods. Finally, we measured all possible confounders related to obesity and colorectal neoplasia. This allowed us to find the most reliable obesity-related factors impacting the risk of colorectal adenoma.

Nevertheless, several limitations need to be a considered in the interpretation of our study. First, it was a single-center, retrospective study. Second, although the cohort was large, the incidence of advanced colorectal neoplasm after baseline polypectomy was low; only 42 (1.2%) participants developed advanced colorectal neoplasm. This might have been insufficient to identify associations between obesity and advanced colorectal neoplasm. However, the incidence of advanced colorectal adenoma is quite low at our center because of the high quality of the colonoscopies. Therefore, our study was able to rule out unmeasured confounders associated with colonoscopy quality, which might affect the incidence of colorectal adenoma. Third, another possible limitation to our study is that adenomas may have been missed at index colonoscopy. However, the adenoma detection rate in the index colonoscopy was 43.2% (1095/2532) for men and 35.7% (312/873) for women and these are higher than recommended benchmarks. The high adenoma detection rates of our study argues against a significant number of missed lesions. Therefore, most adenomas detected on surveillance colonoscopy could be considered as metachronous lesions, not missed lesions.

In conclusion, we found that central obesity is an independent risk factor for metachronous colorectal adenoma, whereas BMI and other metabolic abnormalities were less important. These results suggest that patients who have central obesity and are found to have high risk adenomas at index colonoscopy are at higher risk for metachronous colorectal adenomas, and surveillance colonoscopy should be recommended.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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