

Obesity Markers as Predictors for Colorectal Neoplasia

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Background: The goal of this study was to determine the relations between the risk of colorectal neoplasia and obesity markers: body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR).

Methods: The subjects who underwent screening colonoscopies at a Kyungpook National University Hospital in Daegu from July to December 2010 were enrolled. We defined colorectal neoplasia as tubular adenoma, advanced adenoma, or cancer. We performed a logistic regression analysis to investigate the correlations between obesity and colorectal neoplasia and a receiver operating characteristic (ROC) curve analysis to determine the cut-off obesity marker values for detecting colorectal neoplasia.

Results: Among the total of 268 subjects, 83 (31.0%) subjects had colorectal neoplasia. Subjects with neoplasia had higher BMI, WC, and WHtR than the subjects without any neoplasia. The adjusted odds ratio (aOR) of WHtR ≥ 0.5 with the association of neoplasia was 1.927 (95% confidence interval [CI], 1.041-3.569) in the total subjects. In women, the obesity markers of WC ≥ 85 cm (aOR 4.611; 95% CI, 10.166-18.240) and WHtR ≥ 0.5 (aOR 1.747; 95% CI, 1.149-19.617) were significantly related to neoplasia; however, there was no significant result in men. The ROC analysis showed the optimal cut-off values of BMI as > 23.14 kg/m² ($P=0.002$), WHtR as > 0.50 ($P<0.001$), and WC as > 82.5 cm ($P=0.650$) in men and > 77 cm in women ($P<0.001$).

Conclusion: Obesity is significantly associated with the increased risk of colorectal neoplasia. WC and WHtR have more significant correlations with neoplasia; thus, obese people should undergo regular colonoscopy screenings to detect colorectal neoplasia.

Key words: Body mass index, Colorectal neoplasms, Obesity, Waist circumference, Waist-height ratio

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INTRODUCTION

There is a trend of increasing obese population from the introduction of Westernized dietary habits and hypernutrition. The World Health Organization (WHO) Western Pacific Regional office defines the criterion for obesity as a body mass index (BMI) of ≥ 25 kg/m².¹ According to this criterion, the obese population in Korea increased rapidly after the 1980s and reached to 32.8% of all adult populations by 2012², which is very close to the 34.9% prevalence of obesity among American adults.³ It is a widely known fact that obesity can cause metabolic disorders, such as hypertension, diabetes, and dyslipidemia⁴, and by causing such diseases, obesity is directly responsible for increasing the prevalence of various diseases

and mortality rate.⁵ Recently, a number of studies have reported that obesity is a risk factor for various malignancies, placing greater emphasis on obesity. Among them, colorectal cancer accounts for 10.0% of all cancer cases and represents the 4th and 3rd most common cancer among men and women, respectively, worldwide.⁶ In most colorectal cancer cases, adenomatous colorectal polyps and precancerous lesions progress by an adenoma-carcinoma sequence. Several lifestyle factors are associated with the adenoma-carcinoma sequence. High fat diet, smoking, excessive alcohol consumption, physical activity, obesity and insulin resistance are known to be associated.⁷ Colorectal cancer has the 3rd highest prevalence among all cancers in Korea, following only thyroid and gastric cancer; in 2011, it was found to show an average annual prevalence increase of

5.6%, which is believed to be closely associated with the rapid increase in the prevalence of obesity caused primarily by a decrease in physical activities and Westernized dietary habits from recent socioeconomic advances in Korea.^{8,9} The cost burden associated with the increase in colorectal cancer population is also expected to increase exponentially; thus, in cases where metabolic syndrome is a preventable risk factor for colorectal neoplasia, socioeconomic benefits can be expected from the decrease in the incidence of colorectal cancer by managing obesity through exercise and weight loss strategies. However, although many studies have examined the relationship between obesity and colorectal cancer, very few have examined the relationship between obesity and colorectal neoplasia, such as colorectal polyps, with such studies lacking especially in Korea.

Accordingly, the present study investigated the association of the occurrence of colorectal neoplasia with obesity in average-risk Korean adults. Moreover, the study used these obesity markers in determining whether such markers can effectively predict the risk for colorectal neoplasia.

METHODS

Subjects

The present study conducted a retrospective chart review of Korean adults (20 years or older) who underwent colonoscopy at Kyungpook National University Hospital between July 1 and December 31, 2010. Among these patients, those who satisfied the following criteria were excluded: 1) those who had been diagnosed with gastrointestinal cancer, inflammatory bowel disease, or other systemic diseases, 2) those who have a history of colorectal surgery, 3) those with a family history of colorectal cancer, and 4) those with unreliable test results from inadequate preparation prior to colonoscopy. The present study was conducted with the approval of the Institutional Review Board of the regional hospital.

Methods

Demographic characteristics

The information the patients had filled out personally in the questionnaire was retrospectively reviewed to determine their personal and family medical history and smoking, drinking, and exercise status. The patients were identified to have hypertension, dia-

betes, or dyslipidemia if they had been diagnosed by a physician or were taking medications for the treatment of such diseases. For exercise status, exercising for at least 30 minutes per session with ≥ 3 sessions per week was defined as regular exercise. For smoking status, those who quit smoking or never smoked were defined as non-smokers. For drinking status, high risk drinking was defined as 7 and 5 shots of soju in one sitting for men and women, respectively and sub-divided into moderate drinking (drinking once or less per month), heavy drinking (engaging in high risk drinking at least once a week), and mild drinking (all other cases).¹⁰

Obesity markers: BMI, waist circumference (WC), and waist-to-height ratio (WHtR)

Anthropometric measurements were obtained with the patients wearing only a disposable examination gown, while barefooted. On the basis of the measured weight and height, BMI was calculated using this formula: weight (kg)/height (m)². For WC, the results from measuring the midpoint between the lowest rib and iliac crest were used. Moreover, this was used to calculate the WHtR. Obesity was analyzed based on the criteria of BMI ≥ 25 kg/m² and WC of ≥ 90 and ≥ 85 cm for men and women, respectively, which represent the criteria recommended by the Korean Society for the Study of Obesity. WHtR was analyzed with the subjects divided by a criterion of 0.5, based on a previous study.¹¹

Blood tests

As laboratory findings, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood glucose, glycated hemoglobin, and carcinoembryonic antigen (CEA) levels from blood tests performed on an empty stomach after ≥ 8 hours of fasting were investigated.

Colonoscopy

In preparing for the colonoscopy, 4 L of Colyte-F was used as the colon cleanser to empty the bowel. Afterwards, while maintaining an empty stomach, the procedure was performed by a gastroenterologist with an experience of performing more than 1,000 cases of colonoscopy. Biopsy was performed in all cases that showed any abnormal findings during colonoscopy, and the cases were classified on the basis of the pathological biopsy results as no adenoma,

nonspecific finding, tubular adenoma, advanced adenoma, and cancer depending on how advanced the malignancy was. Hyperplastic polyp and chronic colitis were classified as nonspecific findings. In cases where several lesions were found at once on the same subject, the classification was made on the basis of the most advanced pathological result. The subjects were assigned to the neoplasia group if they had tubular adenoma, advanced adenoma, or colorectal cancer and the control group if they had no adenoma or only nonspecific findings.

Statistical analyses

The analyses were performed with the subjects divided into the neoplasia and control groups according to the criteria presented earlier. Pearson's chi-square test and independent samples *t*-test were used to compare the characteristics between the two groups, while a logistic regression analysis was used to examine the relationship between the obesity markers and colorectal cancer, with 95% confidence intervals (CI). Moreover, a receiver operating characteristic (ROC) curve analysis was used to analyze the accuracy of colorectal neoplasia discovery relative to different possible cut-off points of BMI, WC, and WHtR. The area under the ROC curve (AUC) was also measured, and the values were classified as non-informative ($AUC = 0.5$), less accurate ($0.5 < AUC \leq 0.7$), moderately accurate ($0.7 < AUC \leq 0.9$), highly accurate ($0.9 < AUC \leq 1$), and perfect test ($AUC = 1$).¹² The MedCalc Version 15.11.0 was used for the ROC curve analysis, while the IBM SPSS Statistics Version 22 was used for all other analyses. For all statistical results, *P* value < 0.05 was considered statistically significant.

RESULTS

Comparisons of subject characteristics and obesity markers

Among the total of 286 patients who had undergone a colonoscopy during the study period, 18 were excluded based on the exclusion criteria, leaving 268 patients as the subjects of the final analysis. In the colonoscopy results, neoplasia corresponding to tubular adenoma, advanced adenoma, or colorectal cancer was found in 83 patients, representing a prevalence of 31%. The mean age in the

neoplasia and control groups was 51.1 and 45.8 years, respectively ($P < 0.001$), while the percentage of men was 53.5% and 22.9%, respectively ($P < 0.001$). The mean BMI (kg/m^2) in the two groups was 24.5 and 23.6, respectively ($P = 0.021$), indicating a significantly higher BMI in the neoplasia group. However, when the obesity criterion of $\text{BMI} \geq 25 \text{ kg}/\text{m}^2$ was applied, there was no statistically significant difference in the prevalence of obesity between the two groups. WC (cm) was higher in the neoplasia group than in the control group (85.8 vs 81.8, $P < 0.001$); however, when the obesity criterion of 90 cm for men and 85 cm for women was applied, there was also no statistically significant difference between the two groups. WHtR was also higher in the neoplasia group than in the control group (0.51 vs 0.49, $P = 0.001$), and when the obesity criterion of 0.5 was applied, 69.9% of the neoplasia group and 48.6% of the control group were identified as obese, with the difference being statistically significant ($P = 0.001$).

As compared to the control group, the neoplasia group showed a significantly higher systolic blood pressure (126.1 vs 120.3, $P = 0.006$), diastolic blood pressure (77.7 vs 74.6, $P = 0.017$), triglyceride levels (177.5 vs 134.0, $P = 0.017$), and prevalence of hypertension (38.6% vs 26.5%, $P = 0.047$), while showing lower HDL cholesterol levels (50.5 vs 57.2, $P < 0.001$). There were no statistically significant differences between the two groups with respect to other physical examinations and blood test results, diabetes and dyslipidemia status, and lifestyle factors (Table 1).

Correlations between colorectal neoplasia and obesity markers

The logistic regression analysis was performed with the presence of colorectal neoplasia, as the dependent variable and each obesity marker as independent variables, which were adjusted for metabolic factors known to be associated with obesity, such as sex, age, diabetes, hypertension, and exercise, smoking, and drinking status. When all of the subjects were analyzed, there was no significant correlation between colorectal neoplasia and obesity classified by the criteria of BMI and WC, whereas in cases of obesity with $\text{WHtR} \geq 0.5$, a significant association was found with the odds ratio of having colorectal neoplasia being 1.927 (95% CI, 1.041-3.569).

All factors mentioned above, except sex, were adjusted in performing separate analyses for men and women. The results indicat-

Table 1. General characteristics of the subjects

Characteristic	Neoplasia group (n=83)	Control group (n=185)	Pvalue*
Age (year)	51.1±8.4	45.8±8.6	<0.001
Male	64 (53.5)	99 (22.9)	<0.001
Height (cm)	167.7±8.0	165.8±8.2	0.066
Weight (kg)	69.2±9.7	65.3±12.1	0.006
Body mass index (kg/m ²)	24.5±2.5	23.6±3.1	0.021
BMI ≥ 25 kg/m ²	31 (37.3)	58 (31.4)	0.335
Waist circumference (cm)	85.8±6.6	81.8±9.8	<0.001
WC ≥ 90 cm in men or ≥ 85 cm in women	32 (38.6)	61 (33.0)	0.375
Waist-to-height ratio	0.51±0.41	0.49±0.52	0.001
WHtR ≥ 0.5	58 (69.9)	90 (48.6)	0.001
Systolic blood pressure (mmHg)	126.1±13.6	120.3±16.8	0.006
Diastolic blood pressure (mmHg)	77.7±8.9	74.6±11.3	0.017
HbA1c (%)	5.8±0.7	5.8±0.8	0.972
Glucose (mg/dL)	97.8±17.0	97.0±21.4	0.761
HDL cholesterol (mg/dL)	50.5±13.1	57.2±13.4	<0.001
Total cholesterol (mg/dL)	196.2±31.3	201.2±37.1	0.286
LDL cholesterol (mg/dL)	113.8±31.4	117.7±31.7	0.352
Triglyceride (mg/dL)	177.5±144.8	134.0±113.2	0.017
CEA (ng/mL)	1.9±1.4	1.7±1.2	0.216
Regular exercise	41 (49.4)	93 (50.6)	0.895
Current smoker	23 (27.7)	66 (35.7)	0.201
Moderate to heavy alcohol consumption	59 (71.1)	113 (61.1)	0.114
Hypertension	32 (38.6)	49 (26.5)	0.047
Diabetes	6 (7.2)	16 (8.6)	0.695
Dyslipidemia	7 (8.4)	18 (9.7)	0.736

Data are presented as mean±standard deviation or number (%).

Pearson's Chi-square test was used for discrete variables and independent samples *t*-test for continuous variables.

BMI, body mass index; CEA, carcinoembryonic antigen; HDL, high density lipoprotein; LDL, low density lipoprotein; WC, waist circumference; WHtR, waist-to-height ratio; HbA1c, glycosylated hemoglobin.

ed that women had an odds ratio of 4.611 (95% CI, 10.166-18.240) with obesity corresponding to WC ≥ 85 cm and 4.747 (95% CI, 1.149-19.617) with obesity corresponding to WHtR ≥ 0.5, showing statistically significant differences. Meanwhile, no significant association was seen in relation to obesity corresponding to BMI ≥ 25 kg/m². In men, no significant association was also found between the presence of colorectal neoplasia and any of the obesity markers (Table 2).

Analysis of the cut-off points of the obesity markers for predicting colorectal neoplasia

An ROC curve analysis was performed to determine whether each obesity marker would be effective in predicting colorectal neoplasia, including tubular adenoma, advanced adenoma, and cancer and their corresponding appropriate cut-off points. When

Table 2. Relationship between colorectal neoplasia and obesity markers

Independent variables	OR	95% CI	Pvalue
Total subject (n=268)			
BMI ≥ 25 kg/m ²	1.218	0.657-2.258	0.532
WC ≥ 90 cm in men or ≥ 85 cm in women	1.272	0.677-2.388	0.455
WHtR ≥ 0.5	1.927	1.041-3.569	0.037
Male subjects (n=163)			
BMI ≥ 25 kg/m ²	1.167	0.542-2.511	0.693
WC ≥ 90 cm	0.949	0.422-2.136	0.900
WHtR ≥ 0.5	1.620	0.756-3.469	0.214
Female subjects (n=105)			
BMI ≥ 25 kg/m ²	2.039	0.547-7.602	0.289
WC ≥ 85 cm	4.611	10.166-18.240	0.029
WHtR ≥ 0.5	4.747	1.149-19.617	0.031

Logistic regression analysis was adjusted for sex (removed in sex-subgroup analysis), age, exercise, smoking, alcohol consumption, diabetes, and hypertension.

The presence of colorectal neoplasia was the dependent variable and each obesity marker the independent variables.

BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio.

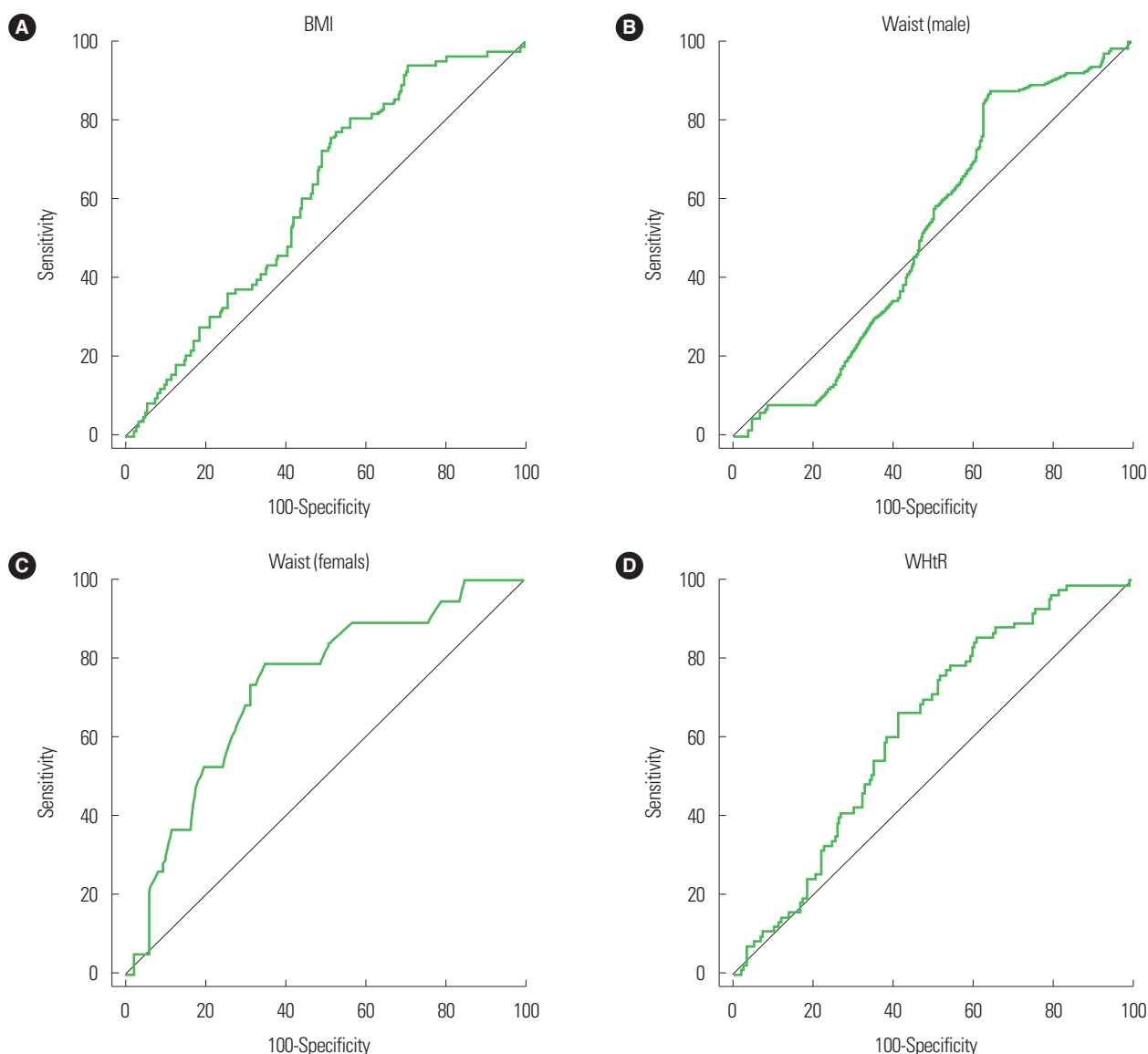


Figure 1. Receiver operating characteristic (ROC) curve using the obesity markers to predict colorectal neoplasia development, including adenoma and cancer. (A) BMI: AUC=0.610 (95% Confidence Interval [CI] 0.549-0.669), $P=0.002$, and Youden index criterion BMI >23.14 kg/m² with sensitivity 75.90% and specificity 48.65%. (B) WC in men: AUC=0.521 (95% CI, 0.441-0.599), $P=0.650$, and Youden index criterion WC >82.5 cm with sensitivity 87.50% and specificity 35.35%. (C) WC in women: AUC=0.731 (95% CI, 0.635-0.813), $P<0.001$, and Youden index criterion WC >77 cm with sensitivity 78.95% and specificity 65.12%. (D) WHtR: AUC=0.626 (95% CI, 0.565-0.684), $P<0.001$, and Youden index criterion WHtR >0.50 with sensitivity 66.27% and specificity 58.38%. BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio.

BMI was >23.14 kg/m², best sensitivity (75.90%) and specificity (48.65%) for predicting colorectal neoplasia were seen, which were statistically significant (AUC = 0.610, $P=0.002$). WC was analyzed separately for men and women; for men, the cut-off point was WC >82.5 cm, which showed no statistical significance (AUC = 0.521, $P=0.650$). Meanwhile, the cut-off point for women was WC >77 cm (sensitivity 78.95% and specificity 65.12%), which showed a statistical significance with a moderately accurate AUC of

0.731 ($P<0.001$). The adequate cut-off point for WHtR was found to be WHtR >0.50 , which was also statistically significant (AUC = 0.626, $P<0.001$) (Fig. 1).

DISCUSSION

The present study was a cross-sectional study that aimed to examine the associations between colorectal neoplasia and obesity.

The study found that obesity was significantly associated with colorectal neoplasia, including tubular adenoma, advanced adenoma, or cancer. Among the obesity markers, WHtR was a better indicator of colorectal neoplasia than BMI or WC; among women, WC was also found to be a useful marker.

The 5-year survival rate for colorectal cancer may vary significantly depending on how advanced the lesion is at the time of diagnosis¹³; as such, there have been continued efforts to identify its risk factors for prevention and early diagnosis. Studies have found that approximately 75% of colorectal cancer cases are caused by modifiable environmental factors, such as obesity, red or processed meat consumption, reduced physical activities, and drinking.¹⁴ Among these risk factors, obesity is considered as the most important risk factor. Obesity increases the risk of colorectal neoplasia, such as adenoma and colorectal cancer, by being involved with endotoxemia, metabolic syndrome, and chronic low grade inflammation associated with insulin, insulin-like growth factors, adipokines, cytokines, and chemokines.¹⁵⁻¹⁷ According to actual epidemiological study reports, a study on Japanese subjects showed that when a BMI of 25 kg/m² was applied, which is the same criterion used in Korea, the risk for colorectal cancer increased by 1.5 fold in the obese population compared to those with normal weight.¹⁸ Moreover, a meta-analysis conducted mostly on Westerners showed that as BMI increased each time by 5 kg/m², the risk for colorectal cancer also increased by 1.13 and 1.06 folds in men and women, respectively. Furthermore, obesity also increased the risk for adenoma and precancerous colorectal lesions in a similar manner as in colorectal cancer, with an increase of 5 kg/m² in BMI, resulting in increased risks for colorectal adenoma by 1.19-3.83 folds¹⁹⁻²³, which is indicative of how important the association between obesity and colorectal neoplasia is.

The results in the present study showed that patients with colorectal neoplasia had higher BMI, WC, and WHtR, which supported the findings of previous studies. However, when the association between obesity and colorectal neoplasia was examined with obesity classified according to the known criteria of BMI, WC, and WHtR and all known risk factors for colorectal cancer being adjusted, there was no statistically significant association between the risk for neoplasia and obesity based on BMI. According to a previous meta-analysis, an increase in BMI, WC, and WHtR tended to in-

crease the risk for colorectal cancer²⁴; however, because different studies used different obesity markers, the results were not always consistent. As a result, which marker is most appropriate is still controversial. Although BMI is the most commonly used marker to measure the degree of obesity, the marker that has a direct influence on the onset of colorectal neoplasia from a physiological perspective is considered to be abdominal obesity. This is because abdominal visceral fat has a high physiological activity level and is easily dissolved; as a result, a high level of free fatty acids is released to interfere with the insulin signaling process, which causes an insulin resistance.¹⁵ Consequently, WC or WHtR, which reflects abdominal obesity better than BMI does, are expected to be more effective in predicting the risk for colorectal neoplasia; further, previous studies conducted in Japan and Korea^{25,26} also showed that obesity markers that reflect abdominal obesity, such as waist-to-hip ratio, were more useful in predicting adenomatous polyps than BMI, which supported the finding in the present study.

Another interesting point in the present study was that men did not show statistical significance with respect to BMI, WC, and WHtR, whereas women showed significant associations with obesity of WC \geq 85 cm showing a 4.6 fold increase in the risk for colorectal neoplasia and obesity of WHtR \geq 0.5 also showing a 4.7 fold increase. These findings were slightly different than the results of previous studies that showed stronger associations in men^{20,23}, which may be attributed to the following factors: First, the present study adjusted for all possible factors, unlike previous studies. Second, the present study examined only Koreans; thus, the results may vary from other studies that included many Caucasians. Since Asians tend to show higher risks for colorectal cancer than other races according to BMI increase²⁷, racial differences cannot be disregarded. A study on Japanese subjects also showed that the association between WHtR and colorectal cancer was more significant in women than in men²⁸, which was similar to the finding in the present study and also serves as an evidence that a racial difference exists. Third, compared to previous studies that used the obesity criteria for Westerners, the present study used more stringent criteria for obesity, which may have led to different results being obtained. In addition, the subjects in the present study were relatively younger than those in previous studies, and others factors, such as female hormones, diet, differences in pathological stages, and genetic

modifications²⁹ can also be considered with respect to the possibility of different results being found.³⁰

In the present study, the ROC curve analysis was used to find the cut-off points of the obesity markers for predicting the onset of colorectal neoplasia. The cut-off point for BMI and WHtR was found to be 23.14 kg/m² and 0.50, respectively, while WC for women was 77 cm. AUC of each was found to be statistically significant. Among these, WHtR showed the highest AUC value among both men and women, while WC showed the highest value among women only; this suggests that in order to predict high risk groups for colorectal neoplasia, the focus should be on abdominal obesity rather than BMI. The cut-off point of WHtR for the most effective prediction of actual risks for cardiovascular diseases was 0.50, and WHtR better reflected the risk for cardiovascular diseases than WC or BMI, which supports the findings in the present study.^{31,32}

The present study has the following limitations: First, because the study investigated patients who had visited a single university hospital on their own, it is possible that the study was biased towards those who would normally be interested in their health, which means that this population may not represent the entire community. Second, because all information related to drinking, smoking, and exercise were based on the questionnaire given by the examiner, it is possible that recall-bias may have been involved. Third, other confounding factors that can influence the onset of colorectal neoplasia, such as dietary habits, level of physical activity among activities of daily living, menopausal status, and location and size of colorectal neoplasia were not excluded. Fourth, the study did not perform serological tests on sex hormones and adipocytokines nor evaluate insulin resistance, which has been suggested as a major pathogenic factor.

Despite those limitations, the present study has certain strengths. We identified possible confounding variables, such as smoking, drinking, and exercise through an objective questionnaire survey and adjusting for those variables. Moreover, it was the first study in Korea to compare the adequacy of risk factors for colorectal cancer by conducting an ROC curve analysis on obesity markers and analyzing the association between obesity and colorectal neoplasia, including colorectal adenoma and colorectal cancer.

In conclusion, obesity is associated with increased risks for colorectal neoplasia; in particular, WHtR measurement is relatively

simple and highly accurate, which can be considered as a meaningful test in screening for high risk groups for colorectal neoplasia. It would be necessary to conduct large-scale prospective studies using a greater variety of obesity markers and to examine whether the treatment of obesity through lifestyle adjustments and drug treatments can lead to a decreased incidence of colorectal neoplasia.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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