Obesity and Metabolic Unhealthiness Have Different Effects on Colorectal Neoplasms

Sun-Hye Ko,[1] Myong Ki Baeg,[2] Seung Yeon Ko,[3] Hee Sun Jung,[4] Pumsoo Kim,[2] and Myung-Gyu Choi[5]

[1]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, South Korea; [2]Department of Internal Medicine, International St. Mary's Hospital, College of Medicine, Catholic Kwandong University, Incheon 22711, South Korea; [3]Department of Surgery, Incheon St. Mary's Hospital, College of Medicine, Catholic University of Korea, Incheon 21431, South Korea; [4]Department of Health Promotion, Seoul St. Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul 06591, South Korea; and [5]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul 06591, South Korea

Context: Obesity and insulin resistance are risk factors for colorectal neoplasms (CRN), but data regarding metabolic status, obesity, and CRN are lacking.

Objective: To investigate the relationship between metabolic status, obesity, and CRN in Koreans who underwent colonoscopy.

Design: Retrospective, cross-sectional.

Participants: Subjects were divided based on metabolic and obesity criteria, as follows: metabolically healthy nonobese (MHNO), metabolically healthy obese (MHO), metabolically unhealthy nonobese (MUNO), and metabolically unhealthy obese (MUO).

Main Outcome Measures: Multiple regression was used to identify CRN and advanced CRN risk factors, with the MHNO group as reference.

Results: A total of 10,235 subjects was included, as follows: 5096 MHNO, 1538 MHO, 1746 MUNO, and 1855 MUO. Of these, 3297 had CRN (32.2%), and 434 (4.2%) had advanced CRN. Number of subjects with CRN in each group were: MHNO 25.8%, MHO 33.9%, MUNO 38.9%, and MUO 42.0% (P for trend < 0.001). Risk of CRN was increased in the MHO [odds ratio (OR) 1.239, 95% confidence interval (CI) 1.082 to 1.418, $P = 0.002$], the MUNO (OR 1.233, 95% CI 1.086 to 1.400, $P = 0.001$), and the MUO groups (OR 1.510, 95% CI 1.338 to 1.706, $P < 0.001$), whereas risk of advanced CRN was increased in the MUNO (OR 1.587, 95% CI 1.222 to 2.062, $P = 0.001$) and the MUO groups (OR 1.456, 95% CI 1.116 to 1.900, $P = 0.006$).

Conclusions: Obesity increased CRN risk with metabolically unhealthy status adding risk. For advanced CRN, metabolically unhealthy status increased the risk but obesity did not. **(*J Clin Endocrinol Metab* 102: 2762–2769, 2017)**

Globally, colorectal cancer (CRC) is the second most common malignancy in women and the third most common in men. It is also the fourth leading cause of cancer death in the world, accounting for >1.3 million new cases and almost 700,000 deaths in 2012 (1). Known risk factors include increasing age; male gender; previous colorectal neoplasms (CRNs); hereditary syndromes, such as Lynch syndrome or familial adenomatous polyposis;

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Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; CRA, colorectal adenoma; CRC, colorectal cancer; CRN, colorectal neoplasm; EGFR, epidermal growth factor receptor; HOMA-IR, homeostasis model assessment of insulin resistance; IGF-1, insulinlike growth factor-1; MHNO, metabolically healthy nonobese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy nonobese; MUO, metabolically unhealthy obese; OR, odds ratio.

and environmental factors, such as smoking, high alcohol consumption, unhealthy dietary patterns, insulin resistance, and obesity (2).

Environmental factors are important because they can be targeted either for primary prevention or to determine those at high risk of CRN. Metabolic risk factors such as diabetes, metabolic syndrome, and obesity are of particular interest because the global incidence of these is rapidly increasing (3–5). Although the pathophysiology underlying the link between metabolic abnormalities and increased CRN risk is not fully understood, meta-analyses have consistently demonstrated that such an association exists (6–9). However, the degree of metabolic disorder is variable because only two-thirds of patients with metabolic syndrome are obese (10, 11), and some obese subjects are metabolically healthy (12). Some recent studies have reported that cardiovascular risk is not increased in metabolically healthy obese (MHO) subjects, whereas others have reported that MHO increases cardiovascular risk (12–14). In regard to CRN risk, studies that investigated the associations between metabolic status, obesity, and CRN have reported conflicting results (15–17). The aim of this study was to investigate the relationship between metabolic status, obesity, and CRN risk in Korean subjects who underwent colonoscopy during routine health screening.

Materials and Methods

Study population

We conducted a retrospective, cross-sectional study of native Koreans who underwent routine health screening at the Health Promotion Center of Seoul St. Mary's Hospital from March 2009 to July 2014. Subjects who underwent screening colonoscopy and for whom results for fasting serum insulin were available were included in this study. We excluded subjects with the following: (1) a previous history of colon polypectomy, (2) malignancies, (3) a history of gastrointestinal surgery other than simple appendectomy or cholecystectomy, (4) missing medical or social history, (5) missing laboratory findings, or (6) incomplete colonoscopies. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, which waived informed consent requirements because this was a retrospective study using blinded records (KC14RISI0574).

Data collection

Social and medical histories were obtained through a standardized self-administered questionnaire. The questionnaire asked about smoking and alcohol consumption, and about medical history concerning prior malignancies, surgery, diabetes, hypertension, dyslipidemia, cardiovascular and cerebrovascular diseases, and previous colon polypectomy. Medication history included aspirin use, antidiabetes medication, antihypertensive medication, and medication for dyslipidemia. Trained personnel took anthropometric measurements, including height, weight, waist circumference, and blood pressure. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest. Blood pressure was measured using a mercury sphygmomanometer on the right arm, using an appropriately sized cuff with the subject seated, and after at least 10 minutes of rest. Body mass index was calculated as weight divided by the square of height (kg/m^2). Body composition was obtained using multifrequency bioelectrical impedance analysis (Inbody 4.0; Biospace, Seoul, South Korea), according to previously established methods (18).

Fasting blood samples were taken in the morning after an overnight fast of at least 12 hours and abstinence of diabetic medication from 6 PM of the previous day. Total blood cell counts were measured using a Sysmex-XE2100 automated blood cell analyzer (Sysmex, Kobe, Japan). Fasting plasma glucose, insulin, total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, aspartate transaminase, and alanine transaminase were measured with a Hitachi 7600 Autoanalyzer (Hitachi, Tokyo, Japan). Glycated hemoglobin was measured with a Tosoh HLC-723 HBG7 analyzer (Tosoh Bioscience, Redditch, UK). Serum carcinoembryonic antigen (CEA) levels were checked using an ADVIA Centaur XRT Immunoassay System (Siemens Health Care Global, Erlangen, Germany). Insulin resistance was computed by the homeostasis model assessment of insulin resistance (HOMA-IR), as follows: fasting insulin (pmol/L) $\times$ fasting glucose (mmol/L)/22.5.

Colonoscopic examinations and definition of CRNs

Colonoscopy (Olympus CIF-H260; Olympus, Tokyo, Japan) was performed by board-certified endoscopists after standard preparation of patients with 4 L polyethylene glycol (Taejoon Pharm, Seoul, South Korea). All polyps encountered during colonoscopy were removed and sent to the pathology department for histological analysis. Polyp size was measured endoscopically by visual estimation and comparison with a 6-mm biopsy forceps. Nonneoplastic polyps such as hyperplastic, inflammatory, lymphoid polyps or mucosal tags were classified as colorectal polyps but not CRN. CRN was defined as the presence of components of adenoma or adenocarcinoma. Advanced adenoma was defined, according to the 2012 American Gastroenterology Association guidelines, as follows: high-grade dysplasia, villous features, $\geq$1 cm in size, or adenocarcinoma. Multiplicity was defined as the presence of at least three CRNs (19).

Definition of metabolic status and obesity

Metabolic health status was defined according to the modified Wildman criteria, and obesity was defined according to the World Health Organization Asian criteria (body mass index $\geq$25 kg/m^2) (11, 20, 21). The modified Wildman criteria are as follows: systolic blood pressure $\geq$130 mm Hg or diastolic blood pressure $\geq$85 mm Hg or use of antihypertensive medication; triglyceride levels $\geq$1.7 mmol/L or use of lipid-lowering drugs; fasting plasma glucose $\geq$100 mg/dL or use of antidiabetes medication; high-density lipoprotein cholesterol levels $<$1.03 mmol/L in men and $<$1.29 mmol/L in women; and HOMA-IR $>$90th percentile in our population ($\geq$3.06). Subjects were defined as metabolically healthy if they met none or one of the modified Wildman criteria and metabolically unhealthy if they met two or more of the criteria. Based on the modified Wildman

and obesity criteria, the subjects were divided into four groups, as follows: metabolically healthy nonobese (MHNO), MHO, metabolically unhealthy nonobese (MUNO), and metabolically unhealthy obese (MUO).

Statistical analysis

Clinical characteristics and parameters are expressed as mean ± standard deviation or numbers (percentage). Categorical variables were analyzed by Pearson's χ^2 test, and continuous variables by analysis of variance. Multiple regression analysis was performed to identify risk factors for CRN and advanced CRN. Odds ratios (ORs) and 95% confidence intervals (CIs) for CRN and advanced CRN were calculated for the MHO, MUNO, and MUO groups using the MHNO group as a reference. Three models were constructed, as follows: model 1 was adjusted for age, gender, and metabolic health/obesity status; model 2 was model 1 additionally adjusted for CEA; and model 3 was model 2 additionally adjusted for smoking and alcohol consumption. Also, a separate analysis was performed with metabolic health status and obesity divided into distinct categories. Finally, a subanalysis of the metabolically unhealthy groups was performed to discover which causes assigned individuals to the metabolically unhealthy groups and to find whether a specific metabolic phenotype conferred added risk to CRN or advanced CRN. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

During the study period, 13,563 Koreans underwent screening colonoscopy and had fasting insulin measured as a part of routine health examinations. Of these, 3328 were excluded: 818 because of previous colon polypectomies, 89 because of previously diagnosed malignancies or abdominal surgery, 1244 with missing social or medical history, 1039 because of missing laboratory data, and 138 because of incomplete colonoscopy. Of the remaining 10,235 subjects, 5096 were in the MHNO group, 1538 in the MHO group, 1746 in the MUNO group, and 1855 in the MUO group (Fig. 1).

The baseline characteristics of the four groups are shown in Table 1. The metabolically unhealthy groups were older than the metabolically healthy groups. There was a higher proportion of females in the MHNO group, whereas the other three groups included more males. There was a significant difference in body mass index between each of all four groups (between each group $P < 0.001$). The MHNO group had a lower proportion of subjects who smoked or drank. The metabolic indices of fasting plasma glucose, glycated hemoglobin, insulin, and HOMA-IR were the lowest in the MHNO group; increased successively in the MHO and MUNO groups; and were highest in the MUO group. CEA levels were increased with poor metabolic health status but were not altered by obesity.

There were 4737 subjects with colon polyps (46.3%). Of these, 3297 had CRN (32.2%), and 434 (4.2%) had advanced CRN. The proportion of subjects with CRN in each group increased in the following order: MHNO (25.8%), MHO (33.9%), MUNO (38.9%), and MUO

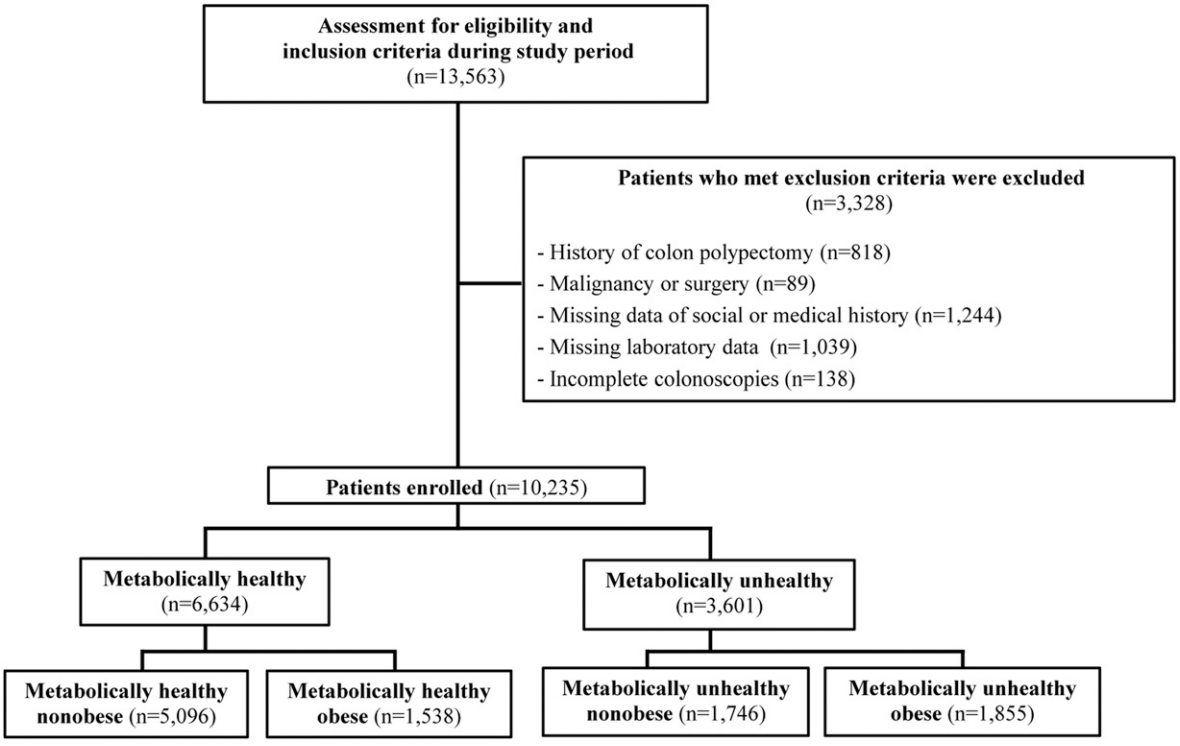

Figure 1. Flow chart of the study design.

Table 1. Clinical and Demographic Characteristics of the Study Population

	MHNO (n = 5096)	MHO (n = 1538)	MUNO (n = 1746)	MUO (n = 1855)	*P*
Age (y)	50.5 ± 10.6	51.2 ± 10.6	56.8 ± 9.8	53.9 ± 10.6	<0.001
Male (n)	2397 (47.0%)	1075 (69.9%)	1081 (61.9%)	1398 (75.4%)	<0.001
Body mass index (kg/m^2)	21.8 ± 2.0	26.8 ± 1.8	23.0 ± 1.6	27.5 ± 2.3	<0.001
Body muscle (%)	41.0 ± 4.3	39.2 ± 4.5	40.5 ± 4.2	38.8 ± 4.3	<0.001
Body fat (%)	25.3 ± 6.5	29.8 ± 6.9	26.4 ± 6.3	30.5 ± 6.6	<0.001
Abdomen–waist ratio	0.89 ± 0.04	0.94 ± 0.04	0.92 ± 0.06	0.95 ± 0.04	<0.001
Diabetes (n)	135 (2.6%)	38 (2.5%)	471 (27.0%)	513 (27.7%)	<0.001
Hypertension (n)	457 (9.0%)	237 (15.4%)	760 (43.5%)	828 (44.6%)	<0.001
Smoking (n)	1850 (36.3%)	695 (45.2%)	823 (47.1%)	947 (51.1%)	<0.001
Drinking (n)	1773 (34.8%)	763 (49.6%)	721 (41.3%)	923 (50.0%)	<0.001
Total cholesterol (mg/dL)	199.7 ± 33.8	203.1 ± 34.7	200.8 ± 40.1	203.4 ± 9.9	<0.001
Triglyceride (mg/dL)	75.3 ± 40.9	97.5 ± 50.0	144.1 ± 90.5	174.0 ± 113.0	<0.001
HDL cholesterol (mg/dL)	57.1 ± 12.4	50.8 ± 9.8	46.6 ± 11.7	43.7 ± 9.9	<0.001
LDL cholesterol (mg/dL)	122.1 ± 31.0	129.6 ± 31.4	122.2 ± 33.7	125.3 ± 34.2	<0.001
Aspartate transaminase (IU/L)	25.2 ± 10.1	27.7 ± 10.6	28.9 ± 24.2	33.0 ± 18.1	<0.001
Alanine transaminase (IU/L)	24.7 ± 15.2	33.3 ± 20.7	31.6 ± 25.2	43.3 ± 32.0	<0.001
Fasting plasma glucose (mg/dL)	87.6 ± 13.4	90.3 ± 10.8	110.1 ± 29.4	111.7 ± 29.6	<0.001
HbA1c (%)	5.4 ± 0.5	5.5 ± 0.4	6.0 ± 1.0	6.1 ± 1.0	<0.001
Fasting insulin (mIU/mL)	4.5 ± 2.9	6.7 ± 3.9	7.2 ± 5.3	11.0 ± 8.5	<0.001
HOMA-IR	1.0 ± 0.7	1.5 ± 0.9	2.0 ± 1.7	3.0 ± 2.5	<0.001
CEA (ng/mL)	1.4 ± 1.3	1.4 ± 0.9	1.7 ± 1.2	1.7 ± 1.1	<0.001

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

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

(42.0%) (*P* for trend <0.001). In the case of advanced CRN, there was a difference between metabolically healthy and unhealthy groups, but obesity did not have an additional effect: MHNO (3.0%), MHO (3.8%), MUNO (6.5%), and MUO (5.9%) (Table 2).

Univariable analysis was performed to investigate the risk factors for CRN and advanced CRN (Table 3). Older age, male gender, smoking history, drinking, elevated CEA, and increased fasting insulin were risk factors for CRN and advanced CRN. Using the MHNO group as the reference, CRN risk was significantly increased in the MHO (OR 1.470, 95% CI 1.300 to 1.662, $P < 0.001$), MUNO (OR 1.830, 95% CI 1.632 to 2.053, $P < 0.001$), and MUO groups (OR 2.077, 95% CI 1.858 to 2.322, $P < 0.001$). For advanced CRN, this increase was noted only in the MUNO group (OR 2.257, 95% CI 1.760 to 2.894, $P < 0.001$) and the MUO group (OR 2.017, 95% CI 1.568 to 2.594, $P < 0.001$).

Multivariable analysis was performed to ascertain the risk factors for CRN and advanced CRN in three different models (Table 4). In all three models, older age and male gender were risk factors for CRN and advanced CRN. All three models also showed that CRN risk was significantly increased in the MHO (model 3, MHO: OR 1.239, 95% CI 1.082 to 1.418, $P = 0.002$) and MUNO groups (model 3, OR 1.233, 95% CI 1.086 to 1.400, $P = 0.001$) and was greatest in the MUO group (model 3, OR 1.510, 95% CI 1.338 to 1.706, $P < 0.001$). For advanced

Table 2. Endoscopic and Histologic Findings for the Study Population Based on Metabolic and Obesity Status

	MHNO (n = 5096)	MHO (n = 1538)	MUNO (n = 1746)	MUO (n = 1855)	*P*
Subjects with polyps	1954 (38.3%)	739 (48.0%)	967 (55.4%)	1077 (58.1%)	<0.001
Number of colorectal polyps	0.7 ± 1.4	1.1 ± 1.7	1.3 ± 2.1	1.5 ± 2.1	<0.001
Subjects with CRN	1317 (25.8%)	521 (33.9%)	680 (38.9%)	779 (42.0%)	<0.001
Number of CRN	0.4 ± 1.0	0.6 ± 1.3	0.8 ± 1.5	0.8 ± 1.5	<0.001
Subjects with multiple CRNs	170 (3.3%)	91 (5.9%)	160 (9.2%)	178 (9.6%)	<0.001
Subjects with advanced CRN	153 (3.0%)	58 (3.8%)	114 (6.5%)	109 (5.9%)	<0.001
CRN >1 cm	151 (3.0%)	58 (3.8%)	110 (6.3%)	104 (5.6%)	<0.001
High-grade CRN	18 (0.4%)	9 (0.6%)	13 (0.7%)	14 (0.8%)	0.092
Villous type	11 (0.2%)	5 (0.3%)	11 (0.6%)	5 (0.3%)	0.063
Carcinoma	14 (0.3%)	5 (0.3%)	16 (0.9%)	8 (0.4%)	0.004
Right-side CRN	540 (10.6%)	197 (12.8%)	276 (15.8%)	302 (16.3%)	<0.001
Left-side CRN	528 (10.4%)	213 (13.8%)	221 (12.7%)	281 (15.1%)	<0.001
Bilateral CRN	249 (4.9%)	111 (7.2%)	183 (10.5%)	191 (10.3%)	<0.001

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

Table 3. Univariable Analysis of CRN and Advanced CRN Risk Factors

	CRN			Advanced CRN		
	OR	95% CI	*P*	OR	95% CI	*P*
Metabolic health and obesity status						
MHNO	1			1		
MHO	1.470	1.300–1.662	<0.001	1.266	0.931–1.722	0.133
MUNO	1.830	1.632–2.053	<0.001	2.257	1.760–2.894	<0.001
MUO	2.077	1.858–2.322	<0.001	2.017	1.568–2.594	<0.001
Age	1.053	1.049–1.058	<0.001	1.057	1.047–1.067	<0.001
Male	2.257	2.066–2.467	<0.001	2.185	1.753–2.722	<0.001
Body mass index	1.080	1.066–1.094	<0.001	1.046	1.015–1.078	0.003
Diabetes	1.882	1.663–2.131	<0.001	1.921	1.500–2.461	<0.001
Hypertension	1.822	1.655–2.006	<0.001	1.859	1.516–2.280	<0.001
Smoking	1.598	1.469–1.737	<0.001	1.640	1.352–1.989	<0.001
Drinking	1.251	1.150–1.360	<0.001	1.134	0.934–1.377	0.203
CEA	1.208	1.160–1.257	<0.001	1.169	1.088–1.256	<0.001
Fasting insulin	1.027	1.019–1.035	<0.001	1.017	1.004–1.030	0.012

CRN, the risk was significantly increased in the metabolically unhealthy groups (model 3, MUNO: OR 1.587, 95% CI 1.222 to 2.062, $P = 0.001$; and MUO: OR 1.456, 95% CI 1.116 to 1.900, $P = 0.006$) but not in the metabolically healthy group (model 3, MHO: OR 1.072, 95% CI 0.774 to 1.484, $P = 0.676$). Finally, the results remained unchanged when the analysis was limited to the metabolically unhealthy groups with the MUNO group as the reference, with the MUO group having a significantly increased risk of CRN (model 3, OR 1.201, 95% CI 1.039 to 1.389, $P = 0.014$), but not advanced CRN (model 3, OR 0.925, 95% CI 0.696 to 1.230, $P = 0.592$) compared with the MUNO group.

A separate multivariable analysis that divided metabolic health status and obesity showed that metabolic unhealthiness increased both CRN and advanced CRN risk (model 3, CRN: OR 1.235, 95% CI 1.119 to 1.362, $P < 0.001$; advanced CRN: OR 1.511, 95% CI 1.225 to 1.866, $P < 0.001$). However, although obesity significantly increased CRN risk, it was not significant for advanced CRN (model 3, CRN: OR 1.216, 95% CI 1.102 to 1.343, $P < 0.001$; advanced CRN: OR 0.954, 95% CI 0.769 to 1.183, $P = 0.954$).

Finally, subanalysis of the metabolically unhealthy groups showed that high blood pressure and hyperglycemia of the Wildman criteria were most likely to be the cause of metabolic unhealthiness. However, there were no significant differences according to specific Wildman criteria in both CRN and advanced CRN of the metabolically unhealthy groups.

Discussion

This study found that both MHO and MUNO increased CRN risk. MUO further increased the risk of CRN compared with MHO or MUNO alone. For advanced CRN, MHO was not a risk factor. However, metabolically unhealthy states (MUNO or MUO) conferred increased risk to advanced CRN (ORs 1.587 and 1.456, respectively), although there was no difference in advanced CRN risk between MUNO and MUO groups. This, combined with the lack of increased risk in the

Table 4. Multivariable Analysis of CRN and Advanced CRN Risk Factors

		MHO		MUNO		MUO	
	MHNO (Reference)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CRN							
Model 1	1	1.211 (1.064–1.377)	0.004	1.247 (1.104–1.409)	<0.001	1.499 (1.332–1.686)	<0.001
Model 2	1	1.227 (1.072–1.405)	0.003	1.239 (1.091–1.406)	0.001	1.505 (1.331–1.700)	<0.001
Model 3	1	1.239 (1.082–1.418)	0.002	1.233 (1.086–1.400)	0.001	1.510 (1.338–1.706)	<0.001
Advanced CRN							
Model 1	1	1.068 (0.782–1.458)	0.678	1.567 (1.213–2.023)	0.001	1.487 (1.150–1.923)	0.002
Model 2	1	1.055 (0.762–1.459)	0.748	1.592 (1.226–2.068)	<0.001	1.443 (1.106–1.881)	0.007
Model 3	1	1.072 (0.774–1.484)	0.676	1.587 (1.222–2.062)	0.001	1.456 (1.116–1.900)	0.006

Model 1: adjusted for age, sex, and metabolic health/obesity status. Model 2: adjusted for age, sex, carcinoembryonic antigen, and metabolic health/obesity status. Model 3: adjusted for age, sex, carcinoembryonic antigen, smoking, drinking, and metabolic health/obesity status.

MHO group, suggests that obesity by itself may not be a risk factor for advanced CRN.

Obesity and insulin resistance have been reported to be risk factors for CRC and colorectal adenoma (CRA) (6, 9, 22, 23). The results of our study partially support this, because we found that obesity and metabolically unhealthy status were risk factors for CRN and that metabolically unhealthy status was a risk factor for advanced CRN. However, MHO status was not a risk factor for advanced CRN, which suggests that obesity by itself is insufficient to promote CRN progression. Our results are supported by those of a recent prospective study, which found that CRC risk was increased in both MUO and MUNO subjects but not in MHO subjects (15). Although the pathophysiology behind this is unclear, we believe that it may be explained by the classic adenoma–carcinoma pathway (24).

The classic colorectal adenoma–carcinoma pathway suggests that CRC arises from CRA through a stepwise sequence involving mutations in *APC*, *K-RAS*, and *TP53* (25). Obesity, which has been associated with colorectal carcinogenesis via increased chronic low-grade inflammation and increased adipokine production (26), has been associated with increased *APC* mutations (27–29). Such *APC* mutations have been regarded as the gatekeepers of the adenoma–carcinoma sequence that occurs early in the adenoma–carcinoma pathway (25). This helps to explain why MHO subjects had an increased overall risk of CRN despite their lack of metabolic abnormalities such as insulin resistance.

However, this hypothesis does not fully explain why only metabolically unhealthy subjects (MUNO and MUO) were at increased risk of advanced CRN. Insulin resistance has been reported to enhance the activity of insulinlike growth factor-1 (IGF-1), which has been implicated in colorectal carcinogenesis (26). Attention has turned to the association between IGF-1 and epidermal growth factor and their receptors (30, 31). Previous reports have shown that IGF-1 receptor activation is essential for the mitogenic and transforming effects of epidermal growth factor receptors (EGFR) and that the IGF-1 receptor is upstream of EGFR (30–32). Metabolically unhealthy individuals would have increased insulin and IGF-1 levels, leading to increased EGFR activation and promoting colorectal carcinogenesis (26). Because EGFR is associated with the activation of *KRAS* (33), this leads to advanced CRA in the classic colorectal carcinoma pathway (25). We can infer that metabolically unhealthy status may be the step after simple obesity in the process of colorectal carcinogenesis.

This hypothesis does not fully explain why some subjects in the MHNO had advanced CRN, including CRC. This is likely to be because colorectal carcinogenesis is multifactorial (2, 25): ~85% of CRCs are sporadic, with 70% being associated with the classic adenoma–carcinoma pathway (25). The remaining 30% are associated with either hereditary forms or other pathways such as *BRAF* that are associated with sessile serrated adenoma (2). We did not investigate family history or differentiate between sessile serrated adenoma and CRA, which may have been the reason that some subjects in the MHNO group had advanced CRN.

Our study had some limitations. First, only inferences about causation could be made for metabolic/obesity status and CRN because this was a retrospective, cross-sectional study. Second, we could not investigate environmental and hereditary factors such as diet or family cancer history. This allows the chance of familial cancer syndrome patients being included in our study. However, as the incidence of CRC syndromes is very low in Korea and we did not discover any polyposis syndrome subjects during colonoscopy, we believe that this would not have significantly altered the results of our study (34, 35). Third, we only analyzed subjects who had both insulin and colonoscopy results, which may have resulted in a selection bias. However, because we included >10,000 subjects, we believe that the risk of selection bias is low. Fourth, as this was a retrospective study, we could not determine whether subjects had type 1 or 2 diabetes. However, as the incidence of type 1 diabetes in Korea is only 0.02% of the entire population (36), this would not have significantly affected our results. Also, we could not ascertain whether subjects had been off from their diabetes medications for a sufficient amount of time. This may have affected the HOMA-IR levels and thus the metabolic health categorization.

Despite these limitations, the main strength of our study is that we used a standardized definition of metabolic/obesity status relevant to our study population, which included >10,000 subjects. We also included all four metabolic/obesity classifications and investigated not only CRC but all CRN. This is in contrast to previous studies that included only metabolically healthy subjects or limited the study to advanced CRN or CRC (15–17). As such, we believe that our study sheds more light on the association between metabolic health, obesity, and all CRNs.

In conclusion, we found that obesity is a risk factor for all CRN, with metabolically unhealthy status adding risk. For advanced CRN, obesity by itself was not a risk factor, but metabolically unhealthy status increased the risk. Further prospective studies are needed to verify the association between obesity, metabolic status, and CRN risk, and to discover whether treatment of obesity or metabolic dysfunction prevents CRN.

Acknowledgments

Address all correspondence and requests for reprints to: Myong Ki Baeg, MD, PhD, International St. Mary's Hospital, College

of Medicine, Catholic Kwandong University, Simgokro 100gil 25 Seo-Gu, Incheon 22711, South Korea. E-mail: baegmk@gmail.com.

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