Research Article

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Risk Factors Associated with Rectal Neuroendocrine Tumors: A Cross-Sectional Study

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Abstract

Background: The incidence of rectal neuroendocrine tumors (NET) has been increasing since the implementation of the screening colonoscopy. However, very little is known about risk factors associated with rectal NETs. We examined the prevalence of and the risk factors for rectal NETs in a Korean population.

Methods: A cross-sectional study was performed on 62,171 Koreans who underwent screening colonoscopy. The clinical characteristics and serum biochemical parameters of subjects with rectal NET were compared with those of subjects without rectal NET using multivariate logistic regression.

Results: Of a total of 57,819 participants, 101 [OR, 0.17%; 95% confidence interval (CI), 0.14–0.20] had a rectal NET. Young age (<50 years; OR, 2.09; 95% CI, 1.06–4.15), male gender (OR, 1.92; 95% CI, 1.15–3.20), alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01–2.42], and a low high-density lipoprotein-cholesterol (HDL-C) level (AOR, 1.85; 95% CI, 1.10–3.11) were independent risk factors for rectal NETs. Cigarette smoking, fatty liver, metabolic syndrome, higher triglyceride level (≥150 mg/dL), and higher homeostasis model assessment of insulin resistance (≥2.5) were not independently associated with rectal NETs, although these factors were more common in individuals with rectal NETs in the univariate analysis.

Conclusions: Young age (<50 years), male gender, alcohol drinking, and a low HDL-C level were risk factors for rectal NETs. Our results suggest that gender, behavioral factors, and dyslipidemia may affect the risk for developing rectal NETs.

Impact: The findings of this study contribute to a better understanding of the influence of gender, behavioral factors, and dyslipidemia in developing rectal NETs. *Cancer Epidemiol Biomarkers Prev; 23(7); 1406–13. ©2014 AACR.*

Introduction

Neuroendocrine tumors (NET) are rare malignancies that are derived from neuroendocrine cells throughout the body (1–3). These tumors are capable of producing biogenic amines and polypeptide hormones that cause characteristic hormonal syndromes. (1–3) Most are slow-growing, but they have the potential to be aggressive, to metastasize, and to be resistant to therapy (3, 4). NETs can develop at various locations and are commonly classified according to their embryonic site of origin: the foregut (lungs, bronchi, stomach, and duodenum), the midgut (jejunum, ileum, appendix, and proximal large bowel), and the hindgut (distal colon and rectum; refs. 2, 5). They are distinct biologically and clinically according to the primary tumor site, and the tumor site is an important factor in determining prognosis and survival (2).

According to a five decade (from 1950 to 1999) analysis of 13,715 NETs, the sites with the greatest incidence of NETs are the gastrointestinal tract (67%) and the bronchopulmonary system (25%). Within the gastrointestinal tract, the most frequently affected sites are the small intestine (39%) and rectum (20%; ref. 6). The small intestine has long been recognized as the most common primary site for gastrointestinal NETs. However, the widespread use of colonoscopy for colorectal cancer screening has led to a rise in the incidence of rectal NETs (7). A recent study comparing rectal and small intestinal NETs between 1992 and 2008 demonstrated that small intestinal NETs were more frequent in the years before 2000, whereas rectal NETs were more common after 2000 (8). Moreover, the Surveillance, Epidemiology, and End Results (SEER) registry database of the National Cancer Institute (which reflects the standard of care for the average U.S. individual) shows that the age-adjusted incidence of rectal NETs has increased about 10-fold over the last 30 years, from 0.1/100,000 in 1973 to 1.0/100,000 in 2004 (4, 9).

Approximately 50% to 60% of patients with rectal NETs are asymptomatic and their tumors are discovered incidentally during a routine medical exam (10, 11).

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Presenting symptoms can include hematochezia, weight loss, constipation, and other changes in bowel habits (11). Rectal NETs have a generally favorable prognosis with an overall 5-year survival rate of 88.3% (6). Upon diagnosis, approximately 80% of rectal NETs are less than 1 cm in size, are located in the submucosa, and have no metastatic spread. Thus, most lesions can be managed by local endoscopic or transanal resection. However, if the neoplasm is 2 cm or greater in size (10% of cases), has evidence of muscular invasion, or if lymph node metastases are present, then radical surgery (low anterior resection or abdominal perineal resection) should be performed (11).

Studies regarding rectal NETs have kept pace with the increase in the incidence of rectal NETs. However, most of these studies were focused on the prognostic factors for rectal NETs. Very little is known about the risk factors associated with rectal NETs due to its rarity as well as the lack of large epidemiologic studies. Although several studies have examined the epidemiology (such as the incidence and race, sex, and age distributions) of NETs (4, 6, 8), most of these studies were performed in Western countries and were not focused on the risk factors for rectal NETs. Furthermore, rectal NETs are known to be exceedingly prevalent among Asian populations within the United States (6, 10), but epidemiologic studies of rectal NETs in Asian countries are lacking. Therefore, the aim of this study was to investigate the prevalence of and risk factors for rectal NETs in a Korean population. We conducted a cross-sectional study of individuals who had undergone colonoscopy as part of their routine preventive health care.

Materials and Methods

Study population

The study population consisted of examinees who had undergone a colonoscopy as part of a comprehensive health screening program at the Total Healthcare Center of Kangbuk Samsung Hospital (Seoul, Korea) between 2010 and 2011 ($N = 62{,}171$). In Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. Approximately 60% of the participants were employees of various companies and local governmental organizations or their spouses and the remaining participants registered individually for the program.

We excluded participants who had an inadequate biopsy (polypoid lesions detected during colonoscopy were not biopsied) or who had a history of prior colorectal surgery, colorectal cancer, or colorectal polyps (because there is a possibility that these subjects could have had a rectal NET). We also excluded subjects with incomplete data. The total number of eligible subjects for the study was 57,819 (Fig. 1).

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent as we only accessed deidentified data retrospectively.

Measurements and colonoscopy examination

Data on medical history and health-related behaviors were collected through a self-administered questionnaire, whereas physical measurements and serum biochemical parameters were measured by trained staff. Details regarding alcohol use included the frequency of intake per week and the average amount of intake per episode. Family history of colorectal cancer was defined as colorectal cancer in one or more first-degree relatives at any age. The weekly frequency of moderate- or vigorous-intensity physical activity and the level of educational attainment were assessed. Regular exercise was defined as $\geq$1 time per week and higher education was defined as a university graduate or higher. The presence or absence of fatty liver was examined through abdominal ultrasound.

Blood samples were taken from the antecubital vein after at least a 10-hour fast. Serum levels of total cholesterol, triglycerides, and uric acid were determined using an enzymatic colorimetric assay; low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) levels were determined using a homogeneous enzymatic colorimetric assay; and serum high-sensitivity C-reactive protein (hsCRP) levels were determined using a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by photometry using a Modular Analytics D2400 (Roche Diagnostics). Serum fasting glucose levels were measured using the hexokinase method on a Cobas Integra 800 apparatus (Roche Diagnostics), and serum insulin levels were measured using an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics). Insulin resistance was assessed with the homeostasis model assessment of insulin resistance (HOMA-IR) according to the following equation: fasting blood insulin (mU/mL) $\times$ FBG (mmol/L)/22.5. Low HDL-C level was defined as HDL-C < 40 mg/dL in men or <50 mg/dL in women.

Colonoscopy was performed by 1 of 13 experienced gastroenterologists using the EVIS LUCERA CV-260 colonoscope (Olympus). All bowel cleansing was performed using 4 L of polyethylene glycol solution (Taejoon Pharm. Inc.). All polypoid lesions were biopsied or removed and histologically assessed by experienced pathologists. Rectal NETs were defined as having one or more of the typical organoid growth patterns characteristic of well-differentiated endocrine neoplams along with relatively uniform nuclei having coarsely clumped chromatin (12). The presence of neuroendocrine differentiation was evidenced by positive immunohistochemical staining for chromogranin or synaptophysin (12).

Statistical analysis

The software program SPSS version 18 (SPSS, Inc.) was used for statistical analyses. The χ^2 or Fisher exact test was used to compare categorical variables. Student t test or the Mann–Whitney U test was used to compare numerical

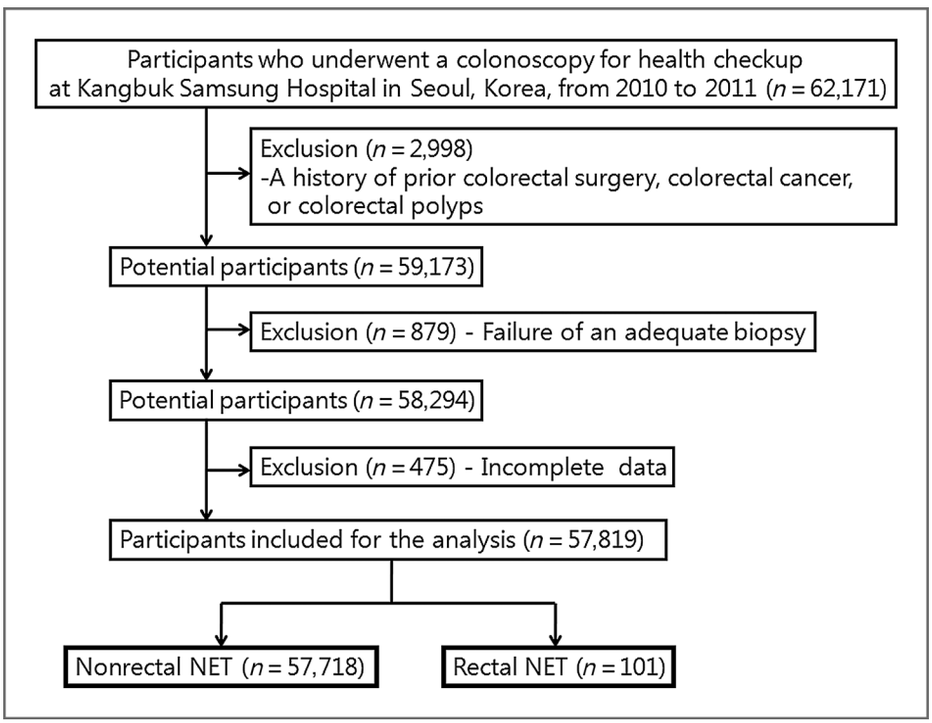

Figure 1. Flow diagram for the selection of study subjects.

variables between the groups. Logistic regression analysis was performed to identify independent risk factors for rectal NETs. Binary logistic regression models were used to estimate ORs and 95% confidence intervals (95% CI) after adjusting for potential confounders. The models were initially adjusted for age and sex, then for smoking, alcohol intake, exercise, educational level, family history of colorectal cancer, body mass index (BMI), fatty liver, metabolic syndrome, HDL-C level, and HOMA-IR. *P* values <0.05 were considered statistically significant.

Results

Of a total of 57,819 participants, 101 (0.17%; 95% CI, 0.14–0.20) had a rectal NET. The clinical characteristics of the 101 subjects with a rectal NET and the 57,718 subjects without a rectal NET are summarized in Table 1. The mean age was significantly younger in subjects with a rectal NET than in those without a rectal NET (41.1 vs. 42.4 years; $P = 0.028$). The proportion of subjects under 50 years of age was also higher in the rectal NET group compared with the non-rectal NET group (91.1% vs. 83.0%; $P = 0.031$). Both groups showed a male predominance, and this trend was more pronounced in the rectal NET group (82.2% vs. 70.6%; $P = 0.011$). The proportion of current or ex-smokers was higher in the rectal NET group (60.4% vs. 49.2%; $P = 0.024$). However, the proportion of subjects who consumed ≥20 g of alcohol per day was higher in the rectal NET group than in the non-rectal NET group (38.6% vs. 26.1%; $P = 0.004$). The presence of fatty liver was more common in the rectal NET group compared with the non-rectal NET group (45.5% vs. 34.8%; $P = 0.024$). There was no difference in terms of the medical history (such as diabetes mellitus and hypertension), family history of colorectal cancer, frequency of regular exercise, educational attainment, BMI, or waist circumference between the two groups. The proportions with a colorectal adenoma between the two groups were also not different.

We compared laboratory findings between participants with and without rectal NETs (Table 2). Mean HDL-C level was lower in the rectal NET group (51.4 vs. 55.2 mg/dL; $P = 0.006$), whereas the median triglyceride level was higher in the rectal NET group (108.0 vs. 96.0 mg/dL; $P = 0.021$). The proportion of subjects with triglycerides ≥ 150 mg/dL and HOMA-IR ≥ 2.5 was higher in the rectal NET group (31.7% vs. 22.1%; $P = 0.021$). The proportion of subjects with HOMA-IR ≥ 2.5 was also higher in the rectal NET group (9.9% vs. 4.5%; $P = 0.025$).

Table 3 shows the results of the binary logistic regression analyses. In the age–sex adjusted analyses, age < 50 years (OR, 2.09; 95% CI, 1.06–4.15; $P = 0.035$), male gender (OR, 1.92; 95% CI, 1.15–3.20; $P = 0.012$), alcohol drinking (OR, 1.53; 95% CI, 1.01–2.34; $P = 0.047$), metabolic syndrome (OR, 1.61; 95% CI, 1.02–2.57; $P = 0.043$), a low HDL-C level (OR, 1.97; 95% CI, 1.25–3.10; $P = 0.003$), and HOMA-IR ≥ 2.5 (OR, 2.30; 95% CI, 1.20–4.44; $P = 0.013$) were associated with an increased risk of rectal NET. However, the correlations with metabolic syndrome and HOMA-IR were no longer significant after multiple adjustments; alcohol drinking [adjusted OR (AOR), 1.56; 95% CI, 1.01–2.42; $P = 0.045$] and a low HDL-C level (AOR, 1.85; 95% CI, 1.10–3.11; $P = 0.021$) still remained as independent risk factors of rectal NET.

Table 1. Comparison of clinical characteristics between participants with and without rectal NETs

	Rectal NET ($n = 101$)	No rectal NET ($n = 57718$)	*P*
Mean age, y	41.1 ± 6.0	42.4 ± 8.2	0.028
Age <50	92 (91.1)	47,913 (83.0)	0.031
Age ≥ 50	9 (8.9)	9,805 (17.0)	
Sex, men	83 (82.2)	40,737 (70.6)	0.011
Smoker (current or ex-smoker)	61 (60.4)	28,373 (49.2)	0.024
Alcohol intake (≥20 g ethanol per day)	39 (38.6)	15,087 (26.1)	0.004
Regular exercise[a]	55 (54.5)	29,994 (52.0)	0.617
Advanced education[b]	77 (76.2)	42,487 (73.6)	0.550
Diabetes mellitus	6 (5.9)	3,364 (5.8)	0.962
Hypertension	12 (11.9)	8,302 (14.4)	0.474
Family history of colorectal cancer	7 (6.9)	2,511 (4.4)	0.204
Adenoma	13 (12.9)	7,604 (13.2)	0.928
BMI (kg/m^2)	24.5 ± 3.1	23.9 ± 3.1	0.053
Fatty liver	46 (45.5)	20,090 (34.8)	0.024
Metabolic syndrome	24 (23.8)	9,273 (16.1)	0.035
Waist circumference (cm)	84.8 ± 8.3	83.5 ± 8.5	0.139
Systolic blood pressure (mmHg)	114 ± 11	115 ± 13	0.796
Diastolic blood pressure (mmHg)	74 ± 9	73 ± 9	0.258

NOTE: Data are presented as mean ± SD or number (%). *P* value by *t* test or Mann–Whitney *U* test for continuous variables and χ^2 test or Fisher's exact test for categorical variables.

[a]≥1 time per week.

[b]≥University graduate or higher.

The median size of the 101 rectal NETs was 4.0 mm (range, 2–12 mm). The number of rectal NETs with sizes of 1 to 4, 5 to 9, and 10 to 12 mm were 51 (50.5%), 46 (45.5%), and 4 (4.0%), respectively.

Discussion

This cross-sectional study is the first and largest to evaluate several risk factors for rectal NETs among adults undergoing screening colonoscopy with proper adjustment for confounding factors.

The present study demonstrated that the prevalence of rectal NETs in adults undergoing screening colonoscopy was 0.17% (101/57,819). To date, only a few studies have investigated the prevalence of rectal NETs diagnosed through screening endoscopy. In 1993, a Japanese survey reported 15 small-size rectal NETs among 21,522 healthy individuals who underwent screening proctosigmoidoscopy (0.07%; ref. 13). Kaminski and colleagues analyzed 50,148 screening colonoscopies in Poland and reported 25 rectal NETs in 24 patients (0.05%), although this was an unpublished study (abstract; ref. 14). In a Korean study, rectal NETs were discovered in 67 patients out of a total of 86,918 patients who underwent endoscopy between 1989 and 2002 (0.08%; ref. 15). However, this study included individuals who underwent endoscopy for anything other than screening purposes. Our study analyzed individuals who underwent screening colonoscopy more recently (in 2010 and 2011) when compared with previous studies. Therefore, widespread use of colonoscopy for screening, improved resolution of endoscopy, increased awareness of rectal NET, and resultant high diagnostic rate may be the reason for the relatively high prevalence in our study. Another possible explanation for the higher prevalence rate found in our study may be that a large proportion of study population was male.

In our study, the maximum size of the 101 rectal NETs was 12 mm and 96% of the tumors measured less than 10 mm. Two prior studies also demonstrated that rectal NETs detected by screening endoscopy are no more than 13 mm in diameter; 39 of 40 carcinoids (97.5%) measured less than 10.1 mm in diameter (13, 14). Our results suggest that screening colonoscopy leads to the detection of rectal NETs of smaller size and more favorable (earlier) stage. This is in line with the steadily improving overall 5-year survival rates in patients with rectal NET over the last 35 years (7).

Our results indicate that rectal NETs may present at early ages. The mean age of participants with rectal NETs was 41 years and participants who were <50 years old had more than twice the risk of being diagnosed with a rectal NET on endoscopy than those who were ≥ 50 years old. Previous epidemiologic studies of rectal NETs have revealed that the average age at diagnosis was 52 to 63 years (4, 6, 8, 10, 16). The mean age at disease onset in our study was younger than the age of diagnosis reported by previous epidemiologic studies. Because rectal NETs frequently cause no or only vague symptoms, diagnosis is often delayed. While the prior epidemiologic studies mentioned above have analyzed data obtained from cancer registries, our study analyzed individuals who

Table 2. Comparison of serum biochemical parameters between participants with and without rectal NETs

	Rectal NET ($n = 101$)	No rectal NET ($n = 57{,}718$)	*P*
Total cholesterol (mg/dL)	200.8 ± 35.6	199.8 ± 34.8	0.782
LDL-C (mg/dL)	126.7 ± 32.8	124.9 ± 32.1	0.572
HDL-C (mg/dL)	51.4 ± 12.5	55.2 ± 13.9	0.006
Triglycerides (mg/dL)	108.0 (72.0–161.5)	96.0 (68.0–141.0)	0.021
≥ 150	32 (31.7%)	12,783 (22.1%)	0.021
Lipoprotein (a) (mg/dL)	25.7 (14.8–43.9)	25.4 (14.6–41.8)	0.690
Apolipoprotein A1 (mg/dL)	131.2 ± 20.8	135.5 ± 22.1	0.050
Apolipoprotein B (mg/dL)	93.5 ± 23.7	90.1 ± 22.9	0.150
hsCRP (mg/dL)	0.05 (0.03–0.10)	0.05 (0.03–0.10)	0.790
Fasting blood glucose (mg/dL)	96.2 ± 15.1	93.9 ± 14.9	0.130
HBA1C (%)	5.7 ± 0.5	5.7 ± 0.5	0.843
HOMA-IR	1.0 (0.6–1.6)	0.9 (0.6–1.3)	0.018
≥2.5	10 (9.9%)	2,584 (4.5%)	0.025
White blood cell (/mm^3)	6498 ± 1617	6,202 ± 1682	0.077
Hemoglobin (g/dL)	15.4 ± 1.3	14.9 ± 1.5	<0.001
Hematocrit (%)	45.3 ± 3.7	43.7 ± 3.9	<0.001
AST (U/L)	26.0 (20.0–34.5)	24.0 (20.0–30.0)	0.166
ALT (U/L)	28.0 (18.0–43.0)	23.0 (17.0–34.0)	0.008
ALP (U/L)	58.0 (51.0–69.0)	60.0 (51.0–71.0)	0.472
γ-GGT (U/L)	33.0 (18.0–54.5)	26.0 (16.0–44.0)	0.026
Total bilirubin (mg/dL)	1.1 ± 0.5	1.0 ± 0.4	0.151

NOTE: Data are presented as mean ± SD, median (interquartile range), or number (%). *P* value by *t* test or Mann–Whitney *U* test for continuous variables and χ^2 or Fisher's exact test for categorical variables.

Abbreviations: ALP, alkaline phosphatase; HBA1C, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; γ-GGT, gamma-glutamyltransferase.

underwent screening colonoscopy. Therefore, our study was able to detect rectal NETs without delay and therefore better reflects the actual age at onset of rectal NETs compared with previous epidemiologic studies. Studies by Hassan and colleagues (10) and Taghavi and colleagues (8) showed a trend similar to our results, although the average age at diagnosis in those studies was older than in ours. Hassan and colleagues (10) demonstrated that subjects who were ≤ 60 years old had an increased risk of developing rectal NETs (OR, 3.2; 95% CI, 1.4–7.4). Taghavi and colleagues (8) reported that patients in the 50- to 59-year-old age group (OR, 0.8; 95% CI, 0.6–0.9) were more likely to be diagnosed with rectal NETs than those in the 60- to 69-year-old (OR, 0.5; 95% CI, 0.4–0.6) and ≥70-year-old age groups (OR, 0.2; 95% CI, 0.2–0.3). The young age of patients diagnosed with rectal NETs may be explained by the implementation of screening colonoscopy. This can be supported by the study by Taghavi and colleagues (8), which demonstrated that rectal NETs were more likely to be diagnosed in the screening colonoscopy era (2000–2008 compared with 1992–1999) among the 50- to 59-year-old age group (OR, 1.4; 95% CI, 1.1–1.9). Our results suggest that the risk of rectal NET development may not be related to aging.

We found that men had a higher risk of rectal NET development than women. Contrary to our results, a female predominance was reported in a U.S. population-based, case–control study with a female/male ratio of 4.3 (95% CI, 1.3–14.5; ref. 10). In addition, a nationwide epidemiologic study from Sweden revealed that women had an estimated OR of 1.4 (95% CI, 1.1–1.8) times that of men (17). On the other hand, in the pan-SEER (1973–1999) dataset, rectal NETs failed to exhibit any significant specific gender predominance (corrected ratio = 1.13; ref. 6). Moreover, several studies reported a male predominance (male/female ratios of 1.7–2.8; refs. 13, 18, 19). The male predominance of rectal NETs appears to be more pronounced in Asian populations (13, 15, 19). There may be differences in susceptibility to rectal NET development between genders according to ethnic group. However, because large-scale epidemiologic studies of rectal NETs in Asian populations are lacking, it is not possible to draw clear conclusions from existing data. Further studies are warranted to elucidate this issue.

In the current study, alcohol drinking (≥20 g of alcohol/day) was an independent risk factor for rectal NETs. On the other hand, cigarette smoking was not associated with rectal NETs in multivariate analysis, although it tended to be more common in individuals with rectal NETs. Behavioral factors may affect the risk of developing rectal NETs. To date, only one study investigated the role of smoking and alcohol in rectal NETs. A U.S. population-based case–

Table 3. Risk factors for rectal NETs using multiple logistic regression models

	Person	Prevalent case	Age–sex AOR (95% CI)	*P*	AOR[a] (95%CI)	*P*
Age, y						
≥50	9,814	9	1			
<50	48,005	92	2.09 (1.06–4.15)	0.035		
Sex						
Women	16,999	18	1			
Men	40,820	83	1.92 (1.15–3.20)	0.012		
Smoking						
Never	29,385	40	1		1	
Ever	28,434	61	1.25 (0.79–1.98)	0.337	1.11 (0.69–1.78)	0.665
Alcohol intake						
<20 g ethanol per day	42,693	62	1		1	
≥20 g ethanol per day	15,126	39	1.53 (1.01–2.34)	0.047	1.56 (1.01-.2.42)	0.045
Regular exercise[b]						
No	27,770	46	1		1	
Yes	30,049	55	1.08 (0.73–1.59)	0.716	1.12 (0.76–1.67)	0.567
Advanced education[c]						
No	15,255	24	1		1	
Yes	42,564	77	0.92 (0.58–1.48)	0.738	0.93 (0.58–1.50)	0.765
Family history of colorectal cancer						
No	55,301	94	1		1	
Yes	2,518	7	1.67 (0.77–3.59)	0.196	1.70 (0.79–3.67)	0.179
BMI (kg/m^2)						
MHU (<18.5)	1,568	1	0.45 (0.06–3.31)	0.432	0.49 (0.07–3.67)	0.494
MHNW (18.5–22.9)	21,173	34	1		1	
MHOW (23.0–24.9)	15,385	26	0.94 (0.56–1.59)	0.820	0.81 (0.47–1.38)	0.436
MHO (≥25.0)	19,693	40	1.09 (0.67–1.75)	0.733	0.73 (0.41–1.29)	0.275
Fatty liver						
No	37,683	55	1		1	
Yes	20,136	46	1.42 (0.94–2.12)	0.093	1.28 (0.80–2.06)	0.302
Metabolic syndrome						
No	48,522	77	1		1	
Yes	9,297	24	1.61 (1.02–2.57)	0.043	1.02 (0.56–1.87)	0.943
Abdominal obesity						
No	40,157	71	1		1	
Yes	17,662	30	1.04 (0.68–1.59)	0.866	0.70 (0.38–1.28)	0.248
Blood pressure						
< 130/85 mmHg	39,405	69	1		1	
≥ 130/85 mmHg	18,414	32	0.96 (0.62–1.47)	0.835	0.77 (0.48–1.24)	0.278
Fasting blood glucose						
<100 mg/dL	44,385	71	1		1	
≥ 100 mg/dL	13,434	30	1.39 (0.90–2.14)	0.134	1.08 (0.66–1.77)	0.761
Low HDL-C level[d]						
No	49,057	76	1		1	
Yes	8,762	25	1.97 (1.25–3.10)	0.003	1.85 (1.10–3.11)	0.021
Triglycerides						
<150 mg/dL	45,004	69	1		1	
≥ 150 mg/dL	12,815	32	1.45 (0.95–2.24)	0.089	1.10 (0.64–1.90)	0.725
HOMA-IR						
<2.5	55,225	91	1		1	
≥2.5	2,594	10	2.30 (1.20–4.44)	0.013	1.92 (0.93–3.96)	0.077

Abbreviations: MHU, metabolically healthy underweight; MHNW, metabolically healthy normal-weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese.

[a]Adjusted for age, sex, smoking status, alcohol intake, regular exercise, educational level, family history of colorectal cancer, BMI, fatty liver, metabolic syndrome, HDL-C level, and HOMA-IR.

[b]≥ 1 time per week.

[c]≥ University graduate or higher.

[d]HDL-C level < 40 mg/dL in men or < 50 mg/dL in women.

control study analyzing 740 patients with NETs and 924 controls found no association between smoking or alcohol drinking and NETs of the small bowel, stomach, lung, pancreas, or rectum (10); however, the study was limited to 54 patients with rectal NETs and hospitalized patients. With regard to NETs at other sites, only two studies have explored the effects of smoking and alcohol in small intestinal NETs. Chen and colleagues (20) compared 17 patients with small bowel NETs and 52 controls and reported insignificant increases in ORs for cigarette smoking (OR, 4.2; 95% CI, 0.8–22.4) and alcohol consumption (OR, 3.1; 95% CI, 0.7–13.9). A European population-based, case–control study analyzing 84 patients with small intestinal NETs and 2,070 controls demonstrated that having ever been a smoker was associated with small intestinal NETs (OR, 1.9; 95% CI, 1.1–3.2), whereas alcohol consumption was not associated with small intestinal NETs (21). These discrepancies indicate that the link between smoking or alcohol drinking and the development of NETs needs to be explored further. In addition, the influence of smoking and alcohol drinking on the prognosis of patients with NETs needs to be investigated.

Interestingly, we found that low HDL-C levels were an independent risk factor for rectal NETs. Although carcinoid syndrome occurs only very rarely in patients with rectal NETs, NETs located in the low rectum bypass the liver and can secrete hormonal products into the systemic circulation (11). It may be possible that hormonal changes in patients with rectal NETs lead to the changes in HDL-C levels. Fatty liver, metabolic syndrome, higher triglyceride levels ($\geq$ 150 mg/dL), and higher HOMA-IR ($\geq$2.5) were more frequent in patients with rectal NETs, although these findings were not significant on multivariate analysis. Metabolic syndrome has been known to associate with common cancers such as colorectal, liver, endometrial, pancreatic, and bladder cancers (22–24). In recent, large-scale studies, low HDL-C levels and elevated triglyceride levels were associated with some cancers, including colorectal cancer (25–27). In addition, several studies have reported that fatty liver is an independent risk factor for colorectal neoplasia (28, 29). Mechanisms linking metabolic syndrome or fatty liver and cancer risk are not fully understood. Excess adiposity results in a state of chronic systemic inflammation, attributed to the production of inflammatory cytokines by both adipocytes and infiltrating immune cells, creating a protumorigenic environment (30). The concentration of adiponectin, which is regarded as having anti-inflammatory effects, is inversely proportional to body fat content and is reduced in individuals with fatty liver (31). The increased levels of inflammatory cytokines and reduced levels of adiponectin may promote a protumorigenic environment. Our study is the first to show that dyslipidemia may be associated with an increased risk of rectal NETs. Future studies with larger sample sizes are required to confirm this finding.

The current study had several limitations. First, this was not a population-based study, but rather was a retrospective study that included individuals who had been seen for a regular health maintenance exam. As a result, there was likely some degree of selection bias; however, because rectal NETs commonly cause no symptoms, our data seem to be more accurate than data obtained from cancer registries. Second, the cross-sectional design precludes the determination of causality. However, the strength of our study was the ability to assess not only medical histories and health-related behaviors, but also the physical measurements and serum biochemical parameters in detail as a means of identifying risk factors for rectal NETs. Finally, we were unable to analyze dietary, occupational, and socioeconomic factors, which could be possible confounders.

In conclusion, the prevalence of rectal NETs in adults undergoing screening colonoscopy was 0.17%. We confirmed that young age (<50 years), male gender, alcohol drinking, and a low HDL-C level were associated with an increased risk of developing rectal NETs. Our results suggest that gender, behavioral factors, dyslipidemia may influence the development of rectal NETs. Further studies are warranted to discover risk factors for rectal NETs. Such studies may contribute to a better understanding of the pathogenesis of rectal NETs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999;340:858–68.

2. Robertson RG, Geiger WJ, Davis NB. Carcinoid tumors. Am Fam Physician 2006;74:429–34.

3. Schnirer I, Yao JC, Ajani JA. Carcinoid–a comprehensive review. Acta Oncol 2003;42:672–92.
4. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.
5. Williams ED, Sandler M. The classification of carcinoid tum ours. Lancet 1963;1:238–9.
6. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–59.
7. Scherübl H. Rectal carcinoids are on the rise: early detection by screening endoscopy. Endoscopy 2009;41:162–5.
8. Taghavi S, Jayarajan SN, Powers BD, Davey A, Willis AI. Examining rectal carcinoids in the era of screening colonoscopy: a surveillance, epidemiology, and end results analysis. Dis Colon Rectum 2013; 56:952–9.
9. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder W, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61–72.
10. Hassan M, Phan A, Li D, Dagohoy CG, Leary C, Yao JC. Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study. Int J Cancer 2008;123:867–73.
11. Wang AY, Ahmad NA. Rectal carcinoids. Curr Opin Gastroenterol 2006;22:529–35.
12. Fahy BN, Tang LH, Klimstra D, Wong WD, Guillem JG, Paty PB, et al. Carcinoid of the rectum risk stratification (CaRRs): a strategy for preoperative outcome assessment. Ann Surg Oncol 2007;14:1735–43.
13. Matsui K, Iwase T, Kitagawa M. Small, polypoid-appearing carcinoid tumors of the rectum: clinicopathologic study of 16 cases and effectiveness of endoscopic treatment. Am J Gastroenterol 1993;88:1949–53.
14. Kaminski M, Polkowski M, Regula J. Prevalence and endoscopic features of rectal neuroendocrine tumors (carcinoids) among 50148 participants of the Polish colorectal–cancer screening programme. Gut 2007;56(Suppl III):A310.
15. Shim KN, Yang SK, Myung SJ, Chang HS, Jung SA, Choe JW, et al. Atypical endoscopic features of rectal carcinoids. Endoscopy 2004;36:313–6.
16. Ellis L, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. Am J Gastroenterol 2010;105:2563–9.
17. Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. Cancer 2001;92:2204–10.
18. Jetmore AB, Ray JE, Gathright JB, McMullen KM, Hicks TC, Timmcke AE. Rectal carcinoids: the most frequent carcinoid tumor. Dis Colon Rectum 1992;35:717–25.
19. Li AF, Hsu C, Tai L, Liang W, Li W, Tsay S, et al. A 35-year retrospective study of carcinoid tumors in Taiwan: differences in distribution with a high probability of associated second primary malignancies. Cancer 2008;112:274–83.
20. Chen CC, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomarkers Prev 1994;3:205–7.
21. Kaerlev L, Teglbjaerg PS, Sabroe S, Kolstad HA, Ahrens W, Eriksson M, et al. The importance of smoking and medical history for development of small bowel carcinoid tumor: a European population-based case-control study. Cancer Causes Control 2002;13: 27–34.
22. Esposito K, Capuano A, Giugliano D. Metabolic syndrome and cancer: holistic or reductionist? Endocrine 2014;45:362–4.
23. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 2012;35:2402–11.
24. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, et al. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. Endocrine 2013;44:634–47.
25. Jafri H, Alsheikh Ali A, Karas RH. Baseline and on-treatment high-density lipoprotein cholesterol and the risk of cancer in randomized controlled trials of lipid-altering therapy. J Am Coll Cardiol 2010; 55:2846–54.
26. Ulmer H, Borena W, Rapp K, Klenk J, Strasak A, Diem G, et al. Serum triglyceride concentrations and cancer risk in a large cohort study in Austria. Br J Cancer 2009;101:1202–6.
27. van Duijnhoven FJ, Bueno-De-Mesquita HB, Calligaro M, Jenab M, Pischon T, Jansen EH, et al. Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition. Gut 2011;60:1094–102.
28. Stadlmayr A, Aigner E, Steger B, Scharinger L, Lederer D, Mayr A, et al. Nonalcoholic fatty liver disease: an independent risk factor for colorectal neoplasia. J Intern Med 2011;270:41–9.
29. Huang KW, Leu HB, Wang YJ, Luo JC, Lin HC, Lee FY, et al. Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy. Colorectal Dis 2013; 15:830–5.
30. Harvey AE, Lashinger LM, Hursting SD. The growing challenge of obesity and cancer: an inflammatory issue. Ann N Y Acad Sci 2011;1229:45–52.
31. Wong VW, Hui AY, Tsang SW, Chan JL, Tse AM, Chan K, et al. Metabolic and adipokine profile of Chinese patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2006;4: 1154–61.