

Esophageal Squamous Cell Carcinoma Patients Have an Increased Risk of Coexisting Colorectal Neoplasms

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See editorial on page 6.

Background/Aims: Esophageal squamous cell carcinoma (ESCC) and colorectal neoplasms (CRNs) share risk factors. We aimed to investigate whether the CRN risk is increased in ESCC patients. **Methods:** ESCC patients who underwent a colonoscopy within 1 year of diagnosis were retrospectively analyzed. Patients were matched 1:3 by age, gender, and body mass index to asymptomatic controls. CRN was defined as the histological confirmation of adenoma or adenocarcinoma. Advanced CRN was defined as any of the following: ≥ 3 adenomas, high-grade dysplasia, villous features, tumor ≥ 1 cm, or adenocarcinoma. The risk factors for both CRN and advanced CRN were evaluated by univariate and multivariate analyses. **Results:** Sixty ESCC patients were compared with 180 controls. The ESCC group had significantly higher numbers of CRNs (odds ratio [OR], 2.311; 95% confidence interval [CI], 1.265 to 4.220; $p=0.006$) and advanced CRNs (OR, 2.317; 95% CI, 1.185 to 4.530; $p=0.013$). Significant risk factors for both CRN and advanced CRN by multivariate analysis included ESCC (OR, 2.157, 95% CI, 1.106 to 4.070, $p=0.024$; and OR, 2.157, 95% CI, 1.045 to 4.454, $p=0.038$, respectively) and older age (OR, 1.068, 95% CI, 1.032 to 1.106, $p<0.001$; and OR, 1.065, 95% CI, 1.024 to 1.109, $p=0.002$, respectively). **Conclusions:** The rates of CRN and advanced CRN are significantly increased in ESCC. Colonoscopy should be considered at ESCC diagnosis. (*Gut Liver* 2016;10:76-82)

Key Words: Colorectal neoplasms; Esophageal neoplasms; Esophageal squamous cell carcinoma; Colonoscopy; Colorectal adenoma and carcinoma

INTRODUCTION

The prognosis for esophageal cancer is generally accepted as poor.^{1,2} However, because of advances in screening and endoscopic imaging,³ more patients are being diagnosed with early-stage esophageal cancer, which has increased the long-term survival rate.⁴ Improvements in therapeutic protocols, such as neoadjuvant or concurrent chemoradiation coupled with esophagectomy, have also increased survival rates for more advanced esophageal cancer.^{5,6}

The increased survival rate for patients with esophageal cancer has led to the discovery of more cases of secondary primary malignancy (SPM).⁷⁻⁹ Although SPMs of the head and neck, stomach, and lung are well known,^{7,10} other SPMs involving the colon, bladder, thyroid, and female breast have also been reported.^{8,9,11,12} The prevalence of colorectal neoplasm (CRN) has been reported to be increased in esophageal adenocarcinoma patients,^{13,14} and colorectal cancers comprise 7% to 16% of esophageal SPMs.^{8,10,12,15} However, studies of the colonoscopic evaluation of patients with esophageal squamous cell carcinoma (ESCC) are limited and have produced conflicting results.^{13,15-17} Colon cancer shares some common demographic and environmental risk factors with ESCC such as gender, smoking, alcohol, and intake of red meat.¹⁸⁻²² Similar genetic markers for these two cancers, such as *p53*, *K-ras*, and *APC* have also been reported.²³⁻²⁶ However, the association between colorectal cancer and ESCC has not been fully investigated.

The aim of this study was to investigate whether the risk for CRN is increased in ESCC patients and whether ESCC is an independent risk factor for the development of CRN.

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MATERIALS AND METHODS

1. Subjects

We retrospectively evaluated the medical records of patients who had been diagnosed with esophageal cancer at Seoul St. Mary's Hospital, a tertiary referral center, from January 1997 to December 2013. We included ESCC patients who had undergone a colonoscopic examination within 1 year of ESCC diagnosis. Patients were excluded if they had any of the following: (1) incomplete colonoscopic examination because of poor bowel preparation or incomplete insertion; (2) history of inflammatory bowel disease; (3) family history of cancer syndromes or polyposis; or (4) previous history of colon polypectomy. The control group subjects were randomly selected by systemic sampling from 13,530 asymptomatic people who had received a colonoscopy for health screening during the same period.

Subjects were excluded from the control group if they had any of the following: (1) incomplete colonoscopic examination because of poor bowel preparation or incomplete insertion; (2) any symptom of colorectal disease (abdominal pain, bowel habit change, hematochezia); (3) previous history of colon cancer; or (4) previous history of colon polypectomy. Use of subject data was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC14RIS10168).

2. Colonoscopy

Colonoscopic examination was performed by experienced endoscopists using standard procedures after routine preparation with 4 L of polyethylene glycol. Small polyps (<0.5 cm) were removed via cold or hot biopsy forceps, and large polyps (≥0.5 cm) were removed by snare polypectomy or endoscopic mucosal resection. The size of the polyps was measured endoscopically based on both visual estimation and comparison with biopsy forceps.²⁷ All retrieved polyps were sent to the pathology department and reviewed by an experienced gastrointestinal pathologist.

3. Definition of CRN, advanced neoplasm, and colorectal cancer

CRN was defined as a histologically confirmed adenoma or adenocarcinoma component. Nonneoplastic polyps such as inflammatory or hyperplastic polyps or mucosal tags were ex-

cluded. Patients were classified into the advanced CRN group if they met either the high-risk adenoma classification of the 2012 American Gastroenterological Association Guidelines²⁸ or if there was a presence of adenocarcinoma: (1) ≥3 adenomas; (2) histological findings of high-grade dysplasia; (3) inclusion of villous features; (4) a tumor ≥1 cm in size; or (5) presence of an adenocarcinoma.

4. Selection of data for analysis

Medical charts of both the patient and control groups were reviewed. These data included age, gender, body mass index (BMI), history of diabetes mellitus, smoking, alcohol consumption, and aspirin intake. Laboratory data included the levels of total cholesterol, triglycerides, and carcinoembryonic antigen. In the ESCC group, the TNM stage was reclassified according to the American Joint Cancer Committee (seventh edition) based on the pathology, operation, and radiology records.²⁹ The location and size of the tumor were noted from the pathology, endoscopy, and radiology reports. In patients who received a colonoscopy, the reasons for the colonoscopy such as routine health screening, evaluation of symptoms (hematochezia, bloating, abdominal pain, diarrhea, anemia, or constipation), and

Table 1. Baseline Characteristics of All Subjects

Characteristic	ESCC patients (n=60)	Controls (n=180)	p-value
Age, yr	63.3±10.1	63.3±10.1	1.000
Average time from ESCC diagnosis to CFS, mo	1.2±2.7		
Male gender	55 (91.7)	165 (91.7)	1.000
BMI, kg/m ²	23.0±3.1	23.0±3.0	0.970
Diabetes	8 (13.3)	20 (11.1)	0.642
Smoking	41 (68.3)	88 (48.9)	0.009
Alcohol	39 (65.0)	113 (62.8)	0.757
Aspirin	32 (53.3)	49 (27.2)	<0.001
Total cholesterol, mg/dL	177.2±30.8	196.0±34.6	<0.001
Triglyceride, mg/dL	139.9±84.9	99.9±55.3	0.004
CEA, ng/mL	2.1±1.3	1.3±1.0	<0.001

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

ESCC, esophageal squamous cell carcinoma; CFS, colonofibroscopy; BMI, body mass index; CEA, carcinoembryonic antigen.

Table 2. Colonoscopic Findings in All Subjects

	ESCC patients (n=60)	Controls (n=180)	OR (95% CI)	p-value
Subjects with colon neoplasms	38 (63.3)	77 (42.8)	2.311 (1.265–4.220)	0.006
Average no. of neoplasms per subject	2.2±2.9	1.1±1.9	-	0.008
Subjects with advanced neoplasms	19 (31.7)	30 (16.7)	2.317 (1.185–4.530)	0.013
Subjects with colorectal cancer	1 (5.8)	0	0.247 (0.198–0.308)	0.250

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

ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

abnormal positron emission tomography findings during the esophageal cancer evaluation were recorded. When polyps were found through colonoscopy, the location, size, and histology of the polyps were noted. In ESCC patients, the time from the esophageal cancer diagnosis to the colonoscopy examination was recorded.

5. Statistical analysis

Comparisons of continuous variables were assessed using Student t-test, and categorical variables were examined using the chi-square test. Multivariate analysis of the risk factors for CRN or advanced CRN was performed using logistic regression. The odds ratios (ORs) and 95% confidence interval (CI) were calculated for each variable in the multivariate analysis. All tests were two-sided and were performed at the 5% level of significance using SAS software (SAS Institute, Cary, NC, USA).

RESULTS

A total of 626 patients were diagnosed with ESCC during the study period; 540 patients were excluded because they did not have a colonoscopic examination. Of the remaining 86 patients, 14 did not have a colonoscopy within 1 year of ESCC diagnosis and 12 were excluded because of poor bowel preparation or incomplete examination, leaving 60 patients in the ESCC group.

Table 1 shows the baseline characteristics of the ESCC and control groups. The mean age of the ESCC group was 63.3 years, and the average time from ESCC diagnosis to colonoscopy was about 1.2 months. The ESCC group had significantly higher percentages of smoking, and aspirin use. The mean total cholesterol level was significantly higher and the triglyceride level significantly lower in the control group. A significantly higher percentage of the ESCC group had CRNs (OR, 2.311; 95% CI 1.265 to 4.220) or advanced CRNs (OR, 2.317; 95% CI, 1.185 to 4.530) (Table 2).

Table 3 shows the analysis of risk factors pertaining to CRN in the ESCC and control groups. Univariate analysis showed that the presence of ESCC, male gender, older age, higher BMI, and higher serum triglyceride level were significant risk factors for CRN. Multivariate analysis showed that the significant risk factors for CRN were ESCC (OR, 2.157; 95% CI, 1.106 to 4.070; p=0.024), older age (OR, 1.068; 95% CI, 1.032 to 1.106; p<0.001), and male gender (OR, 4.442; 95% CI, 1.028 to 19.272; p=0.046). In patients with advanced CRN, univariate analysis showed that the presence of ESCC, older age, history of diabetes, and serum total cholesterol level were significant risk factors. Multivariate analysis showed that the presence of ESCC (OR, 2.157; 95% CI, 1.045 to 4.454; p=0.038) and older age (OR, 1.065; 95% CI, 1.024 to 1.109; p=0.002) were significant risk factors.

Table 4 shows the risk factors for CRN in ESCC patients. In the univariate analysis, the ESCC patients with CRN were significantly older than were those without CRN, but this differ-

Table 3. Risk Factors for Colorectal Neoplasm in All Patients (Esophageal Squamous Cell Carcinoma in Patients and Controls)

Factor	Overall CRN						Advanced CRN					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
ESCC	2.311	1.265-4.220	0.006	2.157	1.106-4.070	0.024	2.317	1.185-4.530	0.014	2.157	1.045-4.454	0.038
Age	1.058	1.028-1.089	<0.001	1.068	1.032-1.106	<0.001	1.070	1.030-1.112	0.001	1.065	1.024-1.109	0.002
Male gender	5.877	1.674-20.625	0.006	4.442	1.028-19.272	0.046	4.63×10 ⁸	0.000	0.998	-	-	-
BMI	1.126	1.031-1.230	0.008	1.077	0.973-1.193	0.151	1.044	0.941-1.159	0.412	-	-	-
Diabetes	2.134	0.941-4.840	0.070	-	-	-	2.464	1.056-5.751	0.037	2.068	0.847-5.048	0.110
Smoking	1.581	0.946-2.640	0.080	-	-	-	1.535	0.804-2.930	0.194	-	-	-
Alcohol	1.169	0.690-1.979	0.561	-	-	-	1.248	0.642-2.426	0.514	-	-	-
Aspirin	0.979	0.574-1.669	0.937	-	-	-	1.435	0.753-2.735	0.273	-	-	-
Total cholesterol	0.993	0.985-1.000	0.053	-	-	-	0.987	0.977-0.997	0.012	0.993	0.983-1.004	0.200
Triglyceride	1.005	1.001-1.009	0.009	1.005	1.000-1.010	0.054	1.001	0.996-1.005	0.759	-	-	-
CEA	1.179	0.927-1.499	0.179	-	-	-	1.063	0.804-1.406	0.669	-	-	-

CRN, colorectal neoplasm; OR, odds ratio; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; BMI, body mass index; CEA, carcinoembryonic antigen.

Table 4. Risk Factors for Colorectal Neoplasm in Esophageal Cancer Patients

Factor	Univariate analysis			Multivariate analysis	
	ESCC without CRN (n=22)	ESCC with CRN (n=38)	p-value	OR (95% CI)	p-value
Age, yr	60.0±2.5	65.3±1.4	0.041	1.048 (0.985–1.115)	0.140
Gender			0.056	6.195 (0.575–66.778)	0.133
Male	18	37			
Female	4	1			
BMI, kg/m ²	22.2±0.7	23.4±0.5	0.138	-	-
Hx of diabetes	3	5	1.000	-	-
Hx of smoking	16	25	0.578	-	-
Hx of alcohol use	13	26	0.465	-	-
Hx of aspirin use	13	19	0.496	-	-
Tumor location			0.966	-	-
Upper	2	3			
Middle	8	13			
Lower	12	22			
Tumor size, mm	32.5±3.8	28.9±3.6	0.520	-	-
T stage			0.572	-	-
1	14	22			
2	2	6			
3	6	8			
4	0	2			
N stage			0.970	-	-
0	12	23			
1	6	9			
2	3	5			
3	1	1			
M stage			0.549	-	-
0	20	37			
1	2	1			
Histological grade			0.809	-	-
Well	4	5			
Moderate	16	31			
Poor	2	2			
TC, mg/dL	179.6±7.2	175.8±4.8	0.650	-	-
TG, mg/dL	128.9±15.3	146.3±14.9	0.450	-	-
CEA, ng/mL	1.8±0.2	2.2±0.2	0.202	-	-
CFS reason			0.942	-	-
Asymptomatic health checkup	15	27			
Symptoms	5	8			
Positive PET/CT	2	3			

Data are presented as mean±SD or number.

ESCC, esophageal squamous cell carcinoma; CRN, colorectal neoplasms; OR, odds ratio; CI, confidence interval; BMI, body mass index; Hx, history; TC, total cholesterol; TG, triglyceride; CEA, carcinoembryonic antigen; CFS, colonofibroscopy; PET/CT, positron emission tomography/computed tomography.

ence was not significant in the multivariate analysis. Univariate and multivariate analyses showed no differences in any factor between ESCC patients with and without advanced CRN. When the CRN risk in ESCC patients who were at stage T1N0 were compared with controls, subjects with T1N0 had a significantly higher risk of CRN (OR, 3.347; 95% CI, 1.331 to 8.420; $p=0.010$).

DISCUSSION

Our study demonstrated a clear association between ESCC and CRN. The presence of ESCC conferred a twofold risk of both CRN and advanced CRN compared with controls. Our study suggests that a screening colonoscopic examination should be considered at the time of ESCC diagnosis.

Multivariate analysis showed that the presence of ESCC conferred a twofold risk of both CRN and advanced CRN compared with controls. This finding is similar to the results of studies reporting an increased CRN risk in patients with esophageal adenocarcinoma or Barrett's metaplasia, which had a similar risk.^{14,30,31} By contrast, only a few studies have investigated the relationship between ESCC and CRN, and the results have been limited.^{13,15-17} Bollschweiler *et al.*¹³ reported a similar twofold increase in colon polyp prevalence in the ESCC group compared with the controls, although a higher risk of colon polyps and CRN were reported in the adenocarcinoma group compared with the ESCC group. Two Asian studies reported a high prevalence of colorectal lesions in 43.4% and 39% of ESCC patients who underwent colonoscopic examination. However, these studies were limited by the lack of a control group and did not specify the adenoma detection rates.^{15,16} Also, one study performed colonoscopies only if a patient's barium examination was positive.¹⁶ Leers *et al.*¹⁷ found no significant increase in the prevalence of CRN in esophageal adenocarcinoma and ESCC patients, although their study was limited by the comparison with historic controls. The strength of our study is that we compared ESCC patients with an age-, gender-, and BMI-matched control group. Therefore, we suggest that all ESCC patients should undergo screen colonoscopy at the time of diagnosis.

The epidemiological and pathophysiological associations between ESCC and CRN remain unclear. Both diseases have some common risk factors such as gender, smoking, alcohol consumption, and intake of red meat.^{18-22,32,33} They also share some common preventive factors such as the use of aspirin and statins.³⁴⁻³⁷ Genetic studies have reported associations between ESCC and genes implicated in classic colorectal tumorigenesis²³⁻²⁶ as well as in other pathways.³⁸⁻⁴⁰ This may also be related to a recent finding which reported increase of CRNs in oral squamous cell carcinoma patients, which are known to be increased in ESCC patients.⁴¹ However, these associations are not strong, and a causal relationship has not been confirmed. As such, the pathogenic associations need further investigation.

Our study identified older age and BMI as risk factors associ-

ated with both CRN and advanced CRN formation. This agrees with the findings of previous studies that have reported a positive association between age, obesity, and risk of CRN.⁴²⁻⁴⁴ In contrast to previous reports, CRN and advanced CRN were not significantly associated with a history of diabetes, smoking, alcohol, or serum total cholesterol or triglyceride levels.^{18,19,45-47}

We investigated the risk factors for CRN in ESCC patients and found that age was the only significant risk factor for CRN in the univariate analysis. A previous study reported that obesity, heavy smoking, and higher alcohol use were associated with higher CRN risk in ESCC patients.¹⁵ We did not quantify the amount of smoking or alcohol intake, which may be the difference between our study and this previous study. The small sample size because of the omission of a large proportion of ESCC patients and the retrospective nature of this study may have also accounted for the lack of positive risk factors.

Some limitations to our study should be noted. First, the ESCC patients had a significantly higher proportion of subjects with smoking history. Though smoking was not a potential risk factor of CRNs in our study, the possibility of confounding may exist. Second, this was a single center, retrospective study, with a small number of subjects selected for colonoscopic evaluation. However, most of the ESCC patients were asymptomatic and had colonoscopy done for routine health checkup which limits the possibility of a selection bias. Also the ESCC patients had a CRN rate of over 60%. When considering that the control group had a CRN rate of over 40%, which is much higher than the recommended adenoma detection rate of 20% to 25%, the higher numbers of CRNs in the ESCC group become even more prominent.⁴⁸ Third, the clinical impact of CRNs in ESCC can be debated as ESCC has poor 5-year survival rates.^{1,2} However, 45% of the ESCC group were T1N0 with a significantly higher CRN risk. As removal of colorectal adenomas have been reported to decrease risk of colorectal cancer,⁴⁹ this suggests that colonoscopic examinations to diagnose and remove CRNs in ESCC patients has clinical significance. Fourth, the retrospective nature of this study limited the collection of potentially important data such as the amount of smoking or alcohol consumption and family history. Future investigations should be carried out prospectively in order to clarify these factors.

In conclusion, this study showed that the risk of CRN and advanced CRN is increased significantly in ESCC patients. Patients with ESCC should have a colonoscopic examination at the time of esophageal cancer diagnosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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