Early gastric neoplasms are significant risk factor for colorectal adenoma
A prospective case-control study

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Abstract
Although gastric cancer patients have a high incidence and risk of colorectal cancer, evidence is lacking regarding whether early gastric neoplasms (EGNs), such as gastric adenomas and early gastric cancer, are risk factors for colorectal adenoma. This study aimed to investigate the incidence of colorectal adenomas in patients with EGN.

This prospective study was conducted between January 2015 and December 2016. Of the 307 patients who underwent gastric endoscopic submucosal dissection for EGN, 110 patients were enrolled in the EGN group, and 110 age- and sex-matched healthy persons from the screening population were included in the control group in a 1:1 ratio. Demographic factors and results of colonoscopy, including quality assessment, were collected, and analyzed.

No significant differences in the quality of colonoscopy, including bowel preparation, cecal intubation rate, and withdrawal time between the 2 groups, were observed. The incidence of colorectal adenoma was significantly higher in the EGN group than in the control group (55.5% vs 26.4%, \( P = .001 \)). Multivariate analysis confirmed that old age (odds ratio: 1.04, 95% confidence interval: 1.01–1.08, \( P = .005 \)) and a history of EGN (odds ratio: 4.99, 95% confidence interval: 2.60–9.57, \( P = .001 \)) were independent risk factors for colorectal adenoma.

This is the first prospective study to reflect the quality indicator of colonoscopy and confirmed that old age and a history of EGN are significant risk factors for colorectal adenomas. Therefore, more stringent colonoscopy surveillance should be considered in elderly patients with EGN.

Abbreviations: ACRA = advanced colorectal adenoma, BMI = body mass index, DM = diabetes mellitus, EGC = early gastric cancer, EGNs = early gastric neoplasms, ESD = endoscopic submucosal dissection, \( H. pylori \) = Helicobacter pylori, NSAIDs = nonsteroidal anti-inflammatory drugs.

Keywords: colonoscopy, colorectal neoplasms, cancer screening, gastric neoplasms.

1. Introduction
Gastric cancer is the fifth most commonly diagnosed cancer and the third leading cause of cancer-related deaths worldwide.[1] The incidence of gastric cancer has been steadily declining since 2011 in Korea, despite having the highest global prevalence.[2] A national gastric cancer screening program leading to increased diagnosis of early gastric neoplasms (EGN), such as gastric adenoma and early gastric cancer, and reduced advanced gastric cancer and showing a remarkable improvement in the 5-year survival rate has been conducted.[3]

Although the exact mechanism is unknown, multiple primary cancers are on the rise resulting in poor quality of life and prognosis in cancer patients. Out of 4.7% of patients having gastric cancer with multiple primary cancer, 77.5% are diagnosed within 5 years, and the most common site is colorectum.[4] A Korean multicenter trial confirmed that patients with gastric cancer have a higher incidence and risk of colorectal cancer.[5] It was also reported that a postgastrectomy gastric cancer patient was a high risk for colorectal neoplasia.[6] But weak evidence exists regarding the relationship between EGN and colorectal adenoma.

Therefore, this study aimed to investigate the incidence of colorectal adenomas in patients with EGN. A prospective study was conducted including patients with EGN who underwent good quality colonoscopy.

2. Methods
2.1 Study population
This prospective single-center study included patients who underwent endoscopic submucosal dissection (ESD) for EGN,
such as gastric adenoma or early gastric cancer, performed between January 2015 and December 2016, and underwent colonoscopy within 6 months before or after the procedure (Fig. 1). Patients with a history of gastric or colorectal cancer, hereditary cancer syndrome, including familial adenomatous polyposis, inflammatory bowel disease, and prior gastric or colorectal surgery, and those with a family history of first-degree relatives with colorectal cancer were excluded. Moreover, we excluded patients with a history of colonoscopy within 5 years and colonoscopy with polypectomy within 3 years to reduce bias. Out of 307 patients who underwent ESD for EGN, 197 were excluded. Out of 110 patients in the EGN group, 93 and 17 were diagnosed with gastric adenoma and early gastric cancer after ESD, respectively. Age- and sex-matched control groups who underwent upper endoscopy and colonoscopy for health screening during the same period were selected (Fig. 2).

2.2. Colonoscopy and data collection
Colonoscopy was performed after bowel preparation with 2 L of CoolPrep (Taejun, Seoul, Korea) by 2 experienced endoscopists. Details of bowel preparation, cecal intubation, and withdrawal time were noted for quality assessment. Bowel preparation was assessed using the Boston bowel preparation score. Cecal intubation is defined as the time when the endoscope tip reached the cecum, and the medial wall of the cecum passed through the ileocecal valve. Withdrawal time is defined as the time for the endoscope to reach the anus from the cecum, excluding the procedure time. The investigators immediately removed the detected lesions using biopsy forceps or snares and recorded the size and location of all colorectal polyps. The colorectal polyps were classified into the proximal colon (cecum, ascending colon, and transverse colon), distal colon (descending colon, sigmoid colon), and rectum. All removed polyps were sent to the pathology department for histological evaluation (Fig. 1). Neoplastic polyps, such as adenoma or adenocarcinoma, were screened. And non-neoplastic polyps, such as inflammatory polyps or hyperplastic polyps, were excluded. Advanced colorectal adenoma (ACRA) was defined as high-grade dysplasia, villous features, a size >1 cm, and >3 adenomas and serrated adenoma with dysplasia. Information on age, sex, body mass index (BMI), diabetes mellitus (DM), lipid profile, alcohol use, smoking, use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), presence of Helicobacter pylori (H. pylori) infection, and location of EGN was recorded.

2.3. Sample size and statistical analysis
The incidence of colorectal adenoma has been previously reported as 35% to 39% in patients with EGN and 16% to 25% in the average-risk population. We assumed the incidence of colorectal adenoma to be 37% in patients with EGN and 20% in the average-risk population, a 2-sided alpha of 0.05, a power of 80%, and a dropout rate of 10%. Finally, each group was determined to contain at least 110 subjects.

Parametric data are expressed as mean ± standard deviation and nonparametric data as median (range). Statistical differences were analyzed using the chi-squared test or Fisher exact test for categorical data and the independent sample t-test for continuous data. Logistic regression analysis was used to estimate the

Figure 1. Gastric adenoma and colorectal adenoma diagnosed in the same patient. (A) Endoscopy shows about 15 mm sized white, elevated gastric adenoma, (B) biopsy revealed low-grade dysplasia of columnar cells differentiate to intestinal-type cells with basally located nuclei (hematoxylin and eosin [H-E] staining, ×100), (C) Colonoscopy shows about 1 cm sized polypoid lesion in the descending colon, (D) Biopsy showed tubular architecture without complexity composed of cells with low-grade dysplasia (H-E staining, ×100).
risk factors of colorectal adenoma and expressed as an OR with a 95% confidence interval (CI) \( P < .05 \), which was considered statistically significant. Statistical evaluation was performed using the SPSS software version 23 (SPSS, Chicago, IL).

2.4. Ethics approval and consent to participate
The study complies with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board Committee of the Chosun University Hospital (2014-09-009-001). All participants provided written informed consent.

3. Results

3.1. Baseline characteristics
A total of 110 participants were enrolled in each of the EGN and control groups. No difference in age and sex between the 2 groups existed because of the matching process used while selecting the control group participants. The average age of the participants was 65 years. Most characteristics were similar in the 2 groups, including BMI, smoking, DM, total cholesterol, NSAIDs, or aspirin use. Alcohol use (51% vs 31%, \( P = .001 \)) was significantly higher in the EGN group than in the control group (Table 1).

3.2. Quality indicators and characteristics of colorectal adenoma
Statistical significance between the 2 groups in bowel preparation (Boston bowel preparation score: \( 7.36 \pm 1.89 \) vs \( 7.18 \pm 1.04 \), \( P = .37 \), cecal intubation rate (100% vs 100%) and withdrawal time (8.9 \pm 2.72 vs 8.55 \pm 2.49, \( P = .29 \)) related to the quality of colonoscopy was not observed. The incidence of colorectal adenomas was significantly higher in the EGN group than in the control group (55.5% vs 27%, \( P = .001 \)). ACRA was also significantly higher in the EGN group than in the control group (22.7% vs 6.5%, \( P = .001 \)). Statistically significant difference in the distribution of colorectal adenoma in both groups was not observed (proximal colon: 73.6% vs 73%, distal colon: 21% vs 16%, and rectum: 6% vs 11%, \( P = .175 \)) (Table 2).

3.3. The risk factors for colorectal adenoma in the EGN group
When analyzing the risk factors for colorectal adenoma in the EGN group, the difference in sex, BMI, smoking, DM, total cholesterol, low-density cholesterol, and alcohol use were not observed between the 2 groups. No statistical difference in factors associated with EGN, such as \( H. pylori \) infection, location, and presence of early gastric cancer, was noted. The incidence of

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**Table 1**

| Basal characteristics of colorectal adenoma in early gastric neoplasm and control groups. |
|-------------------------------------------------|-------------------------------------------------|--------|
| Age (y), mean ± SD | 65 ± 10 | 65 ± 10 | .941 |
| Sex (male) (%) | 74 (67) | 74 (67) | .927 |
| Body mass index, mean ± SD | 24.33 ± 3.14 | 23.60 ± 3.15 | .092 |
| Diabetes mellitus (%) | 19 (17) | 20 (18) | .701 |
| Alcohol (%) | 55 (51) | 34 (31) | .001 |
| Smoking (%) | 19 (17) | 11 (10) | .112 |
| Total cholesterol, mean ± SD | 181.21 ± 34.59 | 190.98 ± 40.93 | .057 |
| NSAID or aspirin use | 18 (16) | 12 (11) | .241 |

EGN = early gastric neoplasm, NSAIDs = nonsteroid anti-inflammatory drugs, SD = standard deviation.
colorectal adenomas was significantly higher in older patients (66.87 ± 8.43 vs 62.76 ± 11.82, \( P = .036 \)) (Table 3).

### 3.4. The risk factors of colorectal neoplasms and advanced colorectal adenoma

Multivariate analysis revealed that old age (colorectal adenoma, odds ratio [OR]: 1.04, 95% CI: 1.01–1.08, \( P = .005 \); ACRA, OR: 1.08, 95% CI: 1.03–1.14, \( P = .001 \)) and history of EGN (colorectal adenoma, OR: 4.99, 95% CI: 2.60–9.57, \( P = .001 \); ACRA, OR: 5.46, 95% CI: 2.10–14.22, \( P = .001 \)) were independent risk factors for colorectal adenoma (Table 4).

### 4. Discussions

This prospective study showed a significantly higher incidence of colorectal adenoma in the EGN group than in the control group (55.5% vs 27%, \( P = .001 \)) and history of EGN as an independent risk factor for colorectal adenoma. Several previous retrospective studies also reported a 37.9 to 57.5% incidence of colorectal adenoma in patients with EGN.\(^{14,9,11,12,14}\) However, these studies have some limitations. First, a selection bias exists because of the retrospective nature of the study. Moreover, prior colonoscopy has not been reviewed, and accurate detection of the adenoma occurrence is difficult. Second, since no evidence for colonoscopy quality control evaluation is available, the results of adenoma detection between the 2 groups are difficult to trust. Although colonoscopy is the most effective screening test for colorectal cancer, the incidence of intermediate cancers is reported to be 5% to 9%.\(^{15}\) In fact, the colonoscopy effect on the prevention of colorectal cancer varies with country or region, and large differences in the detection rate of adenomas are reported among examiners.\(^{16,17}\) Quality indicators such as suboptimal bowel preparation, incomplete cecal intubation, and insufficient withdrawal time can significantly affect adenoma detection rate.\(^{18}\) In our study, high-quality colonoscopy in both groups increased the reliability of the results and reinforced the suggestion that active colonoscopy is needed in patients with EGN.

Our study revealed a history of EGN to be an independent risk factor for colorectal adenoma (OR: 4.99, 95% CI: 2.60–9.57, \( P = .001 \)) and ACRA (OR: 5.46, 95% CI: 2.10–14.22, \( P = .001 \)). Several factors have been suggested for the association between EGN and colorectal adenomas. Although conflicting data exist, a recent systemic review reported a moderate correlation (OR: 1.70, 95% CI: 1.64–1.76) between \textit{H. pylori} infection and colorectal neoplasms, including colorectal adenoma.\(^{19}\) Chronic gastritis due to \textit{H. pylori} infection can increase the production of gastrin, a known trophic factor in the colonic mucosa, and induce systemic inflammation by increasing the production and activity of inflammatory markers such as cyclooxygenase-2. These changes caused by \textit{H. pylori} infection may promote colorectal neoplasms.\(^{20–22}\) However, no association between \textit{H. pylori} infection and colorectal adenoma development was observed in our study. Patients with EGN were mostly transferred to our hospital after being diagnosed at a separate clinic, and it is possible that \textit{H. pylori} eradication has already been performed in hospitals in these cases. In addition, since the prevalence of \textit{H. pylori} in our country is relatively high, the small sample size of our study might not indicate a significant relationship between \textit{H. pylori} infection and colorectal adenoma.

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### Table 2

Quality indicators and characteristics of colorectal adenoma in early gastric neoplasm and control groups.

| Indicator                        | EGN group (n = 110) | Control group (n = 110) | \( P \) |
|----------------------------------|---------------------|------------------------|--------|
| Bowel preparation                | 7.36 ± 1.89         | 7.18 ± 1.04            | .378   |
| Cecal intubation rate (%)        | 100                 | 100                    | .291   |
| Withdrawal time (min), mean ± SD | 8.9 ± 2.72          | 8.55 ± 2.49            | .001   |
| Colorectal adenomas (%)          | 61 (55.5)           | 30 (27)                | .001   |
| Advanced adenoma (%)             | 25 (22.7)           | 7 (6.5)                | .001   |
| Colorectal adenocarcinoma (%)    | 0 (0)               | 0 (0)                  | .247   |
| Location of neoplasm             |                     |                        | .175   |
| Proximal colon (%)               | 81 (73.6)           | 80 (73)                | .756   |
| Distal colon (%)                 | 23 (21)             | 17 (16)                | .354   |
| Rectum (%)                       | 6 (6)               | 13 (11)                | .387   |

EGN = early gastric neoplasm, SD = standard deviation.

### Table 3

The risk factors for colorectal adenoma in the early gastric neoplasm group.

| Indicator                        | Colorectal adenoma (+) (n = 61) | Colorectal adenoma (−) (n = 49) | \( P \) |
|----------------------------------|----------------------------------|----------------------------------|--------|
| Age (y), mean ± SD               | 66.87 ± 8.43                     | 62.76 ± 11.82                    | .036   |
| Sex (male) (%)                   | 44 (72)                          | 30 (61)                          | .226   |
| Body mass index, mean ± SD       | 24.27 ± 3.14                     | 24.29 ± 3.17                     | .895   |
| Diabetes mellitus (%)            | 14 (23)                          | 5 (10)                           | .079   |
| Total cholesterol, mean ± SD     | 182.16 ± 37.23                   | 180 ± 31.35                      | .746   |
| Alcohol use (%)                  | 21 (35)                          | 14 (28)                          | .381   |
| Smoking (%)                      | 12 (19)                          | 7 (14)                           | .458   |
| \textit{H. pylori} infection (%) | 26 (43)                          | 22 (45)                          | .811   |
| Location                         |                                  |                                  | .753   |
| Corpus (%)                       | 17 (28)                          | 15 (30)                          |        |
| Antrum (%)                       | 44 (78)                          | 35 (70)                          |        |
| Presence of EGC                  |                                  |                                  | .995   |
| Adenoma (%)                      | 56 (92)                          | 45 (92)                          |        |
| EGC (%)                          | 5 (8)                            | 4 (8)                            |        |

EGC = early gastric cancer, \textit{H. pylori} = \textit{Helicobacter pylori}, SD = standard deviation.
adenoma. Further large-scale prospective studies are needed to confirm the association between *H. pylori* infection and colorectal neoplasms.

Like colorectal cancer, gastric cancer is known to follow sequential steps of precancerous changes, including atrophic gastritis, intestinal metaplasia, dysplasia, and cancer, based on gene mutation, such as APC, DCC, K-ras, p53, and microsatellite instability.[23–26] An association in each of the sequential steps of gastric cancer with colorectal neoplasms has been reported.[13] Bestas et al.[27] reported that gastric intestinal metaplasia is associated with colorectal neoplasms (39.7% vs 25.3%, *P* = .03). Several studies reported that atrophic and metaplastic changes in the gastric corpus are associated with the development of gastric adenoma or gastric cancer.[28,29] In this regard, we investigated the relationship between the EGN location and colorectal adenoma; however, no statistical difference between the EGN location and colorectal adenoma development. This result might be due to colon-specific environmental factors, such as gut microbiota, in addition to genetic factors of colorectal neoplasms.

In addition, lifestyle factors, such as age, obesity, diabetes, hyperlipidemia, smoking, and alcohol, may be related to colorectal neoplasm.[30–35] Old age is a well-known risk factor for colorectal adenoma.[36] Yang et al reported that 85.1% of patients with gastric adenoma are 50 to 69 years of age, and increasing age over 55 years is a significant independent risk factor for colorectal adenoma (OR: 2.943; 95% CI: 1.558–5.560). This study showed a significantly higher incidence of colorectal adenoma in old age (66.87 ± 8.43 vs 62.76 ± 11.82, *P* = .03) and old age was an independent risk factor for colorectal adenoma (OR: 1.04, 95% CI: 1.01–1.08, *P* = .005). Therefore, colonoscopy should be considered more actively concerning colorectal adenoma for elderly patients diagnosed with EGN. However, caution is needed to apply these results to western. Most of the studies, including this study, were conducted in Japan and Korea, and there is 1 Western study. Cappell MS et al, in their study, reported that gastric adenoma was a significant risk factor for colorectal polyp (OR 3.58, 95% CI: 1.56–8.23, *P* < .006). Additional studies are needed to determine whether there is a difference in the incidence of colorectal adenoma in gastric adenoma patients according to factors such as geographic region and patient’s race.

The present study had some limitations. First, the incidence of colorectal cancer was absent in both groups, and the association between EGN and colorectal cancer could not be assessed. However, considering that most colorectal cancers follow sequential steps of normal epithelium, adenoma, and cancer, the incidence of increased ACRA in the EGN group is a significant finding.[27] Second, the control group was selected from those who visited the health promotion center. Because these people are more concerned about their health and can follow a healthy lifestyle, their risk of colorectal neoplasms might be lower than in the general population. Third, this study confirmed that colorectal adenomas were common in elderly patients with EGN. However, the exact risks of old age and EGN and when and how often colonoscopy should be recommended could not be determined. Fourth, the exact mechanism of the association between EGN and colorectal adenoma could not be elucidated through genetic or experimental studies.

5. Conclusions

This study was conducted as a prospective study with high-quality colonoscopy. The incidence of colorectal adenoma was found to be significantly higher in the EGN group than in the control group. Old age and a history of EGN were independent risk factors for colorectal adenoma. Therefore, clinicians should strictly consider colonoscopy surveillance in elderly patients with EGN.

Author contributions

All authors read and approved the final article. Conceptualization: SeongJung Kim, Jun Lee, DaeYoub Baek Methodology: SeongJung Kim, Jun Lee, DaeYoub Baek Software: SeongJung Kim Data curation: SeongJung Kim, JunHyung Lee, Ran Hong Supervision: Jun Lee, JunHyung Lee, Ran Hong Writing—original draft: SeongJung Kim Writing—review and editing: Jun Lee, DaeYoub Baek

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