



BRIEF ARTICLE

Gastric dysplasia may be an independent risk factor of an advanced colorectal neoplasm

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CONCLUSION: The study emphasizes the need for colon surveillance in patients with gastric dysplasia, regardless of *H pylori* infection.

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Key words: Gastric adenoma or dysplasia; *Helicobacter pylori*; Colorectal neoplasm

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Abstract

AIM: To evaluate the relationship between gastric dysplasia and *Helicobacter pylori* (*H pylori*) and the occurrence of colorectal adenoma, and to define the necessity for colonoscopy in patients with gastric dysplasia or *H pylori* infection.

METHODS: From May 2005 to February 2008, 133 patients with established gastric dysplasia by gastroduodenoscopy (EGD) were additionally investigated by colonoscopy. The authors compared results with those of 213 subjects who underwent both EGD and colonoscopy during the same period at the author's Health Promotion Center as a control group. *H pylori* infection was evaluated in both the gastric dysplasia and control groups.

RESULTS: The mean age of all 346 study subjects was 54.1 ± 10.5 years, and there were 258 (73%) men and 87 (27%) women. No significant difference was found between the *H pylori* positive and negative subjects in terms of the prevalence of colorectal adenoma and advanced colorectal adenoma ($P = 0.261$). Patients with gastric dysplasia showed no elevated risk of colorectal adenoma (OR = 0.910, 95% CI: 0.587-1.411, $P = 0.738$), but had a significantly higher risk of having advanced colorectal adenoma (OR = 3.382, 95% CI: 1.700-6.342, $P = 0.000$).

INTRODUCTION

Colorectal carcinoma is one of the most common cancers and is the second leading cause of cancer-related mortality in the United States^[1], and the fourth leading cause of cancer-related mortality in Korea^[2]. The etiologies and risk factors of colorectal neoplasms have attracted research attention for several decades, especially in association with *Helicobacter pylori* (*H pylori*) or gastric dysplasia. *H pylori* infection is a well-known cause of chronic gastritis, peptic ulcers^[3,4], gastric adenocarcinoma^[5], and gastric lymphoma^[6], and several reports have suggested that *H pylori* infection increases the risk of colorectal adenoma and adenocarcinoma^[7-9]; however, other reports disagree^[10,11]. Furthermore, several have concluded that gastric adenoma and carcinoma may be indicators of colorectal adenoma or carcinoma^[12,13], and it is accepted that both gastric adenoma and colorectal adenoma have a high potential for malignant transformation^[14-16]. The aims of this study were to evaluate relations between gastric dysplasia and *H pylori* infection and the occurrence of colorectal adenoma and to define the need for colonoscopy in patients with gastric dysplasia or *H pylori* infection.

MATERIALS AND METHODS

Patients

From May 2005 to February 2008, 133 consecutive patients with established gastric dysplasia (the gastric dysplasia group), as determined by gastroduodenoscopy (EGD) at our institute, were additionally subjected to colonoscopy, after obtaining informed consent, within 3 wk of EGD. We defined gastric adenoma as gastric dysplasia. The presence of gastric dysplasia and colorectal adenoma were confirmed histologically using specimens obtained by endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or polypectomy. We also enrolled 213 consecutive subjects who underwent both EGD and colonoscopy for the purpose of screening at the Health Promotion Center at Kyungpook National University Hospital as a control group during the same period. We reviewed endoscopic findings and pathology specimens retrospectively. The subjects who were included in the control group had no symptoms and no gastric dysplasia. Patients with any kind of malignancy and those with a previous history of colorectal surgery were excluded. Subjects with either family history of colorectal adenocarcinoma or adenoma or gastric cancer were also excluded. This study was approved by our Institutional Review Board.

Diagnosis of *H pylori* infection

H pylori infection was diagnosed by biopsy, CLO test (GASTREX, Warsaw, Poland), or by using an urea breathing test (UBT, Otsuka, Tokyo). The specimens for the CLO test were obtained from both the antrum and the distal body of the stomach during EGD. Cresyl violet staining was used for the pathologic diagnosis of *H pylori* infection. The cut-off value of the UBT was 2.5‰. *H pylori* infection was diagnosed when two of the above three methods were positive.

Colonoscopic diagnosis

Cecal intubation was successful in all patients. All lesions found during colonoscopy were removed by biopsy, polypectomy, EMR, or ESD. Advanced colorectal adenoma was defined as a size larger than 1 cm, a villous or tubulovillous adenoma histology, or adenoma with high-grade dysplasia.

Statistical analysis

We compared age and sex distributions, the presence or absence of colorectal adenoma, colorectal adenoma sizes and histology, and *H pylori* infection states in the gastric dysplasia and control groups. Variables were compared using the χ^2 or independent *t*-tests, depending on the nature of the data. Fisher's exact test was used when numbers were small. Odds ratios (ORs) and 95% CIs were used to describe associations. ORs with corresponding 95% CIs were obtained by conditional logistic regression analysis. *P* values of < 0.05 were considered statistically significant, and statistical calculations were performed using SPSS version 14.0 software for Window (SPSS Inc. Chicago, IL, USA).

Table 1 Baseline characteristics of gastric dysplasia and control group

	Gastric dysplasia (<i>n</i> = 133)	Control (<i>n</i> = 213)	<i>P</i> -value
Age (mean \pm SD)	61.2 \pm 9.7	49.6 \pm 8.3	0.0005
Sex [M/F, (%)]	97/36 (73/37)	162/51 (76/24)	0.5200
<i>H pylori</i>			0.2610
(+) <i>n</i> = 204	73	131	
(-) <i>n</i> = 142	60	82	
Colorectal adenoma			0.5220
(+) <i>n</i> = 148	55	93	
(-) <i>n</i> = 198	78	120	
Advanced adenoma			0.0007
(+) <i>n</i> = 44	28	16	
(-) <i>n</i> = 302	105	197	

Advanced adenoma: Advanced colorectal adenoma.

RESULTS

Clinical characteristics of the gastric dysplasia and control groups

The mean age of all 346 study subjects was 54.1 ± 10.5 years, and there were 258 men (73%) and 87 women (27%). The gastric dysplasia group was older than the control group ($P = 0.0005$). In the gastric dysplasia group ($n = 133$), colorectal adenoma was diagnosed in 55/133 (41%) and advanced colorectal adenoma in 28/133 (21%). In the control group, colorectal adenoma was diagnosed in 93/213 (44%), and advanced colorectal adenoma in 16/213 (7.5%). No significant difference was observed between the gastric dysplasia and control groups in terms of the prevalence of colorectal adenoma ($P = 0.5220$), and no significant difference was observed between the *H pylori* positive and negative groups in terms of the prevalence of gastric dysplasia, colorectal adenoma, or advanced colorectal adenoma ($P = 0.2610$). Furthermore, no significant difference was observed between the gastric dysplasia and control groups in terms of the sizes of advanced colorectal adenomas (10.50 ± 3.107 mm *vs* 11.92 ± 8.722 mm, respectively, $P = 0.5860$) (Table 1).

Clinical characteristics of the advanced colorectal adenoma positive and negative groups

Mean age in the advanced colorectal adenoma positive group was greater than in the negative group ($P = 0.0002$). However, group sex distributions ($P = 0.0600$) and *H pylori* ($P = 0.1060$) infection statuses were not different significantly different (Table 2).

Comparisons of the colorectal adenoma and advanced colorectal adenoma groups

Those with colorectal adenoma or advanced colorectal adenoma were older than those without (Table 3). Moreover, those with gastric dysplasia showed no increased risk of having colorectal adenoma (OR = 0.910, 95% CI: 0.587-1.411, $P = 0.7380$), but they had a significantly higher risk of having advanced colorectal adenoma (adjusted OR = 3.283, CI: 1.700-6.342, $P = 0.0004$) (Table 3). This result was supported by multivariate analysis (Table 4).

Table 2 Baseline characteristics of advanced adenoma (+) and (-) group

	Advanced adenoma (+) (n = 44)	Advanced adenoma (-) (n = 302)	P-value
Age (mean ± SD)	60.8837 ± 8.55294	53.1419 ± 10.43410	0.0002
Sex [M/F n (%)]	38/6 (86/14)	221/81 (73/27)	0.0600
<i>H pylori</i>			0.1060
(+) n = 204	21	183	
(-) n = 142	23	119	

DISCUSSION

This study shows that the risk of advanced colorectal adenoma is elevated in patients with gastric dysplasia, and thus, supports the notion that colorectal cancer risk is increased by gastric adenoma, as has been reported previously^[12]. In addition our study concurs with the findings of a previous study, in which it was found that two of six patients with diffuse gastric adenoma had colon polyps and 40 of 73 patients (54.8%) with gastric polyps had colorectal adenomatous polyps^[17]. In the present study, 55 of 133 patients (41%) with gastric dysplasia had colorectal adenomatous polyps and 28 of 133 (21%) had advanced colorectal adenomatous polyps. The present study concurs with another study, in which it was found that eight of eleven patients with duodenal adenomas had colonic polyps^[18]. Furthermore, the present study agrees with other studies concerning the elevated risk of gastric polyps in patients with sporadic colonic polyps^[19]. Shemesh *et al*^[20] reported that two of 100 patients with 1-4 colorectal polyps had gastric adenoma, 3 of 80 patients (3.5%) with 5 or more colorectal polyps had gastric adenoma, 3 of 80 patients with colon cancer had gastric adenoma, and one of 100 patients without colorectal adenoma and cancer had gastric adenoma, and these findings are also in line with those of the present study. The progression of colorectal adenoma to colon cancer is known to be associated with an adenoma size larger than 10 mm, more than three lesions, a villous, tubulovillous or high grade dysplastic histology, and the presence of genetic abnormalities^[21-24]. Genetic abnormalities in colon cancer are very similar to those in gastric cancer^[25,26], especially concerning mutations of the *p53*^[27,28], *APC*^[29,30], *DCC*^[31,32], and *K-ras* genes^[33,34]. Genetic abnormalities are well known to be associated with upper gastrointestinal polyps and with hereditary colonic polyposis syndromes^[25,26], which include familial polyposis coli^[25,26], Gardner's syndrome, Peutz-Jeghers' syndrome, Cowden's syndrome, Cronkhite-Canada syndrome, hereditary flat adenoma syndrome, and others. In the present study, we deliberately excluded patients with HNPCC, suspected HNPCC, or FAP to avoid the influence of such genetic factors.

Gastric adenoma or dysplasia have high rates of malignant transformation (up to 75%^[14-16,19-21]). Accordingly, regardless of the existence of colorectal adenoma, treatment of gastric dysplasia by EMR or ESD is inevitable. Moreover, the above-mentioned relations suggest that the pathogeneses of gastric dysplasia and colorectal

Table 3 Statistics of colorectal adenoma and advanced adenoma groups

	Colorectal adenoma			Advanced adenoma		
	aOR	CI	P-value	aOR	CI	P-value
Age (old age)	1.337	0.872-2.049	0.0020	2.872	1.446-5.704	0.0002
Sex (female)	0.629	0.379-1.042	0.0800	0.431	0.176-1.057	0.0640
<i>H pylori</i>	1.037	0.672-1.599	0.9120	0.594	0.315-1.120	0.1390
(positive)						
G. dysplasia	0.910	0.587-1.411	0.7380	3.283	1.700-6.342	0.0004
(presence)						

aOR: Adjusted odds ratio; G. dysplasia: Gastric dysplasia.

adenoma are similar. Several other controversial factors may increase the risk of colorectal cancer development, e.g. an increased serum gastrin level^[35], *H pylori* infection^[6-11] and *Streptococcus bovis* bacteremia^[36]. However, previous studies have concluded that the presence of *H pylori* infection and an elevated serum gastrin level are not associated with elevated risks of colorectal neoplasm development. Recently, some studies have concluded that increased serum gastrin levels due to the use of proton pump inhibitors do not predispose the development of a colorectal neoplasm. In the present study, we included only gastric dysplasia and *H pylori* infection status to examine the risk of colorectal adenoma development. No significant association was found between *H pylori* infection and colorectal adenoma, which concurs with another study^[10,11], and thus, it appears that an agent other than *H pylori* is responsible for co-pathogenesis of colorectal adenoma^[35].

The aim of several studies on colorectal adenoma has been to reduce colorectal cancer mortality and morbidity. To achieve this aim, the early diagnoses and treatment of precancerous lesions, like colorectal adenoma and early colorectal cancer, are of the utmost importance, especially, in those deemed to be at high risk group by early surveillance colonoscopy^[37,38]. Some studies have recommended that gastric cancer patients undergo colonoscopy due to a substantial risk of their developing colon cancer^[13]. In another study, haemoccult studies were recommended for early detection of colorectal tumors in patients with gastric polyp^[39]. In addition, it has been reported that the rates of occurrence of colorectal adenoma in gastric adenoma and carcinoma patients are increasing^[12]. In common with other studies, the present study reveals that gastric dysplasia is an indicator of advanced colorectal adenoma, which is an important risk factor of colorectal cancer. Accordingly, we emphasize the need for colon surveillance in elderly patients with gastric dysplasia because of their elevated risk of developing advanced colorectal adenoma, which is an important risk factor of colorectal cancer, regardless of *H pylori* infection.

Several limitations of the present study should be considered. First, the sample size was small, which introduces the possibility of a type II error, and we could not collect age and sex-matched controls. Second, selection bias is possible due to the retrospective nature of the study. Third, insufficient information was obtained regarding alcohol consumption, smoking status, and

Table 4 Multivariate analysis of colorectal adenoma and advanced adenoma groups

	Colorectal adenoma					Advanced colorectal adenoma				
	B	SE	t	Sig	95% CI	B	SE	t	Sig	95% CI
Age	3.585	1.129	3.176	0.0020	1.365 to 5.805	7.770	1.648	4.714	0.0002	4.529 to 11.01
Sex	-0.085	0.047	-1.810	0.0710	-0.007 to 0.178	-0.132	0.070	1.888	0.0600	-0.269 to -0.006
<i>H pylori</i>	-0.009	0.054	-0.163	0.8710	-0.114 to 0.097	-0.129	0.079	1.623	0.1060	-0.285 to -0.027
G. dysplasia	0.022	0.053	0.421	0.6740	-0.082 to 0.127	0.289	0.077	3.741	0.0004	0.137 to 0.440

serum gastrin, cholesterol, and glucose levels, which were recently proposed as risk factors of gastric dysplasia^[35]. Fourth, the mean age of the gastric dysplasia group was greater than that of the control group, because the patients who visited our health promotion center were much younger than the gastric dysplasia patients. Accordingly, although age-adjusted odds ratios for advanced colorectal adenoma were statistically significance, we cannot exclude the possibility of an age-related bias.

Even though there were several reports that *H pylori* infection increased the risk of colorectal adenoma and adenocarcinoma^[7-9], our report reveals that *H pylori* infection is not a risk factor for advanced colorectal polyps, but that gastric dysplasia and an advanced age are. Thus, we infer that genetic and environmental factors probably importantly contribute to the development of advanced colorectal polyps, because patients are continuously exposed to those factors. However, the environmental factors involved have not been identified as yet. Thus, further diverse complex study models are required to clarify the relationship between gastric dysplasia, *H pylori*, and colorectal adenoma, and identify the environmental factors concerned. Moreover, a large prospective case-controlled study is required to determine whether the presence of gastric dysplasia is an indication for colonoscopy and what intervals would be recommended for patients with gastric dysplasia.

COMMENTS

Background

Over the last decades, several studies have been performed on the etiologies and risk factors of colorectal neoplasms, especially on the association with *Helicobacter pylori* (*H pylori*) and gastric dysplasia. This study was performed to define the necessity of screening colonoscopy in patients with gastric dysplasia or *H pylori* infection.

Research frontiers

Several controversial factors might increase the risk of colorectal cancer development, for example, increased serum gastrin level, *H pylori* infection and *Streptococcus bovis* bacteremia, and so on. In this study, the authors demonstrate the relations between gastric dysplasia and the occurrence of advanced colorectal adenoma.

Innovations and breakthroughs

Even though there were several reports that *H pylori* infection increased the risk of colorectal adenoma and adenocarcinoma, this report reveals that *H pylori* infection is not a risk factor for advanced colorectal polyps; however, gastric dysplasia and an advanced age are. Thus, genetic and environmental factors probably contribute to the development of advanced colorectal polyps, because of continuous exposure to genetic and environmental factors.

Applications

This result could emphasize the need for colon surveillance in elderly patients with gastric dysplasia because of their elevated risk of developing advanced

colorectal adenoma, which is an important risk factor of colorectal cancer, regardless of *H pylori* infection.

Peer review

The authors examined the relation between gastric dysplasia and *H pylori* and advanced colorectal adenoma. However, a large prospective case-controlled study is required to determine whether the presence of gastric dysplasia is an indication for colonoscopy and what intervals would be recommended for patients with gastric dysplasia.

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