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Is gastric intestinal metaplasia a risk factor for colorectal neoplasms?

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ABSTRACT

Colorectal cancers are one of the most common types of cancer. Gastric intestinal metaplasia is considered a precancerous lesion that can progress into gastric cancer. Even though there are previous reports that *Helicobacter pylori* and intestinal metaplasia are related to colorectal adenomas, there are also studies stating the opposite. This study aimed explored the relationship between gastric intestinal metaplasia and colorectal neoplasia. A total of 214 patients between the ages of 19 and 92 who underwent combined gastroscopy and colonoscopy between August 2016 and April 2020 were included in this retrospective study. Medical records including demographic data, gastroscopy and colonoscopy findings and histopathology results of the patients were reviewed and analyzed. The association of intestinal metaplasia and *H. pylori* infection with colorectal neoplasia was evaluated in these patients. The mean age of the patients included in the study was 49.07 ± 15.80, and 125 (58.4%) of the patients were male. A statistically significant correlation was found between intestinal metaplasia and colon neoplasm prevalence ($p = 0.03$). However, such a correlation was not seen between *H. pylori* and colon neoplasia. In conclusion, a positive correlation was found between gastric intestinal metaplasia, which is a precancerous lesion, and colon neoplasia. Even though this correlation indicates higher prevalence rates of colon neoplasia in patients with gastric intestinal metaplasia, how to evaluate these patients in terms of colon neoplasia remains a controversial issue.

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Introduction

Gastric cancer, which has a gradually decreasing incidence in many industrialized countries, still remains the second leading cause of cancer related deaths around the world [1]. Gastric cancer is classified into two main types: intestinal and diffuse. Intestinal type gastric cancer is related to premalignant lesions such as chronic atrophic gastritis (AG) and intestinal metaplasia (IM) [2, 3]. IM, defined as gastric mucosa changing into epithelium with intestinal morphology, is associated with *Helicobacter pylori* (*H. pylori*) infection, and during this infection, gastric mucosa progresses into many stages of chronic gastritis, AG and IM [4, 5].

Colorectal cancers (CRC) are one of the most common cancers worldwide. Colorectal carcinogenesis usually originates from colorectal adenomas that develop from normal mucosa and the adenocarcinoma sequence [6]. This process gives us a chance to early diagnose and intervene before the development of cancer. Colorectal adenomas are considered the most important precancerous lesions for CRC. These two diseases, colorectal adenomas and CRC, are collectively referred to as colorectal neoplasia.

Clarifying the pathogenesis and the risk factors of colorectal cancers is of great importance in the early diagnosis and treatment of this type of cancer [7]. Various previous studies have been conducted on this matter after *H. pylori* infection was accepted as a risk factor for colorectal cancer in the 1990s [8]. While some studies have determined a positive association between *H. pylori* infection and colorectal cancers [9–15], there are studies stating that this was controversial as well [16–19]. In addition, studies investigating the association between gastric IM and colorectal adenomas were also conducted [12, 20]. A recent study reported that there is a significant relationship between gastric intestinal metaplasia and colorectal neoplasia [21]. The aim of this study was to evaluate the relationship between *H. pylori* infection and IM, which is considered a premalignant lesion for gastric cancer, with colon neoplasia.

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Subjects and methods

Ethics statement

Informed consent forms were obtained from the patients prior to the procedure. This study was approved by the Clinical Research Ethics Committee at Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital.

Subjects

A total of 214 patients, who were indicated for combined gastroscopy and colonoscopy with various prediagnoses between August 2016 and April 2020, were included in this retrospective study. Gastroscopic, histopathologic and demographic data of the patients were analyzed and recorded. Patients were separated into two groups according to their endoscopic biopsy results as IM positive and IM negative. Additionally, two groups were created according to the presence of *H. pylori* infection. The association between gastric intestinal metaplasia and *H. pylori* infection was evaluated. Patients with colon and gastric surgery histories, patients who had been administered eradication therapy for *H. pylori*, patients who had undergone previous polypectomies, patients with inflammatory bowel disease and patients with missing data were excluded from the study. The patients were fully sedated under the supervision of an anesthesiologist and were applied upper and lower endoscopy procedures by a single experienced endoscopist after a minimum of 8 h of fasting. The absence of abnormal appearance in the examinations was accepted as normal gastroscopic and colonoscopic examination, and biopsies were not taken. Biopsies were taken from patients whose endoscopic examination was suggestive of IM and from suspicious and abnormal lesions. Gastroscopy and colonoscopy procedures were performed with EG-600WR gastroscope and EC-600WL colonoscope (Fujinon, Tokyo, Japan), respectively.

Statistical analysis

All statistical analyses were performed with the Statistical Package (SPSS) 21.0 software. To evaluate the significance of the difference between the two groups, categorical variables were compared with the Pearson *chi*-square test or Fisher's exact test, and continuous variables were compared using Student's *t*-test. Two tailed $p < 0.05$ value was accepted as statistically significant.

Results

The patients included in the study were between the ages of 19 and 92, the mean age was 49.07 ± 15.80 and the median was 47. Furthermore, 89 (41.6%) of the patients were female and 125 (58.4%) were male. The number of IM positive and IM negative patients were 68 (31.8%) and 146 (68.2%) respectively. A total of 99 (46.3%) patients were positive for *H. pylori*, and 115 (53.7%) were negative. The patients were separated into two groups according to their *H. pylori* infection status (Table 1). There was no significant difference between the *H. pylori* positive and *H. pylori* negative groups in terms of mean age and gender. No correlation was found between *H. pylori* infection and colorectal neoplasm prevalence ($p = 0.310$). Patients in the IM positive group were significantly older than the patients in the IM negative group ($p = 0.000$), and there were a higher number of male patients in the IM positive group. Colorectal neoplasm prevalence was significantly higher in the IM positive group in comparison with the IM negative group ($p = 0.033$). The distribution of patients according to IM status is presented in Table 2. All of the patients were separated into four groups (Table 3): Group A: IM positive, *H. pylori* negative; Group B: IM positive, *H. pylori* negative; Group C: IM negative, *H. pylori* positive; and Group D: IM negative, *H. pylori* negative. There was not any significant difference between these four groups in terms of colon neoplasm prevalence.

Discussion

Colon cancer is one of the leading causes of cancer related mortality and morbidities worldwide. Studies have been conducted regarding its etiology exploring the place of a high-fat animal-based diet, consumption of low-fiber foods, smoking [22]. There have been recent studies focusing on the probability of infectious agents, especially *H. pylori*, being associated as well. *H. pylori* infection is considered as the most important

Table 1. Distribution of demographical characteristics of the patients according to the presence of *Helicobacter pylori* infection and their association with colon neoplasia.

Parameter	Hp positive	Hp negative	*P* value
	(n: 99)	*(n: 115)*	
Age, mean ± SD [years]	47.60 ± 15.44	50.34 ± 16.05	0.206
Gender, *n* (%)			0.546
Male	60(60.6)	65(56.5)	
Female	39(39.4)	50(43.5)	
Colon pathology, *n* (%)			
Normal colon	66(66.7)	84(73)	
Colon neoplasm	33(33.3)	31(27)	0.310

Hp; Helicobacter pylori.

Table 2. Distribution of demographical characteristics of the patients according to the presence of intestinal metaplasia and their association with colon neoplasia.

Parameter	IM (+)	IM	*P* value
	(*n*: 68)	(*n*: 146)	
Age, mean ± SD [years]	57.88 ± 13.98	44.97 ± 14.93	0.000
Gender, *n* (%)			
Male	43(63.2)	82(56.2)	0.328
Female	25(36.8)	64(43.8	
Colon pathology, *n* (%)			
Normal colon	41(60.3)	109(74.7)	
Colon neoplasm	27(39.7)	37(25.3)	0.033

IM; intestinal metaplasia.

Table 3. The association of intestinal metaplasia and *Helicobacter pylori* subgroups with colon neoplasia.

Group	IM	Hp	Normal colon *n* (%) 150 (70.1)	Colon neoplasm *n* (%) 64(29.9)	Value
Group A	+	+	14 (56)	11 (44)	0.098
Group B	+	–	27 (62.8)	16 (37.2)	
Group C	–	+	52 (70.3)	22 (29.7)	
Group D	–	–	57(79.2)	15(20.8)	

Hp; *Helicobacter pylori*, IM; intestinal metaplasia.

risk factor in gastric IM development [4, 23, 24]. Sporadic colorectal cancers mostly originate from adenomatous polyps. With early diagnosis and treatment of colorectal polyps, a significant decrease can be achieved in the incidence and mortality of colorectal cancers [25].

The latest research has focused on the role of infectious agents in the prevention of colorectal cancers and the polyp–cancer spectrum [26, 27]. Although it is not fully understood how *H. pylori* infection increases the risk of colorectal neoplasia, according to the most commonly described pathogenesis, IM occurs after a long term *H. pylori* infection, and IM replaces normal gastric cells both in the corpus and the antrum [28]. The reduced gastric acid secretion triggered by IM causes hypergastrinemia, which may facilitate proliferation of colorectal mucosa, making the colon and rectum more susceptible to carcinogenesis [29, 30].

The association between *H. pylori* infection and colorectal neoplasia was first reported in 1997 [8]. Several previous studies showed that there was a positive correlation between *H. pylori* infection and colorectal neoplasia [10, 31–34]. In addition, this correlation was supported in other studies [35–37], and in a recent study, it was reported that *H. pylori* infection is an independent risk factor for colorectal adenomas [38]. In their 11-study meta-analysis, Zumkeller et al. [39] stated that *H. pylori* infection caused a minor increase in colorectal cancer risk. In our study, it was seen that there was no significant association between *H. pylori* infection and gender and age. Contrary to other reports that there was a correlation between *H. pylori* and colorectal neoplasia, in our study, a correlation was not found between *H. pylori* infection and colon neoplasm risk ($p = 0.310$). This outcome supports the studies reporting that *H. pylori* is not likely to increase the colorectal neoplasia risk.

AG and IM prevalence was found to be significantly higher in males in comparison with females [40]. There were many studies reporting that 50 years of age and above was an independent risk factor, and IM incidence increased in proportion to age [41, 42]. Similar to these studies, in our study, IM incidence was found as 41% in the group aged under 50, and 59% in the group aged 50 and over. Besides, IM incidence was higher in male patients in comparison with female patients.

In a comprehensive case-control study conducted on 156000 registered patients, a positive correlation was presented between IM and colorectal adenomas [12]. In their 2016 study conducted on 1641 patients aged 40 and over in China, Yan *et al.* analyzed gastric and colorectal biopsy results and found that *H. pylori* infection was significantly associated with a higher risk of colorectal adenoma [43]. In addition, an increase in the colorectal adenoma risk was seen in IM positive cases. Moreover, in another study, individuals with IM had a higher risk of having high-grade intraepithelial neoplasia [44]. There are very few studies evaluating the association between *H. pylori* and IM in Turkey. In our study, it was found that the IM positive group of patients had a significantly higher risk of colorectal neoplasia in comparison with the IM negative group of patients. There was not any significant difference in terms of colon neoplasia incidence in the analysis of four subgroups including both IM and HP. This result of the group analysis conducted according to the presence of IM supports other publications stating that IM brings a higher risk of colorectal adenoma. Having a limited number of patients in the groups might be the reason why the subgroup analysis gave this result.

Conclusions

Even though our study supports the idea that *H. pylori* infection increases the risk of colorectal neoplasia, this still remains a controversial issue. However, IM, which is considered a chronic sequela of *H. pylori* and a precursor lesion for gastric adenocarcinoma, was found to be a risk factor for colorectal neoplasia, similar to findings of many previous studies. In our study,

although *H. pylori* infection was not found to be a risk factor for colorectal neoplasia, it can be accepted as a potential risk factor for colorectal neoplasia development with IM. Therefore, patients with *H. pylori* infection and IM could be encouraged for colonoscopic examination in early stages of life to lower the colorectal neoplasia risk. However, it is obvious that there is a need for large-scale studies on this matter.

Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability statement

Endoscopic, histopathological, clinical and demographic data used to support the findings of this study are available from the corresponding author upon reasonable request.

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References

[1] Katanoda K, Yako-Suketomo H. Comparison of time trends in stomach cancer incidence (1973-2002) in Asia, from cancer incidence in five continents, vols IV-IX. Jpn J Clin Oncol. 2009;39(1):71–72.
[2] Ferro A, Peleteiro B, Malvezzi M, et al . Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2015, and incidence by subtype. Eur J Cancer. 2014;50(7):1330–1344.
[3] Park DY, Srivastava A, Kim GH, et al. CDX2 expression in the intestinal-type gastric epithelial neoplasia: frequency and significance. Mod Pathol. 2010;23(1):54–61.
[4] Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med. 2001;345(11):784–789.
[5] Akiyama J, Uemura N. Intestinal metaplasia subtype and gastric cancer risk. J Gastroenterol Hepatol. 2009;24(1):4–6.
[6] Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–767.
[7] Etik DÖ, Turhan N. Perspective of gastroenterologist and pathologist in gastric intestinal metaplasia. Güncel Gastroenteroloji. 2016; 20:375–382.
[8] Meucci G, Tatarella M, Vecchi M, et al. High prevalence of *Helicobacter pylori* infection in patients with colonic adenomas and carcinomas. J Clin Gastroenterol. 1997;25:605–607.
[9] Fujimori S, Kishida T, Kobayashi T, et al. *Helicobacter pylori* infection increases the risk of colorectal adenoma and adenocarcinoma, especially in women. J Gastroenterol. 2005;40(9):887–893.
[10] Brim H, Zahaf M, Laiyemo AO, et al. Gastric *Helicobacter pylori* infection associates with an increased risk of colorectal polyps in African Americans. BMC Cancer. 2014; 14:296.
[11] Inoue I, Mukoubayashi C, Yoshimura N, et al. Elevated risk of colorectal adenoma with *Helicobacter pylori*-related chronic gastritis: a population-based case-control study. Int J Cancer. 2011;129(11):2704–2711.
[12] Sonnenberg A, Genta RM. Helicobacter pylori is a risk factor for colonic neoplasms. Am J Gastroenterol. 2013;108(2):208–215.
[13] Hong SN, Lee SM, Kim JH, et al. *Helicobacter pylori* infection increases the risk of colorectal adenomas: cross-sectional study and Meta-analysis. Dig Dis Sci. 2012;57(8):2184–2194.
[14] Wang F, Sun MY, Shi SL, et al. *Helicobacter pylori* infection and normal colorectal mucosa-adenomatous polyp-adenocarcinoma sequence: a Meta-analysis of 27 case-control studies. Colorectal Dis. 2014;16(4):246–252.
[15] Hu KC, Wu MS, Chu CH, et al. Decreased colorectal adenoma risk after *Helicobacter pylori* eradication: a retrospective cohort study. Clin Infect Dis. 2019;68(12):2105–2113.
[16] Patel S, Lipka S, Shen H, et al. The association of *H. pylori* and colorectal adenoma: does it exist in the US hispanic population?J Gastrointest Oncol. 2014;5(6):463–468.
[17] Limburg PJ, Stolzenberg-Solomon RZ, Colbert LH, et al. *Helicobacter pylori* seropositivity and colorectal cancer risk: a prospective study of male smokers. Cancer Epidemiol Biomarkers Prev. 2002;11(10 Pt 1):1095–1099.
[18] Siddheshwar RK, Muhammad KB, Gray JC, et al. Seroprevalence of *Helicobacter pylori* in patients with colorectal polyps and colorectal carcinoma. Am J Gastroenterol. 2001;96(1):84–88.
[19] Boyuk B, Ozgur B, Atalay H, et al. *Helicobacter pylori* infection coexisting with intestinal metaplasia is not associated with colorectal neoplasms. Prz Gastroenterol. 2019;14(2):133–139.
[20] Qing Y, Wang M, Lin YM, et al. Correlation between *Helicobacter pylori*-associated gastric diseases and colorectal neoplasia. World J Gastroenterol. 2016;22(18):4576–4584.
[21] Wang M, Kong WJ, Zhang JZ, et al. Association of *Helicobacter pylori* infection with colorectal polyps and malignancy in China. World J Gastrointest Oncol. 2020;12(5):582–591.
[22] Gustin DM, Brenner DE. Chemoprevention of Colon cancer: current status and future prospects. Cancer Metastasis Rev. 2002;21(3-4):323–348.
[23] Meira LB, Bugni JM, Green SL, et al. DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. J Clin Invest. 2008;118(7):2516–2525.

[24] Kim N, Park RY, Cho SI, et al. Helicobacter pylori infection and development of gastric cancer in korea: long-term follow-up. J Clin Gastroenterol. 2008;42(5):448–454.
[25] Kahi CJ, Imperiale TF, Juliar BE, et al. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol. 2009;7(7):770–775.
[26] Burnett-Hartman AN, Newcomb PA, Potter JD. Infectious agents and colorectal cancer: a review of *Helicobacter pylori*, *Streptococcus bovis*, JC virus, and human papillomavirus. Cancer Epidemiol Biomarkers Prev. 2008;17(11):2970–2979.
[27] Dejea C, Wick E, Sears CL. Bacterial oncogenesis in the Colon. Future Microbiol. 2013;8(4):445–460.
[28] Kneller RW, You WC, Chang YS, et al. Cigarette smoking and other risk factors for progression of precancerous stomach lesions. J Natl Cancer Inst. 1992;84(16):1261–1266.
[29] Correa P, Piazuelo MB, Wilson KT. Pathology of gastric intestinal metaplasia: clinical implications. Am J Gastroenterol. 2010;105(3):493–498.
[30] Choi DS, Seo SI, Shin WG, et al . Risk for colorectal neoplasia in patients with *Helicobacter pylori* ınfection: a systematic review and Meta-analysis. Clin Transl Gastroenterol. 2020;11(2):e00127.
[31] Selgrad M, Bornschein J, Kandulski A, et al. *Helicobacter pylori* but not gastrin is associated with the development of colonic neoplasms. Int J Cancer. 2014;135(5):1127–1131.
[32] Zhang Y, Hoffmeister M, Weck MN, et al. Helicobacter pylori infection and colorectal cancer risk: evidence from a large population-based case-control study in Germany. Am J Epidemiol. 2012;175(5):441–450.
[33] Shmuely H, Melzer E, Braverman M, et al. Helicobacter pylori infection is associated with advanced colorectal neoplasia. Scand J Gastroenterol. 2014;49(4):516–542.
[34] Hang DV, Minh DT, Hoc TH, et al . *H. pylori* ınfection and colorectal cancers by anatomical Locations. Asian Pac J Cancer Prev. 2020;21(8):2431–2437.
[35] Strofilas A, Lagoudianakis EE, Seretis C, et al. Association of *Helicobacter pylori* infection and Colon cancer. J Clin Med Res. 2012;4(3):172–176.
[36] Guo Y, Li HY. Association between *Helicobacter pylori* infection and colorectal neoplasm risk: a Meta-analysis based on east asian population. J Can Res Ther. 2014;10(8):263–266.
[37] Venerito M, Vasapolli R, Rokkas T, et al. *Helicobacter pylori* and gastrointestinal malignancies. Helicobacter. 2015;20 Suppl 1:36–39.
[38] Chen QF, Zhou XD, Fang DH, et al. *Helicobacter pylori* infection with atrophic gastritis: an independent risk factor for colorectal adenomas. World J Gastroenterol . 2020;26(37):5682–5692.
[39] Zumkeller N, Brenner H, Zwahlen M, et al. *Helicobacter pylori* infection and colorectal cancer risk: a meta-analysis. Helicobacter. 2006;11(2):75–80.
[40] Joo YE, Park HK, Myung DS, et al . Prevalence and risk factors of atrophic gastritis and ıntestinal metaplasia: a nationwide multicenter prospective study in Korea. Gut Liver. 2013;7(3):303–310.
[41] Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc. 2006;63(4):570–580.
[42] Correa P. Human gastric carcinogenesis: amultistep andmultifactorial process—first American cancer society award lecture on cancer epidemiology and prevention. Cancer Res. 1992;52:6735–6740.
[43] Yan Y, Chen YN, Zhao Q, et al. *Helicobacter pylori* infection with intestinal metaplasia: an independent risk factor for colorectal adenomas. World J Gastroenterol. 2017;23(8):1443–1449.
[44] Cummings LC, Cooper GS. Colorectal cancer screening: update for 2011. Semin Oncol. 2011;38(4):483–489.