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The relationship between colorectal cancer and gastric histopathology: case-control study

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ABSTRACT

Aim: The aim of this study was to investigate the gastric histopathological findings (*Helicobacter pylori* (*H. pylori*), intestinal metaplasia (IM), atrophic gastritis (AG), and dysplasia) in the patients with and without colorectal cancer (CRC).

Material and Method: Two hundred ninety five patients (160 CRC patients and 135 control individuals) were included in the study. Gastric histopathological findings of the patients who underwent upper gastrointestinal (GI) endoscopy were analyzed retrospectively.

Results: *H. pylori* positivity and IM rates in the CRC patient group were significantly higher than the control group (58.8%&27.8% and 33.1%&19.5%, p<0.001 and p<0.012, respectively). In addition, AG, lymphoplasmocytic infiltration, and dysplasia rates were also higher in the CRC patients compared to the control group. But, they were not statistically significant (p=0.462, p=0.103, and p=0.195, respectively).

Conclusion: In our study, the frequency of *H. pylori* and IM in patients with CRC was higher than in the control group. Since the prevalence of *H. pylori* infection is high in Turkey and *H. pylori*-related gastric diseases may be potential risk factors for colorectal neoplasia, it is recommended that individuals in the high-risk group to be screened for colonoscopy. Also, upper GI endoscopic examination should be performed to screen for gastric premaling lesions in patients with CRC.

Keywords: *Helicobacter pylori*, colorectal cancer, intestinal metaplasia

INTRODUCTION

Colorectal cancer (CRC) has a prevalence of 4-5% worldwide and is the leading cause of cancer related deaths. Many factors cause the development of carcinogenesis in the colon(1). Diet, obesity, lack of physical activity, tobacco and alcohol use, age, familial history of colorectal polyp or CRC, Lynch syndrome, inflammatory bowel disease, type 2 diabetes, cholecystectomy, exposure of abdominal radiation, older age are risk factors (2-4). The loss of genomic and epigenomic stability leads to the accumulation of mutations that occurs in oncogenes, tumor suppressor genes, and genes related to DNA repair mechanisms, and may lead to the development of CRC. As a result of mutations, CRC is classified as sporadic, hereditary, and familial. Studies have shown that the gut microbiota induces the formation of reactive metabolites and carcinogens. This may induce the formation of colorectal malignancy by causing changes in carbohydrate expression and chronic mucosal inflammation (5).

Helicobacter pylori (*H. pylori*) is a spiral-shaped, microaerophilic, gram-negative bacterium that infects more than half of the world's population (6,7). Its prevalence in the adult population in Turkey is 82.5% and varies according to age, gender and educational status (8). *H. pylori* is the most common chronic bacterial infection in humans and causes chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and invasive gastric cancer (6-8). Many studies have proven that AG and IM are precancerous lesions of gastric cancer. More than 90% of gastric cancer patients have been or are still infected with *H. pylori* (7,9).

H. pylori may cause hypergastrinemia, hypochlorhydria and damage to the colorectal epithelium via IL-8. It is thought that hypergastrinemia is associated with cell proliferation in the rectum and may stimulate colon adenoma and the development of the adenoma-cancer sequence (10,11). In our study, we aimed to investigate

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the relationship between histopathologies (*H. pylori* gastritis, IM, AG, dysplasia), which are risk factors for gastric cancer, and colorectal cancer.

MATERIAL AND METHOD

The study was approved by the Non-interventional Clinical Resarches Ethics Committee of the Eskişehir Osmangazi University (Date: 23.02.2022, Decision No: 2021-320). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study included 295 patients who have been followed between years 2018 and 2021. The data of 160 patients who were diagnosed with colorectal cancer radiologically, histologically and endoscopically and who underwent upper gastrointestinal endoscopy (GIS) were analyzed retrospectively. The control group consisted of 135 individuals without malignancy in endoscopy and colonoscopy. Colorectal cancer localization (cecum, ascending colon, hepatic flexure, transverse colon, descending colon, splenic flexure, sigmoid colon and rectum), histology and staging were performed. Tumor staging of CRCs were performed using the TNM classification established and updated by the American Cancer Committee (AJCC) and the International Association for Cancer Control (UICC). Demographic and laboratory data of the patients and control groups included age, gender, co-morbid diseases, glucose, ferritin, vitamin B12, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), alpha-fetoprotein(AFP), carcinoma antigen 15-3 (CA 15-3). Upper GI endoscopy histopathological data were analyzed for *H. pylori*, intestinal metaplasia, dysplasia, lymphoplasmocytic infiltration, and atrophy. Multiple biopsies were taken from the antrum, incisura angularis, and/or corpus. IM with Alcian blue+PAS mixed and *H. pylori* positivity with Giemsa were detected. All individuals included in the study were divided into Hp(+) Hp(-) group, AG(+) AG(-) group, IM(+) IM(-) group, dysplasia(+) dysplasia(-) group, lymphoplasmacytic infiltration(+) lymphoplasmacytic infiltration(-) group.

Statistical Analysis

The data were evaluated using SPSS 24 program. First of all, the suitability of the quantitative data to the normal distribution was tested with the Kolmogorov - Smirnov test. For the analysis, Mann Whitney U test was used for non-normally distributed data and t-test was used for normally distributed data. In statistical analysis, $p<0.05$ values were considered significant. Chi-square analysis was performed for categorical data. For cases where the expected frequency is less than 5, P values were calculated with the Fisher Exact test. The results were interpreted according to these test results.

RESULTS

Demographic and clinicopathological features of CRC patients and control subjects are shown in (**Table 1**). The mean age of 160 colorectal cancer patients and control groups was 64.4±10.31 and 60.48±10.66, respectively. In CRC patients, tumor localization was most common in rectosigmoid colon 99(55.6%)(sigmoid colon 27.5%; rectum 28.1%) ($p<0.001$). There was no statistical significance between glucose, AFP, CEA and CA 15-3 in laboratory results of CRC patients and control group, but a significant difference was determined for CA 19-9.

Table 1. Demographic and clinicopathological features

	Colorectal cancer group	Control group	P value
Age (year, mean ±SD)	64.4± 10.31	60.48± 10.66	<0.002
Sex			<0.001
Females	61 (38.1%)	82 (61.7%)	
Males	99 (61.9%)	51 (38.3%)	
Tumor localization (%)			<0.001
1. Cecum	25 (15.6%)		
2.Ascending colon	25 (15.6%)		
3.Transverse colon	9 (5.6%)		
4.Descending colon	12 (7.5%)		
5.Colon	44 (27.5%)		
6. Rectum	45 (28.1%)		
łTNM Stage			<0.001
Stage 1	40 (25.0%)		
Stage 2	56 (35..0%)		
Stage 3	26 (16.3%)		
Stage 4	36 (22.5%)		
Differentiation(%)			
Well	41 (13.9%)		
Moderate	95 (32.3%)		
Poor	22 (7.5%)		
*Laboratory Data			
Glucose (mg/dl)	119.63±39.71	115.77 ±36.11	0.313
ǂAFP (ng/ml))	337.67±1056.37	237.47±278.02	0.525
ǂCEA (ng/mL)	430±1320.10	356.65 ±601.80	0.170
ǂCA 19-9 (U/mL)	466.17±1372.21	1398±2718.06	<0.004
ǂCA 15-3 (U/ml)	16.06±10.43	34.27±68.81	0.271
Vitamin B12 (pg/ml)	280.72±173.05	440.89±374.65	<0.001
Ferritin(ng/ml)	219.77±617.80	121.53±561.03	<0.001
The site of the biopsy in the stomach			
1.Antrum	150 (93.8)	98 (73.7)	<0.001
2.Antrum-corpus	10 (6.3)	35 (26.3)	
Co-morbid diseases			0.966
Hypertension	13 (19.4%)	5 (20%)	
Diabetes mellitus	18 (26.9%)	5 (20%)	
Ischemic heart disease	3 (4.5%)	1 (4.0%)	
Other	3 (4.5%)	1 (4.0%)	
No disease	30 (44.8%)	13 (52%)	

* (Mean ±SD)
ǂ Alpha-fetoprotein(AFP); Carcinoembryonic antigen (CEA); Carbohydrate antigen 19-9(CA 19-9); Carcinoma antigen 15-3 (CA 15-3)
Ł Stage 1(T1-2,N0,M0), Stage 2(T3-4,N0,M0), Stage 3(T1-4,N1-2,M0), Stage 4(T1-4,N1-2,M1)

H. pylori positivity in the CRC patient group was higher compared to the control group (94 (58.8%), 37 (27.8%), p<0.001). CRC in intestinal metaplasia was higher and statistically significant in patients compared to the control group (53(33.1%), 26(19.5%), p<0.012). Although atrophy, lymphoplasmocytic infiltration and dysplasia were higher in gastric biopsy histopathologies of CRC patients compared to the control group, they were not statistically significant (p=0.462, p=0.103, p=0.195) (**Table 2**).

Table 2. Gastric histopathology in patients with colon cancer and control group

	Colorectal Cancer Group	Control Group	P value
H. pylori			<0.001
No	66 (41.3%)	96 (72.2%)	
Yes	94 (58.8%)	37 (27.8%)	
Intestinal metaplasia			<0.012
No	107 (66.9%)	107 (80.5%)	
Yes	53 (33.1%)	26 (19.5%)	
Atrophy			0.462
No	155 (96.9%)	131 (98.5%)	
Yes	5 (3.1%)	2(1.5%)	
Lymphoplasmocytic infiltration			0.103
No	123 (76.9%)	113(85.0%)	
Yes	37 (23.1%)	20 (15.0%)	
Dysplasia			0.195
No	150 (93.8%)	131 (97.0%)	
Yes	10 (6.3%)	4 (2.96%)	

There was no significant age difference between *H. pylori* positive and *H. pylori* negative groups in CRC patients. *H. pylori* positivity was significantly higher in male CRC patients(64(68.8%), p<0.046). *H. pylori* positivity in CRC patients was higher in Stage 2,3,4 group according to TNM staging, but it was not statistically significant (p=0.080). According to tumor localization, *H. pylori* was positive at a higher rate in tumors located in the left colon and rectum, but it was not statistically significant (p=0.489).

H. pylori positivity was higher in the moderately differentiated group than in the mildly and poorly differentiated group (55(59.1%)), 25(26.9%), 13(14%), but it was not statistically significant (p=0.945)(**Table 3**). Those with intestinal metaplasia in CRC patients were higher in TNM Stage 2 and moderately differentiated groups, but it was not statistically significant (p=0.413, p=0.399). Cancer localization, age and gender groups were not significant in CRC patients with intestinal metaplasia (p=0.335, p=0.432, p=0.825) (**Table 4**).

Table 3. Association with *H. pylori* tumor characteristics in patients with colorectal cancer

	Colorectal cancer *H. pylori* negative	Colorectal cancer *H. pylori* positive	P value
*TNM Stage			0.080
Stage 1	23 (35.4%)	17 (18.3%)	
Stage 2	18 (27.7%)	38 (40.9%)	
Stage 3	9 (13.8%)	17 (18.3%)	
Stage 4	15(23.1%)	21 (22.6%)	
Differentiation			0.945
Well	16 (24.6%)	25 (26.9%)	
Moderate	40 (61.5%)	55 (59.1%)	
Poor	9 (13.8%)	13 (14%)	
**Tumor localization			0.489
1. Right colon	24 (36.9%)	26 (28.0%)	
2. Left colon	23 (35.4%)	37 (39.8%)	
3. Rectum	18 (27.7%)	30 (32.3%)	
Sex			0.046
Females	31 (47.7%)	29 (31.2%)	
Males	34 (52.3%)	64 (68.8%)	
Age(year, mean ±SD)	64.35±11.40	64.25±9.49	0.738

*Stage 1(T1-2,N0,M0), Stage 2(T3-4,N0,M0), Stage 3(T1-4,N1-2,M0), Stage 4(T1-4,N1-2,M1), ** Right colon (cecum, ascending colon,transverse colon proximal), Left colon (transverse colon distal,descending colon, sigmoid colon)

Table 4. The relationship of intestinal metaplasia with tumor characteristics in patients with colorectal cancer.

	Colorectal cancer intestinal metaplasia No	Colorectal cancer intestinal metaplasia Yes	p value
TNM Stage			0.413
Stage 1	31 (29.2)	9 (17.3)	
Stage 2	35 (33.0)	21 (40.4)	
Stage 3	16 (15.1)	10 (19.2)	
Stage 4	24 (22.6)	12 (23.1)	
Differentiation			0.399
Well	28 (26.4%)	13 (25.0%)	
Moderate	66 (62.3%)	29 (55.8%)	
Poor	12 (11.3%)	10 (19.2%)	
Tumor localization			0.335
1. Right colon	33 (31.1%)	17 (32.7%)	
2. Left colon	37 (34.9%)	23 (44.2%)	
3. Rectum	36 (34.0%)	12 (23.1%)	
Sex			0.432
Females	38 (35.8%)	22 (42.3%)	
Males	68 (64.2%)	30 (57.7%)	
Age (year, mean ±SD)	64.16±10.55	64.55±9.82	0.825

Hp(-) İM(+) group was significantly higher in the control group than in the CRC patient group (79(59.4%), p< 0.001). Hp(+) IM(-) group and Hp(+) IM(+) group were higher and statistically significant in CRC patients compared to the control group (p< 0.001)(**Table 5**).

Table 5. Comparison of *H. pylori* and intestinal metaplasia in patient and control groups

	Colorectal cancer group	Control group	P value
Hp-, İM-	46 (28.7%)	79 (59.4%)	<0.001
Hp+,İM-	61 (38.1%)	28 (21.1%)	
Hp-,İM+	20 (12.5%)	18 (13.5%)	
Hp+,İM+	33 (20.6%)	8 (6.0%)	

DISCUSSION

Many factors affect the process of colonic carcinogenesis. In our study, we investigated the relationship between the gastritis-atrophy-metaplasia-dysplasia-cancer process triggered by *H. pylori* in the gastric mucosa and colon cancer patients. *H. pylori* infection is the type 1 carcinogen and is considered as an important cause of gastric cancer. In our study, the prevalence of *H. pylori* was higher in patients with colorectal cancer compared to the control group (58.8%, 27.8%, p<0.001). Wu Q, et al. (14), Hong SN, et al. (15), Zuo Y. et al. (16) in their meta-analysis of different subgroup populations, including Asian, American, and European populations, and Choi DS, et al. (17) in their meta-analysis of 48 studies including 171,045 patients showed positive correlations in HP infection and CRC risk. Mechanisms that may cause *H. pylori* colorectal cancer development are hypergastrinemia, CagA-positive *H. pylori*, systemic inflammatory response triggered by chronic inflammation induced by *H. pylori*, the effects of chronic *H. pylori* infection and proton pump inhibitor use on gut microbiota. In CRC carcinogenesis, hypergastrinemia due to *H. pylori* causes cell proliferation (18-20). There are studies showing that gastrin and cholecystokinin type B/gastrin receptor (CCKBR) are expressed in colorectal adenocarcinoma and colon polyps (12,20). *H. pylori* was not detected in CRC cancerous tissue in many studies. However, Grahn N, et al. (21) detected *H. pylori* DNA in 27% of cancerous tissue histopathology of patients with CRC (21,22,27). As a result of colonization of Helicobacter organisms in the intestine, *H. pylori* may have a direct carcinogenic effect. Although Fujimori S, et al. (23) showed that *H. pylori* infection induces a significantly higher risk in female patients with CRC in the Japanese population in their study, *H. pylori* positivity was significantly higher in male CRC patients in our study (64 (68.8%), p< 0.046). In the meta-analysis of De Martel C, et al. (24) they investigated the relationship between *H. pylori* infection and gender, and in the study of Wang C, et al. (25) in a large population, *H. pylori* positivity was high in male individuals. In this study, *H. pylori* was at a higher frequency in male patients and was consistent with the literature. In our study, according to tumor localization, *H. pylori* was positive at a higher rate in tumors located in the left colon and rectum, but it was not statistically significant (p=0.489). Although Wang C, et al. (25) found the risk of CRC associated with *H. pylori* infection to be high in the left colon and rectum, Fujimori S, et al. (23), Sonnenberg A, et al. (26) and a few studies found no differences in location (26-28). There was no significant relationship between *H. pylori* positivity, CRC differentiation (poor, moderate, well) and TNM stages.

AG is characterized by chronic inflammation of the gastric mucosa with loss of gastric glandular cells and their replacement by intestinal type epithelium, pyloric type glands and fibrous tissue. The relationship of gastric precancerous lesions (chronic atrophic gastritis, gastric intestinal metaplasia, dysplasia) with the risk of colon carcinogenesis is unknown(29-31). Hypochlorhydria that develops after AG controls not only the colonization and growth of oropharyngeal bacteria, but also changes in the distal intestinal microflora, leading to a significant increase in intestinal bacteria, including Bacteroides fragilis and E. feacalis group (32,33). Strains of the enterotoxigenic Bacteroides fragilis (ETBF) bft gene have been shown to contribute to colon carcinogenesis. In the studies of Wang C, et al. (25) and Lee JY, et al. (34) it increased the risk of CRC when *H. pylori* infection and AG were positive together. In the Montani A. et al. (31) study, although chronic *H. pylori* infection and atrophic gastritis might increase the risk of rectal cancer, they did not increase the risk of CRC. In our study (5 (3.1%), p=0.462) and in the studies of Laiyemo AO, et al. (29) and Lahner E, et al. (36), atrophic gastritis was not found to be associated with the risk of colorectal cancer (35).

IM is the advanced stage of atrophy. It is defined as the replacement of surface in the oxyntic or antral mucosa, foveolar and glandular epithelium with intestinal epithelium. IM has been classified into two types: the small bowel or complete type and the colonic or incomplete type. The development of IM is a long process and the most important risk factor for its development is *H. pylori* infection (6,38). IM causes decreased gastric acid secretion and this causes hypergastrinemia. Hypochlorhydria caused by *H. pylori* positive IM results in bacterial overgrowth and impaired protein absorption. Impairment of protein absorption causes the release of some metabolites (eg H2S, phenols, NH3) arising out of bacterial fermentation of proteins. These metabolites are accepted as risk factors in the development of colon cancer(38,39). In our study, while IM was 53 (33.1%) in the CRC group, it was 26 (19.5%) in the control group and it was statistically significant (p<0.012) (**Table 2**). IM associated with *H. pylori* was higher in the patient group than in the control group (33 (20.6%); 8(6.0%)) (**Table 5**). In the *H. pylori* negative IM group, there was no difference between the patient

and control groups (20 (12.5%); 18(13.5%) (**Table 5**). In several studies including this study, the risk of colorectal carcinogenesis was increased in individuals with IM in gastric histopathology. However, only a few studies and small sample sizes are insufficient to determine the risk of colorectal neoplasia (13,26,40).

Our study has several limitations. First, the serum gastrin level, which is thought to be important in the progression of colorectal carcinogenesis, was not included in our analysis. Second, study data were obtained from two centers but one region. The strengths of our study are that the individuals included in the study (CRC group and control group) were patients who had both endoscopy and colonoscopy scans, *H. pylori* was detected through multiple gastric biopsies, and it was case-controlled.

CONCLUSION

Our study showed that the frequency of *H. pylori* and IM is higher in patients with CRC than in the control group. The relationship between the risk of colon neoplasia and premaling gastric lesions due to *H. pylori* is still unknown, and the results of the few studies on this subject are inconsistent. Because of the high prevalence of *H. pylori* infection in Turkey and because *H. pylori*-related gastric diseases may be potential risk factors for colorectal neoplasia, it is recommended that people in high-risk groups to be screened for colonoscopy. Also, upper GI endoscopic examination should be performed to screen for gastric premaling lesions in patients with CRC. However, multicenter studies in the Turkish population are needed to clarify further this relationship and to understand the underlying pathophysiological mechanism.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Non-interventional Clinical Resarches Ethics Committee of the Eskişehir Osmangazi University (Date: 23.02.2022, Decision No: 2021-320).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Mármol I, Sánchez-de-Diego C, Pradilla Dieste A, Cerrada E, Rodriguez Yoldi MJ. colorectal carcinoma: a general overview and future perspectives in colorectal cancer. Int J Mol Sci 2017; 18: 197.
2. Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer. Nat Rev Dis Primers 2015; 1: 150-65.
3. Simon K. Colorectal cancer development and advances in screening. Clin Interv Aging 2016; 11: 967-76.
4. Brenner AT, Dougherty M, Reuland DS. Colorectal cancer screening in average risk patients. Med Clin North Am 2017; 101: 755-67.
5. Lucas C, Barnich N, Nguyen HTT. Microbiota, ınflammation and colorectal cancer. Int J Mol Sci 2017; 18: 1310.
6. Watari J, Chen N, Amenta PS, et al. *Helicobacter pylori* associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. World J Gastroenterol 2014; 20: 5461-73.
7. Graham DY. History of *Helicobacter pylori*, duodenal ulcer, gastric ulcer and gastric cancer. World J Gastroenterol 2014; 20: 5191-204.
8. Ozaydin N, Turkyilmaz AS, Cali S. Prevalence and risk factors of *Helicobacter pylori* in Turkey: a nationally-representative, cross-sectional, screening with the 13C-Urea breath test. BMC Public Health 2013; 13: 12-5.
9. Alipour M. Molecular mechanism of *Helicobacter pylori*-induced gastric cancer. J Gastrointest Cancer 2021; 52: 23-30.
10. Huang RJ, Choi AY, Truong CT, Yeh MM, Hwang JH. Diagnosis and management of gastric ıntestinal metaplasia: current status and future directions. Review Gut Liver 2019; 13: 596-03.
11. Park YH, Kim N. Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer. J Cancer Prev 2015; 20: 25–40.
12. Smith AM, Watson SA. Gastrin and gastrin receptor activation: an early event in the adenoma-carcinoma sequence. Gut 2000; 47: 820-4.
13. 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: 1443–9.
14. Wu Q, Yang ZP, Xu P, Gao LC, Fan DM. Association between *Helicobacter pylori* infection and the risk of colorectal neoplasia: a systematic review and meta-analysis. Colorectal Dis 2013; 15: 352-64.
15. 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: 2184-94.
16. Zuo Y, Jing Z, Bie M, Xu C, Hao X, Wang B. Association between *Helicobacter pylori* infection and the risk of colorectal cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2020; 99: 218-32.
17. Choi DS, Seo SI, Shin WG, Park CH. Risk for colorectal neoplasia in patients with *Helicobacter pylori* infection: a systematic review and meta-analysis. Clin Transl Gastroenterol 2020; 11: e00127
18. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016; 65: 740-8.
19. Georgopoulos SD, Polymeros D, Triantafyllou K, et al. Hypergastrinemia is associated with increased risk of distal colon adenomas. Digestion 2006; 74: 42–6.
20. Hagymási K, Tulassay Z. *Helicobacter pylori* infection: new pathogenetic and clinical aspects. Review World J Gastroenterol 2014; 20: 6386-99.
21. Grahn N, Hmani-Aifa M, Fransén K, Söderkvist P, Monstein HJ. Molecular identification of Helicobacter DNA present in human colorectal adenocarcinomas by 16S rDNA PCR amplification and pyrosequencing analysis. J Med Microbiol 2005; 54: 1031–5.

22. Papastergiou V, Karatapanis S, Georgopoulos SD. *Helicobacter pylori* and colorectal neoplasia: Is there a causal link? World J Gastroenterol 2016; 22: 649-58.
23. Fujimori S, Kishida T, Kobayashi T, et al. *Helicobacter pylori* infection increases the risk of colorectal adenoma and adenocarcinoma, especially in women. Comparative Study J Gastroenterol 2005; 40: 887-93.
24. De Martel C, Parsonnet J. *Helicobacter pylori* infection and gender: a meta-analysis of population-based prevalence surveys. Dig. Dis. Sci. 2006; 51: 2292-301.
25. Wang C,Yan J, He B, Zhang S, Xu S. Hp-positive chinese patients should undergo colonoscopy earlier and more frequently: the result of a cross-sectional study based on 13,037 cases of gastrointestinal endoscopy. Front Oncol 2021; 11: 698898.
26. Sonnenberg A, Genta RM. *Helicobacter pylori* is a risk factor for colonic neoplasms. Am J Gastroenterol 2013; 108: 208–15.
27. 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: 1095-9.
28. 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: 2704-11
29. Laiyemo AO, Kamangar F, Marcus PM, et al. Atrophic gastritis and the risk of incident colorectal cancer. Cancer Causes Control 2010; 21: 163–70.
30. Inoue I, Kato J, Yoshimura N, et al. Elevated risk of recurrent colorectal neoplasia with *Helicobacter pylori*-associated chronic atrophic gastritis: a follow-up study of patients with endoscopically resected colorectal neoplasia. Mol Clin Oncol 2013; 1: 75–2.
31. Machida-Montani A, Sasazuki S, Inoue M, et al. Atrophic gastritis, *Helicobacter pylori*, and colorectal cancer risk: a case-control study. Helicobacter 2007; 12: 328–32.
32. Epplein M, Pawlita M, Michel A, Peek RM, Cai Q, Blot WJ. *Helicobacter pylori* protein-specific antibodies and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2013; 22: 1964-74.
33. Kanno T, Matsuki T, Oka M, et al. Gastric acid reduction leads to an alteration in lower intestinal microflora. Biochem Biophys Res Commun 2009; 381: 666–70.
34. Lee JY, Park HW, Choi JY, et al. *Helicobacter pylori* infection with atrophic gastritis ıs an ındependent risk factor for advanced colonic neoplasm. Gut Liver 2016; 10: 902–09.
35. Qing Y, Wang M, Lin Y-M, et al. Correlation between *Helicobacter pylori*-associated gastric diseases and colorectal neoplasia. World J Gastroenterol 2016; 22: 4576–84.
36. Lahner E, Vanni AS, Vannella L, et al. No higher risk for colorectal cancer in atrophic gastritis-related hypergastrinemia. Dig Liver Dis 2012; 44: 793-7.
37. 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: 5682–92.
38. Liu KS, Wong IO, Leung WK. *Helicobacter pylori* associated gastric intestinal metaplasia: treatment and surveillance. World J Gastroenterol 2016; 22: 1311-20.
39. Evenepoel P, Claus D, Geypens B, et al. Evidence for impaired assimilation and increased colonic fermentation of protein, related to gastric acid suppression therapy. Aliment Pharmacol Ther 1998; 12: 1011-9.
40. Ünler GK, Teke Özgür G, Göktürk HS, Korkmaz H, Erinanç ÖH. Is there any association between colonic polyps and gastric intestinal metaplasia? Turk J Gastroenterol 2016; 27: 221