Association of Helicobacter pylori Infection With Colon Cancer and Adenomatous Polyps

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KEYWORDS	ABSTRACT
	Background and objective: *Helicobacter pylori* infection is one of the most common chronic bacterial infections in the world, especially in the developing countries. This bacterium is the cause of many diseases such as lymphoma, gastritis, peptic ulcers, and stomach cancer. According to recent reports, *H. pylori* infection can potentially increase the risk of colon cancer. The current study aimed at investigating the association of *H. pylori* infection and the risk of colorectal cancer and adenomatous polyps.
Article Info	**Methods:** The current study was conducted on 50 patients with colon cancer and adenomatous polyps as the case group and 100 subjects with no specific pathologies (i e, polyps, neoplasms, or inflammatory diseases) as the control group. Blood samples were collected from the patients in order to assess the presence of anti-Helicobacter pylori infection antibodies, and the serum titer levels of anti-Helicobacter pylori IgG and IgA antibodies were measured using indirect enzyme-linked immunosorbent assay (ELISA) and a kit procured by Pishtaz Teb Company (Iran).
	Results: A total of 33 patients in the current study had adenomatous polyps and 17 had colon cancer. *H. pylori* infection (IgA >20 U/mL and IgG >10 U/mL) was significantly more prevalent in the patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*= 0.003, *P*= 0.039, respectively).
	Conclusion: The obtained results suggested that *H. pylori* infection can be considered as a risk factor for colon cancer and adenomatous polyps.
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Introduction

Colorectal cancer (CC) is the 3rd leading cancer in the world and its prevalence is rising in the developing countries (1). Colorectal cancer is a heterogeneous tumor involving a population of different cells with distinct properties (2). This cancer develops following the growth of cancer cells in the colon, rectum, and the appendix (3). Both environmental and genetic factors affect the incidence of this cancer (4). According to the Iranian Cancer Association, around one million people in Iran develop colorectal cancer every year. The incidence of this type of cancer increased in Iran over the past 25 years (5) and is currently the 3rd leading type of cancer in females and the 5th in males in the country (6). The diagnosis of colorectal cancer in early stages prevents its progress and prolongs the survival of the patients.

Many studies show that chronic infection with gastric Helicobacter pylori, which is a risk factor for stomach cancer (7), may also be associated with a moderately increased risk of colorectal cancer (8-11). Most colorectal cancers originate from adenomatous polyps. Adenomas are premalignant lesions that partly turn into cancer (12). Many studies show that *H. pylori* infection is associated with an increased serum gastrin. Endocrinological studies show that hypergastrinemia is associated with rectal cell proliferation and stimulates the growth of colorectal cancer

cells and the development of colon adenoma and the adenoma-cancer sequence. These results suggest that *H. pylori* infection can potentially increase the risk of colorectal cancer (13).

Materials and methods

The current case-control study was conducted on 50 patients diagnosed with colon cancer and all types of adenomatous polyps visiting Ayatollah Rouhani Hospital in Babol from 21st March 2015 to 20th march 2016 as the case group and 100 patients undergoing colonoscopy without pathologic findings (including polyps, neoplasms, inflammatory diseases, etc.) as the control group. Any patient in the case and control groups with inflammatory bowel disease (IBD), non-adenomatous polyps, and history of cancer or eradication therapy of *H. pylori* infection prior to colonoscopy was excluded from the study. Both groups were selected with consecutive sampling method.

After obtaining written consent from the patients, the two groups were matched in terms of age, gender, family history of colorectal cancer, clinical symptoms (rectorrhagia, stomach ache, change in bowel habits, vomiting, weight loss, diarrhea, and iron deficiency anemia). There are several *H. pylori* diagnostic tests including invasive tests (endoscopy, biopsy, histopathology, rapid urease, and polymerase chain reaction (PCR) and non-invasive tests (respiratory urease, the enzyme-linked immunosorbent assay (ELISA), and stool antigen); the current study employed the ELISA method due to its high sensitivity, specificity, and simplicity (14). To investigate the presence of anti-Helicobacter pylori antibodies, 1 mL venous blood sample was collected from each subject and sent to laboratories and the serum was isolated and used to measure serum titer levels of anti-Helicobacter pylori IgG and IgA using indirect ELISA and the kit procured by Pishtaz Teb Co. (Iran) (IgA >20 U/mL manufacturer's cut off point for IgA positivity and IgG >10 U/mL manufacturer's cut off point for IgG positivity) and according to the instructions provided by the kit manufacturer (15). Data were analyzed with SPSS version 20 using Chi-square and t test at the significance level of <0.05.

Results

A total of 150 patients took part in the study, including 50 patients diagnosed with colon cancer and adenomatous polyp as the cases and 100 subjects with no reports of tumors or polyps in their colonoscopy or pathology results as the controls. The mean age of the subjects was 51 years; 88 (58.6%) were male and 62 (41.4%) female. None of the subjects had a history of IBD.

Table 1 presents the subjects' demographic details. No significant differences were observed in the prevalence of adenomatous polyps and colon cancer between the genders. No significant differences were observed between the subjects with a history of gastrointestinal cancer in themselves or their families and the ones with no such history in terms of the prevalence of adenomatous polyps and colon cancer. Nonetheless, a significant difference was observed between the subjects aged 50 and below and the ones aged over 50 in the prevalence of adenomatous polyps and colon cancer (*P*=0.048).

Table 1. Demographics, Personal and Family History of Colon Neoplasm in the Studied Groups

Characteristic		Normal N (%)	Polyp N (%)	Cancer N (%)	*P-value*
Gender	Male	55 (55)	22 (66.7)	11 (64.7)	0.431
	Female	45 (45)	11 (33.3)	6 (35.3)	
Age	50≥	51 (51)	24 (72.7)	12 (70.6)	0.048
	>50	49 (49)	9 (27.3)	5 (29.4)	
Cancer history	Negative	96 (96)	31 (93.9)	16 (94.1)	0.860
	Positive	4 (4)	2 (6.1)	1 (5.9)	
Family history	Negative	95 (95)	28 (84.8)	17 (100)	0.065
	Positive	5 (5)	5 (15.2)	-	

A total of 33 patients had adenomatous polyps and 17 had colon cancer. Of the 33 cases of polyps, 16 were located in the right and 17 in the left colon. Of the 17 cases of colon cancer, eight were found in the right and nine in the left colon. No significant differences were observed in terms of the location of adenomatous polyps and cancer (*P*=0.58).

According to Table 2, H. pylori infection with IgA >20 U/mL (manufacturer's cut off point for IgA positivity) was significantly higher in the patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*=0.003). H. pylori infection with IgG>10 U/mL (manufacturer's cut off point for IgG positivity) was also significantly higher in the patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*=0.039).

According to Table 3, H. pylori infection with IgA >20 U/mL was significantly higher in the male patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*=0.001), but no significant differences were observed between the female patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*=0.054). H. pylori infection with IgG >10 U/mL was significantly higher in the male patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*=0.012), but no significant differences were observed between the female patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*=0.247).

Results showed that H. pylori infection with IgA>20 U/mL was significantly higher in the patients with colon cancer and adenomatous polyps aged 50 or below compared with the healthy controls (*P*=0.009). In different age groups, H. pylori infection with IgG >10 U/mL did not differ significantly between the patients with colon cancer and adenomatous polyps and the healthy controls (*P*=0.262).

Table 2. IgA and IgG Serum Levels in the Study Groups

Serum Level, U/mL	Normal N (%)	Polyp N (%)	Cancer N (%)	Total N (%)	*P-value*
* IgA<15	82 (82)	21 (63.6)	7 (41.2)	110 (73.3)	
15 ≤ IgA <20	7 (7)	4 (12.1)	2 (11.8)	13 (8.7)	0.003
IgA≥20	11 (11)	8 (24.2)	8 (47.1)	27 (18)	
IgG** <5	54(54)	14 (42.4)	3 (17.6)	110 (47.3)	
5≤ IgG < 10	14 (14)	5 (15.2)	2 (11.8)	13 (14)	
IgG≥10	32 (32)	14 (42.4)	12 (70.6)	27 (38.7)	0.039

*immunoglobulin A **immunoglobulin G

Table 3. IgA and IgG Serum Levels in the Study Groups Based on Gender

	Serum level U/mL	Normal N (%)	Polyp N (%)	Cancer N (%)	Total N (%)	*P-value*
Male	IgA <15	43(78.2)	16 (72.7)	2 (18.2)	61 (69.3)	
	15≤ IgA <20	6 (10.9)	3 (13.6)	2 (18.2)	11 (12.5)	0.001
	20≥ IgA	6 (10.9)	3 (13.6)	7 (63.6)	16 (18.2)	
Female	IgA <15	39 (86.7)	5 (45.5)	5 (83.3)	49 (79)	
	15≤ IgA <20	1 (2.2)	1 (9.1)	-	2 (3.2)	0.054
	20≥ IgA	5 (11.1)	5 (45.5)	1 (16.7)	11 (17.7)	
Male	IgG <5	32 (58.2)	9 (40.9)	2 (18.2)	43 (48.9)	
	5≤ IgG <10	6 (10.9)	5 (22.7)	-	11 (12.5)	0.012
	10 ≥ IgG	17 (30.9)	8 (36.4)	9 (81.8)	34 (38.6)	
Female	IgG <5	22 (48.9)	5 (45.5)	1 (16.7)	28 (45.2)	
	5≤IgG <10	8 (17.8)	0 (0)	2 (33.3)	10 (16.1)	0.247
	10 ≥IgG	15 (33.3)	6 (54.5)	3 (50)	24 (38.7)	

Discussion

A total of 33 patients had adenomatous polyps, 16 of which were located in the right and 17 in the left colon, and 17 others had colon cancer, eight of which were in the right and nine in the left colon. *H. pylori* infection (either current or past *H. pylori* colonization identified by IgA >20 U/mL and IgG >10 U/mL as instructed by manufacturer and used by same studies) (15) was significantly higher in the patients with colon cancer and adenomatous polyps compared with the healthy controls (*P*=0.003 and *P*=0.039, respectively).

H. pylori are the microorganism repeatedly observed throughout the world. Although most infected people are asymptomatic, the infection becomes chronic when affecting humans. *H. pylori* can infect humans for the whole life (16-18). This organism is rarely eradicated spontaneously with any treatments, and post-therapy recurrence is also reported, especially in countries with a high prevalence of *H. pylori* infection (19). The mechanism by which *H. pylori* increases the risk of colorectal cancer is not yet clearly understood. Inflammation and the loss of cell cycle are among the mechanisms suggested to be involved. CagA has a pathogenic role in *H. pylori*, and the presence of CagA in *H. pylori* is associated with an increased risk of stomach cancer (20, 21). Infection with *H. pylori* causes the secretion of serum gastrin, which can act as a growth hormone for the colonic mucosa cells (22 ,23). *H. pylori* can cause hypergastrinemia alone or together with changes in the normal gastrointestinal flora, suggesting an acceptable mechanism for the carcinogenicity of this organism. In a recent study conducted by Robertson, increased serum gastrin following polypectomy was not associated with an increased risk of adenomatous polyp recurrence (24).

A number of observational studies examined the correlation between positive serum *H. pylori* and the risk of colorectal cancer (9, 25-27). Nonetheless, their results were inconclusive. Two studies reported a positive correlation (24, 25) and four others found no relationships at all between this infection and the cancer (9, 26-28). In a case-control study conducted by Penman et al., (29) on hospitalized patients to assess gastrin levels and the risk of colorectal neoplasia, serum levels of *H. pylori* were similar in the patients with colorectal cancer and the healthy controls. The two groups were also similar in terms of age and gender. In a meta-analysis conducted in 2013 by Chen et al., on the relationship between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma, it was observed that *H. pylori* infection increased the risk of colorectal adenoma and adenocarcinoma. In a study conducted by Fireman et al. (13), the prevalence of *H. pylori* antibodies was significantly higher in the group of patients with colorectal cancer than the healthy controls; however, the difference was only borderline significant (*P*=0.05). In the current study, *H. pylori* infection was significantly higher in the patients with colon cancer and adenomatous polyps compared with the healthy controls. In contrast, in a case-control study conducted by Talley (31) the serum levels of *H. pylori* were clearly higher in the patients with cancer compared with the healthy controls, although not significantly. Two other studies with relatively small sample sizes (n=41 and n=38) found no acceptable differences in serum levels of *H. pylori* between the group of patients with colorectal cancer and the healthy controls (32, 33).

In two studies that used PCR to detect *H. pylori*, the prevalence of *H. pylori* was significantly higher in colorectal adenocarcinoma tissue compared with the healthy colorectal tissue examined (34, 35). In three studies, however, *H. pylori* species was detected in only 1.2% of the malignant adenocarcinoma tissue and 6% of the normal colorectal tissue (36).

In another study, Fujimari et al., (9) reported *H. pylori* infection as a risk factor for colorectal adenoma and cancer, especially in females; in females, *H. pylori* infection increases the risk of colorectal adenoma and cancer at ages 40 to 80 years; the cited study detected *H. pylori* using respiratory urease test. In the study conducted by Liou et al. (37), no relationships were observed between *H. pylori* infection (detected using respiratory urease test) and colorectal adenoma. The current study, however, found a significant rela-

tionship between *H. pylori* infection and colon cancer and adenomatous polyps with the application of IgA and IgG *H. pylori* antibodies.

In the study by Brim et al. (38), no relationships were observed between *H. pylori* infection and the risk of colorectal polyps, while a significant relationship was observed between these two variables in the current study. This disparity of findings may be attributed to the lower prevalence of *H. pylori* infection in the region studied by Brim et al.

In a study conducted by Buso et al. (39), females with *H. pylori* infection had a higher risk of developing colorectal tumor. Fujimori et al., (9) and Jones et al., (34) showed a higher odds ratio (OR) of developing colorectal adenocarcinoma in females infected with *H. pylori* compared with males with such infection; however, the relationship was not significant. The higher risk of colon adenoma in females is associated with hormonal factors. The mean age of the participants was over 50 years in the current study, which was indicative of reduced serum of sex hormone levels. Estrogen and progesterone reduce the risk of colon adenoma and adenocarcinoma. The association of *H. pylori* infection and reduced sex hormones in females increases the risk of colon neoplasia. Nonetheless, the current study found a significant relationship between *H. pylori* infection and colon cancer and adenomatous polyps in males but not in females. The disparity of findings between this and other studies may be due to the lower mean age in the females that participated in the current study.

In another study, Zhang et al., (40) studied *H. pylori* infection and revealed an increased risk of left colon cancer with an OR of 1.22 and therefore suggested that *H. pylori* infection may be somewhat associated with an increased risk of left colon cancer. Buso et al., (39) and Inoue et al., (25) showed that the risk of late-stage adenoma increased significantly in the presence of *H. pylori* infection. Fujimori et al., (9) and Abbass et al., (41) found no relationships between *H. pylori* infection and the location of colorectal neoplasia. Brim et al., (38) also observed no relationships between *H. pylori* infection and the location of colorectal polyps.

In the current study, the prevalence of colon cancer and adenomatous polyps did not differ significantly in the right and left colons.

Brim et al., (39) showed a significant increase in the incidence of colorectal polyps in the older-than-40 African-American population. In the current study, the prevalence of colon cancer and adenomatous polyps was significantly higher in subjects aged over 50 years compared with the ones aged 50 and below.

The main limitation of the current study was the absence of a gold standard method to diagnose *H. pylori* infection such as endoscopic biopsy, urea breath test, and stool antigen test since the sensitivity and specificity of serological method is less than such tests.

Conclusion

The obtained results suggested that *H. pylori* infection can be considered a risk factor for colon cancer and adenomatous polyps. Further prospective studies with larger sample sizes are required to accurately assess the role of *H. pylori* infection in such pathologies. The eradication of this infection and its reassessment in patients after eradication can help to determine the role of this organism in different pathologies. The clinical significance of these findings also cannot be safely interpreted since the pathophysiology of this phenomenon is still unclear and further basic studies should be conducted in this field.

Acknowledgment

Conflict of interest

The authors declare that there was no conflict of interest.

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