Retrospective Study

**Helicobacter pylori** infection with intestinal metaplasia: An independent risk factor for colorectal adenomas

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**Abstract**

**AIM**

To explore the association between *Helicobacter pylori* ([H. pylori](#)) infection status, intestinal metaplasia (IM), and colorectal adenomas.

**METHODS**

We retrospectively reviewed 1641 individuals aged ≥ 40 years who underwent physical examination, laboratory testing, ^13^C-urea breath testing, gastroscope, and an interview to ascertain baseline characteristics and general state of health. Histopathological results were obtained by gastric and colorectal biopsies.

**RESULTS**

The prevalence of *H. pylori* infection and adenomas was 51.5% (845/1641) and 18.1% (297/1641), respectively. *H. pylori* infection was significantly correlated with an increased risk of colorectal adenomas (crude OR = 1.535, 95%CI: 1.044-1.753, *P* = 0.022; adjusted OR = 1.359, 95%CI: 1.035-1.785, *P* = 0.028). Individuals with IM had an elevated risk of colorectal adenomas (crude OR = 1.664, 95%CI: 1.216-2.277, *P* = 0.001; adjusted OR = 1.381, 95%CI: 0.998-1.929, *P* = 0.059). Stratification based on *H. pylori* infection stage and IM revealed that IM accompanied by *H. pylori* infection was significantly associated with an increased risk of adenomas (crude OR = 2.109, 95%CI: 1.383-3.216, *P*
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= 0.001; adjusted OR = 1.765, 95% CI: 1.130-2.757, *P* = 0.012).

**CONCLUSION**

*H. pylori*-related IM is associated with a high risk of colorectal adenomas in Chinese individuals.

**Key words:** *Helicobacter pylori*; Chinese population; Colorectal neoplasms; Intestinal metaplasia; Chronic gastritis

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**Core tip:** This retrospective study revealed *Helicobacter pylori* (*H. pylori*)-related intestinal metaplasia (IM) to be an independent risk factor for colorectal adenomas in Chinese individuals aged ≥ 40 years. Clinically, it may be useful for patients with *H. pylori* infection and IM to undergo colonoscopy screening and surveillance.

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**INTRODUCTION**

Colorectal cancer (CRC) is the fifth most common cancer and the fifth most common cause of cancer death in China[1]. CRC mostly arises from colorectal adenomas through the adenoma-to-carcinoma sequence[2]. Common risk factors, such as age, family history, smoking, alcohol consumption, diet, and lifestyle, contribute to colorectal neoplasm development[3]. It is well known that *Helicobacter pylori* (*H. pylori*) is classified as a class 1 carcinogen, as it infects the gastric mucosa and causes inflammation that drives the progression of the gastritis-atrophy-metaplasia-dysplasia-cancer sequence[4]. *H. pylori* infection was first recognized as a risk factor for colorectal neoplasia in the 1990s[5]. Some reports have indicated a positive association between *H. pylori* infection and colorectal neoplasms[6-13], but this has been disputed by others[14-18]. The pathophysiological mechanism of how *H. pylori* induces colorectal neoplasms is still unclear. A recent study associated the presence of *H. pylori* infection and intestinal metaplasia (IM) with a significantly elevated risk of colorectal adenomas[10]. Therefore, we aimed to conduct a further analysis to evaluate the relationship between *H. pylori*-related IM and colorectal adenomas.

**MATERIALS AND METHODS**

**Patient selection**

From September 2014 to January 2016, 15622 indivi-
duals from an asymptomatic healthy population under-
went health check-ups at the Medical and Health Care Center of The First Affiliated Hospital of Wenzhou Medical University. All individuals underwent physical examination, laboratory testing, and an interview to ascertain baseline characteristics and general state of health. Among this large study group, 1720 individuals aged ≥ 40 years underwent the 13C-urea breath test, gastroscopy, and colonoscopy. Individuals with a previous history of *H. pylori* eradication therapy or polyp resection were excluded from the study. In addition, individuals were excluded if they had inflammatory bowel disease, gastric dysplasia, or malignancies, including gastrointestinal cancer. Ultimately, the data of 1641 individuals were included in our analysis.

**Diagnostic criteria**

The following baseline characteristics were obtained from self-report questionnaires for analysis: age, body mass index (BMI), family history, personal medical history, smoking, and alcohol consumption. Among the 1641 individuals included in the study group, 1550 (94%) had antrum biopsies, 498 (30%) had corpus biopsies, 120 (7%) had cardia biopsies, and 337 (21%) had biopsies at multiple sites. According to the histopathological results of the gastric mucosa, individuals were divided into two groups: IM (+) group and IM (-) group (including normal mucosa, chronic non-atrophic gastritis, and chronic atrophic gastritis). According to results of colorectal biopsies, individuals were divided into three groups: non-polyp group, non-adenomatous polyp group (including hyperplastic polyps and inflammatory polyps), and adenoma group. Polyps located in the cecum, ascending, and transverse colon were classified as "proximal lesions", those located in the descending colon, sigmoid, and rectum were classified as "distal lesions", and those located on both sides were classified as "bilateral lesions". Polyps were grouped based on number: one, two or more. Polyps were also grouped based on size: 0-9 mm and ≥ 10 mm. Gastroscopy and colonoscopy were performed with a GIF-H260 gastroscope and a CF-H260AI colonoscope (OLYMPUS, Tokyo, Japan), respectively. The 13C-urea breath test was used to identify *H. pylori* infection and was performed with an infrared spectrometer with a sensitivity of 97.8%, specificity of 96.8%, and accuracy of 97.5%[19]. All examinations were performed on the same day.

**Statistical analysis**

Statistical analyses were performed using SPSS version 19 (Armonk, NY). Data for continuous variables are expressed as the mean ± SD, and between-group differences were evaluated using the *t* test. Categorical variables were evaluated using a *χ*² test. Odds ratios (ORs) and 95% CIs were obtained by logistic regression analysis. Statistical significance was established for two-sided *P* values < 0.05.
RESULTS

The prevalence of H. pylori infection was 51.5% (845/1641), and the prevalence rates of IM, non-adenomatous polyps, and adenomas were 18.3% (300/1641), 17.4% (286/1641) and 18.1% (297/1641), respectively. Baseline characteristics of patients with colorectal adenomas and non-adenomatous polyps and those without polyps are summarized in Table 1. No significant differences were observed in mean serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), or fasting blood glucose (FBG) levels between the adenoma and non-polyp groups. Additionally, there were no significant differences in TG, TC or LDL between the non-adenomatous polyp and non-polyp groups. The patients’ mean age was 53.17 (8.450) years for the colorectal adenoma group, 51.91 (8.456) years for the non-adenomatous polyp group, and 49.72 (7.974) years for the non-polyp group, with patients in the non-polyp group being significantly younger than for patients in the colorectal adenoma group (P < 0.001) and the non-adenomatous polyp group (P < 0.001). The mean BMI was higher in the colorectal adenoma group (P = 0.05) and non-adenomatous polyp group (P < 0.001), compared to the non-polyp group. The frequency of male sex in the colorectal adenoma group, non-adenomatous polyp group, and non-polyp group was 81.1% (241/297), 73.78% (221/286), and 59.07% (625/1058), respectively. Smoking (P < 0.001) and alcohol consumption (P < 0.001) rates were both higher in the adenoma and non-adenomatous polyp groups than in the non-polyp group. Therefore, age, sex, BMI, smoking, and alcohol consumption were identified as risk factors in the adenoma group, and used to control for confounding effects in the following analyses. For the non-adenomatous polyp group, age, sex, BMI, smoking, alcohol consumption, HDL level, and FBG level were identified as risk factors, and used to control for confounding effects in the following analyses.

Based on H. pylori infection status, we divided individuals into two groups. As reported in Table 2, there were no significant differences in mean age or sex between the H. pylori positive and H. pylori negative groups. In addition, the incidence of adenomas was higher in the H. pylori positive group than in the H. pylori negative group, with a crude OR of 1.535 (95%CI: 1.044-1.753, P = 0.022) and an adjusted OR of 1.359 (95%CI: 1.035-1.785, P = 0.028, Table 3). Moreover, there was no significant association between non-adenomatous polyps and H. pylori infection. The association of polyps with H. pylori infection was highest for single polyp (OR = 1.328, 95%CI: 1.032-1.708, P = 0.027), polyp size of 0-9 mm (OR = 1.352, 95%CI: 1.098-1.666, P = 0.005), and proximally located polyps (OR = 1.457, 95%CI: 1.062-1.998, P = 0.020).

Compared to the IM (-) group, individuals in the IM (+) group were older (P < 0.001), with a higher proportion of men (P = 0.009, Table 4). The frequency of adenoma was more prevalent in the IM (+) group than in the IM (-) group, with a crude OR of 1.664 (95%CI: 1.216-2.277, P = 0.001) and an adjusted OR of 1.381 (95%CI: 0.998-1.929, P = 0.059; Table 3). The frequency of non-adenomatous polyps in the IM (+) group and IM (-) group was 20.3% and 16.8%, respectively, with a crude OR of 1.436 (95%CI: 1.035-1.993, P = 0.030) and an adjusted OR of 1.225 (95%CI: 0.930-1.612, P = 0.148, Table 3). The association of polyps with IM (+) was highest for patients with more than one polyp (OR: 1.766, 95%CI: 1.278-2.441, P = 0.001), a polyp size of 0-9 mm (OR: 1.526, 95%CI: 1.176-1.981, P = 0.001), and proximally located polyps (OR: 1.703, 95%CI: 1.171-2.475, P = 0.005).

The risk for adenoma was significantly higher in the presence of both H. pylori infection and IM. Next, we further classified all individuals into four groups (Table 5): Group A: H. pylori (-) and IM (-); Group B: H. pylori (+) and IM (-); Group C: H. pylori (+) and IM (+); and Group D: H. pylori (-) and IM (+). The risk of adenomas among the four groups of H. pylori-

### Table 1 Baseline characteristics of subjects n (%)

| Parameter          | Non-polyp 1058 | Adenoma 297 | Non-adenomaous polyp 286 | P value | P value |
|--------------------|----------------|-------------|--------------------------|---------|---------|
| Age                | 49.72 (7.974)  | 51.17 (8.450)| 51.91 (8.456)            | < 0.001 | < 0.001 |
| Male/female        | 625/433        | 241/56      | 221/65                   | < 0.001 | < 0.001 |
| BMI                | 23.95 (2.963)  | 24.50 (2.978)| 24.9 (3.017)             | 0.05    | < 0.001 |
| Smoker (+/-)       | 211/847        | 118/179     | 120/166                  | < 0.001 | < 0.001 |
| Alcohol (+/-)      | 140/918        | 78/219      | 67/219                   | < 0.001 | < 0.001 |
| TC                 | 5.457 (1.130)  | 5.481 (1.340)| 5.427 (1.021)            | 0.753   | 0.682   |
| TG                 | 1.879 (1.763)  | 2.025 (2.438)| 2.111 (1.189)            | 0.25    | 0.052   |
| HDL                | 1.325 (0.324)  | 1.285 (0.316)| 1.246 (0.389)            | 0.538   | 0.001   |
| LDL                | 3.269 (0.814)  | 3.259 (0.815)| 3.271 (0.822)            | 0.857   | 0.967   |
| FBG                | 5.060 (1.220)  | 5.118 (1.220)| 5.316 (1.610)            | 0.478   | 0.004   |

*Two-sided P values for the difference between the adenoma and non-polyp groups were based on the χ² test and t test; Two-sided P values for the difference between the non-adenomatous polyp and non-polyp groups were based on the χ² test and t test. BMI: Body mass index; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; FBG: Fasting blood glucose.
related gastric lesions is reported in Table 5. No significant differences were noted between Group A and Group B (crude OR: 1.214, 95% CI: 0.961-1.761, \( P = 0.198 \)). However, the presence of \( H. pylori \)-related IM was significantly associated with an increased risk for colorectal adenomas, with a crude OR of 2.109 (95% CI: 1.383-3.216, \( P = 0.001 \)) and an adjusted OR of 1.765 (95% CI: 1.130-2.757, \( P = 0.012 \)). The progression of non-\( H. pylori \)-related IM did not increase the risk of adenomas, with a crude OR of 1.527 (95% CI: 0.954-2.444, \( P = 0.078 \)) and an adjusted OR of 1.222 (95% CI: 0.741-2.012, \( P = 0.432 \)).
Table 5  Correlation between stage of _H. pylori_-related gastric lesions and adenoma

| H. pylori | IM | Adenoma 297 | Non-polyp 1018 | Crude OR          | P value  | Adjusted OR | ^P value  |
|-----------|----|-------------|----------------|-------------------|----------|-------------|----------|
| Group A   | (-) | (-)         | 113            | 488               | B:A      | 1.214       | 0.394    | 1.190     | 0.876-1.617 | 0.262     |
| Group B   | (+) | (-)         | 113            | 402               | C:A      | 2.109       | 0.001    | 1.765     | 1.330-2.757 | 0.012     |
| Group C   | (+) | (+)         | 42             | 86                | D:A      | 1.527       | 0.078    | 1.222     | 0.741-2.015 | 0.432     |
| Group D   | (-) | (+)         | 29             | 82                |          |             |          |           |            |           |

^Adjusted for age, gender, body mass index, smoking habit, and alcohol consumption by logistic regression analysis. IM: Intestinal metaplasia.

DISCUSSION

Our study, which included asymptomatic individuals who underwent the ^13^C-urea breath test, gastroscopy, and colonoscopy, identified _H. pylori_-related IM as an independent risk factor for colorectal adenomas in Chinese individuals aged ≥ 40 years. Age, sex, BMI, smoking, and alcohol consumption were included as confounders to adjust the correlation between _H. pylori_-related IM and colorectal adenomas. _H. pylori_ infection was significantly associated with an increased risk of colorectal adenomas. These results are consistent with previous studies that reported a positive correlation between _H. pylori_ infection and colorectal adenomas[14-17]. Additionally, individuals with IM had an elevated risk of colorectal adenomas. A large population based case-control study that enrolled 156000 individuals showed a positive association between IM and colorectal adenomas (adjusted OR = 1.24, 95%CI: 1.17-1.32), but without including an analysis of the relationship between _H. pylori_-related IM and colorectal adenomas[18].

Furthermore, a recent study showed that individuals with IM were more likely to have adenomas with high-grade intraepithelial lesions (OR = 3.218, 95%CI: 2.767-3.509)[20]. To our knowledge, no study has analyzed the relationship between _H. pylori_-related IM and colorectal neoplasm. Thus, we conducted an analysis that stratified individuals based on _H. pylori_ infection stage and IM. Based on this stratification, we drew the following conclusion: _H. pylori_ infection without IM did not increase the risk of colorectal adenomas, whereas IM accompanied by _H. pylori_ infection did increase the risk of colorectal adenomas. Therefore, longstanding _H. pylori_ infection may be crucial to the development of colorectal adenomas because IM is usually a chronic sequela of _H. pylori_ infection. Our analysis may also explain the inconsistencies in previous studies, with some of studies having reported a positive correlation between _H. pylori_ infection and colorectal adenomas, while other studies reported either a null or inverse association[14-17]. This may be due to racial differences or discrepancies in the prevalence of _H. pylori_ infection and IM in different regions. Differences among studies could also be associated with: the dominant use of hospital-based data, which may result in a patient selection bias; small sample sizes; different diagnostic tests used for _H. pylori_ identification; differences in prior history of _H. pylori_ eradication therapy or previous colorectal polyp removal among patients; as well as other uncontrolled confounding factors. In addition, our results revealed that the presence of _H. pylori_ infection was significantly associated with an elevated risk of proximal polyps, as previously reported by Hong et al[21] for proximal neoplasms. Conversely, other studies have reported an association between _H. pylori_ and an elevated risk of distal neoplasms[15,22].

Various interpretations have been proposed to explain the mechanisms by which _H. pylori_ infection increases the risk for colorectal adenomas. According to the most commonly described pathogenesis, persistent _H. pylori_ infection elicits hypergastrinemia, which has a trophic effect on epithelial cell growth and proliferation, contributing to colorectal carcinogenesis[23]. Indeed, gastrin and the cholecystokinin type B/gastrin receptor are expressed in human colonic polyps, with activation occurring early in the adenoma-carcinoma sequence[24]. Several epidemiological reports have confirmed a positive relationship between hypergastrinemia and an increased risk for colorectal neoplasms[15,25,26], although these findings have been disputed[27-29]. _H. pylori_ infection, aging, alcohol consumption, smoking, excessive salt intake, and bile reflux are deemed as risk factors correlated with IM[30,31]. Foci of IM tend to appear first at the antrum-corpus junction, extending to both the antrum and the corpus and replacing the normal gastric parietal cells[32]. Reduced gastric acid secretion triggered by IM might cause hypergastrinemia. In addition, hypochlorhydria hampers protein assimilation, which may increase some metabolites and unab sorbed nutrients, resulting in bacterial overgrowth and colonic disorders and contributing to colorectal carcinogenesis[33,34]. Therefore, _H. pylori_-related IM might aggravate colorectal carcinogenesis.

Our study had several limitations that need to be acknowledged. First, we did not measure the serum gastrin level, which is the key mechanism accounting for the contribution of _H. pylori_ to colorectal carcinogenesis. Second, biopsies were taken from multiple (i.e., three or more) sites in only 21% of patients, lowering the rate of gastric disease detection. Third, we used the ^13^C-urea breath test to determine the presence of an infection. However, the ^13^C-urea breath test is less reliable than histological staining, such as Giemsa staining, in evaluating _H. pylori_ colonization in biopsy tissue. Fourth, this was a single...
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center study with a small sample size. A multicenter study with a large sample size should be conducted. In conclusion, our research demonstrated that Chinese people who have *H. pylori*-related IM do have a high risk of colorectal adenomas. Given a high prevalence of colorectal adenocarcinoma in China, it is necessary for patients with *H. pylori* infection and IM to undergo colonoscopy screening and surveillance.

**COMMENTS**

**Background**

Previous studies demonstrated a positive correlation between Helicobacter pylori (*H. pylori*) infection and colorectal neoplasm. A recent study showed that *H. pylori* infection and intestinal metaplasia (IM) both significantly elevated the risk of colorectal adenomas. However, no study has analyzed the relationship between *H. pylori*-related IM and colorectal neoplasm.

**Research frontiers**

Colorectal cancer mostly arises from colorectal adenomas through the adenoma-to-carcinoma sequence. Early diagnosis of adenoma is very important to lower the mortality. It is necessary for individuals with *H. pylori* infection and IM to have colonoscopy screening and surveillance.

**Innovations and breakthroughs**

This study identified *H. pylori*-related IM as an independent risk factor for colorectal adenomas in Chinese individuals aged ≥ 40 years.

**Applications**

The presented research demonstrated that Chinese people who have *H. pylori*-related IM do have a high risk of colorectal adenomas. Given a high prevalence of colorectal adenocarcinoma in China, it is necessary for patients with *H. pylori* infection and IM to undergo colonoscopy screening and surveillance.

**Peer-review**

In this manuscript, the authors aimed to explore the association between *H. pylori* infection status, IM, and colorectal adenoma, and concluded that *H. pylori*-related IM was associated with a high risk of colorectal adenomas in Chinese individuals. The study was well designed and the results were very interesting. Therefore, the reviewer considers that it can be accepted after some English corrections.

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