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***Retrospective Study***

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

Yan Y *et al*. *H. pylori* infection and colorectal adenomas

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**Abstract**

***AIM***

To explore the association between *Helicobacter pylori* (*H. pylori*) infection status, intestinal metaplasia, and colorectal adenoma.

***METHODS***

We retrospectively reviewed 1641 individuals, ≥ 40 years old, who underwent physical examination, laboratory testing, 13C-urea breath testing, gastroscopy, colonoscopy, and an interview to ascertain baseline characteristics and general state of health. Histopathological examination results were gathered 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 to an increased risk of colorectal adenomas (crude OR of 1.535, 95%CI: 1.044-1.753, *P =* 0.022; adjusted OR of 1.359, 95%CI: 1.035-1.785, *P =* 0.028). Individuals with intestinal metaplasia had an elevated risk of colorectal adenomas (crude OR of 1.664, 95%CI: 1.216-2.277, *P =* 0.001; adjusted OR of 1.381, 95%CI: 0.998-1.929, *P =* 0.059). Stratification based on *H. pylori* infection stage and intestinal metaplasia revealed that intestinal metaplasia accompanied by *H. pylori* infectionwas significantly associated with an increased risk of adenomas (crude OR of 2.109, 95%CI: 1.383-3.216, *P =* 0.001; adjusted OR of 1.765, 95%CI: 1.130-2.757, *P =* 0.012).

***CONCLUSION***

*H. pylori*-related intestinal metaplasia was associated with a high risk of colorectal adenomas in Chinese individuals.

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

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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 ≥ 40 years of age. 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*)infection 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 of colorectal neoplasm in the 1990s[5]. Some reports have indicated a positive association between *H. pylori* infection and colorectal neoplasm[5-13], but this has been disputed by others[14-18]. The pathophysiological mechanism of how *H. pylori* induces colorectal neoplasm is still unclear. A recent study associated that the presence of *H. pylori* infection and intestinal metaplasia (IM) with a significantly elevated risk of colorectal adenomas[9]. 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 individuals from an asymptomatic healthy population underwent 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 ≥ 40 years old underwent the 13C-urea breath test, gastroscopy, and colonoscopy. Individuals with a previous history of *H. pylori* eradication therapy and 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: the IM (+) group and the 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: the non-polyp group, the non-adenomatous polyp group (including hyperplastic polyps and inflammatory polyps), and the 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***

The statistical analysis was performed using SPSS version 19 (Armonk, NY). Data for continuous variables were expressed as the mean ± SD, and between-group differences were evaluated using the *t* test. Categorical variables were evaluated using a χ2 test. Odds ratios (ORs) and 95% confidence intervals (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 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 non-polyp group, with patients in the non-polyp group being significantly younger that 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 81.11% (241/297), 73.78% (221/286) and 59.07% (625/1058). 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 polyps (OR: 1.328, 95%CI: 1.032-1.708, *P =* 0.027), polyps 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*-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).

**DISCUSSION**

Our study, which included asymptomatic individuals who underwent the 13C-urea breath test, gastroscopy, and colonoscopy, identified *H. pylori*-related IM as an independent risk factor for colorectal adenomas in Chinese individuals ≥ 40 years of age. 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[5-10]. 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[9]. 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: 0.767-13.509)[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 these 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 to: 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. for proximal neoplasms[21]. 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 neoplasm[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 intestinal metaplasia tend to appear first at the antrum-corpus junction, extending to both the antrum and the corpus, 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 unabsorbed nutrients, resulting in bacterial overgrowth and colonic disorders, 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 was 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%, lowering the rate of gastric disease detection. Third, we used the 13C-urea breath test, which determines the presence of an infection. However, the 13C-urea breath test is less reliable than histological staining, such as Giemsa, in evaluating *H. pylori* colonization in biopsy tissue. Fourth, this was a single 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. The Chinese have a high prevalence of colorectal adenocarcinoma. Therefore, 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 the presence of *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 intestinal metaplasia 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 ≥ 40 years of age.

***Application***

The presented research demonstrated that Chinese people who have *H. pylori*-related IM do have a high risk of colorectal adenomas. The Chinese have a high prevalence of colorectal adenocarcinoma. Therefore, 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, intestinal metaplasia, and colorectal adenoma, and concluded that *H. pylori*-related intestinal metaplasia 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 it can be accepted after some English correction.

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Non-polyp1058 | Adenoma297 | Non- Adenomaouspolyp 286 | 1*P* value | 2*P* value |
| Age | 49.72 (7.974) | 53.17 (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) | 0.250 | 0.052 |
| HDL | 1.325 (0.342) | 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 (1.230) | 5.118 (1.220) | 5.316 (1.610) | 0.478 | 0.004 |

1Two-sided *P* values for the difference between adenoma and non-polyp were based on the χ2 test and *t* test; 2Two-sided *p-*values for the difference between non-adenomatous polyp and non-polyp 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.

**Table 2 Correlation between *Helicobacter pylori* infection and colorectal neoplasms**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | ***H. pylori* (+)****845** | ***H. pylori* (-)****796** | **OR (95%CI)** | ***P* value** |
| Age | 50.91 (8.315) | 50.54 (8.208) | 1.006 (0.994-1.017) | 0.355 |
| female | 292 | 262 | 1 |  |
| male | 553 | 534 | 0.929 (0.757-1.140) | 0.482 |
| Non-polyp | 519 | 539 | 1 |  |
| Non-adenomaous polyp | 158 | 128 | 1.282 (0.986-1.667) | 0.064 |
| adenoma | 168 | 129 | 1.535 (1.044-1.753) | 0.022 |
| Polyps number |  |  |  |  |
|  one | 179 | 140 | 1.328 (1.032-1.708) | 0.027 |
|  Two or more | 147 | 117 | 1.305 (0.995-1.711) | 0.054 |
| Polyps size |  |  |  |  |
|  0-9 mm | 306 | 235 | 1.352 (1.098-1.666) | 0.005 |
|  10 mm+ | 20 | 22 | 0.944 (0.509-1.751) | 0.855 |
| Polyps location |  |  |  |  |
|  Proximal | 108 | 77 | 1.457 (1.062-1.998) | 0.020 |
|  Bilateral | 64 | 57 | 1.166 (0.800-1.700) | 0.424 |
|  Distal | 154 | 123 | 1.300 (0.997-1.696) | 0.053 |

Correlation between *Helicobacter pylori* (*H. pylori*) (+) and *H. pylori* (-) by logistic regression analysis.

**Table 3 Logistic regression model of the association between *Helicobacter pylori* infection, intestinal metaplasia, and colorectal neoplasm after adjustments for confounding factors**

|  |  |  |
| --- | --- | --- |
|  | Non-adenomaous polyp | Adenomas |
|  | **Adjusted aOR 95%CI** | **1*P* value** | **Adjusted bOR (95%CI)** | **2*P* value** |
| *H. pylori* (+) | 1.225 (0.930-1.612) | 0.148 | 1.359 (1.035-1.785) | 0.028 |
| IM | 1.265 (0.896-1.787) | 0.173 | 1.381 (0.988-1.929) | 0.059 |

1Adjusted for age, gender, body mass index (BMI), smoking habit, alcohol consumption, high-density lipoprotein level, and fasting blood glucose level by logistic regression analysis; 2Adjusted for age, gender, BMI, smoking habit, and alcohol consumption by logistic regression analysis. *H. pylori: Helicobacter* *pylori.*

**Table 4 Correlation between gastric lesions and colorectal neoplasm**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | IM (+)300 | IM (-)1341 | OR (95%CI) | 1*P* value |
| age | 53.12(8.490) | 50.19(8.118) | 1.041 (1.026-1.056) | < 0.001 |
| female | 80 | 474 | 1 |  |
| male | 220 | 867 | 1.503 (1.137-1.988) | 0.004 |
| Non-polyp | 168 | 890 | 1 |  |
| adenomas | 71 | 226 | 1.664 (1.216-2.277) | 0.001 |
| Non-adenomaous polyps | 61 | 225 | 1.436 (1.035-1.993) | 0.030 |
| Polyps number |  |  |  |  |
|  one | 66 | 253 | 1.382 (1.006-1.898) | 0.046 |
|  Two or more | 66 | 198 | 1.766 (1.278-2.441) | 0.001 |
| Polyps size |  |  |  |  |
|  0-9 mm | 121 | 420 | 1.526 (1.176-1.981) |  | 0.001 |
|  10 mm+ | 11 | 31 | 1.880 (0.927-3.813) | 0.080 |
| Polyp location |  |  |  |  |
|  Proximal | 45 | 135 | 1.703 (1.171-2.475) | 0.005 |
|  Bilateral | 28 | 85 | 1.595 (1.013-2.510) | 0.044 |
|  Distal  | 59 | 204 | 1.434 (1.029-1.997) | 0.033 |

1Correlation between IM (+) and IM (-) by logistic regression analysis. IM: Intestinal metaplasia.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | *H. pylori* | IM | Adenoma297 | Non-polyp1018 |
| Group A | (-) | (-) | 113 | 488 |
| Group B | (+) | (-) | 113 | 402 |
| Group C | (+) | (+) | 42 | 86 |
| Group D | (-) | (+) | 29 | 82 |
|  | **Crude OR** | ***P* value** | **Adjusted 1OR** | **1*P* value** |
| B:A | 1.214 (0.906-1.626) | 0.194 | 1.190 (0.876-1.617) | 0.262 |
| C:A | 2.109 (1.383-3.216) | 0.001 | 1.765 (1.130-2.757) | 0.012 |
| D:A | 1.527 (0.954-2.444) | 0.078 | 1.222 (0.741-2.015) | 0.432 |

**Table 5 Correlation between stage of *H. pylori*-related gastric lesions**

1Adjusted for age, gender, body mass index, smoking habit, and alcohol consumption by logistic regression analysis. IM: Intestinal metaplasia.