ORIGINAL ARTICLE

Retrospective Study

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

Ye Yan, Yi-Na Chen, Qian Zhao, Chao Chen, Chun-Jing Lin, Yin Jin, Shuang Pan, Jian-Sheng Wu

Ye Yan, Yi-Na Chen, Qian Zhao, Chao Chen, Yin Jin, Shuang Pan, Department of Gastroenterology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

Chun-Jing Lin, Jian-Sheng Wu, Medical and Health Care Center, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

Correspondence to: Dr. Jian-Sheng Wu, Professor, Medical and Health Care Center, The First Affiliated Hospital of Wenzhou Medical University, No. 1 Nan Bai Xiang street, Wenzhou 325000, Zhejiang Province, China. wzwujs@163.com
Telephone: +86-577-55578033
Fax: +86-577-55578033

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 $\geq$ 40 years who underwent physical examination, laboratory testing, ^{13}C-urea breath testing, gastroscopy, colonoscopy, 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*

= 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

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.

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 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 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 indivi-duals 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 aged ≥ 40 years underwent the ^{13}C-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 ^{13}C-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.

Table 1 Baseline characteristics of subjects *n* (%)					
Parameter	Non-polyp 1058	Adenoma 297	Non-adenomaous polyp 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)	0.25	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

[1]Two-sided *P* values for the difference between the adenoma and non-polyp groups were based on the χ^2 test and *t* test; [2]Two-sided *P* values for the difference between the non-adenomatous polyp and non-polyp groups were based on the χ^2 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.

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 81.11% (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 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
Polyp 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
Polyp 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
Polyp 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 [a]OR 95%CI	[1]*P* value	Adjusted [b]OR (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

[1]Adjusted for age, gender, body mass index (BMI), smoking habit, alcohol consumption, high-density lipoprotein level, and fasting blood glucose level by logistic regression analysis; [2]Adjusted 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
Polyp 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
Polyp 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

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

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).

	H. pylori	IM	Adenoma 297	Non-polyp 1018		Crude OR	*P* value	Adjusted [1]OR	[1]*P* value
Group A	(-)	(-)	113	488	B:A	1.214 (0.906-1.626)	0.194	1.190 (0.876-1.617)	0.262
Group B	(+)	(-)	113	402	C:A	2.109 (1.383-3.216)	0.001	1.765 (1.130-2.757)	0.012
Group C	(+)	(+)	42	86	D:A	1.527 (0.954-2.444)	0.078	1.222 (0.741-2.015)	0.432
Group D	(-)	(+)	29	82					

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

[1]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[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 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 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 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 unabsorbed 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

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.

REFERENCES

1   **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]

2   **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767 [PMID: 2188735]

3   **Giovannucci E**. Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am* 2002; **31**: 925-943 [PMID: 12489270]

4   **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

5   **Meucci G**, Tatarella M, Vecchi M, Ranzi ML, Biguzzi E, Beccari G, Clerici E, de Franchis R. High prevalence of Helicobacter pylori infection in patients with colonic adenomas and carcinomas. *J Clin Gastroenterol* 1997; **25**: 605-607 [PMID: 9451672]

6   **Fujimori S**, Kishida T, Kobayashi T, Sekita Y, Seo T, Nagata K, Tatsuguchi A, Gudis K, Yokoi K, Tanaka N, Yamashita K, Tajiri T, Ohaki Y, Sakamoto C. Helicobacter pylori infection increases the risk of colorectal adenoma and adenocarcinoma, especially in women. *J Gastroenterol* 2005; **40**: 887-893 [PMID: 16211345 DOI: 10.1007/s00535-005-1649-1]

7   **Brim H**, Zahaf M, Laiyemo AO, Nouraie M, Pérez-Pérez GI, Smoot DT, Lee E, Razjouyan H, Ashktorab H. Gastric Helicobacter pylori infection associates with an increased risk of colorectal polyps in African Americans. *BMC Cancer* 2014; **14**: 296 [PMID: 24774100 DOI: 10.1186/1471-2407-14-296]

8   **Inoue I**, Mukoubayashi C, Yoshimura N, Niwa T, Deguchi H, Watanabe M, Enomoto S, Maekita T, Ueda K, Iguchi M, Yanaoka K, Tamai H, Arii K, Oka M, Fujishiro M, Takeshita T, Iwane M, Mohara O, Ichinose M. Elevated risk of colorectal adenoma with Helicobacter pylori-related chronic gastritis: a population-based case-control study. *Int J Cancer* 2011; **129**: 2704-2711 [PMID: 21225622 DOI: 10.1002/ijc.25931]

9   **Sonnenberg A**, Genta RM. Helicobacter pylori is a risk factor for colonic neoplasms. *Am J Gastroenterol* 2013; **108**: 208-215 [PMID: 23208272 DOI: 10.1038/ajg.2012.407]

10 **Breuer-Katschinski B**, Nemes K, Marr A, Rump B, Leiendecker B, Breuer N, Goebell H. Helicobacter pylori and the risk of colonic adenomas. Colorectal Adenoma Study Group. *Digestion* 1999; **60**: 210-215 [PMID: 10343134]

11 **Zhang Y**, Hoffmeister M, Weck MN, Chang-Claude J, Brenner H. Helicobacter pylori infection and colorectal cancer risk: evidence from a large population-based case-control study in Germany. *Am J Epidemiol* 2012; **175**: 441-450 [PMID: 22294430 DOI: 10.1093/aje/kwr331]

12 **Shmuely H**, Passaro D, Figer A, Niv Y, Pitlik S, Samra Z, Koren R, Yahav J. Relationship between Helicobacter pylori CagA status and colorectal cancer. *Am J Gastroenterol* 2001; **96**: 3406-3410 [PMID: 11774957 DOI: 10.1111/j.1572-0241.2001.05342.x]

13 **Fireman Z**, Trost L, Kopelman Y, Segal A, Sternberg A. Helicobacter pylori: seroprevalence and colorectal cancer. *Isr Med Assoc J* 2000; **2**: 6-9 [PMID: 10892362]

14 **Patel S**, Lipka S, Shen H, Barnowsky A, Silpe J, Mosdale J, Pan Q, Fridlyand S, Bhavsar A, Abraham A, Viswanathan P, Mustacchia P, Krishnamachari B. The association of H. pylori and colorectal adenoma: does it exist in the US Hispanic population? *J Gastrointest Oncol* 2014; **5**: 463-468 [PMID: 25436126 DOI: 10.3978/j.issn.2078-6891.2014.074]

15 **Georgopoulos SD**, Polymeros D, Triantafyllou K, Spiliadi C, Mentis A, Karamanolis DG, Ladas SD. Hypergastrinemia is associated with increased risk of distal colon adenomas. *Digestion* 2006; **74**: 42-46 [PMID: 17068397 DOI: 10.1159/000096593]

16 **Limburg PJ**, Stolzenberg-Solomon RZ, Colbert LH, Perez-Perez GI, Blaser MJ, Taylor PR, Virtamo J, Albanes D. Helicobacter pylori seropositivity and colorectal cancer risk: a prospective study of male smokers. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1095-1099 [PMID: 12376513]

17 **Siddheshwar RK**, Muhammad KB, Gray JC, Kelly SB. Seroprevalence of Helicobacter pylori in patients with colorectal polyps and colorectal carcinoma. *Am J Gastroenterol* 2001; **96**: 84-88 [PMID: 11197293 DOI: 10.1111/j.1572-0241.2001.03355.x]

18 **Moss SF**, Neugut AI, Garbowski GC, Wang S, Treat MR, Forde KA. Helicobacter pylori seroprevalence and colorectal neoplasia: evidence against an association. *J Natl Cancer Inst* 1995; **87**: 762-763 [PMID: 7563155]

19 **Chen TS**, Chang FY, Chen PC, Huang TW, Ou JT, Tsai MH, Wu MS, Lin JT. Simplified 13C-urea breath test with a new infrared spectrometer for diagnosis of Helicobacter pylori infection. *J Gastroenterol Hepatol* 2003; **18**: 1237-1243 [PMID: 14535979]

20 **Qing Y**, Wang M, Lin YM, Wu D, Zhu JY, Gao L, Liu YY, Yin TF. Correlation between Helicobacter pylori-associated gastric diseases and colorectal neoplasia. *World J Gastroenterol* 2016; **22**: 4576-4584 [PMID: 27182167 DOI: 10.3748/wjg.v22.i18.4576]

21 **Hong SN**, Lee SM, Kim JH, Lee TY, Kim JH, Choe WH, Lee SY, Cheon YK, Sung IK, Park HS, Shim CS. Helicobacter pylori infection increases the risk of colorectal adenomas: cross-sectional study and meta-analysis. *Dig Dis Sci* 2012; **57**: 2184-2194 [PMID: 22669208 DOI: 10.1007/s10620-012-2245-x]

22 **Kapetanakis N**, Kountouras J, Zavos C, Michael S, Tsarouchas G, Gavalas E, Anastasiadou K, Tsiaousi E, Venizelos I, Nikolaidou C, Vardaka E, Kouklakis G, Moschos I. Re: Helicobacter pylori infection and colorectal cancer risk: evidence from a large

population-based case-control study in Germany. *Am J Epidemiol* 2012; **176**: 566-567 [PMID: 22908208 DOI: 10.1093/aje/kws302]

23   **Renga M**, Brandi G, Paganelli GM, Calabrese C, Papa S, Tosti A, Tomassetti P, Miglioli M, Biasco G. Rectal cell proliferation and colon cancer risk in patients with hypergastrinaemia. *Gut* 1997; **41**: 330-332 [PMID: 9378387]

24   **Smith AM**, Watson SA. Gastrin and gastrin receptor activation: an early event in the adenoma-carcinoma sequence. *Gut* 2000; **47**: 820-824 [PMID: 11076881]

25   **Thorburn CM**, Friedman GD, Dickinson CJ, Vogelman JH, Orentreich N, Parsonnet J. Gastrin and colorectal cancer: a prospective study. *Gastroenterology* 1998; **115**: 275-280 [PMID: 9679032]

26   **Seitz JF**, Giovannini M, Gouvernet J, Gauthier AP. Elevated serum gastrin levels in patients with colorectal neoplasia. *J Clin Gastroenterol* 1991; **13**: 541-545 [PMID: 1744390]

27   **Selgrad M**, Bornschein J, Kandulski A, Hille C, Weigt J, Roessner A, Wex T, Malfertheiner P. Helicobacter pylori but not gastrin is associated with the development of colonic neoplasms. *Int J Cancer* 2014; **135**: 1127-1131 [PMID: 24496701 DOI: 10.1002/ijc.28758]

28   **Kikendall JW**, Glass AR, Sobin LH, Bowen PE. Serum gastrin is not higher in subjects with colonic neoplasia. *Am J Gastroenterol* 1992; **87**: 1394-1397 [PMID: 1415093]

29   **Robertson DJ**, Sandler RS, Ahnen DJ, Greenberg ER, Mott LA, Cole BF, Baron JA. Gastrin, Helicobacter pylori, and colorectal adenomas. *Clin Gastroenterol Hepatol* 2009; **7**: 163-167 [PMID: 18929688 DOI: 10.1016/j.cgh.2008.09.006]

30   **Leung WK**, Lin SR, Ching JY, To KF, Ng EK, Chan FK, Lau JY, Sung JJ. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication. *Gut* 2004; **53**: 1244-1249 [PMID: 15306578 DOI: 10.1136/gut.2003.034629]

31   **Kneller RW**, You WC, Chang YS, Liu WD, Zhang L, Zhao L, Xu GW, Fraumeni JF, Blot WJ. Cigarette smoking and other risk factors for progression of precancerous stomach lesions. *J Natl Cancer Inst* 1992; **84**: 1261-1266 [PMID: 1640486]

32   **Correa P**, Piazuelo MB, Wilson KT. Pathology of gastric intestinal metaplasia: clinical implications. *Am J Gastroenterol* 2010; **105**: 493-498 [PMID: 20203636 DOI: 10.1038/ajg.2009.728]

33   **Kanno T**, Matsuki T, Oka M, Utsunomiya H, Inada K, Magari H, Inoue I, Maekita T, Ueda K, Enomoto S, Iguchi M, Yanaoka K, Tamai H, Akimoto S, Nomoto K, Tanaka R, Ichinose M. Gastric acid reduction leads to an alteration in lower intestinal microflora. *Biochem Biophys Res Commun* 2009; **381**: 666-670 [PMID: 19248769 DOI: 10.1016/j.bbrc.2009.02.109]

34   **Evenepoel P**, Claus D, Geypens B, Maes B, Hiele M, Rutgeerts P, Ghoos Y. Evidence for impaired assimilation and increased colonic fermentation of protein, related to gastric acid suppression therapy. *Aliment Pharmacol Ther* 1998; **12**: 1011-1019 [PMID: 9798807]

Baishideng®

0 8>

9 771007 932045