META-ANALYSIS

Meta-analysis of the Correlation between *Helicobacter Pylori* Infection and the risk of Colorectal Neoplasia

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ABSTRACT

Objective • To study the association of *H. pylori* infection with colorectal adenomas.

Methods • Web searches of PubMed, Embase, and Scopus databases for randomized controlled trials, class-experimental studies, and cohort studies on the association between *H. pylori* and colorectal adenomas were performed from May 2000 to May 2023. Literature was screened based on inclusion and exclusion criteria, data were extracted and evaluated for quality, and statistical analyses were performed using RevMan 5.2 software.

Results • A total of 15 studies were included, and meta-analysis showed a statistically significant difference between colorectal neoplastic polyp cases in the *H. pylori-positive* and *H. pylori-negative* groups [OR=1.80, 95%CI: (1.31, 2.47), $P < .01$, $I^2 = 95\%$]. Analysis based on subgroups of different *H. pylori* detection methods showed that the correlation between *H. pylori* infection and colorectal polyp incidence is not affected by their detection

methods, with serological detection subgroup: [OR=0.13, 95%CI: (0.05, 0.21), $P < .01$, $I^2 = 88\%$], and non-serological detection subgroup: [OR=0.13, 95%CI: (0.04, 0.22), $P < .01$, $I^2 = 95\%$]. Subgroup analysis of pathological types showed that *H. pylori* infection is not significantly associated with the development of non-neoplastic polyps [OR=1.47, 95%CI: 0.98-2.22, $P = .06$], whereas it is correlated with the development of neoplastic polyps [95%CI: 1.69-3.22, $P < .01$]. In the subgroup analysis of geographic differences in the population, *H. pylori* infection was correlated with the development of colorectal polyps in different geographic populations ($P < .01$).

Conclusion • *H. pylori* infection is a risk factor for colorectal polyp neoplasia, its infection is associated with colorectal neoplasia, and the correlation is not affected by the different methods of *H. pylori* detection and the different geographic regions of the population. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium with certain requirements for growth conditions. Since its discovery in 1982, more and more effects of *H. pylori* infection on the body have been discovered, and according to many studies, *H. pylori* has been associated with a variety of gastrointestinal disorders involving chronic gastritis, peptic ulcers, gastric lymphoma, and gastric cancer.[1] Colorectal polyps (CPs), as a common lesion in the digestive tract, are elevated lesions of the colorectal mucosa and protrude

superiorly into the intestinal lumen, which are precancerous lesions of CRC, and CPs are an important indicator for early screening of CRC. Colorectal cancer (CRC) is one of the most common cancers in the world, with the third-highest prevalence rate and the second-highest mortality rate.[2]

CRC is currently thought to be strongly associated with factors such as gender, age, lifestyle, dyslipidemia, and co-morbidities.[3] According to the International Agency for Research on Cancer (IARC), it was estimated that in 2023, 150,000 people would be diagnosed globally (8% of all cancer diagnoses) and 52,000 would die from CRC (8.5% of all cancer-related deaths).[4] Approximately 28% of CRC occurs in the rectum, with 22% of rectal CRC cases involving the distal colorectal region and 41% involving the proximal colorectal region.[5] Up to 50% of CRC patients show metastatic disease at diagnosis.[6] The 5-year survival rate for cases of metastatic disease is less than 10%, although researchers have paved the way for advances in treatment options and screening.[7] Currently the preferred treatment option for CRC remains surgery and chemotherapy.[8] *H. pylori* was discovered in 1982 and classified as a class I carcinogen in 1994 as it is the main cause of most

gastric cancers.[9] *H. pylori* infection can lead to the elevation of serum gastrin, activate the overexpression of inflammatory mediators such as IL-1, IL-8, TNF-α, and epidermal growth factor, and induce the increase of COX-2 secretion, and the interaction between the overexpressed cytokines and COX-2 promotes the cell proliferation, angiogenesis, gene mutation, and reduces the apoptosis of the cells, which leads to the development of colorectal polyps and tumors. The carcinogenesis of colorectal polyps is a complex biological phenomenon that results from the interaction between genes and the environment. It is generally believed that most colorectal cancers develop from adenomas, and the process of evolution roughly involves normal intestinal epithelium → hyperplasia/microadenomas → adenomas → adenocarcinomas.[8] *H. pylori* infection leads to the decreased secretion of ghrelin, which is secreted by the gastric mucosa, and the elevated ghrelin prevents the development of CPs.[10] *H. pylori* promotes intestinal inflammation through the production of toxic substances such as lipopolysaccharide (LPS) and cytotoxins, which can promote colorectal adenomatous polyp development by altering the intestinal status.[11] Current research suggests that the pathogenic mechanisms of colorectal adenomas due to *H. pylori* infection mainly include increased gastrin secretion, elevated COX-2 levels, the action of *H. pylori* virulence factors, gastric or colorectal inflammatory responses due to the infection, and alterations in the intestinal flora.[11] *H. pylori* infection can lead to elevated serum gastrin, activate the overexpression of inflammatory mediators such as IL-1, IL-8, TNF-α, and epidermal growth factor; and induce an increase in the secretion of COX-2. Overexpression of cytokines interacting with COX-2 promotes cell proliferation, angiogenesis, gene mutation, and reduces apoptosis, which results in colorectal tumorigenesis. Basic and clinical studies on the pathogenic mechanism of colorectal adenomas caused by *H. pylori* infection have concluded that there may be the following five main pathogenic mechanisms: 1. *H. pylori* infection increases the secretion of gastrin. 2. *H. pylori* infection elevates COX-2 level; 3. Role of *H. pylori* virulence factors; 4. The inflammatory reaction of the stomach or colorectum due to *H. pylori* infection; 5. *H. pylori* infection leads to alteration of the intestinal flora.

However, some other studies have reached different conclusions influenced by the size of the sample size, the method of detecting *H. pylori* infection, the proficiency of the endoscopic operator, and the clinical experience of the pathologist. Whether colorectal cancer is associated with *H. pylori* infection, has not yet been clarified. For this reason, the present study systematically evaluated clinical studies on the association of *H. pylori* infection with colorectal neoplasia and to provide a theoretical basis for the prevention and treatment of colorectal tumors.

MATERIALS AND METHODS
Search strategy

We searched PubMed, Embase, and Scopus databases for randomized controlled trials, clinical trials, and cohort studies published between May 2000 and May 2023, indexing terms related to *H. pylori* and colorectal cancer. The main

MesH used in the search was as follows: "*Helicobacter pylori*" AND "colorectal cancer", with no restrictions on the language of publication. The search strategy used in PubMed was as follows: ("*helicobacter pylori*") AND ("colorectal hyperplastic polyps" OR "colorectal adenomas "OR "colorectal cancer" OR "colorectal polyps").

Literature inclusion and exclusion criteria

Literature screening: inclusion criteria: 1) Literature included in databases such as PubMed, Scopus, and Embase from the time of library construction to May 2023; 2) Literature involving the correlation between *H. pylori* infection and colorectal cancer, as well as studies with sufficient data to extract raw data such as OR values and 95% CI values; 3) *H. pylori* infection was judged by at least one diagnostic method; 4) Colorectal cancer must have a clear pathological diagnosis; 5) The type of study was case-control, cross-sectional, or cohort study; 6) All studies were limited to human subjects.

Exclusion criteria: 1) Abstracts or incomplete and unusable data; 2) Full text was not available by all means; 3) Repeated publications, conference papers, and poor-quality literature; 4) Literature with obvious flaws and too much bias in the study.

Literature screening and information extraction

All relevant literature initially retrieved was extracted and organized according to the above inclusion and exclusion criteria. Researchers who had received training in evidence-based methods independently screened the literature, extracted the information and cross-checked it according to the inclusion and exclusion criteria, and in case of disagreement, an agreement was reached through discussion or adjudication was assisted with another researcher. This included the evaluation of the severity of the patient's condition at the time of admission, diagnostic criteria, *H. pylori* testing modalities, the number of the case group (number of colorectal polyps), the number of the control group (number of healthy controls), and the prevalence of *H. pylori* infection. The process was repeated as detailed above to screen out all the literature, and finally, only those literatures were included in the study that met the above-mentioned inclusion criteria.

Literature quality evaluation

The quality evaluation of randomized controlled trials was conducted using the risk of bias assessment tool recommended by the Cochrane Evaluation Manual 5.1.0.[12] The evaluation included the generation of randomized sequences, allocation scheme concealment, blinding of study subjects and interveners, blinding of evaluators, completeness of outcome data, selective reporting of results and other bias entries. For each entry, the investigator made a judgment of "low risk of bias" and "high risk of bias unclear". If the study fully met the above criteria, the likelihood of all types of bias was low and the quality grade was A. If it partially met the

criteria, the likelihood of bias was moderate and the quality grade was B. If it did not meet the criteria at all, the likelihood of bias was high and the quality grade was C.

Statistical analysis

Meta-analysis was performed using RevMan 5.2 software. Heterogeneity of the literature included in the study was evaluated by the I^2 statistic and Chi^2, if $P < .10$ or $I^2 > 50\%$, it indicated significant heterogeneity, in which case the random effects model was used for the combined analyses, otherwise the fixed effects model was used. The odds ratio (OR) and its 95% confidence interval (CI) were used as the effect indicators of the study for the count data. The possible sources of heterogeneity, such as *H pylori* detection methods, polyp pathologic types, and population regional differences were analyzed by subgroup. To ensure the stability of the results, sensitivity analyses were performed by excluding individual studies for re-analysis, and in addition, the degree of publication bias was assessed by looking at the funnel plots.

RESULTS

### Results of literature search

1134 literatures were obtained by preliminary search, and 3 related literatures were supplemented by other means. A total of 220 references were obtained by EndNote X9. After reading the title, abstract and full text, 205 references that did not meet the inclusion criteria were excluded, and 15 references were finally included. The selection process and research overview of the included references are shown in Figure 1 and Table 1.[13-27] The risk of bias of the included studies was assessed by the assessment form recommended by the Cochrane Evaluator's Handbook, and all included studies were of high quality, with low risk of bias for implementation bias, measurement bias, and follow-up bias (Figure 2).

Meta-analysis results

Analysis of the correlation between *H. pylori* detection methods and the development of colorectal adenoma. Analysis reveals that *H. pylori* infection increases the risk of colorectal adenomas by 1.80-fold, and *H. pylori* infection is significantly correlated with colorectal adenomas [OR=1.80, 95%CI:(1.31, 2.47), $P < .01$, I^2=95%], as shown in Figure 3.

Analysis of correlation between *H. pylori* detection methods and colorectal adenoma. In order to exclude the effect of different methods for detection of *H. pylori* on the relevance of colorectal morbidity, we performed subgroup analyses according to the *H. pylori* detection method, and a total of 8 studies were included in the *H. pylori* serological detection subgroup analysis with I^2=88%, suggesting poor homogeneity among studies, so the random effects model was used for combined effects analysis; a total of 5 studies were included in the *H. pylori* non-serological testing subgroup, with I^2=87%, suggesting poor homogeneity among studies, so a random-effects model was used for the combined-effects analysis.

Figure 1. Flowchart of Literature Screening
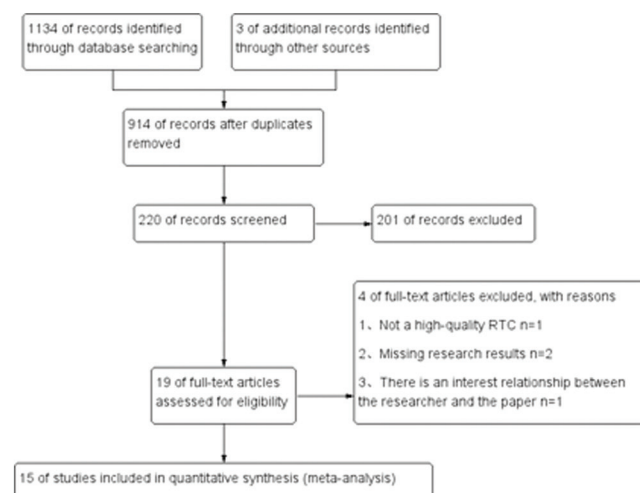
**Table 1.** Basic Characteristics of the Included Literature (n = 15)

| Authors	Test type	Publication time	Detection method	District	Tumor or polyp
Zhuang[13]	Cross section	2022	UBT, histological examination	China	Tumors
Wernly[14]	Cross section	2023	Histology	Austria	Tumors
Shen[15]	Cross section	2023	UBT	China	Tumors
Selgarad[16]	Cross section	2014	IgG	Germany	Tumor/polyp
Brim[17]	Cross section	2014	IgG	America	Tumor/polyp
Nam[18]	Cross section	2013	IgG	Korea	Tumor/polyp
Kountouras[19]	Case control	2013	IgG	Greece	Tumors
Hong[20]	Case control	2012	IgG	Korea	Tumor/polyp
Abbass[21]	Cross section	2011	Histology	America	Tumor/polyp
Meucci[22]	Case control	1997	IgG	Italy	Polyps
Robertson[23]	Cohort study	2009	IgG	America	Polyps
Bae[24]	Cross section	2009	Histological examination	Korea	Polyps
Sonnenberg[25]	Case control	2013	Histological examination	America	Tumor/polyp
Tongtawee[26]	Cross section	2016	Histological examination	Thailand	Tumor/polyp
Georgopoulos[27]	Case control	2006	IgG	Greece	Tumors

Figure 2. Risk of Bias Summary Chart
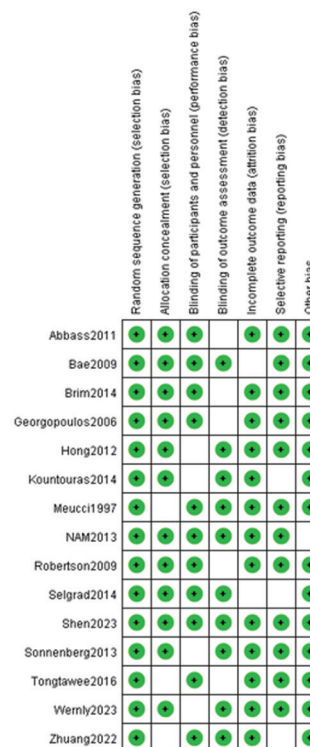
Figure 3. Sensitivity Analysis Regarding the Correlation Between *H. pylori* Infection and Colorectal Adenomas
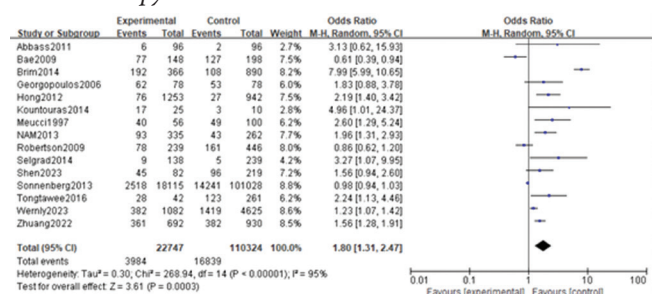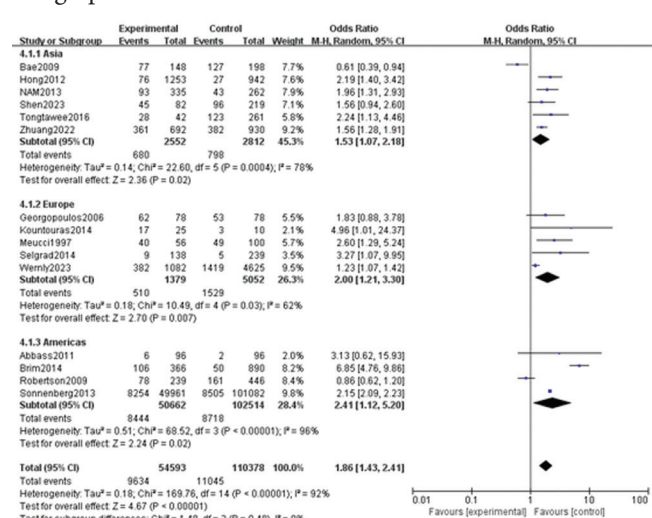

Figure 4. Correlation Analysis Between Different *H. pylori* Detection Methods and Colorectal Adenomas
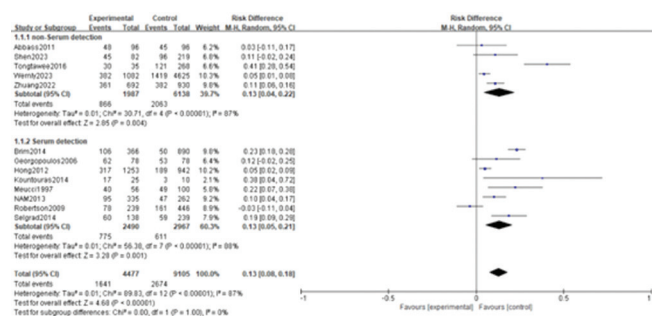
Figure 5. Funnel Plot of Correlation Analysis Between Different *H. pylori* Detection Methods and Colorectal Adenomas
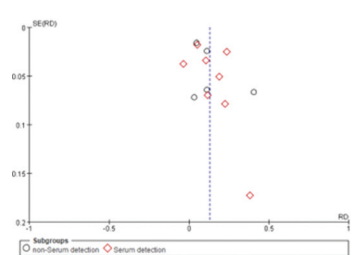
Figure 6. Analysis of the Correlation Between *H. pylori* Infection and Colorectal Adenoma Incidence in Different Geographical Areas

The results showed that both serological detection subgroups or non-serological detection subgroups indicated that *H. pylori* infection is associated with the development of colorectal adenomas, and the differences were statistically significant; serological detection subgroup: [OR=0.13, 95%CI:(0.05, 0.21), $P < .01$, I^2=88%] and non-serological detection subgroup: [OR=0.13, 95%CI:(0.04, 0.22), $P < .01$, I^2=95%], as shown in Figure 4. According to the subgroup meta-analysis of *H. pylori* detection methods, the serological funnel plot showed that the scatter plot of effect size is symmetrically distributed on both sides of the funnel plot, suggesting that there is no significant publication bias. The scatter plot of non-serological effect size is mainly concentrated on the left side of the figure, indicating that there may be publication bias in the selected literature (Figure 5).

Analysis of the correlation between *H. pylori* infection and colorectal adenomas in different geographical populations

In order to exclude the influence of population geographic differences on the results, we performed subgroup analyses of the 15 included papers based on the differences in their geographic population. In the analysis of each subgroup from America, Asia, and Europe, there was heterogeneity in America (I^2=96%), Asia (I^2=78%), and Europe (I^2=62%), so a random-effects model was used. Combined analyses were performed according to the geographic regions, and the results suggested that *H. pylori* infection is associated with the development of colorectal adenomas in populations of different geographic regions, with statistically significant differences ($P < .01$); America: [OR=1.86, 95%CI:(1.43, 2.41), $P < .01$, I^2=88%], Asia: [OR=1.53, 95%CI: (1.07, 2.18), $P = .02$], and Europe: [OR=2.00, 95%CI:(1.21, 3.30), $P < .01$], (as shown in Figure 6). Meta-analysis was performed according to the geographical location of the population, and the distribution of the scatter plots of effect sizes in the funnel plots of the American and Asian subgroups is symmetrical, with no obvious publication bias; the scatter plots of the effect sizes of the studies in the funnel plots of the European subgroups are concentrated to the right, with a certain publication bias (Figure 7).

Analysis of the correlation between *H. pylori* infection and the development of polyps of different pathological types

Based on Morson's histological classification, polyps were analyzed in subgroups according to swelling and non-neoplastic polyps. A total of six studies were included in the subgroup analysis of *H. pylori* infection and non-neoplastic polyps, with I^2=95%, suggesting poor homogeneity among studies, so the analysis was performed using a random-effects model. The results showed that there is no statistically significant difference in the rate of *H. pylori* infection in the non-neoplastic polyp group compared with that in the healthy control group [OR=1.47, 95%CI:0.98-2.22, $P = .06$], suggesting that *H. pylori* infection is possibly not associated with the pathogenesis of colorectal non-neoplastic polyps, whereas a total of 11 studies

Figure 7. Funnel Plot of the Analysis of the Correlation Between *H. pylori* Infection and Colorectal Adenoma Occurrence in Different Geographical Regions
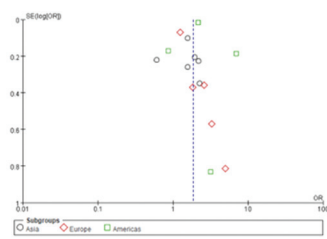

were included in the analysis of the subgroup of colorectal tumorous polyps, with an I^2=94%, suggesting relatively poor homogeneity among studies, so a random-effects model was used to perform a combined-effects analysis. The analysis showed that the occurrence of colon cancer in patients with *H. pylori* infection is 2.33 times higher than that in individuals without *H. pylori* infection [95%CI:1.69-3.22, P < .01] (Figure 8). According to the Meta-analysis of colorectal polyp pathological subgroups, the funnel plot of the tumor subgroup showed that the scatter plots of the effect sizes of the studies are distributed on the right side of the funnel, and the scatter plots of the effect sizes of the studies in the polyp subgroup are distributed on the left side of the funnel, suggesting that there is a certain publication bias (shown in Figure 9).

DISCUSSION

In recent years, with in-depth research on *H. pylori*, the microorganism has been found to be closely related to extra-gastric diseases, among which the relationship between *H. pylori* and CRC has received significant attention. Current research has found that *H. pylori* infection can lead to increased secretion of gastrin and an elevated expression level of COX-2, which induces gastric or colorectal inflammatory response and can change the structure of intestinal flora. In recent years, studies have found a correlation between *H. pylori* infection and colorectal adenoma, and that *H. pylori* infection is associated with the size of colorectal adenomas and can alter the structure of the intestinal flora.[28] Researchers have also explored the risk factors of colorectal adenoma and pointed out that *H. pylori* infection is an independent risk factor for CRC. With 50% of the global population infected with *H. pylori*, its high prevalence has become a global problem, and there are currently wide variations in the prevalence of infection across the world. *H. pylori* has been proven to be a causative factor for gastric diseases such as chronic gastritis, peptic ulcer, gastric cancer, gastric MALT lymphoma, and other intragastric diseases. Banerjee et al.[29] have found the presence of *H. pylori* in rectal adenocarcinoma tissues by immunohistochemistry, suggesting that *H. pylori* infection is not only a risk factor for the development of gastric diseases but also has the potential to play an important role in the occurrence and development of intestinal diseases. The results of a large-sample case-control study from abroad also showed that *H. pylori* infection was correlated with colorectal adenoma.[30] However, there are also some reports suggesting

Figure 8. Analysis of the Correlation Between *H. pylori* Infection and the Development of Colorectal Polyps of Different Pathological Types
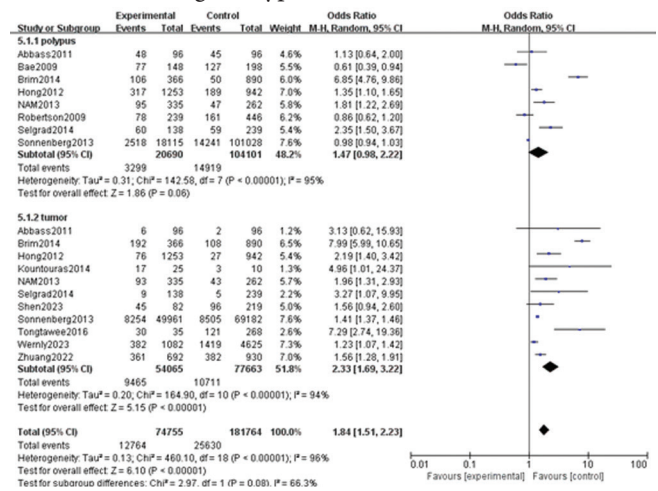
Figure 9. Funnel Plot of the Analysis of the Correlation Between *H. pylori* Infection and the Development of Colorectal Polyps of Different Pathological Types
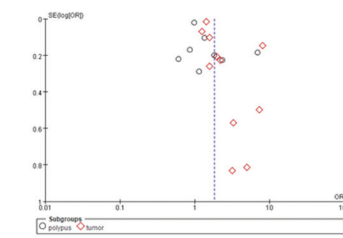
that *H. pylori* infection is not associated with colorectal adenomas. Colorectal Cancer (CRC) is a common tumor of the digestive tract. Its incidence and mortality are increasing year by year, which seriously aggravates the medical burden. The onset of colorectal cancer is affected by multiple factors such as genetics and environment. Its insidious onset and non-specific early manifestations bring about certain clinical challenges such as early diagnosis and treatment. Therefore, it is particularly important to accelerate the research on the etiology and pathogenesis of colorectal cancer, and actively carry out early prevention, effective screening, and targeted therapy of the disease on this basis. In this paper, we have analyzed the possible pathogenic mechanisms of *H. pylori* infection and colorectal adenoma.

A total of 15 papers were included in this study, with 22747 cases in the case group and 110324 controls, for a total of 133,071 cases, and the final results showed that *H. pylori* infection is significantly associated with colorectal adenomas [OR=1.80, 95%CI:(1.31, 2.47), P < .01, I^2=95%].

In this study, we performed subgroup analyses of three possible sources of heterogeneity, namely, *H. pylori* testing methods, different geographical populations, and whether multifactorial analyses were used for polyp pathology types.

The results showed that *H. pylori* infection is correlated with colorectal neoplastic polyp development when analyzed for subgroups of polyp pathology types, suggesting that

H. pylori infection is a risk factor for colorectal neoplasia, whereas no significant correlation is found between *H. pylori* infection and the development of non-neoplastic polyps.

Subgroup analysis for different geographical populations revealed that *H. pylori* infection is correlated with colorectal neoplasia in Europe, Asia, and America, suggesting that differences in geographic settings have less impact on the association between *H. pylori* infection and rectal tumorigenesis. This result is contrary to previous findings, which have mostly analyzed subgroups of Eastern and Western countries. The World Gastroenterology Organisation's global guidelines for *H. pylori* infection in developing countries state that the prevalence of *H. pylori* infection varies considerably according to geographic location, ethnicity, age, and socioeconomic status, being higher in developing countries and lower in developed countries.[31]

The classification of *H. pylori* testing methods into serological and non-serological antibody tests is based on the fact that serological antibody tests are based on current or previous infection, whereas non-serological antibody tests are based on current infection only; the former avoids false-negative results due to partial gastric mucosal atrophy and reduces the incorrect subgrouping of patients with eradicated *H. pylori* infection who were not treated for colorectal adenoma. The subgroup analysis can determine whether the method of *H. pylori* testing has an impact on the results.[32] When analyzed for subgroups of different *H. pylori* testing methods, it was found that the combined effect of both serological and non-serological tests suggested a correlation between *H. pylori* infection and colorectal polyp development. In the pooled analysis of serological tests, the correlation between *H. pylori* infection and colorectal polyp development is higher than that of non-serological tests. Considering that *H. pylori* serological testing reflects the status of the infection over a period of time, and that *H. pylori* antibodies can still be detected in serum several months after some *H. pylori* eradication, the influence of the testing method on the results cannot be excluded.

In this study, the quality of the literature was strictly screened, but there were limitations. This meta-analysis searched only English and published literature, which has some limitations in terms of literature type, but overcame the small sample size and regional limitations. The results of this study indicate that *H. pylori* infection is associated with colorectal neoplasia, especially with the development of colorectal neoplastic polyps, and the correlation is not affected by *H. pylori* detection methods and geographical differences in the population. Based on the results of the current study, it is suggested that *H. pylori* infection may be a risk factor for the development of colorectal polyps, which is of some significance for the prevention and treatment of colorectal polyps and CRC but the specific pathogenesis mechanism has not yet been demonstrated using large-scale, multi-center clinical studies.

ETHICAL COMPLIANCE
Not applicable.

AUTHOR DISCLOSURE STATEMENT
The authors have no potential conflicts of interest to report relevant to this article.

REFERENCE
1. Ralser A, Dietl A, Jarosch S, et al. *Helicobacter pylori* promotes colorectal carcinogenesis by deregulating intestinal immunity and inducing a mucus-degrading microbiota signature. *Gut*. 2023;72(7):1258-1270. doi:10.1136/gutjnl-2022-328075
2. Sun L, Zhang X, Gong P, Zhang L, Zhao Y; Clinical Efficacy of Bevacizumab Plus XELOX Chemotherapy in Colorectal Cancer and Application Value of Mindfulness-Based Stress Reduction Intervention. Clinical Efficacy of Bevacizumab Plus XELOX Chemotherapy in Colorectal Cancer and Application Value of Mindfulness-Based Stress Reduction Intervention. *Altern Ther Health Med*. 2022;28(6):65-71.
3. Peng C, Ouyang Y, Lu N, Li N. The NF-κB Signaling Pathway, the Microbiota, and Gastrointestinal Tumorigenesis: recent Advances. *Front Immunol*. 2020;11:1387. doi:10.3389/fimmu.2020.01387
4. Pannala R, Krishnan K, Melson J, et al. Artificial intelligence in gastrointestinal endoscopy. *VideoGIE*. 2020;5(12):598-613. doi:10.1016/j.vgie.2020.08.013
5. Dalal N, Jalandra R, Bayal N, et al. Gut microbiota-derived metabolites in CRC progression and causation. *J Cancer Res Clin Oncol*. 2021;147(11):3141-3155. doi:10.1007/s00432-021-03729-w
6. Guo CG, Zhang F, Jiang F, et al. Long-term effect of *Helicobacter pylori* eradication on colorectal cancer incidences. *Therap Adv Gastroenterol*. 2023;16:17562848231170943. doi:10.1177/17562848231170943
7. Michalkova R, Kello M, Cizmarikova M, Bardelcikova A, Mirossay L, Mojzis J. Chalcones and Gastrointestinal Cancers: experimental Evidence. *Int J Mol Sci*. 2023;24(6):5964. doi:10.3390/ijms24065964
8. Xu Y, Yang J. The effect of 5A nursing combined with psychological nursing on the immune function, cancer-related fatigue and complications of patients undergoing radical resection of colorectal cancer. *Cell Mol Biol (Noisy-le-grand)*. 2022;68(1):169-176. doi:10.14715/cmb/2022.68.1.21
9. Wang M, Kong WJ, Zhang JZ, et al. Association of *Helicobacter pylori* infection with colorectal polyps and malignancy in China. *World J Gastrointest Oncol*. 2020;12(5):582-591. doi:10.4251/wjgo.v12.i5.582
10. Lam SY, Yu J, Wong SH, Peppelenbosch MP, Fuhler GM. The gastrointestinal microbiota and its role in oncogenesis. *Best Pract Res Clin Gastroenterol*. 2017;31(6):607-618. doi:10.1016/j.bpg.2017.09.010
11. Shmuely H, Melzer E, Braverman M, Domniz N, Yahav J. *Helicobacter pylori* infection is associated with advanced colorectal neoplasia. *Scand J Gastroenterol*. 2014;49(1):35-42. doi:10.3109/00365521.2013.848468
12. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(oct18 2):d5928. doi:10.1136/bmj.d5928
13. Zhuang Z, Yu B, Xie M, Zhang Y, Lv B. Association of Helicobacter pylori enrichment in colorectal adenoma tissue on clinical and pathological features of adenoma. *Clin Res Hepatol Gastroenterol*. 2022;46(6):101961. doi:10.1016/j.clinre.2022.101961
14. Wernly S, Semmler G, Flamm M, et al. The Association between *Helicobacter pylori* and Colorectal Neoplasia. *Med Princ Pract*. 2023;32(1):77-85. doi:10.1159/000528794
15. Shen L, Bian R, Wang W, Zhao J. Association of *Helicobacter pylori* infection with colorectal adenoma in the Chinese urban population: A cross-sectional study. *Microb Pathog*. 2021;158:105111. doi:10.1016/j.micpath.2021.105111
16. Selgrad M, Bornschein J, Kandulski A, et al. *Helicobacter pylori* but not gastrin is associated with the development of colonic neoplasms. *Int J Cancer*. 2014;135(5):1127-1131. doi:10.1002/ijc.28758
17. Brim H, Zahaf M, Laiyemo AO, et al. Gastric *Helicobacter pylori* infection associates with an increased risk of colorectal polyps in African Americans. *BMC Cancer*. 2014;14(1):296. doi:10.1186/1471-2407-14-296
18. Nam KW, Baeg MK, Kwon JH, Cho SH, Na SJ, Choi MG. Helicobacter pylori seropositivity is positively associated with colorectal neoplasms. *Korean J Gastroenterol*. 2013;61(5):259-264. doi:10.4166/kjg.2013.61.5.259
19. Kountouras J, Polyzos SA, Zavos C, et al. *Helicobacter pylori* might contribute to nonalcoholic fatty liver disease-related cardiovascular events by releasing prothrombotic and proinflammatory factors. *Hepatology*. 2014;60(4):1450-1451. doi:10.1002/hep.27168
20. Hong SN, Lee SM, Kim JH, et al. *Helicobacter pylori* infection increases the risk of colorectal adenomas: cross-sectional study and meta-analysis. *Dig Dis Sci*. 2012;57(8):2184-2194. doi:10.1007/s10620-012-2245-x
21. Abbass K, Gul W, Beck G, Markert R, Akram S. Association of Helicobacter pylori infection with the development of colorectal polyps and colorectal carcinoma. *South Med J*. 2011;104(7):473-476. doi:10.1097/SMJ.0b013e31821e9009
22. Meucci G, Tatarella M, Vecchi M, et al. High prevalence of Helicobacter pylori infection in patients with colonic adenomas and carcinomas. *J Clin Gastroenterol*. 1997;25(4):605-607. doi:10.1097/00004836-199712000-00011
23. Robertson DJ, Sandler RS, Ahnen DJ, et al. Gastrin, *Helicobacter pylori*, and colorectal adenomas. *Clin Gastroenterol Hepatol*. 2009;7(2):163-167. doi:10.1016/j.cgh.2008.09.006
24. McJunkin B, Sissoko M, Levien J, Upchurch J, Ahmed A. Dramatic decline in prevalence of *Helicobacter pylori* and peptic ulcer disease in an endoscopy-referral population. *Am J Med*. 2011;124(3):260-264. doi:10.1016/j.amjmed.2010.11.013
25. Sonnenberg A, Genta RM. *Helicobacter pylori* is a risk factor for colonic neoplasms. *Am J Gastroenterol*. 2013;108(2):208-215. doi:10.1038/ajg.2012.407
26. Tongtawee T, Kaewpitoon S, Kaewpitoon N, et al. Helicobacter Pylori Associated Gastritis Increases Risk of Colorectal Polyps: a Hospital Based-Cross-Sectional Study in Nakhon Ratchasima Province, Northeastern Thailand. *Asian Pac J Cancer Prev*. 2016;17(1):341-345. doi:10.7314/APJCP.2016.17.1.341
27. Georgopoulos SD, Polymeros D, Triantafyllou K, et al. Hypergastrinemia is associated with increased risk of distal colon adenomas. *Digestion*. 2006;74(1):42-46. doi:10.1159/000096593
28. Fernández de Larrea-Baz N, Michel A, Romero B, et al. *Helicobacter pylori* Antibody Reactivities and Colorectal Cancer Risk in a Case-control Study in Spain. *Front Microbiol*. 2017;8:888. doi:10.3389/fmicb.2017.00888
29. Banerjee AK, Celentano V, Khan J, Longcroft-Wheaton G, Quine A, Bhandari P. Practical gastrointestinal investigation of iron deficiency anaemia. *Expert Rev Gastroenterol Hepatol*. 2018;12(3):249-256. doi:10.1080/17474124.2018.1404905
30. Jantaree P, Chaithongyot S, Sokolova O, Naumann M. USP48 and A20 synergistically promote cell survival in *Helicobacter pylori* infection. *Cell Mol Life Sci*. 2022;79(8):461. doi:10.1007/s00018-022-04489-7
31. Nieuwenburg SAV, Mommersteeg MC, Wolters LMM, et al. Accuracy of *H. pylori* fecal antigen test using fecal immunochemical test (FIT). *Gastric Cancer*. 2022;25(2):375-381. doi:10.1007/s10120-021-01264-8
32. Choi E, Murray B, Choi S. Biofilm and Cancer: Interactions and Future Directions for Cancer Therapy. *Int J Mol Sci*. 2023;24(16):12836. doi:10.3390/ijms241612836