Risk for Colorectal Neoplasia in Patients With *Helicobacter pylori* Infection: A Systematic Review and Meta-analysis

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OBJECTIVES: **_Helicobacter pylori_ may reportedly be associated with extragastric malignancy beyond gastric cancer. The present study aimed to evaluate the association between _H. pylori_ infection and colorectal neoplasia through a systematic review and meta-analysis.**

METHODS: **The literature search aimed to retrieve all relevant studies published up to September 2019 that examined the risk for colorectal neoplasia including colorectal adenoma, advanced adenoma, and cancer in patients with _H. pylori_ infection. Meta-analysis was performed to calculate pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs). If publication bias was observed, the pooled OR was adjusted using the trim-and-fill method.**

RESULTS: **Forty-eight studies including 171,045 patients were evaluated, of which 24, 8, and 31 reported _H. pylori_-associated risk for adenoma, advanced adenoma, and cancer, respectively. _H. pylori_ infection was associated with a significantly higher risk for colorectal adenoma (pooled OR 1.49 [95% CI 1.37–1.62]). _H. pylori_ infection was also associated with a higher risk for advanced colorectal adenoma (pooled OR 1.50 [95% CI 1.28–1.75]). The risk for colorectal cancer in patients with _H. pylori_ infection was also identified (pooled OR 1.44 [95% 1.26–1.65]). Although publication bias was identified in the analysis for colorectal adenoma, the pooled estimate was not significantly changed after adjustment (pooled OR 1.39 [95% CI 1.27–1.52]).**

DISCUSSION: **Although this meta-analysis based on the observational studies could not show causality, it demonstrated that colorectal adenoma, advanced adenoma, and cancer were all associated with _H. pylori_ infection.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A188, http://links.lww.com/CTG/A182, http://links.lww.com/CTG/A183, http://links.lww.com/CTG/A184, http://links.lww.com/CTG/A185, http://links.lww.com/CTG/A186, http://links.lww.com/CTG/A187

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INTRODUCTION

Approximately one-half of the world's population is infected with *Helicobacter pylori, which* can be colonized in the stomach through the production of urease (1). *H. pylori* infection is a well-known risk factor for various gastrointestinal diseases including peptic ulcer and gastric cancer (2). In addition, *H. pylori* infection is associated with extragastric diseases including immune thrombocytopenic purpura and iron deficiency anemia (3,4).

Interestingly, it has been suggested that *H. pylori* is also associated with extragastric carcinogenesis including colorectal neoplasia (5). One hypothesis that has been proposed is that *H. pylori* may facilitate carcinogenesis through hypergastrinemia caused by atrophic gastritis, followed by a decrease in acid secretion (6). The growth-promoting property of gastrin has been postulated to be associated with the development of several tumors including lung cancer and colorectal cancer (CRC). Although the causal relationship between hypergastrinemia and colorectal neoplasia has not yet been fully evaluated, the association between *H. pylori* infection and colorectal neoplasia has been reported in many recent studies (7–15). In particular, many studies have consistently reported an association between *H. pylori* infection and colorectal adenoma (11–14). However,

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there have been conflicting results regarding the association between *H. pylori* infection and CRC. Several studies have reported a significantly higher proportion of CRCs in patients with *H. pylori* infection than those without *H. pylori* infection (7,9), whereas others have not (8,10). Although new studies examining *H. pylori* infection and CRC continue to be published (16–18), definitive conclusions regarding associations between *H. pylori* infection and CRC remain elusive.

The insignificant impact of *H. pylori* infection on CRC reported in several studies may be because of a small number of patients with CRC, which may affect the precision of the effect size (8,10,13). In this situation, a meta-analysis is useful for summarizing the results derived from all relevant studies and provides more precise estimates. Although several meta-analyses investigating this issue have been conducted previously (5,19–21), an updated meta-analysis is needed because many new studies have been published in the interim (10–18,22–25). Here, we aimed to evaluate the association between *H. pylori* infection and colorectal adenoma, advanced adenoma, and cancer through a systematic review and meta-analysis. It may be helpful to comprehensively understand the risk for colorectal neoplasia in patients with *H. pylori* infection.

METHODS

Search strategy

All relevant studies published between January 1980 and September 2019 that examined the risk of colorectal neoplasia, including colorectal adenoma, advanced adenoma, and cancer, in patients with *H. pylori* infection were identified through a literature search using the MEDLINE, Embase, and Cochrane Library databases. The following search string was used: ([Helicobacter] OR [pylori] OR [Campylobacter]) AND ([colorectal] OR [colon] OR [colons] OR [colonic] OR [rectal] OR [rectum] OR [large bowel] OR [large bowels] OR [large intestine] OR [large intestines] OR [large intestinal]) AND ([neoplasm] OR [neoplasms] OR [neoplasia] OR [cancer] OR [cancers] OR [carcinoma] OR [carcinomas] OR [adenoma] OR [adenomas] OR [polyp] OR [polyps] OR [polypoid] OR [tumor] OR [tumors] OR [tumour] OR [tumours]). The following Medline Subject Headings and Embase subject headings were also used for the literature search: Helicobacter, Colorectal neoplasms (for Medline Subject Headings), and Colorectal tumor (for Embase subject headings). The detailed search strategies used in each database are shown in Appendix 1, http://links.lww.com/CTG/A188. In addition, the references of the screened articles were manually searched to identify additional relevant studies. The date of the most recent search update was September 17, 2019.

Study selection

In the first stage of study selection, duplicate articles retrieved using multiple search engines based on the title, abstract, and bibliographic data were discarded. Next, irrelevant articles were excluded by examining titles and abstracts. Finally, the articles were screened by full-text reviews according to the inclusion and exclusion criteria. The inclusion criteria were as follows: patients (individuals who underwent screening colonoscopy for colorectal neoplasia); intervention (*H. pylori* infection in the stomach); comparator (no *H. pylori* infection in the stomach); outcome (risk for colorectal neoplasia including colorectal adenoma, advanced adenoma, and cancer in patients with *H. pylori* infection); and study design (cross-sectional or case-control study). Investigations involving nonhumans, abstracts or unpublished studies, and those published in a language other than English were excluded. If the study population overlapped among studies, the largest study was selected. Two investigators (D.S.C. and C.H.P.) independently evaluated the studies for eligibility; any disagreements were resolved through discussion and consensus. If no agreement could be reached, a third investigator (S.I.S.) determined the eligibility.

The methodological quality of individual studies was evaluated by 2 investigators (D.S.C. and C.H.P.) using the Newcastle-Ottawa scale, whereby the observational studies were scored across 3 categories: selection (4 questions), comparability of the study groups (2 questions), and ascertainment of exposure or outcome (3 questions) (26). Questions regarding the comparability of the study groups were awarded a maximum of 2 points; all other questions were assigned a score of 1 point. Studies with a cumulative score ≥ 7 were considered to be high quality (27–29).

Data extraction and study endpoint

Using a data extraction form that was developed in advance, the 2 reviewers (D.S.C. and C.H.P.) independently extracted the following information: first author; year of publication; study design; country in which the study was conducted; study period; study population; testing for *H. pylori* infection; and risk for colorectal adenoma, advanced adenoma, and cancer with *H. pylori* infection. Advanced adenoma was defined by the presence of one of the following features in accordance with the current guideline (30): villous component, ≥10 mm in size, and high-grade dysplasia.

The primary endpoint of this meta-analysis was the overall risk for colorectal neoplasia including colorectal adenoma and cancer. The secondary endpoint was the risk for colorectal neoplasia according to the testing method used to diagnose *H. pylori* infection and study design.

Statistical analysis

A meta-analysis was performed to calculate pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A random-effects model was used in this meta-analysis. Study heterogeneity was assessed using 2 methods: Cochran Q test, which was considered to be statistically significant for heterogeneity if P was <0.1, and the I^2 statistic, with values $> 50\%$ suggestive of significant heterogeneity (31). Publication bias was assessed using the Egger regression test (32). Heterogeneity was also visually examined using funnel plots of the logarithmic ORs vs their SEs (33). If publication bias was observed, pooled ORs were adjusted using the Duval and Tweedie trim-and-fill method (34). All P-values were 2-tailed, and $P < 0.05$ was considered to be statistically significant in all tests (except for heterogeneity, and the Egger regression test). In addition, subgroup analyses were conducted according to the inclusion of immunoglobulin [Ig] G anti-*H. pylori* antibody as a test for *H. pylori* infection because IgG anti-*H. pylori* antibody represents past or current infection of *H. pylori*, whereas other tests such as rapid urease test, histologic examination, or culture identify only current *H. pylori* infection. Individual studies that used IgG anti-*H. pylori* antibody and other tests were classified into the IgG anti-*H. pylori* antibody subgroup, whereas those that used *H. pylori* tests other than IgG anti-*H. pylori* antibody were classified into other-than-IgG anti-*H. pylori* antibody subgroup. Subgroup analyses were further performed according to the study design (cross-sectional vs case-control) and population

(hospital-based vs community-based). Sensitivity analysis was also performed after excluding individual studies with a low-quality score or outlier.

Analysis and reporting were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (35). All statistical procedures were performed using Review Manager version 5.3.5 (Cochrane Collaboration, Copenhagen, Denmark), with the exception of publication bias analysis, which was performed using R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection and characteristics

A flow diagram of study selection is shown in Figure 1. A total of 920 studies were identified in the literature search. Among the 920 studies, 46 duplicates across the multiple search engines were discarded. An additional 801 irrelevant studies were excluded based on their titles and abstracts. After full-text review of these 73 studies, 25 were excluded for the following reasons: did not report relevant outcomes (n = 22), neither cross-sectional nor case-control study (n = 1), and unavailable full-text (n = 2).

Ultimately, 48 studies involving a total of 171,045 patients were included in the meta-analysis (6–18, 22–25, 36–66). The characteristics of the included studies are summarized in Table 1 . These studies were published between 1995 and 2019, and their enrollment periods ranged from 1964 to 2016 . Of the 44 studies, 18 were cross-sectional and the remaining 30 were case-control. Serological testing including IgG anti-*H. pylori* antibody was used in 31 studies to diagnose *H. pylori* infection. The urea breath test, rapid urease test, and histological examination were used in 8, 10, and 12 individual studies, respectively.

The Newcastle-Ottawa scale quality scores of the included studies are shown in Table 1, with scores ranging from 4 to 9. Of the 44 included studies, 33 (68.8%) were rated as high quality.

The risk for colorectal adenoma

The risk for colorectal adenoma in patients with *H. pylori* infection is shown in Figure 2. Overall, *H. pylori* infection was associated with a significantly higher risk for colorectal adenoma (pooled OR 1.49 [95% CI 1.37–1.62]; degrees of freedom [*df*] = 23; $P < 0.001$; $I^2 = 63\%$). In the subgroup analysis of studies that used IgG anti-*H. pylori* antibody to diagnose *H. pylori* infection, *H. pylori* infection was associated with an increased risk for colorectal adenoma (pooled OR 1.83 [95% CI 1.47–2.27]; $df = 11$; $P < 0.001$; $I^2 = 67\%$). *H. pylori* infection was also associated with a high risk for colorectal adenoma in a subgroup analysis of studies in which *H. pylori* testing, other than anti-*H. pylori* antibody, was used (pooled OR 1.40 [95% CI 1.28–1.54]; $df = 11$; $P = 0.002$; $I^2 = 62\%$). The risk for colorectal adenoma appeared to be higher in the IgG anti-*H. pylori* antibody subgroup than the other subgroup (test for subgroup difference, $df = 1$; $P = 0.03$; $I^2 = 79\%$).

The risk for advanced adenoma

The risk for advanced adenoma was reported in 8 included studies (12–14,51,55,60,63,64). As shown in Table 1, the studies used the definition of advanced adenoma similar to those proposed in the guideline (30). Figure 3 shows the risk for advanced adenoma in patients with *H. pylori* infection. The pooled OR for *H. pylori*

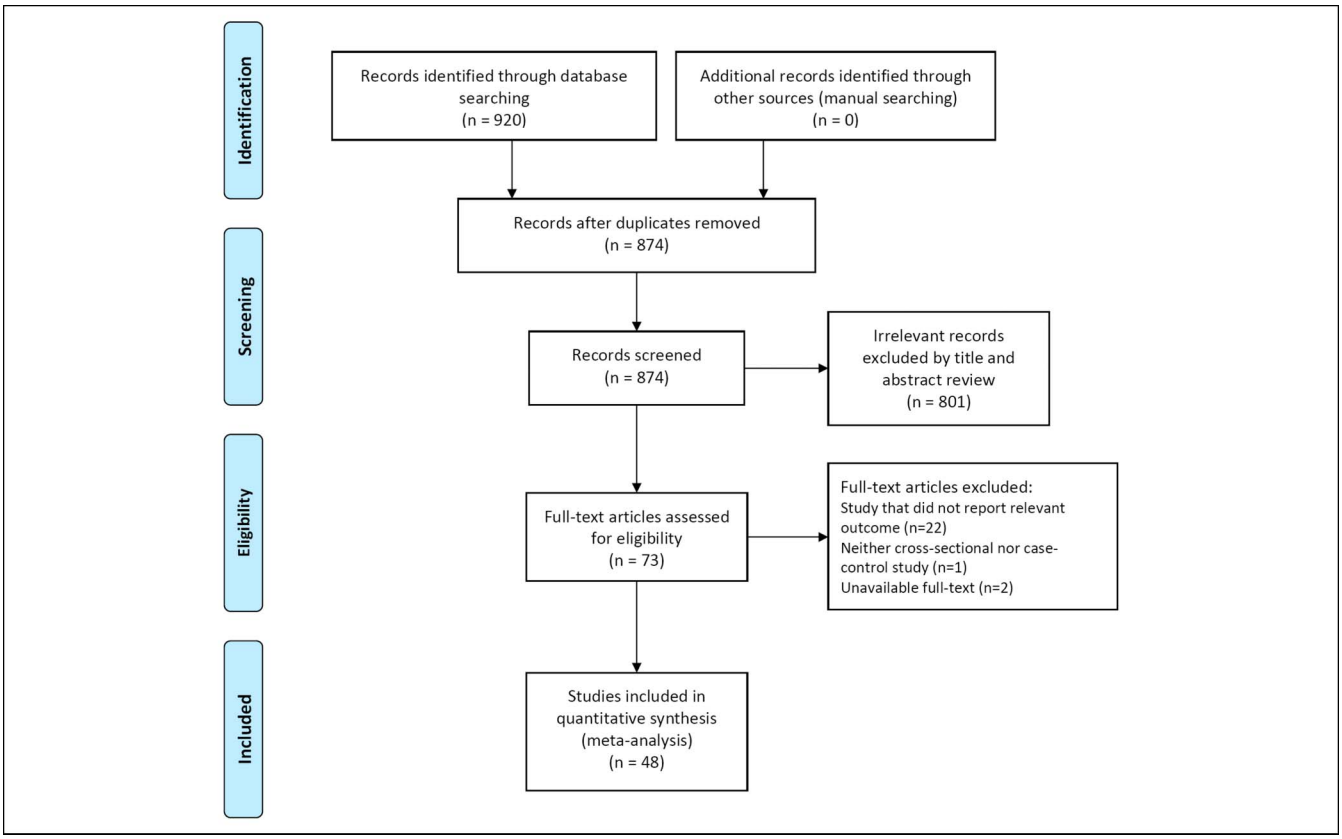

Figure 1. Flow diagram of studies included in the meta-analysis.

Table 1. Baseline characteristics of included studies

Publication yr	First author (reference)	Study design	Country	Study period	No. of participants	Study population	Testing for HP infection	Assessment timing of HP infection	Definition of advanced adenoma	NOS quality score
1995	Ciccotosto (6)	Case-control	Australia	N/A	79	Hospital-based	IgG anti-HP antibody	N/A		4
1997	Meucci (36)	Case-control	Italy	1993–1994	156	Hospital-based	IgG anti-HP antibody	N/A		6
1998	Thorburn (37)	Case-control	USA	1964–1991	466	Community-based	IgG anti-HP antibody	N/A		9
1999	Aydin (38)	Case-control	Turkey	1996–1997	267	Hospital-based	IgG anti-HP antibody	N/A		5
1999	Breuer-Katschinski (39)	Case-control	Germany	1993–1996	196	Hospital-based case community-based control	IgG anti-HP antibody	After the colonoscopy		8
2000	Fireman (40)	Case-control	Israel	1997	102	Hospital-based	RUT or IgG anti-HP antibody	After the colonoscopy		6
2001	Hartwich (41)	Case-control	Poland and Germany	N/A	240	Hospital-based	UBT or histologic examination	N/A		4
2001	Shmuely (42)	Case-control	Israel	1999–2000	112	Hospital-based	IgG anti-HP antibody	After the colonoscopy		8
2001	Siddheshwar (43)	Case-control	UK	1997–1999	368	Hospital-based	IgG anti-HP antibody	After the colonoscopy		6
2002	Konturek (44)	Case-control	Poland	N/A	150	Hospital-based	UBT or IgG anti-HP antibody	N/A		8
2002	Limburg (45)	Case-control	Finland	1985–1995	354	Community-based	IgG anti-HP antibody	N/A		8
2003	Bombski (46)	Case-control	Poland	1998–1999	70	Hospital-based	RUT or histologic examination	N/A		5
2003	Wang (47)	Case-control	China	N/A	387	Hospital-based	IgG anti-HP antibody	N/A		4
2005	Fujimori (48)	Cross-sectional	Japan	1996–2003	669	Hospital-based	UBT, RUT, or histological examination	N/A		8
2005	Mizuno (49)	Cross-sectional	Japan	N/A	307	Hospital-based	IgG anti-HP antibody	N/A		6
2006	Georgopoulos (50)	Case-control	Greece	2000–2001	156	Hospital-based	IgG anti-HP antibody	Before the colonoscopy		8
2006	Liou (51)	Cross-sectional	Taiwan	N/A	462	Hospital-based	UBT	N/A	Villous component (≥20%), >10 mm in size, or severe dysplasia	6
2007	D'Onghia (52)	Case-control	Italy	2004–2005	79	Hospital-based	IgG anti-HP antibody	After the colonoscopy		5
2007	Machida-Montani (53)	Case-control	Japan	1998–2002	339	Hospital-based	IgG anti-HP antibody	After the colonoscopy		8
2007	Zumkeller (54)	Case-control	Germany	2003–2004	851	Hospital-based case community-based control	IgG anti-HP antibody	After the colonoscopy		9

Table 1. (*continued*)

Publication yr	First author (reference)	Study design	Country	Study period	No. of participants	Study population	Testing for HP infection	Assessment timing of HP infection	Definition of advanced adenoma	NOS quality score
2009	Bae (55)	Case-control	Korea	2005–2008	346	Hospital-based	UBT, RUT, or histological examination	Before the colonoscopy	Villous component, >10 mm in size, or high-grade dysplasia	8
2009	Buso (56)	Case-control	Brazil	2005–2007	188	Hospital-based	IgG anti-HP antibody	After the colonoscopy		8
2009	Wu (57)	Case-control	Taiwan	2000–2007	635	Hospital-based	IgG anti-HP antibody	N/A		8
2010	Abbass (58)	Cross-sectional	USA	2008–2009	192	Hospital-based	RUT or histologic examination	N/A		6
2011	Inoue (59)	Case-control	Japan	1996–2004	478	Community-based (health checkup center)	IgG anti-HP antibody	With the colonoscopy		9
2012	Hong (60)	Cross-sectional	Korea	2010	2,195	Community-based (health checkup center)	UBT or histologic examination	Within 6 months from the colonoscopy	Villous component (≥25%), ≥10 mm in size, or high-grade dysplasia	9
2012	Strofilas (61)	Case-control	Greece	N/A	113	Hospital-based	IgG anti-HP antibody	N/A		6
2012	Zhang (7)	Case-control	Germany	2003–2007	3,381	Community-based	IgG anti-HP antibody	N/A		8
2013	Epplein (62)	Case-control	USA	2002–2009	558	Community-based	IgG anti-HP antibody	Before the colonoscopy		7
2013	Nam (63)	Cross-sectional	Korea	2004–2005	597	Community-based (health checkup center)	IgG anti-HP antibody	Within 6 months from the colonoscopy	Villous component, ≥10 mm in size, or high-grade dysplasia	9
2013	Sonnenberg (64)	Cross-sectional	USA	2008–2011	119,142	Community-based	Histologic examination	N/A	Villous component, ≥10 mm in size, or high-grade dysplasia	9
2014	Brim (65)	Cross-sectional	USA	2005–2009	1,256	Hospital-based	Histologic examination or IgG anti-HP antibody	N/A		8
2014	Patel (22)	Cross-sectional	USA	2009–2011	798	Hospital-based	Histologic examination	N/A		8
2014	Selgrad (8)	Cross-sectional	Germany	2008–2013	377	Hospital-based	IgG anti-HP antibody	Before the colonoscopy		8
2014	Shmuely (66)	Cross-sectional	Israel	2008–2010	273	Hospital-based	IgG anti-HP antibody	Same d as the colonoscopy		8
2015	Engin (9)	Case-control	Turkey	N/A	205	Hospital-based	IgG anti-HP antibody	N/A		6
2015	Zuniga (23)	Case-control	USA	2010–2012	943	Community-based (health checkup center)	RUT, stool antigen test, or culture	N/A		9

Table 1. (*continued*)

Publication yr	First author (reference)	Study design	Country	Study period	No. of participants	Study population	Testing for HP infection	Assessment timing of HP infection	Definition of advanced adenoma	NOS quality score
2016	Blase (16)	Case-control	USA	1998–2009	1,166	Community-based	Serology (seropositivity for at least 4 of the 15 HP proteins)	N/A		8
2016	Qing (10)	Case-control	China	2012–2015	120	Hospital-based	RUT or histologic examination	N/A		5
2016	Tongtawee (24)	Cross-sectional	Thailand	2014–2015	303	Hospital-based	RUT or histologic examination	N/A		7
2017	Fernández de Larrea-Baz (17)	Case-control	Spain	2008–2013	3,983	Hospital-based case community-based control	Serology (seropositivity for at least 4 of the 15 HP proteins)	N/A		8
2017	Hu (11)	Cross-sectional	Taiwan	2006–2015	2,475	Community-based (health checkup center)	RUT	Same d as the colonoscopy		9
2017	Kim (12)	Cross-sectional	Korea	2002–2010	8,916	Community-based (health checkup center)	IgG anti-HP antibody	N/A	Villous component, ≥10 mm in size, or high-grade dysplasia	9
2017	Nam (13)	Cross-sectional	Korea	2007–2009	4,466	Community-based (health checkup center)	RUT	N/A	Villous component, ≥10 mm in size, or high-grade dysplasia	9
2017	Yan (25)	Cross-sectional	China	2014–2016	1,641	Community-based (health checkup center)	UBT	Same d as the colonoscopy		9
2018	Kumar (14)	Cross-sectional	USA	2006–2016	8,963	Hospital-based	Histologic examination	N/A	Villous component (≥25%) or high-grade dysplasia	8
2018	Teimoorian (18)	Case-control	Iran	2015–2016	150	Hospital-based	IgG anti-HP antibody	After the colonoscopy		8
2019	ChangxiChen (15)	Cross-sectional	China	2013–2014	1,375	Community-based	UBT	N/A		8

HP, *Helicobacter pylori*; N/A, not available; NOS, Newcastle-Ottawa scale; RUT, rapid urease test; UBT, urea breath test.

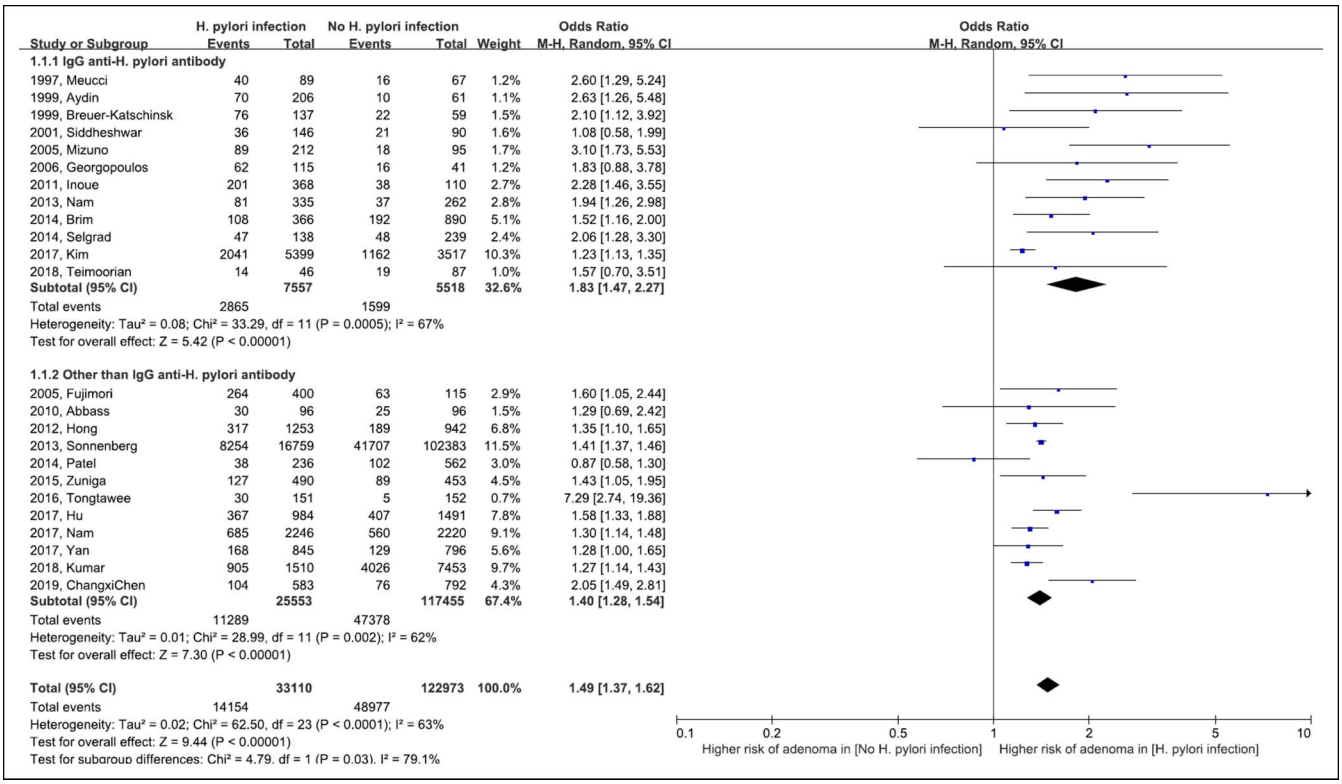

Figure 2. Forest plot of the risk for colorectal adenoma with *Helicobacter pylori* infection. CI, confidence interval; M-H, Mantel-Haenszel.

infection for advanced adenoma was similar to that for colorectal adenoma (pooled OR 1.50 [95% CI 1.28–1.75]; $df = 7$; $P = 0.05$; $I^2 = 49\%$). The pooled OR was 1.71 (95% CI 1.29–2.27) in the IgG anti-*H. pylori* antibody group and 1.45 (95% CI 1.19–1.77) in the other-than-IgG anti-*H. pylori* antibody group. The risk for advanced colorectal adenoma did not differ between the subgroups (test for subgroup difference, $df = 1$; $P = 0.35$; $I^2 = 0\%$).

The risk for colorectal cancer

Figure 4 shows the risk for CRC in patients with *H. pylori* infection. Although 21 of 31 included studies did not report statistically significant results, the results of meta-analysis revealed a significant association between *H. pylori* infection and CRC (pooled OR 1.44 [95% CI 1.13–2.52]; $df = 30$; $P < 0.001$; $I^2 = 58\%$). The results of subgroup analysis according to the *H. pylori* test method did not differ between the subgroups (IgG anti-*H. pylori*

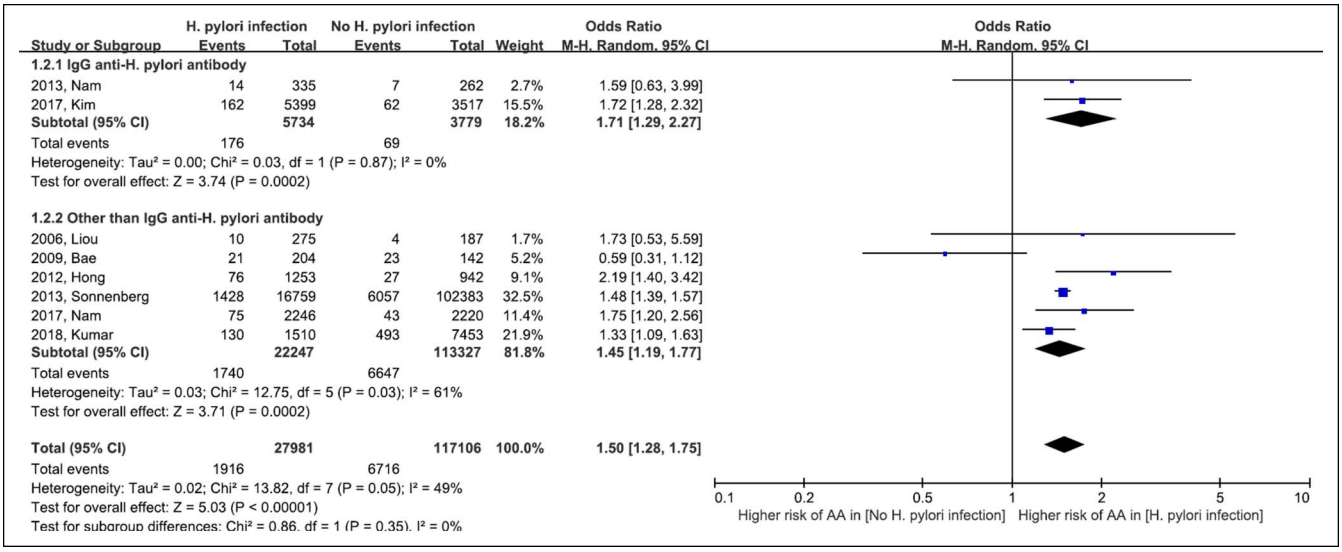

Figure 3. Forest plot of the risk for advanced colorectal adenoma *with Helicobacter pylori* infection. AA, advanced adenoma; CI, confidence interval; M-H, Mantel-Haenszel.

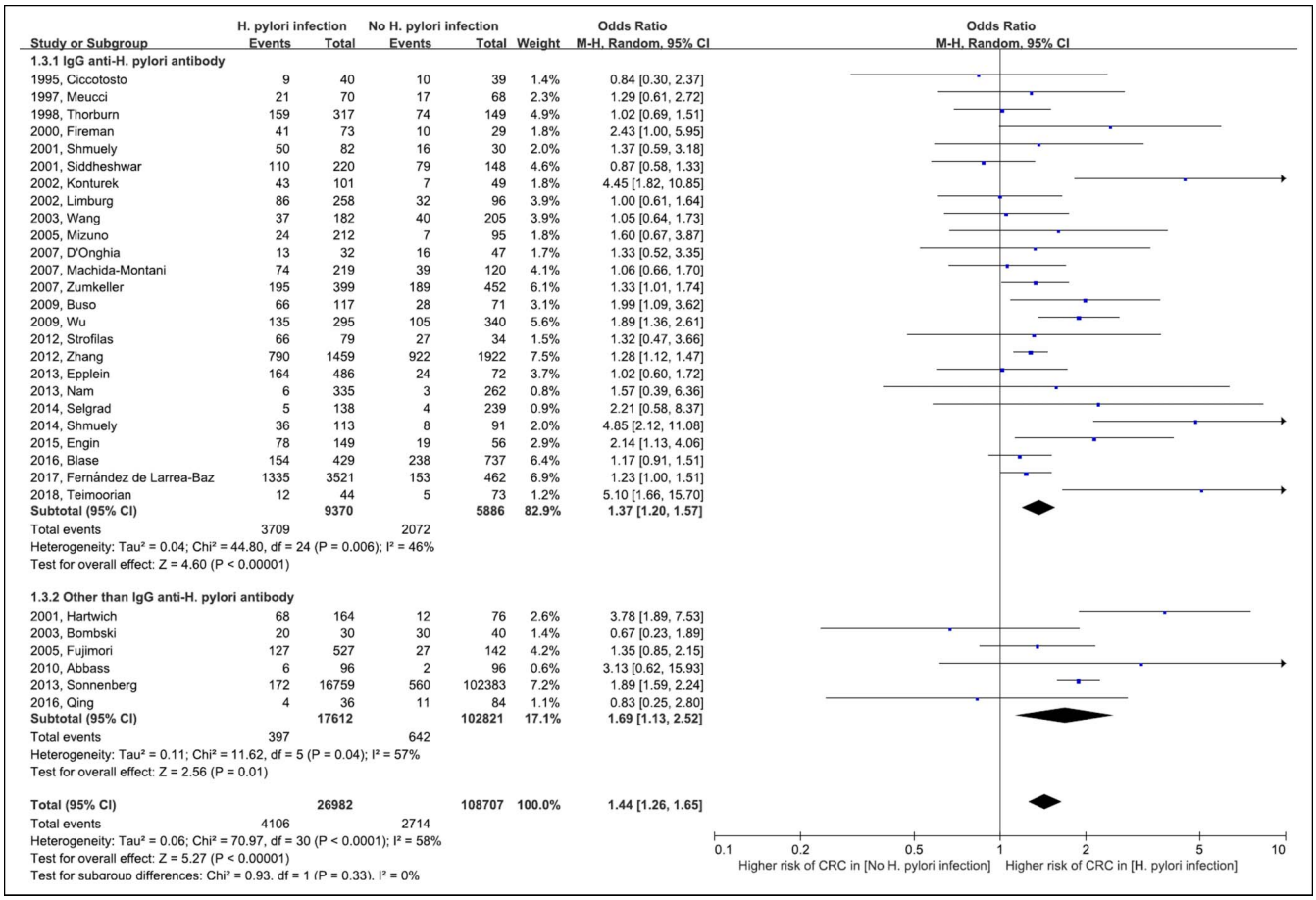

Figure 4. Forest plot of the risk for colorectal cancer with *Helicobacter pylori* infection. CRC, colorectal cancer; CI, confidence interval; M-H, Mantel-Haenszel.

antibody subgroup: pooled OR 1.37 [95% CI 1.20–1.57] vs other-than-IgG anti-*H. pylori* antibody subgroup: pooled OR 1.69 [95% CI 1.13–2.52]; test for subgroup difference: $df = 1$; $P = 0.93$; $I^2 = 0\%$).

Publication bias

Publication bias was assessed for risk for colorectal adenoma, advanced adenoma, and cancer (Figure 5). There was an asymmetry in the funnel plot for colorectal adenoma. Because significant publication bias was also identified in the Egger regression test for colorectal adenoma ($P = 0.046$), the Duval and Tweedie trim-and-fill method was applied to the sensitivity analysis. After this adjustment, the significance of the association between *H. pylori* infection and colorectal adenoma was maintained (pooled OR 1.39 [95% 1.27–1.52]). Meanwhile, publication bias was not identified for advanced adenoma and CRC ($P = 0.980$ and $P = 0.352$, respectively [Egger regression test]).

Subgroup analysis according to study design and population

Additional subgroup analyses according to the design of the included studies (i.e., cross-sectional and case-control) were performed (see Figure S1, Supplementary Digital Content 1, http://links.lww.com/CTG/A182, http://links.lww.com/CTG/A183, http://links.lww.com/CTG/A184). Overall, the results of subgroup analyses were similar to the original analysis. The pooled OR for *H. pylori* infection for colorectal adenoma was 1.44 (95% CI 1.32–1.57) in the cross-sectional studies and 1.78 (95% CI 1.43–2.20) in the case-control study.

Regarding advanced adenoma, the pooled OR was 1.49 (95% CI 1.41–1.58) in the cross-sectional studies. The pooled OR in the 1 case-control study was 0.59 (95% CI 0.31–1.12); however, it is important to note that there was only a single study included in this subgroup analysis. In addition, the pooled OR for *H. pylori* infection for CRC was 1.91 (95% CI 1.46–2.48) in the cross-sectional studies and 1.34 (95% CI 1.17–1.54) in the case-control studies.

In the subgroup analyses according to the study population (see Figure S2, Supplementary Digital Content 1, http://links.lww.com/CTG/A185, http://links.lww.com/CTG/A186, http://links.lww.com/CTG/A187), the pooled OR for *H. pylori* infection for colorectal adenoma was 1.71 (95% CI 1.38–2.11) in the hospital-based population and 1.43 (95% CI 1.37–1.62) in the community-based population. Regarding advanced adenoma, although the pooled OR tended to be lower in the hospital-based population (1.07 [95% CI 0.59–1.94]) than in the community-based population (1.55 [95% CI 1.40–1.71]), there was no significant difference. The pooled OR of *H. pylori* infection for CRC was 1.57 (95% CI 1.30–1.89) in the hospital-based population and 1.27 (95% CI 1.26–1.65) in the community-based population.

Sensitivity analysis

Sensitivity analyses excluding the 15 low-quality studies were performed to assess the robustness of the meta-analyses. Overall,

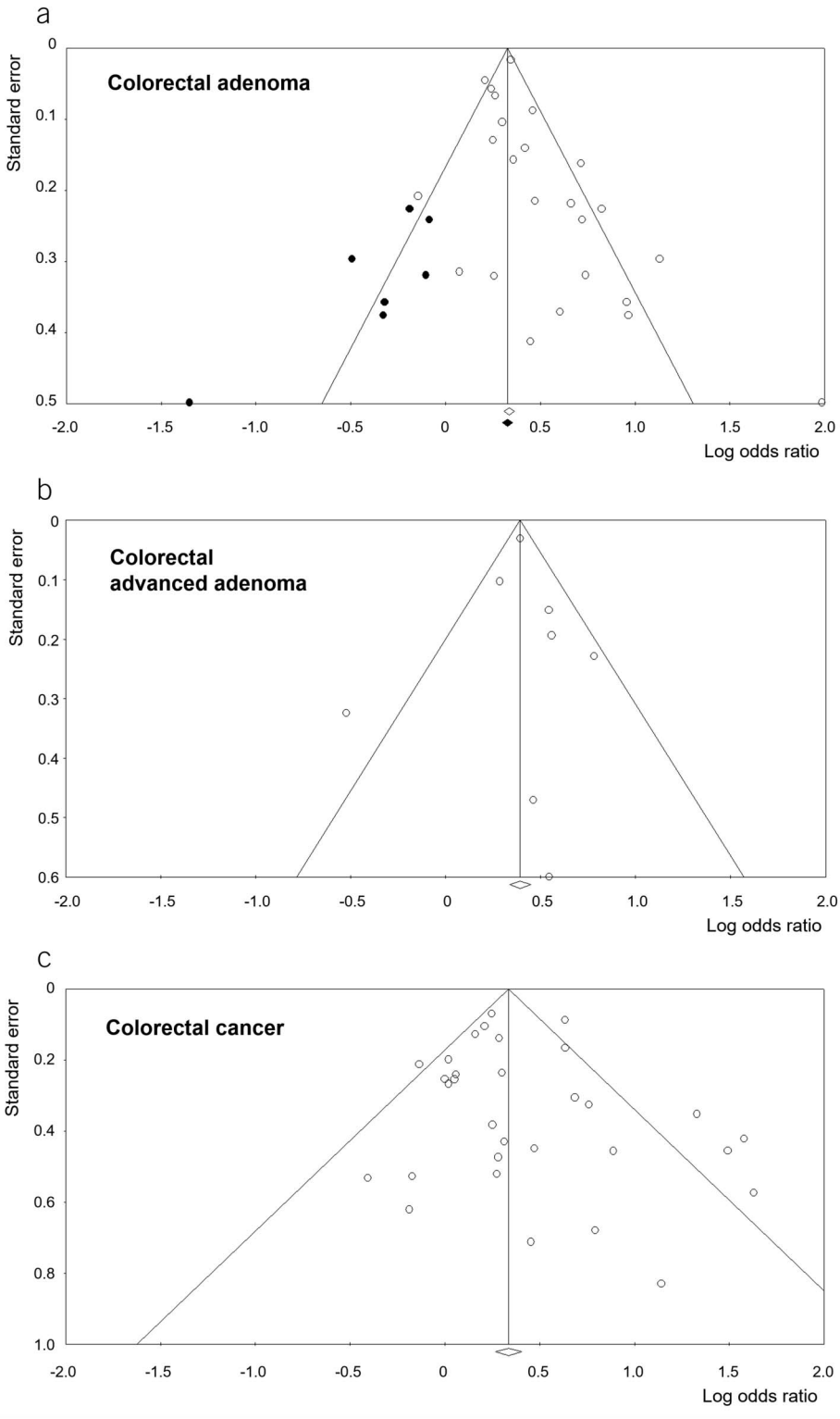

Figure 5. Funnel plots for the analysis of publication bias. (**a**) Colorectal adenoma, (**b**) colorectal adenoma, and (**c**) colorectal cancer. The white diamond represents the pooled logarithmic odds ratio and corresponding 95% confidence interval, among studies. The black diamond represents the pooled logarithmic odds ratio and corresponding 95% confidence interval, among the observed and imputed studies.

the results of sensitivity analysis were similar to those of the original analysis. Even in only high-quality studies, *H. pylori* infection was associated with an increased risk for colorectal adenoma (pooled OR 1.45 [95% CI 1.34–1.57]), advanced adenoma (pooled OR 1.49 [95% CI 1.27–1.76]), and cancer (pooled OR 1.46 [95% CI 1.25–1.71]).

Additional sensitivity analysis was performed after excluding the study by Tongtawee et al. (24) which had an outlier in the analysis of colorectal adenoma. As a result, the pooled OR of *H. pylori* infection for colorectal adenoma was 1.46 (95% CI 1.35–1.57).

DISCUSSION

Several meta-analyses examining the relationship between *H. pylori* infection and colorectal neoplasia have been published (5,19–21). However, these meta-analyses included 9–28 individual studies, which represented only a portion of all relevant studies published to date. Furthermore, some of these meta-analyses included individual studies examining *H. pylori* infection in colorectal tissues, not intragastric *H. pylori* infection (5,21). Through a systematic review, we included only studies that evaluated the association between intragastric *H. pylori* infection and colorectal neoplasia. In addition, we identified 14 new individual studies and included them among the 48 studies in the present meta-analysis. Our large-scale meta-analysis provides reliable pooled estimates with high precision. It also evaluated the impact of diagnostic tools or study design on the association between *H. pylori* infection and colorectal neoplasia through subgroup analyses.

In this study, the risks for colorectal adenoma, advanced colorectal adenoma, and CRC were similar (OR [95% CI]: adenoma vs advanced adenoma vs CRC, 1.49 [1.37–1.62] vs 1.50 [1.28–1.75] vs 1.44 [1.26–1.65]). This finding implied that *H. pylori* infection may be associated with the early stages of colorectal carcinogenesis. If *H. pylori* infection is associated with only the advanced stage of colorectal carcinogenesis (such as advanced adenoma or CRC), the risk for colorectal adenoma may be lowered. Of course, we cannot conclude that *H. pylori* infection facilitates colorectal carcinogenesis because a causal relationship cannot be determined through analysis of cross-sectional or case-control studies. However, *H. pylori* infection usually occurs when individuals are young and continues until old age if not treated (67). Therefore, it is likely that colorectal neoplasia occurred in patients with *H. pylori* infection, rather than the possibility of new *H. pylori* infection in patients who had colorectal neoplasia. In addition, a previous cohort study demonstrated that *H. pylori*-infected individuals had a 73% higher risk for CRC development during the follow-up period compared with noninfected individuals (68).

There are several hypotheses that support the relationship between *H. pylori* infection and colorectal neoplasia, one of the most plausible of which is hypergastrinemia in patients with chronic *H. pylori* infection. Chronic gastritis by *H. pylori* infection can cause gastric mucosal atrophy, followed by intestinal metaplasia, which results in a decrease in gastric acid secretion from the parietal cells and an increase in intragastric pH. As a result, serum gastrin level is increased by a negative feedback mechanism. Hypergastrinemia may facilitate proliferation of colorectal mucosa, making the colon and rectum more susceptible to carcinogenesis (37,41).

Another hypothesis suggesting the association between *H. pylori* infection and colorectal neoplasia is the dysbiosis of the gut microbiome in patients with *H. pylori* infection. In healthy individuals, gastric acid acts as a barrier to various environmental and oral microorganisms. If the gastric acid secretion is decreased, various bacteria can colonize the stomach and gut dysbiosis can be induced (69–71). Although various pathogenetic mechanisms involve colorectal carcinogenesis, changes in the gut microbiome play a very important role in colorectal carcinogenesis (72,73).

The direct carcinogenic effect of *H. pylori* may also be considered as a cause of high risk for colorectal neoplasia in patients with *H. pylori* infection. A previous study reported that *H. pylori* reside in the colorectum and are associated with colorectal neoplasia (74). In that study, the prevalence of *H. pylori* was higher in both colorectal adenoma tissues and CRC tissues than in normal colorectal tissues. Although the study did not evaluate causal relationships, the results suggested an association between colorectal neoplasia and *H. pylori* colonization in the colorectum as well as intragastric *H. pylori* infection.

Our meta-analysis now supports the association between *H. pylori* infection and CRC; however, this was not previously clear. In fact, of the 31 studies that reported a risk for CRC in patients with *H. pylori* infection, only 10 demonstrated a significant difference. Twelve studies reported a tendency toward increased risk for CRC without statistical significance in patients who had *H. pylori* infection. This may be because of the small sample sizes in individual studies examining CRC. By contrast, most individual studies demonstrated a significantly increased risk for adenoma in patients with *H. pylori* infection. Because the prevalence of colorectal adenoma is higher than that of CRC, it would have been easier to demonstrate statistically significant results.

One other issue in determining the association between *H. pylori* infection and colorectal neoplasia is the method used to diagnose *H. pylori* infection. Although serological testing, including IgG anti-*H. pylori* antibody, is a popular screen for *H. pylori* infection, it has a limitation in that it does not guarantee current *H. pylori* infection (75). Therefore, there is a possibility that the impact of *H. pylori* infection on the risk for colorectal neoplasia may depend on the methods used to diagnose *H. pylori* infection—IgG anti-*H. pylori* antibody or other tests. In our subgroup analysis, the risk for colorectal adenoma was higher when *H. pylori* infection was determined using IgG anti-*H. pylori* antibody compared with other tests. It may be because studies that used IgG anti-*H. pylori* antibody included more patients with severe atrophy and intestinal metaplasia. Patients with past *H. pylori* infections, who usually exhibit severe atrophy and intestinal metaplasia, may be positive for IgG anti-*H. pylori* antibody, but negative results in other tests including urea breath test and rapid urease test. For now, however, it can be somewhat difficult to draw definitive conclusions because the risk for CRC did not appear to be influenced by the diagnostic methods in our subgroup analysis.

Although we demonstrated an increased risk for colorectal neoplasia in patients with *H. pylori* infection, whether *H. pylori* eradication has a beneficial effect on colorectal neoplasia is another issue. Generally, it has been known that *H. pylori* eradication lowers the risk for gastric cancer by 35% in the general population and by 50% in high-risk populations (76–78). Although it is not clear whether *H. pylori* eradication prevents the development of colorectal neoplasia, we cautiously speculate that *H. pylori* eradication may reduce the risk for CRC to a similar extent as gastric cancer.

Although this study was the largest meta-analysis to date and provided precise estimates, it had several limitations. First, all included studies were observational in nature. Although most studies included consecutive patients during the study period, potential selection bias may be a concern. Moreover, 15 of the 48 included studies were assessed to be of low quality. Although sensitivity analysis including only high-quality studies revealed

that the pooled estimates were similar to the original results, the meta-analysis findings should be cautiously interpreted. Second, significant heterogeneity was identified in the meta-analyses. This may have been caused by some deviation in the studies from the pooled estimates. However, the direction of effect size was consistent among most of the individual studies. Third, there was a publication bias in the analysis for colorectal adenoma. Small studies tended to report relatively high effect size. This is an obvious limitation to our meta-analysis; however, pooled estimates were not significantly changed after adjusting missing studies by the trim-and-fill method. Fourth, we could not adjust for potentially confounding variables in the meta-analysis because not all included studies provided adjusted ORs.

Despite these limitations, our study findings provide a better understanding of the risk for colorectal neoplasia, including colorectal adenoma and CRC, in patients with *H. pylori* infection. Although our meta-analysis based on the observational studies could not show causality, it demonstrates that colorectal adenoma, advanced adenoma, and cancer were all associated with *H. pylori* infection.

CONFLICTS OF INTEREST

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Specific author contributions: Conception and design: C.H.P., acquisition of data: D.S.C. and C.H.P., analysis and interpretation of data: D.S.C., S.S.I., and C.H.P., statistical analysis: C.H.P., drafting manuscript: D.S.C., critical revision of the article for important intellectual content: S.I.S. and W.G.S., and final approval of the article: all authors.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ *Helicobacter pylori* infection is a well-known risk factor for various gastrointestinal diseases including peptic ulcer and gastric cancer.
- ✓ It has been suggested that *H. pylori* is associated with extragastric malignancies.

WHAT IS NEW HERE

- ✓ The meta-analysis demonstrated the association, rather than causality, between *H. pylori* infection and colorectal neoplasms including colorectal adenoma, advanced adenoma, and cancer.
- ✓ The relative risks for colorectal adenoma, advanced adenoma, and cancer in patients with *H. pylori* infection were similar.

TRANSLATIONAL IMPACT

- ✓ This meta-analysis may be the basis of study on prevention of colorectal neoplasms through the treatment of *H. pylori* infection.

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