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

**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,
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 [(colon) OR [colloid] OR [polyp] OR [polyps] OR [polypoid] OR [tumor] 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 reviewers (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 $\geq 7$ 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, $\geq$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 $P<0.1$, 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 [IgG 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; \(P < 0.001; F = 63\%\)). 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]; \(df = 11; P < 0.001; F = 67\%\)). \( H. pylori \) 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-IgG antibody, was used (pooled OR 1.40 [95% CI 1.28–1.54]; \(df = 11; P = 0.002; F = 62\%\)). 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, \(df = 1; P = 0.03; F = 79\%\)).

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 \( H. pylori \) infection was 1.49 [95% CI 1.37–1.62]; degrees of freedom \([df]\) = 23; \(P < 0.001; F = 63\%\)).
| 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          | Bombiski (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 | Villous component (>20%), >10 mm in size, or severe dysplasia | 8                |
| 2006          | Liou (51)                | Cross-sectional | Taiwan  | N/A          | 462                | Hospital-based   | UBT                      | N/A                               |                                  | 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          | Zumikeller (54)          | Case-control | Germany  | 2003–2004    | 851                | Hospital-based case community-based control | IgG anti-HP antibody | After the colonoscopy |                                  | 9                |
| 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 | N/A                           | 8                |
| 2009          | Wu (57)                  | Case-control | Taiwan  | 2000–2007    | 635                | Hospital-based   | IgG anti-HP antibody | N/A                           | N/A                           | 8                |
| 2010          | Abbass (58)              | Cross-sectional | USA     | 2008–2009    | 192                | Hospital-based   | RUT or histologic examination | N/A                           | N/A                           | 6                |
| 2011          | Inoue (59)               | Case-control | Japan   | 1996–2004    | 478                | Community-based (health checkup center) | IgG anti-HP antibody | With the colonoscopy | N/A                           | 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                           | N/A                           | 6                |
| 2012          | Zhang (7)                | Case-control | Germany | 2003–2007    | 3,381              | Community-based | IgG anti-HP antibody | N/A                           | N/A                           | 8                |
| 2013          | Epplein (62)             | Case-control | USA     | 2002–2009    | 558                | Community-based | IgG anti-HP antibody | Before the colonoscopy | N/A                           | 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                           | N/A                           | 8                |
| 2014          | Patel (22)               | Cross-sectional | USA     | 2009–2011    | 798                | Hospital-based   | Histologic examination | N/A                           | N/A                           | 8                |
| 2014          | Selgrad (8)              | Cross-sectional | Germany | 2008–2013    | 377                | Hospital-based   | IgG anti-HP antibody | Before the colonoscopy | N/A                           | 8                |
| 2014          | Shmuely (66)             | Cross-sectional | Israel  | 2008–2010    | 273                | Hospital-based   | IgG anti-HP antibody | Same d as the colonoscopy | N/A                           | 8                |
| 2015          | Engin (9)                | Case-control | Turkey  | N/A          | 205                | Hospital-based   | IgG anti-HP antibody | N/A                           | 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                           | N/A                           | 9                |
| 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.
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; I² = 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; I² = 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; I² = 58%). The results of subgroup analysis according to the \(H. pylori\) test method did not differ between the subgroups (IgG anti-\(H. pylori\) and Colorectal Neoplasia 7

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

**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.**
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: \( d_f = 1; P = 0.93; I^2 = 0\%\).

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% CI 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,
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 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
Guarantor of the article: Chan Hyuk Park, MD, PhD.
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.L., 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.

TRANSITIONAL 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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