Helicobacter pylori and Esophageal Cancer Risk: A Meta-analysis

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Abstract We conducted this meta-analysis to examine the association between *Helicobacter pylori* and esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma. We searched the PubMed database, the ISI database, and the references of the selected articles. Case-control or nested case-control studies were selected if they used serology or endoscopic methods to detect *H. pylori* in the stomach and if control subjects were not restricted to upper gastrointestinal tract cancer or peptic ulcer disease patients. A total of 19 studies were used for this analysis. Summary odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using the DerSimonian-Laird method. *Q* statistics and I^2 statistics were calculated to examine heterogeneity. Subgroup analyses were conducted by CagA status. For EAC, the summary OR (95% CI) was 0.56 (0.46-0.68). There was little heterogeneity among studies (I^2 = 15%). Further analysis showed that colonization with CagA-positive strains was inversely associated with EAC risk (OR, 0.41; 95% CI, 0.28-0.62) but colonization with CagA-negative strains was not (OR, 1.08; 95% CI, 0.76-1.53). For esophageal squamous cell carcinoma, the summary OR (95% CI) was 1.10 (0.78-1.55). However, there was substantial heterogeneity among studies (I^2 = 73%), with statistically significant associations in both directions. Our results suggest an inverse association between CagA-positive *H. pylori* colonization and risk of EAC. The prominent decline of *H. pylori* colonization in the past few decades may be partly responsible for the recent increase in EAC incidence in Western countries.

Since its discovery in the early 1980s (1), *Helicobacter pylori* has been associated with several benign and malignant gastrointestinal tract diseases. *H. pylori* is now a known cause of gastric and duodenal ulcers, noncardia gastric adenocarcinoma, and gastric MALT lymphoma (2). In addition, epidemiologic studies have investigated the association between *H. pylori* and other gastrointestinal malignancies, including pancreatic cancer (3, 4), colorectal cancer (5, 6), and esophageal cancer. Of these, the association with esophageal cancer has been examined in a larger number of studies and relatively consistent patterns of association are emerging. Systematic reviews will help in establishing such patterns.

With over 450,000 new cases annually, esophageal cancer is the 8th most common incident cancer in the world (7). The two main histologic types of esophageal cancer, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), have distinct geographic and demographic patterns. ESCC constitutes the large majority of all esophageal cancer cases in the world (7, 8) and more than 90% of the cases in some high-risk areas of the world, such as China (9) and Iran (10). EAC constitutes the minority of esophageal cancer cases in the world, but approximately half of the cases in some Western countries, such as the United States and the United Kingdom, are of this type (11–13). There is also a large body of evidence suggesting that the risk factors for these two cancer types may be different. For example, alcohol consumption is a strong risk factor for ESCC but its association with EAC is unclear (14, 15). Therefore, the associations of any potential causal factors should be evaluated separately for these two cancer types.

H. pylori resides in the stomach and can be detected with a number of invasive methods, such as histologic examination or urease test on gastric antral biopsies, or by noninvasive methods, such as serologic tests (16). Of these, positive serologic tests indicate past or current colonization, whereas other methods indicate only current colonization of *H. pylori* in the stomach. Because of the low cost, the ability to detect previous exposure, and the availability of serum in epidemiologic studies, serologic tests are especially useful in such studies.

There are different strains of *H. pylori*. The genome of CagA-positive strains contains the *cag* pathogenicity island. This island includes approximately 31 putative genes, including *cagA*—the gene that encodes the CagA protein (17). CagA-positive strains confer a higher risk of noncardia gastric cancer than CagA-negative strains (18). Likewise, the association

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Table 1. Study characteristics

First author	Study location	Year*	Study type	HP Dx	HP+ definition†	EAC‡			
						Case		Control	
						HP+	*CagA+*	*HP+*	*CagA+*
1. Talley (42)	USA	1991	Clin	S	HPSe+	—	—	—	—
2. Oberg (35)	USA	1999	Clin	H	Hist+	5/37	—	32/229	—
3. Peek (36)‖	USA	1999	Clin	S, H	HPSe+ or Hist+	11/30	3/30	20/48	25/48
4. Vieth (45)	Germany	2000	Clin	H	Hist+	66/138	—	468/712	—
5. Weston (48)	USA	2000	Clin	H	Hist+	3/20	—	96/217	—
6. El Omar (27)	USA	2003	Pop	S	HPSe+	35/108	5/68	84/210	46/224
7. Wu AH (50)	USA	2003	Pop	S	HPSe+ (HPSe+ or CagA+)	49/80 (52/80)	18/80	230/356 (249/356)	106/356
8. Wang KX (46)¶	China	2003	NR	S	HPSe+	—	—	—	—
9. Ye (53)	Sweden	2004	Pop	S	HPSe+ (HPSe+ or CagA+)	18/97 (47/97)	42/97	198/499 (304/499)	293/499
10. de Martel (23)	USA	2005	Pop	S	HPSe+	19/51	9/18	74/150	44/71
11. Wu DC (52)	Taiwan	2005	Pop	S	HPSe+	—	—	—	—
12. Wang Z (47)**	China	2006	Pop	S	HPSe+	—	—	—	—
13. Siman (41)	Sweden	2007	Pop	S	HPSe+ (HPSe+ or CagA+)	4/12 (7/12)	6/12	24/47 (35/47)	32/47
14. Kamangar (33)	China	2007	Pop	S	HPSe+ (HPSe+ or CagA+)	—	—	—	—
15. Anandasabapathy (20)	USA	2007	Clin	H	Hist+	4/25	—	10/30	—
16. Iijima (31)	Japan	2007	Clin	S, H,U	HPSe+, Hist+, or U+	—	—	—	—
17. Derakhshan (25)	Iran	2008	Clin	S	HPSe+	9/19	—	28/38	—
18. Fruh (28)	USA	2008	Clin	S	HPSe+	36/100	29/100	43/101	30/101
19. Anderson (21)	Ireland	2008	Pop	S	HPSe+	55/123	57/123	157/253	150/253

Abbreviations: Clin, clinic based; Pop, population based; NR, not reported; HP Dx, HP detection method; S, serology; H, histology; U, rapid urease test.

*Publication year.

†Definition for *H. pylori* positivity: Hist+, positive histologic examination of tissue samples; HPSe+, seropositivity for antibodies to whole cell; CagA+, sero-positivity for antibodies to CagA; U+, positive rapid urease test.

‡Number of subjects with a positive test/total number of subjects.

§Group- or individual-matching of controls to cases for age/reporting adjusted ORs for the association between *H. pylori* or CagA and cancer.

‖EAC cases include Barrett's with high-grade dysplasia.

¶Because the authors reported that there was no difference in age and gender between cases and controls, this study was analyzed as a matched study.

********H pylori*–positive numbers by case status were not reported.

Table 1. Study characteristics (Cont'd)

ESCC[‡]				Matched/adjusted[§]	Controls
Case		Control			
HP+	*CagA+*	*HP+*	*CagA+*		
20/41	—	96/252	—	No/yes	Asymptomatic volunteers and patients with benign esophageal, lung, or musculoskeletal disorders
—	—	—	—	No/no	Patients with foregut symptoms and benign diseases
—	—	—	—	No/no	Patients endoscoped for reasons other than GERD or Barrett's
—	—	—	—	No/no	Patients with non–ulcer dyspepsia and no endoscopic signs of GERD
—	—	—	—	No/no	Patients with GERD symptoms but no Barrett's esophagus
31/53	7/26	84/210	46/224	Yes/no	Matched to cases for age, sex, and study center
—	—	—	—	Yes/yes	Matched to cases for age, sex, neighborhood of residence, and race
33/63	—	145/310	—	NR[¶]/no	Healthy subjects
32/85 (64/85)	63/85	198/499 (304/499)	293/499	Yes/yes	Randomly selected population-based controls, frequency matched to EAC cases for age and sex
—	—	—	—	Yes/yes	Randomly selected from the study cohort, matched to cases for age, sex, race, and study site
28/127	—	74/171	—	No/yes	Parents of children randomly selected from the study area
?/107	—	?/107	—	Yes/yes	Neighborhood controls, randomly selected and matched to cases for age and sex
15/37 (24/37)	24/37	68/129 (87/129)	82/129	Yes/yes	Randomly selected from the study cohort, matched to cases for age, sex, and date of enrollment
231/335 (254/335)	178/335	662/992 (727/992)	552/992	No/yes	Randomly selected from the baseline participants in the study cohort
—	—	—	—	No/no	Barrett's patients with no dysplasia
60/73	—	56/73	—	Yes/yes	Endoscoped patients with no localized lesion, matched to cases for age and sex
—	—	—	—	Yes/yes	Dyspeptic patients with no peptic ulcer or tumor in their endoscopy
—	—	—	—	Yes/yes	Healthy GERD-free, non–blood-related family members and friends of other cancer/surgical patients
—	—	—	—	Yes/yes	Randomly selected population-based controls, frequency matched to EAC cases for age and sex

between CagA-positive and CagA-negative strains with other cancers may be different (19) and should be considered in analyses.

We conducted this meta-analysis to summarize the published literature on the association between *H. pylori*, detected by different methods, and esophageal cancer. We analyzed and report the results separately for ESCC and EAC. We also report the associations by CagA status.

Materials and Methods

Selection of studies

We conducted a comprehensive search by examining the PubMed and ISI-Web of Knowledge databases for all case-control or cohort studies that have been published on the association between *H. pylori* colonization in the stomach and risk of esophageal cancer. All results were updated on February 12, 2008. The following terms were used in the PubMed Database search: ["Helicobacter pylori" [MeSH] OR (Campylobacter pylori) OR (H Pylori) OR (H. Pylori)] AND ["Esophageal Neoplasms" [MeSH] OR (Cancer of Esophagus) OR (Cancer of the Esophagus) OR (Esophageal Cancer) OR (Esophagus Cancer) OR (Esophagus Neoplasm) OR (Neoplasms, Esophageal)]. The same terms were used to search text words in the ISI Database. The search was repeated by replacing Esophagus with Oesophagus, and Esophageal with Oesophageal. In addition, references cited in the identified articles were searched manually. Both authors reviewed the search

results to reduce the possibility of missing the published articles. Where data were missing, we contacted the authors for the relevant information. Using these approaches, reports on *H. pylori* in relation to esophageal cancer were found in 35 full-text articles (19–53).

Inclusion criteria were (*a*) testing for the presence of *H. pylori* in the stomach using invasive or noninvasive methods and (*b*) including control subjects without upper gastrointestinal cancers or peptic ulcer disease. Based on these criteria, three studies were excluded because they examined the presence of *H. pylori* only in esophageal tissue samples (but not in the stomach; refs. 30, 43, 49). Six studies were excluded because they had no control subjects or because all control subjects had upper gastrointestinal tract cancers or peptic ulcers (22, 26, 34, 37–39). Six more studies (19, 24, 32, 40, 44, 51) were excluded because the *H. pylori* assay results were also reported in other publications (23, 27, 36, 41, 50, 53). Finally, one study was excluded because cancers of the proximal 5 cm of stomach were considered as esophageal cancer (29). Therefore, a total of 19 studies were used for calculating summary statistics.

Data extraction and statistical analysis

We compared *H. pylori* positivity in esophageal cancer cases and controls. *H. pylori* positivity was defined as having evidence for *H. pylori* colonization by direct (invasive) examination of the gastric antral tissue or being seropositive for IgG antibodies against whole-cell antigen. In an additional analysis, we used a broader definition of *H. pylori* positivity, defined as having evidence for *H. pylori* colonization by direct examination of the gastric antral tissue, being seropositive for IgG antibodies against *H. pylori* whole-cell antigen, or being seropositive for IgG antibodies against CagA. We chose this broader definition because individuals who are seronegative for antibodies against whole-cell antigen but are seropositive for antibodies against CagA may in fact be positive for *H. pylori* (54). Where data were available, we compared the presence of CagA-positive strains (versus no *H. pylori*), and the presence of CagA-negative strains (versus no *H. pylori*) between case and control subjects. In all studies, CagA positivity was determined using IgG antibodies.

We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for the association between each of the exposures noted above and esophageal cancer. ORs and 95% CIs were calculated for each individual study and for all studies combined. We used both random-effects models (DerSimonian-Laird method) and fixed-effects models (Mantel-Haenszel method) to calculate summary ORs and 95% CIs. Because these two methods provided qualitatively similar results, we chose random-effects models, which are more conservative than fixed-effects models (55), to present forest plots and subgroup analyses described in the text.

We conducted several subgroup analyses. In a number of studies, the control subjects were selected from among clinic patients who were endoscoped because of upper gastrointestinal tract symptoms.

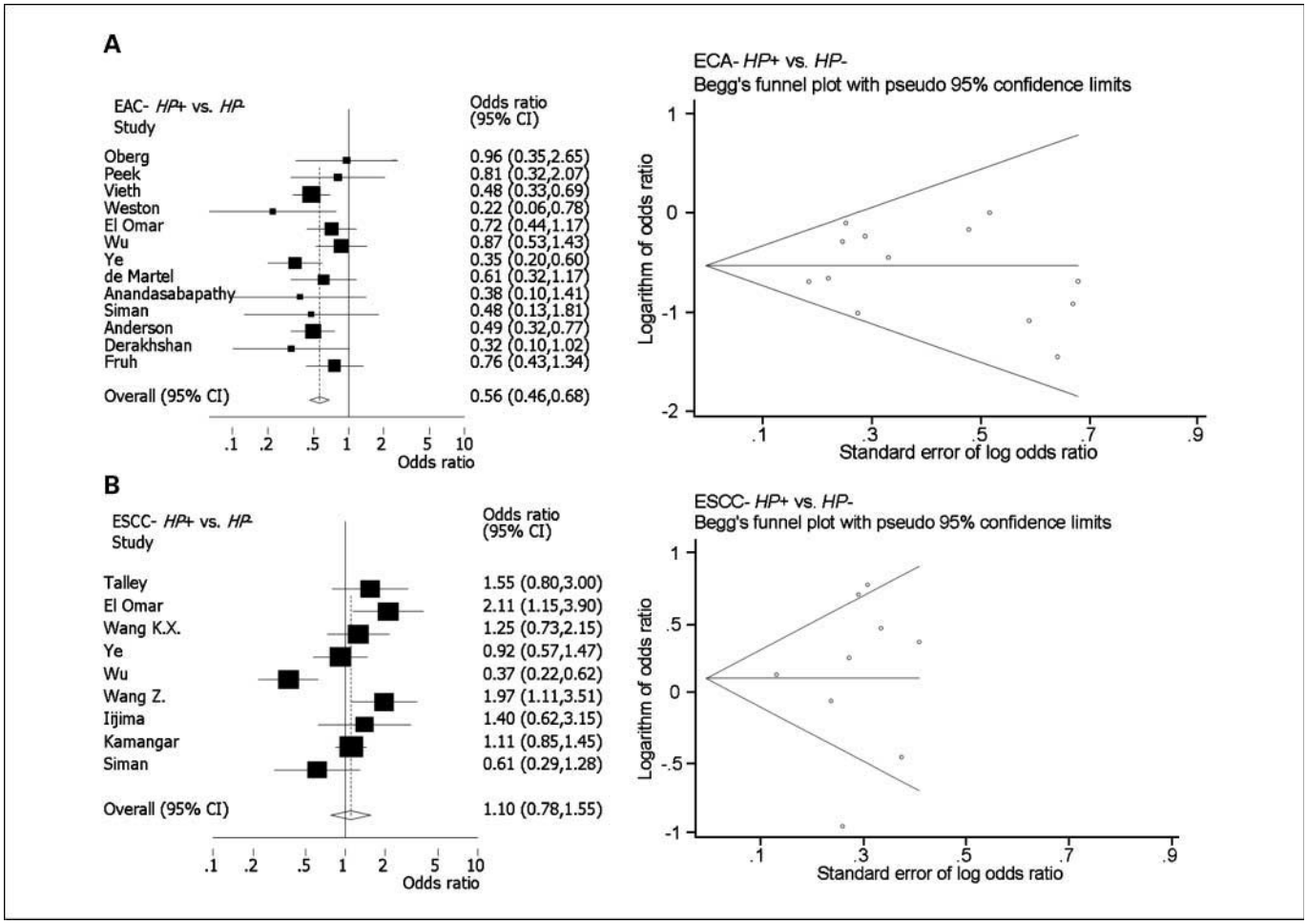

Fig. 1. Forest plot and Begg's funnel for the association between *H. pylori* and esophageal cancer. Studies are sorted in order of publication year. *A*, esophageal adenocarcinoma. *B*, esophageal squamous cell carcinoma.

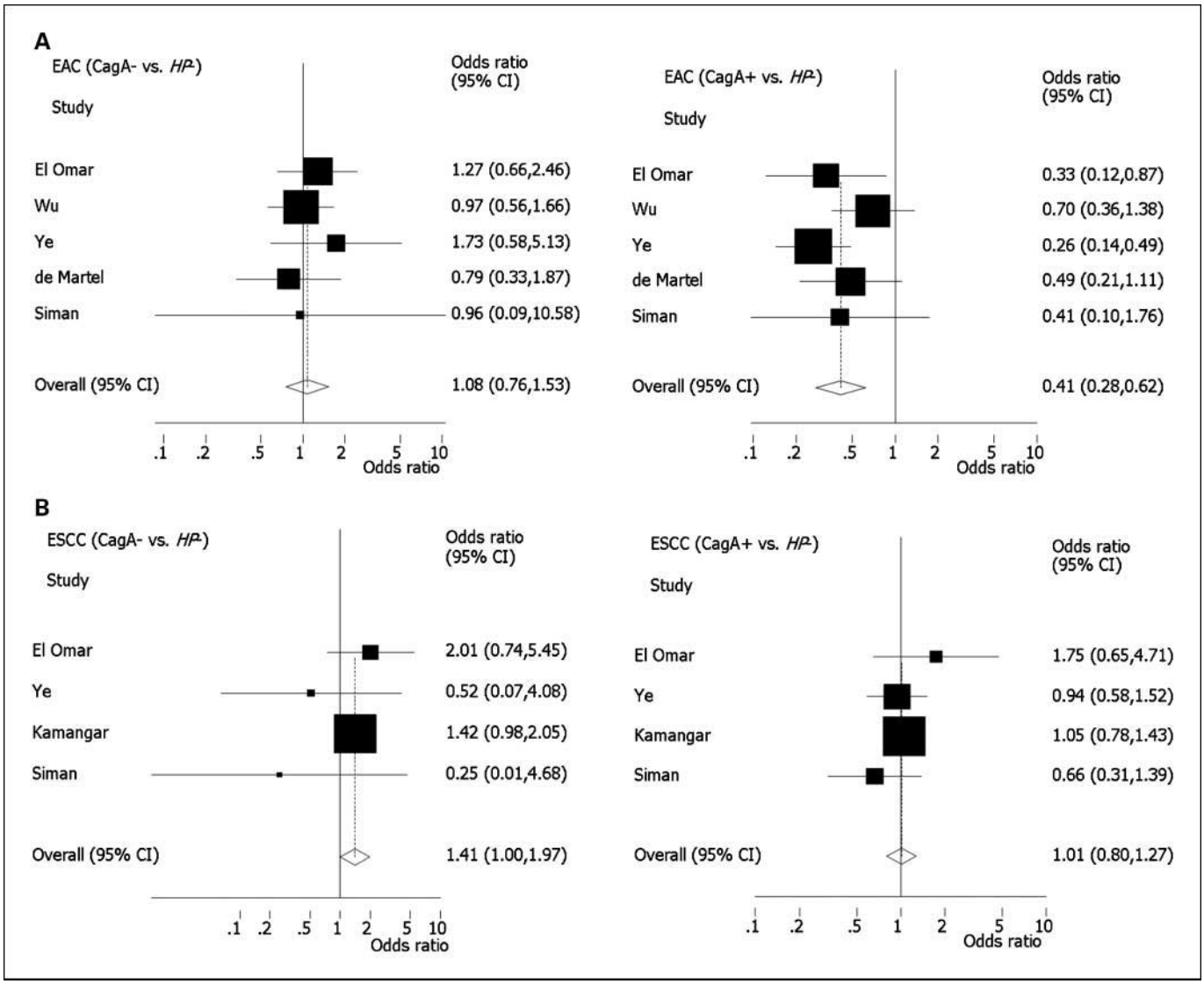

Fig. 2. The association between CagA-positive and CagA-negative strains and esophageal cancer. Studies are sorted in order of publication year. *A*, esophageal adenocarcinoma. *B*, esophageal squamous cell carcinoma.

Use of such control subjects may bias results because the *H. pylori* colonization rate in such control subjects may be different from the rate in the general population. Therefore, subgroup analyses were done that included only population-based studies. We also did subgroup analyses for studies from Western (European and American) and Eastern (Asian) countries, which may have different *H. pylori* positivity rates in their general populations. High prevalence of *H. pylori* colonization among controls may conceal an association between *H. pylori* and disease, especially if the association is not very strong. Only serologic studies are able to detect past exposure to *H. pylori*. Therefore, we also calculated summary ORs (95% CIs) for the subgroup of studies that had used serologic tests. *H. pylori* colonization rate is usually higher in older subjects, mostly because of cohort effects. Therefore, subgroup analyses were done for studies that had used age-matched controls (group-matched or individual-matched). Differentiating between EAC and gastric cardia adenocarcinoma can be challenging. To differentiate between the two, some studies required the presence of Barrett's esophagus for diagnosis of EAC. We conducted a subgroup analysis using these studies. Because the association between *H. pylori* and esophageal cancer could potentially be confounded by other factors, e.g., socioeconomic status, we also calculated and present the summary of adjusted ORs (95% CIs) for studies that provided adjusted results.

We plotted Begg's funnel plot to examine small study effects (56). We also used Begg and Mazumdar's method (57) to calculate *P* for rank correlation and Egger's weighted regression method (58) to calculate *P* for bias. For sensitivity analysis, we excluded smaller studies and recalculated the summary ORs (95% CIs) using only larger studies.

To examine heterogeneity among studies, the *Q* statistic (using Mantel-Haenszel weights) and the I^2 statistic (59) were calculated. All analyses were done using STATA software, version 10.0 (StataCorp LP). Throughout the article, two-sided *P* values <0.05 were considered as statistically significant.

Results

Summary characteristics of the 19 studies that were included in this analysis are presented in Table 1. Most studies used serologic tests to determine prior or current stomach colonization with *H. pylori* and to determine CagA status. Approximately half of the studies were population based, whereas the other half were clinic based.

Esophageal adenocarcinoma

Figure 1A and Table 2 show the results for the association between *H. pylori* and EAC. A total of 13 studies with 840 cases and 2,890 controls were included in this analysis. The OR point estimate for each individual study was below 1 (Fig. 1A), and the overall random effects and fixed effects ORs (95% CIs) were 0.56 (0.46-0.68) and 0.55 (0.47-0.66), respectively. For the overall association, the I^2 statistic was 15%, suggesting little heterogeneity, and the *P* value associated with the *Q* statistic was 0.29, showing no statistically significant heterogeneity (Table 2).

Begg's funnel plot for the association between *H. pylori* and EAC is also shown in Fig. 1A. This figure shows the logarithm of the odds ratio (*Y* axis) versus its SE (*X* axis). Smaller studies have larger SEs; therefore, points representing these studies are in the right-hand side of the graph. The distribution of the dots on this graph was reasonably symmetric, suggesting no strong evidence for publication bias. Also, there was no evidence for bias using either Begg and Mazumdar's method (*P* for rank correlation = 0.76) or Egger's weighted regression method (*P* for bias = 0.71). After excluding small studies, defined as those having a SE >0.5, the summary OR (95% CI) for *H. pylori* positivity was 0.58 (0.47-0.73).

Table 2 also shows the results of subgroup analyses. Similar to the overall association, every subgroup analysis showed an inverse association between *H. pylori* positivity and EAC risk. For population-based studies, the OR (95% CI) was 0.58 (0.43-0.76). The ORs (95% CIs) for Western and Eastern studies were 0.57 (0.47-0.70) and 0.32 (0.10-1.02), respectively. Only one study (25) was from an Eastern country. The summary OR (95% CI) for studies that used serologic tests was 0.59 (0.48-0.73). Among the studies that matched for age, the summary OR (95% CI) was 0.58 (0.46-0.75). The summary OR (95% CI) for studies that included Barrett's esophagus in their diagnostic criteria (20, 36, 45, 48, 53) was 0.44 (0.33-0.58). Analysis of adjusted ORs (95% CIs) yielded a summary OR (95% CI) of 0.50 (0.34-0.74). There was no evidence for significant heterogeneity in the subgroup analyses, except for the adjusted analyses, which showed a marginally significant *Q* statistic ($P = 0.04$).

When we used the broader definition of *H. pylori* positivity (being positive for *H. pylori* or CagA), there was little change in the results, and the overall random-effects OR (95% CI) was 0.56 (0.45-0.69). There was also an inverse association between *H. pylori* and EAC in all subgroup analyses (results not shown).

Eight of the studies reported on antibodies to CagA, and in five of these, the simultaneous status of IgG antibodies to both CagA and whole-cell antigen was known. In this latter group of studies, the summary ORs (95% CIs) for carrying CagA-negative and CagA-positive *H. pylori* strains, versus being *H. pylori* negative, were 1.08 (0.76-1.53) and 0.41 (0.28-0.62), respectively. These two summary ORs were statistically significantly different from each other ($P < 0.01$). Figure 2A shows the associations between CagA-negative and CagA-positive strains and EAC separately. All five studies show inverse associations for CagA-positive strains, but the results for CagA-negative strains are mixed.

Esophageal squamous cell carcinoma

Figure 1B and Table 3 show the results for the association between *H. pylori* and ESCC. Nine studies, with a total of 921 cases and 2,743 controls, were included in this analysis. As shown in Fig. 1B, the results varied substantially, on both

Table 2. Summary statistics for the association between *H. pylori* and esophageal adenocarcinoma

	No. studies	*Q* statistic*	*P*†	I^2 (%)‡	Random effects OR (95% CI)	Fixed effects OR (95% CI)
H. pylori (840/2,890)§						
All studies	13	14.19	0.29	15	0.56 (0.46–0.68)	0.55 (0.47–0.66)
Large studies (SE < 0.5)	8	9.64	0.21	27	0.58 (0.47–0.73)	0.57 (0.48–0.68)
Population-based studies	6	7.32	0.20	32	0.58 (0.43–0.76)	0.57 (0.46–0.71)
Western studies	12	13.28	0.28	17	0.57 (0.47–0.70)	0.56 (0.47–0.67)
Eastern studies	1	—	—	0	0.32 (0.10–1.02)	0.32 (0.10–1.02)
Studies used serologic tests	10	10.03	0.35	10	0.59 (0.48–0.73)	0.56 (0.47–0.67)
Studies with age-matched controls	8	9.17	0.24	24	0.58 (0.46–0.75)	0.58 (0.47–0.71)
Studies that required Barrett's esophagus for EAC diagnosis	5	3.77	0.44	0	0.44 (0.33–0.58)	0.43 (0.33–0.56)
Adjusted results	7	13.25	0.04	55	0.50 (0.34–0.74)	0.52 (0.41–0.66)
H. pylori (the broader definition)‖	13	16.60	0.17	28	0.56 (0.45–0.69)	0.57 (0.46–0.71)
CagA-negative strains¶	5	1.64	0.80	0	1.08 (0.76–1.53)	1.07 (0.75–1.52)
CagA-positive strains**	5	4.78	0.31	16	0.41 (0.28–0.62)	0.40 (0.28–0.56)

*χ^2 *Q* statistic for homogeneity in random effects model.
†*P* value for the *Q* statistic in random effects model.
‡Higgins I^2 statistic for heterogeneity in random-effects model.
§Being positive for antibodies against whole-cell or being positive for *H. pylori* in invasive tests; numbers inside parenthesis refer to number of cases/controls.
‖Being positive for antibodies against whole-cell or CagA, or positive for *H. pylori* in invasive tests.
¶This row compares subjects with CagA-negative strains versus those who are *H. pylori* negative.
**This row compares subjects with CagA-positive strains versus those who are *H. pylori* negative.

Table 3. Summary statistics for the association between *H. pylori* and esophageal squamous cell carcinoma

	No. studies	*Q* statistic*	*P*†	I^2 (%)‡	Random effects OR (95% CI)	Fixed effects OR (95% CI)
H. pylori (921/2,743)§						
All studies	9	29.76	<0.01	73	1.10 (0.78–1.55)	1.07 (0.91–1.26)
Large studies (SE <0.5)	9	29.76	<0.01	73	1.10 (0.78–1.55)	1.07 (0.91–1.26)
Population-based studies‖	6	27.52	<0.01	82	1.00 (0.62–1.60)	1.01 (0.84–1.21)
Western studies	4	8.21	0.04	63	1.17 (0.71–1.95)	1.16 (0.87–1.56)
Eastern studies	5	21.17	<0.01	81	1.05 (0.63–1.77)	1.03 (0.85–1.25)
Studies used serologic tests	9	29.76	<0.01	73	1.10 (0.78–1.55)	1.07 (0.91–1.26)
Studies with age-matched controls	6	10.47	0.06	52	1.28 (0.89–1.83)	1.27 (1.00–1.61)
Adjusted results	7	13.54	0.04	56	0.99 (0.67–1.45)	1.04 (0.84–1.29)
H. pylori (the broader definition)‖	9	30.66	<0.01	74	1.26 (0.88–1.80)	1.20 (1.01–1.42)
CagA-negative strains¶	4	2.77	0.43	0	1.41 (1.00–1.97)	1.37 (0.98–1.90)
CagA-positive strains**	4	2.60	0.46	0	1.01 (0.80–1.27)	1.01 (0.80–1.27)

*χ^2 *Q* statistic for homogeneity in the random-effects model.
†*P* value for the *Q* statistic in the random-effects model.
‡Higgins I^2 statistic for heterogeneity in the random-effects model.
§Being positive for antibodies against whole cell or being positive for *H. pylori* in invasive tests; numbers inside parenthesis refer to number of cases/controls.
‖Being positive for antibodies against whole cell or CagA, or positive for *H. pylori* in invasive tests.
¶This row compares subjects with CagA-negative strains versus those who are *H. pylori* negative.
**This row compares subjects with CagA-positive strains versus those who are *H. pylori* negative.

sides of the neutral line, and the ORs (95% CIs) ranged from 0.37 (0.22-0.62) to 2.11 (1.15-3.90), statistically significant in opposite directions. The overall summary ORs (95% CIs) using the random-effects and fixed-effects models were 1.10 (0.78-1.55) and 1.07 (0.91-1.26), respectively. Indices of heterogeneity are shown in Table 3. For the overall analysis, the *Q* statistic was significant ($P < 0.01$) and the I^2 statistic showed a high variation (73%) among study results.

Begg's funnel plot for the association between *H. pylori* and ESCC is shown in Fig. 1B. The distribution of the dots around the summary line was symmetric, and there was no evidence of bias using either Begg's method ($P = 0.47$) or Egger's method (P for bias = 0.84). All studies had a SE of <0.5.

Subgroup analysis results are shown in Table 3. The summary OR (95% CI) for population-based studies was 1.00 (0.62-1.60). The ORs (95% CIs) for Western and Eastern studies were 1.17 (0.71-1.95) and 1.05 (0.63-1.77), respectively. The OR (95% CI) for studies that used serologic tests was 1.10 (0.78-1.55). The summary OR (95% CI) for studies that matched for age was 1.28 (0.89-1.83). When the adjusted ORs were analyzed, the overall OR (95% CI) was 0.99 (0.67-1.45). Similar to the overall analysis, the I^2 and *Q* statistics suggested high and statistically significant heterogeneity in the subgroup analyses.

When the broader definition of *H. pylori* positivity was used, the random-effects OR for the overall association changed only slightly and remained nonsignificant. However, when studies were classified by geographic region, there was a statistically significant association between *H. pylori* and ESCC in Western studies, with an OR (95% CI) of 1.65 (1.17-2.32). Other subgroup analyses yielded results that were qualitatively similar to those found with the earlier definition of *H. pylori* positivity (results not shown).

Four studies reported on CagA results, and in all of them the simultaneous status of antibodies to CagA and whole-cell were known. Two of these studies dominated the results (Fig. 2B). The summary ORs (95% CIs) for carrying CagA-negative and CagA-positive strains, versus being *H. pylori*–negative, were 1.41 (1.00-1.97) and 1.01 (0.80-1.27), respectively. These two summary OR point estimates were not statistically significantly different from each other.

Discussion

The results of this meta-analysis suggest that colonization of the stomach with CagA-positive strains of *H. pylori* may protect against EAC.

H. pylori has coexisted with modern humans since their origin (60), and once it could be found in the stomachs of most humans. With advances in sanitation and use of antibiotics, however, this bacterium is rapidly disappearing from human populations (61), especially in Western countries. In the United States, for example, data from the third National Health and Nutritional Examination Survey (1988-1991) showed that serum samples from 57% of the population older than 70 years of age, versus 17% of the population between 20 and 29 years of age, were positive for IgG antibodies against *H. pylori* (62). More recent data from the National Health and Nutritional Examination Survey 1999-2000 show a positive IgG seroprevalence of only 5% in children younger than 10 years old who were born in the 1990s (63). Given that *H. pylori* colonization in most people occurs before the age of 10 years (64), these numbers show a substantial decline in *H. pylori* in a period of 70 years. This decrease mostly reflects a cohort effect (65) rather than eradication of *H. pylori* in individuals over time.

With changes in the prevalence of *H. pylori*, incidence rates of diseases caused, or prevented, by this organism change. *H. pylori* is a known cause of noncardia gastric cancer (66).

Incidence rates of this cancer have been sharply declining in most parts of the world in the past few decades (7). In contrast, rates of EAC have steeply increased in Western countries during this same period (13, 67). Once a rare cancer, EAC now constitutes approximately half of all esophageal cancer cases in some Western populations (11–13). Our results suggest that CagA-positive strains of *H. pylori*, which constitute the majority of *H. pylori* strains, may protect against EAC, and that increasing EAC rates may be partly due to the decline of *H. pylori* in human populations. In parallel with EAC rates, the incidence rates of gastric cardia adenocarcinoma, another cancer inversely associated with *H. pylori* prevalence (68), are increasing in some Western countries (67). However, it is unclear whether this latter inverse association is real or it merely reflects misclassification of EAC for gastric cardia adenocarcinoma (33, 69). Another observation consistent with the hypothesis that *H. pylori* disappearance is contributing to the increased EAC rates is that EAC rates are still low in most developing countries (9, 10), where *H. pylori* is still common.

H. pylori may decrease risk of EAC by reducing acid production in the stomach and hence reducing acid reflux to the esophagus (19). It may also reduce EAC risk by decreasing the production of the hormone ghrelin, which is mostly secreted from the stomach and stimulates appetite (70). A reduction in the level of ghrelin may lead to lower rates of obesity, an important risk factor for EAC (71).

The protective association of *H. pylori* with EAC or gastric cardia adenocarcinoma may be part of a broader phenomenon. The long history of coexistence of this organism with humans, despite its disease-causing potential, may suggest that *H. pylori* also has some beneficial effects to humans (61), including possible roles in reducing diarrheal diseases and asthma (63, 72, 73). Therefore, in this article, we have used the term *H. pylori* "colonization," rather than "infection," to describe the presence of *H. pylori* living in the stomach. The reciprocal link of *H. pylori* with both EAC and asthma may be due to lower acid reflux, which is a risk factor for both diseases, or it could be due to modulation of the hormones leptin and ghrelin, which have immunoregulatory effects (reviewed in refs. 72, 74).

The decline of *H. pylori* colonization can only partly explain the sharp increase in EAC incidence rates. With an OR of 0.5, even if *H. pylori* entirely disappeared, EAC incidence could increase at most by 2-fold; thus, part of the nearly 4-fold increased incidence observed in some populations (67) must be due to other reasons. Recent epidemiologic studies have found three important risk factors for EAC, namely gastroesophageal reflux, obesity, and smoking (14, 15, 71, 75). Whether, and how much, a change in the prevalence of these factors has contributed to the surge of EAC cases in the past few decades is still debated.

We conducted several analyses to examine the robustness of the association between *H. pylori* and EAC. The point estimate of the OR for each individual study in the meta-analysis was lower than 1, and there was little heterogeneity among these studies. Subgroup analyses also showed remarkably consistent ORs. When data analysis was limited to population-based studies, to studies from Western or Eastern countries, to studies that used serologic tests to determine exposure, to studies that matched for age, to larger studies, or to studies that included Barrett's esophagus in their diagnostic criteria, the summary OR remained lower than 0.60. When we used adjusted estimates, the summary OR was 0.50. Therefore, the results were quite robust. Likewise, using the broader definition of *H. pylori* positivity had very little or no impact on the results. We did not find any evidence for publication bias by using funnel plots or formal statistical tests.

CagA-positive strains of *H. pylori* have been disappearing faster than the CagA-negative ones (76). Interestingly, the inverse association between *H. pylori* and EAC was seen only with CagA-positive strains. Forest plots showed that this pattern was consistent across studies. It should be noted, however, that only 5 of the 13 selected studies could be used for comparing the effects of CagA-positive and CagA-negative strains. Therefore, more studies may still be needed to confirm this pattern. As discussed earlier, CagA-positive strains confer higher risk of noncardia gastric cancer than CagA-negative strains (18). Therefore, CagA-positive strains may also have stronger associations with other diseases that are caused, or prevented, by *H. pylori*. CagA protein can be delivered into gastric epithelial cells, and it may increase the risk of gastric cancer by increasing the turnover of the gastric epithelium (17). CagA-positive strains are also more likely to have the s1 allele of *vacA*, which encodes a molecule that affects epithelial cells (77) and may increase gastric cancer risk (78), and are also more likely to express the *babA* product, which controls adherence of *H. pylori* organisms to Lewis^b antigens on gastric epithelial cells (77). The biological reasons for the inverse association between CagA-positive *H. pylori* and EAC need to be further investigated.

We found no overall association between *H. pylori* and ESCC risk. However, the point estimates differed substantially and qualitatively among studies, resulting in large heterogeneity indices. Limiting studies to population-based studies, studies from Western or Eastern countries, studies that used serologic tests, studies that matched for age, or studies using adjusted results made little change in summary estimates and did not reduce heterogeneity. Therefore, the source of the observed heterogeneity is unclear. Gastric colonization with CagA-positive strains was not associated with ESCC risk. Compared with *H. pylori*–negative subjects, CagA-negative strains were associated with a marginally significant increased risk of ESCC. However, the bulk of the data for the latter analysis came from only two studies, and further studies are needed to make more definitive conclusions. An association was observed in studies from Western countries when we used the broader definition of *H. pylori* positivity. Again, there were only four studies in this analysis, and further data are needed to have more confidence in the results.

One other meta-analysis has previously examined the association between *H. pylori* and esophageal cancer (79). Our meta-analysis differs from this previous evaluation in several respects. One difference is the choice of published articles. The two meta-analyses share only six articles that examined the association between *H. pylori* and EAC, and only four articles that examined the association between *H. pylori* and ESCC. We excluded several of the publications used in the previous meta-analysis because they included duplicate data from the same study; we substituted newer papers from some studies; and we included several additional recent studies. We also conducted multiple subgroup analyses to examine the robustness of our data to the choice of study methods and other factors. We also examined the effects of CagA-positive and

CagA-negative strains of *H. pylori* separately versus *H. pylori*–negative subjects, rather than comparing CagA-positive subjects versus all other subjects. Despite these differences, both meta-analyses found that *H. pylori* protects against EAC and is not significantly related to ESCC risk. Also, both meta-analyses found that the association of *H. pylori* with EAC was largely homogeneous across studies, but there was substantial and statistically significant heterogeneity in results with respect to ESCC.

The strengths of this meta-analysis include the evaluation of 19 published studies with a large number of cases and controls, presenting multiple subgroup analyses, and using several methods to examine study heterogeneity and publication bias. This meta-analysis also has limitations. Combining observational studies conducted in different populations with various qualities of design to obtain summary ORs and 95% CIs can sometimes be misleading (80) and summary statistics need to be interpreted with caution (81). However, as mentioned above, at least for EAC, there was little evidence of heterogeneity and the results were robust to multiple subgroup analyses.

In conclusion, we found an inverse association between CagA-positive strains of *H. pylori* and risk of esophageal adenocarcinoma. The prominent decline of *H. pylori* colonization, especially CagA-positive strains, may be responsible for part of the recent increase in esophageal adenocarcinoma rates in Western countries.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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