

A systematic review and meta-analysis of the role of *Helicobacter pylori* eradication in preventing gastric cancer

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Abstract

Background Increasing evidence has suggested that *Helicobacter pylori* (*H. pylori*) eradication might prevent the development of gastric cancer (GC). This systematic review and meta-analysis aimed to better explore the role of *H. pylori* eradication in preventing GC, with particular reference to patients with precancerous lesions at baseline histology.

Methods Searches for human studies were performed through October 2016 and risk ratios (RRs), were obtained. Heterogeneity between studies was estimated using the Cochran Q test and *I*² values, whereas the possibility of publication bias was estimated with funnel plots. Additionally, we performed subgroup and sensitivity analyses.

Results In 26 studies suitable for meta-analysis (10 randomized controlled trials and 16 cohort studies) 52,363 subjects were included. The risk of GC among patients in whom *H. pylori* was successfully eradicated was significantly lower than that among controls: pooled RRs [95% CI] 0.56 [0.48-0.66], *Z*= -7.27, *P*=0.00001. This finding applied separately for randomized controlled trials (0.65 [0.51-0.84], *Z*= -3.33, *P*=0.0009) and for cohort studies (0.51 [0.42-0.62], *Z*= -6.63, *P*=0.00001). Concerning *H. pylori* eradication in patients with precancerous lesions, subgroup analyses showed that patients with non-atrophic or atrophic gastritis benefited from *H. pylori* eradication for the risk of GC development, whereas those with intestinal metaplasia or dysplasia did not.

Conclusion *H. pylori* eradication is associated with a significantly lower risk of GC; this finding has significant implications for the prevention of this cancer. The benefit is maximized when *H. pylori* eradication is applied at early stages of the infection.

Keywords *H. pylori*, eradication, gastric cancer, prevention, meta-analysis

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Introduction

Despite a decline of gastric cancer (GC) in many countries in the developed world, GC remains among the most common causes of cancer death globally [1]. In fact, there is an increase in global mortality from the disease due to population growth and increasing life expectancy in the developing world [2]. Two

major types are evident: The intestinal and the diffuse type. The intestinal type, the more common variant, shows a strong association with *Helicobacter pylori* (*H. pylori*) infection, as well as other factors such as cigarette smoking and diet (salted foods). The diffuse type is less common and is attributed to host-factor influences, such as mutations in the E-cadherin gene.

H. pylori infection affects approximately 50% of the global population [3] and it is the principal trigger of gastric carcinogenesis. It is believed to predispose to GC by inducing precancerous changes, i.e., atrophic gastritis (AG) and intestinal metaplasia (IM) [4,5]. There is evidence that subjects infected by *H. pylori* were between three and six times more prone to develop GC than uninfected controls [6-8]. These data were taken into account by the International Agency for Research on Cancer, which declared *H. pylori* as a class I human carcinogen [9]. Eradication of *H. pylori* can result in amelioration of gastric inflammation, halt the progression of gastric mucosal damage, prevent further *H. pylori*-induced DNA damage, improve gastric acid secretion, and restore the microbiome toward normal [10]. Because we can treat

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H. pylori with a course of antibiotic treatment, identifying and treating *H. pylori* infection could represent a strategy for reducing the disease burden of GC [11]. Thus, an earlier meta-analysis [12] that pooled randomized controlled trials (RCTs) conducted in asymptomatic infected individuals reported that *H. pylori* treatment could reduce the risk of GC in Asians.

As more data concerning the relationship of *H. pylori* treatment and GC prevention have become available from recent studies, we undertook the present meta-analysis to update and better define this relationship. We gave particular attention to studies that examined the role of *H. pylori* eradication in reducing the cancer risk in patients with precancerous lesions at baseline histology, i.e., AG, IM, and dysplasia (DYS).

Materials and methods

Study identification and extraction of data

The three authors performed extensive PubMed, MEDLINE and Embase database medical literature searches for human studies through October 2016, using suitable key words (“stomach neoplasms”[MeSH Terms] OR (“stomach”[All Fields] AND “neoplasms”[All Fields]) OR “stomach neoplasms”[All Fields] OR (“gastric”[All Fields] AND “cancer”[All Fields]) OR “gastric cancer”[All Fields]) AND (“helicobacter pylori” [MeSH Terms] OR (“helicobacter” [All Fields] AND “pylori” [All Fields]) OR “helicobacter pylori” [All Fields] OR “h pylori” [All Fields]) AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “treatment” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]) OR eradication [All Fields]) AND (“prevention and control”[Subheading] OR (“prevention” [All Fields] AND “control” [All Fields]) OR “prevention and control” [All Fields] OR “prevention” [All Fields]). A full manual search of all review articles, recently published editorials and retrieved original studies was also performed. Two of the authors (TR and PP) independently extracted data from suitable studies using a standard form. Any disagreement was settled by further discussion. The meta-analysis was performed in agreement with PRISMA [13].

Selection criteria

Inclusion and exclusion criteria were defined prior to the literature search. Hence, the following criteria had to be met for studies to be included in this meta-analysis: 1) published as full articles or abstracts; 2) written in English; and 3) randomized controlled trials (RCTs) or observational studies with data on the association of *H. pylori* eradication and GC prevention. Exclusion criteria were the following: 1) studies not meeting the inclusion criteria; 2) studies without data for retrieval; 3) duplicate studies; and 4) the less informative publication of two on the same study.

Statistical analysis

Authors’ agreement on study selection was measured by the κ coefficient. The pooled risk ratio (RR) and the 95% confidence interval (CI) were calculated and results of individual studies were compared by employing the Mantel-Haenszel method (fixed-effects model) [14] or the DerSimonian and Laird method (random-effects model) [15]. Forest plots were constructed for the visual display of RRs of individual studies. Heterogeneity between studies was measured with the Cochran Q test [16] and was judged significant when the Q test had a P-value of less than 0.10 [17,18]. In addition, the I^2 statistic was employed to estimate the rate of inconsistency in individual studies that could not be interpreted by chance [19]. When statistically significant heterogeneity was not present, pooled RRs (95% CI) were calculated using the fixed-effects model. If significant heterogeneity was present, pooled RRs (95% CI) were calculated using the random-effects model [17-19]. We also used cumulative meta-analysis to explore whether the association between *H. pylori* eradication and GC remained steady [18]. The Comprehensive Meta-Analysis software, version 2 (BIOSSTAT INC., Englewood, NJ, USA), was used in all calculations throughout this meta-analysis.

Sensitivity analyses and publication bias

In case of significant heterogeneity, except for the random-effects model, sensitivity analyses were employed to judge the consistency of the results. Thus, to explore any significant influence of single studies on the pooled RR results, we performed the exclusion method by repeating the meta-analysis after excluding single studies one at a time [18]. Furthermore, as different populations and study designs may incorporate various

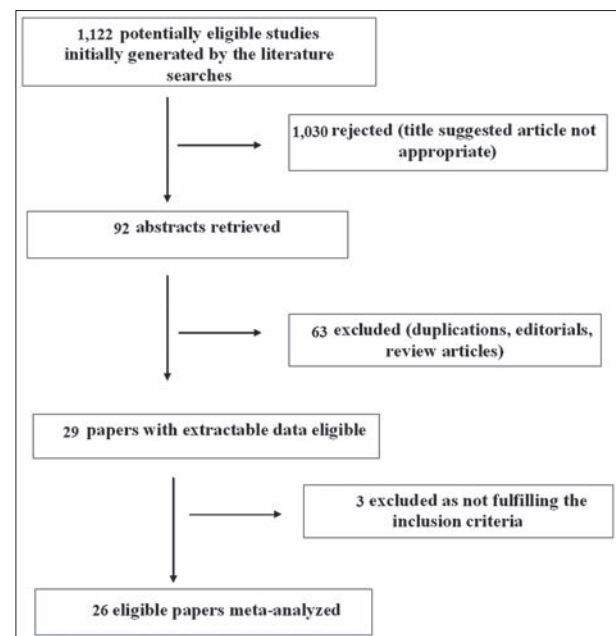


Figure 1 Flow diagram of the studies identified in this meta-analysis

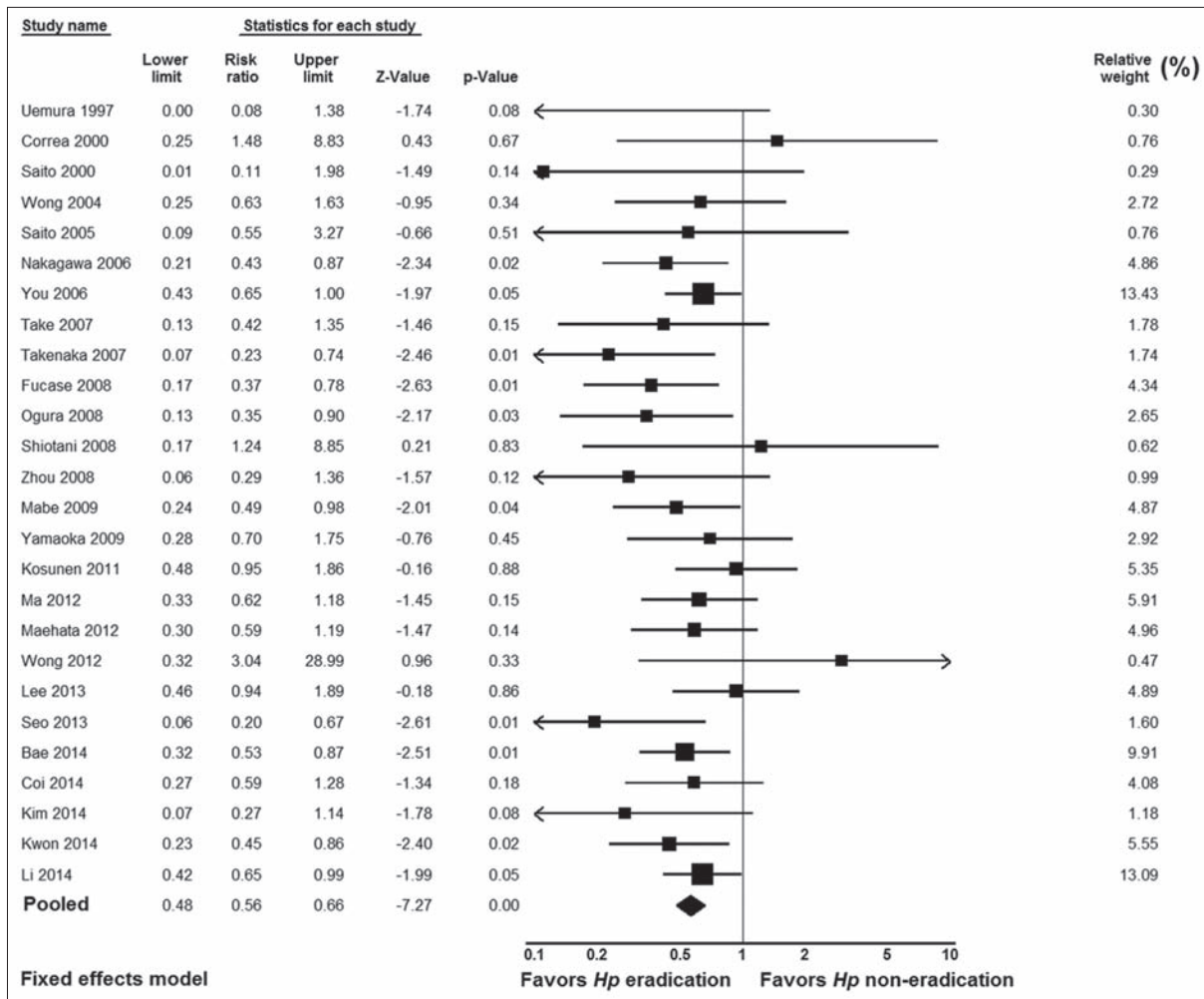


Figure 2 Forest plot showing individual and pooled risk ratios and 95% confidence intervals in studies comparing gastric cancer risk in *Helicobacter pylori* (*Hp*)-eradicated patients and in controls

biases, we employed subgroup analyses by stratifying all factors that could influence the overall results. In addition, we further explored possible heterogeneity using meta-regression analyses (methods of moments) [20]. The possibility of publication bias was examined by constructing funnel plots. These were constructed by plotting the log RRs vs. Standard Error (SE) of individual studies [20,21]. Their symmetry was measured by Egger’s regression test and the Begg and Mazumdar adjusted rank correlation test [22,23]. The adjustment for publication bias, i.e., calculation of the number of studies missing from the meta-analysis, was achieved by using the nonparametric “trim and fill” rank-based method of Duval and Tweedie [24].

Results

Descriptive assessment and characteristics of the studies

Agreement between the authors regarding the selection of suitable articles and data extraction was high: $\kappa=0.93$, 95%

CI 0.83-1. A flow chart explaining the study selection is shown in Fig. 1. Of the 1122 titles initially found by the literature searches, 26 studies were found suitable for meta-analysis, 8 RCTs and 18 observational (cohort) studies [25-50]. There were 24 studies from Far East countries (13 from Japan, 5 from China, 5 from Korea, 1 from Taiwan), 1 from Colombia and 1 from Finland. Table 1 shows the characteristics of the 26 eligible studies for meta-analysis.

GC risk in *H. pylori* treated patients and non-treated (controls)

A total of 22,619 patients and 29,744 controls were included in the 26 meta-analysis studies. There was no significant heterogeneity in the included studies: $Q=23.09$, $df(Q)=25$, $I^2=0\%$, $P=0.57$. Therefore, we applied the fixed-effects model, which yielded significant results: i.e., pooled RR result 0.56, 95% CI 0.48-0.66, test for overall effect $Z= -7.27$, $P=0.00001$ (Fig. 2). No publication bias was found, as seen in the funnel plot and its symmetry calculation: $P=0.11$ by adjusted rank correlation test and 0.14 by Egger’s regression test (Fig. 3).

Table 1 The main characteristics of the studies included in the meta-analysis

1 st author (Ref.)	Year	Region	Study design	Publication type	Follow up mean duration (yrs)	Eradication group		Control group (Non-eradicated)	
						Gastric cancer (n)	Total (n)	Gastric cancer (n)	Total (n)
Uemura [25]	1997	Japan	Cohort	Published paper	4	0	65	6	67
Correa [26]	2000	Colombia	Randomized control trial	Published paper	6	3	491	2	485
Saito [27]	2000	Japan	Cohort	Published paper	2	0	32	4	32
Wong [28]	2004	China	Randomized control trial	Published paper	7.5	7	817	11	813
Saito [29]	2005	Japan	Randomized control trial	Abstract	4	2	379	3	313
Nakagawa [30]	2006	Japan	Cohort	Published paper	2	8	356	129	2,469
You [31]	2006	Japan	Randomized control trial	Published paper	14.6	34	1,130	52	1,128
Take [32]	2007	Japan	Cohort	Published paper	3.9	9	953	4	178
Takenaka [33]	2007	Japan	Cohort	Published paper	3.2	6	1,519	5	288
Fucase [34]	2008	Japan	Randomized control trial	Published paper	3	9	255	24	250
Ogura [35]	2008	Japan	Cohort	Published paper	3.2	6	404	13	304
Shiotani [36]	2008	Japan	Cohort	Published paper	2.7	4	41	3	6
Zhou [37]	2008	China	Randomized control trial	Abstract	10	2	276	7	276
Mabe [38]	2009	Japan	Cohort	Published paper	5.6	47	3,781	9	352
Yanaoka [39]	2009	Japan	Cohort	Published paper	9.3	5	473	55	3656
Kosunen [40]	2011	Finland	Cohort	Published paper	10	11	3,650	37	11,638
Ma [41]	2012	China	Randomized control trial	Published paper	14.7	15	1,130	24	1,128
Maehata [42]	2012	Japan	Cohort	Published paper	3	15	177	13	91
Wong [43]	2012	China	Randomized control trial	Published paper	5	3	255	1	258
Seo [44]	2013	Korea	Cohort	Published paper	2	4	41	3	6
Bae [45]	2014	Korea	Cohort	Published paper	5	34	485	24	182
Choi [46]	2014	Korea	Randomized control trial	Published paper	3	10	439	17	441
Kim [47]	2014	Korea	Cohort	Published paper	4.3	2	49	16	107

Table 1 Continued..

1 st author (Ref.)	Year	Region	Study design	Publication type	Follow up mean duration (yrs)	Eradication group		Control group (Non-eradicated)	
						Gastric cancer (n)	Total (n)	Gastric cancer (n)	Total (n)
Kwon [48]	2014	Korea	Cohort	Published paper	3.2	18	214	13	69
Lee [49]	2014	Taiwan	Cohort	Published paper	5	15	4,121	16	4,121
Li [50]	2014	China	Randomized control trial	Published paper	15	51	1,086	33	1,086
Total						320	22,619	524	29,744

Table 2 Sub-group analyses by stratifying the data according to study design, geographical region and kind of prevention (primary vs. secondary)

Sub-groups (n studies)	RR (95% CI)	Z value	P value	Heterogeneity			
				Q value	Df (Q)	I ² %	P value
Core analysis							
Study design							
RCTs (n=8)	0.65 (0.51-0.84)	-3.33	0.0009	3.73	7	0	0.81
Cohort (n=18)	0.51 (0.42-0.62)	-6.63	0.00001	17.2	17	11.8	0.44
Geographical region							
Colombia (n=1)	1.48 (0.25-8.83)	0.43	0.67	-	-	-	-
Finland (n=1)	0.95 (0.48-1.86)	-0.16	0.88	-	-	-	1
Far East (n=24)	0.54 (0.46-0.63)	-7.51	0.000001	19.42	23	0	0.68
Kind of prevention (primary vs. secondary)							
Primary (n=16)	0.63 (0.52-0.77)	-4.62	0.000004	13.23	15	0	0.58
Secondary (n=10)	0.46 (0.36-0.60)	-5.91	0.000001	6.44	9	0	0.69

RR, risk ratio; CI, confidence interval; RCT, randomized control trial

Subgroup and sensitivity analyses

We performed subgroup analyses to examine whether the significant result found for all 26 studies would apply separately when the data were stratified according to study design (i.e., RCTs vs. cohort studies), geographical region, and kind of prevention, i.e., primary vs. secondary, according to whether or not early GC endoscopic resection was performed before *H. pylori* treatment was given to prevent the development of metachronous cancer. The results of these subgroup analyses are shown in Table 2. There were significant results for both groups of study design: i.e., 0.65 (0.51-0.84), Z= -3.33, P=0.0009 for RCTs, and 0.51 (0.42-0.62), Z= -6.63, P=0.00001 for cohort studies. Concerning geographical region, there were significant results for the Far East studies (0.54 [0.46-0.63], Z=-7.51, P=0.000001), whereas the results were not significant for the American study from Colombia (1.48 [0.25-8.83], Z=-0.43, P=0.67) or the European study from Finland (0.95 [0.48-1.86], Z= -0.16, P=0.88). There were significant results for both primary (0.63 [0.52-0.77], Z= -4.62, P=0.000004) and secondary prevention

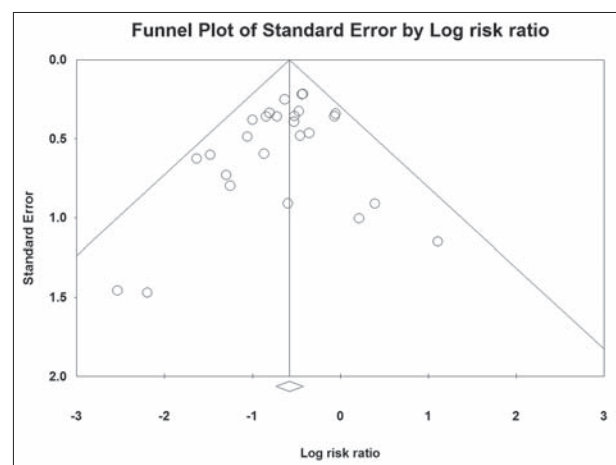


Figure 3 Funnel plot of all studies included in the meta-analysis. There is no evidence of publication bias (P=0.11 by Begg and Mazumdar adjusted rank correlation test and 0.14 by Egger's regression test)

(0.46 [0.36-0.60], Z= -5.91, P=0.000001). Additionally, more sensitivity analyses were utilized to detect the presence of

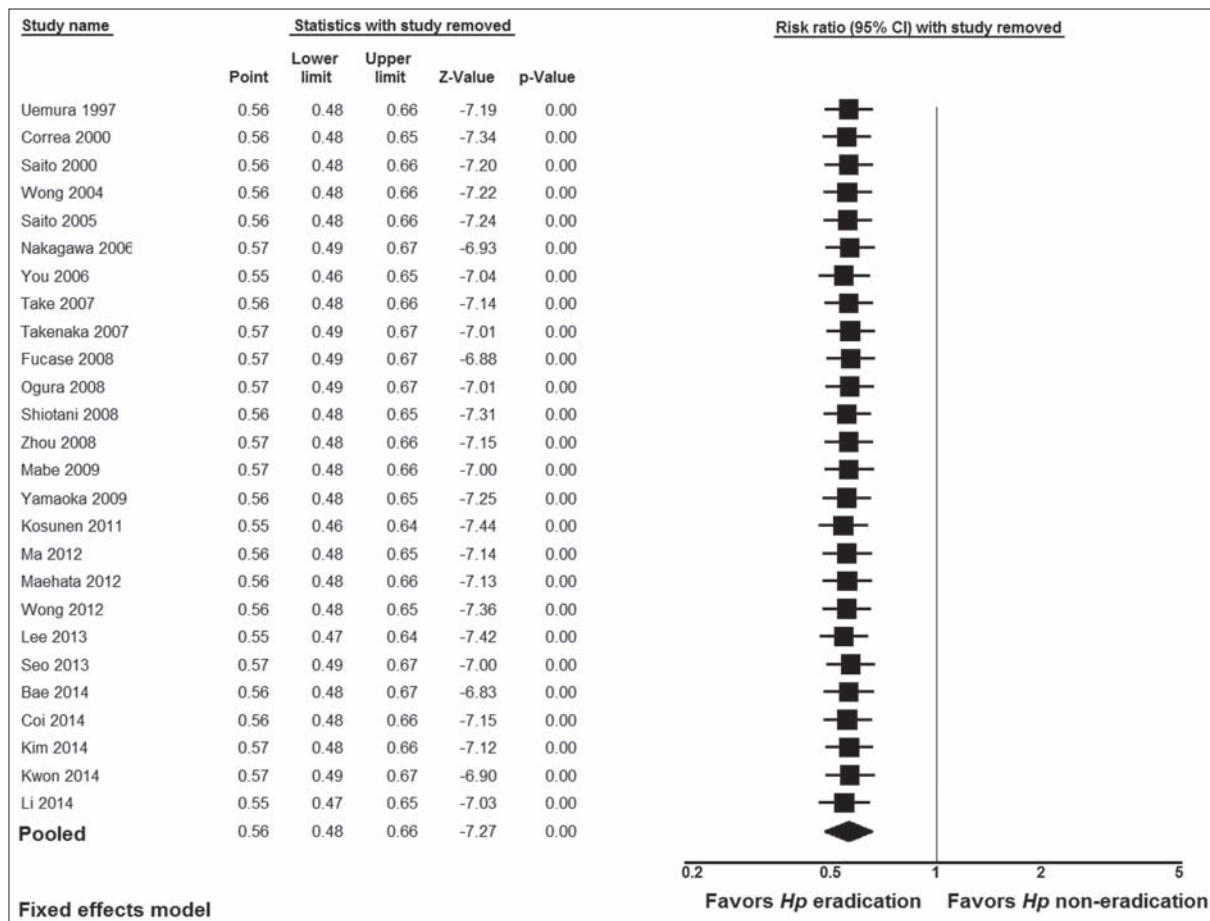


Figure 4 Exclusion sensitivity plot showing the effect of exclusion of any study on the magnitude of the summary estimate

any biases related to included populations and different study designs. The exclusion of any study did not alter the summary results substantially (Fig. 4). Furthermore, the results of the cumulative meta-analysis did not change over the years (Fig. 5). In addition, the meta-regression analyses showed no significant results for publication year ($Z=0.67$, $P=0.49$), but significant results for mean duration follow up ($Z=1.96.57$, $P=0.049$) (Fig. 6). The latter was expected as more cancers were noted in subjects who had longer duration of follow up.

GC risk according to baseline histology

Five studies [26,28,31,43,46] examined the GC risk according to baseline histology and the results are shown in Fig. 7. These studies stratified baseline histology into two groups: i.e., a group of subjects with chronic non-AG (NAG) or AG, and a group of subjects with IM or DYS. The RR [95% CI] was significant in the NAG/AG group (0.28 [0.08-0.96], $Z= -2.03$, $P=0.04$), but not in the IM/DYS group (0.84 [0.55-1.28], $Z= -0.83$, $P=0.41$).

Discussion

Despite the decline in its incidence in recent decades, GC remains a major health concern in many parts of the world. The development of GC constitutes a complex cascade of events, characterized mainly by interactions between *H. pylori* infection, host factors and environmental influences, such as diet [51]. Indeed, *H. pylori* plays a crucial role in this process, as most non-cardia GCs develop from *H. pylori*-infected mucosa [52]. In the gastric mucosa, *H. pylori* initiates a cascade of events, which may lead to chronic AG and then to IM, DYS, and finally carcinoma [53]. Such a proposal is supported by a substantial number of studies performed in countries with a high incidence of GC. Indeed, in these countries *H. pylori* eradication has been proposed as a potentially important primary preventive strategy to reduce GC incidence. The results of this meta-analysis showed that *H. pylori* eradication significantly reduces the risk of GC development, in comparison to non-eradication. This evidence was robust, as evidenced by the various sensitivity and other analyses. In addition, these results confirm earlier meta-analyses [12,54]. These significant

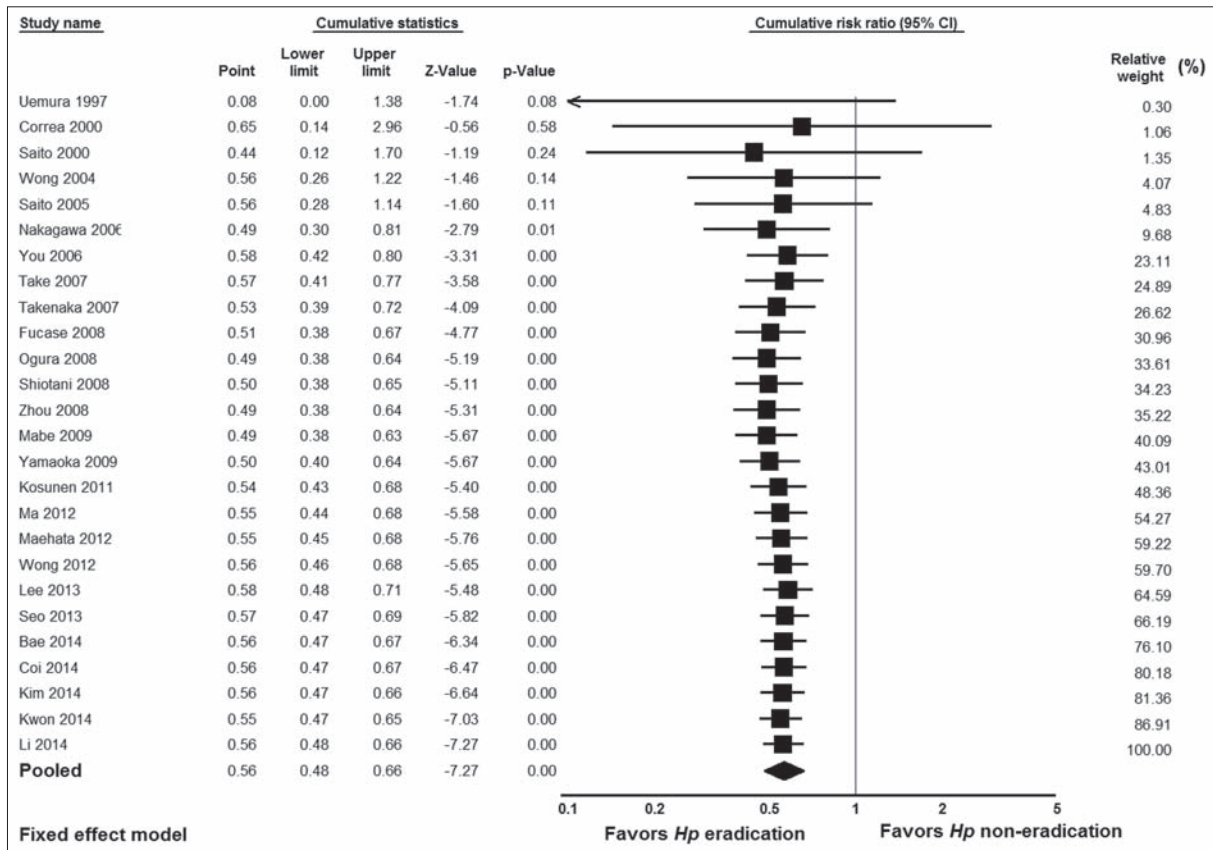


Figure 5 Cumulative meta-analysis of studies ordered by year of publication

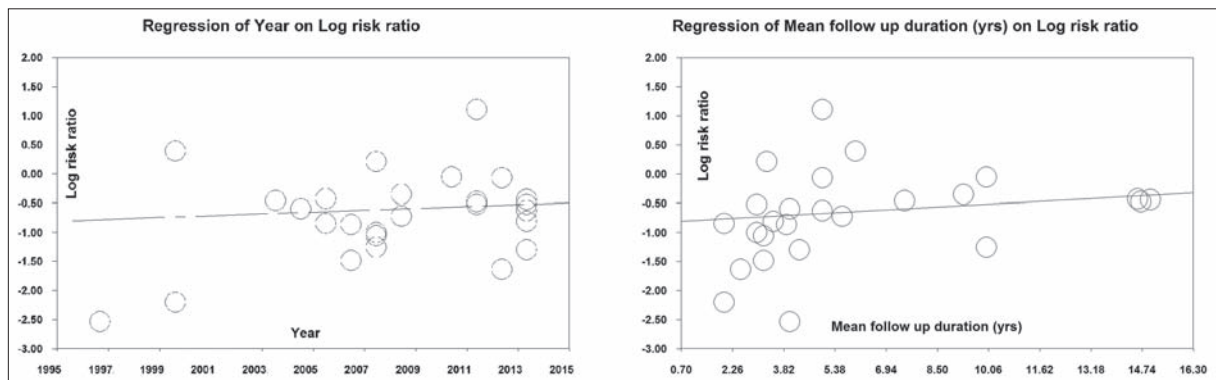


Figure 6 (A) Meta-regression analysis showing regression of publication year on log risk ratio. (B) Meta-regression analysis showing regression of mean follow-up duration on log risk ratio. Circles represent each study in the meta-analysis

results applied for primary prevention and also for secondary prevention, i.e., when evaluating the effect of *H. pylori* treatment on the risk of metachronous GC development after resection of early GC. These results support the notion that mass *H. pylori* screening and eradication is a viable preventive strategy and should be implemented in high-risk populations, especially in those with an incidence rate higher than 150/100,000 person-years [55]. The number needed to treat varies depending on the GC risk in various populations being studied. Thus, it was calculated that it could be as low as 15 infected men from areas

with a high risk of GC, such as China or Japan, in comparison to 250 in infected women from a low-risk area, such as the USA [12].

Some studies [26,28,31,43,46], examined the effect of *H. pylori* eradication on GC risk according to baseline histology. In these studies, baseline histology was stratified into two groups, i.e., a group of subjects with early histological events, namely chronic NAG or AG and a group of subjects with advanced histological events, namely IM or DYS. We meta-analyzed these data, and the results showed that the RR

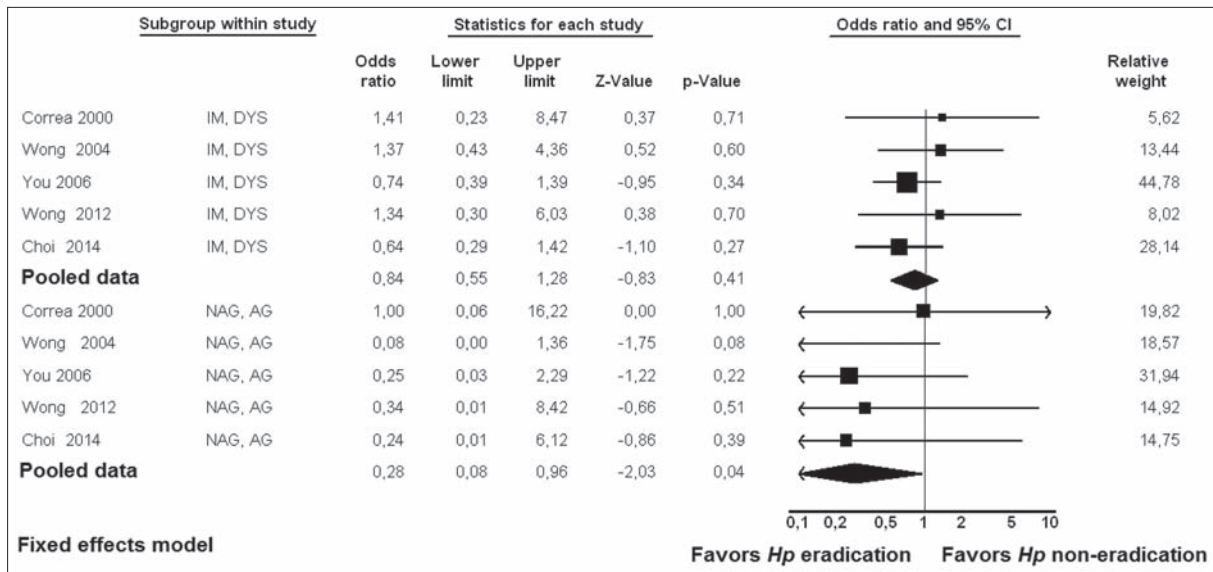


Figure 7 Forest plot showing individual and pooled risk ratios with 95% confidence intervals in studies comparing gastric cancer risk in *Helicobacter pylori* (*Hp*)-eradicated patients and in controls, according to baseline histology
 NAG, non atrophic gastritis; AG, atrophic gastritis; IM, intestinal metaplasia; DYS, dysplasia

Summary Box

What is already known:

- The International Agency for Research on Cancer declared *Helicobacter pylori* (*H. pylori*) as a class I human carcinogen and individuals who tested positive for *H. pylori* are at increased risk of developing gastric cancer (GC) compared with uninfected controls
- A growing body of evidence has suggested that *H. pylori* eradication might prevent GC development
- An earlier meta-analysis reported that *H. pylori* treatment could reduce the risk of GC in Asians

What the new findings are:

- This meta-analysis evaluated updated data concerning the effect of *H. pylori* eradication on GC risk and in particular examined the effect of *H. pylori* eradication on GC risk according to baseline histology
- The results support the notion that *H. pylori* is a significant risk factor for GC and that *H. pylori* eradication is associated with a reduction in the incidence of GC
- *H. pylori* eradication represents a primary preventive strategy in a subset of subjects with non-atrophic or atrophic gastritis. However, *H. pylori* eradication in patients who have already developed advanced pre-neoplastic lesions, i.e., intestinal metaplasia or dysplasia, does not prevent GC development

[95% CI] was significant in the NAG/AG group (0.28 [0.08-0.96], P=0.04), whereas in the IM/DYS group it was not (0.84 [0.55-1.28], P=0.41). These results suggest that *H. pylori* eradication represents a primary preventive strategy in a subset of subjects with NAG or AG. In contrast, *H. pylori* eradication in patients who have already developed advanced pre-neoplastic lesions, i.e., IM or DYS, does not prevent GC development. All this supports the notion that IM represents the “point of no return”, as was suggested previously [56,57] and was advocated by the recent Maastricht guidelines [58]. If we take into account that IM starts approximately in the fourth decade of life [59], all this could potentially mean that the implementation of *H. pylori* infection screening and treatment could be more effective well before the risk for GC starts increasing [60]. Thus, in Korea it was shown that *H. pylori* eradication might be most effective in the second decade of life [61].

The stability of the results over time, as shown in the cumulative meta-analysis chart and the lack of heterogeneity and publication bias, strengthens the results of this meta-analysis. However, there is a limitation in that 24 of the 26 meta-analyzed studies (92%) were conducted in far-eastern countries (13 in Japan, 5 in Korea, 5 in China, 1 in Taiwan) and only two were from other parts of the world (1 in Colombia, 1 in Finland). Therefore, more studies from non-far-eastern countries are needed to better define the role of *H. pylori* eradication in preventing GC. Additional limitations could be the fact that only studies written in English were included in this meta-analysis and the fact that baseline histology was available only in five studies. The latter stresses the need for more studies that take the baseline histology into account.

In conclusion, the results of this meta-analysis support the notion that *H. pylori* is a significant risk factor for GC. In addition, the results confirmed that *H. pylori* eradication is associated with a reduction in the incidence of GC and

may therefore be the most viable strategy for GC prevention. However, as these results come mainly from East Asian countries, they must be interpreted with caution for European and North American countries; more studies from these parts of the world are needed to better define the role of *H. pylori* eradication in preventing GC.

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