

Accepted Manuscript

Association Between *Helicobacter pylori* Eradication and Gastric Cancer Incidence: a Systematic Review and Meta-analysis

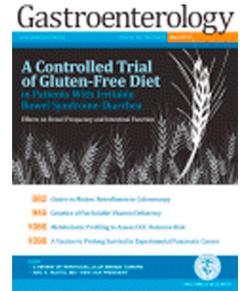
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PII: S0016-5085(16)00120-7
DOI: [10.1053/j.gastro.2016.01.028](https://doi.org/10.1053/j.gastro.2016.01.028)
Reference: YGAST 60255

To appear in: *Gastroenterology*
Accepted Date: 24 January 2016

Please cite this article as: Lee Y-C, Chiang T-H, Chou C-K, Tu Y-K, Liao W-C, Wu M-S, Graham DY, Association Between *Helicobacter pylori* Eradication and Gastric Cancer Incidence: a Systematic Review and Meta-analysis, *Gastroenterology* (2016), doi: 10.1053/j.gastro.2016.01.028.

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Title: Association Between *Helicobacter pylori* Eradication and Gastric Cancer

Incidence: a Systematic Review and Meta-analysis

Short title: *Helicobacter pylori* eradication and gastric cancer incidence

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Conflict of Interest disclosure: Dr. Graham is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies and has received research support for culture of *H.*

pylori. He is a consultant for Otsuka Pharmaceuticals regarding diagnostic breath testing and for BioGaia in relation to probiotic therapy for *H. pylori* infection. Other authors do not have conflicts of interest. Other authors report no conflict of interest.

Grant Support: This study was supported by the Health Promotion Administration, Ministry of Health and Welfare (MOHW103-TDU-212-114009), National Taiwan University Hospital (104-P01), and National Research Program for Biopharmaceuticals (104-2325-B-002-029). The funding source had no role in study design, data collection, analysis or interpretation, report writing or the decision to submit this paper for publication.

Contributors: The study was conceived by YC Lee, WC Liao, and MS Wu, with input from all the other listed contributors. YC Lee and TH Chiang contributed equally in this work. WC Liao and MS Wu contributed equally in this work. TH Chiang, YK Tu, and WC Liao conducted the statistical analyses. TH Chiang and CK Chou reviewed the literature. YC Lee, TH Chiang, WC Liao, YK Tu, and DY Graham drafted the article and all authors commented on drafts and approved the final version.

Funding: This study was supported by the Health Promotion Administration, Ministry of Health and Welfare, National Taiwan University Hospital, and National Research Program for Biopharmaceuticals.

ABSTRACT

Background & Aims: Eradication of *Helicobacter pylori* infection has been reported to reduce the risk of gastric cancer among asymptomatic individuals in high-risk areas. The magnitude of benefit of *H pylori* eradication in populations with different levels of gastric cancer risk and in different clinical scenarios is unclear. We performed a systematic review and meta-analysis of randomized controlled trials and observational studies to investigate the effects of *H pylori* eradication on the incidence of gastric cancer.

Methods: We searched PubMed, Cochrane Library, and ClinicalTrials.gov, reviewing titles and abstracts of studies of the effects of eradication of *H pylori* infection on risk of gastric cancer, through May 2015. We also searched bibliographies of included studies, related reviews, and abstracts presented at Digestive Disease Week.

Twenty-four eligible studies (22 research manuscripts and 2 abstracts) were included in our meta-analysis (715 incident gastric cancers among a total of 48,064 individuals/340,255 person-years). We assessed the effects, as well as their modification by baseline gastric cancer incidence, study design (randomized trial vs observational study), clinical scenario (asymptomatic infected individuals vs individuals after endoscopic resection of early gastric cancer), demographic characteristics of patients (age and sex), and duration of follow up.

Results: Results: After adjustment for baseline gastric cancer incidence, individuals with eradication of *H pylori* infection had a lower incidence of gastric cancer than those who did not receive eradication therapy (pooled incidence rate ratio, 0.53; 95% confidence interval (CI), 0.44–0.64). There was little heterogeneity among studies. Baseline gastric cancer incidence modified the benefit of *H pylori* eradication ($P=.037$ for interaction); the incidence rate ratio of gastric cancer decreased in a non-linear fashion with increasing baseline incidence of gastric cancer ($P=.018$, in comparison with the linear model). The benefit also modestly increased with age ($P=.023$ for interaction), but this might be due to correlation between age and baseline gastric cancer incidence. Eradication provided significant benefit for asymptomatic infected individuals (pooled incidence rate ratio, 0.62; 95% CI, 0.49–0.79) and individuals after endoscopic resection of gastric cancers (pooled incidence rate ratio, 0.46; 95% CI, 0.35–0.60). The benefits of *H pylori* eradication did not differ with study design, sex, or follow-up period.

Conclusions: In a systematic review and meta-analysis, we associated eradication of *H pylori* infection with a reduced incidence of gastric cancer. The benefits of eradication vary with baseline gastric cancer incidence, but apply to all levels of baseline risk.

Key words: stomach, tumor, risk factor, antibiotic

INTRODUCTION

Gastric cancer is a major global health threat¹⁻³ and is the third leading cause of cancer deaths worldwide causing an estimated more than 720,000 deaths per year globally.⁴ *H pylori* is the most important etiologic factor for gastric cancer. *H pylori* infects approximately 50% of the global population,⁴ and it is estimated that 89% of non-cardia gastric cancers, which accounts for 78% of gastric cancer cases, are attributed to *H pylori* infection.^{5, 6} *H pylori* promotes gastric carcinogenesis through multiple mechanisms. *H pylori* causes chronic gastric inflammation that may progress to the precancerous changes of atrophic gastritis and intestinal metaplasia. The risk of gastric cancer increases in relation to the severity and extent of those precancerous changes.⁷ Chronic *H pylori* infection may also contribute to gastric mucosal genetic instability⁸ by reducing gastric acid secretion (hypochlorhydria), which can promote the growth of gastric microbiome that processes dietary components into carcinogens.⁷ Eradication of *H pylori* may result in resolution 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.⁸ Since *H pylori* can be eradicated with a short-course of antibiotic treatment,⁴ identifying and eradicating *H pylori* infection could represent a viable strategy to reduce the enormous disease burden of gastric cancer.⁹

There has been increasing interest in mass *H pylori* eradication to prevent gastric cancer. However, the benefit of eradication varies in relation to baseline gastric cancer risk,¹⁰ which varies widely across regions and populations,⁴ and the extent to which mass *H pylori* eradication will affect gastric cancer incidence remains unclear. A recent meta-analysis combining six randomized controlled trials (RCTs) conducted in asymptomatic infected individuals reported that *H pylori* eradication reduced the risk of gastric cancer in Asians, but the effect might not be generalizable to areas with a lower incidence rate of gastric cancer.¹⁰ However, that study used the risk (*i.e.*, the number of gastric cancer cases at the end of follow-up divided by the number of individuals at baseline) for the intervention and comparison groups in each study to conduct meta-analysis and expressed the results with risk ratios; this approach does not take into account differences in follow-up duration and loss to follow-up. Controversies also exist regarding whether eradication could still provide protection against gastric cancer once atrophic gastritis and/or intestinal metaplasia develops. One RCT conducted in asymptomatic infected individuals showed that eradicating *H pylori* reduced the incidence of gastric cancer only in subjects without premalignant gastric lesions but not in those with atrophic gastritis, suggesting there may be a point of no return beyond which irreversible molecular changes renders eradication ineffective or less effective in preventing progression to cancer.¹¹ However, other

RCTs reported that *H pylori* eradication could reduce subsequent cancer incidence among individuals with atrophic gastritis¹² and those with early gastric cancer¹³ who often harbor significant atrophic gastritis and/or intestinal metaplasia in the stomach, arguing against the existence of an absolute point of no return. Collectively, the magnitude of the benefit of *H pylori* eradication among diverse populations, who have different interaction between host genetic and bacterial virulent factors and thus harbor different levels of gastric cancer risk,¹⁴ remains unclear and the knowledge gap remains wide.

A better understanding of the size of the benefit to be expected following eradicating *H pylori* in populations with differing levels of gastric cancer risk is crucial in deciding whether and how mass eradication of *H pylori* should be implemented. We conducted a systematic review and meta-analysis of RCTs and cohort studies conducted in both asymptomatic *H pylori* carriers (*i.e.*, primary prevention) and in individuals undergoing endoscopic resection of early gastric cancer (*i.e.*, tertiary prevention) to investigate the association between *H pylori* eradication and gastric cancer incidence.

METHODS

Search strategy and selection criteria

We performed a systematic review in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.¹⁵ Two investigators (THC and CKC) independently searched PubMed, Cochrane Library, and ClinicalTrials.gov and reviewed titles/abstracts for studies that examined eradication of *H pylori* and subsequent risk of gastric cancer until the end of May 2015 without language or date restriction by using the terms of “*Helicobacter pylori*” and “gastric cancer” (see **Appendix** for the search strategy). We manually searched bibliographies of included studies, related reviews, and abstracts presented at Digestive Disease Week in the USA for additional references. RCTs and cohort studies that compared individuals receiving *H pylori* eradication with those not receiving eradication with respect to incident gastric cancer or metachronous recurrence after endoscopic resection of gastric cancer were eligible for meta-analysis. For studies that assessed other chemopreventive interventions in addition to *H pylori* eradication, we used the arm that received *H pylori* eradication alone and the arm that received placebo or no treatment for meta-analysis; arms that received other interventions with/without *H pylori* eradication were excluded. Studies that did not include a comparison group (*i.e.*, receiving placebo or no treatment) or evaluated patients who had undergone partial gastrectomy were excluded from

meta-analysis.

Data extraction and assessment for study quality

Two investigators (THC and CKC) independently reviewed full manuscripts of eligible studies and extracted information into an electronic database, including author, publication year, country where the study was conducted, study design, sample size, duration of follow-up, participants' characteristics, inclusion and exclusion criteria, diagnostic criteria for *H pylori* infection, the number of subjects in both intervention and comparison groups, the number of incident gastric cancers in both intervention and comparison groups, the modality used during endoscopic resection for early gastric cancer in the tertiary prevention trials, and the final outcomes. The same reviewers independently evaluated the risk of bias of included RCTs with the Cochrane risk of bias tool¹⁶ and assessed the quality of cohort studies with the Newcastle-Ottawa scale.¹⁷ Disagreement was resolved by joint review of the manuscript to reach consensus. When multiple articles for a single study were found, we used data from the latest publication.

Data synthesis and analysis

To account for differences in follow-up durations, we used incidence rate of gastric cancer for conducting meta-analysis. Random effects models were used for all meta-analyses to account for potential heterogeneity among studies. Two

approaches were undertaken for data synthesis. We first conducted random-effects meta-analysis proposed by DerSimonian and Laird with the use of the incidence rate ratio as the measure of effect size.¹⁸ Pre-planned subgroup meta-analyses were undertaken for studies of low, intermediate, and high baseline incidence of gastric cancer (defined by the tertiles of incidence rates in the groups not receiving eradication in the included studies). Subgroup analyses were also conducted with regard to study designs (*i.e.*, RCT or cohort study) and clinical scenarios (*i.e.*, asymptomatic *H pylori* carriers or patients with prior endoscopic resection of gastric cancer). We used meta-regression to evaluate whether incidence rate ratio differed by tertiles of baseline cancer incidence, study designs, and clinical scenarios. Potential small study bias was evaluated by funnel plots and by Egger's test¹⁹ and Begg's test.²⁰ Heterogeneity was evaluated by I^2 and Cochran's Q.²¹

Second, as traditional meta-analysis can introduce bias when using continuity corrections for studies with no event in one of the study arms,²² we also conducted meta-analysis using generalized linear mixed models.²³ We used random effect Poisson regression to model the effect of *H pylori* eradication on gastric cancer incidence with the number of cases as the outcome and the person-year as the offset in the model. The study-by-treatment interaction was included as the random effect in the regression model.

We further evaluated whether the effect of *H pylori* eradication on subsequent gastric cancer incidence was modified by the baseline gastric cancer incidence with the inclusion of interaction terms between the treatment and baseline gastric cancer incidence as fixed effects in the model; baseline gastric cancer incidence was treated as a continuous variable in the analysis because the incidence rate was apparently a continuous variable and categorizing a continuous variable might result in loss of information.²⁴ This approach also enabled us to assess how the benefit of eradication changed linearly/nonlinearly with varying baseline gastric cancer incidence. If significant interaction between treatment and baseline gastric cancer incidence existed, the relation between incidence rate ratio and baseline cancer incidence was modeled using restricted cubic splines with three knots to explore potential non-linear relationship as well as the threshold value for a significant treatment effect. Likewise, we examined whether study design (*i.e.*, RCT vs. cohort), clinical scenario (*i.e.*, asymptomatic infected individuals vs. individuals after endoscopic resection of early gastric cancer), demographic characteristics (*i.e.*, age and gender), and follow-up duration would modify the effect of *H pylori* eradication on subsequent gastric cancer incidence. All *p* values were two-sided, and $p < 0.05$ was considered to indicate statistical significance.

For sensitivity analysis, we first excluded studies that were published as abstracts. Second, we repeated the analysis with the exclusion of each study in turn to evaluate whether any study had excessive influence on the results of our meta-analysis.

All meta-analyses were conducted using the statistical software package Stata 14 (StataCorp, College Station, Texas, US).

RESULTS

Literature search

We identified 8,061 articles for review of title and abstract (**Figure 1**). After initial screening, full-text of potentially eligible articles was retrieved for detailed assessment. Twenty-four eligible studies including 22 full-text manuscripts and two abstracts were included for meta-analysis, with 715 incident gastric cancers among a total of 48,064 individuals/340,255 person-years. Study characteristics and outcomes are summarized in **Table 1**. Among included studies, 14 studies^{11, 25-37} were conducted in asymptomatic infected individuals and 10 studies^{13, 38-46} in individuals who had undergone endoscopic resection of early gastric cancers. Most studies were conducted in Asia; only two studies were conducted in other regions (Colombia and Finland).^{25, 36} The mean age at enrollment ranged from 42 to 63 years in all studies except a cohort study³⁰ from Japan which focused on elderly patients (68 to 90 years).

Except two studies^{26, 28} reported in the abstract form, all included studies were considered as high or moderate quality (**Appendix Table 1 and 2**).

Traditional random-effects meta-analysis

Among all 24 studies, gastric cancer developed in 253 of 20,484 infected individuals who received eradication therapy, compared with 462 of 27,580 infected individuals who did not receive anti-*H pylori* treatment. No significant small study bias was found (Begg's test, $p=0.17$, and Egger's test, $p=0.18$; **Appendix Figure 1**).

Individuals receiving eradication had a lower incidence rate of gastric cancer than those without eradication; the pooled incidence rate ratio was 0.54 [95% confidence interval (CI): 0.46 to 0.65] without significant heterogeneity ($I^2=0\%$, $p=0.67$) (**Figure 2**).

The baseline gastric cancer incidence (*i.e.*, incidence rate of gastric cancer in the group not receiving eradication) in each study varied widely from 34.3 to 10,256.4 per 100,000 person-years (**Table 1**). All studies of the intermediate and the highest tertiles of incidence were conducted in Asia. Of the 8 studies in the highest tertile of baseline incidence, one study assessed the preventive effect of eradication in individuals with gastric adenoma at baseline³⁰, and others evaluated cancer incidence after endoscopic resection of early gastric cancer. As shown in **Figure 2**, in studies categorized into the intermediate (314.3 to 2,941.2 per 100,000 person-years)

and highest tertiles (2,970.0 to 10,256.4 per 100,000 person-years) of baseline gastric cancer incidence, individuals receiving anti-*H pylori* treatment had a significantly lower incidence of gastric cancer as compared with those who did not receive treatment; the pooled incidence rate ratios were 0.49 (95% CI: 0.38-0.64) and 0.45 (95% CI: 0.32-0.64), respectively. The benefit of *H pylori* eradication was non-significant in studies of the lowest tertile of gastric cancer incidence (34.3-253.6 per 100,000 person-years); the pooled incidence rate ratio was 0.80 (95% CI: 0.56-1.15).

Meta-regression analysis reaffirmed that the quantitative benefit of *H pylori* eradication was greater in studies with higher baseline incidence rates of gastric cancer. Using studies of the lowest tertile of baseline incidence as reference, the pooled incidence rate ratios for eradication vs. non-eradication were reduced by 43.5% (95% CI: 4.3%-66.6%) in the highest tertile and by 38.4% (95% CI: 1.7%-61.4%) in the intermediate tertile, respectively.

Subgroup analyses according to different clinical scenarios (**Figure 3**) showed that the quantitative benefit of eradication seemed greater among individuals after endoscopic resection of gastric cancers (pooled incidence rate ratio: 0.46, 95% CI: 0.35-0.60) than among asymptomatic infected individuals (pooled incidence rate ratio: 0.62, 95% CI: 0.49-0.79), but the difference was not significant ($p=0.12$ by

meta-regression). The benefit of *H pylori* eradication was comparable in RCTs and cohort studies, with pooled incidence rate ratios of 0.60 (95% CI: 0.44-0.81) and 0.52 (95% CI: 0.41-0.64), respectively ($p=0.44$ by meta-regression).

Mixed-effect Poisson regression meta-analysis

Results of the mixed-effect Poisson regression meta-analysis were similar with those of the traditional meta-analyses. Individuals who received *H pylori* eradication had a lower incidence of gastric cancer than those who did not receive eradication therapy; the pooled incidence rate ratio was 0.53 (95% CI: 0.44-0.64) with little heterogeneity across studies (**Table 2, model 1**). Interaction analyses showed that baseline gastric cancer incidence significantly modified the benefit of eradication (**model 2**); the incidence rate ratio of gastric cancer decreased in a non-linear fashion with rising baseline incidence rate ($p=0.018$ in comparison with linear model) (**Figure 4**). The upper 95% confidence interval of incidence rate ratio for eradication decreased to below 1 when baseline gastric cancer incidence exceeded 150 per 100,000 person-years, and the incidence rate ratio continued to decrease with rising baseline incidence up to around 1,200 per 100,000 person-years and then stabilized. With exclusion of two studies^{25, 39} that did not provide information on age of participants, age also seemed to modestly modify the benefit of eradication (**model 5**, p -value interaction=0.023); the incidence rate ratio decreased by 3% (95% CI:

0%-5%) with every one year increase in the median age of participants. However, the interaction between age and eradication became non-significant (p-value interaction=0.25) when interaction between eradication and baseline incidence was also entered into the model; therefore, the impact of age on the effect of eradication might be due to the fact that studies with older patients tended to have higher baseline gastric cancer incidence. The benefit conferred by *H pylori* eradication did not differ by study design, clinical scenario, the percentage of male subjects, or follow-up duration (**model 3, 4, 6 or 7**). No material difference in results was noted in pre-specified sensitivity analyses, and no individual study had excessive influence on the summary estimate.

DISCUSSION

This meta-analysis is the first to evaluate the association between *H pylori* eradication and the incidence of gastric cancer across different levels of baseline gastric cancer risk and in different clinical scenarios. Our results support the concept that *H pylori* eradication effectively reduces the incidence of gastric cancer, and the magnitude of the protective effect is greater among individuals with higher baseline gastric cancer risk.

In the two previous meta-analyses that also evaluated the effect of *H pylori* eradication on gastric cancer prevention, the estimated relative risks were closer to 1 and had wider confidence intervals (0.65, 95% CI: 0.43-0.98⁴⁷, and 0.66, 95% CI: 0.46-0.95¹⁰, respectively) compared with our estimates. Several reasons might explain why our meta-analysis showed greater benefit with better precision. The two previous meta-analyses summarised only five and six RCTs, respectively. Furthermore, those RCTs were conducted in asymptomatic carriers; most of those individuals likely belonged to the subgroup with the lowest gastric cancer risk among all *H pylori*-infected individuals.^{11, 25, 26, 28, 29} Therefore, the evidence base in previous meta-analyses was relatively limited. Secondly, previous meta-analyses used risk ratios to conduct meta-analysis, but risk ratios did not account for differences in follow-up durations between/within studies and thus could yield less precise pooled estimates. Our pooled rate ratio (0.63, 95% CI: 0.50-0.81) for asymptomatic carriers (baseline incidence from 68.7 to 314.3 per 100,000 person-year in the included RCTs) was similar to those from previous meta-analyses but with a narrower confidence interval. We were also able to identify that *H pylori* eradication provided even greater benefit among high-risk individuals. Taken together, our meta-analysis has a wider evidence base and greater statistical power with more precise estimates; therefore,

our results should better reflect the full spectrum of the potential benefit of implementing mass *H pylori* eradication for gastric cancer prevention.

The novel finding that the protective effect of *H pylori* eradication increased along with increasing gastric cancer incidence argues against an absolute point-of-no-return and has important implications. Atrophic gastritis and intestinal metaplasia from *H pylori*-induced chronic inflammation are the major histologic risk factors for gastric cancer,^{7, 9, 25} underscoring the need to prevent the occurrence of these precancerous conditions or reduce subsequent progression to cancer. Three previous studies^{11, 36, 38} suggested that eradicating *H pylori* might not reduce the risk of gastric cancer in individuals who has already developed atrophic gastritis and/or intestinal metaplasia, but those studies either used premalignant gastric lesions as surrogate endpoints^{36, 37} or had only limited sample size in the subgroups of atrophic gastritis and/or intestinal metaplasia;¹¹ therefore, those studies might have inadequate statistical power. One meta-analysis suggested that only subjects with non-atrophic gastritis and atrophic gastritis could benefit from *H pylori* treatment on gastric cancer risk but not subjects with intestinal metaplasia or dysplasia;⁴⁸ however, that study was inevitable limited by the patchy distribution of intestinal metaplasia in stomach and the variation in biopsy methods across studies. Our meta-analysis shows that *H pylori* eradication is associated with a reduction of gastric cancer risk

even among high-risk individuals, supporting that *H pylori* eradication is beneficial in individuals with atrophic gastritis and/or intestinal metaplasia. Other lines of evidence also support our finding. First, almost all gastric cancer patients have atrophic gastritis and/or intestinal metaplasia,¹³ and our meta-analysis showed that eradicating *H pylori* after endoscopic resection of early gastric cancer reduced the risk of metachronous cancer by 54%. Second, our population-based mass eradication program on Matsu Island of Taiwan found that *H pylori* eradication could reduce the severity or reverse the presence of atrophic gastritis among subjects with premalignant gastric lesions at baseline and reduced gastric cancer incidence by 25%, from 40.3 to 30.4 per 100,000 person-years.³⁷

The notable finding that *H pylori* eradication confers greater protection against gastric cancer for individuals with a higher baseline cancer risk might be attributed to the phenomenon that the risk of gastric cancer increases exponentially over time in those high-risk individuals.⁴⁹ Therefore, the difference in subsequent cancer risk between eradicated and non-eradicated groups in an individual study is likely to be greater if eradication is provided when the cancer risk has increased to a higher level, and studies on high-risk individuals might have superior statistical power than studies on low-risk individuals.⁵⁰ Indeed, even with relatively limited sample size and follow-up duration, the benefit of *H pylori* eradication was evident in the included

studies that assessed individuals undergoing endoscopic resection of early gastric cancer, who belonged to the subset of individuals at the highest risk of gastric cancer.⁵¹

Without effective preventive measures, the current high incidence of gastric cancer is projected to remain stable or even increase by 2030.⁴ The International Agency for Research on Cancer has indicated the urgent need for effective preventive measures and for a critical assessment of *H pylori* eradication as a preventive strategy.⁵² Our results support that mass *H pylori* screening and eradication is a viable preventive strategy and should be implemented in high-risk populations/areas, especially in those with an incidence rate higher than 150/100,000 person-years. While we found that the protective effect of *H pylori* eradication is less conspicuous in low-incidence individuals, this finding does not argue against implementing *H pylori* eradication for gastric cancer prevention in low-incidence populations. Overall, our results clearly show that eradication protects against gastric cancer; the 95% confidence interval of the pooled incidence rate ratio crossing one when incidence rate is below 150/100,000 person-years reflects limited statistical power due to smaller effect size and relative paucity of evidence from low-incidence areas. Furthermore, *H pylori* infection can be reliably identified with non-invasive methods and eradicated with an overall success rate above 90%^{53, 54} through selecting a regimen with or without

clarithromycin according to the 15%-20% threshold of macrolide resistance in a specific population.⁹ In light of the unequivocal benefit of *H pylori* eradication, future long-term placebo controlled trials for high-risk population would be unethical. How *H pylori* eradication should be implemented in low-incidence populations/areas should be further evaluated. For instance, in areas with intrinsically lower rates of gastric cancer (e.g., much of Europe and North America), there are high-risk populations (such as immigrants from high-risk areas) and thus eradication may need to be focused; simulation studies have shown that such a strategy would be cost-effective in the long run.⁵⁵

Our meta-analysis addresses the limitations of existing research and has several strengths. Most of previous studies were underpowered; it is estimated that even in a high-risk population with an annual incidence rate of 200 per 100,000 person-years, 17,625 individuals per group with a follow-up duration of 10 years are need for an RCT to demonstrate a 50% reduction in gastric cancer incidence with eradication against placebo.⁴⁹ Our meta-analysis evaluated the association between *H pylori* eradication and the incidence of gastric cancer across diverse populations/scenarios with different levels of baseline gastric cancer risk, comprising 20,484 treated and 27,580 untreated individuals with a total follow-up of 340,255 person-years. The agreement between results from different meta-analytic methods supports that the

results are robust. Our results provide a more comprehensive and precise estimate of the potential benefit of implementing *H pylori* eradication among populations at different levels of gastric cancer risk and should have better generalizability.

Our study also has some limitations. First, all but two of the included studies were conducted in East Asia; therefore, whether the results can be extrapolated to other high-risk areas remains unclear. Second, the presence and severity of atrophic gastritis and intestinal metaplasia were not uniformly assessed and reported in the included studies (*i.e.*, they lacked risk stratification: **Appendix Table 3**). Therefore, it remains speculative to translate the magnitude of benefit for subjects with early gastric cancer to those who have precancerous changes in their gastric mucosae. Also, we could not further clarify how the extent and severity of those precancerous conditions modifies the preventive effect of *H pylori* eradication. However, accurate determination of the extent and severity of atrophic gastritis and intestinal metaplasia requires endoscopic examination and histological assessment; routine ascertainment of this information before eradication is neither feasible nor necessary for most *H pylori*-infected individuals. Third, the outcome assessment may be different between primary and tertiary prevention studies; the former may obtain the information from cancer registries (most cancers had clinical symptom) while the latter may mainly from endoscopic surveillance (most cancers were asymptomatic). However, gastric

cancer was characteristic for its rapid progression with a preclinical detectable phase of only about 1.4 years.⁵⁶ Without treatment, gastric cancers early in stage will eventually progress to the symptomatic stage in a short time period such that the difference between these two approaches would be minimal. This interpretation was also supported by our subgroup analysis that showed no significant difference between the different clinical scenarios. Lastly, this meta-analysis was conducted using summary statistics rather than individual data. The modest interaction between age and *H pylori* eradication may be influenced by collinearity between age and baseline gastric cancer incidence. However, there might be some covariates that could influence the effect of eradication, but were not reported and thus could not be adjusted. Access to and examination of data from individual participants should allow further identification and control of potential confounding factors.

In conclusion, our meta-analysis confirmed that *H pylori* eradication is associated with a reduction of the incidence of gastric cancer. Although the level of benefit varies, it presents across all levels of baseline gastric cancer risk. *H pylori* eradication may be the most viable strategy for gastric cancer prevention.

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Author names in bold designate shared co-first authorship.

FIGURE LEGENDS

Figure 1. Flow chart of literature search and selection

Figure 2. Summary incidence rate ratio of gastric cancer associated with *H pylori* eradication by traditional random-effects meta-analysis, stratified by baseline incidence of gastric cancer

Figure 3. Summary incidence rate ratio of gastric cancer associated with *H pylori* eradication by traditional random-effects meta-analysis, stratified by clinical scenario (asymptomatic infected individuals vs. individuals after endoscopic resection of early gastric cancer)

Figure 4. Non-linear relation between incidence rate ratio of gastric cancer associated with *H pylori* eradication and baseline gastric cancer incidence.

IRR, incidence rate ratio; CI, 95% confidence interval. Circles indicate incidence rate ratios in individual studies; size of bubble is proportional to precision (inverse of variance) of incidence rate ratio. Note that the upper bound of 95% CI starts to decrease less than 1 and becomes statistically significant when the baseline

incidence exceeds the threshold value of approximately 150 per 100,000 person-years.

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TABLES

Table 1. Characteristics of studies evaluating the effect of *H pylori* eradication on the primary and tertiary prevention of gastric cancer

Author, Year	Country	Mean age (year)	Male (%)	Mean follow-up (month)	Treatment group			Comparison group		
					Total, n	GC, n	GC incidence, /100,000 PY	Total, n	GC, n	GC incidence (baseline incidence), /100,000 PY
Studies on asymptomatic infected individuals (primary prevention)										
Randomized controlled trial										
Correa et al, 2000	Colombia	51.1	46.0	72	491	3	101.8	485	2	68.7
Wong et al, 2004	China	42.2	54.0	90	817	7	114.2	813	11	180.4
Saito et al, 2005,	Japan	NA	NA	48	379	2	131.9	313	3	239.6
You et al, 2006	China	50.7	51.4	176	1130	34	205.1	1128	52	314.3
Zhou et al, 2008,	China	53.4	47.8	120	276	2	72.5	276	7	253.6
Wong et al, 2012	China	52.9	46.1	60	255	3	235.3	258	1	77.5
Cohort study										
Saito et al, 2000	Japan	79.2	54.7	24	32	0	0	32	4	6250.0
Take et al, 2007	Japan	50	88.7	47	953	9	241.1	178	4	573.8
Takenaka et al, 2007	Japan	53.6	71.3	38	1519	6	124.7	288	5	548.2
Ogura et al, 2008	Japan	62.9	56.5	38	404	6	469.0	304	13	1350.4
Mabe et al, 2009	Japan	52.9	71.7	67	3781	47	222.6	352	9	457.9

Yanaoka et al, 2009	Japan	49.8	99.9	112	473	5	117.3	3656	55	156.7
Kosunen et al, 2011	Finland	55.3	50.0	121	3650	11	29.0	11638	37	34.3
Lee et al, 2013	Taiwan	49.2	45.8	60	4121	15	72.8	4121	16	77.7
Studies on individuals after endoscopic resection of early gastric cancer (tertiary prevention)										
Randomized controlled trial										
Fukase et al, 2008	Japan	68	76.5	36	272	9	1102.9	272	24	2941.2
Choi et al, 2014	Korea	60	67.7	36	444	10	750.8	457	17	1240.0
Cohort study										
Uemura et al, 1997	Japan	69	72	36	65	0	0	67	6	2985.1
Nakagawa et al, 2006	Japan	NA	NA	24	356	8	1123.6	2469	129	2612.4
Shiotani et al, 2008	Japan	66	84	33	80	9	4090.9	11	1	3305.8
Maehata et al, 2012	Japan	69	72.3	36	177	15	2824.9	91	13	4761.9
Seo et al, 2013	Korea	62	67.6	27	61	6	4371.6	13	3	10256.4
Kwon et al, 2014	Korea	61	67.1	40	214	10	1401.9	69	10	4347.8
Bae et al, 2014	Korea	63	78.5	56	485	34	1470.0	182	24	2970.0
Kim et al, 2014	Korea	64	74.3	58	49	2	844.5	107	16	3093.8

Abbreviation: GC=gastric cancer; PY=person year; NA=not available

Table 2. Effects of *H pylori* eradication and other variables on the incidence rate of gastric cancer

Variables included into models ^a							
	Eradication	Eradication × baseline risk	Eradication × cohort study ^b	Eradication × tertiary prevention ^c	Eradication × age ^d	Eradication × gender ^e	Eradication × follow-up duration ^f
Model 1							
Incidence rate ratio	0.53 (0.44-0.64)						
Model 2							
Incidence rate ratio	0.63 (0.50-0.81)						
Interaction p value		0.037					
Model 3							
Incidence rate ratio	0.60 (0.44-0.80)						
Interaction p value			0.340				
Model 4							
Incidence rate ratio	0.61 (0.48-0.78)						
Interaction p value	-			0.097			
Model 5							
Incidence rate ratio	0.52 (0.43-0.63)						
Interaction p value					0.023		
Model 6							
Incidence rate ratio	0.53 (0.44-0.64)						

Interaction p value		0.103
Model 7		
Incidence rate ratio	0.51 (0.42-0.61)	
Interaction p value		0.064

^a Study-specific effects are omitted from the table.

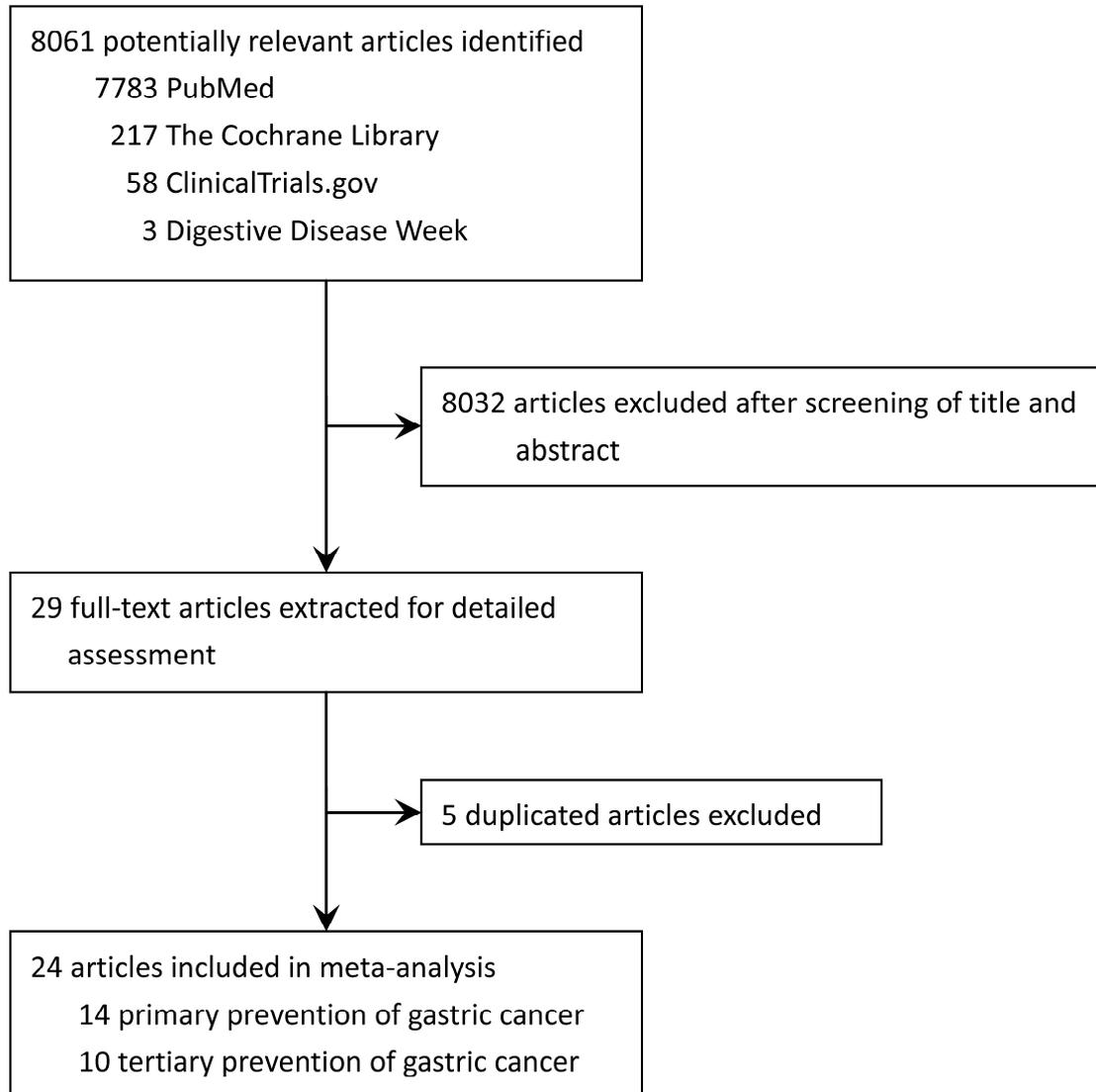
^b Randomized controlled trial as reference.

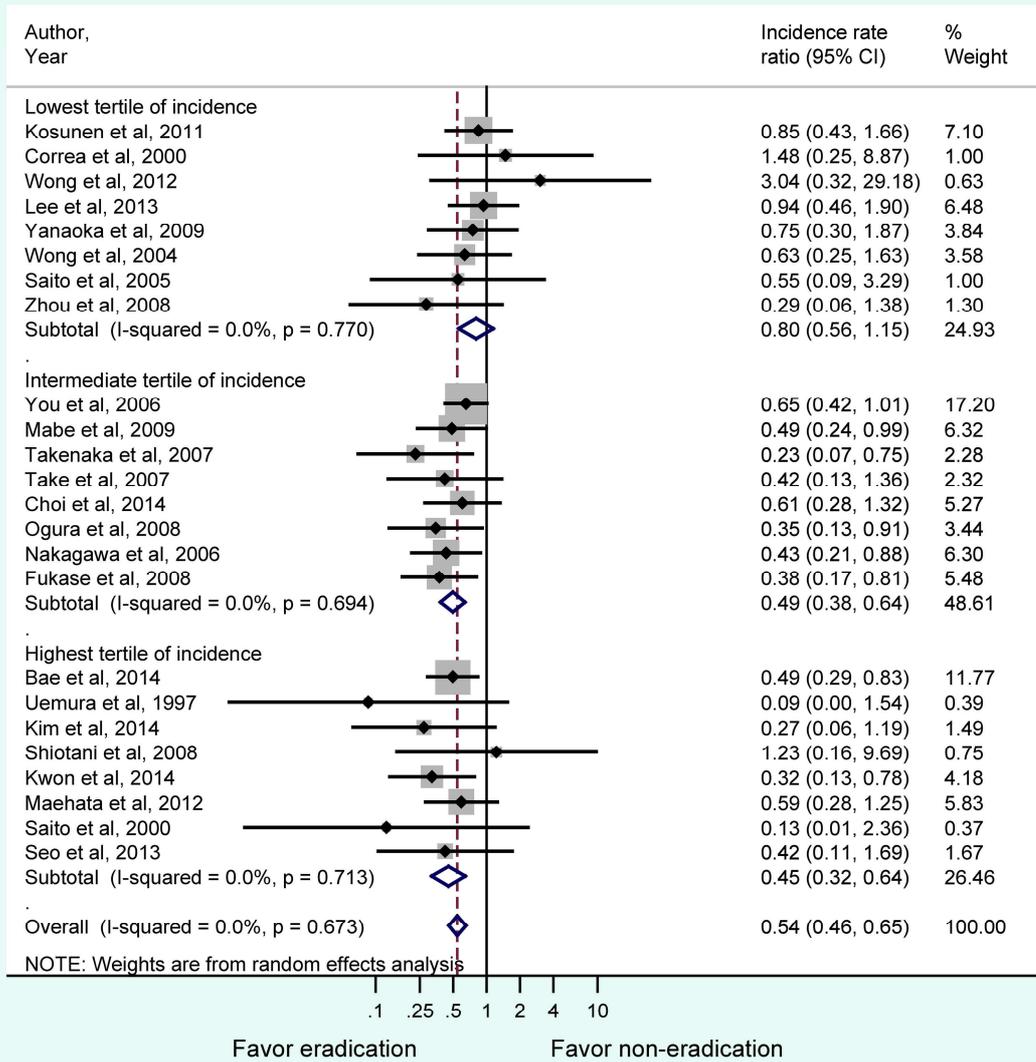
^c Primary prevention as reference.

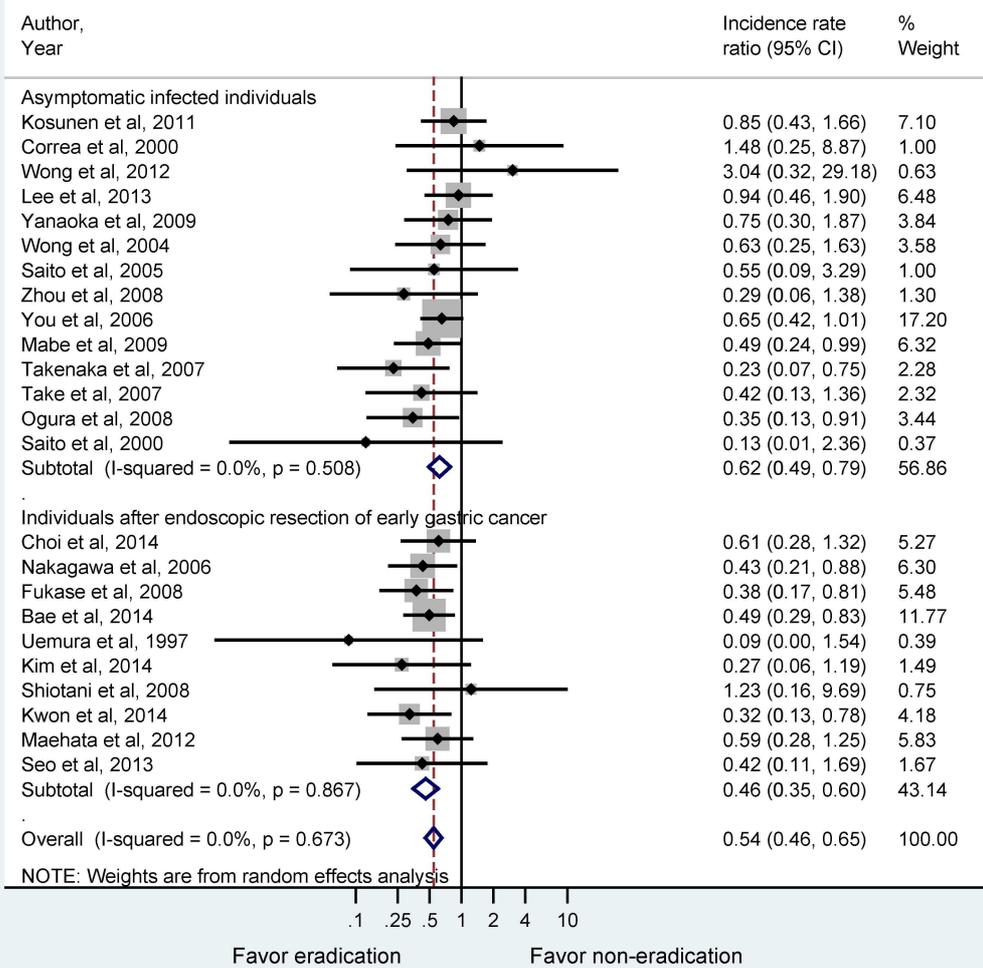
^d Median age in individual studies (Saito et al²⁶ and Nakagawa et al⁴⁰ excluded due to lack of information).

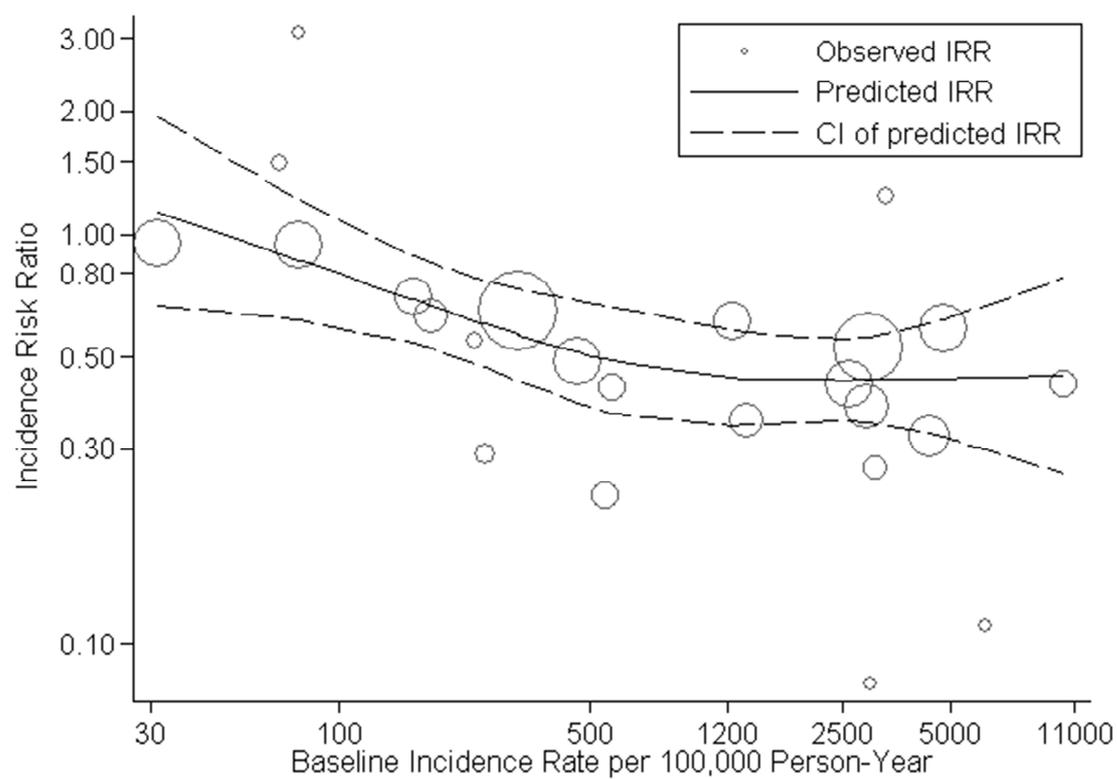
^e Percentage of male subjects in individual studies (Saito et al²⁶ and Nakagawa et al⁴⁰ excluded due to lack of information).

^f Median follow-up duration in individual studies.









APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lee YC, Chiang TH, Chou CK, *et al.* Association Between *Helicobacter pylori* Eradication and Gastric Cancer Incidence: a Systematic Review and Meta-analysis

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Search strategy**PubMed:**

("helicobacter pylori"[MeSH Terms] OR ("helicobacter"[All Fields] AND "pylori"[All Fields]) OR "helicobacter pylori"[All Fields]) AND ("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])

Cochrane Library:

Category: helicobacter pylori gastric cancer
(<http://onlinelibrary.wiley.com/cochranelibrary/search>)

ClinicalTrials.gov:

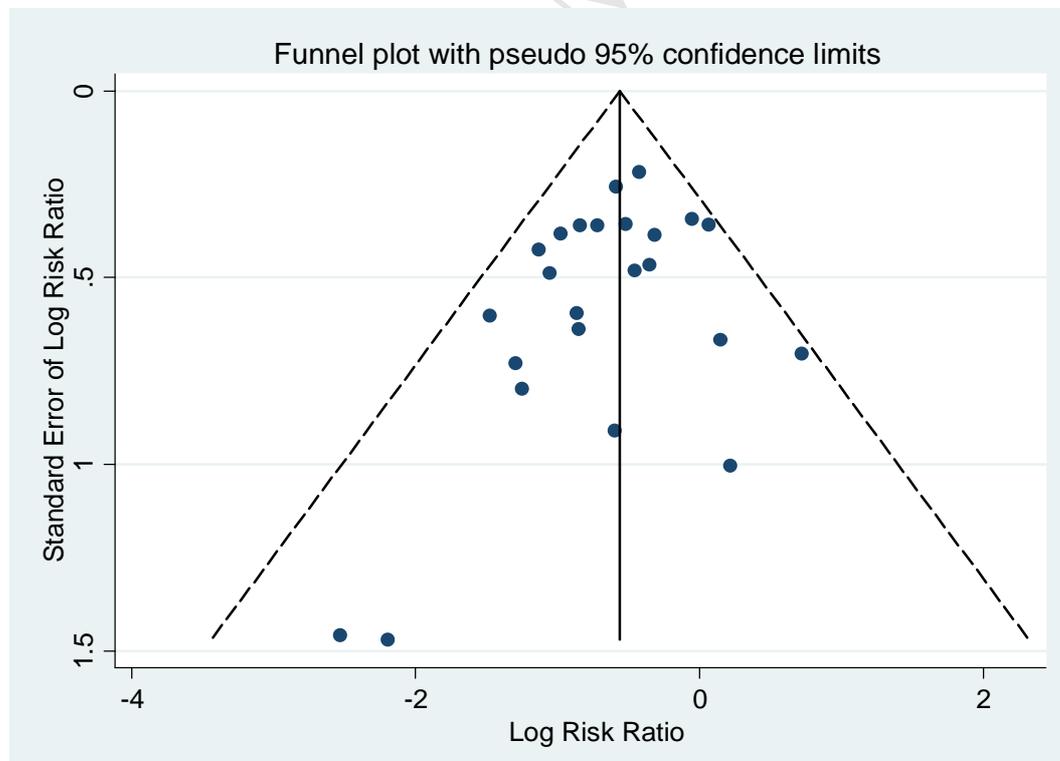
Category: helicobacter pylori gastric cancer
(<https://clinicaltrials.gov/ct2/results?term=helicobacter+pylori+gastric+cancer&Search=Search>)

Digestive Disease Week:

Category: helicobacter pylori gastric cancer
(<http://www.ddw.org/search?query=helicobacter+pylori+gastric+cancer>)

Appendix Figure 1. The funnel plot of all 24 eligible studies does not show asymmetry.

Statistical analysis confirmed no evidence of publication bias with Begg's test ($p=0.17$) and Egger's test ($p=0.18$).



AppendixTable 1. Cochrane risk of bias tool assessment for RCTs

Author, Year	Adequate sequence generation?	Was treatment allocation concealed?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Correa et al, 2000,	■	■	□	□	■	■
Wong et al, 2004	■	■	■	■	■	■
Saito et al, 2005,	NA	NA	■	NA	■	■
You et al, 2006	■	■	■	■	■	■
Zhou et al, 2008,	NA	NA	■	NA	■	■
Wong et al, 2012	■	■	■	■	■	■
Fukase et al, 2008	■	NA	□	■	■	■
Choi et al, 2014	■	NA	□	■	■	■

□ = quality measure not fulfilled; ■ = quality measure fulfilled; NA = not available.

Appendix Table 2. Newcastle-Ottawa scale for cohort study quality

Author, Year	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Saito et al, 2000	★	★	★	★		★		
Take et al, 2007	★	★	★	★	★	★		
Takenaka et al, 2007	★	★	★	★	★	★	★	
Ogura et al, 2008	★	★	★	★	★	★		★
Mabe et al, 2009	★	★	★	★		★		★
Yanaoka et al, 2009	★	★	★	★	★★	★	★	★
Kosunen et al, 2011	★	★	★	★	★	★	★	★
Lee et al, 2013	★	★	★	★		★		★
Uemura et al, 1997	★	★	★	★	★	★	★	★
Nakagawa et al, 2006	★	★	★	★	★	★	★	★
Shiotani et al, 2008	★	★	★	★		★	★	★
Maehata et al, 2012	★	★	★	★	★	★		★
Seo et al, 2013	★	★	★	★		★		★
Kwon et al, 2014	★	★	★	★	★★	★	★	★

Bae et al, 2014	★	★	★	★	★	★	★	★
Kim et al, 2014	★	★	★	★	★	★	★	★

Appendix Table 3. Additional study information on the primary and tertiary prevention of gastric cancer

Author, year	Location	Baseline gastric mucosal status, proportion of atrophic gastritis,%	Baseline gastric mucosal status, proportion of intestinal metaplasia,%	Baseline gastric mucosal status, proportion of dysplasia,%	Risk ratio of gastric cancer (95% CI)	Method to confirm <i>H. pylori</i>	Eradication regimen
Studies on asymptomatic infected individuals (primary prevention)							
RCT							
Correa et al, 2000	Colombia	22.8	67.9	9.2	1.48 (0.25-8.83)	A	T
Wong et al, 2004	China	7.9	28.7	0.6	0.63 (0.25-1.63)	A+D	T
Saito et al, 2005,	Japan	NA	NA	NA	0.55 (0.09-3.27)	NA	T
You et al, 2006	China	44.8	33.0	20.1	0.65 (0.43-1.00)	D	O
Zhou et al, 2008,	China	49.1	49.5	0	0.29 (0.06-1.36)	A+D	T
Wong et al, 2012	China	22.2	23.4	54.4	3.04 (0.32-28.99)	C	T
Cohort							
Saito et al, 2000	Japan	NA	NA	NA	0.11 (0.01-1.98)	A	T
Take et al, 2007	Japan	100	0	0	0.42 (0.13-1.35)	E	T or O
Takenaka et al, 2007	Japan	NA	NA	NA	0.23 (0.07-0.74)	B+C+D+E and/or A	T or O

Ogura et al, 2008	Japan	NA	NA	NA	0.35 (0.13-0.90)	E or two of A,B,C	T
Mabe et al, 2009	Japan	NA	NA	NA	0.49 (0.24-0.98)	D	T
Yanaoka et al, 2009	Japan	NA	NA	NA	0.70 (0.28-1.75)	B	T or O
Kosunen et al, 2011	Finland	NA	NA	NA	0.95 (0.48-1.86)	B	NA
Lee et al, 2013	Taiwan	59.9	31.7	8.4	0.94 (0.46-1.89)	C	T
Studies on individuals after endoscopic resection of early gastric cancer (tertiary prevention)							
RCT							
Fukase et al, 2008	Japan	99.6	66.7	NA	0.38 (0.18-0.79)	A or D	T
Choi et al, 2014	Korea	75.5	90.7	NA	0.61 (0.28-1.31)	A or D	T
Cohort							
Uemura et al, 1997	Japan	NA	NA	NA	0.08 (0.00-1.38)	B	O
Nakagawa et al, 2006	Japan	NA	NA	NA	0.43 (0.21-0.87)	NA	T
Shiotani et al, 2008	Japan	NA	NA	NA	1.24 (0.17-8.85)	A+B	T
Maehata et al, 2012	Japan	4.2	NA	NA	0.59 (0.30-1.19)	One of A,B,C,D	T
Seo et al, 2013	Korea	NA	NA	NA	0.43 (0.12-1.49)	A+C+D	T
Kwon et al, 2014	Korea	97.5	NA	NA	0.32 (0.14-0.74)	Two of A,B,D	T
Bae et al, 2014	Korea	NA	98	NA	0.53 (0.32-0.87)	One of A,C,D	T
Kim et al, 2014	Korea	NA	NA	NA	0.27 (0.07-1.14)	Two of A,B,D	T

Abbreviation: RCT=randomized controlled trial; NA=not available; CI=confidence interval; A=histology; B=serology; C=¹³Carbon-urea breath test; D=rapid urease test; E=bacterial culture; T=triple therapy; O=dual therapy