Gastroenterology 2016;150:1113–1124

CLINICAL—ALIMENTARY TRACT

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

Yi-Chia Lee,[1,2,*] **Tsung-Hsien Chiang**,[1,3,4,*] Chu-Kuang Chou,[1,5] Yu-Kang Tu,[2] Wei-Chih Liao,[1,2] Ming-Shiang Wu,[1,6] and David Y. Graham[7]

[1]Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [2]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [3]Department of Integrated Diagnostics and Therapeutics, National Taiwan University Hospital, Taipei, Taiwan; [4]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [5]Division of Gastroenterology and Hepatology, Chia-Yi Christian Hospital, Chia-Yi, Taiwan; [6]Department of Primary Care Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; and [7]Department of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine Houston, Texas

This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this examination, successful learners will be able to: (1) estimate the benefit of *Helicobacter pylori* eradication on gastric cancer risk; (2) list factors that modify the effect of *H pylori* eradication on gastric cancer risk; (3) describe the risk reduction in gastric cancer associated with *H pylori* eradication.

See Covering the Cover synopsis on page 1049.

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:** 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: 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 nonlinear 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.

Keywords: Stomach; Tumor; Risk Factor; Antibiotic.

Gastric cancer is a major global health threat[1–3] and is the third leading cause of cancer deaths worldwide causing an estimated >720,000 deaths per year globally.[4] *Helicobacter 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 noncardia 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 can progress to the precancerous changes of atrophic gastritis and intestinal metaplasia. The risk of gastric cancer increases in relation to the severity

*Authors share co-first authorship.

Abbreviations used in this paper: **CI, confidence interval; RCT, randomized controlled trial.**

Most current article

0016-5085
http://dx.doi.org/10.1053/j.gastro.2016.01.028

and extent of those precancerous changes.[7] Chronic *H pylori* infection can also contribute to gastric mucosal genetic instability[8] 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* can 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] Because *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 6 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 (ie, 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 might 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 gastritis[12] and those with early gastric cancer[13] 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 after 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 (ie, primary prevention) and in individuals undergoing endoscopic resection of early gastric cancer (ie, 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 Supplementary Material for the search strategy). We manually searched bibliographies of included studies, related reviews, and abstracts presented at Digestive Disease Week in the United States 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 (ie, 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 tool[16] 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