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RESEARCH LETTERS

Long-Term Impact of *Helicobacter pylori* Eradication Therapy on Gastric Cancer Incidence and Mortality in Healthy Infected Individuals: A Meta-Analysis Beyond 10 Years of Follow-Up

Gastric cancer remains the third commonest cause of cancer death worldwide,[1] and the bacterium *Helicobacter pylori* is strongly implicated in its pathogenesis.[2] In previous meta-analyses of randomized controlled trials (RCTs), we found that eradication of *H pylori* in healthy asymptomatic individuals reduces future incidence of, as well as mortality from, gastric cancer.[3,4] In the most recent meta-analysis, including 7 RCTs that recruited 8323 participants, the number needed to treat (NNT) was 72 (95% CI, 56–199) to prevent 1 future gastric cancer and 135 (95% CI, 88–658) to prevent 1 death from gastric cancer.[4] Recently, 2 of the RCTs included in this meta-analysis reported follow-up data out to 20 years or more.[5,6] Given the increasing duration of follow-up in some trials, we hypothesized that the treatment effect would be even stronger than that observed previously. We, therefore, re-analyzed data from this meta-analysis, restricting the analysis to only 4 RCTs with 10 or more years of follow-up.[5–8]

We updated the previous meta-analysis,[4] incorporating data from 2 recently reported updates from trials conducted in Colombia and China, now with 20 years[5] and 26.5 years[6] of follow-up, respectively. Our primary outcome of interest was effect of *H pylori* eradication therapy, compared with placebo or no treatment, on subsequent occurrence of gastric cancer. Our secondary outcome was effect of eradication therapy on gastric cancer–related mortality. We extracted all data independently as dichotomous outcomes (eg, presence or absence of gastric cancer). We used a modified intention-to-treat analysis, excluding individuals found to be ineligible after randomization (eg, subjects in whom gastric cancer was detected at baseline or any participants found to be *H pylori*–negative) and those who did not receive the intervention as assigned and, due to the fact that the outcome of interest was relatively rare, we assumed all subjects lost to follow-up did not develop gastric cancer, but retained them in the study denominator. We pooled data with a random effects model to provide a conservative estimate of the effect of eradication therapy on subsequent occurrence of gastric cancer. We expressed the impact of eradication therapy, compared with placebo or no treatment, as a relative risk (RR) of occurrence of gastric cancer with 95% CIs, and calculated the NNT, with 95% CI, using the following formula: NNT = 1 / (assumed control risk from the meta-analysis × (1 – RR)). We assessed heterogeneity between studies using the I^2 statistic, with a cutoff of ≥50% to define significant heterogeneity. We used Review Manager, version 5.4.1 (The Cochrane Collaboration, 2020) to generate forest plots of pooled RRs for primary and secondary outcomes with 95% CIs.

One criticism of the NNT from RCT data is that most of the benefit may relate to preventing gastric cancer in the very elderly, when the utility, in terms of life gained, is questionable. To address this, we used International Agency for Research on Cancer data on cumulative risk of gastric cancer in those younger than 75 years to provide the actual assumed control risk for gastric cancer according to both geographical region and the Human Development Index (HDI), a measure of social and economic development of countries.[9] This assumes that any benefit of *H pylori* eradication persists beyond the duration of follow-up of RCTs and can be used to calculate more conservative estimates for region and HDI-specific NNTs using the formula described above, but substituting the actual assumed control risk for the one derived from the meta-analysis.

The 4 trials reported data between 10 and 26.5 years among 5292 healthy individuals.[5–8] In total, there were 69 gastric cancers (2.6%) occurring in 2660 subjects assigned to eradication therapy and 127 gastric cancers (4.8%) in 2632 participants receiving placebo or no treatment (RR, 0.54; 95% CI, 0.41–0.72) (Figure 1*A*), with no heterogeneity among trials ($I^2 = 0\%$). The NNT to prevent 1 gastric cancer was 45 (95% CI, 35–74). Three trials reported mortality from gastric cancer[6–8]; there were 47 deaths (2.1%) among 2242 individuals randomized to eradication therapy and 71 deaths in 2233 (3.2%) receiving placebo or no treatment (RR, 0.66; 95% CI, 0.46–0.95) (Figure 1*B*), again with no heterogeneity among studies ($I^2 = 0\%$). The NNT to prevent 1 death from gastric cancer was 92.5 (95% CI, 58–629).

From International Agency for Research on Cancer data we estimated the NNT to prevent 1 gastric cancer for men younger than 75 years in North America, Northern Europe, Central or Eastern Europe, and Eastern Asia to be 345 (95% CI, 269–567), 311 (95% CI, 242–510), 100 (95% CI, 78–165), and 57 (95% CI, 45–94), respectively (Supplementary Table 1). For men younger than 75 years in countries with very high and high HDI, NNT was 121 (95% CI, 94–198) and 86 (95% CI, 67–141), respectively.

This update of a previous meta-analysis, including only the 4 RCTs with ≥10 years of follow-up,[5–8] demonstrates an even stronger effect of eradication therapy in preventing gastric cancer and gastric cancer–related mortality in terms of NNT in healthy *H pylori*–positive individuals. This may well be an underestimate of the benefit, as some trials used

Abbreviations used in this paper: HDI, Human Development Index; NNT, number needed to treat; RCT, randomized controlled trial; RR, relative risk.

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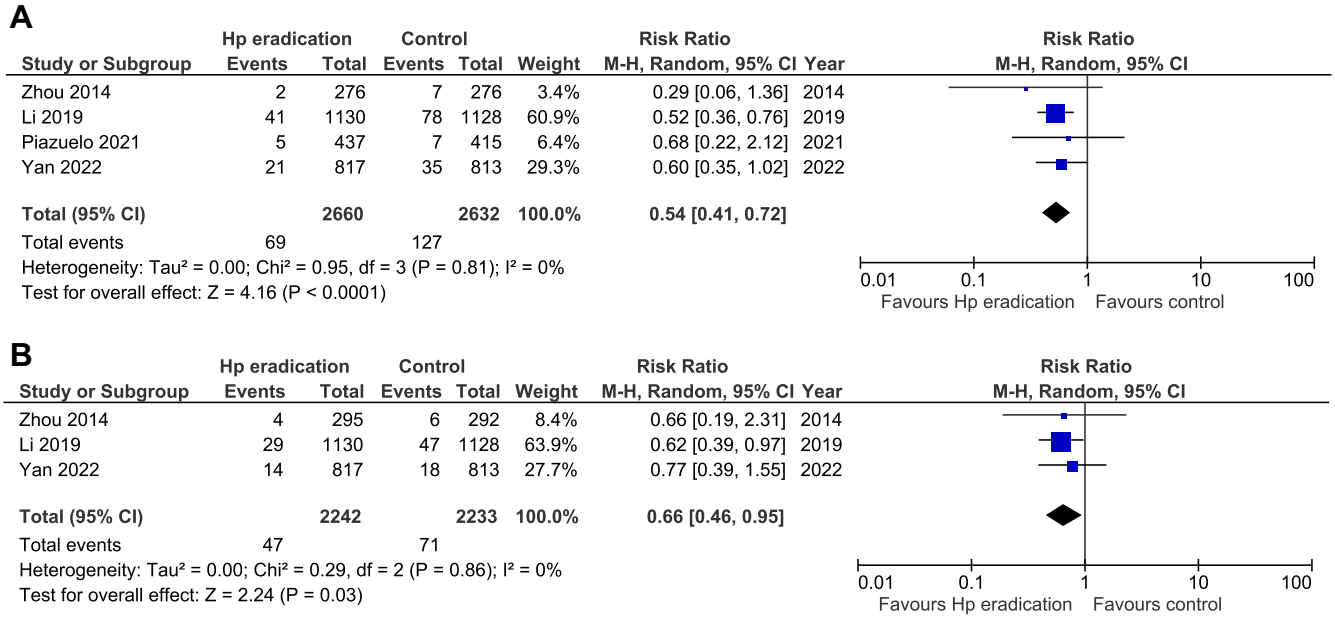

Figure 1. (*A*) Forest plot of RCTs of *Helicobacter pylori* eradication therapy with ≥10 years of follow-up: effect on subsequent occurrence of gastric cancer (modified intention-to-treat analysis). (*B*) Forest plot of RCTs of *H pylori* eradication therapy with ≥10 years of follow-up: effect on subsequent mortality from gastric cancer (modified intention-to-treat analysis).

eradication regimens that are no longer recommended due to suboptimal eradication rates,[7] some offered eradication therapy to individuals in the placebo or no-treatment arms after a certain period of time had elapsed,[5] and in others an increasing proportion of participants in the placebo or no-treatment arms tested negative for *H pylori* as duration of follow-up increased,[6] suggesting that some subjects sought out eradication therapy subsequently.

Our confidence in the estimate of the efficacy of eradication therapy in preventing gastric cancer and death from gastric cancer in healthy *H pylori*–infected individuals has improved further and the magnitude of the effect, in terms of NNT, has increased. The effect was strongest in Eastern Asian countries. Many countries now have a high HDI, and even in these countries the NNT to prevent 1 gastric cancer in people younger than 75 years appears reasonable.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2022.05.027.

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Conflicts of interest

The authors disclose no conflicts.

Supplementary Table 1. Numbers Needed to Treat Calculated From Cumulative Risk of Gastric Cancer in Individuals Younger Than 75 Years According to Geographical Region or Human Development Index[9]

Population	Cumulative risk of gastric cancer in individuals younger than 75 y, %	NNT	95% CI
North American men	0.63	345	269–567
North American women	0.35	621	484–1020
Northern European men	0.70	311	242–510
Northern European women	0.34	639	499–1050
Central or Eastern European men	2.17	100	78–165
Central or Eastern European women	0.84	259	202–425
Eastern Asian men	3.80	57	45–94
Eastern Asian women	1.49	146	114–240
Men in countries with a very high HDI	1.80	121	94–198
Women in countries with a very high HDI	0.73	298	232–489
Men in countries with a high HDI	2.54	86	67–141
Women in countries with a high HDI	1.03	211	165–347