Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer?

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CRD summary
This generally well-conducted review concluded that Helicobacter pylori eradication treatment appeared to reduce gastric cancer risk, but the generalisability of the findings may be limited. Also, they are based on evidence of variable reliability. These conclusions are an accurate reflection the results of the review and appear to be reliable.

Authors' objectives
To determine whether Helicobacter pylori eradication treatment can reduce the risk of gastric cancer.

Searching
PubMed, EMBASE, the Cochrane Library and Google Scholar were searched without language, completion or publication status restriction up to January 2009. Search terms were reported. Also searched were online trial registries including the Cochrane Central Register of Controlled Trials, metaRegister of Controlled Trials and the National Institutes of Health. Abstracts from three relevant conferences were handsearched up to 2008. References of included studies were also checked.

Study selection
Randomised controlled trials (RCTs) which compared an eradication treatment for Helicobacter pylori with no treatment in Helicobacter pylori-positive patients were eligible for inclusion. Included trials had to report the number of gastric cancer cases detected during follow-up.

All trials were conducted in areas with a high incidence of gastric cancer (incidences in the general populations of the study areas varied from 50 to 160 cases per 100,000 persons per year). All except one of the included trials were conducted in Asia, with the majority undertaken in China. The majority of trials used progression of neoplastic lesions rather than incidence of gastric cancer as a primary outcome. Eradication treatment regimes included differing combinations and doses of the following agents: amoxicillin, metronidazole, bismuth subsalicylate, omeprazole, lansoprazole, clarithromycin. Patients in included trials had baseline symptoms ranging from superficial gastritis to dysplasia, with most having either gastric atrophy or intestinal metaplasia. All except one trial used biopsy to evaluate histology. In all but one trial patients had mean ages ranging from 42 to 51 years. An equal number of men and women were included in the trials.

Two reviewers independently selected the studies for inclusion in the review, and disagreements were resolved through consensus among eight reviewers.

Assessment of study quality
Two reviewers independently assessed the studies for validity, using the criteria of randomisation, allocation concealment, blinding, follow-up, control group, definition of outcome measures, adequate power, use of intention-to-treat analysis, baseline assessment, and description of treatment regimens. Data extraction also included items related to validity, such as validation of diagnosis by external reviewers. Disagreements were resolved through consensus among eight reviewers.

Data extraction
Intention-to-treat data on the number of cases of gastric cancer in each treatment group, together with losses to follow-up and length of follow-up, were extracted from the trials.

Two reviewers independently performed the data extraction. Where necessary further information was requested from study authors.
Methods of synthesis
A Mantel-Haenszel fixed-effect meta-analysis was used to calculate a pooled relative risk with 95% confidence intervals (CI). A sensitivity analysis using a random-effects model was also undertaken. Sensitivity analyses were performed to investigate the impact of each individual study on the pooled outcome. A further sensitivity analysis investigated the effect of including a trial excluded from the primary analysis on the grounds of clinical heterogeneity (patients had early gastric cancer at baseline, were older, and a greater proportion were male). Subgroup analyses based on the outcome definition were employed (progression of pre-neoplastic lesions or incidence of gastric cancer). Assessment of statistical heterogeneity was not reported.

Results of the review
Seven randomised controlled trials (RCTs) were included in the review (n=7,239 patients). Five of the trials reported adequate allocation concealment. Two trials were triple blinded, although five trials reported using blinded outcome assessors. Three trials used an intention-to-treat analysis. Two trials were adequately powered. Four trials were placebo-controlled. Median follow-up was six years (range three to 10 years). Eradication rates in the treatment groups ranged from 73% to 89%, while spontaneous eradication in the control groups ranged from 5% to 15%, where reported.

In the treatment groups, 37 of 3,388 (1.1%) patients developed gastric cancer, compared to 56 of 3307 (1.7%) of patients in control groups. The pooled relative risk was 0.65 (95% CI: 0.43 to 0.98, six RCTs), indicating a statistically significant benefit of treatment. Inclusion of the previously excluded study gave a relative risk of 0.57 (95% CI: 0.40 to 0.81; seven RCTs). A subgroup analysis of trials that used progression of pre-neoplastic lesions as an outcome was not statistically significant (relative risk 0.66, 95% CI: 0.41 to 1.04; five RCTs). However, the two trials which used gastric cancer incidence as a primary outcome showed a statistically significant benefit of treatment (relative risk 0.46, 95% CI: 0.26 to 0.82).

Authors' conclusions
*Helicobacter pylori* eradication treatment seemed to reduce gastric cancer risk. However, it was noted that all except one trial was performed in Asia, which may limit their generalisability, only two trials assessed gastric cancer incidence, and only two trials were double-blinded.

CRD commentary
The review question was clear and was supported by specific inclusion criteria. The search included a number of relevant databases and other sources. This, along with the lack of restrictions on language or publication status, reduced the possibility that some relevant studies were missed, as well as reducing the risk of publication or language biases. The authors used methods designed to reduce reviewer bias and error at all stages of the review process. A thorough validity assessment used appropriate criteria, was fully reported and was used to inform the synthesis. The decision to use meta-analysis appeared appropriate. Although statistical heterogeneity was not assessed, an appropriate investigation of clinical heterogeneity was undertaken. The authors’ conclusions are an accurate and appropriately cautious reflection of the results of the review, and appear to be reliable.

Implications of the review for practice and research
**Practice:** The authors stated that their findings supported the 2008 Asia-Pacific international guidelines, which recommend screening and treating patients for *Helicobacter pylori* as a gastric cancer risk reduction strategy in populations with a high incidence of the condition.

**Research:** The authors stated that further intervention studies are unrealistic and that future research should focus on the identification of people at higher risk of gastric cancer because of genetic susceptibility and environmental factors, who would benefit from preventative *Helicobacter pylori* eradication therapy.

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