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TOPIC HIGHLIGHT

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Helicobacter pylori eradication for preventing gastric cancer

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Abstract

Helicobacter pylori (*H. pylori*) infection is a major risk factor for gastric cancer (GC) development, which is one of the most challenging malignant diseases worldwide with limited treatments. In the multistep pathogenesis of GC, *H. pylori* infection slowly induces chronic active gastritis, which progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia, and dysplasia, and then finally to GC. Although eradication of *H. pylori* is a reasonable approach for the prevention of GC, there have been some contradictory reports, with only some long-term follow-up data showing efficacy of this approach. The inconsistencies are likely due to the insufficient number of participants, relatively short follow-up periods, poor quality of study designs, and the degree and extent of preneoplastic changes at the time of *H. pylori* eradication. This review analyzes recent high-quality studies to resolve the discrepancies regarding the eradication of *H. pylori* for GC prevention. The relationship between *H. pylori* eradication and GC/precancerous lesions/metachronous GC is examined, and the cost-effectiveness of this strategy in the prevention of GC is assessed. Although it is assumed that eradication of *H. pylori* has the potential to prevent GC, the feasibility and appropriate timing of this strategy for cancer prevention remain to be determined. As a result, additional well-designed trials with longer follow-up periods are needed to clarify this issue.

Key words: *Helicobacter pylori*; Gastric cancer; Cancer prevention

Core tip: The treatment of gastric cancer (GC) is challenging. Elimination of a major risk factor, *Helicobacter pylori* (*H. pylori*) infection, represents an important approach for the prevention of GC. However, the feasibility and appropriate timing of this strategy remain to be determined. This review highlights the most recent literature and presents a comprehensive evaluation of what is currently known about *H. pylori* infections and GC.

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INTRODUCTION

Gastric cancer (GC) represents one of the most challenging malignant diseases worldwide and is the second leading cause of death with the highest incidence rates observed in Eastern Asia, Japan, Eastern Europe, and the Andean regions of South America[1]. GC develops from the progression of chronic gastritis to gastric atrophy, intestinal metaplasia, dysplasia, and finally invasive carcinoma[2]. Although the development of GC involves a multifactorial pathway, the pathogenesis is believed to begin from a single infectious agent[3,4], *Helicobacter pylori* (*H. pylori*), which is classified as a Group 1 carcinogen

by the World Health Organization (WHO) and International Agency for Research on Cancer (IARC)[5]. *H. pylori* is a leading worldwide infectious agent, accounting for as many as 650000 new cases of non-cardiac GC annually[6], and epidemiological data support a strong causal relationship between *H. pylori* infection and GC[7-11], as well as some animal studies[12-14]. Different countries have different consensus reports about *H. pylori* eradication treatment[15-20]. Among these guidelines, the most consistent recommendation with a high level of evidence is endoscopic resection of early GC[21]. *H. pylori* eradication is recommended to improve gastric atrophy[22]. Although it may seem intuitive that removing the organism would eliminate the risk of GC, only a small proportion of infected individuals develop GC[23]. Furthermore, massive eradication therapy may lead to activation of antibiotic-resistant strains of *H. pylori* in the general population, as well as an over-consumption of medical resources. Therefore, this review integrates information available from recent studies in order to evaluate the benefit of *H. pylori* eradication for GC prevention.

H. PYLORI ERADICATION AND GC

The first well-designed trial to investigate eradication of *H. pylori* for the prevention of GC was performed in 1991 by Correa *et al*[24] and involved Colombian individuals at high risk for GC. Although the cancer incidence was similar in both treated and untreated groups after a 6-year follow-up, this trial showed significant increases in the regression rates of cancer precursor lesions. In 2004, Wong *et al*[25] assigned 1630 patients from the Fujian province in China with *H. pylori* infections to an eradication or a non-eradication group. During the 7.5-year follow-up period, GC was similar in both groups, occurring in 11 out of 813 patients from the non-eradication group and seven of 817 patients from the eradication group. However, the incidence of GC in a subgroup without precancerous lesions receiving *H. pylori* eradication therapy was significantly lower, compared with the non-eradication group; several other trials reported similar results[26-27].

A meta-analysis by Fuccio *et al*[28] examined six randomized trials assessing GC and the progression of preneoplastic lesions during 4-10 years follow-up. Their results indicated that 27 of 3388 patients (1.1%) in the *H. pylori* antibiotic treatment group developed GC, compared to 56 of 3307 (1.7%) not undergoing treatment; the overall relative risk was 0.65. However, this meta-analysis comprised mainly studies performed in Asia, and only two of the studies were of a double-blind design. With a cohort study of 80225 patients, Wu *et al*[29] found that the earlier *H. pylori* is eradicated after peptic ulcer disease, the smaller the risk of GC, with no risk for patients receiving early *H. pylori* eradication as compared to the general population. A later interventional trial in Shandong, China showed that 2 wk antibiotic treatment for *H. pylori* in 3365 patients significantly reduced GC incidence by 39%, during a total follow-up of 14.7 years[30].

Altogether, most of these studies focused on people with gastric precancerous lesions, such as gastric atrophy and intestinal metaplasia (IM), because of the low incidence of GC. However, GC has a long pre-malignancy phase that may mask the ultimate effects of *H. pylori* eradication. Therefore, some results of previous studies are inconclusive, partly due to the insufficient number of participants and the relatively short follow-up[31,32]. Nonetheless, the above studies provide clinical evidence suggesting that successful eradication of this organism is related to a reduction in the risk of GC, although it does not prevent GC completely.

H. PYLORI ERADICATION AND PRECANCEROUS LESIONS

H. pylori infection can cause chronic gastritis. This chronic condition can lead to gastric mucosal atrophy and IM[2], which are considered to be precancerous lesions of GC[2,33-35]. Therefore, improvement or elimination of atrophy and IM with *H. pylori* eradication could potentially inhibit gastric carcinogenesis. Although the effect of *H. pylori* eradication on the incidence of precursor lesions is unknown, many studies have identified alterations in gastric atrophy and IM after *H. pylori* eradication. These reports had contradictory results, with several studies showing improvements in atrophy and IM[36-38], and others showing no improvement in the gastric mucosa after eradication[39-41]. There is also evidence that *H. pylori* eradication can lead to regression of atrophy in other conditions[42]. However, these studies were limited to data from short-term follow-up, small sample sizes, and few points of observation in their design, which may have contributed to the contradictory results.

A study by our team followed chronic atrophic gastritis patients with *H. pylori* infections, with only 92 of 179 patients receiving *H. pylori* eradication. Although the grade of IM increased in the untreated *H. pylori*-infected group after 3 years, the grade of atrophy significantly decreased in the eradication group, suggesting that *H. pylori* eradication may improve gastric atrophy and prevent the progression of IM[43]. However, a more recent meta-analysis that systematically reviewed the long-term effects of *H. pylori* eradication on gastric histology showed that *H. pylori* eradication can improve atrophy but not IM[22]. Recently, a trial from Matsu Island demonstrated that population-based eradication of *H. pylori* infection was associated with a significant reduction in gastric atrophy within the relatively short study period[44]. Evidence for the prevention of GC by reducing the occurrence of precancerous lesions was presented by Kodama *et al*[45], who evaluated the gastric mucosa at five points in the stomach according to the updated Sydney system and showed that atrophy at all sites and IM in the lesser curvature of the corpus were gradually and significantly decreased 10 years after the *H. pylori* eradication.

It is noteworthy to mention that GC can still develop even after successful eradication therapy. One famous

case report describes two patients who were included in one of the first study cohorts that received eradication therapy for peptic ulcer disease, but nevertheless developed GC during long-term follow-up (one at 4 years and the other at 14 years after the *H. pylori* eradication)[46]. Both patients had suffered from IM when the gastric ulcer disease was first discovered. Furthermore, malignant lesions that develop after eradication therapy have a similar characteristic appearance to and therefore may have a common carcinogenesis with cancers that occur in the presence of *H. pylori* infection, although biological features may be changed by the eradication therapy[47,48]. These results suggest that *H. pylori* eradication does not result in the regression of all precancerous lesions, which may depend on the degree and extent of preneoplastic changes at the time of eradication. Moreover, decreased *H. pylori* colonization density may occur in these lesions even without active intervention, with further progression of premalignant lesions less dependent on *H. pylori* infection. Therefore, the key question is whether and when precancerous lesions can be reversed with *H. pylori* eradication. Ongoing clinical studies are focusing on a "point of no return", defined as a situation when certain alterations are no longer reversible by *H. pylori* eradication and GC progression continues.

H. PYLORI ERADICATION AFTER ENDOSCOPIC RESECTION OF EARLY GASTRIC CANCER

Following endoscopic resection of early gastric cancer (EGC), secondary cancers are often found at sites other than the resection site during follow-up, with the rates ranging from 3% to 4% per year[21,49,50], rendering them more likely to be detected in trials compared to the low incidence of GC. Japanese guidelines recommend treatment for *H. pylori* infection in patients following resection of EGC[51,52]. In 1997, Uemura *et al*[53] assigned patients undergoing endoscopic resection for GC to an *H. pylori* eradication group or a non-eradication group. Secondary GC was detected in 10 of 67 patients from the non-eradication group (15%) *vs* none of the 65 patients from the eradication group during about 5 years follow-up, suggesting that *H. pylori* eradication inhibits the development of new carcinomas. Although this was a pioneer study, it was not a randomized controlled trial. Fukase *et al*[21] reported the first multicenter, open-label, randomized study on the incidence of developing metachronous GC following endoscopic resection of EGC. In this study, 544 patients from 51 Japanese institutions were randomly assigned to an *H. pylori* eradication group or a non-eradication group and were followed up over 3 years with annual endoscopy to detect any recurrence of GC. This trial demonstrated a 65% risk reduction for the development of metachronous GC with *H. pylori* eradication. Long-term results of this trail were encouraging[54]. However, two recently published retrospective studies failed to validate these findings, suggesting that *H. pylori* eradication does not significantly prevent metachronous GC[49,55]. Nonetheless, a large retrospective study showed that recurrence rates and recurrence-free survival differed significantly between the non-eradication and eradication groups[56]. As for subtotal gastrectomy, Cho *et al*[57] reported that there was no difference in the development of metachronous GC according to the treatment allocation or final *H. pylori* status, which should be evaluated in further studies because bile reflux was reported to act as a carcinogen for later GC development[58,59].

Unlike gastric resection, endoscopic resection preserves the abnormal mucosa and gastric environment, which may promote the occurrence of secondary cancer in cases with atrophic gastritis or IM caused by *H. pylori* infection. Some available evidence suggests that *H. pylori* eradication reduces the incidence of metachronous GC in patients with a history of gastric adenoma. However, opposing results also indicate that the progression of atrophic gastritis and IM to GC can indeed occur following *H. pylori* eradication. Thus, there must be additional factors, such as genetic and epigenetic alterations, that lead to the progression of these preneoplastic lesions.

COST-EFFECTIVENESS OF *H. PYLORI* ERADICATION FOR GC PREVENTION

Several studies have indicated that the screening and eradication of *H. pylori* is a cost-effective strategy for the prevention of GC in middle-aged adults, even if the treatment prevents only 20%-30% of *H. pylori*-associated cancers[60,61]. Parsonnet *et al*[62] carried out a cost-benefit analysis of *H. pylori* screening and eradication in individuals aged 50 years. With an assumption that *H. pylori* treatment prevents 30% of GC, cost-effectiveness was estimated to be $25000 per year of life saved, and < $50000 per year of life saved for high-risk individuals, such as Japanese-Americans, even at a 5% treatment efficacy. The authors concluded that the screening and eradication of *H. pylori* was therefore a cost-effective strategy for preventing GC, especially in high-risk populations. Another study reported that the screening and eradication of *H. pylori* in young adults has the potential to prevent one in every 4-6 cases of GC in China, and would be considered cost-effective using the GDP per capita threshold[63]. A study from Shin *et al*[64] evaluated the long-term cost-effectiveness of *H. pylori* eradication in a selective population with a high risk of developing GC with estimated model variables based on an extensive review of published reports. Their analysis suggests little difference in *H. pylori* eradication costs ($29780 *vs* $30594 for no eradication) or in saving of lives (mean life expectancy from eradication: 13.60 years *vs* 13.55 years for no eradication). Although screening and eradication appear to be a cost-effective way to prevent GC, shortcomings in the therapeutic armamentarium along with a concern for antibiotic resistance should prevent recommendation of this global screen-and-treat strategy.

A prophylactic *H. pylori* vaccine could be an attractive

alternative strategy for the control of *H. pylori* infections. A 2009 study evaluated the potential socioeconomic benefit of a putative *H. pylori* vaccine in three different simulated scenarios: no intervention, vaccination of infants, and vaccination of school-age children[65]. Results of their direct transmission model indicated that the use of a prophylactic *H. pylori* vaccine was cost-effective in the United States, with vaccination in infancy providing the greatest benefit over at least 40 years, at a cost per quality-adjusted life year of $17684.

CONCLUSION

H. pylori infection induces progressive inflammatory changes in the gastric mucosa that may lead to GC. As the treatment of GC represents a significant medical burden and poor outlook[66], *H. pylori* screening and eradication is likely to be one of the most promising and cost-effective approaches in GC prevention. However, the collective results of previous studies have failed to identify a significant reduction in GC; possibly due to the variable prevalence of *H. pylori* infection between countries and the long course of GC. Nevertheless, younger individuals with no precancerous lesions should consider *H. pylori* eradication for GC prevention, although high-risk groups should combine this therapy with endoscopic surveillance or treatment. Following endoscopic resection of EGC, *H. pylori* eradication should be used to prevent the development of metachronous gastric carcinoma, although study of the benefits in a wider population is needed.

H. pylori, which is often acquired during childhood and associated with low socioeconomic status, is recognized as a necessary but insufficient cause of GC, because the pathogenesis of gastric carcinogenesis is multifactorial. Although the mass eradication of *H. pylori* is potentially feasible, doubts remain about the advisability of such a policy. Differences in the socioeconomic composition of countries and the undesirable side effects of antibiotic use as well as increased incidence of other diseases necessitate further investigation into mass eradication of *H. pylori* as a preventative strategy[67-70]. In addition, the feasibility and appropriate timing of this strategy for cancer prevention remains to be determined. Further systematic data collection comprising large randomized controlled trials designed in multiple geographical areas and with extended follow-up periods is needed to elucidate the role of *H. pylori* eradication for GC prevention in patients with or without precancerous lesions.

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