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World J Gastroenterol 2006 August 28; 12(32): 5101-5107
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Eradication of *H pylori* for the prevention of gastric cancer

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Received: 2005-12-02 Accepted: 2006-01-14

Abstract

Infection with *H pylori* is the most important known etiological factor associated with gastric cancer. While colonization of the gastric mucosa with *H pylori* results in active and chronic gastritis in virtually all individuals infected, the likelihood of developing gastric cancer depends on environmental, bacterial virulence and host specific factors. The majority of all gastric cancer cases are attributable to *H pylori* infection and therefore theoretically preventable. There is evidence from animal models that eradication of *H pylori* at an early time point can prevent gastric cancer development. However, randomized clinical trials exploring the prophylactic effect of *H pylori* eradication on the incidence of gastric cancer in humans remain sparse and have yielded conflicting results. Better markers for the identification of patients at risk for *H pylori* induced gastric malignancy are needed to allow the development of a more efficient public eradication strategy. Meanwhile, screening and treatment of *H pylori* in first-degree relatives of gastric cancer patients as well as certain high-risk populations might be beneficial.

Key words: Gastric cancer; *H pylori*; Eradication

Trautmann K, Stolte M, Miehlke S. Eradication of *H pylori* for the prevention of gastric cancer. *World J Gastroenterol* 2006; 12(32): 5101-5107

http://www.wjgnet.com/1007-9327/12/5101.asp

INTRODUCTION

Despite decreasing incidence and mortality rates, gastric cancer remains the second most frequent malignancy worldwide, with the majority of cases diagnosed at an advanced stage[1]. A number of environmental factors, e.g. diets high in salt and N-nitrosamines and low in fruits and vegetables have been shown to contribute to gastric cancer development[2]. Furthermore, it is now well recognized that chronic infection with *H pylori* is tightly associated with the development of gastric cancer, primarily noncardiac gastric cancer. The clinical course of *H pylori* infection is highly variable and the likelihood of developing gastric cancer is determined by both microbial and host factors (Figure 1). Based on the large number of experimental and epidemiological studies, it seems reasonable to conclude that the eradication of *H pylori* should prevent gastric cancer. However, convincing results from clinical trials are not yet available. Hence, current clinical decision-making has to be based on indirect evidence: data from animal models and studies supporting the beneficial effect of eradication on the development of gastric cancer precursor lesions[3]. This article reviews the existing evidence that *H pylori* eradication prevents gastric cancer with a highlight on recent publications relevant for the clinician.

PATHOGENESIS AND EPIDEMIOLOGY

Pathogenesis

According to Correa's model, gastric cancer development is a multistep process where the gastric mucosa is slowly transformed from normal epithelium to chronic gastritis, to multifocal atrophy, to intestinal metaplasia of various degrees, to dysplasia and finally to invasive cancer[4]. However, this sequence of events does not precede diffuse type gastric cancer and has even been debated for the intestinal type[5] since less than 10% of patients with these lesions ultimately develop gastric cancer[6]. Most *H pylori* infected individuals show antral predominant gastritis, which predisposes them to duodenal ulcers, but rarely causes gastric cancer. On the contrary, patients with corpus-predominant gastritis are likely to develop gastric ulcers, gastric atrophy, intestinal metaplasia and eventually gastric cancer. Our group, among others, has found that the pattern and the morphological distribution of gastritis correlate strongly with the gastric cancer risk[7,8]. We showed that the expression of *H pylori* associated gastritis in patients with gastric cancer is high in the corpus and is frequently associated with intestinal metaplasia and atrophy[9]. Based on these findings we developed a gastric carcinoma risk index, which evaluates grade and activity of corpus-dominant *H pylori* gastritis as well as the occurrence of intestinal metaplasia in the antrum or corpus to determine a patient's risk for developing gastric carcinoma[10]. In a subsequent case control study, the gastric carcinoma risk index had a sensitivity of 93% and a specificity of 85% for diagnosing individuals with gastric carcinoma[11].

Epidemiology

Infection with *H pylori* occurs worldwide, but the prevalence varies greatly among countries and among different populations within the same country[12]. The overall prevalence of *H pylori* infection is closely linked to current socioeconomic conditions[13]. Although the incidence of the infection in industrialized countries has decreased substantially over recent decades, it will remain endemic for at least another century, unless intervention occurs[14]. In the early 1990s a series of prospective case control studies[15-18] demonstrated a close link between *H pylori* infection and gastric cancer, which prompted the World Health Organization to announce the bacterium a class I (definite) carcinogen in 1994. Since then data from various studies have accumulated that further strengthen the association between *H pylori* infection and gastric cancer. One of the most compelling studies was conducted in Japan, where Uemura *et al*[19] prospectively followed 1526 patients over a period of 7.8 years. A total of 2.9 percent of *H pylori* infected individuals developed gastric cancer compared to none in the *H pylori* negative control group. Among individuals with *H pylori* infection, those with severe gastric atrophy (odds ratio: 4.9), corpus-predominant gastritis (odds ratio: 34.5) and intestinal metaplasia were at significantly higher risk for gastric cancer.

According to most retrospective, cohort and case control studies, the overall odds ratio for *H pylori* infection and gastric cancer is around two to six[19-23]. However, these numbers are likely to represent a gross underestimation of the real risk. Among the confounding factors that make risk appear lower in most studies are the long latency between the initiation of the carcinogenetic process and the clinical occurrence of cancer as well as the inclusion of individuals with antral predominant/duodenal ulcer phenotype[24]. If selection of patients and methodology is optimized, the odds ratio for *H pylori* infected individuals may increase to a factor of around 20[25-27].

RISK FACTORS

Bacterial virulence factors

H pylori displays a considerable amount of genetic variation. Even strains within an individual host commonly change over the course of the infection[28,29]. A number of bacterial virulence factors have been discovered that influence disease outcome in infected individuals. The majority of *H pylori* strains express and secrete VacA, a vacuolating cytotoxin, which is inserted into the gastric epithelial-cell and mitochondrial membranes, possibly providing the bacterium with nutrients and inducing apoptosis of the host cell[12,30]. VacA has also been found to modulate the host immune system *via* T-cell inhibition[31,32]. Studies indicate that expression of VacA increases bacterial fitness and in some western countries VacA *s1* and VacA *m1* genotypes are associated with more severe forms of gastritis, atrophy, intestinal metaplasia and perhaps gastric cancer[33-36]. Another major focus of research is the analysis of the *cag* pathogenicity island (*cag PAI*), a genomic fragment comprising 31 genes that support the translocation of the 120-kD CagA protein into the gastric epithelial cell[37,38]. CagA has been shown to induce cytokine production along with a growth factor-like response in the host cell and to disrupt the junction-mediated gastric epithelial cell barrier function[39,40]. In western countries, patients carrying CagA+ *H pylori* strains are more likely to develop adenocarcinomas of the distal stomach than patients infected with CagA- strains[41]. In particular, one recent meta-analysis of case-control studies concluded that infection with CagA+ strains increases the risk over *H pylori* infection alone[42]. However, similar findings are not reported from Asia, where about 95% of all infected individuals carry CagA+ strains[3,43,44].

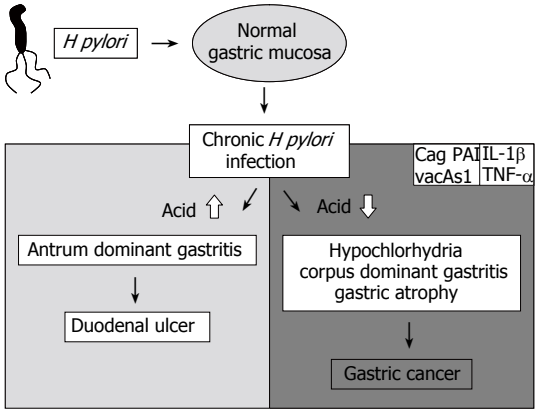

Figure 1 Variable course of *H pylori* infection.

Host genetic factors

H pylori leads to inflammation of the gastric mucosa in virtually all infected individuals. However, most *H pylori* infected humans do not develop gastric cancer even if they are infected with so-called more virulent strains, indicating that host factors play a crucial role. The fact that first-degree relatives of gastric cancer patients have a significantly increased risk for developing gastric cancer compared to patients without a family history further emphasizes the importance of genetic factors. For example, our group found some important gastric cancer related genes to be more prevalent in the gastric mucosa of first-degree relatives[45-49].

The infection with *H pylori* triggers an extensive systemic and local inflammatory response. Gastric epithelial cells respond by producing enhanced levels of interleukin-1β, interleukin-2, interleukin-6, interleukin-8 and tumor-necrosis-factor-α[50-52]. El-Omar and co-workers were the first to show that patients with certain Interleukin-1 gene cluster polymorphisms, which lead to enhanced production of the proinflammatory cytokine IL-1β are at increased risk for *H pylori* induced hypochlorhydria and gastric cancer[53]. Further studies found that proinflammatory polymorphisms of the IL-1 receptor antagonist, tumor necrosis factor-α and IL-10 are also associated with an increased risk for the development of noncardia gastric adenocarcinoma[54,55]. Interestingly, the combination of pro-inflammatory polymorphisms in the interleukin-1β gene and infection with more virulent *H pylori* strains seems to increase the gastric cancer risk even more[56]. Most of the important studies exploring host

Table 1 Gastric cancer prevention studies

Study	Design	Follow-up	Patients	Treatment	Outcome
Uemura *et al* 1997	Nonrandomized intervention trial	2 yr	132 Japanese patients with endoscopically removed early stage gastric cancer and *H pylori* infection	*H pylori* eradication therapy or no treatment	Reduced rate of gastric cancer development after eradication of *H pylori*
Saito *et al* 2000	Nonrandomized intervention trial	2 yr	64 Japanese patients with gastric adenoma and *H pylori* infection	*H pylori* eradication therapy or no treatment	Reduced rate of metachronous gastric cancer development after eradication of *H pylori*
Correa *et al* 2000	Prospective, randomized, placebo controlled trial	6 yr	852 individuals from a high risk region in Colombia with *H pylori* infection and precancerous lesions	*H pylori* eradication therapy and/or ascorbic acid/beta-carotene or placebo	Significant increase in the rate of regression of precursor conditions after cure of *H pylori* and/or treatment with dietary supplements
Wong *et al* 2004	Prospective, randomized, placebo controlled trial	8 yr	1630 individuals from a high risk region in China with *H pylori* infection; with or without precancerous lesions	*H pylori* eradication therapy or placebo	Significant reduction in gastric cancer risk after cure of *H pylori* only for patients without precancerous conditions
Take *et al* 2005	Nonrandomized intervention trial	3.4 yr	1342 Japanese patients with peptic ulcer disease	*H pylori* eradication therapy	Significant increase in gastric cancer risk for patients with persistent *H pylori* infection

genetics were performed in Caucasian populations and still need to be confirmed in other ethnic groups[3]. However, there is emerging evidence that similar associations can be found in Asian populations. For example, one study from Japan showed that proinflammatory IL-1β polymorphisms in *H pylori* infected Japanese individuals are significantly associated with hypochlorhydria and atrophic gastritis[57]. Recent data by Goto *et al*[58] also indicate that a common polymorphism in the coding gene for SHP-2 that interacts with the CagA protein can increase the risk for gastric atrophy in Japanese patients infected with CagA+ *H pylori* strains. The authors speculate that this might explain why only a proportion of CagA+ individuals develop gastric atrophy even though this strain is almost universal in Asian countries.

IN VIVO STUDIES

Animal models

A number of animal models have been developed to study the mechanisms by which *H pylori* induces gastric carcinogenesis. Using the Mongolian gerbil model, several studies provided evidence that *H pylori* infection is in fact a potent carcinogen and able to induce gastric cancer by itself[59-62]. The studies by Watanabe *et al*[59] and Honda *et al*[60] found that 37% and 40% of infected animals developed well-differentiated intestinal adenocarcinomas 62 and 72 wk after inoculation of the bacterium. Both studies used *cagA* and *vacA* positive *H pylori* strains for infection of the animals. The risk of gastric carcinogenesis in Mongolian gerbils increases significantly through combination of *H pylori* infection with other known carcinogens such as N-methyl-N-nitrosourea (NMU) and N-methyl-N-nitro-N-nitrosoguanidine (MNNG)[63-65]. Studies using *H pylori* or *H. felis* infected mice found that the gastric cancer development is strongly determined by host specific factors, for example specific patterns of immune response. Some mouse strains develop a vigorous Th-1 response to the infection while others have a predominant Th-2 immune response and seem to be more resistant to mucosal damage. Those with the strong TH-1 response continue to develop atrophy, metaplasia and eventually invasive cancer in a gender specific manner[66].

There is evidence from animal models, that eradication of *H pylori* is able to prevent gastric carcinogenesis. The incidence of gastric adenocarcinoma in nitrosamine administered Mongolian gerbils with *H pylori* infection was significantly lower in animals receiving *H pylori* eradication[67,68]. Mouse models have also provided important evidence of beneficial effects from the administration of anti-inflammatory drugs, where atrophy and metaplasia have been reversed, in some cases completely[69].

Clinical studies

Cure of *H pylori* infection results in several physiologic effects that are likely to reduce gastric cancer risk. These include reduction in cell turnover, elimination of DNA damage by a reduction of reactive oxygen species, increased gastric acid secretory capacity and restoration of ascorbic acid secretion into the gastric juice[1,70,71]. However, evidence from well-designed clinical studies supporting the cancer protective effect of *H pylori* eradication remains sparse (Table 1). Among the first clinical data to support the hypothesis that *H pylori* eradication is able to prevent gastric cancer development were case-control studies from Sweden on patients undergoing hip replacement procedures. Akre *et al*[72] showed that significantly reduced rates of gastric cancer occurred in such patients who frequently receive high doses of prophylactic antibiotics, incidentally eradicating *H pylori* infection. As discussed earlier in this review, the study by Uemura *et al*[19] provides some of the strongest evidence for the causative role of *H pylori* infection in gastric cancer development. Here, gastric cancer developed in 2.9% of all *H pylori* infected patients compared with 0% of those without infection. Notably,

no case of cancer developed in a subgroup of 253 *H pylori* infected patients who received eradication therapy at an early time point after enrollment in the study. The same group of investigators found that eradication of *H pylori* was able to prevent relapse after endoscopic resection of early stage gastric cancer[73]. Another study by Saito *et al*[74] showed that *H pylori* eradication had a favorable impact on gastric cancer development in patients with gastric adenoma. More recently, Take *et al*[75] published the results from a large prospective Japanese intervention trial. The authors endoscopically followed 1342 patients with peptic ulcer disease for a mean period of 3.4 years. All patients initially received *H pylori* eradication therapy. The risk of developing gastric cancer was significantly higher in the group of patients who failed eradication therapy compared to those who were cured for the infection.

The first prospective randomized controlled study to examine the effect of *H pylori* eradication on gastric cancer development was published by Wong *et al*[76] in 2004. The authors randomized 1630 individuals from a high-risk region in China with confirmed *H pylori* infection to eradication therapy or placebo. After a follow-up period of 7.5 years, they found no difference in gastric cancer incidence between those receiving *H pylori* eradication therapy and those who were not given treatment (7 *vs* 11 cases, $P = 0.33$). However, further subgroup analysis of the data demonstrated a significant benefit ($P = 0.02$) from eradication therapy in patients without baseline intestinal metaplasia at the time of study enrollment.

Unfortunately, several international prospective randomized controlled trials, designed to evaluate the long-term effect of *H pylori* eradication on gastric cancer development had to be abandoned. For example, the PRISMA study[77], initiated in 1998 by our group to test the effect of *H pylori* eradication therapy in a high-risk population in Germany and Austria was discontinued due to insufficient recruiting. As might be expected, most eligible patients for those studies are not willing to enter the placebo arm after the nature of such a trial has been explained to them. Apart from ethical issues, the required follow-up time of 10 to 20 years for these trials remains an additional problem. A growing number of studies are therefore using surrogate markers for gastric cancer development, namely gastric atrophy and intestinal metaplasia as primary study endpoints.

There is consistent evidence that *H pylori* eradication cures gastritis and numerous studies have shown that atrophy and metaplasia do not progress in patients after *H pylori* eradication compared to control groups who remain *H pylori* positive[78-86]. However, many of the available studies addressing the reversibility of gastric atrophy and intestinal metaplasia have yielded conflicting and inconsistent results, possibly because most of them are nonrandomized, not controlled, have short follow-up periods and only include small numbers of patients[1,3]. One of the few randomized controlled trials for the prevention of gastric dysplasia was conducted by Correa *et al*[87] in 2000. The authors found significant regression of gastric atrophy and intestinal metaplasia after *H pylori* eradication alone and in combination with β-carotene and ascorbic acid. Sung *et al*[88] prospectively followed a total of 587 *H pylori* infected patients, randomized to receive either eradication therapy or placebo, endoscopically for one year. Decrease in acute and chronic gastritis was significantly more frequent after *H pylori* eradication, but after the relatively short follow-up period, changes in intestinal metaplasia were similar between the two groups. The majority of available studies suggest, however, that regression of atrophic gastritis and, to a lesser extent, intestinal metaplasia can occur at least in a subset of patients with sufficient follow-up[3,89].

In conclusion, there is little randomized controlled trial evidence to suggest that *H pylori* eradication decreases the risk of gastric cancer development. However, regression of gastric cancer precursor lesions may occur in some patients. At present, there are no markers that help to predict such a response in the individual patient. Therefore, eradication at the earliest possible time point in the disease process seems favorable. The optimal age for testing of *H pylori* infection still needs to be determined but available data suggest that eradication at a younger age might be a more favorable approach. Future research has to focus on identification of host and bacterial specific markers that will help to predict the development of gastric cancer in the *H pylori* infected individuals. Better identification of individuals at high risk for gastric cancer will allow for more effective prevention and eradication strategies. Meanwhile, screening and treatment of *H pylori* in first-degree relatives of gastric cancer patients as well as certain high-risk populations might be beneficial.

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