MINI-REVIEW

Helicobacter Pylori Eradication as a Preventive Tool Against Gastric Cancer

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Abstract

***Helicobacter pylori* (*H. pylori*), which increases the risk of gastric diseases, including digestive ulcers and gastric cancer, is highly prevalent in Asian countries. There is no doubt that eradication of the bacterium is effective as a treatment of digestive ulcer, but eradication aiming to reduce the gastric cancer risk is still controversial. Observational studies in Japan demonstrated that the eradication decreased the gastric cancer risk among 132 stomach cancer patients undergoing endoscopical resection (65 treated with omeprazol and antibiotics and 67 untreated). In Columbia, 976 participants were randomized into eight groups in a three-treatment factorial design including *H. pylori* eradication, resulting in significant regression in the *H. pylori* eradication group. A recent randomized study in China also showed a significant reduction of gastric cancer risk among those without any gastric atrophy, intestinal metaplasia, and dysplasia. Efficacy of eradication may vary in extent among countries with different incidence rates of gastric cancer. Since the lifetime cumulative risk (0 to 84 years old) of gastric cancer in Japan is reported to be 12.7% for males and 4.8% for females (Inoue and Tominaga, 2003), the corresponding values for *H. pylori* infected Japanese can be estimated at 21.2% in males and 8.0% in females under the assumptions that the relative risk for infected relative to uninfected is 5 and the proportion of those infected is 0.5. Both the fact that not all individuals are infected among those exposed and the knowledge that only a small percentage of individuals infected with the bacterium develop gastric cancer, indicate the importance of gene-environment interactions. Studies on such interactions should provide useful information for anti-*H. pylori* preventive strategies.**

Key Words: *Helicobacter pylori* - eradication - gastric cancer

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Introduction

Helicobacter pylori (H. pylori) is a gram-negative bacterium expressing urease to buffer the pH in the acidic conditions of the human stomach. The virulence of *H. pylori* mainly depends on cytotoxic proteins such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) in the CagA pathogenicity island (Montecucco and Rappuoli, 2001). *H. pylori* is classified into strains with and without CagA, and further those that are CagA-positive are subdivided into Western and East Asian types (Azuma, 2004a). When CagA is translocated from *H. pylori* to human gastric epithelial cells through the type IV secretion system, it is phosphorylated by Src family kinases, and then combines with Src homology 2 domain-containing protein tyrosine phosphatase (SHP-2), a target molecule of CagA. The SHP-2-binding activity is associated with the degree of virulence. The East Asian type reportedly combines with SHP-2 more strongly than the Western type (Higashi et al., 2002).

The bacterium is highly prevalent in many developing countries, including examples in Asia (Bardhan, 1997; Lunet et al., 2003; Matsuhisa et al., 2003). It is well established that *H. pylori* infection is a cause of gastric diseases including gastric cancer (Munoz, 1994; Asaka et al., 1997). Recent findings showed that East Asian CagA-positive strains, in particular, are closely related to gastric cancer risk (Azuma

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et al., 2004b). Accordingly, a high prevalence is not always related to a high incidence rate of gastric cancer (Lunet et al., 2003). In Japan, Korea, and China with high gastric cancer incidences, where East Asian CagA-positive *H. pylori* is a dominant form, an effective strategy against infection is a high priority.

The bacterium is transmitted through oral-oral and/or fecal-oral routes, and the infection chance depends largely on sanitary conditions, especially in childhood (Brown, 2000). As sanitary conditions have been improved, mainly due to use of flush toilets and modern sewage systems, the proportion of the infected has been decreasing in a birth cohort manner, resulting in a higher proportion in the older generations and a lower proportion in the younger generations. The decreasing proportion of *H. pylori* infected persons will definitely contribute to a long term reduction in gastric cancer incidence in the countries with a high incidence rate of *H. pylori* related gastric cancer.

H. pylori eradication may be one of preventive strategies against gastric cancer (Plummer et al, 2004), whose effect could appear in a shorter term. An animal experiment showed that eradication reduced the stomach cancer incidence at any time, though the effect was larger in the case of earlier eradication (Nozaki et al., 2003). The present paper focuses on the epidemiologic background of eradication as a preventive tool against gastric cancer. This includes: 1) gastric cancer risk among the infected; 2) histologic changes in gastric mucosa after eradication; 3) adverse effects due to eradication; 4) reduction in gastric cancer risk through eradication; 5) lifetime cumulative risk of gastric cancer for Japanese; and 6) genetic traits for persistent *H. pylori* infection and gastric cancer.

Gastric Cancer Risk Among the Infected

It is well known that chronic atrophic gastritis is a high risk condition without reference to *H. pylori* infection. For example, a follow-up study of 5,373 stomach-unresected Japanese participants without a cancer demonstrated a significantly elevated risk for those with gastric atrophy (Inoue et al., 2000). An association between gastric atrophy and *H. pylori* infection has also been documented from cross-sectional or case-control studies (Asaka et al., 1992; Fukao et al., 1993; Fontham et al., 1995; Watanabe et al., 1997a), as well as cohort studies (Kuipers et al., 1995; Kikuchi ea al., 2000a). Accordingly, the hypothesis that *H. pylori* infection causes gastric atrophy, resulting in the elevation of gastric cancer risk, is widely accepted. Those uninfected with gastric atrophy seem to have a similar or higher risk to the infected with gastric atrophy, simply because the uninfected are in an progressed condition (Fig. 1).

Direct associations between *H. pylori* infection and gastric cancer have been examined for many regions and ethnic groups (Eslick et al., 1999). Case-control studies on the association have been conducted in Japan (Asaka et al., 1994; Fukuda et al., 1995; Kikuchi et al., 1995; Kato et al., 1996; Kikuchi et al., 2000b), Korea (Kim et al., 1997; Lee

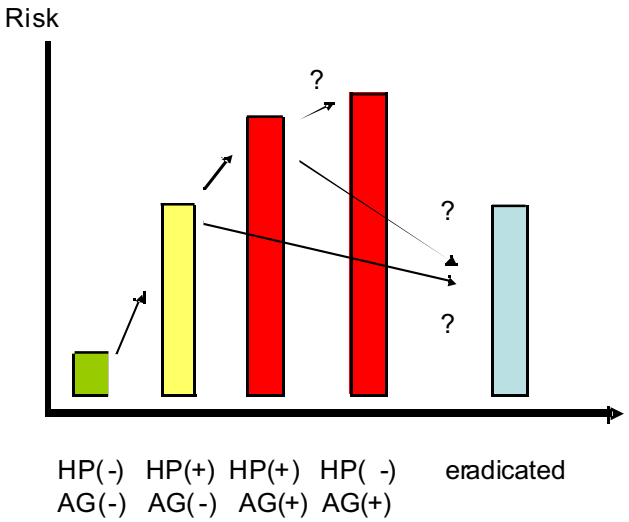

Figure 1. Gastric Cancer Risk according to *Helicobacter pylori* Infection Status and Atrophic Gastritis

et al., 1998), Taiwan (Wu et al., 1998), China (Hu et al., 1994), and India (Sivaprakash et al., 1996). While there were some studies reporting no association with gastric cancer, the summary statistic derived from meta-analysis indicated that there was no doubt on the presence of an association (Eslick et al., 1999).

Studies on links with the CagA seropositive condition have also been conducted in many countries. In Japan,CagA seropositives showed a larger odds ratio (OR), OR=10.4, 95% confidence interval (CI), 4.2-29.7 than *H. pylori* seropositives (high-molecular-weight cell-associated protein; OR=1.3, 95%CI, 0.7-2.5) (Maeda et al., 2000), and a significantly elevated risk for the CagA positives (OR=2.2, 95%CI, 1.04-4.65) among infected individuals was also reported (Shimoyama et al, 1998). Two other studies resulted in no additional risk elevation observed among the infected (Kikuchi et al., 1999; Yamaoka et al., 1999) but a meta-analysis of the association with CagA seropositivity, including data from non-Asian countries found a more marked association with CagA seropositivity than *H. pylori* seropositivity (Huang et al., 2003).

Twelve nested case-control studies (case-control studies in a cohort study) using blood samples before diagnosis were summarized in meta-analysis, providing a summary odds ratio of 2.36 (95%CI, 1.98-2.81) with 1,228 gastric cancer cases and 3,406 controls (*Helicobacter* and Cancer Collaborative Group 2001), including studies in Japan (Watanabe et al., 1997b), Taiwan (Lin et al., 1995), and China (Yuan et al., 1999; Limburg et al., 2001). When stratified, the odds ratio was 2.97 (95%CI, 2.34-3.77) for non-cardia cases and 0.99 (95%CI, 0.71-1.35) for cardia cases.

In a cohort study at a clinic in Japan, patients with active duodenal ulcers, active gastric ulcers, gastric hyperplastic polyps or nonulcer dyspepsia were tested by histologic examination, a rapid urease test, and serologic test. Those who were positive in any of the three tests were defined as

infected, and those with no positive results as uninfected. No gastric cancer patients were diagnosed in 280 uninfected persons, while 36 out of 1,246 infected were diagnosed as having gastric cancer during 7.8 years of mean follow-up (Uemura et al., 2001). In a follow-up study of 3,386 participants of gastric cancer screening in China, presence of *H. pylori* infection was associated with progression to dysplasia or gastric cancer (You et al., 2000).

Histologic Changes in Gastric Mucosa after Eradication

Eradication of *H. pylori* reduces inflammation of gastric mucosa (Asaka et al., 2003), and gastric atrophy is reported to gradually improve (Watanabe et al., 2003). Since intestinal-type gastric cancer is preceded by a series of pathological changes starting from superficial gastritis to intestinal metaplasia and dysplasia (Correa et al., 1990), the effect of eradication on gastric cancer risk reduction could be measured by changes in shift in histology. A double-blind, placebo-controlled eradication trial was conducted for the infected health volunteers in Mexico (Ley et al., 2004). One year follow-up demonstrated the changes in worst biopsy diagnosis to be similar between the eradication and control groups, but an index score relating to the histology was improved in the eradication group. In a placebo-controlled randomized trial with 295 treated and 292 control individuals, a significant reduction in acute and chronic gastritis, but not in intestinal metaplasia, was observed for the eradicated group (Sung et al., 2000).

H. pylori infection may persist in gastric cancer patients after partial gastrectomy (Katsube et al., 2002), which is followed by severe mucosal changes such as cystic dilatation, atrophic gastritis, intestinal metaplasia, and dysplasia (Weinstein et al., 1985). The changes are reportedly themselves associated with *H. pylori* infection (Safatle-Ribeiro et al., 1999). In a study of 12 patients who underwent distal gastrectomy with Billroth I anastomosis for early gastric cancer (Hamaguchi et al., 2004),eradication led to disappearance of mucosal edema and erythema with a reduction in mononuclear cell infiltration, as well as decreases in both the Ki-67 label index, indicating cell proliferation, and interleukin 8 levels.

Adverse Effects due to Eradication

Reflux esophagitis after *H. pylori* eradication was first reported by Labenz et al., in 1997. Subsequent clinical studies showed conflicting results including examples indicating beneficial effects of the eradication treatment (Befrits et al., 2000). The results from large-scale randomized controlled studies supported no increase in adverse effects. No association was observed for 1,165 asymptomatic *H. pylori*-positive patients in the United States (Laine et al., 2002) and for 1,558 participants a *Helicobacter* project in northeast Bristol, United Kingdom (Harvey et al., 2004). An association with beneficial effects of eradication was demonstrated for 2,324 *H. pylori*-positive participants out of 32,929 invited from the lists of 36 general practices in the north of England (Moayyedi et al., 2000). A study in Denmark was conducted with a pre-randomization method, in which 21,607 inhabitants were randomized into Group 1 (screening and eradication) and Group 2 (only questionnaire survey) before informed consent. The participants were 5,749 out of 10,007 inhabitants in Group 1 and 6,781 out of 10,696 inhabitants in Group 2. The 1-year follow-up found that the prevalence of dyspepsia decreased from 24.3% to 20.5% in Group 1 (including 17.5% of *H. pylori*-positive participants), and increased from 20.3% to 21.5% in Group 2. The reduction of dyspepsia in Group 1 was similar in the *H. pylori*-positive participants and *H. pylori*-negative participants (Wildner-Christensen et al., 2003).

Several non-randomized studies on adverse effects have been conducted for Japanese, but none are available for other Orientals. In one, 286 patients with gastritis or peptic ulcers undergoing eradication treatment were followed using annual endoscopy, as well as infected patients with the same disease who visited the hospital during the same period (Hamada et al., 2000). The accumulated incidence of reflux esophagitis at 3 years was 18% for the eradication group and 0.3% for the controls. Those with hiatal hernia or corpus gastritis had a higher risk of reflux esophagitis. Two studies reported beneficial effects of the eradication. One of 162 *H. pylori*–positive reflux esophagitis patients with peptic ulcers showed that the eradicated patients had a significantly higher rate of improvement (60.8%) than the eradication-failure cases (38.9%) (Ishiki et al., 2004). The other study compared symptoms between 241 successfully eradicated and 241 age-gender-disease (gastric ulcer, duodenal ulcer, or gastroduodenal ulcer) -matched controls not treated by eradication therapy. The rate for improved reflux symptoms was significantly higher in the eradicated group (65.4%) than in the controls (30.4%) (Miwa et al., 2002). One case series study of 82 patients (32 with gastric adenomas, 20 with non-ulcer dyspepsia, 14 with gastric ulcers, 12 asymptomatic requesting eradication, and 4 undergoing endoscopic mucosal resection for gastric cancer) found 3 out of 55 patients without esophagitis to develop mild reflux esophagitis and esophagitis was improved in 5 out of 27 patients with the disease (Yachida et al., 2001).

Reduction in Gastric Cancer Risk through Eradication

Although the risk elevation among *H. pylori* infected individuals is well documented, information on the degree of risk reduction in gastric cancer incidence due to *H. pylori* eradication is still limited. In a non-randomized study in Japan, none out of 65 gastric cancer patients who underwent eradication treatment after endoscopic gastric cancer resection were sunsequently diagnosed as having a new gastric cancer, in contrast to six out of 67 corresponding patients without eradication treatment (Uemura et al., 1997).

In order to confirm the risk reduction through *H. pylori*

eradication, randomized controlled studies are required. Several studies are still ongoing in the world, but the first report appeared in 2000, in which 976 with multifocal non-metaplastic atrophy, intestinal metaplasia, or dysplasia, among 1,219 participants in Colombia, were randomized into eight groups defined by a factorial design of *H. pylori* eradication, ascorbic acid supplementation, and beta-carotene supplementation (Correa et al., 2000). The eradication treatment consisted of amoxicillin (500 mg), metronidazole (375 mg), and bismuth subsalicylate (262 mg) three times per day for 14 days. The participants who received the intervention as allocated were 852; 194 with multifocal nonmetaplastic atrophy, 579 with intestinal metaplasia, and 79 with dysplasia. After 72 months follow-up, a significant regression to a lower risk condition was observed for the eradication group relative to the controls; RR=4.8 (95% confidence interval (CI), 1.6-14.2) among those with multifocal nonmetaplastic atrophy at entry, and RR=3.1 (95% CI, 1.0-9.3) among those with intestinal metaplasia at entry. The relative risk of progression for the eradication group was not statistically significant; RR=0.8 (95% CI, 0.4-1.9) and RR=0.4 (95% CI, 0.2-0.9), respectively. In total, five gastric cancer patients were found; four from those with intestinal metaplasia and one from those with dysplasia. The allocated treatments for the five patients were not described in the paper. Although this intervention study failed to demonstrate an effect on gastric cancer risk, it was clear that the eradication caused regression, and it is possible that it prevented progression to a high risk condition, which suggests that eradication makes a reversible change to the lower risk condition, and possibly prevents development of a higher risk condition.

Next reported was a study in China (Wong et al., 2004). The authors randomized 1,630 subjects into a placebo control group and an eradication group receiving 2-weeks of omeprazole (20mg), a combination of amoxicillin and cluvulanate potassium (750mg), and metronidazole (400mg) twice a day as the first-line treatment, and 1-week of colloidal bismuth subcitrate (240mg), metronidazole (600mg), clarithromycin (500mg) and omeprazole (20mg) twice a day as the second-line treatment. Out of 817 participants allocated into the eradication group, the therapy was successful in 624 with the first-line treatment and 60 of 85 who agreed to receive the second-line treatment, in total 83.7%. A follow-up of 7.5 years after eradication treatment found that 11 out of 813 controls and 7 out of 817 eradicated participants were diagnosed as gastric cancer. In a subgroup without any of atrophy, intestinal metaplasia, and dysplasia at enrollment, 6 and 0 gastric cancer patients were found for the controls and the eradicated, respectively (p=0.02 by a log-rank test).

Thus the available evidence supports a conclusion of merits for the eradication. However, the size of the the gastric cancer risk reduction can not presently be precisely estimated (Fig. 1) and this presumably may vary among the ethnic groups, and among individuals exposed to different secondary risk factors.

Lifetime Cumulative Risk of Gastric Cancer in Japanese

Lifetime cumulative risk (LCR) is the probability of suffering a given disease from birth to a defined age (e.g., 84 years old), estimated from age-specific incidence rate at a calendar period under the assumption that there is no difference in the rate among those with a different birth year.

The lifetime cumulative risk (0 to 84 years old) of gastric cancer for Japanese has been estimated to be 12.7% for males and 4.8% for females (Inoue and Tominaga 2003). The estimates were for those including both *H. pylori* infected and uninfected. The proportion of the infected depends on age from 10% for those aged 10-19 years to 60-80% for those aged 60 years or over. When the proportion is P, the lifetime cumulative risk of the whole population (LCR_{whole}) is roughly calculated by $\{P \times RR + (1 - P)\} \times LCR_{uninfected}$, where RR is the relative risk of the infected relative to the uninfected, and $LCR_{uninfected}$ is the lifetime cumulative risk for the uninfected. Accordingly, the $LCR_{uninfected}$ is $LCR_{whole} / \{P \times RR + (1 - P)\}$, and $LCR_{infected}$ is $RR \times LCR_{uninfected}$.

Table 1 shows the $LCR_{uninfected}$ and $LCR_{infected}$ values depending on LCR_{whole}, RR, and P. In the case of RR=5 and P=0.5, the $LCR_{infected}$ was calculated to be 21.2% for males with a LCR_{whole}=12.7%, and 8.0% for females with a LCR_{whole}=4.8%. The infected were found to have a high cumulative risk if the assumptions (RR=5 and P=0.5) are plausible. The RR of *H. pylori* infection for gastric cancer may be underestimated because those with gastric atrophy due to the infection in the past is usually included in the uninfected controls of case-control studies. The RR=5 is not an unrealistic estimate (You et al., 2001). It should also be noted that LCR of *H. pylori*-eradicated individuals is not equal to $LCR_{infected}$.

Genetic Traits for Persistent *H. pylori* Infection and Gastric Cancer

The virulence or strains of the bacterium may influence the infection rate, as well as the disease risk of the infected (Montecucco and Rappuoli, 2001). However, it is also a fact that there are uninfected individuals among the exposed. Although lifestyle and other non-genetic factors can be associated with the *H. pylori* infection and the persistence, genetic factors of the host could also affect the susceptibility. A twin study showed that the concordance of anti-*H. pylori* antibody status was higher in monozygotic twin pairs than in dizygotic twin pairs (Malaty et al., 1994), strongly indicating genetic roles in persistent *H. pylori* infection. To date, associations with HLA types and polymorphisms of *secretor*, *Lewis*, *interleukin 1B* (*IL-1B*), *myeloperoxidase* and *tumor necrosis factor A* (*TNF-A*) have been reported (Hamajima., 2003a). Among them, the polymorphisms of *IL-1B* and *TNF-A* are considered to be candidates for genetic traits pertaining to *H. pylori* infection.

IL-1β, which is induced by *H. pylori* infection (Jung et al., 1997), is a proinflammatory cytokine with multiple

Table 1. Lifetime Cumulative Risk (LCR) of Gastric Cancer according to the Status of *Helicobacter pylori* Infection.

LCR_{whole}	RR	Infected	$LCR_{infected}$	$LCR_{uninfected}$
3%	3	50%	4.5%	1.5%
3%	3	70%	3.8%	1.2%
3%	5	50%	5.0%	1.0%
3%	5	70%	3.9%	0.8%
3%	10	50%	5.5%	0.5%
3%	10	70%	4.1%	0.4%
4.8%	3	50%	7.2%	2.4%
4.8%	3	70%	6.0%	2.0%
4.8%	**5**	**50%**	**8.0%**	**1.6%**
4.8%	5	70%	6.3%	1.3%
4.8%	10	50%	8.7%	0.9%
4.8%	10	70%	6.6%	0.7%
10%	3	50%	15.0%	5.0%
10%	3	70%	12.5%	4.2%
10%	5	50%	16.7%	3.3%
10%	5	70%	13.2%	2.6%
10%	10	50%	18.2%	1.8%
10%	10	70%	13.7%	1.4%
12.7%	3	50%	19.1%	6.4%
12.7%	3	70%	15.9%	5.3%
12.7%	**5**	**50%**	**21.2%**	**4.2%**
12.7%	5	70%	16.7%	3.3%
12.7%	10	50%	23.1%	2.3%
12.7%	10	70%	17.4%	1.7%
15%	3	50%	22.5%	7.5%
15%	3	70%	18.8%	6.3%
15%	5	50%	25.0%	5.0%
15%	5	70%	19.7%	4.9%
15%	10	50%	27.3%	2.7%
15%	10	70%	20.5%	2.1%

RR: relative risk. The bold figures are plausible combinations for males (LCRwhole=12.7%) and females (LCRwhole=4.8%).

biological effects (Dianarello, 1996). It is a strong inhibitor of gastric acid secretion, possibly leading to *H. pylori* spread from the pylorus to the corpus. Such spread increases the risk of gastric atrophy and gastric cancer (El-Omar, 2001). *IL-1B* coding IL-1β has been reported to have polymorphisms, among which the tightly linked T-31C and C-511T polymorphisms (*-31C* with *-511T* and *-31T* with *-511C*) (Hamajima et al., 2001) are considered to be functional. TNF-α is also a proinflammatory cytokine, which has a similar function to IL-1α. *TNF-A*, T-857C and T-1031C were reported to have a consistent association with *H. pylori* seropositivity (Hamajima et al., 2003b).

There are a limited number of reports concerning the associations between eradication success and polymorphisms. Only an association with a Lewis gene polymorphism was found (Matsuo et al 2003).

Concerning gastric cancer risk, many polymorphisms have been examined (Gonzalez et al., 2002). Among them, *IL-1B* polymorphisms showed rather consistent results among Caucasians, with *IL-1B -511T* allele carriers reported to have a higher risk of stomach cancer (El-Omar et al., 2000, corrections 2001; Machado et al., 2001). However, in Japan and Korea, the association appears less clear (Kato et al. 2001, Lee et al., 2004)

Comments

This review summarizes the available information useful to evaluate *H. pylori* eradication as a tool for gastric cancer prevention. Although the evidence may be regarded inconclusive by some researchers, accumulated epidemiological and biological findings strongly indicate that *H. pylori* eradication reduces the risk. Questions remain concerning who will experience benefit and how large the size of the risk reduction is for the whole population and for subgroups defined by family history, smoking habit, genotypes, and so forth. No one can answer these questions at present, but if the individuals seek eradication after explanation of the potential risk and benefit, the accumulated evidence could justify preventive health services for such persons.

In the 1996 Maastricht Consensus Report, eradication was strongly recommended for infected patients who had undergone partial gastrectomy for early gastric cancer (The European *Helicobacter Pylori* Study Group, 1997). At present, Japanese health insurance does not cover eradication, resulting in restricted access to preventive eradication. Such high risk patients should be treated even outside of the health insurance system.

The risk of gastric cancer varies among individuals with different lifestyle and genotypes. Large studies including lifestyle questioning and genotyping on the effect of the eradication are now required in geographical areas where the gastric cancer incidence is high.

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