Review Article

Helicobacter Pylori and Gastric Cancer: Clinical Aspects

Zhi-Qiang Song, Li-Ya Zhou

Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China

Abstract

Objective: Although *Helicobacter pylori* (*H. pylori*) is considered as the main etiological factor for gastric cancer, the strategy of screening and treating the oncogenic bacterium is still controversial. The objective was to evaluate the status and progress of the cognition about the relationship between *H. pylori* infection and gastric cancer from a clinical aspect.

Data Sources: The data used in this review were mainly from the PubMed articles published in English from 1984 to 2015.

Study Selection: Clinical research articles were selected mainly according to their level of relevance to this topic.

Results: Gastric cancer is the fifth most common malignancy and the third leading cause of cancer deaths worldwide. The main etiological factor for gastric cancer is *H. pylori* infection. About 74.7–89.0% gastric cancer was related to *H. pylori* infection. Up to date, some regional gastric cancer prevention programs including the detection and treatment of *H. pylori* infection are under way. Current data obtained from the randomized controlled trials suggest that population-based *H. pylori* screening and treatment is feasible and cost-effective in preventing gastric cancer; however, a population-based *H. pylori* eradication campaign would potentially lead to bacterial resistance to the corresponding antibiotics, as well as a negative impact on the normal flora.

Conclusions: The important questions of feasibility, program costs, appropriate target groups for intervention, and the potential harm of mass therapy with antibiotics must first be answered before implementing any large-scale program.

Key words: Clinical; Eradication; Gastric Cancer; *Helicobacter pylori*; Screening

Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer deaths worldwide.[1,2] The most recent estimates from GLOBOCAN 2012[3] indicate that nearly one million new gastric cancer cases and more than 720,000 deaths from gastric cancer occurred worldwide in 2012, accounting for 7.0% of the total new cancer cases and 9.0% of the total cancer deaths. Among the new gastric cancer cases, Asia contributed approximately 74% to the global burden and nearly one-half of the worldwide cases (405,000) were in China. Many other countries, especially in Latin America and Eastern Europe, also have relatively high rates of gastric cancer.

Over the past 50 years, incidence rates of gastric cancer have steadily declined in most countries, regardless of their background risk. Yet despite an anticipated continued reduction of approximately 2.0% per year, the future burden of gastric cancer, in numbers of cases and deaths, is expected to rise as the world's population increases and ages.[1,4]

The main etiological factor for gastric cancer is the infection of *Helicobacter pylori* (*H. pylori*), the first bacterium recognized as oncogenic.[4] A meta-analysis[5] of 12 prospective studies showed a relative risk of 2.4 (95% confidence interval [*CI*], 2.0–2.8) between *H. pylori* positive patients and gastric cancer. The International Agency for Research on Cancer classified *H. pylori* as a Group 1 carcinogen in 1994[6] based on a thorough review of relevant laboratory and epidemiological studies and reconfirmed this classification in 2009.[7]

Possible Mechanisms by Which *Helicobacter Pylori* Induces Gastric Cancer

H. pylori infects the gastric mucosa during childhood and establishes a chronic long-lasting inflammation that, if not

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Address for correspondence: Prof. Li-Ya Zhou, Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China
E-Mail: zhouliya123456@163.com

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treated, remains for decades. This persistent inflammation of gastric mucosa will eventually cause gastric cancer in <3.0% of the infected individuals.

H. pylori colonizes the gastric mucosa, where it expresses an array of proteins that allow it to establish a persistent infection. Most of these factors interact with receptors in gastric epithelial cells to signal different cellular pathways that eventually lead to changes in the expression of the genes involved in inflammation, cellular proliferation, invasion, and metastasis. Inflammation might also lead to chronic long-lasting exposure to reactive oxygen and reactive nitrogen species, which cause DNA damage, genetic instability, and gene mutations, eventually lead to carcinogenesis.

Decades of gastric inflammation might also induce epigenetic changes, such as methylation of genes, which also leads to carcinogenesis. Virulence factors such as CagA, VacA, and lipopolysaccharide interact and modulate different cellular signaling pathways to induce a proinflammatory response or alter tight junctions and cell polarity, which finally favor metastasis. A proinflammatory response would result in increased mucosal levels of cytokines such as interleukin (IL)-1, IL-8, tumor necrosis factor-α, and prostaglandin E_2.[8-10]

Relationship between *Helicobacter Pylori* Infection and Gastric Cancer

Investigators have attempted to estimate the proportion of gastric cancer cases that could have been avoided if exposure to *H. pylori* infection is absent. de Martel *et al*.[11] estimated a population attributable fraction (PAF) by using a prevalence of *H. pylori* infection of 90% in gastric cancer cases and a relative risk of 5.9, and obtained a PAF estimate of 74.7%. Plummer *et al*.[12] estimated a revised PAF based on a prevalence of *H. pylori* infection of 94.6% in gastric cancer cases and a relative risk of 17.0, which resulted in a PAF of 89.0%.

These data clearly indicate the close relationship between *H. pylori* infection and gastric cancer (mainly in noncardia gastric cancer). *H. pylori* infection is the most important etiological factor for gastric cancer.

Evidence Relating to the Effectiveness of *Helicobacter Pylori* Eradication in Gastric Cancer Prevention

Three placebo-controlled trials of therapy to eradicate *H. pylori* were performed in relation to the incidence of gastric cancer. Two of the studies were performed in China[13,14] and one in Japan.[15] The meta-analysis[1] showed that the summary relative risk is 0.64 (95% *CI*, 0.44–0.94). This summary estimate is dominated by the results from the study described below.

In 2012, Ma *et al*.[14] reported the long-term follow-up results of the Shandong Intervention Trial, a masked, randomized trial in which 2258 *H. pylori* seropositive adults drawn from a general population in China were randomly assigned in a 2 × 2 × 2 factorial design to three interventions: 2 weeks of *H. pylori* eradication therapy, garlic supplements, and supplemental vitamins for 7.3 years, or their placebos. Gastroscopies with stomach biopsies were scheduled at study entry and at follow-up times approximately 5 and 9 years after randomization. The investigators had previously reported the results of the 9-year gastroscopy study, which indicated that antibiotic eradication therapy significantly reduced the prevalence of precancerous gastric lesions (odds ratio [*OR*], 0.60; 95% *CI*, 0.47–0.75).[16] At that time, there were 19 gastric cancers detected in participants assigned to eradication therapy and 27 in those assigned to the control group ($P = 0.14$). After the 9-year gastroscopy study, participants remained under active clinical follow-up without protocol-specified endoscopy, and by 15 years after randomization, there were 34 gastric cancers in the participants assigned to *H. pylori* eradication and 52 in those assigned to the corresponding control (*OR*, 0.61; 95% *CI*, 0.38–0.96).

Another two randomized controlled trials reported results after 5 years[17] and 10 years[18] of follow-up. The relative risk was 0.65 (95% *CI*, 0.19–2.28) after 5 years and 0.29 (95% *CI*, 0.06–1.36) after 10 years.

There are two published randomized placebo-controlled trials of eradication therapy in patients with precancerous stomach lesions. One trial yielded a relative risk of 1.48 (95% *CI*, 0.25–8.83).[19] The other had a four-group factorial design using the following two treatments: *H. pylori* eradication treatment and the use of a cyclooxygenase-2 (COX-2) inhibitor.[20] The relative risk based on the groups without using a COX-2 inhibitor was 3.04 (95% *CI*, 0.32–28.99), and the relative risk based on all the data was 2.00 (95% *CI*, 0.50–7.97). The meta-analysis[1] showed that the combined relative risk for these two trials was 1.79 (95% *CI*, 0.60–5.33).

To evaluate the benefit of *H. pylori* eradication for gastric cancer prevention, Lee *et al*.[21] conducted a mass eradication of *H. pylori* infection over 4 years (2004–2008) in a Chinese population >30 years of age with a high prevalence of *H. pylori* infection. Participants with a positive ^{13}C-urea breath test underwent endoscopic screening and one to two courses of eradication therapy. The prevalence of gastric atrophy was 59.9% in 2004 (immediately before chemoprevention) and 13.7% in 2008 (after chemoprevention), yielding an effectiveness of 77.2% (95% *CI*, 72.3–81.2%) in reducing gastric atrophy. Compared with the 5-year period before chemoprevention and endoscopic screening, the effectiveness in reducing gastric cancer incidence during the chemoprevention period was 25% (rate ratio, 0.753; 95% *CI*, 0.372–1.524).

A recent meta-analysis[22] of all six published randomized trials of *H. pylori* treatment among asymptomatic infected individuals yielded an estimated effectiveness

of 34% (95% *CI*, 5.0–54.0%) in preventing new gastric cancer. Fifty-one (1.6%) gastric cancers occurred among 3294 individuals who received eradication therapy versus 76 (2.4%) in 3203 control subjects with no heterogeneity between studies. If the benefit of eradication therapy was assumed to persist lifelong the number needed to treat was as low as 15 for Chinese men and as high as 245 for US women.

Two randomized trials were performed on *H. pylori* eradication therapy on the incidence of second gastric cancers, one in Japan[23] and the other in the Republic of Korea.[24] The two trials resulted in 19 cases of second gastric cancers in the treated group compared with 41 cases in the control group. The relative risk estimate was 0.47 (95% *CI*, 0.28–0.80).[1]

Three studies compared the number of second gastric cancers between patients in whom *H. pylori* had been successfully eradicated and patients in whom eradication of *H. pylori* had failed; relative risks of 0.59 (95% *CI*, 0.30–1.19),[25] 0.53 (95% *CI*, 0.32–0.87),[26] and 0.45 (95% *CI*, 0.23–0.86)[27] were observed; however, these studies are not randomized controlled trials, so the possibility of selection bias cannot be excluded.

In the latest review article, Ford *et al*.[28] found that the limited, moderate-quality evidence that searching for and eradicating *H. pylori* reduces the incidence of gastric cancer in healthy, asymptomatically infected Asian individuals, however, it may be inadequate to extrapolate this data to other populations.

These results, taken together, suggest that treating *H. pylori* infection protects against gastric cancer, but they do not provide a final conclusion. Given that other randomized trials are in progress, it would be prudent to draw any conclusions about the benefit of *H. pylori* eradication therapy on gastric cancer unless further evidence is available from these trials.

Status of Regional Gastric Cancer Prevention Efforts

In Japan, gastric cancer prevention efforts have primarily focused on early detection using barium contrast imaging and gastroscopy.[29] The emphasis is now shifting toward treating *H. pylori* infection, and in 2013, the Japanese government approved national health insurance coverage for antibiotic treatment for *H. pylori* infection in patients who had been endoscopically diagnosed with chronic gastritis. According to this strategy, patients with gastritis are investigated for *H. pylori* infection and those who test positive receive eradication therapy followed by periodic surveillance. If this strategy is implemented, deaths from gastric cancer in Japan may dramatically decrease in 10–20 years.[30]

In Changhua County, Taiwan, China, organized gastric cancer prevention is included in a community-based integrated screening program that provides stool testing for *H. pylori* antigen (as well as fecal immunochemical screening for colorectal cancer) targeting the adult population aged 50–69 years. Individuals who were positive for *H. pylori* were offered endoscopic screening and antibiotic treatment. Both primary prevention (*H. pylori* eradication treatment) and secondary prevention (endoscopic screening) were implemented for detecting gastric cancer, and preliminary results showed that this strategy was applicable and effective. On positive identification, participants benefited from antibiotic treatment for peptic ulcer and chronic gastritis, and from chemoprevention for gastric cancer.[21]

The Republic of Korea, where the age-standardized gastric cancer incidence rate is the highest worldwide, has an established nationwide program that provides screening with either an upper gastrointestinal series (barium swallow) or an endoscopy every 2 years to individuals ≥40 years old. In 2012, over 12 million people were invited for screening and approximately one-half participated.[31]

In Latin America, Chile introduced an opportunistic gastric cancer screening program that focuses on symptomatic population ≥40 years old. The program provides endoscopic examination for *H. pylori* detection, biopsy, and treatment.[1]

Potential Impact of Bacterial Resistance after Population-based *Helicobacter Pylori* Treatment

There is evidence of a positive correlation between antibiotic consumption and bacterial resistance to the corresponding antibiotic, as well as a negative impact on the normal flora, which are now considered as an important problem in many diseases.

A study was conducted to assess the resistance rates of *H. pylori* to certain antibiotics (macrolides and fluoroquinolones) and the link to outpatient antibiotic use in 17 European countries.[32] Data on consumption were expressed as the defined daily dose (DDD) per 1000 inhabitants per day, and *H. pylori* strains were collected in centers across Europe. A good correlation was obtained for fluoroquinolones. The correlation was not statistically significant for macrolides when analyzed together but was significant when only long-acting macrolides were considered.

Another research in this area conducted in Finland by Seppälä *et al*.[33] studied the effect of macrolide consumption on erythromycin resistance of *Streptococcus pyogenes* (*S. pyogenes*). In the early 1990s, after an increase in *S. pyogenes* resistance to macrolides, the policy on outpatient antibiotic use was changed throughout the country, especially policies limiting macrolide use for respiratory and skin infections. After this decision, *S. pyogenes* resistance to erythromycin was monitored for 7 years. The researchers observed a decrease in the DDD per 1000 inhabitants per day from 2.40 to 1.38, and the percentage of *S. pyogenes* macrolide resistance decreased by nearly 50%, but only after a 5-year delay.

The results of these two studies point out that a positive relationship exists between antimicrobial use and the development of resistance.

In addition to *H. pylori* resistance, the resistance of other bacteria which is induced by *H. pylori* eradication therapy must also be considered, especially that of fecal flora. In a study of the stool, throat, and nostril flora of 85 patients who received clarithromycin, metronidazole, and omeprazole for 1-week, the researchers focused on four bacterial species.[34] A dramatic increase in resistance was observed 2 weeks after the treatment among all strains that were previously susceptible as follows: Streptococci (80%), staphylococci (72%), enterococci (67%), and bacteroides (27%). After 1 year, the probability of persistence of resistant organisms was 51% for streptococci, 39% for staphylococci, 14% for enterococci, and 14% for bacteroides.

A mass *H. pylori* eradication campaign might add greatly to this burden; however, the precise impact of eradication measures should be calculated in different areas, according to the prevalence of the infection, to determine what the real additive effect would be.[1]

Cost-effectiveness of Population *Helicobacter Pylori* Screening and Treatment Strategy

A screening program also needs to be affordable and the benefits of the strategy must justify the costs. In 1996, Parsonnet *et al*.[35] first reported a health economic model that suggested that population *H. pylori* screening and treatment could be a cost-effective strategy by which to prevent gastric cancer. Other related studies[36-39] obtained similar results. These models studied a variety of populations and made different assumptions, but all found population *H. pylori* screening and treatment to be cost-effective using a threshold of $50,000 per life year saved. Most studies evaluated screening using serology.[40]

Current data suggest that population *H. pylori* screening and treatment is feasible and cost-effective in preventing gastric cancer.[4,41] Future economic models should use current systematic review data on the efficacy of *H. pylori* eradication to prevent gastric cancer.

Conclusions

Given the strong causal link between *H. pylori* and gastric cancer, billions of people who are already infected with the organism represent a vast reservoir of potential cancer cases that will emerge in the coming decades unless effective preventive measures are implemented. When viewed in the context of the epidemiological and laboratory evidence for the carcinogenic activity of chronic *H. pylori* infection, the recently reported results from randomized trials appear to provide compelling support for a large gastric cancer preventive effect of *H. pylori* eradication.[42-45] Nevertheless, important questions of feasibility, program costs, appropriate target groups for intervention, and the potential harm of mass therapy with antibiotics must first be answered before implementing any large-scale program. The answers to these questions will most likely require region-specific data and cost-benefit analyses.[1,46]

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Conflicts of interest

There are no conflicts of interest.

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