REVIEW ARTICLE

Is Eradication of *Helicobacter pylori* the Feasible Way to Prevent Gastric Cancer? New Evidence and Progress, but Still a Long Way to Go

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Epidemiological, animal and biological studies provide compelling evidence for the role of *Helicobacter pylori* infection in gastric carcinogenesis. The finding that *H. pylori*-induced chronic atrophic gastritis is the major cause of gastric cancer suggests that eradication of the bacterium may prevent this malignancy. Computer-simulation studies have confirmed the cost-effectiveness of eradication in high-risk subjects; however, unresolved issues complicate active testing for and treatment of *H. pylori* infection among asymptomatic carriers. Concerns include the enormous costs for developing countries to implement strategies, the inconclusiveness of data from randomized controlled studies, the potential induction of antimicrobial resistance, and the uncertain effect of eliminating this organism on the spectrum of modern disease. Although current evidence is insufficient to recommend universal testing and treatment, it is possible to identify highly susceptible individuals who are most likely to benefit from treatment. Novel biomarkers for predicting risk are under extensive investigation, including genetic, epigenetic and proteinomic factors. The emerging evidence suggests that treatment of *H. pylori* infection in asymptomatic carriers may decrease the burden of gastric cancer. However, confirmation of long-term benefits remains a long way off. [*J Formos Med Assoc* 2008;107(8):591–599]

Key Words: cancer prevention, cost effectiveness, *Helicobacter pylori*, stomach neoplasms

Gastric malignancy is associated with high morbidity rates and poor prognoses, and accounts for almost 10% of new cancers worldwide.[1] In some countries, especially those in Far East Asia such as China, Japan and Korea, this disease is one of the leading causes of cancer-related deaths.[2] Although the global incidence is declining, gastric cancer still affects public health substantially and results in the growth of an already considerable economic burden.[1,2]

To help prevent gastric cancer, numerous investigators have sought to identify risk factors associated with gastric cancer, to build mathematical models for predicting the efficacy of intervention, and to test the precision of models in clinical trials.[3] Most studies have been based on

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Received: March 24, 2008
Revised: May 31, 2008
Accepted: July 8, 2008

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the fact that *Helicobacter pylori* is one of the major causes of gastric cancer.

H. pylori Infection and Risk of Gastric Cancer

H. pylori is a Gram-negative bacterium that selectively colonizes the gastric mucosa. Infection rates vary, with a mean of 20–40% in developed countries and 60–80% in developing countries.[4] After infection, the bacterium persists for the lifetime of the host. Prolonged infection may lead to chronic gastritis, peptic ulcer, gastric cancer, and/or mucosa-associated lymphoid tissue (MALT) lymphoma.[1]

On the basis of epidemiologic studies, the World Health Organization classified *H. pylori* as a class I (definite) carcinogen in humans in 1994.[4] Several meta-analyses have shown a strong and consistent association between *H. pylori* infection and noncardiac gastric cancer (Table 1).[5–8] An updated consensus has indicated that chronic atrophic gastritis caused by *H. pylori* is the major precursor of gastric cancer.[9] In a recent study, the attribution fraction of noncardiac gastric cancer was 74% in developed countries and 78% in developing countries. These percentages represented 592,000 cases, or 5.5% of all cancers.[10]

In addition to epidemiologic observations, data from animal studies have solidified the causal relationship between *H. pylori* infection and gastric cancer.[11] Furthermore, biological studies have clarified the underlying molecular mechanisms.[12–15] To sum up, epidemiologic, animal and biological studies have provided consistent evidence to confirm the role of *H. pylori* infection in gastric carcinogenesis.[16]

Health Economic Models to Estimate the Efficacy of *H. pylori* Eradication

The strong link between *H. pylori* infection and gastric cancer presents a unique opportunity for clinicians to actively intervene to improve public health. One approach is to test asymptomatic carriers of *H. pylori* and offer eradication therapy before irreversible changes occur. Such population-based intervention may theoretically eliminate gastric cancer. However, the problems of large samples, long-term follow-up, and ethical issues hinder the performance of randomized controlled trials to measure outcomes such as changes in the incidence of gastric cancer.[17] A good alternative to predict the late benefits of *H. pylori* eradication is cost-effectiveness analysis with computer simulation. This method allows researchers to calculate the incremental cost-effectiveness ratio, or the ratio of change in cost to change in effects, without the aforementioned limitations (Table 2).[18–24]

Table 1. Meta-analyses of the association between *Helicobacter pylori* infection and the risk of gastric cancer

Investigators	Years	Studies	Summary OR (95% CI)	Sources of heterogeneity
Huang et al[5]	1990–1996	5 cohort, 14 case control	1.92 (1.32–2.78)	Early or advanced gastric cancer, cardiac or noncardiac gastric cancer, population- or hospital-based control subjects, patient age
Eslick et al[6]	1983–1999	8 cohort, 34 case control	2.04 (1.69–2.45)	Patient age, intestinal- or diffuse-type gastric cancer
Xue et al[7]	1995–1998	11 case control*	3.00 (2.42–3.72)	Not available
Wang et al[8]	1980–2006	19 case control	3.38 (2.15–5.33)†	Early or advanced gastric cancer, sample size, differentiated- or undifferentiated-type early gastric cancer

**Only studies in China were included; †OR expresses the prevalence of H. pylori infection in the comparison between patients with early gastric cancer and control subjects without non-neoplasm. OR = odds ratio; CI = confidence interval.*

Most cost-effectiveness analyses have focused on populations with a low prevalence of *H. pylori* and a low risk for gastric cancer.[18–22] Parsonnet et al[18] estimated the benefit of a test-and-treat strategy in the United States. Assuming 30% risk reduction in gastric cancer with eradication, they found that the benefit would be optimized if chemoprevention were implemented in patients aged 50–70 years and if it targeted high-risk populations (e.g. Japanese Americans). Fendrick et al[19] evaluated testing, treating, retesting, and/or retreating *H. pylori* infection in the United States. Testing and treating at an initial age of 40 years was most cost-effective, although the incremental cost-effectiveness ratio of retesting and/or retreating remained acceptable. Knowing that *H. pylori* that expresses cagA protein increases the risk of gastric cancer threefold, Harris et al[20] analyzed testing and treating in the United States. Screening for cagA-positive strains alone did not improve cost-effectiveness compared with screening for all *H. pylori* strains.

In a randomized trial, Mason et al[21] evaluated the economic impact of a test-and-treat approach for *H. pylori* infection in the United Kingdom. The program would have been cost-effective even if the mortality rate were reduced by only 10%. Roderick et al[22] also confirmed the cost-effectiveness of population screening for *H. pylori* in the United Kingdom. However, the benefit was sensitive to the efficacy of eradication on lowering the incidence of gastric cancer, to the risk associated with complicated peptic ulcers, and to the effect of opportunistic testing in patients with dyspepsia. These factors indicated substantial uncertainty.

In areas in which gastric cancer is highly prevalent, traditional screening is based on secondary prevention (e.g. testing and endoscopy). For instance, photofluorography and measurement of serum pepsinogen concentrations can help to identify high-risk individuals and to refer them for confirmatory endoscopy.[25] Wang et al[23] suggested that testing and treating of *H. pylori* infection was feasible in China if eradication could prevent 50% of gastric cancers. In Taiwan, we previously incorporated the results of local preventive programs and compared testing and treating for *H. pylori* infection with traditional testing and endoscopy.[24]

Table 2. Health economic models to predict the efficacy of *Helicobacter pylori* eradication to prevent gastric cancer

Investigators	Location	Study design	Strategy	ICER for strategy 2 *vs.* 1 (cost/yr of life saved)*	Optimal age for screening (yr)
Parsonnet et al, 1996[18]	US	Literature review	(1) No screen, (2) test and treat	US$25,000	50–70
Fendrick et al, 1999[19]	US	Literature review	(1) No screen, (2) test and treat, or (3) test, treat, retest, and/or retreat	US$6264	40
Harris et al, 1999[20]	US, abroad	Literature review	(1) No screen, (2) test and treat for all *H. pylori* strains, or (3) test and treat only for cagA+ strains	US$25,100	50
Mason et al, 2002[21]	UK	Randomized controlled trial ($n = 2329$)	(1) No screen, (2) test and treat	£14,200	40–49
Roderick et al, 2003[22]	UK	Literature review	(1) Opportunistic *H. pylori* treatment, (2) test and treat	£5860	40
Wang et al, 2003[23]	China	Literature review	(1) No screen, (2) test and treat	¥1374	30–40
Lee et al, 2007[24]	Taiwan	Prospective uncontrolled trial ($n = 1654$)	(1) No screen, (2) test and treat, (3) pepsinogen test and endoscopic confirmation	US$17,044	30

**In all studies, strategy 2 was the strategy of choice. ICER = incremental cost-effectiveness ratio.*

Given a reduction in the initial transition rate (i.e. from normal mucosa to chronic active gastritis), our results suggest that eradication of *H. pylori* early in life can substantially reduce the risk of mortality and improve cost-effectiveness.

Clinical Trials of *H. pylori* Eradication to Prevent Gastric Cancer

Population-specific characteristics can confound the cost-effectiveness of *H. pylori* eradication. Therefore, the applicability of models should be confirmed in local clinical trials. The chemoprevention trials reported to date can be categorized according to differences in their target populations and outcome measures (Table 3).[26–42] Areas with high incidences of gastric cancer are East Asia and the Andean regions of South America, whereas North America, Northern Europe, Africa and Southeast Asia have relatively low rates.[1] It is reasonable that most population-based chemoprevention trials have been conducted in developing countries to increase the statistical power for detecting benefits of *H. pylori* eradication.

One limitation is that most of the data supporting the efficacy of *H. pylori* eradication have been based on surrogate outcomes of histologic regression. If one considers the endpoint of a reduction in gastric cancer, only one randomized trial, conducted in China, has demonstrated risk reduction; the change was 37% after 7.5 years.[41] Although this result was not statistically significant, subgroup analysis showed a substantial reduction in the incidence of gastric cancer for subjects without premalignant changes (e.g. atrophic gastritis, intestinal metaplasia, and dysplasia). The results suggested a point of no return in that the benefits of *H. pylori* eradication might diminish at an advanced stage, when many types of molecular damage become irreversible.

For developed countries with a low risk of gastric cancer, attention has focused on saving costs related to managing dyspepsia.[34–39] In a mass screening program conducted in the United Kingdom, Moayyedi et al[34,35] and Ford et al[36] found that dyspepsia-related expenditure declined after *H. pylori* was eradicated and that the savings were greater than the initial cost of a test-and-treat strategy. In their randomized trial in the United Kingdom, Lane et al[38] confirmed that testing and treating reduced the costs associated with dyspepsia by 30% at 2 years after eradication.

H. pylori Infection and Changes in the Modern Disease Spectrum

Among developed countries, the parallel epidemics of obesity and metabolic disorders have suggested that the decline in *H. pylori* infections might be an etiology.[43] *H. pylori* infection is characterized by chronic and persistent intragastric inflammation, which may induce changes both local to and remote from the primary site. Curing *H. pylori* infection may attenuate local inflammation and, in turn, affect appetite and energy expenditure.[44–47] The remote effects of *H. pylori* infection are related to a prominent immune response involving type 1 T-helper cells. This response may stimulate the secretion of insulin counter-regulatory hormones and, therefore, contribute to the pathogenesis of atherosclerosis and colon neoplasms.[48,49] Whether the decline in *H. pylori* infection can explain changes in modern disease entities deserves further observation, especially in developing countries.

Major Scientific Challenge: Why Are Some *H. pylori*-infected People More Susceptible to Disease Than Others?

Although *H. pylori* has been identified as a major cause of a wide range of gastrointestinal diseases, only a few infected patients develop advanced intragastric pathology, such as peptic ulcers (10–15%) or gastric malignancies (1–3%).[50] This observation points to a couple of major scientific challenges: what mechanisms lead to cancer or ulcer in susceptible carriers of *H. pylori* and vice

Table 3. Population-based clinical trials of the test-and-treat strategy for *Helicobacter pylori* infection

Investigators	Location	Design	Population	Outcome measure	Follow-up (yr)	Result
Gail et al, 1998;[26] You et al, 2006[27]	Linqu County, Shandong, China	Randomized	General ($n=3365$)	Histologic regression	1[26] or 7.3[27]	NA,[26] positive[27]
Correa et al, 2000;[28] Ruiz et al, 2001;[29] Mera et al, 2005[30]	Pasto and Tuguerres, Narino, Colombia	Randomized	Patients with atrophic gastritis or intestinal metaplasia ($n=976$,[28] 132,[29] or 795[30])	Histologic regression	3,[28] 6,[29] or 12[30]	Positive
Sung et al, 2000;[31] Zhou et al, 2003;[32] Leung et al, 2004[33]	Yantai County, Shandong, China	Randomized	*H. pylori* carriers ($n=587$,[31] 552,[32] 435[33])	Histologic regression	1[31] or 5[32,33]	Positive
Moayyedi et al, 2000;[34,35] Ford et al, 2005[36]	Leeds and Bradford, UK	Randomized	*H. pylori* carriers ($n=2324$,[34] 1773,[35] 914[36])	Incidence of gastric cancer incidence,[34] cost for dyspepsia[35,36]	2[34,35] or 10[36]	NA,[34] positive[35,36]
Lane et al, 2002,[37] 2006;[38] Harvey et al, 2004[39]	Bristol, UK	Randomized	*H. pylori* carriers ($n=1558$)	Dyspepsia, health-resource use and cost, and QoL,[37] cost for dyspepsia,[38] GERD[39]	2	NA,[37] positive,[38] negative[39]
Guo et al, 2003[40]	Zhuanghe County, Liaoning, China	Prospective, uncontrolled	General ($n=1781$)	Incidence of gastric cancer	6	NA
Wong et al, 2004[41]	Changle County, Fujian, China	Randomized	*H. pylori* carriers ($n=1630$)	Incidence of gastric cancer	7.5	Negative*
Lee et al, 2006[42]	Matsu, Lienchiang County, Taiwan	Prospective, uncontrolled	*H. pylori* carriers ($n=2658$)	Incidence of gastric cancer	1	NA

**The effect of H. pylori eradication was positive only in a subgroup of patients with no precancerous lesions on presentation. NA = not applicable; QoL = quality of life; GERD = gastroesophageal reflux disease.*

versa; and, what mechanisms prevent pathologic changes in other infected individuals?

Three main gastric phenotypes after *H. pylori* infection are known. The first is mild pan-gastritis, which involves no alteration in gastric physiology and, therefore, no clinically significant disease. The second is corpus-predominant gastritis, which is associated with gastric atrophy, hypochlorhydria and an increased risk of gastric cancer. The third phenotype is antrum-predominant gastritis, which is associated with high secretion of gastric acid and an increased risk of duodenal ulcer disease.[51]

This disease paradigm suggests that intragastric inflammatory responses are related to an interaction between host genetic makeup and bacterial virulence factors, one which determines the final outcomes after *H. pylori* infection.[52] Many researchers have focused on the role of strain-specific virulence factors for *H. pylori*-related disease, including cagA, vacA, iceA, babA, oipA and sabA.[14] At the same time, host genetic susceptibility may determine interindividual variation in the magnitude of cytokine responses and may contribute to the diversity of clinical outcomes. A series of pro- and anti-inflammatory cytokine polymorphisms are considered crucial to these outcomes. Potential candidate genes include those encoding interleukin (IL)-1β, IL-8, IL-10, tumor necrosis factor-4 and toll-like receptor 4.[53] Despite recent progress in identifying susceptible hosts, in determining bacterial genotypes, and in elucidating their association with advanced intragastric pathology, a geographical difference exists, and no conclusive data have been noted. Moreover, the underlying molecular mechanisms remain unclear. Further in-depth studies in this field are warranted.

Concerns About Implementation on the Population Level

H. pylori eradication is the most practical means of preventing gastric cancer and peptic ulcer. However, some concerns must be addressed. First, the efficacy of population-based intervention for gastric cancer remains inconclusive in terms of long-term outcomes. Second, such an approach may be enormously costly and especially cumbersome for widespread implementation in developing countries.[54] Third, as with the treatment of other infectious pathogens, induction of antimicrobial resistance is a critical issue.[55] Asymptomatic carriers of *H. pylori* are usually less receptive to treatment than others are, and adverse effects can seriously affect their drug compliance. Low compliance not only wastes medical resources but also potentially accelerates the emergence of drug-resistant strains due to premature discontinuation of treatment. Finally, the interest in *H. pylori* infection has recently extended from its role in the etiology of diseases of the stomach and duodenum to those of the esophagus.[39,56] *H. pylori* infection may increase, decrease, or have no effect on gastric acid secretion, which depends on the pattern of gastritis.[57,58] For high-risk subjects with atrophic gastritis, eradicating *H. pylori* infection may restore gastric acid secretion and thus increase the risk of gastroesophageal reflux, although the evidence remains inconclusive.[56]

Whether active treatment of *H. pylori* will accelerate the clinical course of certain modern diseases remains unknown. Given the stated limitations, the identification of highly susceptible persons is crucial to selective testing and treatment. For example, El-Omar et al[59] found that relatives of gastric cancer patients have a higher prevalence of gastric atrophy and hypochlorhydria. Similarly, Sheu et al[60] showed that relatives of gastric cancer patients have greater gastric cycloxygenase-2 expression and higher incidence of precancerous lesions after *H. pylori* infection. Both studies highlighted the increase in host susceptibility in such subjects and, consequently, eradication of *H. pylori* infection is recommended.[61] Moreover, in Taiwan, the high prevalence of virulent triple-positive *H. pylori* infection (cagA-, vacAs1- and babA2-positive)[62] may further justify prophylactic treatment. Second, subjects with precancerous lesions also have a higher risk for gastric cancer but the benefit of *H. pylori* eradication has not been confirmed by randomized controlled trials. The concept of "a point of no return"[41,63] implies

that screening for *H. pylori* infection may be more beneficial 10–20 years before the take-off age for gastric cancer.[62] Nonetheless, some well-designed studies have shown the reversibility of advanced gastric lesions.[30,64] Currently, novel biomarkers for risk prediction, including genetic, epigenetic and proteinomic factors, are under extensive investigation.[65]

Alternatives to Eradication: Vaccination and Socioeconomic Improvement

From the viewpoint of preventive medicine, vaccine development is the best way to control an infectious process. However, no vaccine against *H. pylori* is currently available. In addition, studies concerning acquisition and re-infection rates of *H. pylori* have varied greatly. Direct person-to-person contact has been suggested as the primary route of transmission in developed countries, whereas fecal–oral exposure to contaminated water is implicated in developing countries.[66] Risk factors for transmitting *H. pylori* include overcrowding, poor hygiene and sharing of beds by siblings.[67] As socioeconomic conditions improve in developing regions, declining incidence of *H. pylori* infection can reasonably be expected to lower the incidence of gastric cancer, similar to that which has happened in Western countries. Nevertheless, even if such a downward trend were to happen, it may take a long time to accomplish without active intervention in areas of highly prevalent infection.

Discussion and Conclusion

The discovery of a previously unappreciated microbial basis for peptic ulcer and gastric malignancy brings new challenges, namely, defining the etiologic effect of *H. pylori* infection and designing strategies for preventing these common gastroduodenal disorders.[68] Today, eradication of *H. pylori* is considered as the first-line treatment of peptic ulcer disease and MALT lymphoma. In 2005, the Nobel Prize for Medicine that was awarded to Marshall and Warren was a formal recognition of their discovery that many peptic ulcers were due to an infectious condition that can be cured with antibiotics.

Elucidation of the central role of *H. pylori* in carcinogenesis has increased expectations in our ability to prevent gastric cancer by eradication of this bacterium. However, the effect of primary prevention in patients with premalignant gastric lesions and the long-term results of randomized clinical trials are still inconclusive. There is a clear need for studies with large numbers of patients, long follow-up, and careful control of the types of cancer and underlying gastric mucosal conditions. The current evidence does not enable us to accurately assess the benefits of universal testing and treatment. However, it is sufficient for targeted intervention, that is, identifying subjects who are susceptible to *H. pylori*-related diseases. Active screening of the general population in areas with high incidence of gastric cancer appears logical but is not yet evidence-based. The test-and-treat approach should be validated in randomized controlled trials and, thus, still has a long way to go.

Acknowledgments

This article was supported by research grants from the National Science Council (NSC 96-2314-B-002-092-MY3) and the Bureau of Health Promotion, Department of Health, Taiwan (DOH97-TD-M-113-95002).

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