ERADICATING GASTRIC CANCER

Introduction

Gastric cancer develops in a stepwise manner along the inflammation–metaplasia–dysplasia–carcinoma pathway. Similar to several infection-associated cancers, such as liver cancer (associated with viral hepatitis B and C) and cervical cancer (associated with human papilloma virus), Helicobacter pylori infection is the main trigger of this carcinogenic cascade. Observational studies with baseline serological testing and more than 10 years of follow up have found that chronic H. pylori infection is related to about 90% of gastric cancers and thus removal of this bacterium from a population has been postulated to eradicate the occurrence of gastric cancer. This hypothesis has stimulated numerous investigations indicating not only the magnitude of benefit obtained from a short-course antibiotic treatment but also the principles to help policymakers design preventive services that maximize the effectiveness of using this strategy. The application of this antibiotic-based approach for gastric cancer prevention has been hindered by a lack of answers to four important questions (Table 1). There are now satisfactory answers to these questions.

Table 1 Questions about the elimination of gastric cancer through H. pylori eradication

| Q1: What is the magnitude of benefit of H. pylori eradication to reduce gastric cancer risk? |
| Q2: How can H. pylori be effectively eradicated? |
| Q3: After H. pylori eradication, who should receive endoscopic surveillance? |
| Q4: When can a mass eradication program be implemented in a given population? |

A1: The degree of benefit gained from H. pylori eradication depends on the baseline risk of gastric cancer

In addition to H. pylori infection, lifestyle habits including high salt intake, tobacco, excessive alcohol use, and low consumption of fruits and vegetables are positively associated with gastric cancer risk. The inter-population variation in these factors implies that the magnitude of eradication-associated benefit is also population-specific. A meta-analysis showed that the magnitude of the protective effect of H. pylori eradication depends on the baseline risk of gastric cancer and is greater in individuals with higher baseline risk. There are two explanations for this finding: First, in high-risk individuals, the extent of host–bacterial interaction leading to inflammatory reaction is greater, so that removal of H. pylori from the gastric mucosa may reduce the level of inflammation-related damage. Second, the statistical power of studies on high-risk individuals might be superior to that of studies on low-risk individuals, increasing the significance of the clinical benefit demonstrated in currently available studies with limited follow-up time. Therefore, even in those with premalignant lesions or endoscopically/surgically resected early-stage gastric cancer, there is no absolute point of no return; in high-risk populations, active testing and treatment for H. pylori infection should be routinely practiced.

A2: Effective H. pylori therapy can be chosen on rational grounds

Highly effective antibiotic regimens are available for most populations. Therapeutic failure can be due to: the lack of compliance, presence of antibiotic resistance, and inadequate control of gastric acidity. With assurance of patient compliance, the efficacy of an eradication therapy (typically a proton pump inhibitor combined with one to three kinds of antibiotics) can be predicted from previous population estimates of antibiotic resistance or individual history of antibiotic exposure, and used to select a rational H. pylori therapy. Failure to take antibiotic resistance into account and simply increasing the number of antibiotics or prolonging the duration of multi-antibiotic regimens may result in population over-exposure to unnecessary antibiotics, leading to the emergence of antibiotic-resistant bacteria in that population. Failure to adequately control gastric acid (i.e. raise pH to >5) can reduce the antibiotic effect and thereby the efficacy of the eradication treatment.

A3: Individual risk for gastric cancer can be defined after H. pylori eradication

As in screening programs commonly adopted for the prevention of other types of cancers, repeated endoscopic screening may be used to reduce gastric cancer mortality. Better survival (the benefit gained from this relatively short-term approach to therapy) can be attributed to early detection of a cancer. However, such a cancer prevention program is not necessarily successful for every population. Improvement in survival due to early detection may be outweighed by the emergence of new cases resulting from a failure to eliminate risk factors. Technical issues may reduce the effectiveness in a population: for example, the lack of trained endoscopists and insufficient endoscopic resection may hinder the effectiveness of a screening program that uses endoscopy as the primary screening tool. Therefore, to efficiently eradicate gastric cancer, we need a dual approach that includes both primary prevention based on H. pylori eradication and secondary prevention based on repeated endoscopy in individuals with residual gastric cancer risk even after eradication therapy.

Before H. pylori eradication, the endoscopic features of gastric mucosa are typically diffuse redness, swelling, enlarged fold, sticky mucus, and/or spotty redness, while after H. pylori eradication, the mucosa is rarely normal looking, and frequently undergoes
residual changes such as map-like redness. Improvements such as decreased inflammatory cell infiltration in the gastric mucosa and increased density of gastric glands in atrophic mucosa may be evident microscopically and reach a plateau over time. Collectively, these findings may indicate that *H. pylori* eradication in adult patients cannot completely eliminate gastric cancer risk owing to the possible irreversibility of infection-related inflammation-associated genetic and epigenetic damage. This hypothesis has been confirmed by a recent meta-analysis, including 20,484 treated and 27,580 untreated individuals with a total follow-up of 340,255 person-years. In this meta-analysis, *H. pylori* eradication reduced gastric cancer risk by only about 50%.

To allocate limited endoscopic resources efficiently, accurate risk-stratification following *H. pylori* eradication should be performed by using: (i) endoscopic or histological classification systems, such as the updated Sydney system, the Operative Link for Gastritis Assessment (OLGA), and the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM); (ii) serological tests, such as serum pepsinogen level; and (iii) molecular approaches, such as measuring epigenetic changes in endoscopically biopsied samples. These approaches, alone or in combination, may reduce the number of unnecessary endoscopies and increase cost-effectiveness.

**A4: The strategy of mass eradication is achievable in any given population**

The gastric cancer incidence has been gradually declining globally not only because of improvement in sanitation and hygiene but also because *H. pylori* testing and treatment nowadays are routine in patients with peptic ulcer and dyspeptic symptoms. Consequently, a program to eradicate *H. pylori* with the intention of accelerating the decline in gastric cancer incidence in a given population should focus on the high-risk or intermediate-risk subpopulation and be integrated with programs dealing with other pressing healthcare issues.

For example, in Taiwan, the mass eradication program was first implemented on Matsu Island, an offshore island with about a fivefold higher incidence of gastric cancer than that of the general Taiwanese population. In that population, the eradication program was initiated in 2004, and urea-breath-test-positive individuals were prescribed antibiotics. Five years after the intervention, the prevalence of atrophic gastritis (the surrogate endpoint) declined from 59.9% to 13.7%, yielding a significant reduction of 77.2%. The 5-year average incidence of gastric cancer (the definite endpoint) went from 40.3 to 30.4 per 100,000 person-years, with a 24.7% reduction of gastric cancer.

In 2012, another mass eradication program was launched in Changhua County, whose population had an intermediate risk of gastric cancer with incidence rate of about 17 per 100,000 person-years. The colorectal cancer incidence rate in that population was approximately fourfold that of gastric cancer; therefore, a novel method was designed to combine the fecal immunochemical test for detecting occult blood with the stool antigen test for detecting *H. pylori*. It was hoped that, in addition to having a primary prevention effect, the combining of occult blood and stool *H. pylori* antigen testing would encourage greater screening attendance and thereby increase the health benefit without needing more than the resources allocated to the stool-sample-based program.

Another program will be carried out in Taitung County, in the eastern part of Taiwan, where the gastric cancer incidence is about twofold higher than the average rate for the Taiwanese population. Also, in this area, there is a high prevalence of oral cancer, especially in the aboriginal population, because alcohol, betel nut, and cigarette consumption is very common. Therefore, the integration of two screening programs (one to prevent gastric cancer by mass eradication of *H. pylori* infection and one to prevent oral cancer by oral inspection and health-behavior education, especially targeting the younger population) is highly desirable.

**Conclusions**

The availability of an effective treatment for *H. pylori* eradication and its role in gastric cancer prevention, the ability to properly allocate endoscopic resources, and the applicability of an organized preventive program have important implications for establishing a healthcare policy that can nearly eliminate the threat of gastric cancer.

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