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Strategy for Eliminating Gastric Cancer in Japan

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Abstract

A study conducted by the Japan Gast Study Group showed that eradication of *Helicobacter pylori* reduced the risk of gastric cancer by about one-thirds. However, it did not completely prevent the onset of latent gastric cancer among those at high risk (i.e., with atrophic gastritis). To prevent deaths from gastric cancer, it is necessary to eradicate *H. pylori* infections. We propose a program of risk stratification based on presence of *H. pylori* infection with or without atrophic gastritis followed by targeted interventions. Those at no risk for gastric cancer (no *H. pylori*, no atrophic gastritis) need no therapy or follow-up. Those at low risk (*H. pylori* infected, nonatrophic gastritis) need only *H. pylori* eradication therapy. The smaller groups at high or very high risk need eradication and cancer surveillance. We estimated the costs and the benefits of this strategy. Gastric cancer screening by simultaneous measurement of serum pepsinogen and *H. pylori* antibody combined with eradication of *H. pylori* in all individuals at risk would initially increase national healthcare expenditure, but this would be offset by markedly reducing the cost of treating gastric cancer. The proposed strategy should prevent about 150,000 deaths from gastric cancer during the 5 years after its adoption. If the loss caused by these deaths is also taken into account, the economic effect of this strategy becomes enormous. It would probably reduce the incidence of gastric cancer by more than 80–90% within 10 years. The Japanese government should take the initiative to implement this strategy as soon as possible.

Keywords

Helicobacter pylori; gastric cancer prevention; eradication; cost-effectiveness

Introduction

A clinical study conducted by the Japan Gast Study Group (JGSG) showed that the strategy of *Helicobacter pylori* eradication for patients who had had endoscopic mucosal resection for early gastric cancer reduced led to a reduction in the incidence of metachronous gastric carcinomas by approximately one-third (1). As expected the majority of subjects in that

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study had histologic evidence of atrophic gastritis. Based on the finding of this study, the Japanese Society for Helicobacter Research revised the Japanese Guideline for the Management of *H. pylori* Infection to expand the indications for eradication therapy to those with *H. pylori* infection with the goal of treating and/or preventing *H. pylori*-related diseases (2).

It is estimated that about 60 million Japanese individuals are currently infected with *H. pylori* (3). *H. pylori* infection is now recognized as the primary cause of gastric cancer such that eradication of the microorganism will eventually result in the virtual elimination of the development of gastric cancer such that implementation of the new guidelines for the management of *H. pylori* infection will result in a major cost savings in Japan. In 2009 the cost of treating gastric cancer was estimated at 3 billion dollars per year (4).

H. pylori infection is a necessary but not sufficient cause of gastric cancer and it has long been recognized that the risk increases in proportion to the extent and severity of atrophic gastritis/gastric atrophy. The JGSG study focused on the highest risk group, (i.e., those with atrophic gastritis who had already experienced a gastric cancer) and, as predicted *H. pylori* eradication reduced the risk of subsequent gastric cancers, but did not reverse the underlying atrophy such that the while the risk was reduce, it was not eliminated (1,5).

To completely prevent gastric cancer from Japan will not only require eradication of the infection and prevention of acquisition of the infection, but also the institution of a gastric cancer risk assessment program for those whose infection has been successfully eliminated. Thus, the national strategy for the elimination of gastric cancer must combine primary prevention (*H. pylori* eradication) with effective screening for secondary prevention. While the initial cost of a combination approach is high, the duration of any surveillance program is limited as new high risk cases are prevented such that the initial costs are largely offset by the marked reduction in the number of patients requiring treatment for gastric cancer.

The present study estimated the cost of *H. pylori* eradication (primary prevention) combined with endoscopic follow-up (secondary prevention), as well as the effectiveness of this combination for reducing gastric cancer deaths in Japan.

Gastric cancer screening in Japan

The national cancer screening program of Japan has conventionally employed barium gastrography to detect gastric cancers (6). However, only approximately 10% of the at risk population who need screening actually underwent examination in 2008 (7). The current screening program also suffers from the low sensitivity of barium gastrography for detecting early gastric cancer (8,9). The plan of the national cancer screening program is for all Japanese persons aged 40 years or older to be examined annually for gastric cancer. However, there is little evidence to support this recommendation. In 2006, 1,637 persons age less than 50 years died of gastric cancer. This accounted for only 3.3% of all deaths from this malignancy in that year (Figure 1) (10). The major association with risk of gastric cancer is the presence of atrophic gastritis which increases with age. A shift in focus screening programs based on risk (i.e., presence of atrophic gastritis) would be more

efficient as it would avoid screening those at little or no risk and thus target the at risk population independent of age.

The role of *H. pylori* eradication in the prevention of gastric cancer

We based our estimate as to the extent to which *H. pylori* eradication would prevent the development of gastric cancer on the prevalence of the precursor lesion atrophic gastritis and the incidence of gastric cancer (12). The incidence of intestinal metaplasia in Japanese *H. pylori* carriers at each age (11) was used as a surrogate for the presence of atrophic gastritis. The details are described elsewhere (13). In brief, the age-dependent incidence of intestinal metaplasia was multiplied by the age-dependent incidence rate of gastric cancer, divided by 700 (the maximum estimated incidence rate of gastric cancer per 100,000 population). This result was then subtracted from 100 to estimate the extent of gastric cancer prevention. Because of the low prevalence of atrophic gastritis in men and women below age 40, *H. pylori* eradication therapy alone would result in nearly 100% prevention of development of gastric cancer in those age groups. *H. pylori* eradication would also reduce the incidence of gastric cancer by 93% from 40 to 49 years, by 76% from 50 to 59 years, by 50% from 60 to 69 years, and by 45% among those age 70 years. In women, higher rates of risk reduction can be expected, with a decrease of 98% at 40 to 49 years, 92% at 50 to 60 years, 84% at 60 to 69 years, and 73% at ages 70 years (Table 1). Thus, *H. pylori* detection (by serology, urea breath testing, or stool antigen or a combination) followed by eradication therapy for all carriers would be expected to achieve nearly 100% prevention of gastric cancer in persons aged less than 40 years. Accordingly, a national test-and-treat system should be implemented for Japanese individuals age less than 50 years.

Future of gastric cancer screening

The preferred gastric cancer prevention program should be simple, effective, and low cost as it be carried out on a large number of people. The current barium gastrography does not meet these requirements. We propose that the combination of assessing *H. pylori* status and atrophic gastritis status can achieve these objectives simply and cheaply. Atrophic gastritis can be assessed by measurement of serum pepsinogen levels and *H. pylori* status by a variety of methods including stool antigen, urea breath test and *H. pylori* serology. We here propose the combination of serum pepsinogen and *H. pylori* antibody testing although the final program would need to evaluate whether confirmatory testing for either or both was cost effective.

Serum pepsinogen was proposed to replace barium gastrography for gastric cancer screening in Japan (14,15) but this strategy was questioned because of the low detection rate of diffuse type gastric cancer (16,17). However, it has subsequently been shown that the combination of pepsinogen testing and measurement of *H. pylori* antibody as superior diagnostic accuracy compared to barium gastrography (9,18).

The combination of tests allows for risk stratification. Risk can be estimated by the pattern of test results. For example, patients can be grouped as negative for both pepsinogen and *H. pylori* (A), negative for pepsinogen and positive for *H. pylori* (B), positive for both pepsinogen and *H. pylori* (C), or positive for pepsinogen and negative for *H. pylori* (D).

Persons in Group A have little mucosal atrophy, and no *H. pylori* infection and are at an extremely low risk of developing gastric cancer. Those in Group B have at most mild mucosal atrophy and are also at low risk of gastric cancer. In contrast, Group C has prominent mucosal atrophy and a high risk of gastric cancer. Group D is very small, but has severe mucosal atrophy associated with intestinal metaplasia and the highest risk of developing gastric cancer (9,18,19). The majority of individuals in Group D had *H. pylori* infections which damaged the gastric mucosa so severely that it was almost totally replaced by intestinal metaplasia and made the stomach unsuitable for the microorganism to inhabit. The loss of the infection explains the antibody negativity. An alternate explanation is the presence of classical autoimmune gastritis. An example of this process is a study by Ohata et al. who followed up asymptomatic subjects (21% in Group A, 50% in Group B, 28% in Group C, and 1% in Group D at baseline); none of those in Group A developed gastric cancer (20).

Proposed follow-up schedule after screening (Figure 2)

We propose that all Japanese persons aged 50 years or more should undergo simultaneous measurement of serum pepsinogen and *H. pylori* status (e.g., *H. pylori* antibody) so as to be grouped (A–D) according to the results. Those in Group A need no follow-up because current data indicate that persons in this group have little risk of developing gastric cancer (19,20,21). *H. pylori* eradication therapy is indicated for all persons in Groups B, C, and D. Persons in Group B have at best, only mild atrophic changes, as indicated by a normal serum pepsinogen level (i.e., nonatrophic gastritis). In this group, eradication of *H. pylori* reduces the risk of developing gastric cancer to nearly zero (20) and like Group A do not require follow-up after successful *H. pylori* eradication. In contrast, those in Groups C and D are candidates for periodic endoscopic follow-up even after successful eradication of *H. pylori*. The initial follow-up also is used to confirm the extent and severity of atrophic gastritis. Because persons in these groups have atrophic gastritis, follow-up endoscopy will be covered by the national health insurance system in Japan.

National strategy for eliminating gastric cancer in Japan

The increase of the elderly population in Japan has been rapidly accelerating especially since the Japanese baby boomers have reached 60 years old. Although the incidence and mortality of gastric cancer have both been decreasing, this increase of the elderly population has resulted in a continuing increase in the number of deaths from gastric cancer, which will probably rise to 70,000 around the year 2020 when the incidence of gastric cancer among Japanese baby boomers will reach a peak. Incidence and mortality data are relative values that are useful for comparison between different countries or regions, but should be interpreted with caution. Rather than relative values, absolute values such as the incidence and number of deaths are important when determining national policies. In Japan, about 3 billion dollars are spent annually on the treatment of gastric cancer (4) and the annual cost will probably exceed 5 billion dollars after 10 years if effective measures are not taken to reduce national healthcare expenditure. Introduction of molecular targeting therapy for cancer has also accelerated the increase in the cost of treatment. For example, the cost of treating colorectal cancer, for which molecular targeting therapy is used most aggressively,

now exceeds 20,000 dollars per patient. The cost of treating gastric cancer is currently estimated at 7,000 dollars per patient, but this will increase when a new molecular targeting agent becomes available and will approximate the cost of treating colorectal cancer (22). Obviously, we cannot prevent the increase in the cost of treating gastric cancer without taking effective measures for prevention this cancer.

Eradication of *H. pylori* in all carriers according to the new guideline published by the Japanese Society for Helicobacter Research (2) would considerably reduce the incidence rates of all *H. pylori*-related diseases, which include gastric cancer, gastritis, gastroduodenal ulcer, and idiopathic thrombocytopenic purpura and eventually result in a marked decrease in national healthcare expenditure despite the high initial costs. Another effect of such a program that should be as important as reducing costs is the reduction of morbidity and mortality due to *H. pylori*-related diseases. Theoretically, eradication of *H. pylori* in all carriers could prevent about 150,000 deaths from gastric cancer during the subsequent 5 years (13). Periodic endoscopic follow-up of treated *H. pylori* carriers should allow early detection of gastric cancer in most cases and improve the prognosis of the group which will also result in a marked decrease of gastric cancer deaths and will probably lead to the elimination of gastric cancer by the middle of the 21st century.

Gastric cancer is still considered to be a national disease in Japan. To eliminate it, the Japanese government should take the initiative and educate the public, so that people come to understand that *H. pylori* infection is responsible for most cases of gastric cancer. In the national gastric cancer screening program, barium gastrography should be immediately replaced by simultaneous measurement of serum pepsinogen and *H. pylori* antibody to identify persons at high risk of developing gastric cancer. Aggressive prophylactic measures should be taken by combining *H. pylori* eradication for all individuals at risk with periodic endoscopic follow-up of treated *H. pylori* carriers. Prophylaxis with a test-and-treat system (for example, by requesting all persons aged 20 years to undergo *H. pylori* antibody testing) should be attempted for persons aged less than 50 years. These strategies will prevent most new cases of gastric cancer.

We would be able to eliminate gastric cancer at a lower cost by adopting the basic concepts employed for hepatitis control in the recent Hepatitis Prevention and Control Act in Japan¹³. It is clear that we should take similar measures against gastric cancer as those adopted for liver cancer because these two malignancies are both infection-related. Thus, there is an urgent need to organize an advisory committee that can assist the government in drafting a gastric cancer prevention and control act.

Conclusions

Eradication of *H. pylori* combined with endoscopic follow-up of high risk patients after eradication therapy should reduce the incidence of gastric cancer by more than 80 to 90% within 10 years. Although gastric cancer screening by simultaneous measurement of pepsinogen and *H. pylori* antibody combined with eradication of *H. pylori* in all individuals at risk will initially increase national healthcare expenditure, it will also achieve great savings by remarkably reducing the cost of treating gastric cancer. The combination of these

primary and secondary prevention measures will prevent about 150,000 deaths from gastric cancer during 5 years after initiation. As has been done with the Hepatitis Prevention and Control Act, the Japanese government should take the initiative to devise a gastric cancer prevention and control act.

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Figure 1.

Numbers of age related gastric cancer death in 2006 in Japan: Gastric cancer death in Japan is abruptly increased after 50 years.

Figure 2.

Surveillance of gastric cancer after screening: Simultaneous measurement of serum pepsinogen and *H. pylori* status so as to be grouped (A–D) according to the results is recommended for all Japanese persons aged 50 years or more as surveillance of gastric cancer in Japan.

Table 1Possible rate of gastric cancer prevention by eradication of *H. pylori*

Age group	Male	Female
0–29	99.9%	99.9%
30–39	97.3%	98.8%
40–49	92.7%	97.6%
50–59	76.2%	91.9%
60–69	49.8%	83.5%
70~	44.5%	73.1%