Review

Strategies for eliminating death from gastric cancer in Japan

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Abstract: In Japan, efforts have been directed toward improving the detection of early gastric cancer by double contrast radiography and endoscopy, since early cancer has a good prognosis, resulting in Japan having the world’s best diagnostic system for early gastric cancer. The 5-year survival rate of gastric cancer patients in Japan is much higher than in Western countries by the development of endoscopic treatment for early gastric cancer. In February 2013, Japanese national health insurance cover for H. pylori eradication therapy was expanded to patients with H. pylori-associated gastritis, a type of chronic gastritis. H. pylori-associated gastritis causes gastric and duodenal ulcers and gastric polyps, therefore, providing treatment for this gastritis is likely to substantially decrease the prevalence of both gastric and duodenal ulcer and gastric cancer. Patients with gastritis are tested for H. pylori infection and those who are positive receive eradication therapy followed by periodic endoscopic surveillance. If such an approach is pursued further in Japan, gastric cancer deaths will show a dramatic decline after 10–20 years.

Keywords: gastric cancer prevention, Helicobacter pylori (H. pylori), H. pylori-associated gastritis, elimination of gastric cancer

Introduction

Gastritis with infiltration of neutrophils or lymphocytes develops within a few months in almost 100% of persons who are infected by H. pylori. Such gastritis is termed chronic active gastritis and is said to be specific to H. pylori infection. Persistent inflammation gradually increases the fragility of the gastric mucosa and progression to atrophic gastritis occurs over time. The speed of progression from chronic gastritis to atrophic gastritis varies among geographic regions and ethnic groups, and it takes 10–20 years in about 80% of Japanese patients.1) After atrophic gastritis has developed, the annual incidence of progression to intestinal type gastric cancer is 0.1% to 0.4%.2,3) In addition, excessive strong gastric acid secretion and stress increase the risk of gastric and duodenal ulcer in patients with H. pylori-associated gastritis. Moreover, H. pylori-associated gastritis is closely associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, functional dyspepsia (FD), hyperplastic gastric polyps, idiopathic thrombocytopenic purpura (ITP), and diffuse type gastric cancer.4,5) Since H. pylori-associated gastritis is the underlying cause of almost all gastric diseases, treating it with bacterial eradication therapy is likely to prevent most gastric conditions, including gastric cancer. In Japan, national health insurance cover for H. pylori eradication therapy to treat H. pylori-associated gastritis finally became available in February 2013 for the first time in the world. The possibility of eliminating H. pylori-associated gastric diseases, including gastric cancer will be promoted by the approval of the health insurance. This article describes a strategy for the elimination of gastric cancer in Japan.

Current gastric cancer screening program in Japan

Gastric cancer was the most common fatal malignancy in Japan before and after World War II until it was replaced by lung cancer in 1995.6) In order to decrease deaths from gastric cancer, various efforts have been made so far. For example, gastric
cancer screening with double contrast radiography has been offered to the general public by the Japan Cancer Society since 1960. In 1982, gastric cancer screening was also initiated under national health insurance plans based on the Health and Medical Service Act for the Aged.

In Japan, gastric cancer screening is currently performed annually in people aged 40 or older, comprising an interview and a double contrast radiography. It might be proved that the mass screening program had the effectiveness in reducing stomach cancer mortality in Miyagi prefecture.\(^7\) According to national data, the number of individuals undergoing gastric cancer screening was about 0.4 million in 1964 and it increased tenfold to about 4 million in the 1970s. The number increased further to exceed 6 million in the 1990s and then remained steady for a number of years. It has decreased somewhat recently. The gastric cancer detection rate achieved by screening has remained stable around 0.1%, showing little change over the last 30 years.\(^8\) Recently, the gastric cancer screening rate has decreased (9.6%, about 0.4 million in 2010).\(^9\) Screening based on double contrast radiography has a problem with respect to the low sensitivity for detecting early gastric cancer, and exposure to radiation may become a major issue. Although gastric cancer screening using endoscopy is more effective than gastric X-ray examination in assessing early gastric cancer ratio,\(^10\) it is reported that both radiographic and endoscopic screening may prevent gastric cancer deaths.\(^11\)

In 1994, \textit{H. pylori} was classified as a group 1, a definite carcinogen by the International Agency for Research on Cancer of the World Health Organization.\(^12\) The most serious deficiency with regard to preventing gastric cancer is the lack of primary prevention measures in Japan. Of course, the cause of gastric cancer had not been identified in the 1960s when screening for this cancer was started in Japan. However, it has now been proved that over 95% of gastric cancers develop due to \textit{H. pylori} infection.\(^13\) As a general rule for cancers caused by infectious agents, such as liver cancer and cervical carcinoma, primary prevention of infection should precede screening, which is only secondary prevention.

By the efforts of many clinical and basic researchers in Japan, the concept of early gastric cancer was first proposed in 1963. At that time, early gastric cancer was defined as infiltration of tumor cells limited to the mucosa and submucosa irrespective of lymph node metastasis.\(^15\) The prognosis of early gastric cancer is far better than that of advanced gastric cancer and the 5-year survival rate of patients with early cancer is over 90%.\(^17\) Therefore, many studies performed in Japan have focused on effective methods for the diagnosis of early gastric cancer. As a result, early cancer now accounts for nearly 60% of all gastric cancers detected in Japan. This is not seen in any other country and highlights the improved methods for diagnosis of early gastric cancer that have been adopted in Japan. In other countries including the US and Europe, the 5-year survival rate of gastric cancer patients is reported to be only 10% to 25%\(^6\),\(^18\),\(^19\) (Fig. 1). This difference does not necessarily indicate that the treatment of gastric cancer is superior in Japan to other countries, but is because early cancer accounts for a small proportion of all cases in other countries.

Endoscopic surgery is commonly performed in patients with early gastric cancer to resect intramucosal cancer in Japan. In contrast, intramucosal gastric cancer is not even recognized as a disease entity in Western countries; hence, endoscopic surgery is uncommon. Even if physicians in Europe and the US accept this concept of early gastric cancer, they will still need to develop techniques for performing diagnosis and endoscopic surgery.\(^20\) The skill of Japanese physicians with regard to early diagnosis and endoscopic treatment of gastric cancer is unsurpassed and makes a great contribution to the management of patients with this cancer in Japan. To improve the prognosis of gastric cancer in other countries, it seems to be necessary for the concept of early gastric cancer to be accepted and for a high level of technical skill in the management of early gastric cancer to be established like that in Japan, which could promote the elimination of gastric cancer by combining \textit{H. pylori} eradication therapy with surveillance.

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\caption{Five years survival rates (%) of gastric cancer in various countries.}
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The effect of *H. pylori* eradication for gastric cancer prevention

After it became clear that *H. pylori* infection is an important risk factor for gastric cancer, the issue of whether *H. pylori* eradication therapy can decrease the incidence of gastric cancer has attracted increasing attention. Intervention studies to assess the preventative effect of *H. pylori* eradication on gastric cancer have been conducted in healthy individuals worldwide. However, the incidence of gastric cancer is very low in Western countries and the study populations enrolled in those countries were not large enough to detect a significant effect of eradication therapy, resulting in the discontinuation of most studies.21)

You et al. reported a study of 3,365 Chinese patients who were randomized to an *H. pylori* eradication group, a garlic group, or a vitamin group and then were followed for 7.3 years in 2006. They found no difference of gastric cancer among the three groups.22) However, longer follow-up for 15 years subsequently revealed a significant reduction of gastric cancer in the *H. pylori* eradication group (odds ratio, 0.61; p = 0.032).23) Because the incidence of progression from *H. pylori*-positive atrophic gastritis to gastric cancer is very low, it has been suggested that it would be difficult to demonstrate a significant difference unless the sample size is increased or the observation period is longer. In recent years, You et al. have reported a significant difference due to *H. pylori* eradication after long-term (10 years or more) observation. In order to define the preventive effect on gastric cancer of *H. pylori* eradication therapy, they are now conducting a large-scale randomized placebo-controlled study involving approximately 200,000 people in Linqu County, which has a high incidence of gastric cancer (Unpublished data, presented in IARC Meeting, 2013). This is a massive project in which subjects are allocated to either an *H. pylori* eradication group or a non-eradication group and then are followed endoscopically for almost 10 years to assess the development of gastric cancer. If this study is completed successfully, it is likely to determine how effective *H. pylori* eradication therapy is for reducing the incidence of gastric cancer.

In contrast, we conducted a clinical trial with a small sample size and short follow-up period that involved patients who had undergone endoscopic mucosal resection for early gastric cancer, a population in which gastric cancer is very likely to develop. The annual incidence of gastric cancer has been reported to be only 0.1% to 0.4% in *H. pylori*-positive patients,23,3) while the incidence of metachronous recurrence after endoscopic surgery for early gastric cancer is far higher (3% to 5%).24,25) To investigate the ectopic recurrence of gastric cancer, 544 patients who had received endoscopic treatment for early gastric cancer were randomly allocated to *H. pylori* eradication or non-eradication groups and were followed up for 3 years by annual endoscopic examination. Metachronous recurrence was detected in 9 and 24 subjects from the eradication group and the non-eradication group, respectively, and there was a significantly lower relapse rate in the eradication group (p < 0.01 according to intention-to-treat analysis).26) *H. pylori* eradication therapy reduced the incidence of differentiated gastric cancer by at least two-thirds irrespective of whether the patients had atrophic gastritis, intestinal metaplasia, or early gastric cancer. Data obtained up to 8–10 years after completion of this study were also analyzed, revealing a persistent difference in the incidence of metachronous gastric cancer between the *H. pylori* eradication and non-eradication groups. Thus, our findings indicate that the preventive effect of *H. pylori* eradication therapy on gastric cancer persists for a long time.27)

A large-scale cohort study involving about 80,000 Taiwanese patients with peptic ulcer was reported, in which patients were followed up for 10 years after *H. pylori* eradication therapy.28) The subjects were assigned to an early eradication group that received *H. pylori* eradication therapy at the time of diagnosis or a late eradication group that received eradication therapy at 1 year or more after diagnosis. It was found that the incidence of gastric cancer was markedly lower in the early eradication group than in the late eradication group. This study is important because it not only demonstrated that *H. pylori* eradication therapy reduces the incidence of gastric cancer, but also showed that earlier eradication is more effective.

It has been shown that 95% of gastric cancer in Korea is associated with *H. pylori*.14) The National Cancer Screening Program in Korea was initiated to provide gastric cancer screening for people aged 40 or older by double contrast radiography or endoscopy in 1999. The screening rate of 46% achieved in Korea is significantly higher than that in Japan,29) and such widespread screening may decrease gastric cancer deaths. Indeed, 5-year survival rate of gastric cancer patients was 47% in 2002, when X-ray studies were mainly used for screening, while it increased to 67%
in 2010 when endoscopic screening was predominant. The detection rate of gastric cancer endoscopy has been reported to be 4 times greater than with double contrast radiography (0.26% vs. 0.07%). In Korea, there have been demands for the government to approve national health insurance coverage for *H. pylori* eradication therapy in patients with chronic gastritis but there is no public knowledge-based application system like that in Japan; hence, a new clinical study involving about 100,000 subjects is required and this will be completed after 7 years at the earliest.

**Health insurance cover for *H. pylori* eradication therapy in Japan**

Cancers can be broadly classified into lifestyle-related tumors and infection-related tumors. In Western countries, infections only cause a low percentage (10% or less) of all cancers. In Japan, however, it has become clear that approximately 25% of cancers are infection-related, including liver cancer caused by hepatitis viruses, cervical cancer due to papillomaviruses, and gastric cancer related to *H. pylori*. Although cervical cancer is uncommon and only accounts for 1.3% of all cancers, gastric cancer and liver cancer account for about 17% and 6.5%, respectively, and the total for these three cancers is nearly 25% (Fig. 2). Since it has become clear that most gastric cancer cases are due to *H. pylori* infection rather than lifestyle factors, it is time for a major revision of the strategies for fighting this cancer. When cancer is suspected to be related to infection, proactive preventative measures are likely to lead to a dramatic reduction in the incidence and a significant decrease of cancer mortality. In Japan, preventative measures for liver cancer have been focused on hepatitis virus infection since 2002, leading to a reduction of mortality. However, the annual number of gastric cancer deaths has remained at around 50,000 for the last few decades, suggesting that current preventative measures are inadequate. Even though there is a difference in the causative agent between liver cancer (hepatitis viruses) and gastric cancer (bacteria), the preventive measures for gastric cancer should not be markedly different from those for liver cancer because both are related to infection. Thus, the fundamental preventative approach to gastric cancer should be shifted from conventional secondary prevention based on double contrast radiography screening to primary prevention by *H. pylori* eradication therapy.

The Japanese Society for Helicobacter Research published a guideline which recommended that all *H. pylori*-infected persons should receive eradication therapy in 2009. In response to this, the Ministry of Health, Labour and Welfare (MHLW) approved the expansion of national health insurance cover for *H. pylori* eradication therapy to include three new indications (gastric MALT lymphoma, post endoscopic resection of early gastric cancer, and ITP), in addition to gastric and duodenal ulcer. This was the first time in the world that a national health scheme had included *H. pylori* eradication therapy for indications other than gastric and duodenal ulcer, and it represented an innovative approach. To achieve expansion of health insurance cover for *H. pylori* eradication therapy to include chronic gastritis, the presidents of the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society, and the Japanese Society for Helicobacter Research submitted a joint petition to the Minister of the MHLW. Following this public knowledge-based application, *H. pylori* eradication therapy became available to patients with chronic gastritis on February 21, 2013. The MHLW notification states that eradication therapy is covered by national health insurance when a patient with endoscopically diagnosed chronic gastritis is positive for *H. pylori*.

One year after this expansion of insurance coverage, the prescription of *H. pylori* eradication therapy was 5-fold higher than before, with an estimated 1.5 million prescriptions per year.33)

**Strategy and expected effect of eliminating gastric cancer in Japan**

In order to eliminate gastric cancer in Japan, the strategy for adolescents should differ from that for elderly persons. This is because eradication of
H. pylori in adolescents achieves nearly 100% prevention of gastric cancer, while the incidence of this cancer increases with advancing age. We recommend a screen-and-treat approach as the strategy for adolescents, which would involve testing for H. pylori infection in junior high school and high school followed by immediate eradication therapy if there was a positive result. Eradication of this infection in adolescents should prevent H. pylori-related diseases such as gastric ulcer and gastric polyps, as well as preventing nearly 100% of gastric cancers. In the future, it should be possible to reduce the prevalence of most H. pylori-related gastric diseases in Japan, including gastric cancer and gastric ulcer, which is likely to attract attention from around the world. It is estimated that approximately 5% of all teenagers in Japan are positive for H. pylori, suggesting that the cost of this approach would not be so high. Some local governments have already scheduled H. pylori screening for junior high school students. In Maniwa City of Okayama Prefecture, free H. pylori screening for junior high school students was initiated in August 2013 based on measurement of H. pylori antibodies in urine specimens. Students who are positive for H. pylori receive eradication therapy that costs 6,000 yen, and 80% of the cost is paid by Maniwa City out of an annual budget of 600,000 yen. Other municipal governments, such as Wakkanai City, Fukusima Town, Bihoro Town of Hokkaido Prefecture are starting to take a similar approach to Maniwa City. Because the diagnosis and treatment of H. pylori-associated gastritis is only covered by national health insurance for adults, these actions of municipal governments deserve appreciation.

The expansion of insurance cover for eradication therapy to include H. pylori-related gastritis allows more individuals with abdominal symptoms to undergo diagnosis and treatment of H. pylori-associated gastritis. To qualify for health insurance coverage, endoscopy must be performed first for diagnosis of gastritis, and most patients are likely to have chronic gastritis on endoscopy. Such mandatory endoscopy based on the national health scheme may also increase the detection of gastric cancer. All patients with endoscopic gastritis are then supposed to receive H. pylori eradication therapy. For patients with atrophic gastritis, periodic endoscopic follow-up is recommended every 1 or 2 years even after eradication therapy, while patients with no or mild atrophy and those who are negative for H. pylori can be followed by optional screening (such as complete medical check-up) instead of strategic screening (Fig. 3).

Although it is still not clear how effective eradication therapy will be at reducing the development of gastric cancer in patients with H. pylori-associated gastritis, prediction can be based on experience with gastric and duodenal ulcer for which H. pylori eradication therapy has been covered by the Japanese national health scheme since 2000. As a result, the incidence of gastric and duodenal ulcer has decreased dramatically by about 60% over 10 years. In particular, duodenal ulcer decreased to 50,000 cases per year in 2011, representing an almost 70% decrease of its incidence during the 10 years of

Fig. 3. Strategy for elimination of gastric cancer deaths in Japan.
insurance coverage. In the near future, duodenal ulcer may disappear from Japan. The medical cost of treating gastric and duodenal ulcer also decreased by 47% during the same period. Now that insurance cover is available for *H. pylori* eradication therapy, providing eradication therapy (etiologic treatment) for *H. pylori*-associated gastritis is likely to lead to a long-term reduction in the incidence of gastric cancer, although it is unclear whether the outcome for gastric cancer will be comparable to that for gastric and duodenal ulcer. Eradication therapy for *H. pylori*-associated gastritis should reduce the development of gastric and duodenal ulcer and gastric polyp as well as gastric cancer, expecting that a greater reduction of medical costs will be achieved by expanding insurance cover to patients with *H. pylori*-associated gastritis than by offering insurance to patients with gastric and duodenal ulcer.

Because the baby boomer generation is a huge population that is turning 65 and entering the cancer-prone years, the number of gastric cancer deaths in Japan is likely to reach 60,000 in 2020 without any countermeasures. In contrast, if the gastric cancer elimination project is successful and even 50% of persons with *H. pylori* infection receive eradication therapy, the number of gastric cancer deaths will be reduced to about 30,000 in 2020.5) The cost of gastric cancer treatment in Japan is currently around 300 billion yen per year and will exceed 500 billion yen annually if measures are not taken for a decade or so.35) However, if the incidence of gastric cancer is reduced by *H. pylori* eradication, medical costs should be lowered substantially.37) A good model may be peptic ulcer for which *H. pylori* eradication therapy was first covered by the Japanese national health scheme in 2000. Since then, the incidence of peptic ulcer has decreased dramatically by about 60% over 10 years. The medical costs of treating ulcers have decreased by no 47% during that period.5)

**Conclusion**

A gastric cancer elimination project that combines *H. pylori* eradication therapy and endoscopic examination is both appropriate and feasible for Japan, where excellent methods of diagnosis and endoscopic treatment for early gastric cancer are already available. In 2013, *H. pylori* eradication therapy for chronic gastritis was covered by the Japanese national health insurance scheme for the first time in the world, making a dramatic decrease of gastric cancer-related deaths more feasible.

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Profile

Masahiro Asaka was born in Hokkaido in 1948 and graduated from Hokkaido University School of Medicine in 1972. He worked at Hokkaido University Hospital majoring in internal medicine, especially gastroenterology. He received Ph D in 1980 and worked as a research fellow at Baylor College of Medicine in Houston in 1981 and got a position of Instructor of Medicine in 1982. He became Professor of Internal Medicine at Hokkaido University Graduate School of Medicine. He was elected as Director of Hokkaido University Hospital in 2007. He has been a Professor of Cancer Preventive Medicine, Hokkaido University Graduate School of Medicine since 2011. He is a member of the editorial board of many gastroenterology journals including Digestive Diseases, Helicobacter and The GI Forefront, for which he is Chief Editor. He is a member of the American Gastroenterological Association and the American College of Gastroenterology and the Japanese Society of Gastroenterology. He received Princess Takamatsu Cancer Award in 2009, Asahi Cancer Award in 2009, Japan Medical Association Prize in 2011. He won a prize of European Helicobacter Study Group, the Marshall and Warren Medal in 2013.