Chapter 3.8.

Gastric cancer prevention in Japan

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Summary

- Gastric cancer incidence has drastically decreased in Japan because of reductions in its two major traditional risk factors, *H. pylori* infection and the intake of salt-preserved food.
- The high prevalence of these risk factors in older generations has led to gastric cancer occurring more frequently in patients in older age groups.
- Population-based gastric cancer screening has contributed to the high survival rate of gastric cancer in Japan compared with other countries.
- Given the ongoing transition to new generations with fewer risk factors for gastric cancer, Japan should consider a flexible transformation of its national gastric cancer prevention strategies and shift from a total-population approach to a high-risk population approach.
- Serological testing of anti-*H. pylori* IgG antibody in combination with pepsinogen I and II testing and eradication treatment are good candidates but have yet to be recommended, because the long-term effect of this approach on reducing gastric cancer incidence warrants verification.

3.8.1 Descriptive epidemiological trends

The incidence of gastric cancer in Japan, which was once the highest in the world, has decreased substantially in recent years. According to IARC's estimates for 2022, when ranked by age-standardized rates (world), gastric cancer was the fifth most common cancer type in Japan in terms of both incidence and mortality [1, 2]. In 2022, gastric cancer accounted for 12.6% of all cancer cases and 10.3% of all cancer deaths in

Japan, which is consistent with the global rates of 13.1% of all cancer cases and 6.6% of all cancer deaths.

The long-term trends (Fig. 3.8.1) show that the number of incident cases of gastric cancer in Japan has decreased drastically after a peak in about 2010–2015. In contrast, the number of gastric cancer deaths has remained stable, with a gradual decrease in recent years. The age-standardized rates (world) for both incidence and mortality have decreased constantly over time, with steeper decreases in recent years [1, 2].

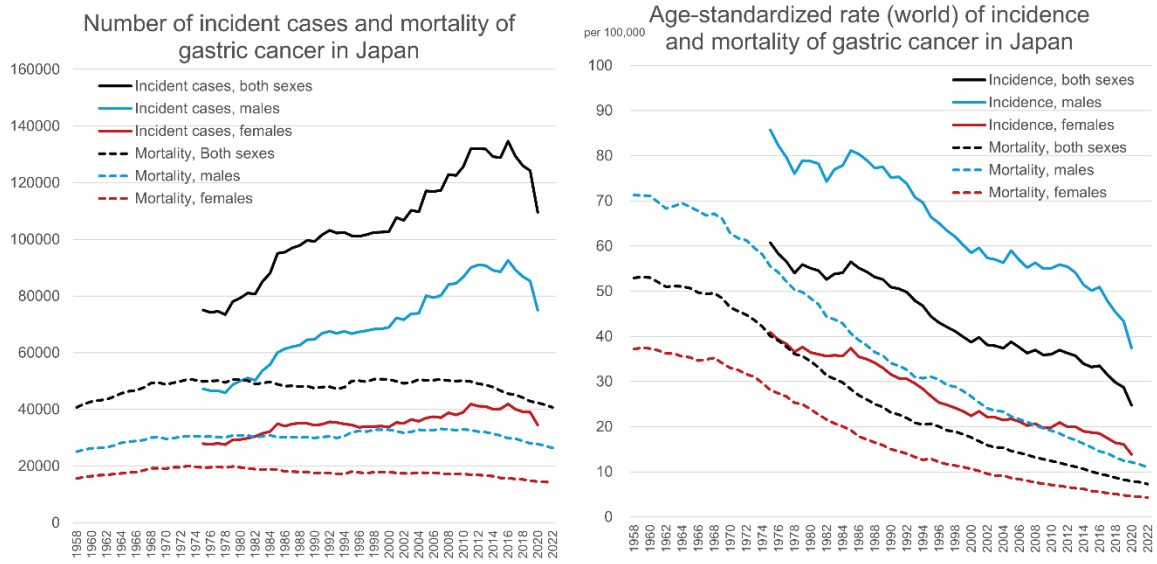

Fig. 3.8.1. Time trends of gastric cancer incidence and mortality in Japan. Compiled from Institute for Cancer Control (2024) [3] (incidence) and from Ministry of Health, Labour and Welfare (2024) [4] (mortality).

By age distribution, gastric cancer incidence and mortality show increases in both the number and the proportion of cases and deaths in people aged ≥ 75 years (Fig. 3.8.2). This is mainly due to the increasing rise in the number of cases and deaths in people aged ≥ 75 years, which indicates that gastric cancer will, in time, become a cancer type that is diagnosed predominantly in older people. Japan has become a “super-ageing society”. In 2007, > 21% of the population were aged ≥ 65 years. This percentage has continued to rise and is contributing in part to the increase in cases of gastric cancer [5].

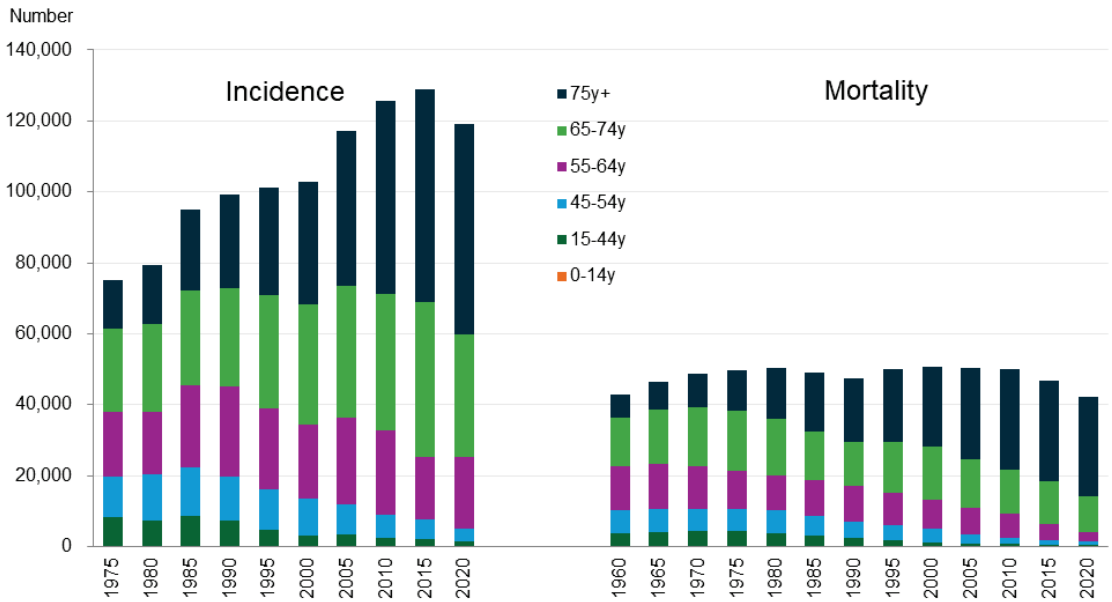

Fig. 3.8.2. Time trends of the number of gastric cancer cases and deaths in Japan in both sexes, by age group. Compiled from Institute for Cancer Control (2024) [3] (incidence) and from Ministry of Health, Labour and Welfare (2024) [4] (mortality).

3.8.2 Clinico-epidemiological features of gastric cancer

Gastric cancer in Japan has two notable characteristics. First, the occurrence is more common in the distal part of the stomach, which is in contrast to countries in North America and northern and western Europe, where occurrence in the proximal part of the stomach is more common. The latest global cancer registry data show that the subsite location in the distal portion has not changed substantially for decades and is substantially attributable to *H. pylori* infection [6].

Second, although the prognosis for gastric cancer is generally poor globally, better survival rates are observed in Japan. The ongoing Global Surveillance of Trends in Cancer Survival (CONCORD) programme has monitored global cancer survival rates for a long time, now involves more than 70 countries, and includes 75% of all cancer cases worldwide, with high representativeness. According to the latest CONCORD-3 report, the 5-year relative survival rate for patients with gastric cancer in 2000–2014 generally ranged from 20% to 40%, versus 60.3% in Japan [7]. This better overall survival in Japan is due to the high proportion of gastric cancers diagnosed at an early stage. In the National Cancer Registry Report 2020 [8], 59% of gastric cancers in Japan were

localized when they were diagnosed, which is relatively high compared with the 31.3% reported by the United States Surveillance, Epidemiology, and End Results (SEER) Program in 2020 [9].

3.8.3 Risk factors and prevention

The incidence of gastric cancer has decreased constantly in Japan (see Section 3.8.1), and the disease has now become a cancer of older people. Therefore, the question arises as to whether this trend is attributable merely to ageing or whether it is a birth cohort effect. However, in either case, *H. pylori* infection and intake of foods preserved by salting have made particular contributions to the history of gastric cancer in Japan.

H. pylori *infection*

H. pylori infection is the most important cause of gastric cancer, particularly non-cardia gastric cancer. *H. pylori* infection is generally acquired during childhood, typically before age 5 years. Therefore, infection status is strongly dependent on hygiene status during childhood, which is dependent mainly on eating behaviours, such as mouth-to-mouth feeding [10]. These factors during infancy greatly determine the infection rate in adulthood.

In Japan, which had the highest incidence rate of gastric cancer in the last century, the *H. pylori* infection rate has decreased with a birth cohort effect [11, 12]. The infection rate peaked at nearly 70–80% for people born in 1930–1940 and decreased with age to nearly 5% for people born in about 2000. Each respective birth cohort shows no marked change in infection rate with increasing age. Estimates in Japanese children and adolescents follow the trend seen in Japanese adults; the prevalence of *H. pylori* infection in children and adolescents was about 10% in individuals born in 1985 but decreased to < 3% in individuals born in 2011 [13] (Fig. 3.8.3).

Thus, gastric cancer prevention strategies must account for generational differences. National-level improvements in hygiene, including improvements in water and sewage systems, and in overall socioeconomic status, which are in turn generally influenced by a history of hygiene and health policy at the national level, will lead to a substantial decline in the overall prevalence of *H. pylori* infection in all age groups, even in countries with a high infection rate [14]. In Japan, *H. pylori* infection will eventually become a rare event, leading to an overall decrease in gastric cancer incidence.

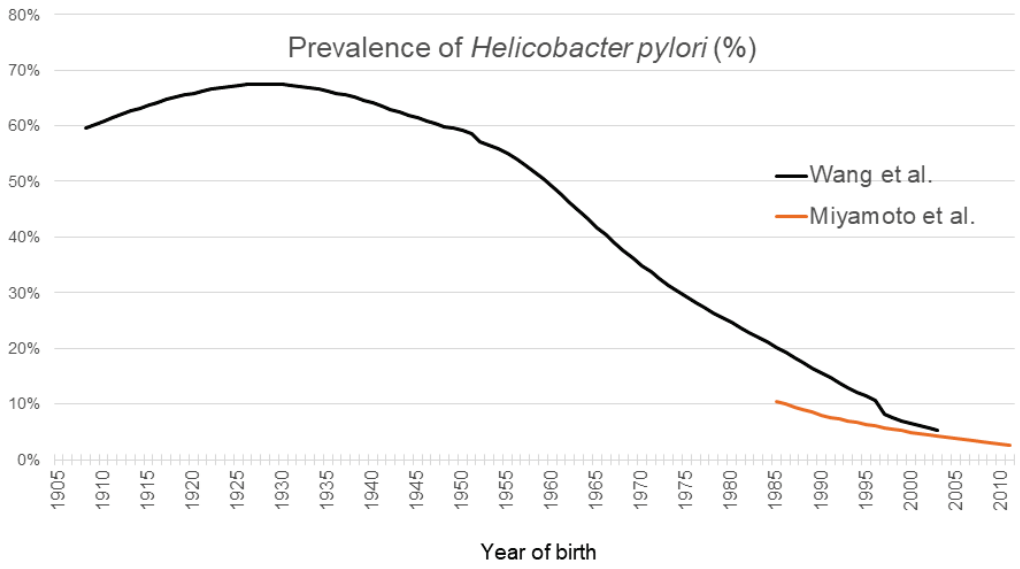

Fig. 3.8.3. Decreasing trend in the prevalence of *H. pylori* infection in Japan by birth year, 1908–2011. Compiled from Wang et al. (2017) [11] and Miyamoto et al. (2019) [13].

Intake of foods preserved by salting

Salt consumption, in general, is known to be linked not only to gastric cancer but also to hypertension and stroke [15]. These diseases are associated with the amount of salt intake and have historically been the major diseases in Japan. A high intake of foods preserved by salting increases the risk of gastric cancer but not the risk of stroke, which tends to be positively associated with the amount of salt intake [16, 17].

Salt reduction means reducing the amount of salt intake and the intake of highly salt-concentrated preserved foods. Salt-preserved foods were more commonly consumed before refrigeration became available [18, 19], and the dissemination of refrigeration has substantially affected the decrease in gastric cancer mortality in Japan. Expanded use of industrial refrigeration in both storage and transportation has led to increased consumption of fresh food and has reduced the need for salting and pickling, which are both positively associated with gastric cancer [18, 19]. Home refrigeration has shifted food preservation techniques from salt preservation to frozen storage [18, 19]. In Japan, the popularization of electric refrigerators in the 1960s was strongly inversely correlated with the decrease in gastric cancer incidence [18].

Japan has also achieved a decrease in salt consumption at the local community level. In the late 1950s, deaths from stroke in Japan were the highest in the world. It became apparent that the number of strokes in different parts of the country was directly related to the amount of salt consumed. The Japanese government initiated a campaign to reduce salt intake, and this eventually decreased over the subsequent decade. A resulting reduction in blood pressure was observed, along with a substantial reduction in stroke mortality [20] and eventually also in gastric cancer incidence and mortality.

3.8.4 Population-based gastric cancer screening

Gastric cancer screening in Japan began with indirect X-ray photography, which had been used in mass screening for pulmonary tuberculosis in the 1950s. The first population-based gastric cancer screening was conducted in Nagano Prefecture and Miyagi Prefecture in the late 1950s and 1960s [21] (Fig. 3.8.4).

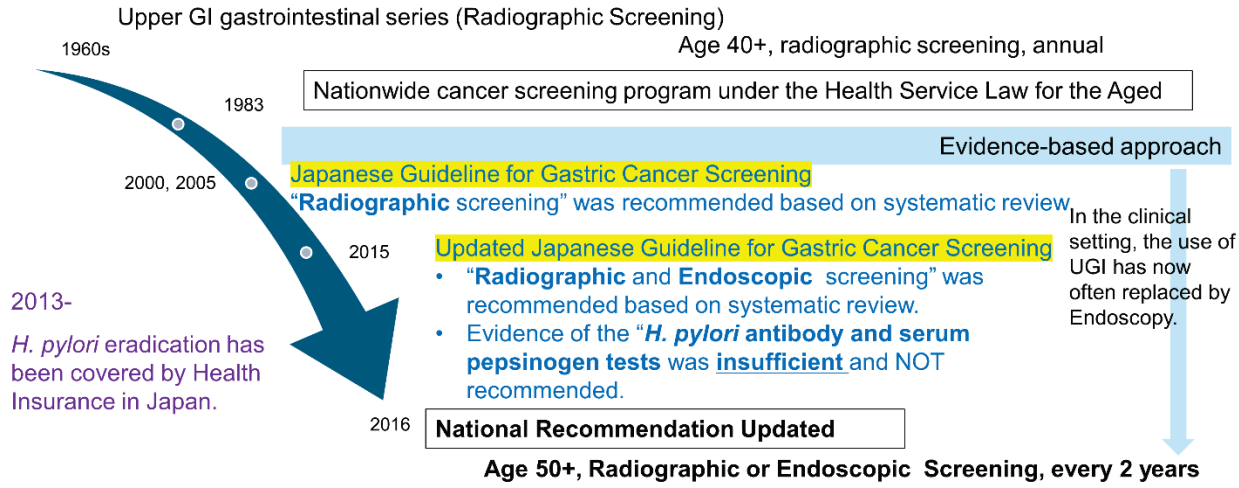

Fig. 3.8.4. Population-based gastric cancer screening in Japan. GI, gastrointestinal; UGI, upper gastrointestinal series. Compiled from Hamashima et al. (2018) [22] and Hamashima (2014) [23].

In the 1960s, in addition to the widespread use of the gastric cancer screening bus, the barium double-contrast method was introduced and was widely used as a gastric cancer screening method, with the establishment of gastric X-ray diagnostics. The number of participants undergoing gastric cancer X-ray screening increased steadily, partly as a result of the start of government subsidies in 1966. The project evolved into a

nationwide gastric cancer screening programme in 1983, under the Health Service Law for the Aged, and later was included in health promotion activities organized by municipalities, under the Health Promotion Act in 2008. The number of people undergoing gastric cancer X-ray screening continued to increase steadily. However, this increase started to slow down in about 1998, when gastric cancer screening was removed from the Geriatric Health Service and was moved to be part of the general financial responsibility of each municipality [21, 24].

The introduction of double-contrast radiography into gastric cancer screening made it possible to detect early gastric cancer. This technique continued to evolve, with improving diagnostic accuracy. In the Japanese Guidelines for Gastric Cancer Screening in 2005, it was reported to be the only screening modality to have reduced gastric cancer mortality [25]. By the late 1990s, radiography was gradually being replaced by endoscopy as the primary modality in the clinical setting.

Initially, the use of endoscopy in population-based screening for gastric cancer was not recommended because of a lack of evidence for effectiveness in reducing mortality [25]. However, after studies in Japan and the Republic of Korea, which provided evidence that gastroscopy screening effectively reduces mortality, the 2014 edition of the Japanese Guidelines for Gastric Cancer Screening [26] recommended endoscopy for both organized and opportunistic screening. This latest guideline recommends biennial endoscopic screening in individuals aged ≥ 50 years [22]. Each municipality is responsible for implementing its own population-based gastric cancer screening programme.

Even with the increasing proportion of municipalities adopting endoscopic screening, various issues have hindered implementation, including insufficient endoscopists, insufficient endoscopy processing capabilities, insufficient quality control systems, and budget constraints [27]. Further efforts are required to ensure the nationwide adoption of endoscopic gastric cancer screening, improve participation rates, and optimize diagnostic accuracy control.

3.8.5 Risk stratification approach

In Japan, groups at high risk of gastric cancer are commonly stratified by serological testing of anti-*H. pylori* immunoglobulin G (IgG) antibody (HP) in combination with pepsinogen I and II testing (PG) [28]. This method has attracted attention as a risk stratification tool, and its use has become more widespread in recent years, after national health insurance coverage in Japan was expanded in 2013 to include *H. pylori* eradication treatment for chronic gastritis. The approach stratifies Japanese people into four groups: (A) HP-negative and PG-negative, (B) HP-positive and PG-negative, (C) HP-positive and PG-positive, and (D) HP-negative and PG-positive. Compared with group A, the long-term risk of gastric cancer is highest in group D, followed by group C and group B [29].

Given the current variation in the prevalence of *H. pylori* infection by birth year (high in older age groups and low in younger age groups) and the efforts to address the inadequate endoscopy processing capacity in gastric cancer screening in Japan, it is worthwhile to considering a risk stratification approach by *H. pylori* infection status, in which screening is omitted or is conducted at longer intervals in individuals who have never had *H. pylori* infection. However, evidence for the effectiveness of this risk stratification method combined with endoscopy in the setting of population-based screening remains insufficient, and it is yet to be recommended.

3.8.6 *H. pylori* eradication for gastric cancer prevention

Eradication of *H. pylori* has drawn attention as a strategy to minimize gastric cancer risk. Since 2013, when eradication therapy for *H. pylori*-associated gastritis was included in national health insurance coverage (Box 3.8.1), a relatively large number of individuals with *H. pylori* infection have received this treatment, i.e. about 1.4–1.6 million people annually [30]. A recent systematic review and meta-analysis of published studies in Japan showed that eradication effectively prevents gastric cancer in the Japanese population irrespective of symptoms [33]. However, because of insufficient evidence on long-term effects after eradication, well-designed, extensive cohort studies are warranted to determine the long-term efficacy and safety of *H. pylori* eradication in reducing gastric cancer incidence at the population level [33].

The development of antimicrobial resistance and treatment failure fuel the global burden of *H. pylori*-associated gastric complications [34]. Antimicrobial susceptibility testing can improve the success rate of eradication treatment and avoid the spread of resistant bacteria due to inappropriate antibiotic use, and it has been included in the *H. pylori* diagnosis treatment guideline in Japan.

Box 3.8.1. History of health insurance coverage for *H. pylori* eradication therapy

In November 2000, based on the results of various clinical studies, *H. pylori* eradication therapy was approved in Japan for treating *H. pylori*-positive gastric and duodenal ulcers. This was the first time that eradication therapy was approved under Japan's public medical insurance system.

At about this time, it became clear that most gastric cancers are caused by *H. pylori* infection, and it was time for a substantial review of the *H. pylori* control measures. Since 2002, in Japan, measures to prevent liver cancer had focused on addressing hepatitis virus infections, resulting in a significant decrease in liver cancer mortality. However, the annual number of gastric cancer deaths had remained at about 50 000 for the past several decades, without substantial increases or decreases, suggesting that current prevention measures were inadequate. It was considered that primary prevention through *H. pylori* eradication therapy, as well as secondary prevention, should be promoted as a fundamental preventive method for gastric cancer.

In 2009, the Ministry of Health, Labour and Welfare approved the expansion of national health insurance coverage for *H. pylori* eradication therapy and added three new indications – gastric mucosa-associated lymphoid tissue (MALT) lymphoma, post-endoscopy treatment for early-stage gastric cancer, and idiopathic thrombocytopenic purpura – in addition to gastric and duodenal ulcers.

This was the first time in the world that *H. pylori* eradication therapy was covered by health insurance for indications other than gastric and duodenal ulcers. The Japanese Society of Gastroenterology, the Japanese Society for Gastrointestinal Endoscopy, and the *Helicobacter* Society of Japan jointly submitted a request to the Ministry of Health, Labour and Welfare to expand the insurance coverage of *H. pylori* eradication therapy for chronic gastritis. As a result, *H. pylori* eradication therapy for

patients with chronic gastritis became available on 21 February 2013.

After the insurance coverage had been extended, prescriptions for *H. pylori* eradication therapy were 5 times the previous numbers, with an estimated 1.5 million people being treated per year [30–32].

3.8.7 Conclusions and future directions

Gastric cancer incidence has drastically decreased in Japan because of reductions in its two major traditional risk factors, *H. pylori* infection and the intake of salt-preserved food. The high prevalence of these risk factors in older generations has led to gastric cancer occurring more frequently in patients in older age groups. Population-based gastric cancer screening has contributed to the high survival rate of gastric cancer in Japan compared with other countries. Given the ongoing transition to new generations with fewer risk factors for gastric cancer, Japan should consider a flexible transformation of its national gastric cancer prevention strategies and shift from a total-population approach to a high-risk population approach. Serological testing of anti-*H. pylori* IgG antibody in combination with pepsinogen I and II testing and eradication treatment are good candidates but have yet to be recommended, because the long-term effect of this approach on reducing gastric cancer incidence warrants verification.

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