Gastric Cancer

With Special Focus on Studies from Japan

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Preface

Helicobacter pylori was declared a human carcinogen in 1994. Evidence has now accumulated to show that at least 95% of gastric cancers are etiologically related to *H. pylori*. In Japan, there has been a progressive and rapid decline in the prevalence of *H. pylori* infection, and the number of gastric cancer deaths has begun to decline in recent years. Japanese insurance policy approved eradication therapy for *H. pylori*-positive gastritis after endoscopic examination in February 2013. The high incidence of gastric cancer in Japan initially resulted in the establishment of a countrywide gastric cancer screening program to detect early and treatable cancers. Population-based endoscopic gastric cancer screening started in September 2014. On *H. pylori* eradication in Japan, potassium-competitive acid blocker (P-CAB) has been approved in February 2015. P-CAB is able to achieve longer and stronger acid suppression, and the superiority of P-CAB-based triple therapy over proton pump inhibitors (PPIs) has been confirmed.

The book comprises of five parts: epidemiology, pathogenesis, risk clarification, therapy, and prevention focusing on gastric cancer in Japan. In the first part, the two chapters indicate gastric cancer epidemiology in Japan and outside Japan. There are three chapters describing *H. pylori* virulence factors and epigenetic and proteomic modulations related to gastric carcinogenesis and clinicopathological features of gastric cancer. *H. pylori* eradication reduces or eliminates mucosal inflammation and reverses or reduces *H. pylori*-associated molecular events such as aberrant activation-induced cytidine deaminase expression, double-strand DNA breaks, impaired DNA mismatch repair, and aberrant DNA methylation. However, increased risk of gastric cancer remains even after *H. pylori* eradication. The theme of the third part is risk clarification and cancer screening before and after eradication. For high-risk groups, especially those with severe atrophy, long-term follow-up endoscopic surveillance for gastric cancer becomes more important than eradication and should be offered. There are three chapters on treatment of gastric cancer regarding current status of endoscopic treatment, operation, and chemotherapy in Japan. Endoscopic submucosal dissection (ESD), which was developed to make possible the en bloc removal of large, flat, superficial cancer lesions, has become a standard technique in Japan and other East Asian countries. The final part consists of two

chapters about gastric cancer prevention. Earlier eradication of *H. pylori* is considered to be more effective in preventing gastric cancer by inhibiting the progression of mucosal atrophy. Japanese gastric cancer elimination projects including test and treat in young generation are thought to promote a decrease of gastric cancer-related deaths.

Kurashiki, Okayama, Japan Akiko Shiotani

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Abstract Gastric cancer remains one of the most common cancers in the world, being the third most common cause of cancer death and the fifth most common malignancy. Incidence rate of gastric cancer is highest in East Asia including Japan, Korea, and China. More than half of new gastric cancer cases in the world have been diagnosed in East Asia. Gastric cancer is not a disease of the past in Japan like other developed Western countries. Although mortality and morbidity rates of gastric cancer have been dramatically declining in Japan, the absolute number of gastric cancer deaths has remained constant for a few decades. The number of deaths has begun to decline in recent years. Interestingly, gastric cancers detected in Japan have characteristic features. Mortality rates in Japan are considerably lower than incidence rates due to the impact of diagnosis and treatment of early-stage gastric cancers.

Keywords Gastric cancer · Early gastric cancer · Mortality · Morbidity · *H. pylori* · Salt · Diet · Atrophy · Intestinal metaplasia

1.1 Mortality

Over time in Japanese trends of age-standardized cancer mortality rates, mortality rates of gastric cancer in both male and female have been dramatically declining throughout the observation period (Fig. 1.1) [1]. This phenomenon is in contrast with the rising mortality rates of other cancers such as lung, colon, prostate, and breast. Gastric cancer has been the leading cause of cancer death for a long time, but it has now dropped to second place in male and fourth place in female. In 1950 gastric cancer deaths accounted for about 48% of cancer deaths, while in 2011 they accounted for about 14% [2]. Mortality rates of gastric cancer worldwide have been declining for decades. This decrease is due to changes in food preservation methods (from salted to refrigerated or frozen) and to everyday availability of fresh vegetables and fruits.

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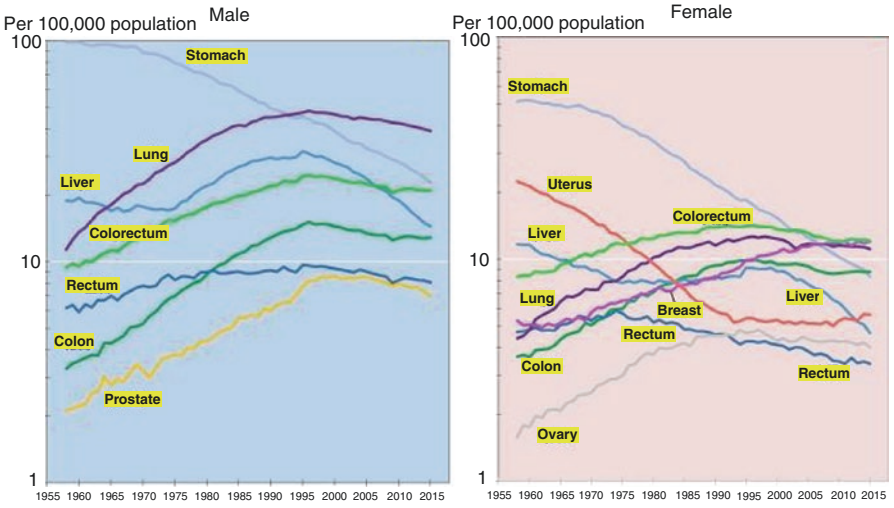

Fig. 1.1 Age-standardized mortality rate of cancer by site in Japan. Source: Center for Cancer Control and Information Services, National Cancer Center, Japan

An age-standardized mortality rate of gastric cancer performed in Japan every 10 years, from the 1960s to the 2010s, shows decrease of mortality rate in all ages over time (Fig. 1.2a) [1]. In the 1960s, the peak of mortality rate was between 75 and 79 years old. However, every 10 years, the peak age has increased, currently reaching over 85 years old. When the mortality rate of each age class is represented by the birth year, the mortality rate is lower for late births in the same age group (Fig. 1.2b) [1]. Infection rates of *H. pylori* in Japanese individuals born before 1950 were uniformly high; however, even the mortality rate of those generations was affected by their birth years [3]. Therefore, a change in lifestyle contributed to the decline in mortality rates of gastric cancer. A decline in the prevalence rate of *H. pylori* appears to be a factor that influenced mortality rates only later.

Although age-standardized mortality rate of gastric cancer has declined, the absolute number of gastric cancer deaths has remained constant between 50,000 and 55,000 over the past 50 years (Fig. 1.3) [1]. A trend of the number of gastric cancer deaths by age in Japan reveals that they peaked from 65 to 75 years old until the 1990s (Fig. 1.4) [1]. Subsequently, in the 2000s the number of gastric cancer deaths in individuals over 85 years old increased dramatically. The shift of gastric cancer patients and death to an extremely elderly population are attributable to the rapid aging of Japanese population (Fig. 1.5) [4]. Originally the effect of decreasing the number of deaths caused by a decline in the age-adjusted mortality rate was offset by an increase in the number of gastric cancer deaths among a super elderly population.

The absolute number of deaths from gastric cancer was 48,632 in 2013, 47,903 in 2014, 46,659 in 2015, and 45,509 in 2016. These numbers show a decreasing trend following the introduction of insurance coverage for *H. pylori* eradication as a consequence of *H. pylori*-induced gastritis [1]. A fall of 9.2% over the last 4 years

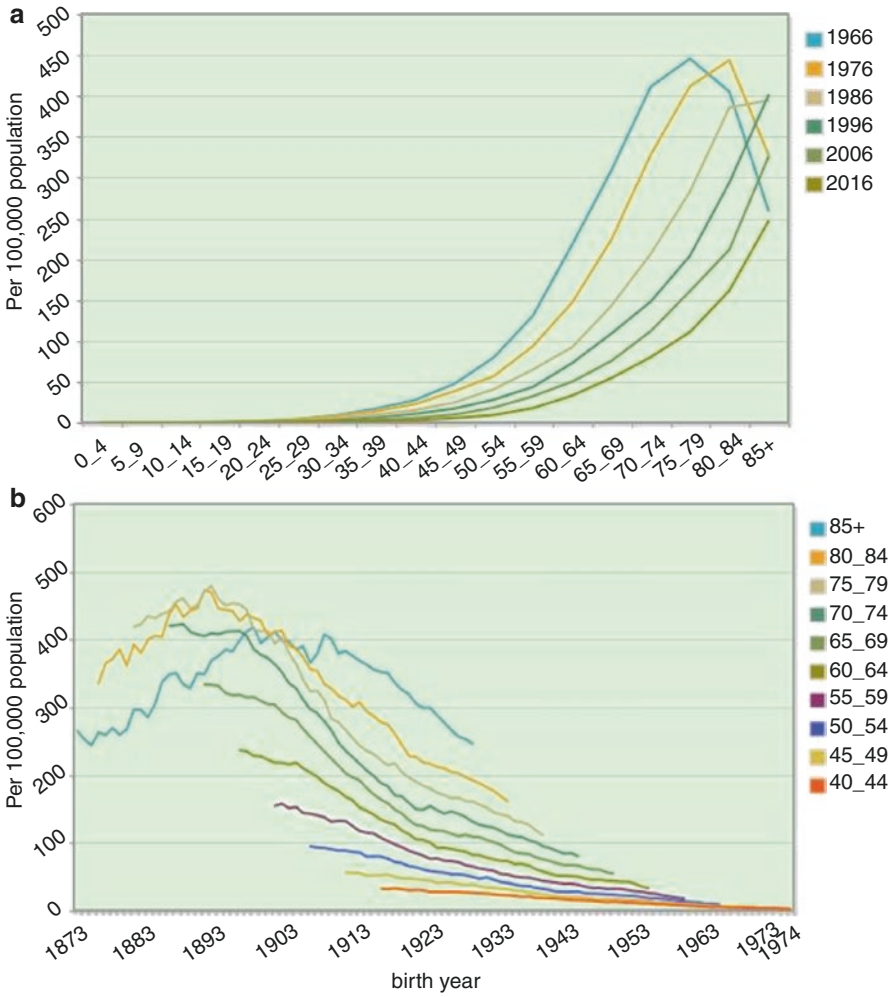

Fig. 1.2 Trend of age-standardized mortality rate by age and by birth year in Japan. Source: Center for Cancer Control and Information Services, National Cancer Center, Japan

showed a significant decrease, compared to the expected number of gastric cancer deaths using previously observed data shown by the National Cancer Center (Fig. 1.6) [4, 5]. From 300,000 to 600,000, patients have *H. pylori* eradicated every year after insurance approval in year 2000. Six million patients with gastritis have had *H. pylori* eradicated in the 4 years following the availability of insurance coverage. It is estimated that 12 million Japanese have had *H. pylori* eradicated so far [5]. It seems that reduction of gastric cancer incidence following *H. pylori* eradication over a 10-year period has contributed to the recent decrease in the number of gastric cancer deaths.

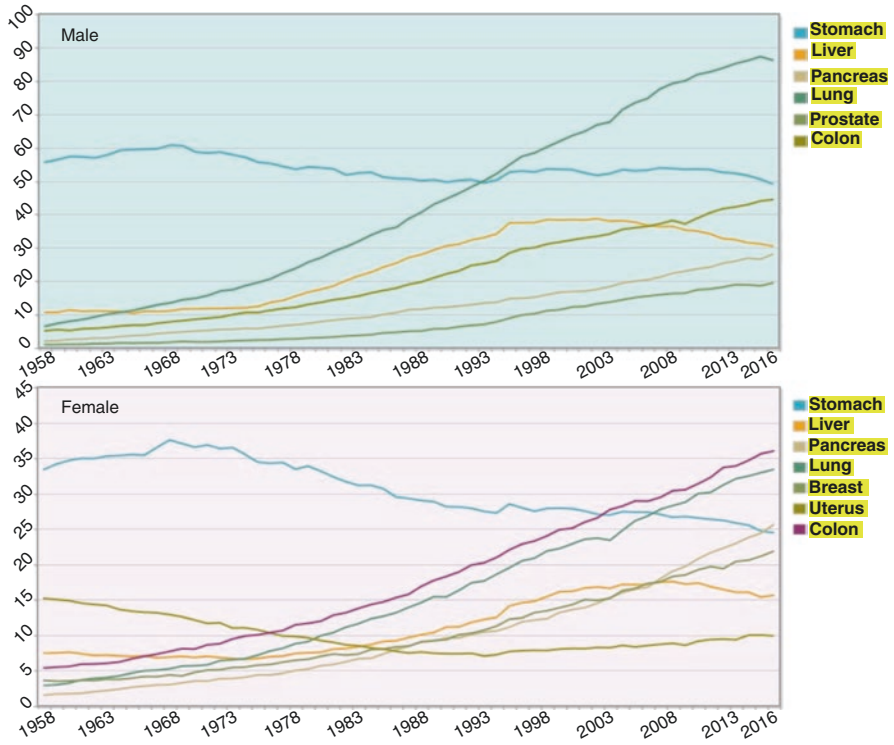

Fig. 1.3 Absolute number of cancer deaths by site in Japan. Source: Center for Cancer Control and Information Services, National Cancer Center, Japan

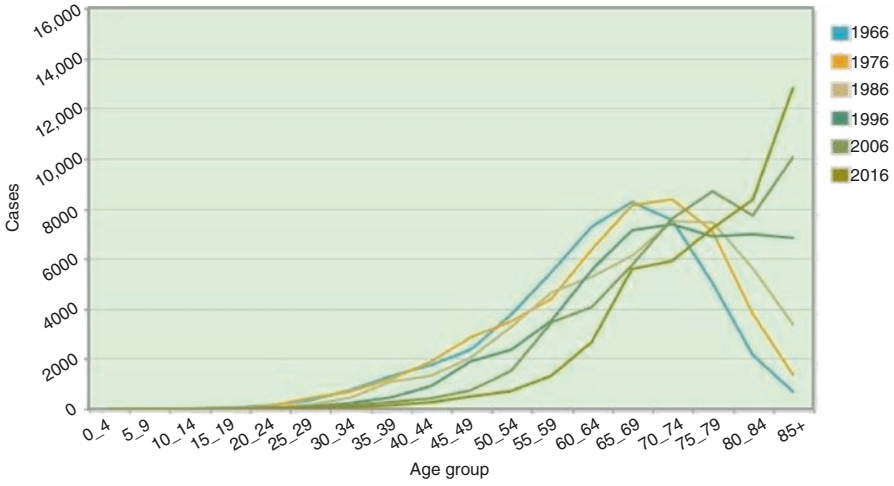

Fig. 1.4 Trend of the absolute number of gastric cancer deaths by age in Japan. Source: Center for Cancer Control and Information Services, National Cancer Center, Japan

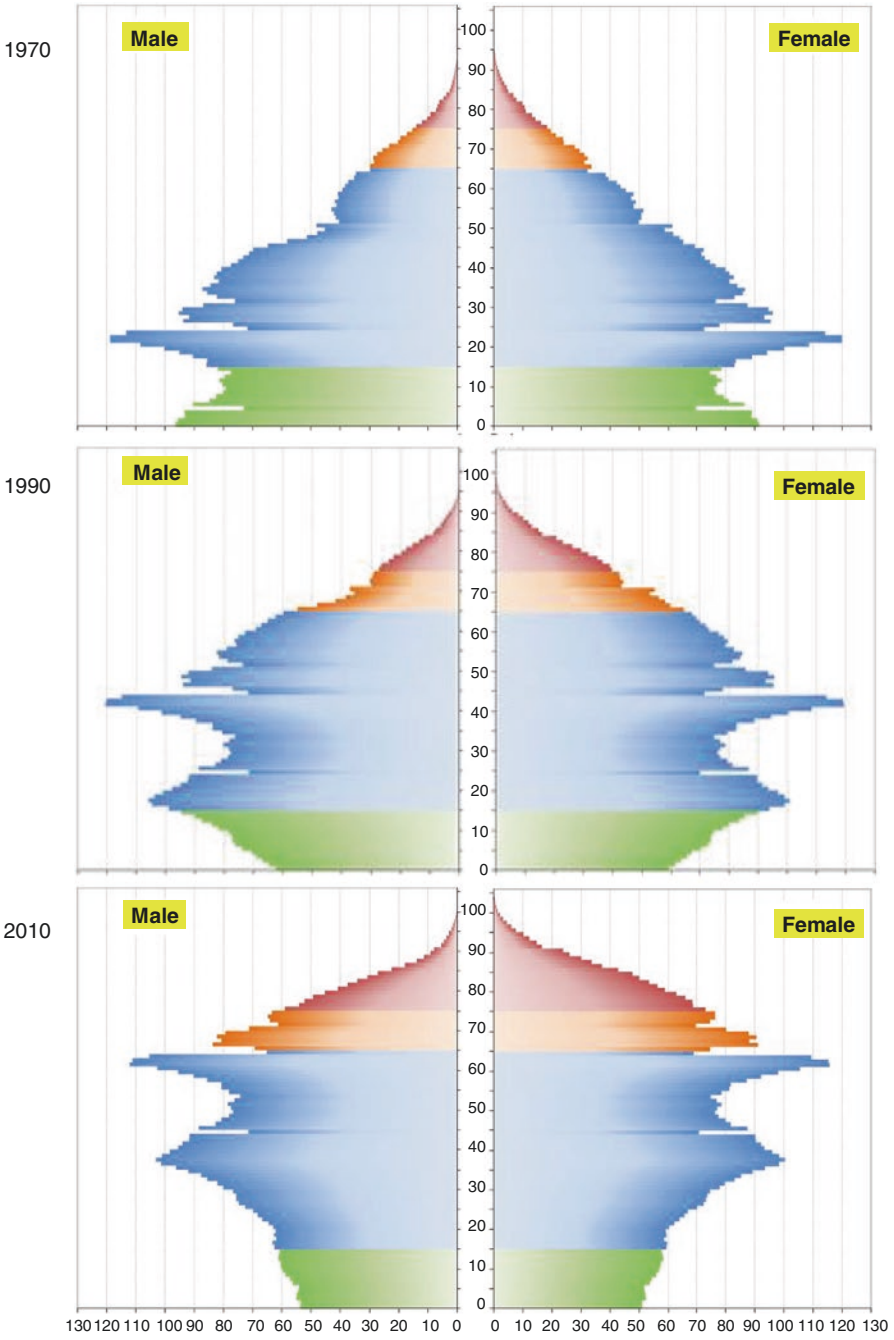

Fig. 1.5 Population pyramid of Japan from 1940 to 2010

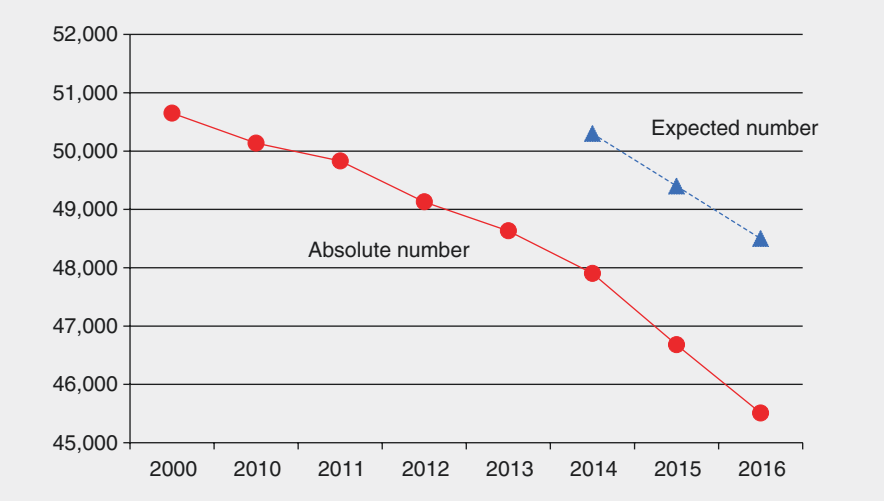

Fig. 1.6 The difference between absolute and expected number of deaths from gastric cancer in Japan

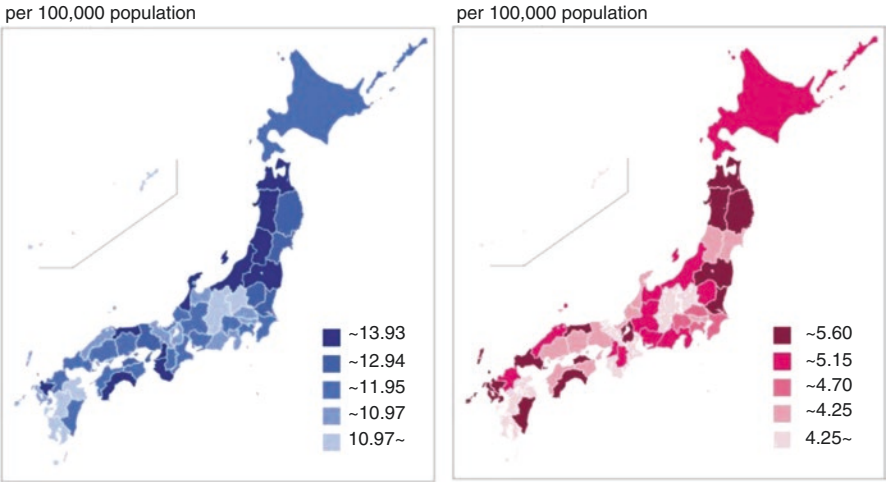

Fig. 1.7 Age-standardized mortality of gastric cancer by prefecture in Japan. Source: Center for Cancer Control and Information Services, National Cancer Center, Japan

The distribution of gastric cancer varies across geographical regions. The mortality rate of gastric cancer in Japan is high in both males and females, highest in the northeast region by Akita Prefecture and Yamagata Prefecture, and lowest in the southwest area by Okinawa Prefecture (Fig. 1.7) [1]. This regional difference is also associated with food culture. For example, high salt consumption is prevalent in high-risk areas of gastric cancer [6]. Although the prevalence rate of *H. pylori* in