

# Changing epidemiology of *Helicobacter pylori* in Japan

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**Abstract** *Helicobacter pylori* (*H. Pylori*) is known as the most important cause of gastric cancer. The prevalence of *H. pylori* infection varies widely by geographic area, age, and socioeconomic status. In Japan, *H. pylori* infection has been highly correlated with the incidence rate of gastric cancer, and a reduction in *H. pylori* infection is therefore crucial for decreasing the incidence of gastric cancer, especially at the population level. Infection occurs during childhood, commonly before 5 years of age. In Japan, where gastric cancer has ranked as the most common cancer by incidence and mortality for the last several decades, the prevalence of *H. pylori* infection has dramatically declined by birth cohort effect, mainly due to improvements in the general hygiene environment in childhood. Older generations born before around 1950 show a high prevalence of around 80–90 %, decreasing with age to reach around 10 % or less in those born around the 1990s, and less than 2 % for children born after the year 2000. This change will have generational effects on gastric cancer prevention strategies, both primary and secondary. The risk-stratified approach to gastric cancer prevention should be considered in Japan and other countries which have similarly experienced rapid economic development.

**Keywords** *Helicobacter pylori* · Gastric cancer · Epidemiology · Japan

## Recent epidemiological trends in gastric cancer

A recent global estimate shows gastric cancer as the fifth-most common cancer worldwide, with 951,600 new cases in 2012 [1]. Occurrence was most frequent in the East Asian region. Globally, most developed countries and regions have observed a steady decline in this cancer with economic development and better sanitary conditions over the last century. A similar trend has also been observed in East Asia, including Japan.

Japan no longer has the highest gastric cancer rate, as it once did, and the latest age-standardized incidence rate places Japan third, after South Korea and Mongolia [1] (Fig. 1). Gastric cancer rates in Japan have constantly declined over time in all age groups [2, 3] (Fig. 2). In spite of this decreasing trend, the number of incident cases has been increasing due to “aging”, and the number of deaths has remained unchanged. Both in incidence and mortality, we can clearly discern that most incident cases and deaths are in patients aged 60 years and over, and are prominent among those aged 70 years and over [2, 4] (Fig. 3). In short, gastric cancer in Japan has constantly declined, and has now become a “cancer of the elderly”. The question therefore arises as to whether this trend is caused merely by “aging” or by a birth-cohort effect; and if the latter, by what factor.

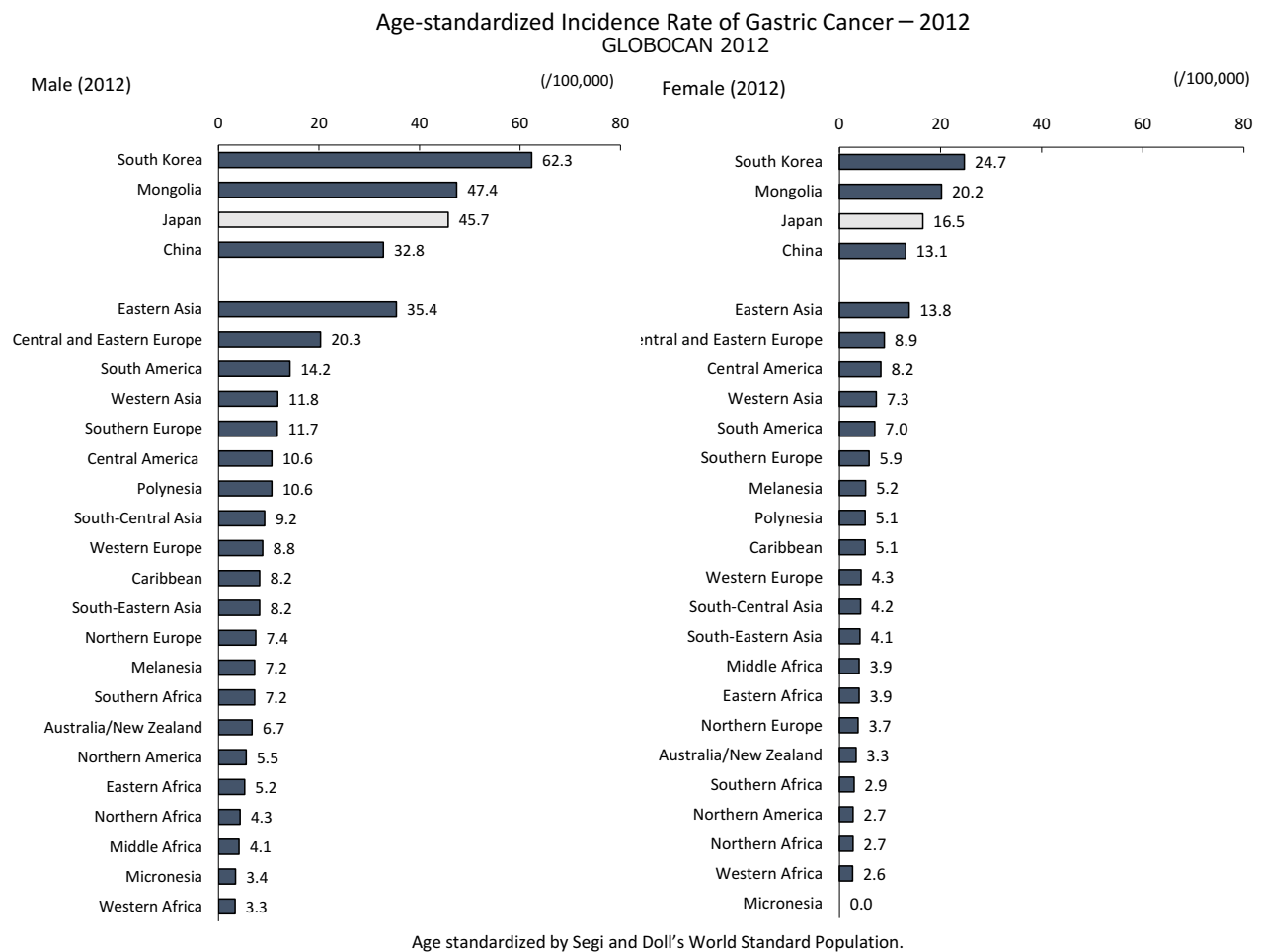
## *Helicobacter pylori* (*H. pylori*) infection

Needless to say, *H. pylori* is known as the most important cause of gastric cancer. *H. pylori* has been identified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) [5, 6], and is typically associated with non-cardia gastric carcinoma. Approximately 90 % of non-cardia gastric cancer worldwide is estimated

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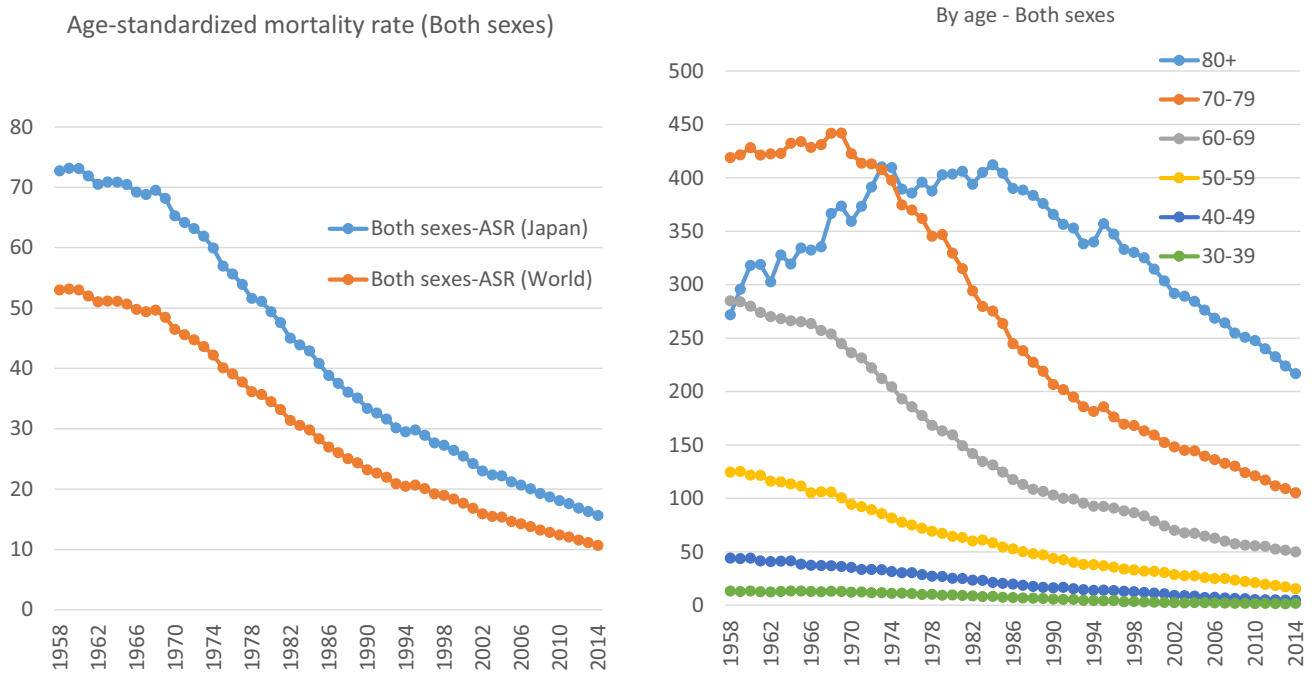
**Fig. 1** Age-standardized Incidence Rate of Gastric Cancer-2012 (GLOBOCAN 2012, International Agency for Research on Cancer) [1]

to be explained by this infection [7]. The pathogenic relationship between *H. pylori* and gastric cancer has been reported in various studies, and these have shown that *H. pylori*-associated carcinogenesis is primarily due to the gastric inflammatory response and resulting oxidative stress [6, 8, 9].

The prevalence of *H. pylori* infection varies widely by geographic area, age, and socioeconomic status. Prevalence in less developed regions may reach 70 % or higher, compared with 40 % or less in more developed regions. In Japan, as well as Eastern Asia in general, *H. pylori* infection has been highly correlated with incidence rate of gastric cancer [10], and a reduction in *H. pylori* infection is therefore crucial for decreasing the incidence of gastric cancer, especially at the population level. The incidence rate is generally more reflective of the prevalence of *H. pylori* in older age groups in Japan, which are prone to gastric cancer, and so the high prevalence of *H. pylori* in Japan in the elderly corresponds to a high incidence of gastric cancer [10]. In contrast, countries with low gastric cancer rates, such as Australia and the US, have a very low

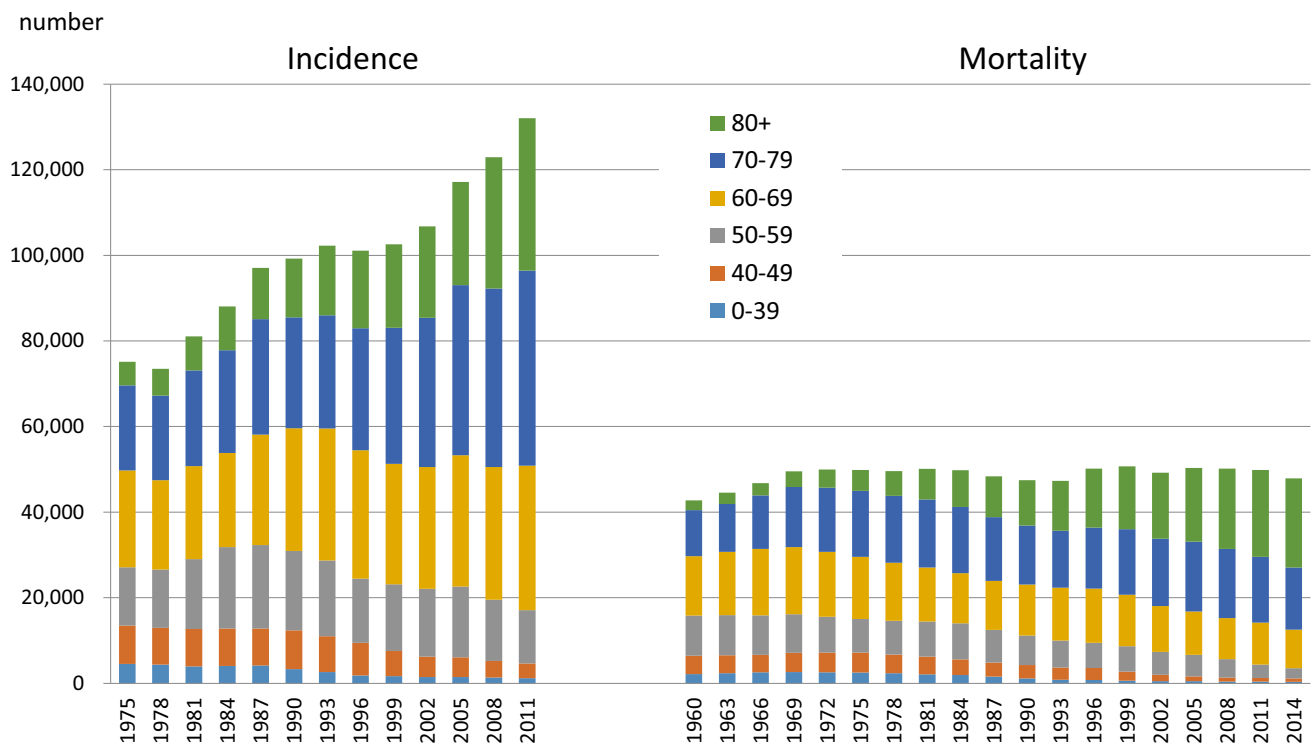
prevalence in younger age groups. Most countries with decreased gastric cancer rates show a lower prevalence of *H. pylori* in younger age groups [10].

A comparison of the prevalence of *H. pylori* infection in various Asian countries revealed that the prevalence in Japan shows a mixed pattern of developed and developing countries, namely a developed country pattern (low prevalence) for those aged under 29 years and a developing country pattern (high prevalence) for those aged over 40 [11]. Korea shows a similar pattern although the prevalence of *H. pylori* in younger age groups is slightly higher than in Japan [12]. Prevalence of *H. pylori* infection and gastric cancer rates do not necessarily correlate in other parts of the world, due to differences in the virulence factors of the bacteria [13]. Despite a high prevalence in young as well as old age groups in other countries in Eastern Asia (China, Mongolia), south-eastern Asia (Vietnam, Malaysia, Singapore, Brunei, Thailand, Myanmar), southern Asia (Bhutan, Bangladesh, Nepal, India), Central Asia (Kazakhstan, Iran, Iraq, Pakistan) and western Asia (Saudi Arabia, Turkey) [11], rates of gastric cancer are not high.



**Fig. 2** Time trend of gastric cancer mortality in Japan. ASR (Japan): Age standardized by Japanese model population in 1985. ASR (World): Age standardized by Segi and Doll’s world standard

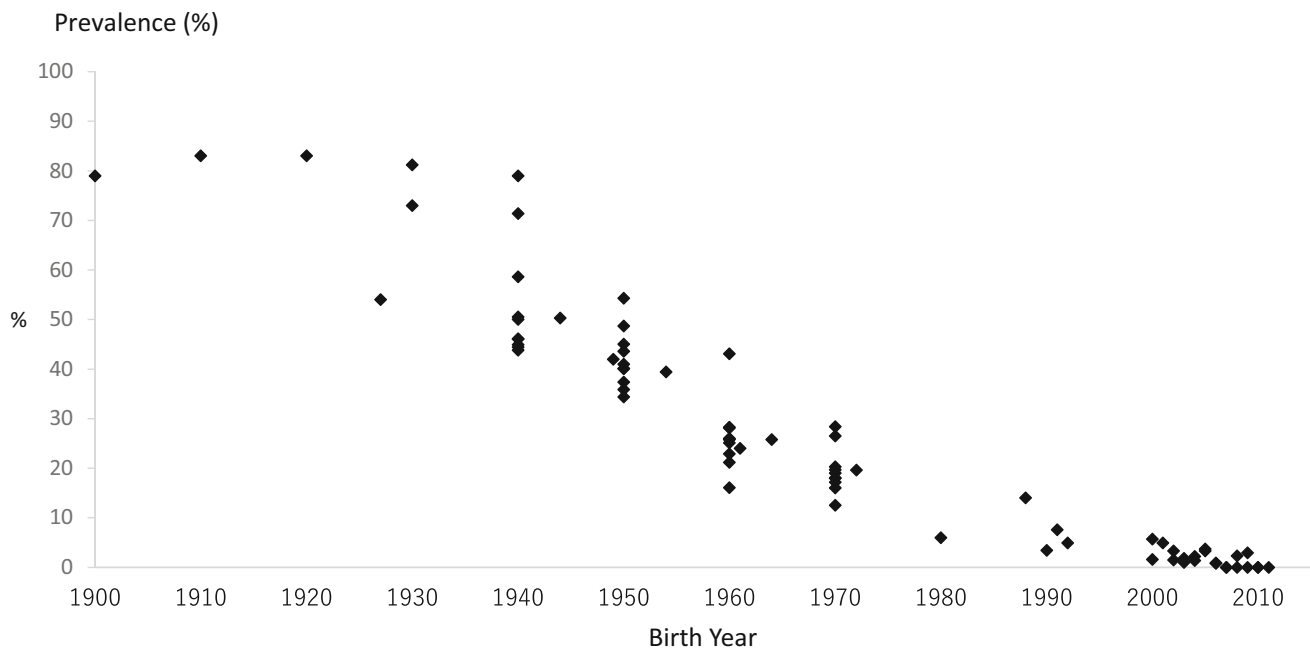
population Data source: Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan [http://ganjoho.jp/reg\\_stat/statistics/dl/index.html](http://ganjoho.jp/reg_stat/statistics/dl/index.html)



**Fig. 3** Number of incidence and mortality of gastric cancer in Japan Data source: Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan [http://ganjoho.jp/reg\\_stat/statistics/dl/index.html](http://ganjoho.jp/reg_stat/statistics/dl/index.html)

Economic development and an improved hygienic environment may contribute to a decline in the prevalence of *H. pylori* infection in infancy and childhood. Furthermore, the

prevalence trend of *H. pylori* in younger age groups is the key to predicting the future course of gastric cancer incidence in high-risk countries.



**Fig. 4** Prevalence of *Helicobacter pylori* infection in Japan by birth-year Data source: [15–21]

### Effect of birth cohort in Japan

It is known that the acquisition of *H. pylori* infection occurs mostly under the age of 5 years. Infection status is suggested to be dependent on sanitary conditions during early childhood and lifestyle eating behavior (mouth to mouth transmission). Therefore, a sanitary environment around infancy greatly impacts the prevalence of *H. pylori* infection in adulthood [14]. Many reports on prevalence have reported their results by age group. For the reasons above, however, data by birth cohort or birth year rather than age group may facilitate understanding, and even help in predicting the future of gastric cancer.

The earliest study on the *H. pylori* prevalence in Japanese asymptomatic population was reported by Asaka et al. [15], which showed  $\approx 80\%$  for those born before 1950s,  $\approx 40\%$  for those born in 1950s,  $\approx 25\%$  for those born in 1960s,  $\approx 20\%$  for those born in 1970s and  $\approx 5\%$  for those born in 1980s. Ueda et al. reported the prevalence of *H. pylori* infection based on health checkups in a multi-institutional study across Japan in 1997–2013, which broadly included Hokkaido, Aomori, Yamagata, Gunma, Aichi, Saga and Kagawa [16]. The study showed a clear decline by birth cohort, particularly in those born after 1950–1959. Similar declining trends in prevalence by birth-year were also reported by the HERPACC III Study (2005–2013) in Nagoya using joinpoint regression analysis [17]: the prevalence of *H. pylori* infection was 50% for those born in 1920s, 40% for those born in 1950s, 20% for those born in 1960s, and 15% for those born in 1980s. Tamura et al.

reported that prevalence in an urban area of Japan (Nagoya) in 2008–2010 also showed clear decline, from 50% for those born in 1940s to 20% for those born in 1970s [18]. Hirayama et al. reported a similar prevalence using annual health check-up data from a major company in Japan (28% overall; 18% for those born in 1970s, 23% for those born in 1960s, 37% for those born in 1950s, and 46% for those born in 1940s), with no clear difference by sex [19].

Akamatsu et al. examined the prevalence of *H. pylori* in Japanese high school students [20] and found the low prevalence of *H. pylori*, 5% for those born around 1990. Okuda et al. targeted Japanese children born after 2000 [21] and reported a very low prevalence for those born between 2000 and 2010. This study reported that *H. pylori* prevalence in Japanese children is less than 2%; parent-to-child infection is thought to be the main infection route; and that the possibility of new infection other than by vertical infection in Japanese children is low.

When taken together, older generations born before around 1950 show a high prevalence of around 80–90%. Prevalence decreases with age to reach around 10–20% in those born during the 1980s, 5% in those born around 1990 and less than 2% in children born after 2000 (Fig. 4) [15–21].

### Conclusion

This accumulating evidence indicates that the prevalence of *H. pylori* infection in Japan will undoubtedly decline substantially in future in all age groups, to the extent that it

will be recognized as a rare event. This change will have generational effects on gastric cancer prevention strategies, both primary and secondary. The risk-stratified approach to gastric cancer prevention should be considered in Japan [22] and other countries which have similarly experienced rapid economic development.

**Compliance with ethical standards** This is a review article of published studies and the article does not contain any studies with human or animal subjects performed by the author.

**Conflict of interest** Manami Inoue is the beneficiary of a financial contribution from the AXA Research fund as chair holder of the AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo, from November 1, 2012. The AXA Research Fund has no role in this work.

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