

## ORIGINAL ARTICLE

# Gastric cancer deaths by age group in Japan: Outlook on preventive measures for elderly adults

Masahiro Asaka<sup>1</sup>  | Masanobu Kobayashi<sup>1</sup> | Takahiko Kudo<sup>1</sup> | Kozo Akino<sup>1</sup> |  
Yuichiro Asaka<sup>1</sup> | Kenji Fujimori<sup>2</sup> | Shogo Kikuchi<sup>3</sup> | Sayo Kawai<sup>3</sup> | Mototsugu Kato<sup>4</sup>

<sup>1</sup>Advanced Research Promotion Center, Health Sciences University of Hokkaido, Ishikari-gun, Japan

<sup>2</sup>Department of Health Administration and Policy, Tohoku University School of Medicine, Aichi, Japan

<sup>3</sup>Department of Public Health, Aichi Medical University, Aichi, Japan

<sup>4</sup>Department of Internal Medicine, Hakodate National Hospital, Nagakute, Japan

## Correspondence

Masahiro Asaka, Health Sciences University of Hokkaido, Ishikari-gun, Japan  
Email: maasaka@hoku-iryo-u.ac.jp

## Abstract

In February 2013, Japan became the first country in the world to cover *Helicobacter pylori* eradication for chronic gastritis under its National Health Insurance (NHI) system. Now that eradication therapy is covered by NHI, its usage has increased dramatically, and gastric cancer deaths have begun to decrease. We undertook a detailed epidemiological analysis to investigate effects of expanded NHI coverage for *H. pylori* eradication therapy on gastric cancer deaths in specific age groups. Numbers of gastric cancer deaths were determined by referencing data from Ministry of Health, Labour and Welfare reports and “Cancer Statistics in Japan – 2018” published by the Foundation for Promotion of Cancer Research. Gastric cancer deaths across all age groups have been clearly decreasing since 2013, but deaths of people aged 80 years and older are still increasing. The number of gastric cancer deaths in people aged in their 80s was 2 times higher than in people aged in their 70s and 4 times higher than in people aged in their 60s. The number of people in their 80s who had an endoscopy was less than half that of people in their 60s and 70s. The eradication therapy has increased dramatically, and gastric cancer deaths are clearly decreasing in Japan. However, this decrease in deaths has not extended to elderly adults aged in their 80s, which suggests that measures to prevent gastric cancer in people aged 80 years and older will be critical to achieving the mission of eliminating gastric cancer in Japan.

## KEYWORDS

cancer prevention, elderly adults, gastric cancer, *Helicobacter pylori*

## 1 | INTRODUCTION

Gastric cancer kills 50 000 people per year in Japan, making it the third deadliest cancer by number of deaths. Salt, smoking, and charred fish and meat, as well as genetic factors, have conventionally been considered important causes of gastric cancer, but it is now known that 98% of gastric cancer cases in Japan are caused by *Helicobacter pylori*, and it would not be unreasonable to basically

consider the majority of gastric cancer cases as an infection caused by *H. pylori*.<sup>1</sup>

The International Agency for Research on Cancer (IARC) of the WHO classified *H. pylori* as a carcinogen in 1994.<sup>2</sup> In 2008, a multicenter randomized clinical study undertaken by the Japanese JAPANGAST Study Group showed that *H. pylori* eradication reduces the risk of second gastric cancer after endoscopic mucosal resection of early gastric cancer to approximately one-third that of patients

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. Cancer Science published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association

who do not undergo eradication therapy.<sup>3</sup> These results indicate the benefit of *H. pylori* eradication in preventing gastric cancer. In 2014, the IARC officially recognized the preventive effect of *H. pylori* eradication against gastric cancer and called for countries to devise country-specific gastric cancer prevention plans that incorporate *H. pylori* eradication.<sup>4</sup>

Prevention plans in Japan have traditionally emphasized secondary prevention by barium X-ray to detect gastric cancer at an early stage. However, annual gastric cancer deaths in Japan held steady at approximately 50 000 for a period of almost 40 years, and the introduction of screening tests barely affected the number of deaths.<sup>5</sup> In February 2013, Japan became the first country in the world to cover *H. pylori* eradication for chronic gastritis (*H. pylori* gastritis) under its National Health Insurance (NHI) system. This expansion of coverage enables physicians to test for *H. pylori* in patients with endoscopy-proven chronic gastritis and undertake NHI-covered eradication therapy in patients who test positive. Use of *H. pylori* eradication therapy has increased dramatically since then, and the treatment has been carried out approximately 9 million times over the 5 years after being covered by NHI.<sup>6-8</sup> As a result, gastric cancer deaths in Japan have begun to decrease.<sup>7</sup>

We undertook an epidemiological analysis to investigate the effects of expanded NHI coverage for *H. pylori* eradication therapy on gastric cancer deaths using data from Japanese Ministry of Health, Labour and Welfare (MHLW) reports and "Cancer Statistics in Japan - 2018" published by the Foundation for Promotion of Cancer Research.

## 2 | MATERIALS AND METHODS

### 2.1 | Sourcing of cancer mortality data and statistical analysis

Data on deaths from gastric cancer and other cancers were obtained from vital statistics published by the MHLW and "Cancer Statistics in

Japan - 2018" published by the Foundation for Promotion of Cancer Research.<sup>9</sup> Changes in the number of deaths were plotted on graphs using Microsoft Excel. The expected and the observed number of deaths from gastric cancer were compared using a  $\chi^2$  test.

To evaluate time trends in gastric cancer deaths, the number of deaths from 1958 to 2018 were analyzed using a Joinpoint regression analysis program obtained from the NCI.<sup>10,11</sup>

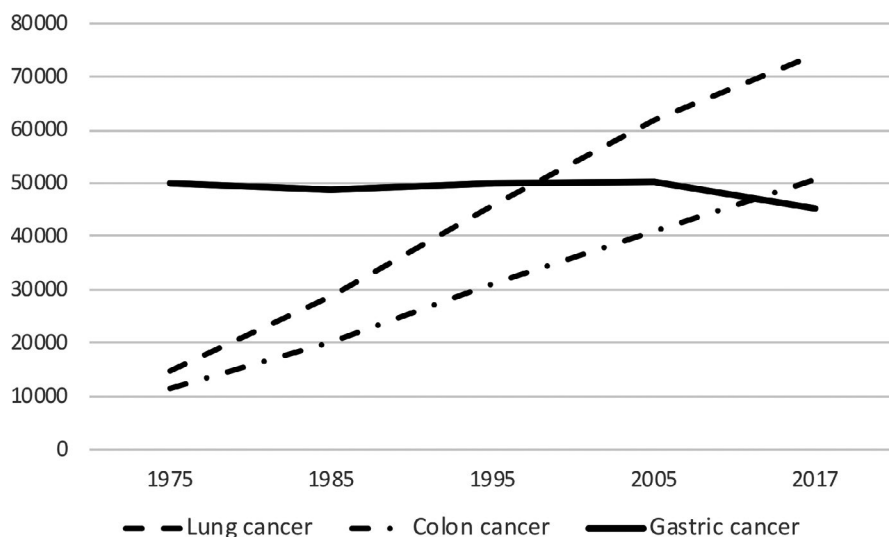
## 3 | RESULTS

### 3.1 | Changes in cancer deaths in Japan over time

In 1975, gastric cancer was the deadliest cancer in Japan by number of deaths, killing approximately 3.5 times more people than lung cancer and 4 times more people than colorectal cancer. Gastric cancer deaths in Japan later held steady at approximately 50 000 per year, but lung cancer and colorectal cancer deaths continued to increase, and surpassed gastric cancer deaths in 1996 and 2014, respectively (Figure 1).

### 3.2 | Deaths from gastric cancer

The number of deaths from gastric cancer was 48 427 in 2013, 47 903 in 2014, 46 659 in 2015, 45 531 in 2016, 45 210 in 2017, and 44 192 in 2018 showing a decreasing trend after widening of the NHI indications for *H. pylori* eradication therapy. The decrease in the number of gastric cancer deaths to 44 192 in 2018, where all *P* values for  $\chi^2$  tests were less than  $1.0 \times 10^{-10}$ , represented a fall of 11.8% in the 6 years after the indications for *H. pylori* eradication therapy were expanded (Figure 2). We also carried out Joinpoint analyses. The 3 joinpoints model on mortality from 1958 to 2017 shows that the tendency of gastric cancer mortality changed around 2010, and the mortality of gastric cancer has decreased since then (Figure 3).



**FIGURE 1** Annual number of lung, colon, and gastric cancer deaths in Japan, 1975-2017

Approval of Insurance

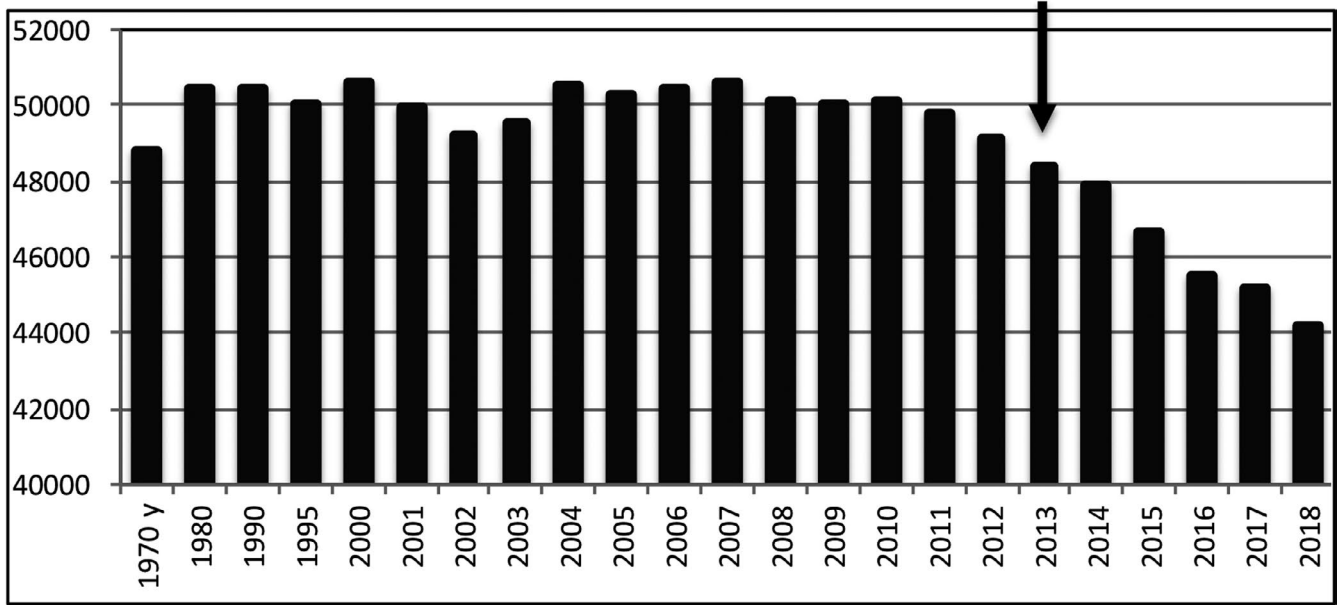
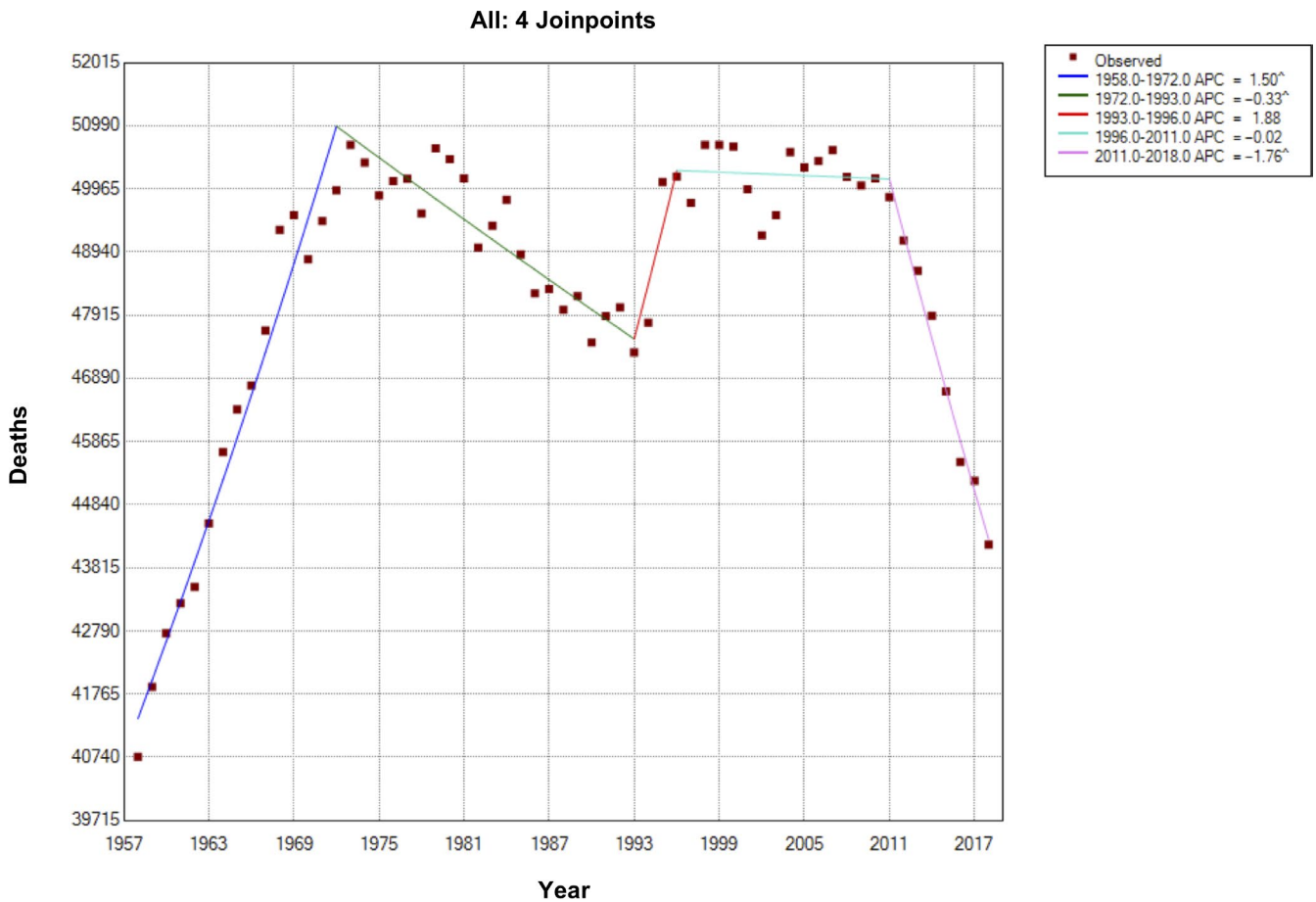


FIGURE 2 Changes in gastric cancer deaths in Japan, 1970-2018



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: 4 Joinpoints.

FIGURE 3 Result of Joinpoint analysis in gastric cancer deaths in Japan, 1957-2017

### 3.3 | Changes in lung cancer and colorectal cancer deaths over time

Analysis of lung cancer deaths by age group revealed that, around 1974, most deaths occurred in people aged in their 70s, followed by people in their 60s, and there were very few deaths among people aged 80 years and older. Deaths among people aged 80 years and older began to increase when overall lung cancer deaths began to increase rapidly in the 1980s, and came to surpass the number of deaths in any other age group in 2007. The number of deaths in this age group was over 30 000 in 2014, and is still increasing today (Figure 4). Colorectal cancer deaths have shown a similar trend to lung cancer deaths. The number has soared over the years. Deaths among people aged 80 years and older increased rapidly, and surpassed the number of deaths in any other age group in 2002. The number of deaths in this age group was over 20 000 in 2010, and is still increasing today (Figure 5).

### 3.4 | Changes in gastric cancer deaths in Japan over time

Gastric cancer deaths across age groups have changed in different ways than lung cancer and colorectal cancer deaths. Deaths of people younger than 50 years have been decreasing since around the 1960s, and are still decreasing today. Deaths of people aged in their 60s and 70s have gradually decreased since around the 1980s. In contrast, deaths of people aged 80 years and older have been continually

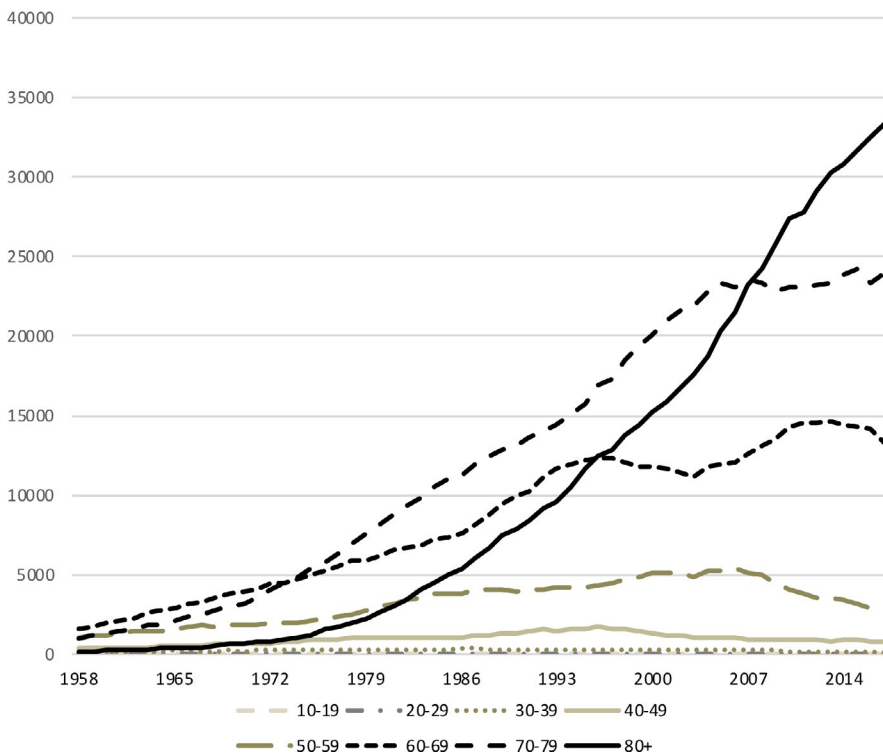
increasing. They surpassed the number of deaths in any other age group in 2004, and continue to increase to this day (Figure 6).

When gastric cancer deaths by age group are plotted onto a histogram, it shows that deaths of people younger than 80 years have been decreasing since around 1970, whereas overall gastric cancer deaths across all age groups have remained unchanged at approximately 50 000 per year for nearly 40 years. However, overall gastric cancer deaths have clearly been decreasing since eradication therapy for *H. pylori* gastritis became covered by NHI, despite the increase in deaths of people aged 80 years and older (Figure 7). Gastric cancer deaths in people younger than 80 years decreased by 23.4% from 2011 to 2018.

The proportion of people aged 80 years and older in the total population of Japan has been consistently increasing since the 1960s, and this increase matches the increase in the number of deaths from lung cancer, colorectal cancer, and gastric cancer in the 80 and older age group (Figure 8).

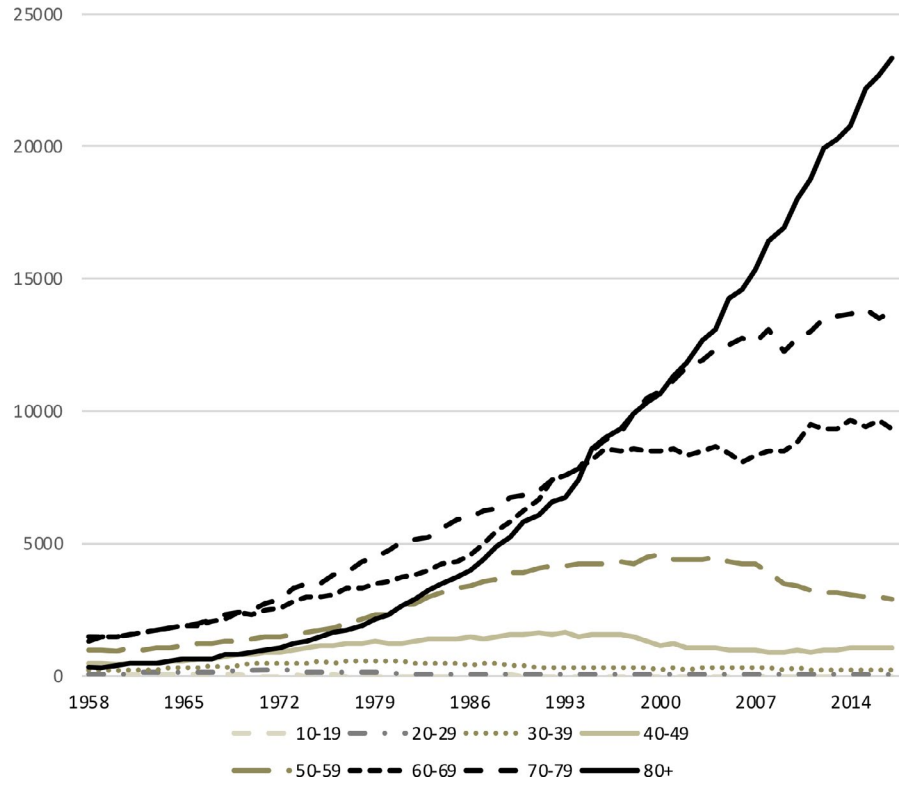
### 3.5 | Number of deaths and mortality rate from gastric cancer by age group in 2018

A total of 44 189 people died of gastric cancer in Japan in 2018. People aged 80 years and older accounted for 49% of those deaths ( $n = 21\ 596$ ). The mortality rate per 100 000 population was just 14.6 deaths in the 50-59 years age group, but increased dramatically to 155.6 in the 80-84 years age group, 213.6 in the 85-89 age group, and 269.5 in the 90 and older age group, with the highest rate seen in the 90 and older age group (Figure 9).

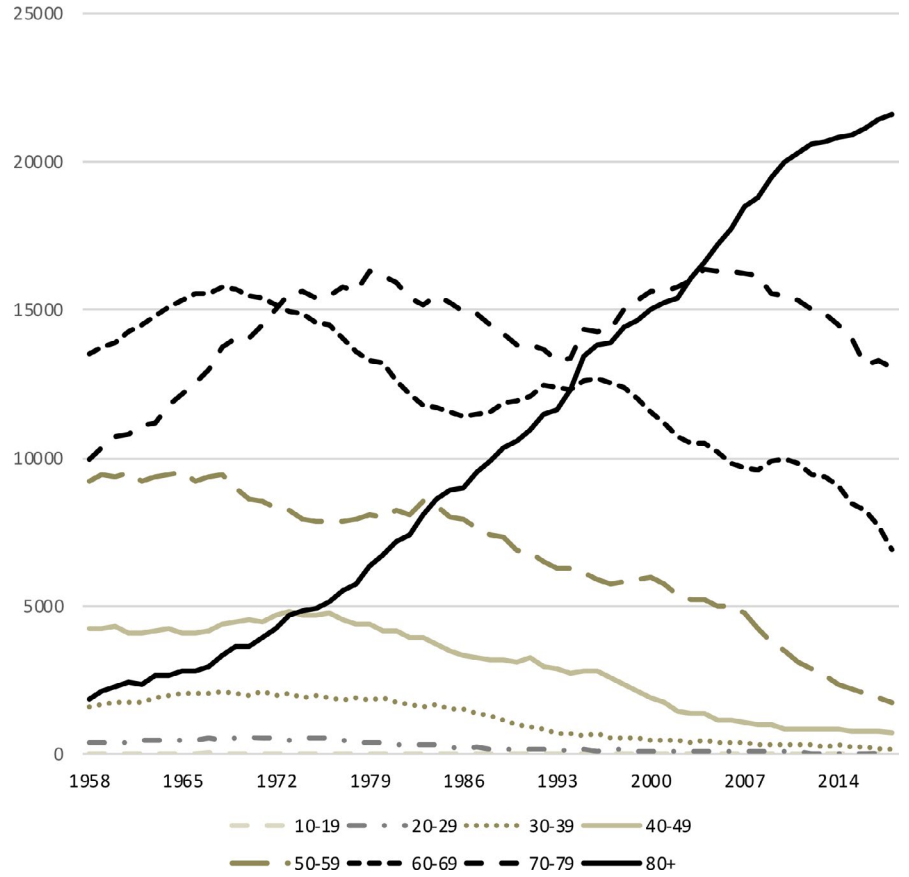


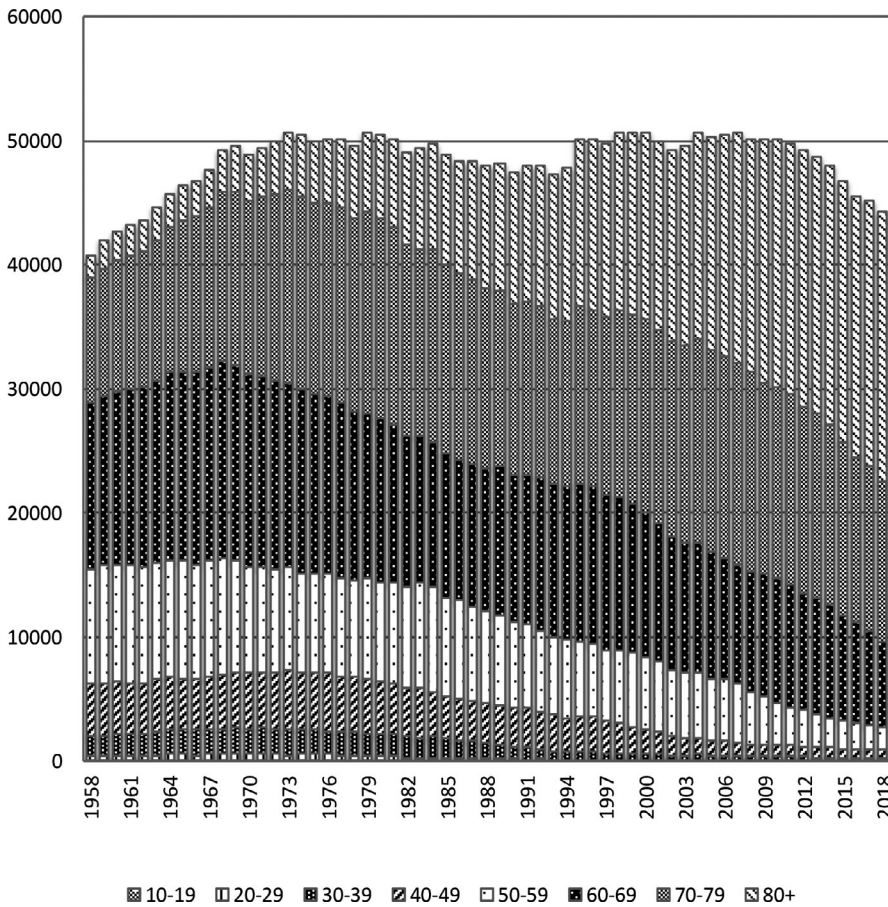
**FIGURE 4** Number of age-related lung cancer deaths in Japan, 1958-2014

**FIGURE 5** Number of age-related colon cancer deaths in Japan, 1958-2014

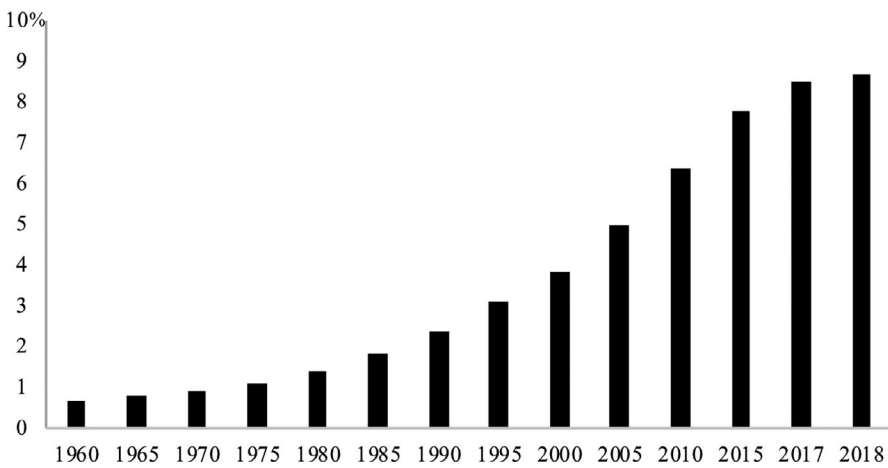


**FIGURE 6** Number of age-related gastric cancer deaths in Japan, 1958-2014





**FIGURE 7** Number of age-related gastric cancer deaths in Japan: stratified analysis, 1958-2018



**FIGURE 8** Rate of total population of people aged over 80 years in Japan

#### 4 | DISCUSSION

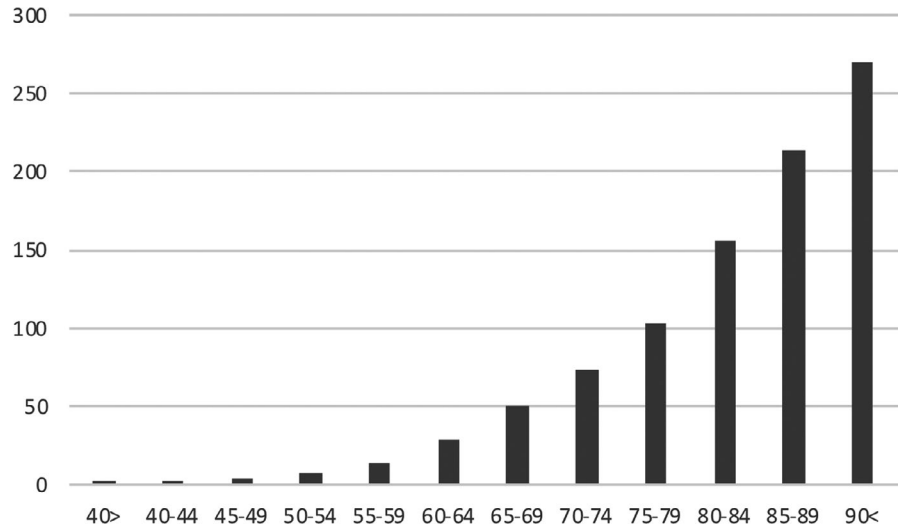
In the 6 years since *H. pylori* eradication therapy became covered by NHI for the indication of chronic gastritis, its usage has increased dramatically, and gastric cancer deaths are clearly decreasing. Approximately 1.5 million patients received eradication therapy each year after the indications for *H. pylori* eradication therapy were expanded to include chronic gastritis, with approximately 6 million patients being treated by eradication therapy over 4 years.<sup>7</sup> According to NHI criteria, the diagnosis of gastritis must be established by endoscopy before eradication therapy is carried out and this increased requirement for endoscopy could lead to detection

of gastric cancer in many patients. The fact that patients diagnosed with *H. pylori* gastritis required gastroscopy to receive eradication therapy resulted in a rapid increase in gastroscopy procedures along with the prescription of *H. pylori* eradication therapy.

The current deadliest cancers in Japan by number of deaths are lung cancer, colorectal cancer, and gastric cancer, in that order. Back in 1975, gastric cancer was by far the deadliest cancer in Japan, killing approximately 3.5 times more people than lung cancer and 4 times more people than colorectal cancer. The ranking has switched considerably over the 40 years since that point, and lung cancer is now the deadliest cancer and gastric cancer the third deadliest. Lung cancer deaths have soared, and surpassed gastric cancer deaths in 1996.



**FIGURE 9** Age-specific gastric cancer mortality rates per 100 000 people in Japan, 2018



One trend of note is the increase in the proportion of lung cancer deaths among elderly adults aged 80 years and older.<sup>12</sup> Although lung cancer deaths among people younger than 80 years plateaued around 2002, deaths among people aged 80 years and older have continued to increase, and this is causing the overall number of lung cancer deaths to increase (Figure 3). Colorectal cancer deaths have similarly been increasing over the years, but deaths of people younger than 80 years stopped increasing around 2004. However, deaths of people aged 80 years and older have continued to increase rapidly, and this is causing the overall number of colorectal cancer deaths to increase (Figure 4). Gastric cancer deaths show a clearly different pattern from lung and colorectal cancer deaths. The annual number of gastric cancer deaths in Japan held steady at approximately 50 000 for approximately 40 years. Analysis by age group showed that deaths of people aged 80 years and older soared during this time, surpassed the number of deaths in any other age group in 2005, and continued to increase after that point. Deaths of people younger than 80 years began decreasing in the late 1970s, and clearly began decreasing further when *H. pylori* eradication therapy for *H. pylori* gastritis started to be covered by NHI in 2013 (Figure 5). It can be concluded that the increase in deaths of people aged 80 years and older cancelled out this decrease in deaths in almost all age groups, and was what caused the overall number of deaths to remain at approximately 50 000 for 40 years. Since 2013, however, the overall number of deaths in all age groups, including people aged 80 years and older, has actually been decreasing (Figures 2 and 6). Joinpoint regression analysis of the period from 1958 to 2016 showed that gastric cancer deaths began changing in 2010 and have decreased since that point.<sup>7</sup> This is likely attributable not to eradication therapy directly, but rather to the fact that a larger proportion of gastric cancers are now detected at an early stage due to increased use of endoscopy. The fact that endoscopy was made mandatory for diagnosis and treatment of *H. pylori* infection to be covered by NHI is likely a significant factor in this.

Unlike with lung cancer and colorectal cancer, the number of gastric cancer deaths in people younger than 80 years has been decreasing for a long time. One cause of this could be reduced salt

intake among Japanese people. Efforts to reduce salt intake in the Japanese diet began around 1965, and continue to this day.<sup>13</sup> Salt alone does not readily cause gastric cancer, but salt intake is known to be positively correlated with the carcinogenic potential of *H. pylori* in infected patients.<sup>14,15</sup> The *H. pylori* infection rate among Japanese people aged 40 years and older was over 70% until the 1980s,<sup>16,17</sup> which suggests that high salt intake increased the incidence of gastric cancer. A decrease in salt intake, along with the dramatic increase in usage of *H. pylori* eradication therapy after its approval for *H. pylori* gastritis in 2013, produced a powerful shift toward emphasizing primary prevention of gastric cancer, and this in turn caused a further clear decrease in gastric cancer deaths. However, deaths of elderly adults aged 80 years and older have continued to increase at the same time. The average lifespan of Japanese people is increasing, and Japan ranks second best in the world for longevity. This has caused the proportion of the population aged 80 years and older to increase, to the point where it is approaching 10% (Figure 7). These changes in population composition roughly correspond to changes in deaths from lung cancer, colorectal cancer, and gastric cancer among people aged 80 years and older seen on the graph, and support the premise that very elderly adults have come to account for a larger proportion of all cancer deaths in recent years. Deaths of people aged 80 years and older account for the largest proportion of deaths among all age groups for each of the 3 deadliest cancers in Japan (lung cancer, colorectal cancer, and gastric cancer), and account for nearly 50% of total deaths from these cancers combined. This suggests that measures targeting very elderly adults are necessary to drastically reduce cancer deaths, not only from gastric cancer but also from lung cancer and colorectal cancer. However, it will likely be a major challenge to devise measures targeting elderly adults aged 80 years and older because people in this age group often have many comorbidities, use a large number of medications, have reduced physiological function, have limited cognitive function, and vary greatly in their individual characteristics.<sup>18</sup>

Gastric cancer mortality per 100 000 population was calculated for each age group using statistics from 2018. Mortality

increased along with age group, and was more than 5 times higher in people in the 90 and older age group than in the 65–69 years age group (Figure 8).<sup>9</sup> This continued increase in deaths with age even past 80 years will make measures against gastric cancer in elderly adults considerably challenging. In fact, people aged 80 years and older undergo fewer endoscopies even after correction for age.<sup>19</sup> Therefore, there are fewer opportunities to detect gastric cancer early when it is highly likely to be curable in people aged 80 years and older. Reducing gastric cancer deaths among people aged 80 years and older will require increasing the frequency of endoscopies in this age group. To achieve this, Ab tests for *H. pylori* should proactively be carried out in very elderly adults, and endoscopy undertaken for those who test positive. Doing so might enable greater detection of early gastric cancer that could be cured by minimally invasive endoscopic surgery in people aged 80 years and older.

The number of gastric cancer deaths excluding those of people aged 80 years and older, who have a high mortality rate and are not easy to target with preventive measures, decreased by 23.4% from 2011 to 2018. Japan's baby boomer generation, which account for a massive proportion of the population, have now reached 70 years of age, the typical age when cancer tends to develop. Consequently, if nothing is done to address gastric cancer deaths, they could reach 60 000 in 2020.<sup>4</sup> However, 9 million people underwent *H. pylori* eradication therapy in the 5 years after it was covered by NHI for *H. pylori* gastritis,<sup>6,7</sup> and in the sixth year, the number of gastric cancer deaths fell significantly by 11.8% from the 40-year plateau of approximately 50 000 deaths.<sup>7</sup> This decrease jumps to 23.4% for people younger than 80 years. Our research showed that prevention of all cancers, not only gastric cancer, is extremely difficult in people aged 80 years and older, which indicates that cancer prevention measures must be considered separately for people younger than 80 years and people aged 80 years and older. However, it is unclear whether our results apply to cancer prevention programs in all countries. Since the time that *H. pylori* eradication therapy was approved by NHI for gastritis, members of the Japanese Society for Helicobacter Research, the Japanese Society of Gastroenterology, and the Japan Gastroenterological Endoscopy Society have led the effort to eliminate gastric cancer through this therapy.<sup>20</sup> It is now apparent that the road to eliminating gastric cancer through eradication therapy, which once seemed so straightforward, is in fact blocked by the obstacle of very elderly adults aged 80 years and older. To save very elderly adults from death by gastric cancer, it will be necessary to actively promote endoscopy as a secondary preventive measure beyond primary preventive measures, such as *H. pylori* eradication. Adoption of the practice of screening for *H. pylori* is a critical step to achieving this goal, and it appears that endoscopy must be made mandatory for those who test positive.

There are several limitations in this study. First, total numbers of deaths of gastric, colon, and lung cancers are used in this study, and they might be affected by many factors. In this study, the effect of factors with strong influence is taken into account, and the effect of other factors might be tiny and negligible. Second, instead of mortality rate, total numbers of deaths were used in this study. It is true

that mortality rate is more often used as a marker in studies like the present one. As the present study discusses a prevention strategy, however, the numbers of deaths, which indicate the size of what is to be prevented, seem appropriate as a marker.

## ACKNOWLEDGMENT

We thank Yingsong Lin, Department of Public Health, Aichi Medical University, for his contribution to the Joinpoint analysis.

## CONFLICT OF INTEREST

We declare no competing interests.

## ORCID

Masahiro Asaka  <https://orcid.org/0000-0001-7768-3434>

## REFERENCES

- Blaser MJ. Helicobacter pylori and the pathogenesis of gastroduodenal inflammation. *J Infect Dis*. 1990;161:626-633.
- Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. *IARC Monogr Eval Carcinog Risks Hum*. 1994;61:1-241.
- Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet*. 2008;372:392-397.
- IARC Working Group Reports 2013 Volume 8, Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer. [http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/Helicobacter\\_pylori\\_Eradication.pdf](http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/Helicobacter_pylori_Eradication.pdf)
- Hamashima C, Shibuya D, Yamazaki H, et al. The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol*. 2008;38:259-267.
- Fujimori K. Evaluation of *H. pylori* eradication by electronic receipt analysis in Japan. *GI Forefront*. 2015;11:138-140.
- Tsuda M, Asaka M, Kato M, et al. Effect on Helicobacter pylori eradication therapy against gastric cancer in Japan. *Helicobacter*. 2017;22:e12415.
- Hiroi S, Sugano K, Tanaka S, Kawakami K. Impact of health insurance coverage for Helicobacter pylori gastritis on the trends in eradication therapy in Japan: retrospective observational study and simulation study based on real-world data. *BMJ*. 2017;7:e015855.
- Trends in site-specific crude mortality rate 1965–2014. *Cancer Statistics in Japan-2018*, Tokyo, Japan, 2018; pp 40. [http://ganjoho.jp/data/reg\\_stat/statistics/brochure/2018/cancer\\_statistics\\_2018.pdf](http://ganjoho.jp/data/reg_stat/statistics/brochure/2018/cancer_statistics_2018.pdf)
- Katanoda K, Kamo K, Saika K, et al. Short-term projection of cancer incidence in Japan using an age-period interaction model with spline smoothing. *Jpn J Clin Oncol*. 2014;44:36-41.
- Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19:335-351.
- Population dynamics survey; Vital Statistics Japan 2018, Ministry of Health, Labour and Welfare.
- Japanese salt intake. 2015 For people, for life, for the future <https://www.mhlw.go.jp/stf/houdou/0000041733.html>
- Fox JG, Dangler CA, Taylor NS, et al. High-salt diet induced gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. *Cancer Res*. 1999;59:4823-4828.
- Kato S, Tsukamoto T, Mizoshita T, et al. High salt diets dose-dependently promote gastric chemical carcinogenesis in Helicobacter



- pylori-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. *Int J Cancer*. 2006;119:1558-1566.
16. Asaka M, Kimura T, Kudo M, et al. Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic Japanese population. *Gastroenterology*. 1992;102:760-766.
  17. Kamada T, Haruma K, Ito M, et al. Time trend in *Helicobacter pylori* infection and atrophic gastritis over 40 years in Japan. *Helicobacter*. 2015;20:192-198.
  18. Iwamoto M, Nakamura F, Higashi T. Estimated life expectancy and risk of death from cancer by quartiles in the older Japanese population: 2010 vital statistics. *Cancer Epidemiol*. 2014;38:511-514.
  19. NDB Database (Ministry of Health, Labour and Welfare website). <http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000139390.html>.
  20. Asaka M, Kato M, Sakamoto N. Roadmap to eliminate gastric cancer with *Helicobacter pylori* eradication and consecutive surveillance in Japan. *J Gastroenterol*. 2014;49:1-8.

**How to cite this article:** Asaka M, Kobayashi M, Kudo T, et al. Gastric cancer deaths by age group in Japan: Outlook on preventive measures for elderly adults. *Cancer Sci*. 2020;111:3845-3853. <https://doi.org/10.1111/cas.14586>