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ORIGINAL ARTICLE

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Effect on *Helicobacter pylori* eradication therapy against gastric cancer in Japan

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Abstract

Background: In Japan, there have been approximately 50 000 deaths from gastric cancer annually for over 40 years with little variation. It has been reported that most gastric cancers in Japan are caused by *Helicobacter pylori* infection. *H. pylori* eradication therapy was approved for patients with chronic gastritis by the Japanese national health insurance scheme in February 2013 for patients with an endoscopic diagnosis of chronic gastritis is positive for *H. pylori*. We examined the effect on gastric cancer death rate 4 years after expansion of health insurance coverage.

Aim: We conducted an epidemiological study and analyzed trends in prescription for *H. pylori* eradication therapy. We used the electronic medical claims database from Hokkaido, Japan to evaluate the impact of expansion of national health insurance coverage for *H. pylori* eradication therapy on deaths from gastric cancer.

Methods: Data on deaths from gastric cancer were obtained from the Japanese Ministry of Health, Labour and Welfare and the Cancer Statistics in Japan (2015). Analysis of electronic claims records was performed using the National Database, mainly focusing on Hokkaido. Prescriptions for *H. pylori* eradication therapy and the number of patients treated for gastric cancer were also extracted from the Hokkaido database.

Results: Approximately 1.5 million prescriptions for *H. pylori* eradication therapy were written annually. Gastric cancer deaths fell each year: 48 427 in 2013, 47 903 in 2014, 46 659 in 2015, and 45 509 in 2016, showing a significant decrease after expansion of insurance coverage for *H. pylori* eradication therapy ($P<.0001$).

Conclusions: Prescriptions for *H. pylori* eradication therapy increased markedly after approval of the gastritis indication by the national health insurance scheme and was associated with a significant decrease in gastric cancer deaths.

KEYWORDS
gastric cancer, gastric cancer deaths, prevention of gastric cancer

1 | INTRODUCTION

Helicobacter pylori causes chronic gastric mucosal inflammation which underlies various disorders of the stomach,[1-5] including atrophic gastritis from which intestinal type gastric cancer can develop. It has also been reported that *H. pylori* gastritis is etiologically associated with gastroduodenal ulcers, gastric mucosa-associated lymphoid tissue lymphoma, functional dyspepsia, hyperplastic gastric polyps, idiopathic thrombocytopenic purpura, and undifferentiated gastric cancer.[2,6,7] The International Agency for Research on Cancer of the World Health Organization designated *H. pylori* as a carcinogen for gastric cancer in 1994.[8] A multicenter randomized study performed by the Japan GAST Study Group showed that *H. pylori* eradication therapy decreased the incidence of secondary gastric cancer by approximately two-thirds in patients undergoing endoscopic mucosal resection of early gastric cancer,[9] demonstrating a preventive effect of *H. pylori* eradication therapy against gastric cancer. It has been suggested that *H. pylori* infection causes more than 95% of all gastric cancers in Japan and Korea.[10-12]

It has long-placed emphasis on secondary prevention of gastric cancer with use of barium studies for early detection. The IARC recommended that suitable policies for preventing gastric cancer including *H. pylori* eradication therapy should be designed for each country worldwide.[13]

Japan has long-placed emphasis on secondary prevention of gastric cancer with use of barium studies for early detection.[14] However, the number of gastric cancer deaths has remained stable at approximately 50 000 per year over the past 40 years in Japan, showing almost no change after the start of screening with barium studies.[15,16] *H. pylori* eradication therapy for chronic gastritis (*H. pylori* gastritis) was approved for coverage by the Japanese national health insurance (NHI) scheme in February 2013. According to the Ministry of Health, Labour and Welfare (MHLW) notification, eradication therapy is only covered by NHI when a patient has endoscopically diagnosed chronic gastritis and is positive for *H. pylori*. After this change, prescription of *H. pylori* eradication therapy increased markedly and approximately 6 million patients have been treated in the 4 years since approval.[17] This raises the possibility that deaths from gastric cancer may have begun to decrease in Japan.

We conducted an epidemiological study using official reports of the MHLW and the Cancer Statistics in Japan (2015) published by the Foundation for Promotion of Cancer Research. We analyzed the trends in prescribing *H. pylori* eradication therapy and the number of patients who received treatment for gastric cancer by reviewing electronic medical claims data to evaluate the impact of expanded health insurance coverage for *H. pylori* eradication therapy on death from gastric cancer.

2 | METHODS

2.1 | Prescription of *H. pylori* eradication therapy

Prescription of *H. pylori* eradication therapy throughout Japan was calculated using the claims database for Hokkaido (the north island of Japan) combined with the National Database (NDB). We investigated the prescriptions for primary eradication therapy for *H. pylori*. The number of patients receiving primary eradication therapy throughout Japan was calculated by determining the actual number of treatment pack formulation for primary eradication using data from the NDB.[18] The NDB contains information about claims and specific health examinations, and allows easy retrieval of claims data. Using the anonymized electronic medical claims in this database, we extracted the number of prescription of treatment packs for primary eradication therapy (packs containing Lansap and Rabecure) from the first open data published by the MHLW (April 2014 to March 2015).[18] During this period, 7 223 983 treatment packs of medication were prescribed for primary eradication therapy. Since the duration of treatment is 7 days, this was sufficient medication for primary eradication therapy in 1 031 998 patients.

The claims database for Hokkaido contains anonymized claims data from the NHI scheme and the medical care system for very elderly patients (aged 75 years or older) in all cities, towns, and villages of Hokkaido. Information has been collected for this database independently of the NDB by the Hokkaido government and Hokkaido University in collaboration since 2009 when the use of electronic medical claims has become widespread. In this study, we also investigated prescriptions of *H. pylori* eradication therapy in Hokkaido using the Hokkaido claims database.

The number of patients receiving primary eradication therapy with pack formulations and those receiving equivalent medications prescribe separately as current regimens for *H. pylori* eradication therapy have become more diversified. Accordingly, we investigated the use of two treatment pack formulations (Lansap and Rabecure packs) and concurrent use of a proton-pump inhibitor (PPI) and/or a potassium-competitive acid blocker (P-CAB), amoxicillin, and clarithromycin as primary eradication therapy. The number of prescriptions was calculated for omeprazole, lansoprazole, esomeprazole, and rabeprazole as PPIs, along with the number for vonoprazan as a P-CAB. If medications were available as generic formulations, these were also included in calculation. Separate prescription for amoxicillin and clarithromycin for primary eradication therapy was defined as separate prescription for 7 days from the same day in combination with a PPI or P-CAB for the same period. Therefore, the number of Lansap and Rabecure packs prescribed from April 2014 to March 2015 was calculated from the Hokkaido claims database. Then we calculated the annual prescription of *H. pylori* eradication therapy in Hokkaido by combining the use of pack formulations (Lansap and Rabecure packs) and the concurrent use of PPI/P-CAB, amoxicillin, and clarithromycin prescribed for the same period as primary eradication therapy. A total of 27 841 received *H. pylori* eradication therapy in Hokkaido during this period based on the number of prescriptions.

Using the same approach, we extracted the number of patients receiving primary eradication therapy with treatment pack formulations and for separately prescribed drugs between April 2010 and March 2017 from the Hokkaido claims database and calculated the number of patients receiving primary eradication therapy throughout Japan based on the extracted data.

2.2 | Calculation of deaths from gastric cancer

The number of deaths from gastric cancer was determined from data provided by the MHLW, the National Cancer Center Japan, and the Cancer Statistics in Japan (2015) published by the Foundation for Promotion of Cancer Research to evaluate the influence of *H. pylori* eradication therapy being approved for health insurance coverage on death from this cancer. Information on deaths from gastric cancer was extracted from Vital Statistics data (1958 to 2016) in the Cancer Registry and Statistics (Cancer Information Service, National Cancer Center, Japan),[19] and the annual numbers were graphed using Excel. Gastric cancer mortality predicted by a model that used age, calendar year, and their interactions as explanatory variables was obtained from Cancer Incidence by Age Group: Monitoring Cancer Incidence in Japan (national estimates from 1975 to 2012) and actual cancer mortality was extracted from the from Vital Statistics (actual data from 1975 to 2015).[20] Then the expected and the observed number of deaths from gastric cancer were compared using a chi-square test. The expected mortality was provided by National Cancer Center.[21]

To evaluate whether the discrepancy between the expected and the observed deaths of gastric cancer is transient or not, joinpoint analysis[21] was performed using annual gastric cancer mortality from 1958 to 2016 using a program provided by National Cancer Institute (https://surveillance.cancer.gov/joinpoint/download).

3 | RESULTS

3.1 | Prescription of *H. pylori* eradication therapy

The number of patients receiving primary *H. pylori* eradication therapy from April 2010 to November 2016 was calculated from the number of prescriptions in the Hokkaido database (Figure 1); 27 841 patients received primary eradication therapy in Hokkaido from April 2010 to November 2016. Similarly, it was calculated that the number of patients receiving primary eradication therapy in Hokkaido was 12 410 in 2010, 11 459 in 2011, 11 280 in 2012, 27 324 in 2013, 27 841 in 2014, and 31 979 in 2015. When the number of patients receiving primary *H. pylori* eradication therapy throughout Japan was estimated from these data, it was 613 675 in 2010, 566 648 in 2011, 602 564 in 2012, 1 459 615 in 2013, 1 487 233 in 2014, 1 557 318 in 2015 and 1 400 641 in 2016 (Figure 2).

Thus, the number of patients receiving *H. pylori* eradication therapy showed a rapid increase after the indications for *H. pylori* eradication therapy were expanded to include *H. pylori* gastritis in February 2013. Approximately 6 million patients received *H. pylori* eradication therapy over 12 years after NHI rebates for such therapy became available in 2000, while 4.3 million patients have undergone

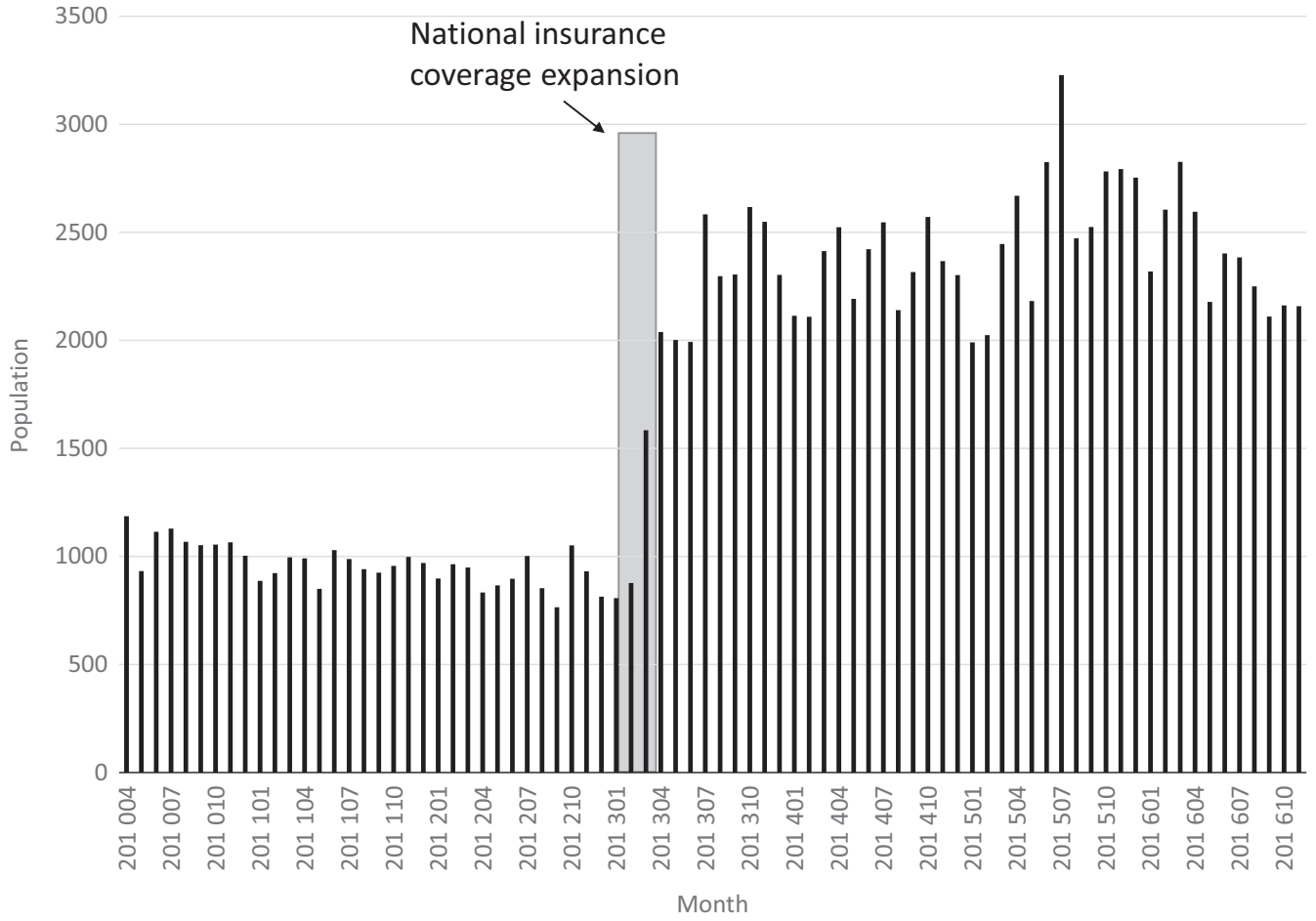

FIGURE 1 Numbers of *Helicobacter pylori* eradication in Hokkaido

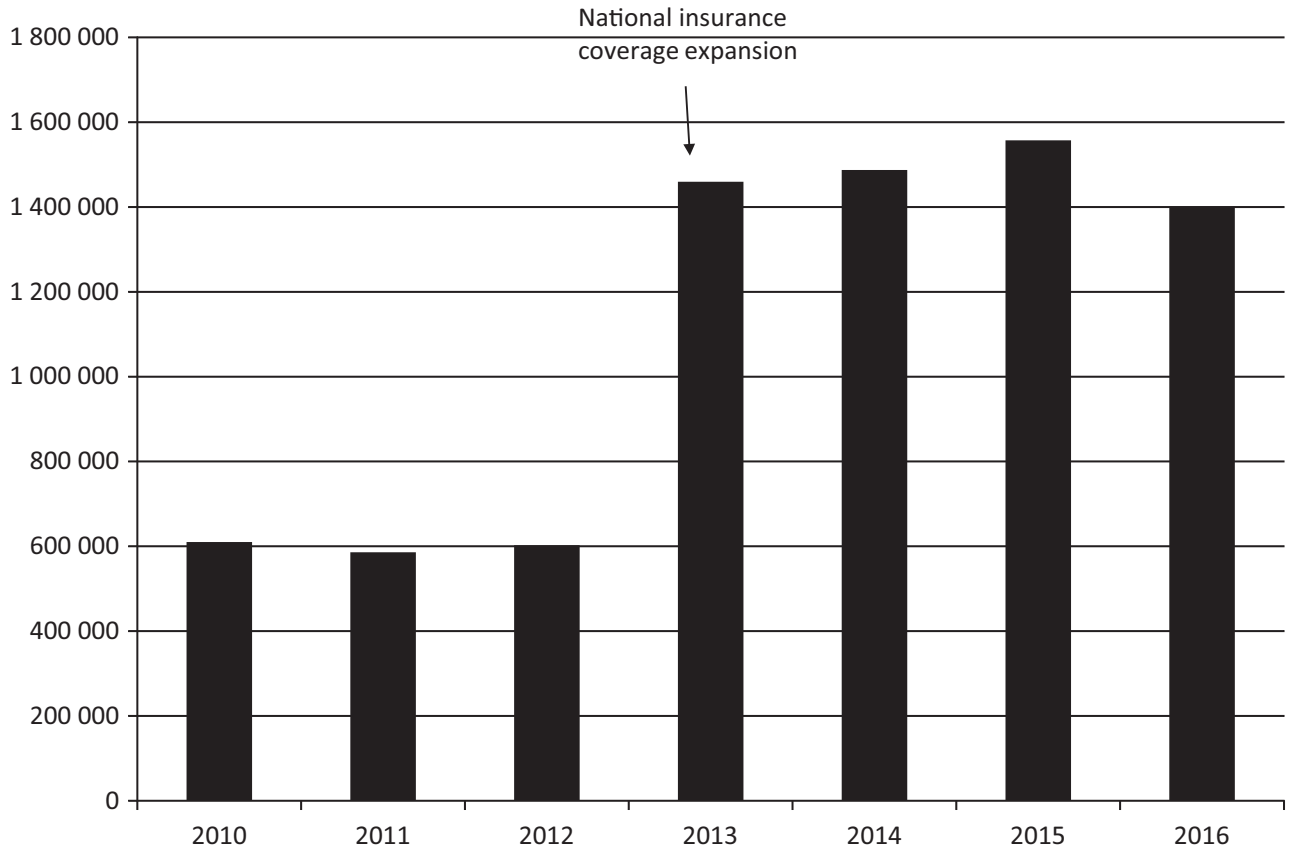

FIGURE 2 Numbers of *Helicobacter pylori* eradication in Japan

H. pylori eradication therapy in the 3 years since the indications were expanded. It can, therefore, be presumed that approximately 10 million patients have undergone eradication therapy to date. When primary eradication therapy for *H. pylori* was defined as prescription of one of the two treatment pack formulations [Lansap (triple therapy pack for *H. pylori* eradication that contains lansoprazole, amoxicillin hydrate, clarithromycin) and Rabecure (triple therapy pack for *H. pylori* eradication that contains rabeprazole, amoxicillin hydrate, and clarithromycin)], as well as the antibiotics plus omeprazole, lansoprazole, esomeprazole, and rabeprazole or vonoprazan, it was found that the annual prescription of *H. pylori* eradication therapy increased 2.42 times (1 351 172/557 796) compared with before the indications for eradication therapy were expanded. This trend was stable.

3.2 | Death from gastric cancer

The number of deaths from gastric cancer was 48 632 in 2013, 47 903 in 2014, 46 659 in 2015, and 45 509 in 2016 showing a decreasing trend after widening of the NHI indications for *H. pylori* eradication therapy, according to cancer mortality data (1958 to 2014) from the Vital Statistics in the Cancer Registry and Statistics[19] (Figure 3). The decrease in the number of gastric cancer deaths to 45 509 in 2016 represented a fall of 9.2% in the 4 years after the indications for *H. pylori* eradication therapy were expanded (Figure 3). The expected deaths of gastric cancer using the previously observed data are shown by the National Cancer Center on its homepage.[21] From 2013 to 2016, discrepancies were observed between the observed and the expected gastric cancer deaths. Observed/Expected deaths (O/E ratio) were 48 632/50 000 (0.97) in 2013, 47 903/50 300 (0.95) in 2014, 46 659/49 800 (0.94) in 2015, and 45 509/48 500 (0.94) in 2016, where all *P*-values for chi-square tests were less than 1.0×10^{-10}. We performed, joinpoint analyzes. The three joinpoints model on mortality from 1958 to 2016 shows that tendency of gastric cancer mortality changed around 2010, and the mortality of GC has decreased since then.

4 | DISCUSSION

Prescription of *H. pylori* eradication therapy increased markedly in the 4-year period after Japanese NHI coverage for *H. pylori* eradication therapy was expanded to include chronic gastritis, and the number of deaths from gastric cancer decreased significantly during the same period. The increase in the prescription of eradication therapy is attributable to the fact that treatment became available for all of million Japanese patients with *H. pylori* gastritis thanks to insurance coverage, in addition to the conventional NHI indications such as gastroduodenal ulcer, gastric mucosa-associated lymphoid tissue lymphoma, postendoscopic resection of early gastric cancer, and idiopathic thrombocytopenic purpura. After eradication therapy for *H. pylori* gastritis was also approved, patients with *H. pylori* gastritis could receive eradication

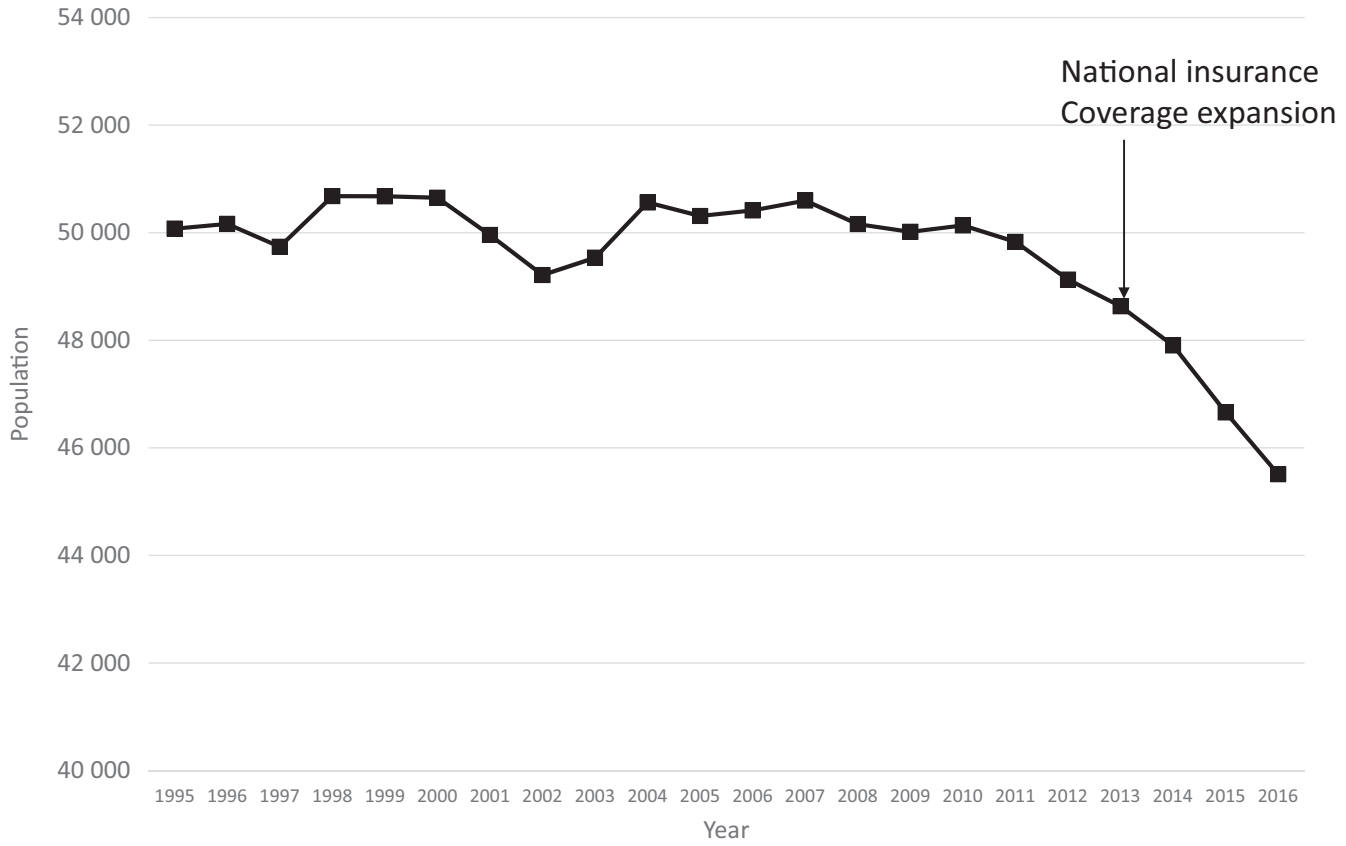

FIGURE 3 Changes of gastric cancer deaths in Japan

therapy if the diagnosis of *H. pylori* gastritis was confirmed by endoscopy. In other words, 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. 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.

Helicobacter pylori eradication therapy for gastroduodenal ulcer was approved for coverage by the Japanese NHI scheme in 2000. Subsequently, the incidence of gastroduodenal ulcer decreased dramatically by approximately 60% over 10 years,[22] and medical costs for treatment of gastroduodenal ulcer were also reduced by 47% during this period. If the incidence of *H. pylori* gastritis can be reduced by eradication therapy, the incidence of atrophic gastritis (a premalignant condition for gastric cancer) will also decrease. Although it is unclear whether the outcome for improvement of gastric cancer will be comparable to that for gastroduodenal ulcer, if the incidence of atrophic gastritis decreases, a reduction in the incidence of intestinal type gastric carcinoma that develops from atrophic gastritis would also be expected.[13] The present study showed that the number of deaths from gastric cancer, which has remained stable over past 40 years, decreased during the last 4 years along with an increase in the prescription of *H. pylori* eradication therapy. According to NHI criteria, the diagnosis of gastritis must be established by endoscopy before eradication therapy is performed and this increased requirement for endoscopy could lead to detection of gastric cancer in many patients.

The baby-boom generation is a large population that has reached the cancer-prone age over 65 years old. It was predicted that the number of deaths from gastric cancers would be 60 000 in 2020 if no new measures were taken.[22] However, the present research revealed that the annual number of deaths from gastric cancer (which remained at about 50 000 over the period of 40 years before the expansion of health insurance coverage) showed a significant decrease of about 9.2% over 4 years after expansion of the indications for *H. pylori* eradication. It is estimated that if patients with *H. pylori* infection continue to receive eradication therapy, the number of deaths from gastric cancer will be reduced by 40% to about 30 000 per year in 2020, along with a protective effect against future development of this cancer.[13]

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DISCLOSURES OF INTERESTS

None of the authors have any conflict of interests to declare.

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