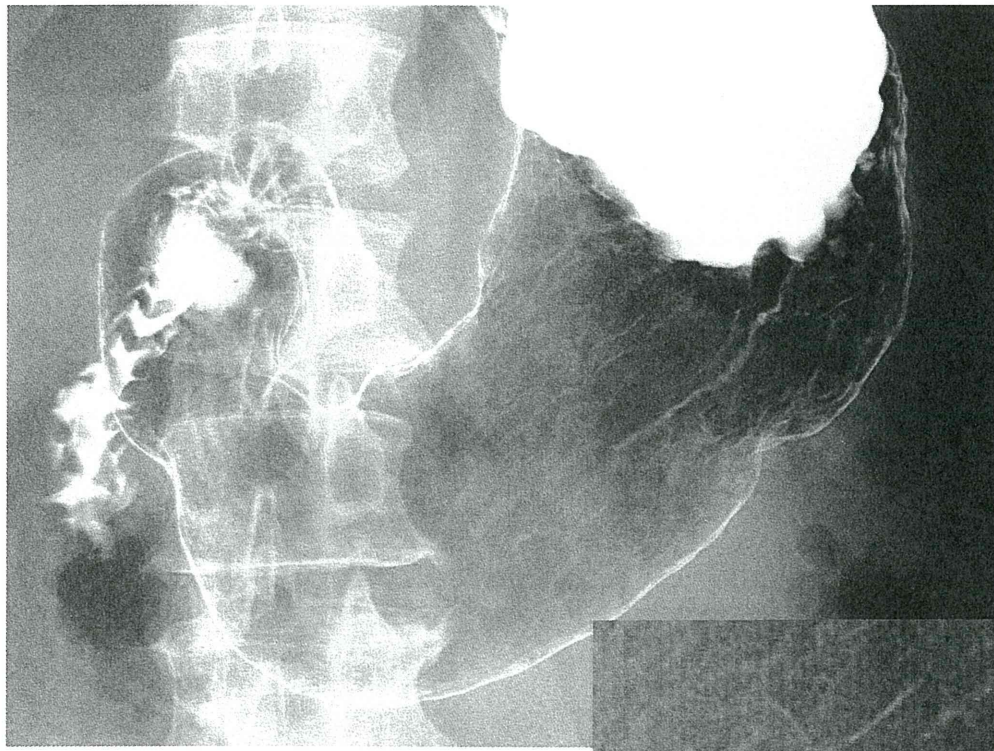

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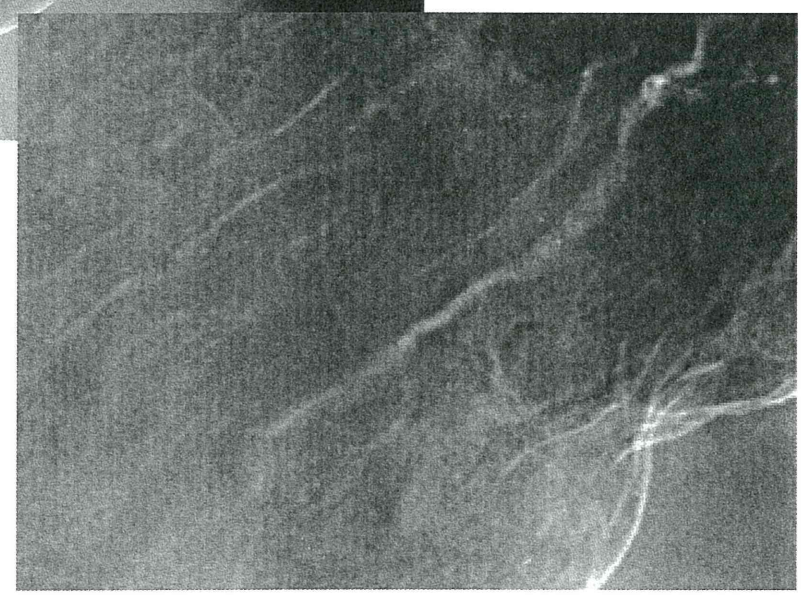
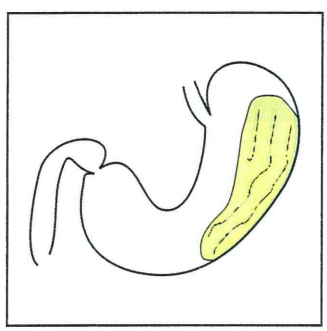




⑪過去の感染と考えられる症例(いわゆる偽A群)

50歳代　男性　バリウム濃度　180～195w/v%　発泡剤3.5g

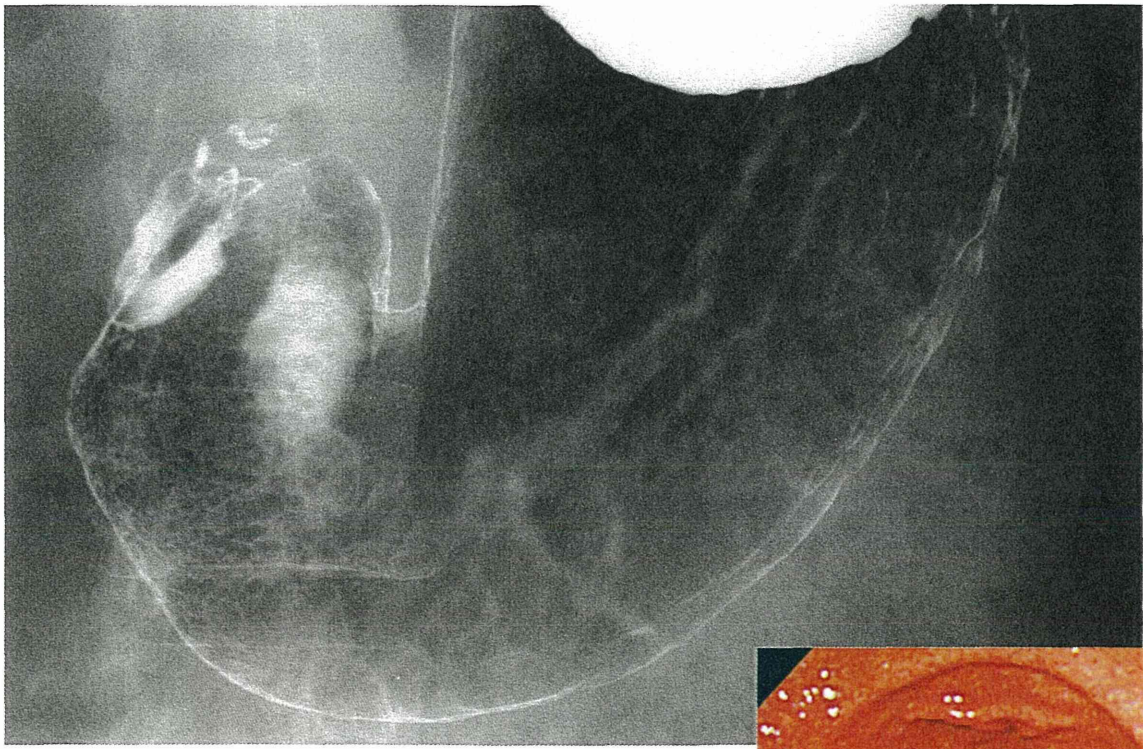
表面胃粘膜像は前庭部では平滑であるが，体部ではやや不均一である。このような場合には，平滑型というよりも中間型とする。ひだは，蛇行は軽度で，立ち上がりもスムーズで，丈も高くないが，表面が平滑でなく，太さもやや太い（4～5mm）ので，正常型でも異常型でもない。このような場合，ひだの形は中間型とする。ひだの分布は中等度萎縮，4分割法で1～3区域である。Hp陽性の所見はないのでHp陰性と診断するが，未感染ではなく過去の感染疑いと診断する。

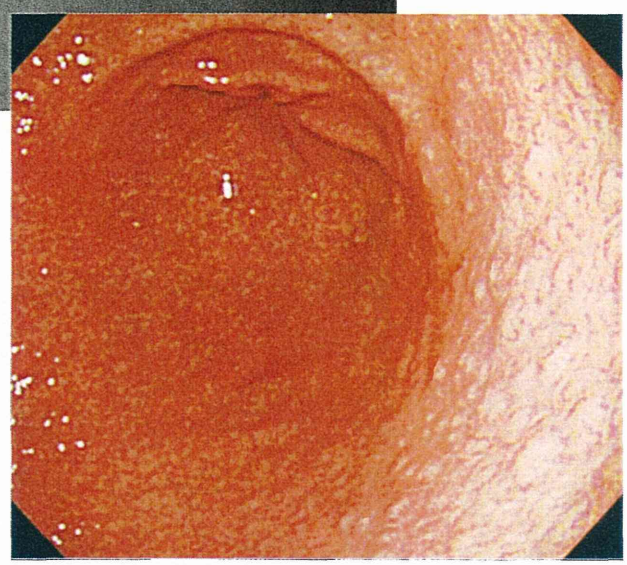
本症例はHp除菌歴はない。血清Hp抗体価：6.9U/mL，PG法：陰性。抗体価の判定は陰性であるが陰性高値であった(抗体価3.0～9.9を陰性高値と呼び，現在または過去の感染の可能性がある)。以上より，除菌歴はないが，血清学的に過去の感染が疑われ，X線診断と矛盾しない。本症例は，ABC胃がんリスク検診ではA群に分類されるが，実際は過去の感染であり，いわゆる偽A群である。胃X線検査は偽A群を診断できるというメリットがある。

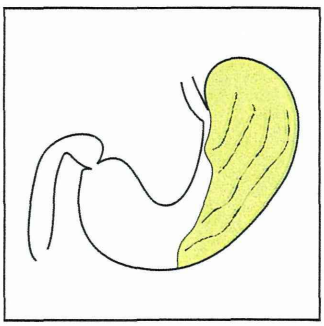
(註) 本アトラスの他のA群症例では，抗体価が3.0未満の陰性低値です。

ひだ萎縮(分布)	ひだ形状	ひだ幅(太さ)	胃粘膜像	Hp感染	PG検査	ABC分類
中等度萎縮・2区域	中間型	太い～中間	中間型	陰性*	陰性	A

*Hp抗体価 6.9u/mL







⑫鳥肌胃炎

40歳代　男性　バリウム濃度200w/v%(ゾル型)　発泡剤3.5g

表面胃粘膜像は前庭部では顆粒様である。顆粒の大きさは大小不同である。体部から胃角部の粘膜表面は平滑であるが，前庭部の所見により粗糙型と判定する。ひだは，蛇行はなく，立ち上がりもスムーズで，丈も高くないので一見正常ひだのように見えるが，太さが一定でなく，表面が平滑ではない。このひだは中間型と判定する。ひだの分布は軽度萎縮，4分割法で3～4区域である。以上より，Hp陽性で萎縮は乏しいと診断する。

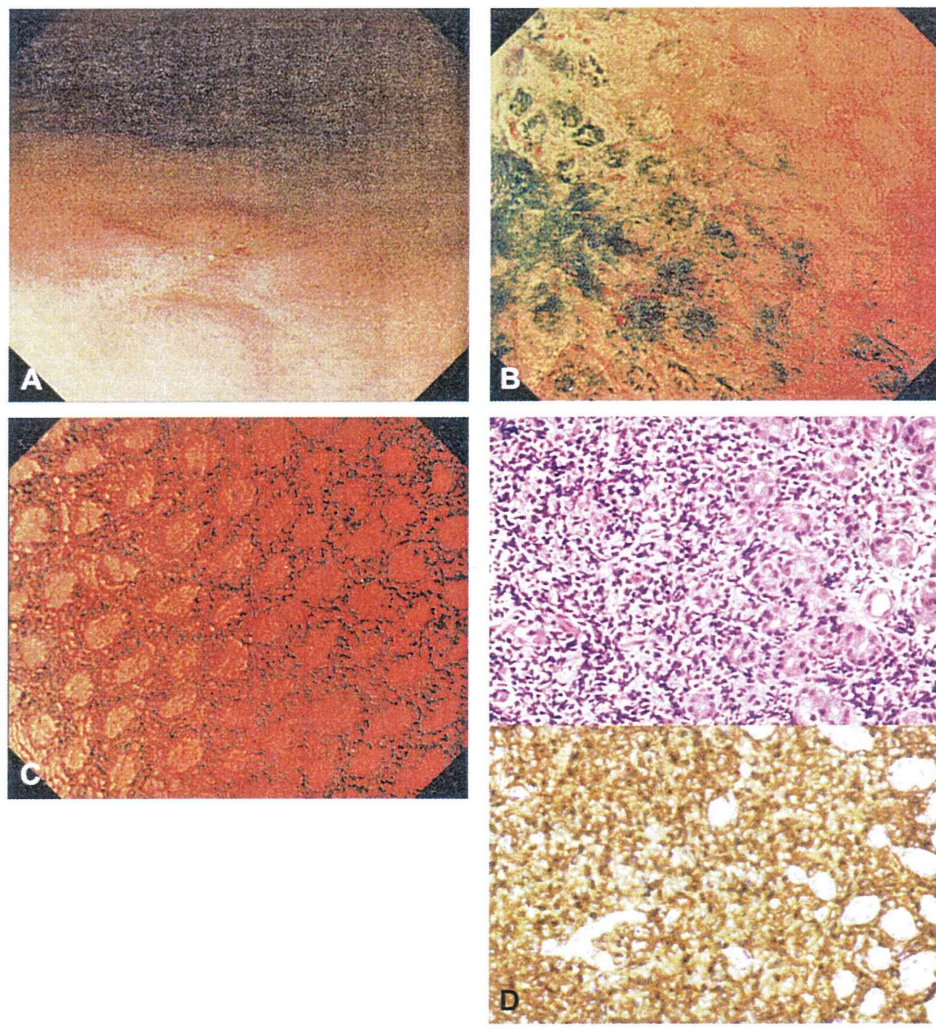
血清Hp抗体陽性，PG法陰性。以上より，Hp感染あり・萎縮なし（ABC胃がんリスク検診B群）で，X線診断と矛盾しない。本症例は，内視鏡検査(**下図**)で鳥肌様の胃粘膜を認め，いわゆる鳥肌胃炎であった。大小不同の顆粒様隆起を認め，胃X線所見と一致した。このように，前庭部に顆粒様所見を有するも胃体部にHp陽性所見の乏しいものは鳥肌胃炎を疑う。

ひだ萎縮(分布)	ひだ形状	ひだ幅(太さ)	胃粘膜像	Hp感染	PG検査	ABC分類
萎縮なし～軽度・3～4区域	中間型	中間	粗糙型	陽性	陰性	B

AT THE FOCAL POINT

Lawrence J. Brandt, MD, *Associate Editor for Focal Points*

In vivo cellular imaging of gastric mucosa-associated lymphoid tissue lymphoma in a *Helicobacter pylori*-negative patient



A 64-year-old woman was referred to our hospital for evaluation of a gastric lymphoma. Conventional EGD revealed a small, pale area surrounded by non-atrophic–appearing gastric mucosa in the distal half of the gastric corpus (**A**), and magnified endoscopic images with narrow-band imaging showed a focal, nonstructural area. To assess the cellular imaging of the lesion in vivo, we applied 1% methylene blue and 1% crystal violet through the working channel of the endoscope. An irregular increase of nuclear density with congested microvessels in the stroma and severe destruction of gastric glands were observed (**B**). These findings were markedly different from those of normal mucosa in which cells formed uniform circles with small round nuclei (**C**). Histopathology confirmed the diagnosis of mucosa-associated lymphoid tissue lymphoma (MALT) because of a dense proliferation of small lymphoid cells with lymphoepithelial lesions and immunophenotype (Wotherspoon grade 5) (H&E and CD 20, orig. mag. × 40)

(**D**). Serology was negative for *Helicobacter pylori* but positive for API2-MALT1 fusion; a "watch and wait" strategy has therefore been taken.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

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Commentary

MALT lymphomas (or MALTomas) are extranodal marginal-zone lymphomas, and most are low-grade lesions that are often localized and manifest indolent clinical behavior. MALTomas may occur in various organs, including the orbit, conjunctiva, salivary glands, skin, thyroid gland, lungs, stomach, and intestine. The majority of MALTomas occur in the stomach, and more than 90% of such cases are associated with *H pylori* infection; other weaker associations of MALTomas are Sjögren's syndrome (salivary glands), Hashimoto's thyroiditis (thyroid), and Crohn's disease or celiac disease (intestine). Prognosis and therapy are individualized based on staging. Eradication of *H pylori* is standard therapy for all *H pylori*-positive gastric MALTomas, and long-term responses to anti-*H pylori* treatment alone have been reported; MALTomas that are not eradicated by treatment of *H pylori* infection are incurable but are associated with a long course. Chemotherapy, radiotherapy, and surgical intervention might be required, depending on disease staging. A characteristic chromosomal translocation in MALToma, t(11;18)(q21;q21), results in a fusion transcript protein, API2-MALT1, that activates NF-kappa B signaling via the apoptotic inhibitor API2 gene; t(11;18)(q21;q21) may be an important prognostic factor for patients with gastric MALTomas. This case prompts me again to reflect on the changes of life. My childhood memories are filled with the visions and taste sensations of *malts* but connote milkshakes made of germinated cereal grains, the enzymes of which sweetened the grains' starches into sugars and punctuated a Sunday ball game with my friends. Assuredly, later on I found equal enjoyment in the *malts* used to make beer and wine. In my life as a gastroenterologist, however, the term *MALT* has only ominous implications. Oh well, to quote Alan Watts (a contemporary philosopher who popularized Eastern philosophy for a Western audience), "The only way to make sense out of change is to plunge into it, move with it, and join the dance."

Lawrence J. Brandt, MD
Associate Editor for Focal Points

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REVIEW

Roadmap to eliminate gastric cancer with *Helicobacter pylori* eradication and consecutive surveillance in Japan

Masahiro Asaka · Mototsugu Kato · Naoya Sakamoto

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Abstract In Japan, the annual number of deaths from gastric cancer is approximately 50,000 and there has been no change over the last 50 years. So far, all efforts have been directed toward improving the detection of early gastric cancer by barium X-ray and endoscopy, since early cancer has a good prognosis, resulting in Japan having the best diagnostic capability for early gastric cancer worldwide. The 5-year survival rate of gastric cancer patients exceeds 60 % in Japan and is much higher than that in Europe and the US (20 %) because of this superior diagnosis of early gastric cancer. In February 2013, national health insurance coverage for *Helicobacter pylori* eradication therapy to treat *H. pylori*-associated chronic gastritis became available in Japan. *H. pylori*-associated gastritis leads to development of gastric and duodenal ulcers and gastric polyps. Therefore, providing treatment for gastritis is likely to substantially decrease the prevalence of both gastric and duodenal ulcers and polyps. Because treatment for *H. pylori*-associated gastritis, which leads to atrophic gastritis and gastric cancer, is now covered by health insurance in Japan, a strategy to eliminate gastric cancer-related deaths by taking advantage of this innovation was planned. According to this strategy, patients with gastritis will be investigated for *H. pylori* infection and those who are positive will receive eradication therapy followed by periodic surveillance. If this strategy is implemented, deaths from gastric cancer in Japan will decrease dramatically after 10–20 years.

Keywords Gastric cancer · *Helicobacter pylori* · Elimination of gastric cancer · Eradication of *Helicobacter pylori*

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Introduction

After the discovery of *Helicobacter pylori* (*H. pylori*) in 1983 [1], the causal relationship between this bacterium and gastritis and/or gastric cancer has been steadily elucidated. In 1994, *H. pylori* was classified as a definite carcinogen by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) [2]. Subsequently, many clinical studies were conducted in various countries to determine whether eradication of *H. pylori* could contribute to the prevention of gastric cancer. However, the very low incidence of gastric cancer among the subjects meant that sufficient data for statistical analysis were not obtained. In 2008, randomized multicenter clinical study conducted in Japan revealed that eradication of *H. pylori* reduced the incidence of secondary gastric cancer by about two-thirds after endoscopic mucosal resection (EMR) of early gastric cancer [3], suggesting the usefulness of *H. pylori* eradication for prevention of gastric cancer. However, this study also showed that *H. pylori* eradication did not completely eliminate gastric cancer. Therefore, to eliminate gastric cancer, periodical surveillance would be required after *H. pylori* eradication. Thus, to achieve the elimination of gastric cancer in Japan, the

important issue is how to combine primary prevention through *H. pylori* eradication with secondary prevention through surveillance. Fortunately, the Ministry of Health, Labour and Welfare of Japan (MHLW) approved national health insurance coverage for eradication therapy in patients with gastritis caused by *H. pylori* infection (chronic active gastritis) on February 21 in 2013 for the first time in the world. Here, we present a roadmap for the elimination of gastric cancer in Japan, focusing on eradication of *H. pylori*.

Current status and characteristics of screening for gastric cancer in Japan

Approximately 60 % of gastric cancer patients worldwide are found in only three East Asian countries (Japan, China, and Korea), and the disease seems to be endemic to this area [4]. Gastric cancer was the most common cause of cancer death in Japan until it was replaced by lung cancer in 1995 [5]. Thanks to concerted efforts by clinical and fundamental researchers, the concept of early gastric cancer was proposed in Japan in 1963. At that time, early gastric cancer was defined as a lesion with infiltration of tumor cells limited to the mucosa or submucosa, irrespective of lymph node metastasis [6, 7].

The prognosis of early gastric cancer is far better than that of advanced cancer, with a 5-year survival rate exceeding 90 % [8]. Therefore, many studies in Japan have focused on how to diagnose effectively early gastric cancer. As a result, early cancer now accounts for nearly 60 % of all gastric cancers detected in Japan. This has not been reported in any other country and suggests high diagnostic capability for early cancer in the country. The survival rate of gastric cancer patients depends on the stage of their tumor. It exceeds 90 % for stage I (including early gastric cancer), while it is under 20 % for stage IV. Thus, a higher stage means a worse prognosis [9], hence it is important to detect as many early cancers as possible for improvement of gastric cancer mortality. The efforts made so far have led to an overall 5-year survival rate of better than 65 % for gastric cancer patients in Japan [9]. In other countries, including the US and Europe, the 5-year survival rate of gastric cancer patients is reported to be only 10–25 % (Fig. 1) [10–12]. This is not because treatment of gastric cancer is superior in Japan to that in other countries, but because the detection rate of early cancer is much lower outside Japan. In other words, the stage distribution of gastric cancer patients receiving treatment in Japan is likely to be different from that in other countries where there is little emphasis on detecting early gastric cancer. In the US and Europe, intramucosal carcinoma is not even considered to be cancer and is classified as dysplasia [13]. Thus, researchers in the US and Europe have speculated that the

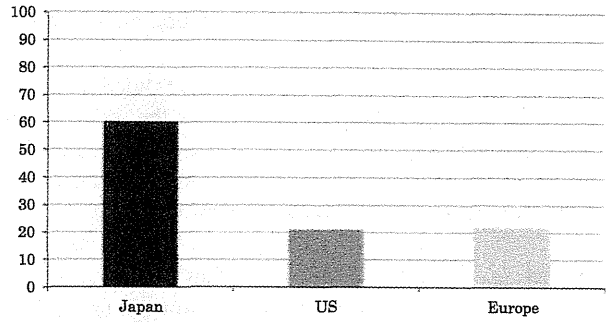

Fig. 1 Five-year survival rate in Japan, US and Europe (%)

diagnosis and treatment of precancerous lesions as early gastric cancer improves the prognosis in Japan compared with other countries. There is undoubtedly a difference of diagnostic criteria between Japan and the US/Europe. While Japanese pathologists make a diagnosis of gastric cancer based on the presence of atypical nuclei in gastric mucosal cells and atypical glandular or ductal structures, pathologists in the US and Europe will diagnose gastric dysplasia instead of gastric cancer when atypical glandular and ductal structures do not extend beyond the muscularis mucosa [13]. This difference in the diagnostic criteria for gastric cancer between Japan and the US/Europe is an issue that seems to be difficult to resolve [14]. However, based on the findings that 30–60 % of lesions diagnosed as dysplasia show progression to gastric cancer within a few years [15–17] and that examination of larger biopsy specimens leads to diagnosis of more lesions as cancer [18], high-grade dysplasia should be classified as intramucosal gastric cancer and be treated aggressively in order to improve the prognosis of gastric cancer.

In Japan, endoscopic surgery is commonly performed for intramucosal gastric cancer, a form of early gastric cancer, while such treatment is uncommon in Europe and the US where intramucosal lesions are not regarded as cancerous. Even if physicians in Europe and the US accept the concept of early gastric cancer, they need to develop techniques for diagnosis and endoscopic surgery [17]. Possibly because of inadequate diagnostic techniques for early gastric cancer, the prognosis of gastric cancer is poor in other countries. The skill of Japanese physicians with regard to early diagnosis and endoscopic treatment of gastric cancer is unsurpassed and contributes greatly to the management of patients with this cancer in Japan. To achieve improvement of the prognosis of gastric cancer in other countries, it would be necessary for the concept of early gastric cancer to be accepted and the same level of technical skill in the management of early gastric cancer as in Japan to be established, which could lead to the promotion of gastric cancer elimination by combining *H. pylori* eradication therapy with surveillance.

Prevention of gastric cancer by eradication of *H. pylori*

As it has become clear that *H. pylori* infection is an important risk factor for gastric cancer, the issue of whether *H. pylori* eradication therapy can decrease the incidence of gastric cancer has attracted increasing attention. Intervention studies to assess the preventative effect of *H. pylori* eradication on gastric cancer have been conducted in healthy individuals worldwide. However, the incidence of gastric cancer is very low in the US and Europe, and the study populations were not large enough to detect a significant effect of eradication therapy, resulting in the discontinuation of most studies [19].

In 2004, a report on a large intervention study performed in China was published [20]. This study involved 1,630 *H. pylori*-infected residents of Fujian province in China where the mortality rate due to gastric cancer is high. During the follow-up period, gastric cancer developed in 7 and 11 subjects from the eradication and placebo groups, respectively, and there was no significant difference between the two groups ($p = 0.33$). However, among patients without precancerous lesions (atrophy, intestinal metaplasia, or dysplasia), there were no cases of gastric cancer in the *H. pylori* eradication group and there was a significantly lower incidence of gastric cancer compared with the placebo group ($n = 6$) ($p = 0.02$). Interestingly, all of the cancers diagnosed after *H. pylori* eradication were advanced and there were no cases of early gastric cancer, which was a surprising result in view of the situation in Japan where at least 60 % of gastric cancers are diagnosed at an early stage. Such an outcome suggests that the endoscopists involved in this study might not be skilled in the diagnosis of early gastric cancer. Accordingly, the patients who were classified as having atrophic gastritis or intestinal metaplasia may well have included many patients with early gastric cancer. *H. pylori* infection is strongly associated with early gastric cancer rather than advanced cancer [21], suggesting that investigation of the prevention of gastric cancer by *H. pylori* eradication therapy is problematic outside Japan because early gastric cancer is unlikely to be diagnosed.

Assessment of the design of a new prospective study on the basis of previous studies indicated that a clinical trial with a small sample size and short follow-up period should enroll patients with early gastric cancer who have undergone EMR, since they represent the population most likely to develop advanced gastric cancer. The annual incidence of gastric cancer has been reported to be only 0.1–0.4 % in *H. pylori*-positive patients with atrophic gastritis [22, 23], while the annual incidence of metachronous recurrence is far higher (3–5 %) in patients who have undergone endoscopic surgery for early gastric cancer [24, 25]. We investigated the metachronous recurrence of gastric cancer in 544 patients who had undergone endoscopic treatment for early gastric cancer. They were randomly allocated to *H. pylori* eradication or non-eradication groups and were followed up by annual endoscopic examination for 3 years. As a result, metachronous recurrence was detected in 9 and 24 subjects from the eradication group and the non-eradication group, respectively, and the former had a significantly lower relapse rate ($p < 0.01$ according to intention-to-treat analysis) [3]. This prospective study had an adequate sample size to provide a definitive answer to the long controversial issue of whether gastric cancer could be prevented through *H. pylori* eradication. It demonstrated that *H. pylori* eradication therapy reduced the incidence of intestinal type gastric cancer by at least two-thirds and this effect was noted irrespective of whether patients had atrophic gastritis, intestinal metaplasia, or early gastric cancer. Thus, it was confirmed that most gastric cancer is associated with *H. pylori* infection and that the disease can be effectively prevented by eradication of this microorganism.

In 2009, a large-scale cohort study was reported, in which about 80,000 patients in Taiwan were followed up for 10 years after *H. pylori* eradication therapy [26]. The patients were assigned to an early eradication group (*H. pylori* eradication therapy was provided at the time of diagnosis) or a late eradication group (eradication therapy was performed at 1 year or more after diagnosis). It was found that the incidence of gastric cancer was markedly lower in the early eradication group than in the late eradication group. This study is important because it demonstrates that *H. pylori* eradication therapy inhibits the development of gastric cancer and that earlier eradication is more effective.

In 2006, You et al. [27] reported a study of 3,365 patients in China who were randomized to an *H. pylori* eradication group, a garlic group, or a vitamin group and were followed for 7.3 years, with the result being no inhibition of gastric cancer in any of the groups. However, longer follow-up for 15 years subsequently revealed significant inhibition of gastric cancer in the *H. pylori* eradication group (odds ratio, 0.61; $p = 0.032$) [28]. Although there was no significant preventive effect on gastric cancer of eradication therapy in the original randomized study, longer observation revealed a significant effect.

The above-mentioned three studies performed in East Asia provide strong evidence that *H. pylori* eradication therapy is effective for inhibiting gastric cancer. In Japan, Maehata et al. investigated the long-term clinical outcome following *H. pylori* eradication therapy and whether it prevented metachronous gastric cancer. They reported that eradication therapy inhibited the development of metachronous gastric cancer for 5 years, but there was no significant difference after longer follow-up [29]. However, the mean observation period of this study was only 3 years and

the 10-year prognosis was assessed in very few patients, leading to lack of reliability. That is, the findings about the short-term prognosis may well be accurate, but no conclusion can be drawn regarding the long-term outcome.

After the JGSG study was completed and data obtained at 8–10 years were analyzed, it was found that there was still a difference in the incidence of metachronous gastric cancer between the *H. pylori* eradication and non-eradication groups [30]. This indicates that the preventive effect of eradication therapy on gastric cancer persists for a long time.

Health insurance coverage for *H. pylori* eradication therapy in Japan

Cancers are classified into two broad categories, which are lifestyle-related and infection-related cancers. In the US and Europe, cancers related to infection account for a low percentage (10 % or less) of all cancers [31, 32]. In Japan, however, it has become clear that infection-related cancers account for approximately 25 %, including liver cancer caused by hepatitis viruses, cervical cancer due to papillomavirus, and gastric cancer related to *H. pylori*. Although cervical cancer is uncommon and accounts for a low percentage (1.3 %) of all cancers, gastric cancer and liver cancer account for about 17 and 6.5 %, respectively, and the total for these three cancers is nearly 25 % [33]. Since it has become clear that most gastric cancer is due to *H. pylori* infection rather than lifestyle factors, it is time for major revision of the preventative strategies for gastric cancer. When it is suspected that a cancer is caused by infection, proactive preventative measures are likely to lead to a dramatic decrease in the incidence of that cancer, resulting in a significant decrease of cancer mortality. In Japan, preventative measures for liver cancer have been focused on hepatitis virus infection since 2002, leading to a reduction of mortality [34, 35]. However, the annual number of deaths from gastric cancer has remained at around 50,000 for the last few decades [36], suggesting that the current preventative measures are inadequate (Fig. 2). Even though there is a difference in the causative agent between liver cancer (viruses) and gastric cancer (a bacterium), preventive measures for gastric cancer should not be completely different from those for liver cancer. Thus, the fundamental measures for preventing gastric cancer should be shifted from conventional secondary prevention based on barium X-ray screening to primary prevention focused on *H. pylori* eradication therapy.

In 2009, the Japanese Society for Helicobacter Research published a guideline in which it is recommended that all *H. pylori*-infected people receive bacterial eradication therapy [37]. In response to this, the MHLW approved the extension of national health insurance coverage to *H. pylori*

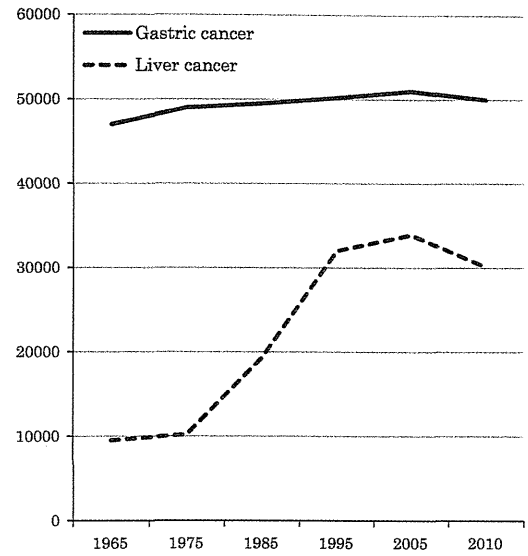

Fig. 2 Changes of deaths of gastric cancer and liver cancer in Japan

eradication therapy for three indications [i.e., patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, patients who have undergone endoscopic surgery for early gastric cancer, and patients with idiopathic thrombocytopenic purpura (ITP)], in addition to patients with gastric and duodenal ulcer. This was the first time in the world that insurance coverage has been provided for *H. pylori* eradication therapy for indications other than gastric and duodenal ulcer and represents an innovative approach. Regarding the potential expansion of health insurance coverage for eradication therapy to include patients with chronic gastritis, the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society, and the Japanese Society for Helicobacter Research submitted a joint petition to the Minister of the MHLW. This public knowledge-based application led to the inclusion of *H. pylori* eradication therapy for patients with chronic gastritis on February 21, 2013. The MHLW notification states that eradication therapy is covered by the national health insurance scheme when a patient with endoscopically diagnosed chronic gastritis is positive for *H. pylori*.

Within a few months of being infected, gastritis with neutrophil and lymphocyte infiltration develops in almost 100 % of patients who have *H. pylori* infection. Such gastritis is called chronic active gastritis and is said to be specific to *H. pylori* infection [38]. Gastritis caused by *H. pylori* develops as a biological defense to the infection, resulting in the production of inflammatory cytokines such as IL-1 and IL-8 and the expansion of gastric mucosal inflammation [39]. Persistent inflammation gradually increases the fragility of the gastric mucosa and *H. pylori*-associated gastritis progresses to atrophic gastritis over time. It has been demonstrated that progression takes

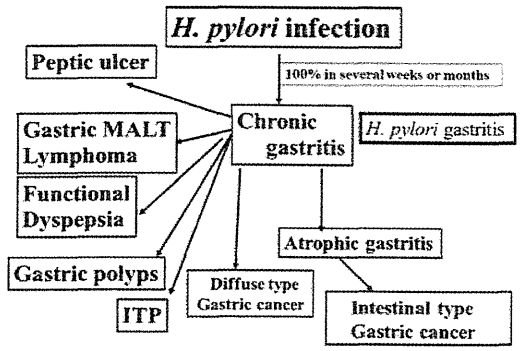

Fig. 3 Progress of *H. pylori* infection

10–20 years in about 80 % of Japanese patients [40], and some cases of atrophic gastritis then progress to intestinal type gastric cancer. Correa's hypothesis has been widely accepted, which states that gastritis progresses to intestinal metaplasia, dysplasia, and then gastric cancer [41], and it has been virtually proved by the discovery of *H. pylori*. The effects of gastric acid and stress on a background of *H. pylori*-associated gastritis can lead to the development of peptic ulcer. In contrast, gastritis that is not associated with *H. pylori* usually does not progress to ulceration even when stress occurs. It has become obvious that *H. pylori*-associated gastritis is also closely associated with gastric MALT lymphoma, functional dyspepsia (FD), hyperplastic gastric polyps, idiopathic thrombocytopenic purpura (ITP) and diffuse type gastric cancer (Fig. 3) [42, 43] Thus, *H. pylori*-associated gastritis is the underlying cause of almost all gastric diseases, hence treatment of this gastritis through bacterial eradication therapy is likely to prevent most gastric conditions, including gastric cancer.

Kodama et al. observed the 10-year course by obtaining biopsy specimens from 5 different sites of the gastric mucosa, and found that the activity score and inflammation improved immediately after *H. pylori* eradication therapy and then remained stable for the next 10 years. They reported that atrophic change took longer to improve leukocytic infiltration, but nearly 80 % of the changes had resolved after 10 years [44]. Their findings revealed that eradication therapy improved atrophic changes of *H. pylori*-associated gastritis, as well as leukocytic infiltration, indicating that this therapy is useful for the prevention of gastric cancer.

Strategy and roadmap for the elimination of gastric cancer in Japan

In order to eliminate gastric cancer in Japan, the strategy for adolescents should be different from that for elderly persons. This is because bacterial eradication in adolescents achieves nearly 100 % prevention of gastric cancer, but the incidence of this cancer increases with advancing age [43, 45]. We recommend a test-and-treat approach as the strategy for adolescents, which includes *H. pylori* testing of junior high school and high school students, followed by immediate *H. pylori* eradication therapy for those with a positive result. Eradication in adolescents should be able to prevent *H. pylori*-related diseases such as gastric ulcer and gastric polyps, as well as preventing the development of nearly 100 % of gastric cancers. It is estimated that approximately 5 % of all teenagers in Japan are positive for *H. pylori* [46], suggesting that the cost of this approach would not be so high. Some local governments have already scheduled free *H. pylori* testing for junior high school students.

The recent expansion of health insurance coverage allows individuals with symptoms such as gastric heaviness to present to hospital for the diagnosis and treatment of *H. pylori*-associated gastritis. To obtain health insurance coverage, endoscopy must be performed first for the diagnosis of gastritis, and most patients seem to have chronic gastritis by the time they undergo endoscopy. We expect that many patients with gastric cancer will be discovered during this endoscopic examination. This project thus includes a form of endoscopic screening supported by medical insurance. All patients in whom gastritis is diagnosed are supposed to receive *H. pylori* eradication therapy. In patients with obvious atrophic gastritis, periodic endoscopic follow-up is recommended every 1 or 2 years even after eradication therapy, while patients with no or mild atrophy and those who are negative for *H. pylori* infection can be followed by optional screening (such as personal medical check-up) instead of strategic screening (Fig. 4).

In Japan, the success rate of *H. pylori* eradication therapy is decreasing every year because of the increase in bacteria resistant to clarithromycin, but secondary eradication therapy with metronidazole achieves a high success rate (>95 %). That may be because resistance to metronidazole is very low in Japan (about 5 %) where health

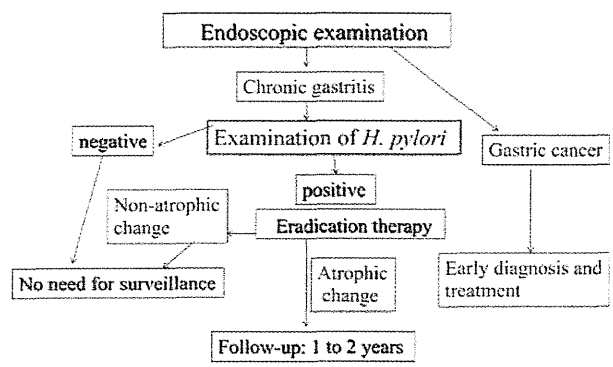

Fig. 4 Strategy for elimination of gastric cancer deaths in Japan

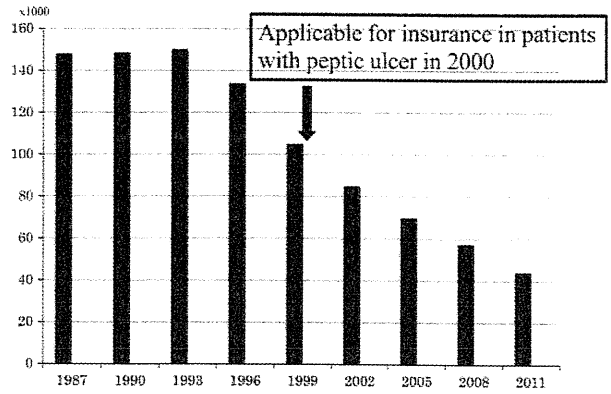

Fig. 5 Changes in incidence of peptic ulcer in Japan

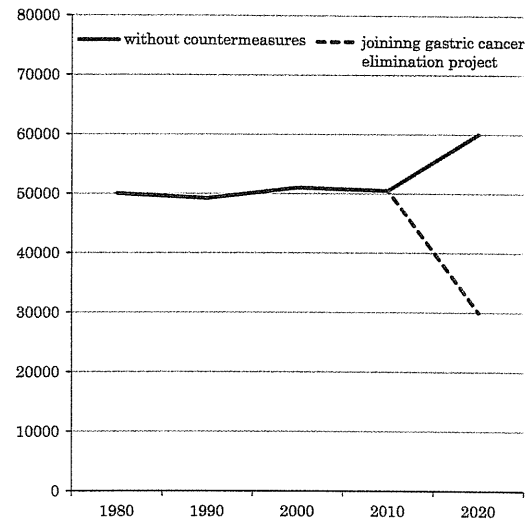

Fig. 6 Anticipation of gastric cancer deaths with or without countermeasures in Japan

insurance coverage for administration of metronidazole is limited and its use remains uncommon [36]. A recent report indicated that third-line eradication therapy with sitafloxacin was effective for 70 % of the patients in whom secondary eradication therapy was ineffective [47].

Although it is not clear to what extent the use of eradication therapy in patients with *H. pylori*-associated gastritis will inhibit the development of gastric cancer, a good model may be peptic ulcer for which *H. pylori* eradication therapy was first covered by the Japanese national health scheme in 2000. Since then, the incidence of peptic ulcer has decreased dramatically by about 60 % over 10 years (Fig. 5) [48]. In addition, the medical costs of treating ulcers have decreased by no 47 % during that period. Although it is unclear whether the results obtained with gastric cancer will be comparable to those for peptic ulcer, *H. pylori* eradication therapy (etiologic treatment) for *H. pylori*-associated gastritis will lead to a long-term decrease of gastric cancer. Such treatment will inhibit the development of peptic ulcer and gastric polyps as well as gastric cancer, suggesting a greater reduction of medical costs than that achieved by providing insurance coverage for *H. pylori* eradication therapy in patients with peptic ulcer.

There are two potential outcomes of the gastric cancer elimination project suggested here with regard to gastric cancer-related deaths in Japan. One is a definite decrease in the incidence of gastric cancer resulting from the widespread use of *H. pylori* eradication therapy (a direct effect of this therapy). The other is a decrease in the number of deaths resulting from an increase in the diagnosis of early gastric cancer owing to mandatory endoscopy at the time of presentation for chronic gastritis. The target would be to eventually increase the proportion of early gastric cancer from the current 60 % to around 90 %, which would make it possible to increase the 5-year survival rate for gastric cancer patients in Japan to approximately 90 %. Because the baby boomer generation represents a huge population turning 65 years old and entering the cancer-prone years, the number of deaths from gastric cancer is likely to reach 60,000 in 2020 without any countermeasures. In contrast, if the gastric cancer elimination project is successful and about 50 % of persons with *H. pylori* infection receive eradication therapy, the number of deaths from gastric cancer will decrease to about 30,000 in 2020 (Fig. 6).

Conclusion

H. pylori eradication therapy for chronic gastritis achieved the world's first coverage by the Japanese national health insurance scheme in 2013, making a dramatic decrease of gastric cancer-related deaths more realistic. Combining *H. pylori* eradication therapy with endoscopic surveillance can prevent the development of gastric cancer. Even if gastric cancer develops, most patients are likely to be diagnosed while it is at an early stage, possibly resulting in a large decrease of gastric cancer deaths.

Success with the elimination of gastric cancer in Japan could lead other countries with a high incidence of gastric cancer (China, Korea, and Latin American countries) to consider a similar strategy, suggesting the potential for elimination of gastric cancer around the world.

Conflict of interest Masahiro Asaka belongs to the donation-funded department by Eizai Co. LTD at Hokkaido University Graduate School of Medicine.

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Prevalence of *Helicobacter pylori* Infection by Birth Year and Geographic Area in Japan

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Keywords
H. pylori, prevalence, gastric cancer, birth cohort.

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Abstract

Background: *Helicobacter pylori* (*H. pylori*)-related diseases are responsible for a tremendous amount of morbidity and mortality in Japan. We estimated the prevalence of *H. pylori* infection by sex, birth year, and geographic area among Japanese adults.

Materials and Methods: This cross-sectional study included 14,716 subjects aged 20 years or more who underwent a health checkup between May 1997 and March 2013 in seven geographic areas throughout Japan. Relevant information on the demographics and status of *H. pylori* infection was retrieved from the electronic database. The univariate log-binominal regression model was used to estimate the prevalence of *H. pylori* infection, taking birth year into consideration. The multivariate log-binominal regression model was used to compare the prevalence of *H. pylori* infection between seven geographic areas.

Results: The overall prevalence of *H. pylori* infection was 37.6% in women and 43.2% in men. Among seven geographic areas, Hokkaido showed the lowest prevalence (29.4%), while Yamagata Prefecture represented the highest (54.5%). The prevalence of H. pylori infection was highest in the 1940–1949 birth cohort and then decreased in the ensuing birth cohorts; the risk ratio (RR) was 0.85 (95% confidence interval (CI) 0.84–0.87) for changes in the 10-year birth cohort. Individuals in Yamagata Prefecture had the highest RR of acquiring H. pylori infection in all three birth cohorts (RR = 1.53 for 1940, RR = 1.69 for 1950, and RR = 1.85 for 1960) when compared with those in Hokkaido.

Conclusions: The prevalence of *H. pylori* infection increases with age and exhibits geographic variation in Japan. There has been a striking decrease in the prevalence of *H. pylori* infection, especially in younger Japanese populations.

An estimated half the population of the world is infected with *Helicobacter pylori* (*H. pylori*). *H. pylori* infection causes digestive diseases such as gastro/duodenal ulcers and chronic gastritis and increases the risk of noncardiac gastric cancer [1]. *H. pylori*-related diseases are responsible for a tremendous amount of morbidity and mortality in Japan. One of the more striking features of *H. pylori* infection is geographic variation, with developing countries having a much higher prevalence compared with developed countries [2]. Although

Japan is a developed country, both the prevalence of *H. pylori* infection and incidence of gastric cancer are among the highest in the world.

The prevalence of *H. pylori* infection used to be very high in asymptomatic Japanese. The most-cited study, published in 1992, showed that the prevalence of serum anti-*H. pylori* antibody increased with age and that individuals born before 1950 had a prevalence as high as 70–80% [3]. However, as with other developed countries, the prevalence in Japan has been continuously decreasing over the past several decades. Using random samples collected at three points in time, Fujisawa et al. reported that the overall seroprevalence of *H. pylori* was 72.7% in 1974, 54.6% in 1984, and 39.3% in 1994 [4]. This finding suggested that a marked decrease in *H. pylori* infection had occurred in Japan.

Despite many studies of *H. pylori* prevalence in selected areas of Japan [5–9], it remains unclear whether its prevalence differs across geographic areas. Moreover, very few studies have reported the prevalence of *H. pylori* infection by birth year. We believe that the epidemiology of *H. pylori* infection sheds light on the geographic differences in the prevalence of *H. pylori*-associated diseases. Using data collected from a large number of health checkup participants, we estimated the updated prevalence of *H. pylori* infection among Japanese adults by sex, birth year, and geographic area.

Methods

Study Population

This is a cross-sectional, multi-institutional study of *H. pylori* prevalence in Japanese adults. Our study included individuals aged 20 years or more who underwent a health checkup provided by their municipal government or private health screening center/clinic, between May 1997 and March 2013, in Hokkaido (Yubari), Tokyo, and nine other prefectures (Aomori, Yamagata, Gunma, Aichi, Shiga, Okayama, Hiroshima, Kagawa, and Oita) throughout Japan. Of these areas, data collected from outpatients residing in four areas (Tokyo, Okayama, Hiroshima, and Oita) were excluded, and thus, the remaining seven areas were eligible for the present study. In addition, individuals with a history of *H. pylori* eradication therapy were excluded. Information on identification number, sex, birth date, type of health checkup, inspection date, *H. pylori* infection status, history of *H. pylori* eradication therapy, and serum pepsinogen (I and II) levels were retrieved from the electronic database. *H. pylori* infection was determined using serologic, urinary, or stool antigen tests. The serologic test was performed for quantifying *H. pylori* -IgG antibody using ELISA-kit "E-plate Eiken *H. pylori* antibody" (Eiken Kagaku, Tokyo, Japan). The recommended cutoff point of antibody titers was used to define *H. pylori* infection. A stool antigen test was performed using TFB Meridian HpSA ELISA2, and the urine antibody test performed using RAPIRUN (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). If an individual underwent a diagnostic test for *H. pylori* periodically, we selected the result of the first test. Furthermore, for individuals who had undergone more than one diagnostic test, results of the serologic test were given top priority. Our study was approved by the Ethics Committee of Hokkaido University.

Statistical Method

Continuous variables were summarized as the mean (standard deviation), and categorical variables were presented as numbers and percentages. The prevalence of *H. pylori* infection was estimated using a univariate log-binomial regression model that included birth year as a factor [10]. The risk ratio (RR) represented the comparison of the proportion of being *H. pylori*—positive in the case of a 10-year increase in birth cohort. Using multivariate log-binomial regression models, we compared the prevalence of *H. pylori* infection for the seven areas in three birth cohorts (1940, 1950, and 1960). Four factors (area, birth year, sex, and clinical test method) and the interaction term between area and birth year were added in the models. The reference group for area, sex, and clinical test method is Hokkaido, female, and health checkup provided by municipal government, respectively.

All tests were two-sided, and p values less than 0.05 were considered to indicate statistical significance. Statistical analyses were carried out using SAS 9.3 (SAS institute Inc., Cary, NC, USA).

Results

Figure 1 shows the flowchart of selection of the study subjects. After the exclusions described in Methods, data collected from 14,716 people were eligible for the present analysis. Table 1 presents the characteristics of the study population. Of the 14,715 people who underwent diagnostic tests for *H. pylori* infection, data on the serologic test were available for 11,470 (77.9%) people. The status of *H. pylori* infection was determined by a urine antibody test in Hokkaido (Yubari) and by a stool antigen test in Aichi Prefecture. The overall prevalence of *H. pylori* infection was 37.6% in women and 43.2%

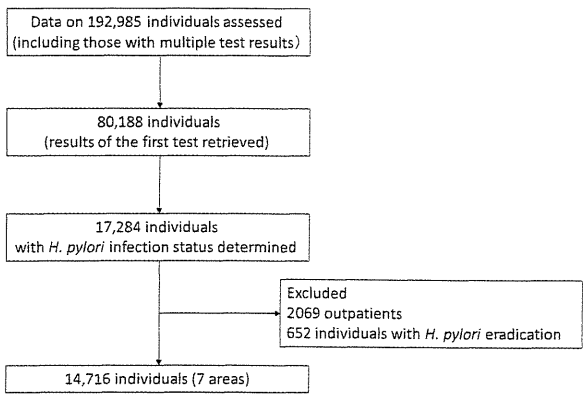

Figure 1 A flowchart of selection of study subjects.

in men. The mean birth year was 1950 among *H. pylori*-positive subjects and 1956 among *H. pylori*-negative subjects. Among seven geographic areas, Hokkaido showed the lowest prevalence of *H. pylori* infection (29.4%), while Yamagata Prefecture represented the highest (54.5%). Aomori and Shiga also had a high prevalence compared with other prefectures. The prevalence of *H. pylori* infection was slightly higher among individuals who underwent a health checkup provided by the municipal government compared with that among those who underwent a health checkup provided by private health screening centers/clinics.

The results of univariate analysis showed that the prevalence of *H. pylori* infection was highest in the 1940–1949 birth cohort and then decreased in the ensuing birth cohorts; the RR was 0.85 (95%CI 0.84–0.87) for changes in the 10-year birth cohort (Fig. 2). Figure 3 shows the results of multivariate log-binomial regression analysis. Individuals in Yamagata Prefecture had the highest RR of acquiring *H. pylori* infection of all three birth cohorts (RR = 1.53 for 1940, RR = 1.69 for 1950, and RR = 1.85 for 1960) when compared with those in Hokkaido.

Discussion

Despite the retrospective nature of our study, we collected a large amount of updated data on the status of *H. pylori* infection from healthy checkup participants who resided in various geographic areas in Japan. We found that the prevalence of *H. pylori* infection showed geographic variations. We also examined the effect of birth year on the prevalence of *H. pylori* infection and found a clear birth cohort effect that was occurring in Japan: Individuals who belonged to young birth cohorts had a decreased prevalence compared with old birth cohorts.

One striking feature of *H. pylori* is geographic variation. Although differences in prevalence have been observed in different geographic regions within a coun-

Table 1 Characteristics of the study subjects

Characteristics	Category	*H. pylori* -positive (n = 5879)	*H. pylori*-negative (n = 8837)	Total (n = 14716)
Sex	Women	3184 (37.6%)	5293 (62.4%)	8477 (57.6%)
	Men	2695 (43.2%)	3544 (56.8%)	6239 (42.4%)
Birth year	Mean (SD)	1950 (11)	1956 (16)	1954 (14)
Geographic area	Hokkaido	420 (29.4%)	1008 (70.6%)	1428 (9.7%)
	Aomori	389 (49.7%)	393 (50.3%)	782 (5.3%)
	Yamagata	1969 (54.5%)	1646 (45.5%)	3615 (24.6%)
	Gunma	1586 (32.3%)	3328 (67.7%)	4914 (33.4%)
	Aichi	684 (30.6%)	1553 (69.4%)	2237 (15.2%)
	Shiga	664 (51.2%)	634 (48.8%)	1298 (8.8%)
	Kagawa	167 (37.8%)	275 (62.2%)	442 (3%)
Diagnostic method	Serology	4963 (43.3%)	6507 (56.7%)	11470 (77.9%)
	Urine antibody	232 (23%)	776 (77%)	1008 (6.9%)
	Stool antigen test	684 (30.6%)	1553 (69.4%)	2237 (15.2%)
Type of health checkup	Health checkup provided by municipal government	4153 (38.1%)	6752 (61.9%)	10905 (74.1%)
	Health checkup provided by private health screening center/clinic	1726 (45.3%)	2085 (54.7%)	3811 (25.9%)

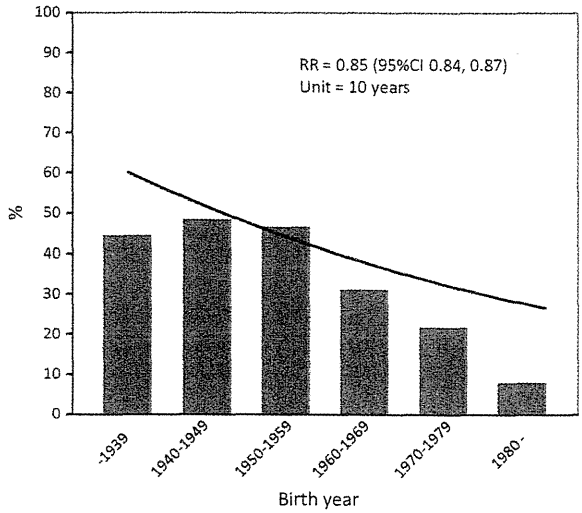

Figure 2 The effect of birth year on the prevalence of *H. pylori* infection: a univariate analysis.

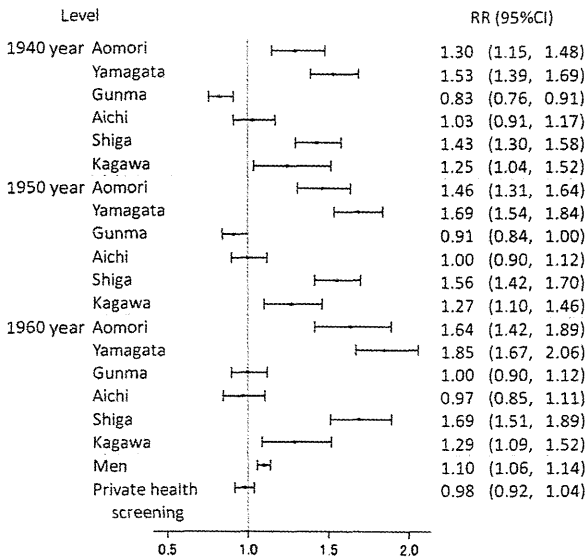

Figure 3 The effect of area, birth year, sex, and clinical test method on *H. pylori* prevalence : a multivariate analysis. Bars represent the RR with a 95% CI for *H. pylori* prevalence. The RR is estimated by the use of the multiple log-binominal regression model including area, birth year, sex, and clinical test method as factors and the interaction term between area and birth year. The prevalence of *H. pylori* infection in each area (Aomori, Yamagata, Gunma, Aichi, Shiga, and Kagawa) is compared to that in Hokkaido at 1940, 1950, and 1960 years. The reference group for area, sex, and clinical test method is Hokkaido, women, and health checkup provided by municipal government, respectively. RR, multivariate-adjusted risk ratio; CI, confidence interval.

try [11], few studies have examined the effect of geographic areas on *H. pylori* prevalence in Japan. Our finding showed that geographic variation in the prevalence of *H. pylori* infection existed in Japan, with Yamagata Prefecture having the highest prevalence among the seven prefectures examined. Previous studies have indicated that genetic diversity of *H. pylori* strains, socioeconomic status, and environmental factors may play a role in *H. pylori* infection [12–15], contributing to the geographic variation. Given that *H. pylori* colonization occurred mainly in children under 5 years old and persisted in one's whole life without eradication, socioeconomic status during childhood may be the major contributing factor underlying of *H. pylori* infection. In Yamagata Prefecture, three generations under one roof was common and this may be, in part, associated with a high prevalence of *H. pylori* infection. In contrast, Hokkaido (Yubari) had a complete water supply system since 1950s, which may account for the low prevalence. Another important factor is the genetic diversity of *H. pylori* strains. It has been shown that the virulence factors of *H. pylori*, such as CagA and Vac A, varied across regions in the world [12]. The majority of the *H. pylori*-positive subjects in Japan possess CagA, while those in other developed countries are colonized by an almost equal proportion of CagA-positive and CagA-negative strains [12]. CagA-positive *H. pylori* strains induce more intense inflammation in the stomach, and individuals with CagA-positive *H. pylori* strains had a significantly increased risk of gastric cancer [12]. Further studies are needed to address the question of which factor is most important in determining the geographic variation.

In this study, the prevalence of *H. pylori* infection increased with age. Our findings confirmed that birth cohorts have different risks of acquiring *H. pylori* infection. The birth cohort effects reflect a decrease in the rate of acquisition of *H. pylori* infection in successive generations of children as sanitation and living standards improved. This phenomenon has been consistently observed in cross-sectional studies of *H. pylori* infection [13,16,17]. One thing to note here is that the prevalence of *H. pylori* infection among individuals who were born before 1940 was lower than expected. There are several possible reasons. The first possibility is that in the elderly, *H. pylori* may disappear with the progression of gastric atrophy. Another possibility is that incidental *H. pylori* eradication might have occurred as a result of the widespread use of antibiotics in the elderly for the treatment of diseases such as upper respiratory diseases.

A decline in the age-standardized incidence of gastric cancer has been noted in many countries, including Japan. An examination of secular trends in *H. pylori* prevalence and gastric cancer incidence showed that the decline in *H. pylori* prevalence was in parallel with

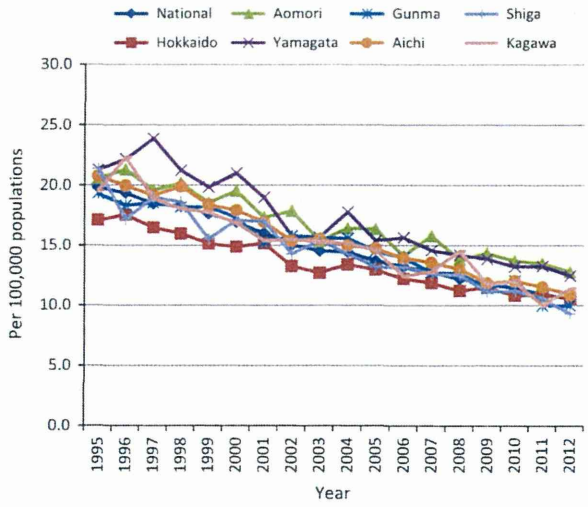

Figure 4 Age-adjusted mortality rates of gastric cancer in selected areas in Japan; 1995–2012. Source: Vital statistics, provided by Center for Cancer Control and Information Services, National Cancer Center, Japan. Website access: http://ganjoho.jp/professional/statistics/statistics.html#05

a decline in gastric cancer incidence [18]. Using a population-based microsimulation model, Yeh et al. estimated that approximately 50% of the observed decrease in distal gastric cancers from 1978 to 2008 in the United States could be attributable to the decline in *H. pylori* prevalence [19]. Similarly, when comparing the prevalence of *H. pylori* infection and age-adjusted mortality rates of gastric cancer in seven areas, we found that *H. pylori* prevalence generally correlated with gastric cancer mortality rates. Although the age-adjusted mortality rates have been declining in all seven areas, Aomori and Yamagata Prefectures had consistently higher rates compared with other areas throughout the period from 1995 to 2012(Fig. 4). Apart from *H. pylori* infection, salt intake is an important risk factor for gastric cancer [20]. There has been strong evidence indicating a synergistic effect of *H. pylori* and salt intake for gastric cancer among Japanese [21]. Despite a continuous decrease in salt intake per day, it was still high when compared with other Western countries [22]. We speculate that the high salt intake and high prevalence of *H. pylori* infection may account for the highest gastric cancer mortality rates observed in Yamagata Prefecture.

Our study has several limitations. First, our study included a small number of young people. There has been a marked decrease in the prevalence of *H. pylori* infection in younger generations over the past several decades in Japan. According to a recent survey, the prevalence was only 12.1% among those aged 1–18 years [23]. A clearer picture of the birth cohort effect for *H. pylori* infection would emerge by including data from young generations. Second, heterogeneities would be expected because we collected data in different prefectures. For example, the characteristics of study subjects and the period for which data were collected might differ across areas. The diagnostic tests also varied across areas. These variations may cause uncertainty in precisely estimating *H. pylori* prevalence. Third, data were retrieved from health checkup participants who may represent a health-conscious group. Therefore, the generalizability of our findings to the general Japanese population may be of a concern, and further studies involving a random sample of the general population are warranted.

In summary, the prevalence of *H. pylori* infection increases with age and exhibits geographic variations in Japan. There has been a striking decrease in the prevalence of *H. pylori* infection in younger Japanese populations. If the decline in *H. pylori* prevalence across various age groups continues, gastric cancer incidence is expected to be continuously decreasing in the coming years.

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V. *H. pylori* 感染症関連疾患と除菌治療の意義

早期胃癌の内視鏡治療後胃

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After endoscopic treatment of early stage gastric cancer

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Abstract

Almost all gastric cancers including intestinal type and diffuse type develop from background of *H. pylori* infection of the gastric mucosa. In treatment of gastric cancer, the development of endoscopic technique expanded the indication of endoscopic treatment for early gastric cancer. Residual cancers due to incomplete resection occur within two years after endoscopic treatment. However, metachronous cancers continue to occur for long-term after endoscopic treatment of primary cancer. Multi-center, randomized controlled trial in Japan showed that *H. pylori* eradication significantly reduced the incidence of metachronous cancer after endoscopic resection. Severe atrophy is high risk factor on metachronous gastric cancer after successful eradication. Because *H. pylori* eradication after endoscopic treatment of early gastric cancer have been covered under public health insurance, positive eradication therapy for *H. pylori* infection is expected to reduce metachronous cancer.

Key words: *H. pylori* eradication, cancer prevention, metachronous cancer

はじめに

胃癌は*H. pylori*感染に伴う慢性炎症を背景として発生する疾患の一つである．世界保健機関(WHO)の下部組織である国際癌研究機関(IARC)は1994年に疫学的成績から，*H. pylori*を胃癌のdefinite carcinogen(明確な発癌因子)に指定した[1]．その後，*H. pylori*の感染モデルであるスナネズミを用いた動物実験，ヒトでの前向き研究などから，*H. pylori*感染と胃癌の因果関係は明らかとなった[2]．胃癌は*H. pylori*の持続感染を背景として，長期にわたる炎症が続き，遺伝子変異が蓄積されてやがて発癌に至ると考えられる．すなわち，胃癌の成因は*H. pylori*感染だけではないが，*H. pylori*感染という必要条件に更にほかの環境因子などが加わることで，発癌率

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が高くなる[3]. 炎症のない背景粘膜から*de novo*型に胃癌が発生することはまれで, その割合は1%に満たないとされる[4,5]. したがって, *H. pylori*感染は胃癌の最も重要な成因といえる.

*H. pylori*除菌によって胃粘膜の炎症が改善することで, 胃癌の発生や発育進展がなんらかの影響を受けることが推測される. 動物実験では*H. pylori*除菌に胃癌の予防効果を有することが認められ, 感染期間が短いほど除菌による胃癌の抑制効果が強いことも示されている[6]. ヒトにおいては4つのコホート試験において, *H. pylori*除菌の胃癌発症の抑制効果が報告された[7-10]. また, 無作為比較試験のメタ解析で明らかな有意ではなかったが, *H. pylori*除菌の胃癌抑制の可能性が示された[11]. 早期胃癌の内視鏡治療後に起こる異時性多発癌に対しては, 我が国での多施設による無作為化試験で, *H. pylori*除菌が有意に異時癌の発生を抑制することが証明された[12]. その成績により2010年にほかの2疾患とともに, 早期胃癌に対する内視鏡治療後胃として公知申請によって*H. pylori*の除菌治療が保険適用となった[13]. しかし, *H. pylori*除菌後の経過観察中に, 胃癌が発見される症例が存在することも明らかになっており, 除菌成功後の経過観察が重要である.

1. 胃癌の内視鏡治療

以前の胃癌治療は, 外科切除あるいは外科切除の適応外に二分されていた. 外科切除としては早期胃癌でも進行胃癌でも, 広範囲胃切除と系統的リンパ節郭清が行われてきた. しかし, 外科サイドでは患者の侵襲度, QOL, 治療効果, コストなどを考慮して, 画一的な手術法から個々の症例の胃癌病期に応じて, 腹腔鏡下手術から拡大手術まで外科的治療の選択幅が広がった. 一方, 内視鏡機器の発展や内視鏡技術の開発によって, 粘膜内癌に対しての内視鏡切除術が確立されてきた. 胃癌学会の胃癌治療ガイドラインでは内視鏡治療の適応をリンパ節転移の可能性がほとんどなく, 腫瘍が一括切除できるものとして, 2cm以下の粘膜内癌で, 組織型が分化型で潰瘍合併のないものとしている[14].

最近では内視鏡的粘膜下層剥離術(endoscopic submucosal dissection: ESD)が開発されたことにより, 従来の内視鏡的粘膜切除術(endoscopic mucosal resection: EMR)では一括切除が不可能であった2cm以上の大きさの病変に対しても一括切除が可能となった. そのため, 分化型M癌であれば大きさに制限はなく, 3cm以下の潰瘍合併の分化型M癌, 3cm以下の潰瘍非合併の分化型SM1癌, 2cm以下の未分化型M癌に対して, 内視鏡治療の適応拡大がなされている[15]. EMRでは, 一般的には2チャネルスコープを用いて, 病変の下に局注を施行した後に, 把持鉗子とスネアーにて病変部を絞扼・切除するが, ESDでは局注後はナイフを用いて病変周囲を全周切開し, 次に病変の粘膜下層部を切って, 胃壁から病変を剥離させる方法である. 従来のEMRに比べ, 技術的に難しく偶発症が多い欠点はあるが, ESDによって内視鏡的に切除できる病変の大きさに制限がなくなった. 胃癌における内視鏡治療の重要性は増している.

2. 内視鏡治療後の遺残再発と異時性多発癌

内視鏡治療後に, 胃癌再発病変として遺残再発や異時性多発癌を認めることは少なくない. 内視鏡切除後の遺残再発については, 経過観察中に切除瘢痕に接して癌を再び認めたものと定義でき, 不十分な内視鏡治療が原因とされる. 分割切除の場合には標本の再構築による組織学的検討が不十分になるために, 完全切除された場合に比べ遺残再発のリスクが高い. 一方, 内視鏡切除後の経過観察中に, 切除した部位とは別の部位に異時癌(二次癌)を認めることがある. 異時癌の発生は内視鏡治療後長期にわたって一定の割合で続く一方で, 内視鏡治療が不完全なために起こる同部位再発(遺残再発)は80%近くが1年以内で, ほとんどが2年以内に発見されるとの特徴がある[16-20]. 遺残再発の場合にはある程度の腫瘍量が残っていることと注意深い経過観察のため, ほとんどの遺残再発が短期間内で内視鏡的に発見されていると考える.