(×100 magnification on a 19-inch monitor) was obtained by BLI in the BLI-bright mode. Thereafter, images were digitized (1280×1024 pixels) and stored. All lesions were treated by endoscopic submucosal dissection or surgical resection and then diagnosed histopathologically, and results of the magnifying endoscopy study were compared with results of the histopathology study.

We also produced a set of images of flat or slightly depressed, small (< 10 mm), reddened lesions from 40 gastric lesions (Fig. 3). All lesions were biopsied. No biopsy specimen of a reddened lesion showed evidence of malignancy. We then calculated the SVM output value for the various lesion types on the images, as described above.

The study was conducted with full approval of the ethics committee of Hiroshima University and according to the guidelines of the Declaration of Helsinki, and patients and/or family members provided informed consent for the endoscopic examination and pathologic study of resected specimens.

Validation Images

We gathered validation images from among the BLI-derived magnifying endoscopy images of the histologically confirmed gastric cancers. In the same manner, we obtained images of tissue surrounding the lesions and of reddened lesions. The validation set did not include images that were considered unsuitable for evaluation (exclusion criteria: out-of-focus images, images that were blurred, images with halation).

On each BLI-derived magnified image, a region of interest (ROI) was selected manually (Fig. 4). Validation images of cancerous lesions, reddened lesions, and surrounding tissue were extracted from these ROIs. Thus, we obtained 100 images each of cancerous and surrounding tissues and 40 images of reddened lesions.

Training Images

The training images were obtained from a different group of patients examined at Hiroshima University Hospital. In gathering the training images of cancers, we selected images of histologically confirmed cancers with either an irregular microvascular pattern or an irregular microsurface pattern. In gathering the training images of surrounding tissue, we selected images of histologically confirmed noncancerous tissue with a regular microvascular pattern and a regular microsurface pattern. The set

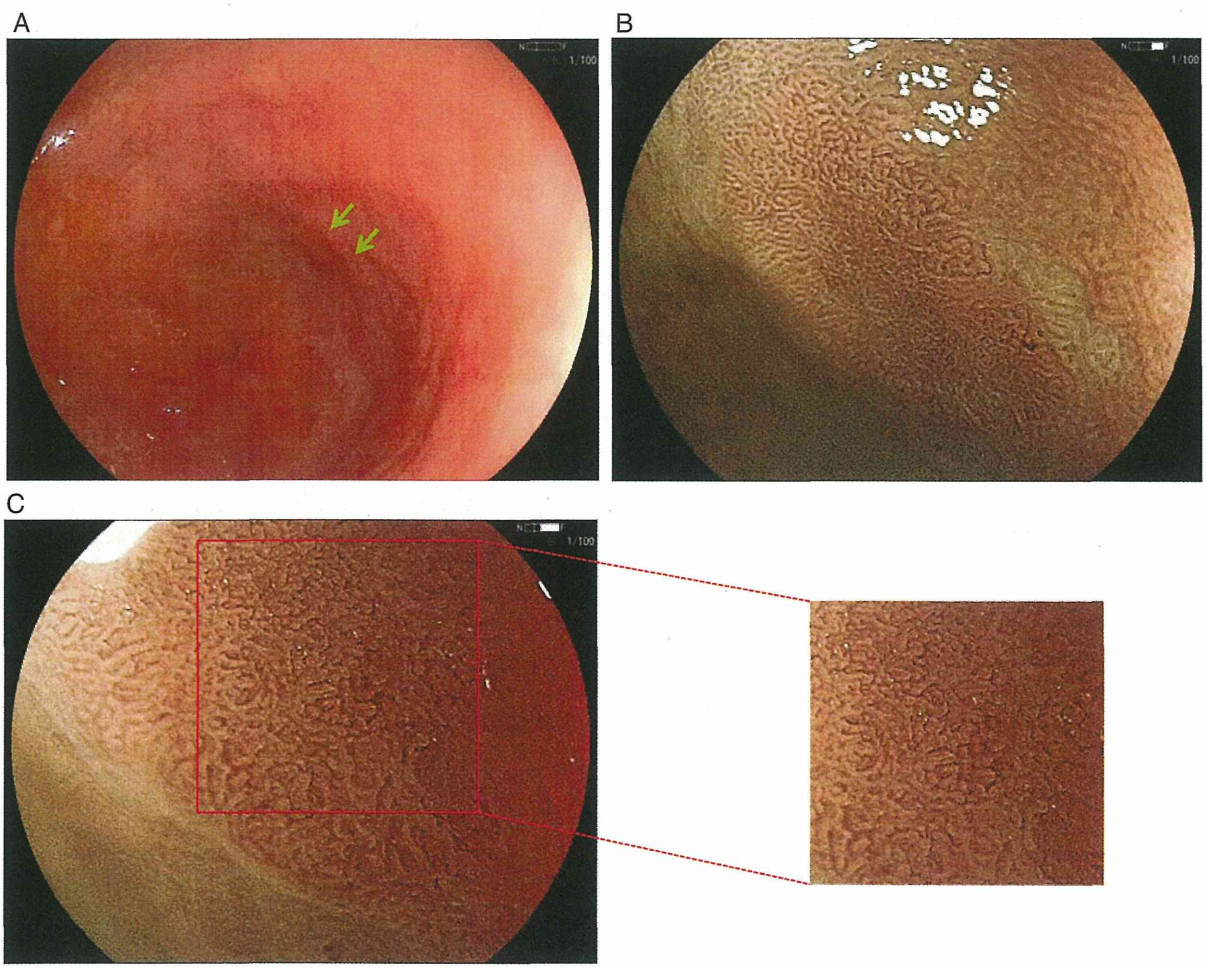

FIGURE 3. Images of a slightly depressed, reddened lesion in the antrum viewed under white light (A), in BLI bright mode at ×50 magnification on a 19-inch monitor (B) and in BLI bright mode at ×100 magnification on a 19-inch monitor (C). The ROI (C) was selected on the BLI-derived magnifying image. The arrows indicate a slightly depressed, reddened lesion. BLI indicates blue-laser imaging; ROI, region of interest. full color online

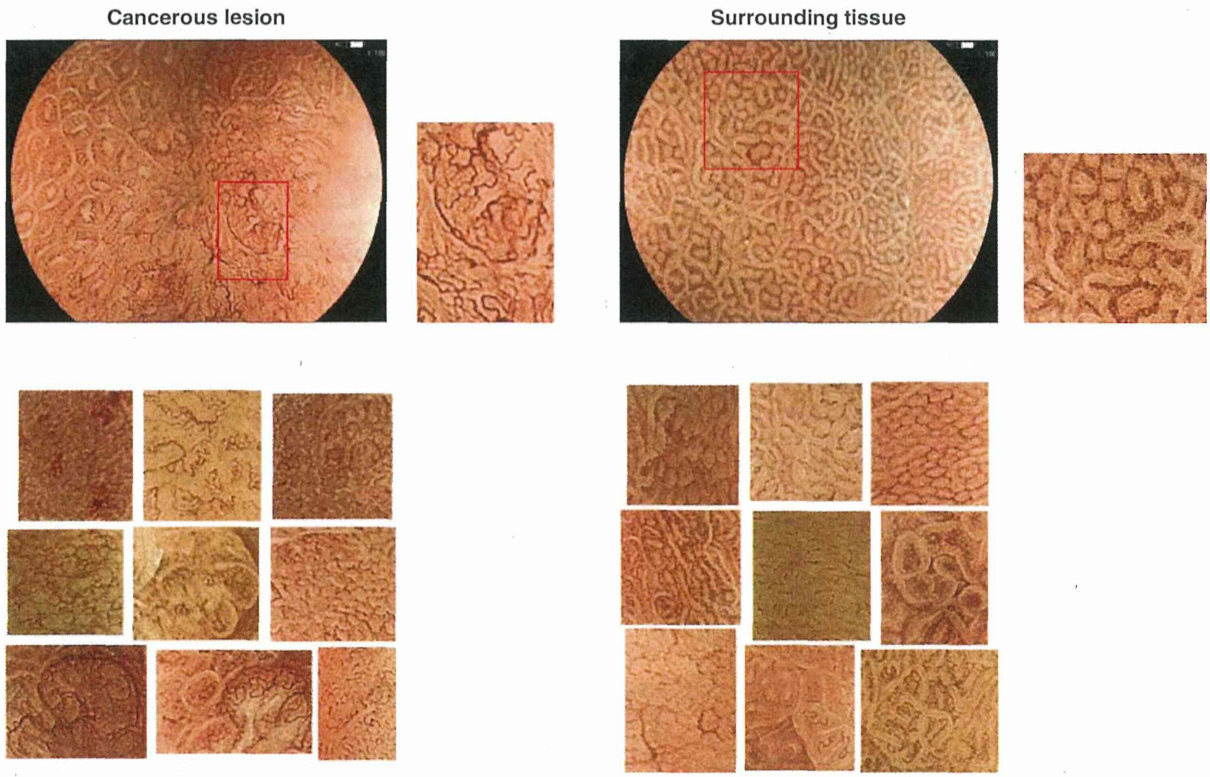

FIGURE 4. Examples of blue-laser imaging–derived magnifying endoscopy images of a cancerous lesion and surrounding tissue. Regions of interest are cut out for analysis. full color online

of training images comprised 587 cutout images of gastric cancer and 503 cutout images of surrounding tissue.

Statistical Analysis

Values are reported as mean ± SD. Differences in SVM output values for differentiated-type cancer and undifferentiated-type cancer were analyzed by the Mann-Whitney U test, and a P value of <0.01 was considered statistically significant. The significance level after Bonferroni correction for multiple testing was $P = 0.00333$ (0.01/3). For general statistical analysis, we used the R statistical environment (http://www.cran.r-project.org).

RESULTS

Clinical Application of Our Quantitative Analysis System

In applying our new software for quantitative analysis and identification of the various types of tissue, the average SVM output value was 0.846 ± 0.220 for images of cancerous lesions, 0.381 ± 0.349 for images of reddened lesions, and 0.219 ± 0.277 for images of surrounding tissue. The SVM output value for cancerous lesions was significantly higher than that for reddened lesions ($P = 1.453 \times 10^{-17}$) and surrounding tissue ($P = 3.740 \times 10^{-41}$) (Fig. 5A). The average SVM output value for differentiated-type cancer was 0.840 ± 0.207 and for undifferentiated-type cancer was 0.865 ± 0.259 (Fig. 5B).

Images of cancerous lesions, reddened lesions, and surrounding tissue with SVM output values are shown in Figure 6.

DISCUSSION

In this study, we used magnifying endoscopy with BLI for diagnosis of early gastric cancer. One advantage of the laser light source is that narrow-band illumination with a single-wavelength laser is ideal for imaging targeted objects. In addition, the lasers are of high power and the lighting system is efficient, is long lasting, and consumes low power. Moreover, lasers of various wavelengths can be used with the new endoscopy system, and the output power can be controlled independently. The addition of excitation light to a laser-based endoscopy system may become the basis for next-generation endoscopy systems, such as those to be used for endoscopic molecular imaging.[8–10]

The endoscopy system we used suitably visualized microvessels and structures in the superficial portion of the mucous membrane affected by early gastric cancer. Using the new laser light source in the white-light mode, we obtained images comparable to those obtained with a conventional xenon lamp. The endoscopic images obtained in the BLI mode and the BLI-bright mode differed in terms of the surface and vascular patterns. The BLI mode, with its shorter wavelength, is used to acquire mucosal surface information. The BLI-bright mode, which is brighter, allows for an overall view in addition to highlighting surface characteristics. With the BLI mode, we achieved clear and detailed visualization of microsurface structures and microvascular patterns of the superficial mucosa. Under the brightness of the BLI-bright mode, the mucosal surface was clearly exposed (Fig. 7).

Yao et al[3] devised the VS classification system, which is based on separate evaluations of the microvascular (V)

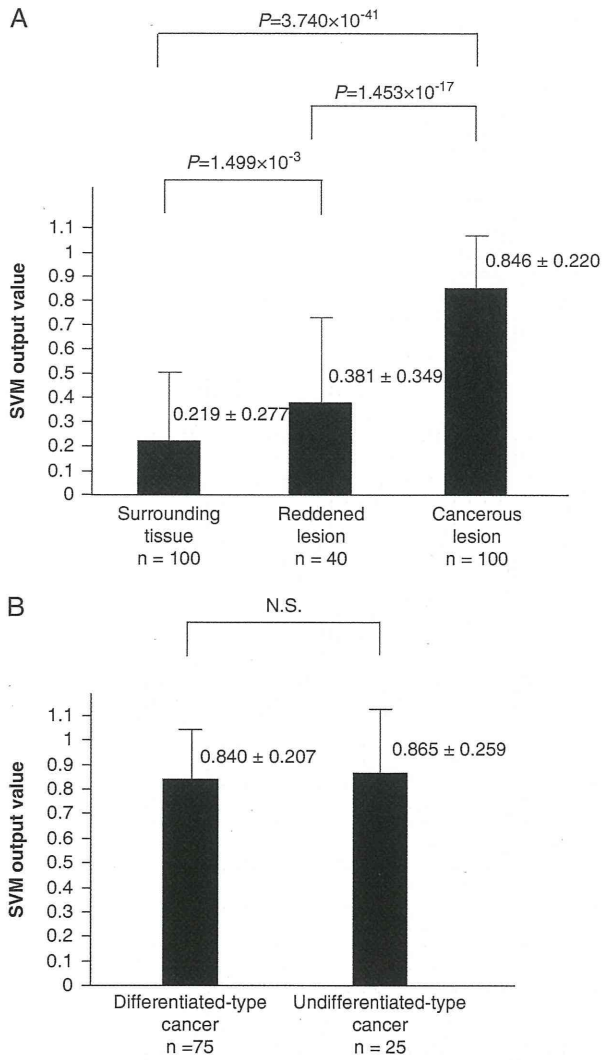

FIGURE 5. A, SVM output values for images of cancerous lesions, reddened lesions, and surrounding tissue. Values are mean ± SD. B, SVM output values for images of differentiated-type cancer and undifferentiated-type cancer. Values are mean ± SD. N.S. indicates not significant; SVM, support vector machine.

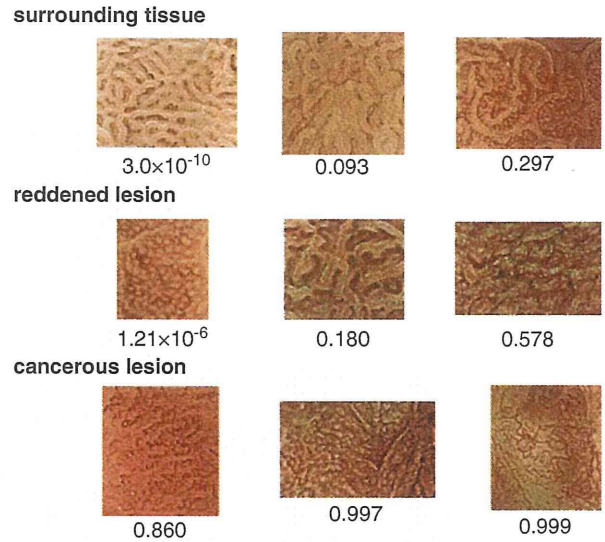

FIGURE 6. Images of cancerous lesions, reddened lesions, and surrounding tissue with support vector machine output values (shown below each image). full color online

and microsurface (S) patterns, which are then combined for a diagnosis of gastrointestinal pathologies. Accordingly, the microvascular and microsurface patterns are classified as regular, irregular, or absent. Yao and colleagues showed early gastric cancers to be associated with the presence of either an irregular microvascular pattern with a demarcation line or an irregular microsurface pattern with a demarcation line.

The main purpose of gastrointestinal endoscopy is the detection and qualitative diagnosis of lesions. Endoscopic diagnosis is based on differentiation between non-neoplastic, neoplastic, and malignant lesions. However, it can be difficult to distinguish between the lesion types by routine endoscopic examination.[11] In its early stages, gastric cancer appears as a shallow depression or a small, flat lesion, which happens also to be the most common macroscopic appearance of a noncancerous erosion or superficial inflammation in the stomach. Therefore, pathologic examination of biopsy samples is necessary for differentiation of early cancer from a noncancerous lesion. Because a large number of these types of lesions are encountered during endoscopy, it is unrealistic to examine all of them pathologically. Thus, only those suspected of being cancerous are biopsied. As previously reported, magnifying endoscopy combined with NBI is remarkably useful for differential diagnosis of superficial gastric lesions identified under white light.[2,12,13]

In this study, we calculated the SVM output value for reddened lesions identified by magnifying endoscopy with BLI because these lesions are difficult to distinguish from cancer under conventional gastrointestinal endoscopy. We applied a quantitative analysis system to images obtained by magnifying endoscopy with BLI and confirmed the ability of the system to differentiate between early gastric cancer, gastritis surrounding cancer, and gastritis characterized by localized reddened mucosa. We found the SVM output values for reddened lesions and surrounding tissue to differ significantly from the SVM output value for cancerous lesions identified by means of magnifying BLI and our quantitative analysis system.

Research into image recognition is ongoing in various laboratories, and various methods have been studied. Face recognition technology is a practical example of applied image recognition. A bag-of-features (or bag-of-visual words, bag-of-keypoints) is a representation of images used mainly for generic object recognition or category recognition. Bag-of-features for object recognition was proposed by Csurka et al[14] in 2004 and has since been used widely for general object recognition and image retrieval.[15,16] SIFT[17] is a new method that is invariant not only to image scaling and rotation but also to change in illumination. These characteristics make SIFT superior to several other descriptors including steerable filters, different invariants, moment invariants, and complex filters.[18] These advantages allow application of SIFT in various object-recognition and face-recognition fields.[18–20] However, neither the weakness of SIFT nor its advantages and disadvantages in face recognition have been reported.

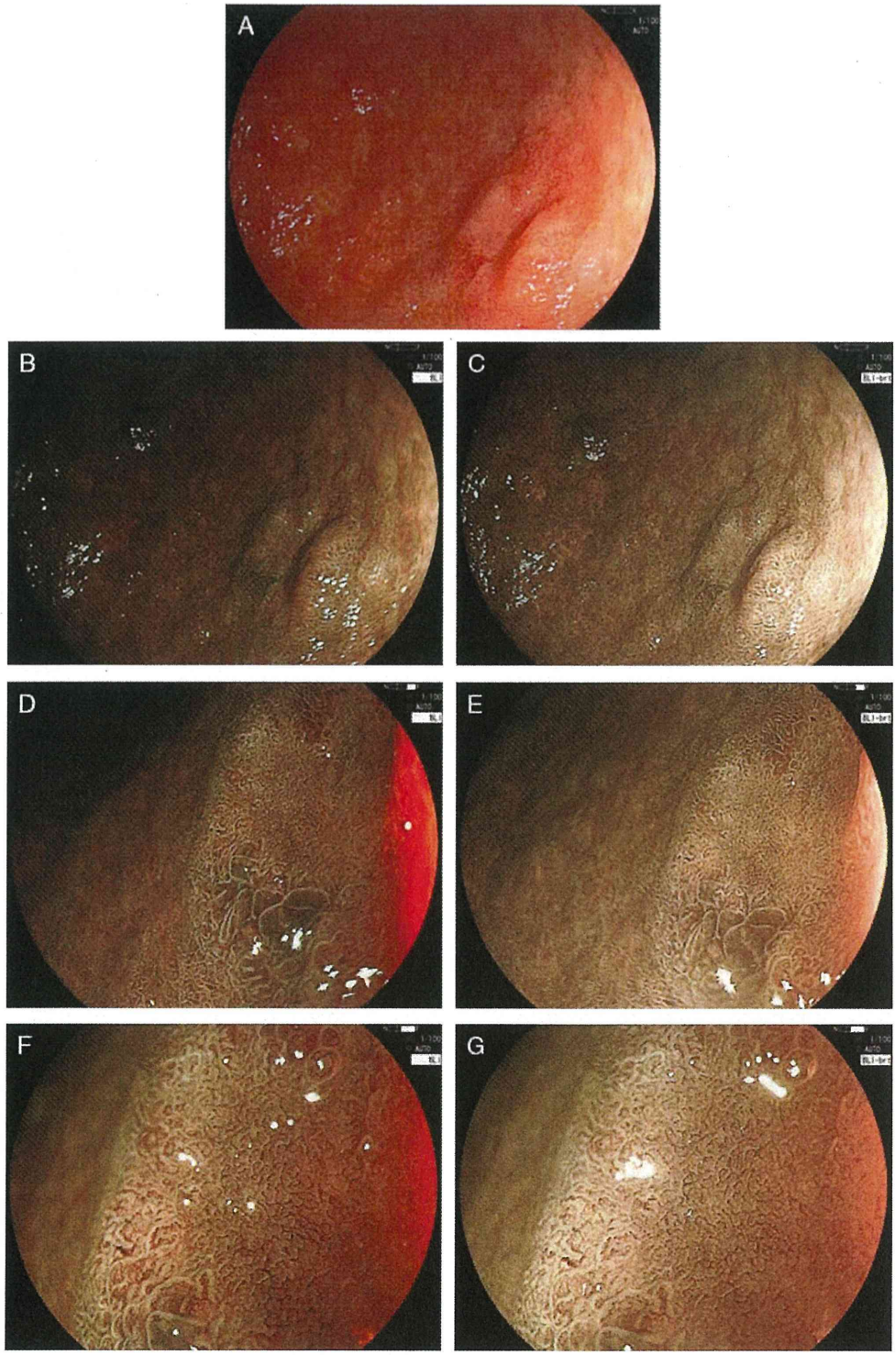

FIGURE 7. Images of gastric adenocarcinoma (A) identified as a flat depression in the antrum with the new endoscopy system in the white-light mode. The image is comparable to a white-light image obtained with a conventional xenon lamp. The same lesion depicted without magnification in the (B) BLI mode and (C) BLI-bright mode. Note that the lesion appears brighter under BLI-bright than under BLI. The same lesion depicted at ×50 magnification on a 19-inch monitor in the (D) BLI mode and (E) BLI-bright mode. In both modes, the microsurface structure and the microvascular pattern of the superficial mucosa are clearly visualized. The lesion depicted at ×100 magnification on a 19-inch monitor in the (F) BLI mode and (G) BLI-bright mode. In both modes, the detailed microsurface structure and microvascular pattern of the superficial mucosa are clearly visualized. The BLI-mode image is of greater contrast than the BLI-bright-mode image. BLI indicates blue-light image. full color online

Our study was limited in some respects. One is that we used images that were chosen by endoscopic specialists. We are in the process of developing a computerized system that will allow automatic selection of ROIs. The system can scan the endoscopic images and automatically extract the region that is most malignant among them.[21] Further development that will allow magnifying observation without a zoom lens by a high-resolution charge-coupled device or complementary metal oxide semiconductor image sensors will permit novices to use the computer-aided system without needing to identify the discriminatory features of lesions. They will simply need to bring gastric lesions into clear focus when they believe a BLI image should be expressed quantitatively.

Although further study and development are needed, we conclude that magnifying endoscopy with BLI and computer-based analysis will allow quantitative diagnosis of gastric lesions.

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Time Trends in *Helicobacter pylori* Infection and Atrophic Gastritis Over 40 Years in Japan

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Keywords
Gastric atrophy, intestinal metaplasia, smoking, salt intake, *Helicobacter pylori*, gastric cancer.

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Abstract

Background: *Helicobacter pylori* infection produces progressive mucosal damage that may eventually result in gastric cancer. We studied the changes that occurred in the presence and severity of atrophic gastritis and the prevalence of *H. pylori* infection that occurred coincident with improvements in economic and hygienic conditions in Japan since World War II.

Materials and Methods: The prevalence of *H. pylori* infection and histologic grades of gastric damage were retrospectively evaluated using gastric biopsy specimens obtained over a 40-year period. Gastric atrophy and intestinal metaplasia were scored using the updated Sydney classification system.

Results: The prevalence of *H. pylori* and severity of atrophy were examined in 1381 patients including 289 patients examined in the 1970s (158 men; mean age, 44.9 years), 787 in the 1990s (430 men; 44.2 years), and 305 in the 2010s (163 men; 53.2 years). Overall, the prevalence of *H. pylori* infection decreased significantly from 74.7% (1970s) to 53% (1990s) and 35.1% (2010s) ($p < .01$). The prevalence of atrophy in the antrum and corpus was significantly lower in the 2010s (33, 19%, respectively) compared to those evaluated in either the 1970s (98, 82%) ($p < .001$) or 1990s (80, 67%) ($p < .001$). The severity of atrophy and intestinal metaplasia also declined remarkably among those with *H. pylori* infection.

Conclusions: There has been a progressive and rapid decline in the prevalence of *H. pylori* infection as well a fall in the rate of progression of gastric atrophy among *H. pylori*-infected Japanese coincident with the westernization and improvements in economic and hygienic conditions in Japan since World War II.

In 1983, Warren and Marshall [1] cultured *Helicobacter pylori* and suggested that it was responsible for gastritis and the gastritis-related diseases, peptic ulcer disease, and gastric cancer [2,3]. In 1994, the World Health Organization classified *H. pylori* as a group I carcinogen [4] and confirmed that designation in 2012 [5]. *Helicobacter pylori* is now recognized as etiologically responsible for gastritis-associated peptic ulcer disease, the majority of gastric cancers as well as gastric MALT lymphoma. Proof of these etiological associations capped decades of work on the natural history of gastritis and its relation to disease [6–16].

Helicobacter pylori causes progressive gastric damage that is initially most prominent in the antrum and subsequently advances into the corpus [17,18]. Gastric cancer risk is associated with the extent and severity of

atrophic injury, which is recognized by loss of normal glandular elements (atrophy), and the development of metaplastic epithelia (pseudopyloric or spasmolytic-polypeptide expressing type and intestinal type) [17,19]. The population risk of developing gastric cancer increases with the rate of development of these atrophic changers [17]. In Western countries such as the United States, the incidence of gastric cancer was noted to decline rapidly such that it fell from being the most common cancer in the first quarter of the 20th century to an uncommon disease by the beginning of the 21st century [20]. This change in incidence was initially associated with a marked increase in duodenal ulcer which then also declined as the prevalence of *H. pylori* infection declined [20]. The different *H. pylori*-related disease is associated with different patterns of gastritis (i.e., atrophic pangastritis or corpus predominant gastritis in gastric ulcer and gastric cancer and antral predominant with duodenal ulcer) suggesting that the rapid changes in disease manifestation were accompanied by similar changes in the rate of development of atrophic gastritis [17,19–22].

The incidence and mortality rate of gastric cancer have declined in the past several decades in Japan [23]. However, there have been few studies regarding the trends in *H. pylori* infection and the pattern and severity of gastritis over this same time period [24–28]. This study focused on correlating the long-term changes in the prevalence of *H. pylori* infection with the histologic expression of the infection in Japan over a 40-year period starting with the 1970s.

Methods

Patient Selection

We retrospectively analyzed records of patients undergoing upper gastrointestinal endoscopy based on three 3-year periods (i.e., 1975–1978, 1991–1994, and 2010–2013). The records were obtained from Hiroshima University Hospital (1975–1978 and 1991–1994) and Kawasaki Medical School (2010–2013) both located in the western portion of Honshu Island. The patients were among those who received upper endoscopy for investigation of dyspepsia or for screening of gastric cancer. Additional entry criteria included age older than 18 years at the time of endoscopy and no localized lesions in the upper gastrointestinal tract such as esophagitis, peptic ulcer, or malignancies. Exclusion criteria included: 1, history of previous *H. pylori* eradication therapy; 2, patients who, in the previous 8 weeks, had received drugs that may have affected the histologic evaluation before (e.g., nonsteroidal anti-inflammatory drug: NSAID, proton-pump inhibitor, or antibiotics). Written informed consent for the procedures was obtained from all patients. The study protocol was approved by the Ethics Committee of the Hospitals.

Histologic Assessment

Two biopsy specimens were each obtained from the lesser curvature of the middle antrum and the anterior and posterior regions of the corpus for evaluation of gastritis and *H. pylori* infection. Biopsy specimens were cut into 4-μm-thick slices and were stained using the hematoxylin and eosin, Giemsa, or Gimenez methods. Histologic slides were independently assessed by two gastroenterologists experienced in the evaluation and scoring of gastritis with no knowledge of the clinical findings of the patients (KH and TK). These two gastroenterologists are very versed in the pathology of alimentary tract, especially, the updated Sydney system. Disagreements were resolved by joint review. The presence of *H. pylori* was identified using Giemsa or Gimenez staining. Atrophy and intestinal metaplasia were scored as present or absent, and the severity of mucosal atrophy and intestinal metaplasia was scored on a scale of 0–3 according to the updated Sydney system of classification: 0 = normal, 1 = mild, 2 = moderate, and 3 = severe.

Smoking Rate and Salt Intake in Japanese Population

The Ministry of Health, Labour and Welfare has investigated the smoking prevalence every year from 1965 for men and woman over 20 years old [29]. We extracted the mean smoking rate according to gender from 1965 to 2012. Salt intake in the Japanese population has been investigated by the Ministry of Health, Labour and Welfare since 1975. Before that time, the salt intake was estimated from the consumption trend of salty foods. We used the data published from the years 1950 to 2010 [30].

Statistical Evaluation

The age-specific prevalence of *H. pylori* infection as well as the atrophic gastritis and intestinal metaplasia scores were separately calculated in the three periods (i.e., 1970s, 1990s, and 2010s) considering seven age groups: 18–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years. The statistical significance for each group was examined using the chi-square test.

p-values $< .05$ were considered statistically significant. 95% confidence intervals (CI) were also calculated.

Results of gastritis scores are expressed as mean ± standard error and as mean and 95% CI, and age of subjects is expressed as mean ± standard deviation. The changes were also analyzed by ANOVA on ranks for the severity (Sydney score) of antral atrophy, antral intestinal metalasia, corpus atrophy, and corpus intestinal metaplasia for those with *H. pylori* infections both for the entire group from each of the three time periods and separately for three age groups (20–39, 40–59, and 60–79) comparing the three time periods. Pairwise multiple comparisons were performed using Dunn's method (Sigma Stat California, USA 3.5). $p < .05$ was considered significant.

Results

The total number of patients underwent upper routine endoscopy from 2010 to 2013 was 5307, 5691, and 5089, respectively (We don't have these data for 1975–1978, 1991–1994). Among these total patients, as not a random sample, we selected our study patients who gastroenterologists need to evaluate the histologic gastritis or *H. pylori* infection for taking gastric biopsy specimens or the patient wished to inspect. A total of 1381 subjects were entered including 289 (158 men, 131 women; mean age, 44.9 ± 16 years) in the 1970s group, 787 (430 men, 357 women; mean age, 44.2 ± 17 years) in the 1990s group, and 305 (163 men, 142 women; mean age, 53.2 ± 17 years) in the 2010s group. The overall prevalence of *H. pylori* infection was significantly lower (107/305) among those studied in the 2010s (35.1%; 95% CI = 29–40%) compared to those evaluated in either the 1970s (216/289, 74.7%; 95% CI = 69–79%; $p < .001$) or 1990s (417/787, 53%; 95% CI = 49–56%; $p < .05$). In the 1970s, the prevalence of *H. pylori* infection increased with age but reached a plateau by age 30 consistent with the notion that the disease is primarily acquired in childhood and the incidence for any birth cohort tends to be stable after about age 20. However, evaluation of the trends in 2010s shows that overall the rate of acquisition was low leading to a low overall prevalence which was relatively constant for the first two decades followed by an increase reflecting the higher rates of acquisition that had previously occurred among birth cohorts born before approximately 2000 (Fig. 1).

Prevalence of mucosal atrophy and intestinal metaplasia across the 1970s, 1990s, and 2010s in *H. pylori*-positive patients is shown in Table 1. The prevalence of atrophy in the antrum was significantly lower in the 2010s (33%, 35/107) compared to those evaluated in either the 1970s (98%, 212/216) ($p < .001$) or 1990s (80%, 333/417) ($p < .001$). Atrophy was also lower in the corpus and was significantly lower in the 2010s

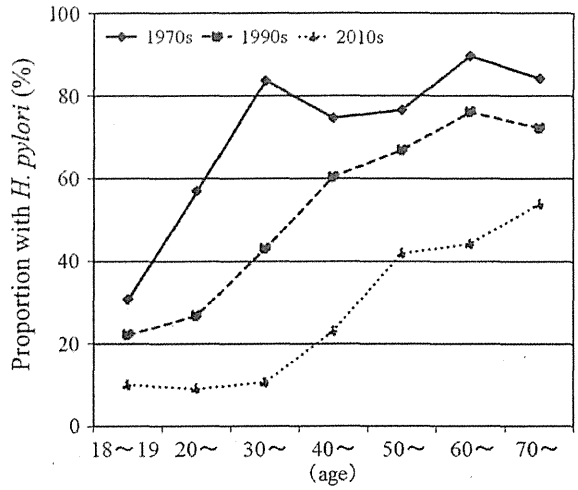

Figure 1 Age-specific prevalence of *Helicobacter pylori* from the 1970s to the 2010s in Japan. The pattern was typical for that of a developing country in the 1970s and then showed a progressive shift to the right as the rate of acquisition steadily declined in childhood. The base line prevalence currently appears to be stable at about 10%.

Table 1 Prevalence of mucosal atrophy and intestinal metaplasia across the 1970s, 1990s, and 2010s in *Helicobacter pylori*-positive patients

	1970s (n = 216)	1990s (n = 417)	2010s (n = 107)
Atrophy (n)			
Antrum	98% (212)	80% (333)*	33% (35)**,##
Corpus	82% (177)	67% (280)*	19% (20)**,##
Intestinal metaplasia (n)			
Antrum	63.9% (138)	37.4% (156)*	15% (16)**
Corpus	32.4% (70)	21.3% (89)	4.7% (5)*

**$p < .001$ versus 1970s, *$p < .05$ versus 1970s, ##$p < .001$ versus 1990s.

(19%, 20/107) compared to those evaluated in either the 1970s (82%, 177/216) ($p < .001$) or 1990s (67%, 280/417) ($p < .001$). Finally, the prevalence of intestinal metaplasia in the antrum was significantly lower in the 2010s (15%, 16/107) compared to those evaluated in the 1970s (63.9%, 138/216) ($p < .001$) and that in the corpus was also significantly lower in the 2010s (4.7%, 5/107) compared to those evaluated in the 1970s (32.4%, 70/216) ($p < .05$).

The severity and extent of mucosal damage were investigated by assessing the prevalence of gastric mucosal atrophy and intestinal metaplasia in relation to age. Among those with *H. pylori* infection, the severity of mucosal atrophy and intestinal metaplasia significantly declined during the 1970s, 1990s, and 2010s (Figs 2 and 3).

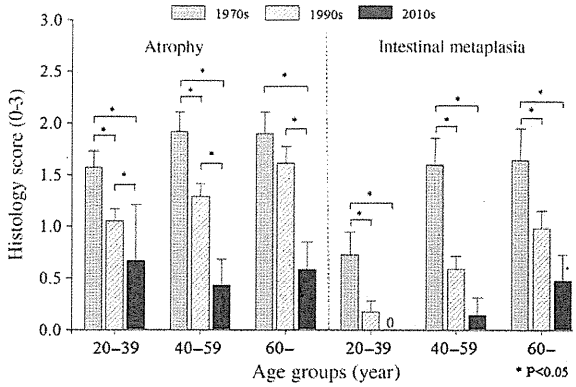

Figure 2 Mean ± 95% CI of atrophy and intestinal metaplasia scores of antral mucosal biopsies in *Helicobacter pylori*-positive patients according to age group. Both mucosal atrophy and metaplasia in the antrum significantly decreased in time period setting in all age group.

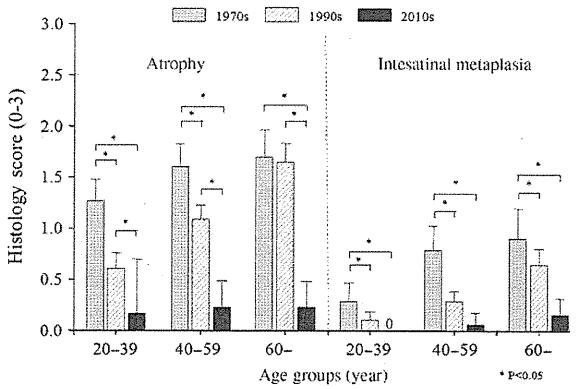

Figure 3 Mean ± 95% CI of atrophy and intestinal metaplasia scores of corpus mucosal biopsies in *Helicobacter pylori*-positive patients according to age group. Both mucosal atrophy and metaplasia in the corpus significantly decreased in time period setting in all age group.

Discussion

A significant decline in the prevalence of *H. pylori* infection in recent years in Japan has been documented previously and corresponds to improvements in national hygienic conditions and a trend toward nuclear families [24–28]. To our knowledge, this is the first report describing the recent trends while separately addressing the reduction in the prevalence of *H. pylori* infection in addition to the decline in severity of gastritis among *H. pylori*-infected Japanese adults. We show that among *H. pylori*-infected individuals, the age-specific severity of atrophy and intestinal metaplasia has declined remarkably over 40 years of observation. Sipponen et al. [31] reported the prevalence of gastritis in Finland over 15 years using biopsy specimens of patients obtained in 1977 (702 patients), 1985 (1309 patients), and 1992 (1447 patients). They reported a decreasing prevalence of gastritis associated with a decreasing rate of *H. pylori* infections. Valle et al. [32] had previously reported the long-term course and consequences of *H. pylori* gastritis in a 32-year follow-up study (1952–1983) in Finland. They showed that the appearance of parietal cell antibodies during follow-up was associated with progression of severe corpus atrophy which was accompanied by disappearance of *H. pylori* infection. Imai and Murayama [33] examined autopsies and resected stomachs of Japanese patients in two different periods (1957–1962 and 1978–1980) and showed that although there was a downward tendency in the prevalence of *H. pylori* infection among middle-aged individuals, the prevalence of intestinal metaplasia generally remained high. In contrast, our more recent data clearly show a long-term trend toward a reduction in the prevalence of *H. pylori* infection as well as a change in the pattern of damage among those with *H. pylori* infection. This trend was evident despite the introduction of proton-pump inhibitors whose use would tend to enhance the rate of progression among those with *H. pylori* infection [34,35].

The eventual outcome of an *H. pylori* infection is related to the interaction between the virulence of the *H. pylori* strain, the genetic background of the host, and environmental factors such as diet [20]. Both smoking and salt intake have been shown to promote more rapid development of atrophic gastritis and intestinal metaplasia [36–38]. In a previous study, we investigated the relationship between *H. pylori* infection, smoking, atrophic gastritis, and intestinal metaplasia and found that atrophy and the histologic grade of intestinal metaplasia grades were higher in *H. pylori*-positive smokers than among nonsmokers [36]. Figure 4 shows the change in the fall in prevalence of smoking in the Japanese population over the past 40 years. High salt intake has long been established as risk factors for gastric cancer [39],

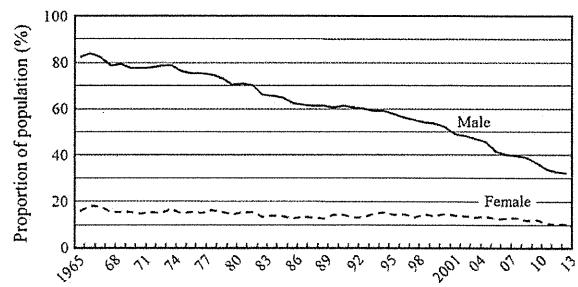

Figure 4 Time trend over 40 years showing the prevalence of smoking according to the sex in Japanese population. The smoking rate in the Japanese population has decreased remarkably over the past 40 years [29].

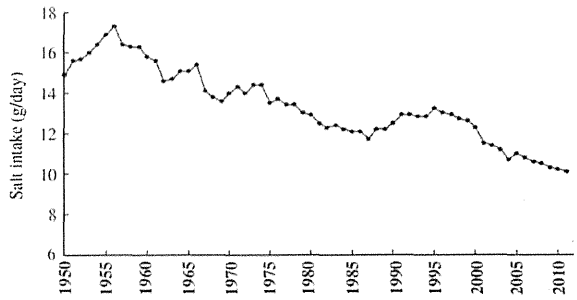

Figure 5 Time trend of daily salt intake levels in the past 60 years in the Japanese population. Salt intake in the Japanese population has decreased remarkably in the past 60 years [30].

and the daily salt intake in Japanese population has been decreasing over the past 60 years (Fig. 5). In addition, the reduction in salt intake and smoking, the Japanese diet has changed markedly since World War II such that the fat and protein intake are now similar to that Western countries [40]. The introduction of refrigeration and improvements in transportation have also resulted in a more varied diet and elimination of seasonal variation in availability of fruits and vegetables.

Our prior animal studies using the *H. pylori-infected* Mongolian gerbil showed that excessive salt enhanced gastric corpus gastritis [37] and that long-term administration of a high-protein or casein diets suppressed corpus atrophic gastritis [41]. In that study, we proposed that the high-protein diet enhanced gastrin secretion which stimulated G cells to increase acid secretion which in turn limited the *H. pylori* infection to the antrum similar to what is seen in patients with duodenal ulcer [42]. Whatever the mechanism, the change in the Japanese diet to one with an increase in the intake of protein, fresh fruits, and vegetable and decreased use of salt likely contributed greatly to the observed changes in the development of atrophic gastritis demonstrated among *H. pylori*-infected Japanese.

As noted earlier, the most common *H. pylori* strains circulating in Japan are CagA positive of the East Asian CagA genotype [43]. These strains are thought to be highly virulent, and recent studies [44–46] have confirmed that these strains remain most common. The fact that the extent and severity of atrophic changes have declined rapidly despite the presence of these highly virulent *H. pylori* strains emphasizes the predominate importance of environmental factors in determining the outcome of *H. pylori* infections. The time-related decline in the rate of acquisition of atrophic changes among Japanese with *H. pylori* infection has occurred despite no change in host genetics or the prevalence of what is considered a highly virulent *H. pylori* strain [43]. As in Western countries, the change in the velocity in the development of atrophic damage among those with *H. pylori* has occurred coincident with changes in the environmental factors associated with decreased severity of gastritis such as westernization of the diet and use of refrigeration [20].

There are two limitations to this study. Firstly, our study is a retrospective analysis what reviewed biopsy specimens collected from a nonrandom sample. Secondly, considerable difficulties persist in the classification and grading of gastric atrophy with a substantial interobserver variability. In this study, the presence and severity of gastric atrophy and intestinal metaplasia were assessed by gastroenterologists experienced in gastric histopathology. The two gastroenterologists in this study are very versed in the pathology of alimentary tract, especially, the updated Sydney system. Two assessments were made one for atrophy and the other for the presence of intestinal metaplasia. Intestinal metaplasia is not subject to difficulties with intraobserver variation and served as a separate measure of the presence of corpus and antral atrophy making misclassification bias less likely.

In conclusion, our data clearly showed a trend of a fall in the prevalence of *H. pylori* infection of the last 40 years that was additional coupled with a decrease in the extent and severity of mucosal atrophy and intestinal metaplasia among those with *H. pylori* infections. These results are consistent with prior experience that decline in the incidence of gastric cancer may occur more rapidly than the decline in *H. pylori* infection.

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Competing interests: Dr. Graham is an unpaid consultant for Novartis in relation to vaccine development for treatment or prevention of *H. pylori* infection. Dr. Graham is a paid consultant for RedHill Biopharma regarding novel *H. pylori* therapies and has received research support for culture of *H. pylori*. He is a consultant for Otsuka Pharmaceuticals regarding diagnostic breath testing. Dr. Graham has received royalties from Baylor College of Medicine patents covering materials related to ^{13}C-urea breath test.

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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%

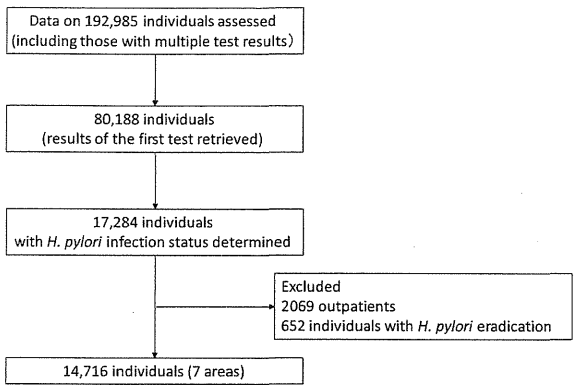

Figure 1 A flowchart of selection of study subjects.

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%)

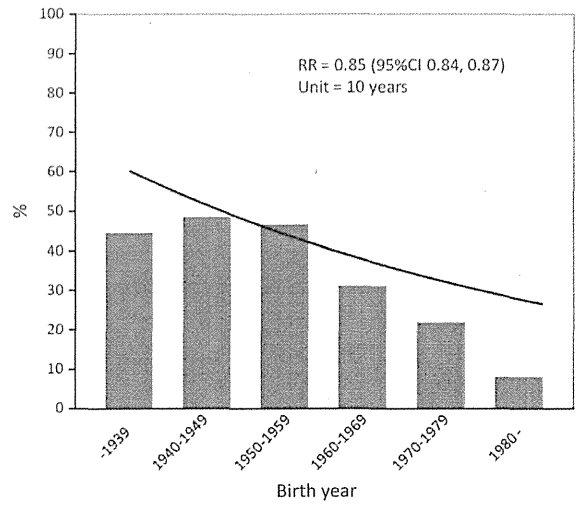

Figure 2 The effect of birth year on the prevalence of *H. pylori* infection: a univariate analysis.

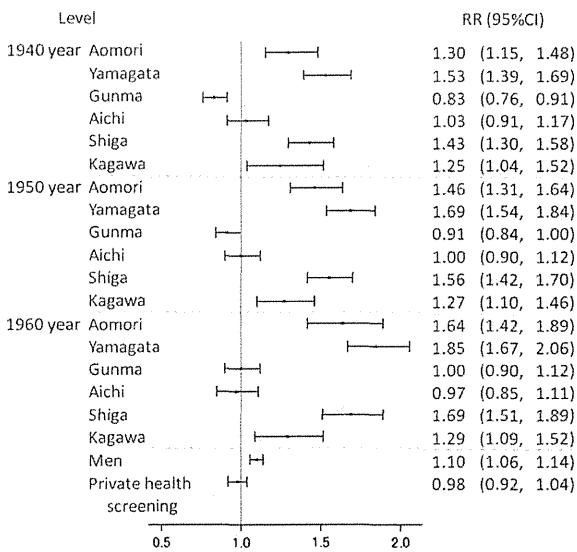

Figure 3 The effect of area, birth year, sex, and clinical test method on *H. pylori* prevalence : a multivariate analysis. Bars represent the RR with a 95% CI for *H. pylori* prevalence. The RR is estimated by the use of the multiple log-binominal regression model including area, birth year, sex, and 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

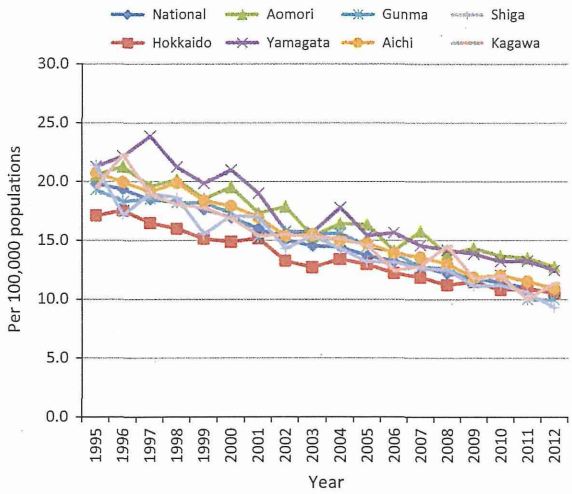

Figure 4 Age-adjusted mortality rates of gastric cancer in selected areas in Japan; 1995–2012. Source: Vital statistics, provided by Center for Cancer Control and Information Services, National Cancer Center, Japan. Website access: http://ganjoho.jp/professional/statistics/statistics.html#05

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.

Acknowledgments and disclosures

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Review

Strategies for eliminating death from gastric cancer in Japan

By Masahiro ASAKA[*1,†] and Katsuhiro MABE[*1]

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Abstract: In Japan, efforts have been directed toward improving the detection of early gastric cancer by double contrast radiography and endoscopy, since early cancer has a good prognosis, resulting in Japan having the world's best diagnostic system for early gastric cancer. The 5-year survival rate of gastric cancer patients in Japan is much higher than in Western countries by the development of endoscopic treatment for early gastric cancer. In February 2013, Japanese national health insurance cover for *H. pylori* eradication therapy was expanded to patients with *H. pylori*-associated gastritis, a type of chronic gastritis. *H. pylori*-associated gastritis causes gastric and duodenal ulcers and gastric polyps, therefore, providing treatment for this gastritis is likely to substantially decrease the prevalence of both gastric and duodenal ulcer and gastric cancer. Patients with gastritis are tested for *H. pylori* infection and those who are positive receive eradication therapy followed by periodic endoscopic surveillance. If such an approach is pursued further in Japan, gastric cancer deaths will show a dramatic decline after 10–20 years.

Keywords: gastric cancer prevention, *Helicobacter pylori (H. pylori)*, *H. pylori*-associated gastritis, elimination of gastric cancer

Introduction

Gastritis with infiltration of neutrophils or lymphocytes develops within a few months in almost 100% of persons who are infected by *H. pylori*. Such gastritis is termed chronic active gastritis and is said to be specific to *H. pylori* infection. Persistent inflammation gradually increases the fragility of the gastric mucosa and progression to atrophic gastritis occurs over time. The speed of progression from chronic gastritis to atrophic gastritis varies among geographic regions and ethnic groups, and it takes 10–20 years in about 80% of Japanese patients.[1] After atrophic gastritis has developed, the annual incidence of progression to intestinal type gastric cancer is 0.1% to 0.4%.[2),3] In addition, excessive strong gastric acid secretion and stress increase the risk of gastric and duodenal ulcer in patients with *H. pylori*-associated gastritis. Moreover, *H. pylori*-associated gastritis is closely associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, functional dyspepsia (FD), hyperplastic gastric polyps, idiopathic thrombocytopenic purpura (ITP), and diffuse type gastric cancer.[4),5] Since *H. pylori*-associated gastritis is the underlying cause of almost all gastric diseases, treating it with bacterial eradication therapy is likely to prevent most gastric conditions, including gastric cancer. In Japan, national health insurance cover for *H. pylori* eradication therapy to treat *H. pylori*-associated gastritis finally became available in February 2013 for the first time in the world. The possibility of eliminating *H. pylori*-associated gastric diseases, including gastric cancer will be promoted by the approval of the health insurance. This article describes a strategy for the elimination of gastric cancer in Japan.

Current gastric cancer screening program in Japan

Gastric cancer was the most common fatal malignancy in Japan before and after World War II until it was replaced by lung cancer in 1995.[6] In order to decrease deaths from gastric cancer, various efforts have been made so far. For example, gastric

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cancer screening with double contrast radiography has been offered to the general public by the Japan Cancer Society since 1960. In 1982, gastric cancer screening was also initiated under national health insurance plans based on the Health and Medical Service Act for the Aged.

In Japan, gastric cancer screening is currently performed annually in people aged 40 or older, comprising an interview and a double contrast radiography. It might be proved that the mass screening program had the effectiveness in reducing stomach cancer mortality in Miyagi prefecture.[7] According to national data, the number of individuals undergoing gastric cancer screening was about 0.4 million in 1964 and it increased tenfold to about 4 million in the 1970s. The number increased further to exceed 6 million in the 1990s and then remained steady for a number of years. It has decreased somewhat recently. The gastric cancer detection rate achieved by screening has remained stable around 0.1%, showing little change over the last 30 years.[8] Recently, the gastric cancer screening rate has decreased (9.6%, about 0.4 million in 2010).[9] Screening based on double contrast radiography has a problem with respect to the low sensitivity for detecting early gastric cancer, and exposure to radiation may become a major issue. Although gastric cancer screening using endoscopy is more effective than gastric X-ray examination in assessing early gastric cancer ratio,[10] it is reported that both radiographic and endoscopic screening may prevent gastric cancer deaths.[11]

In 1994, *H. pylori* was classified as a group 1, a definite carcinogen by the International Agency for Research on Cancer of the World Health Organization.[12] The most serious deficiency with regard to preventing gastric cancer is the lack of primary prevention measures in Japan. Of course, the cause of gastric cancer had not been identified in the 1960s when screening for this cancer was started in Japan. However, it has now been proved that over 95% of gastric cancers develop due to *H. pylori* infection.[13),14] As a general rule for cancers caused by infectious agents, such as liver cancer and cervical carcinoma, primary prevention of infection should precede screening, which is only secondary prevention.

By the efforts of many clinical and basic researchers in Japan, the concept of early gastric cancer was first proposed in 1963. At that time, early gastric cancer was defined as infiltration of tumor cells limited to the mucosa and submucosa irrespective of lymph node metastasis.[15),16] The prognosis

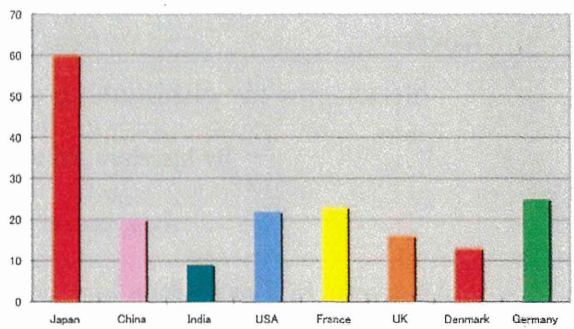

Fig. 1. Five years survival rates (%) of gastric cancer in various countries.

of early gastric cancer is far better than that of advanced gastric cancer and the 5-year survival rate of patients with early cancer is over 90%.[17] Therefore, many studies performed in Japan have focused on effective methods for the diagnosis of early gastric cancer. As a result, early cancer now accounts for nearly 60% of all gastric cancers detected in Japan. This is not seen in any other country and highlights the improved methods for diagnosis of early gastric cancer that have been adopted in Japan. In other countries including the US and Europe, the 5-year survival rate of gastric cancer patients is reported to be only 10% to 25%[6),18),19] (Fig. 1). This difference does not necessarily indicate that the treatment of gastric cancer is superior in Japan to other countries, but is because early cancer accounts for a small proportion of all cases in other countries.

Endoscopic surgery is commonly performed in patients with early gastric cancer to resect intramucosal cancer in Japan. In contrast, intramucosal gastric cancer is not even recognized as a disease entity in Western countries; hence, endoscopic surgery is uncommon. Even if physicians in Europe and the US accept this concept of early gastric cancer, they will still need to develop techniques for performing diagnosis and endoscopic surgery.[20] The skill of Japanese physicians with regard to early diagnosis and endoscopic treatment of gastric cancer is unsurpassed and makes a great contribution to the management of patients with this cancer in Japan. To improve the prognosis of gastric cancer in other countries, it seems to be necessary for the concept of early gastric cancer to be accepted and for a high level of technical skill in the management of early gastric cancer to be established like that in Japan, which could promote the elimination of gastric cancer by combining *H. pylori* eradication therapy with surveillance.