Higher Proportions of a Healthy Gastric Mucosa in Healthy Japanese Adults with Later Birth Year: Analysis of 41,957 Participants

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Research Article

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Abstract

Purpose: In Japan, most gastric cancers are associated with gastric mucosal atrophy caused by chronic infection with *Helicobacter pylori* (*H. pylori*). To recognize the condition of the gastric mucosa and to determine the infection status of *H. pylori* are important for predicting the individual risk of gastric cancer. The present study aimed to determine the proportion of Japanese adults with a healthy gastric mucosa (without *H. pylori* infection) among 12 birth-year groups encompassing 1935 to 1990.

Methods: The gastric mucosa was classified as healthy or having gastritis based on routine double-contrast upper gastrointestinal barium X-ray radiography examination (UGI-XR). The participants were 41,957 healthy Japanese adults. Serum or urine *H. pylori* antibody levels were also assessed.

Results: In total, 25,424 participants had a healthy mucosa without a history of *H. pylori* eradication. The proportions of participants with a healthy mucosa by birth year were 19.8% (57/288), 27.1% (306/1,128), 32.4% (569/1,756), 37.6% (1,808/4,811), 49.2% (3,207/6,522), 60.1% (3,966/6,550), 71.2% (5,224/7,342), 77.2% (5,114/6,624), 80.6% (3,342/4,149), 85.0% (1,404/1,652), 85.3% (302/354), and 94.7% (125/132) in 1935, 1940, 1945, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, and after 1990, respectively (p for trend < 0.01). All participants with a healthy mucosa showed negative results in *H. pylori* antibody tests.

Conclusion: The proportion of participants with a normal gastric mucosa increased linearly with birth years. Prevalence of a morphologically healthy gastric mucosa may have been increasing, in parallel with prevalence of *H. pylori* infection has been decreasing.

Introduction

In Japan, double-contrast upper gastrointestinal barium X-ray (UGI-XR) has been used for organized gastric cancer screening based on national policy since 1983. In 2005, Japanese guidelines for gastric cancer screening highlighted evidence suggesting that UGI-XR can help to reduce gastric cancer death [Hamashima et al. 2008]. After its discovery in the stomach (Warren and Marshall, 1983), *Helicobacter pylori* (*H. pylori*) was determined to be a carcinogen leading to gastric cancer (WHO 1994). In Japan, most gastric cancers are associated with chronic infection and atrophy caused by *H. pylori* (Uemura et al. 2001). The prevalence of gastric cancer is very low in those with *H. pylori*-negative healthy mucosa (Matsuo et al. 2011), while one-sixth to one-fourteenth of those with *H. pylori* infection have gastric cancer until 85 years of age (Kawai et al. 2021). Therefore, when judging the need for further examination after gastric cancer screening with UGI-XR, it is important to recognize the condition of the gastric mucosa individually, as this can aid in predicting the risk of gastric cancer. Thus, diagnosis of the background gastric mucosa has become a proactive strategy (Nakajima 2019).

Since Asaka et al. (1992) reported the prevalence of *H. pylori* infection in the Japanese population based on serum levels of *H. pylori* antibodies, there have been many reports on the prevalence of *H. pylori* infection. These studies reported *H. pylori* prevalence is decreasing in Japan and consequently age-adjusted incidence of gastric cancer is decreasing. However, most studies only used *H. pylori* antibodies in the serum or urine as the method of detection (Wang et al. 2017). Few epidemiological studies have observed difference in morphological gastric mucosal status using UGI-XR depending on birth years to date.

The present study aimed to determine the proportion of Japanese adults with a healthy gastric mucosa among 12 birth-year groups encompassing 1935 to 1990. The subjects were 41,957 participants who underwent UGI-XR in a health check center.

Materials And Methods

Ethics

All authors had access to the study data and reviewed and approved the final manuscript. Our study was approved by the Ethics Committee of Ibarakiken Medical Center (2020-001) on March 31, 2020. This cross-sectional study was conducted in accordance with the World Medical Association Declaration of Helsinki, and informed consent was obtained from the participants. Before the participants underwent UGI-XR and/or endoscopic examination at our institute, separate informed consent was obtained; moreover, they were provided with the choice to opt out of the study. The participants were also informed that they had the right to refuse the use of their data for this study at any time. For easy communication, our contact information including, address, phone number, and email address were provided along with the informed consent. The same information was displayed on the notice board at the entrance of the institute and where the medical examination was conducted. The choice to opt out was approved by the ethics committee.

Patients

Participants were selected from among 216,152 patients who underwent UGI-XR annually or biannually at Ibarakiken Medical Center between April 2007 and March 2020. The twelve birth-year groups were 1935, 1940, 1945, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, and after 1990 (Fig. 1). The study included 41,957 participants across 12 birth-year groups, with others being excluded for a history of gastrectomy (n=208) or history of gastric acid suppressant use (n=277).

Assessments

Ibarakiken Medical Center is a health check-up center. Our institute assesses the gastric mucosal background in patients who undergo double-contrast screening (UGI-XR) and determines the need for endoscopy. UGI-XR was performed using a digital radiographic system with an X-ray image intensifier (I.I.-DR) (DREX-AA28M2/I, Toshiba) between 2007 and 2015, and with the X-ray flat panel detector (FPD) (DIAVISTA, Hitachi) between 2016 and 2019. UGI-XR was performed using two or three types of barium with 210% W/V barium contrast, 5 g of gas-forming agent, and 130 mL total volume. Among 14 UGI-XR images taken daily, six double-contrast images were selected to assess the gastric mucosal background. These included a frontal image in the supine position, a right anterior oblique view in the near supine position, a left anterior oblique view in the near supine position, a frontal view in the prone position with the head down, a right anterior oblique view in the supine standing position for the upper body, and an anterior oblique view in the near supine position ("barium-divided" image).

The mucosa was considered healthy when the areae gastricae and folds were smooth in all mucosal surfaces of the stomach (Fig. 2a, Fig. 3a-e), based on radiological criteria (Nakajima 2019; Ito et al. 2015; Yamamichi et al. 2014). Active and inactive (Fig. 2b, c) *H. pylori*-associated gastritis were diagnosed daily, and the gastric mucosa was classified into two groups: healthy mucosa and gastritis. Mucosal findings were assessed using high-performance monitors, including GS310-EIZO between 2007 and 2012 and RX440-EIZO between 2013 and 2019. *H. pylori* antibodies were detected in urine using an immunochromatographic method (Rapirin, Otsuka) between April 2007 and August 2013 and in serum using a chemiluminescent enzyme immunoassay (negative: <4.0 U/mL, Sphere-Light *H. pylori* J, Fuji-Wako) starting from September 2014.

Radiographs were interpreted according to consensus decisions. The gastric mucosa was assessed first, followed by *H. pylori* antibody results. Statistical analyses were performed using EZR (Kanda 2013) or R (<http://cran.r-project.org>), including the Cochran-Armitage test.

Results

In total, 26,073 participants were found to have a healthy mucosa, and 649 individuals had a history of *H. pylori* eradication. Finally, data were analyzed for 25,424 participants with a healthy gastric mucosa. The proportions of participants with a healthy mucosa by birth year were 19.8% (57/288), 27.1% (306/1,128), 32.4% (569/1,756), 37.6% (1,808/4,811), 49.2% (3,207/6,522), 60.1% (3,966/6,550), 71.2% (5,224/7,342), 77.2% (5,114/6,624), 80.6% (3,342/4,149), 85.0% (1,404/1,652), 85.3% (302/354), and 94.7% (125/132) in 1935, 1940, 1945, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, and after 1990, respectively (Table 1, Figure 4). The proportion of participants with a healthy mucosa increased linearly with birth year ($p < 0.001$). No *H. pylori* antibodies were detected among participants with a healthy mucosa.

Table 1
Proportion of participants with a healthy gastric mucosa by birth year

Birth- year	Total number of participants	Number of participants with a healthy gastric mucosa (%)
1935	288	57 (19.8%)
1940	1,128	306 (27.1%)
1945	1,756	569 (32.4%)
1950	4,811	1,808 (37.6%)
1955	6,522	3,207 (49.2%)
1960	6,550	3,966 (60.6%)
1965	7,342	5,224 (71.2%)
1970	6,624	5,114 (77.2%)
1975	4,149	3,342 (80.6%)
1980	1,652	1,404 (85.0%)
1985	354	302 (85.3%)
After 1990	132	125 (94.7%)
Total	41,308	25,424 (61.6%)

Discussion/conclusions

This study assessed the morphological condition of the gastric mucosa among healthy Japanese adults every five years between 1935 and 1990, with all participants born after 1990 included in a single group. The proportion of participants with a healthy mucosa increased linearly with birth year: the proportions of healthy mucosa and gastritis were 19.8% and 80.2%, respectively, in 1935, and they were 80.6% and 19.4%, respectively, in 1975. These results demonstrate that the incidence of gastritis has decreased over this period.

Asaka et al. (2001) assessed the prevalence of atrophic gastritis with *H. pylori* infection, reporting that atrophic gastritis and intestinal metaplasia were strongly associated with *H. pylori*.

All participants who had a healthy mucosa were negative for urine or serum *H. pylori* antibodies. Wang et al. (2017) reported the prevalence of *H. pylori* infection by birth year among the Japanese population based on a systematic review and meta-regression analysis. They reported that *H. pylori* infections were decreasing, with the highest prevalence observed in the 1923–1933 birth cohort. The authors suggested that the discrepancies in the prevalence of infection were dependent on spreading of atrophic mucosa or small samples. Wang et al. (2015) determined the prevalence of *H. pylori* infection in 20-year-old individuals from 1895 to 1990, reporting results similar to ours, except in the 1935 birth cohort.

Two types of gastritis were known before the discovery of *H. pylori* infection: type A gastritis, which is characterized by diffuse, atrophic gastritis, except in the antrum, with high gastrin levels and autoantibodies in gastric parietal cells; and type B, which refers to diffuse gastritis that spreads from the antrum with advancing age (Strickland and Mackay 1973). Type B gastritis is now considered to be associated with persistent *H. pylori* infection, while type A gastritis is classified as autoimmune gastritis. Since we diagnosed a healthy gastric mucosa first in the diagnostic procedure, the presence of autoimmune gastritis exerted no effect on the results.

Most *H. pylori* infections occur during early childhood by person-to-person transmission (Brown 2000; Okuda 2007; Naito 2008; Rowland 2006). The youngest individuals in this study were 18-year-old-adults born after 1990; therefore, the proportion of participants with a healthy mucosa may rarely change after diagnosis. The proportion of gastritis decreased linearly with birth year from 1935 to 1990. The decreasing trend in proportion of gastritis and prevalence of *H. pylori* infection indicate that future generation may rarely have gastritis caused by *H. pylori* infection.

Several reports have suggested that the prevalence of *H. pylori* infection depends on the environment during childhood, especially the condition of drinking water (Klein 1991; Mendall 1992; Olmos 2000). In Japan and the Ibaraki prefecture, the water supply increased between 1960 and 1990 (<https://www.mhlw.go.jp/content/000624219.pdf>; <http://mobile.pref.ibaraki.jp/hokenfukushi/seiei/suido/seiei/suido/02abot/documents/h25ibarakikennosuidou.pdf>). Taken together these results and the results from our study, there may be a relationship between the decline of *H. pylori*-associated gastritis and the water supply.

In Japan, organized gastric cancer screening using UGI-XR for residents over 40 years of age was officially launched in 1983. Although we did not analyze whether *H. pylori*-associated gastritis played a role in the pathogenesis of gastric cancer, gastric cancer screening was performed for gastritis in a majority of participants. Wang et al. (2015) reported that gastric cancer mortality rates in the Japanese population decreased in younger birth cohorts. Indeed, the age-adjusted incidence rate and mortality rate in Japan have decreased since 1975 (Table 2) (Hori et al. 2015). Organized gastric cancer screening is now practiced in residents over 50 years of age. The high proportion of participants with a healthy mucosa in the later birth year suggests that it is necessary to reconsider screening procedures to account for changes in the prevalence of *H. pylori* infection.

Table 2

Age-adjusted incidence and mortality rates for gastric cancer per 100,000 people according to the 1985 Japanese population model

Year	1960	1965	1970	1975	1980	1985	1990	1995	2000	2005	2010	2015
Age- adjusted incidence rate				84.0	76.5	78.6	70.8	62.1	54.4	54.5	51.1	47.5
Age- adjusted mortality rate	73.1	70.5	65.3	56.9	49.4	40.8	33.4	29.8	25.5	21.2	18.1	14.8

This study has several limitations. First, only participants from one institution were assessed. However, the participants were from the whole Ibaraki area and the sample size is relatively large. Sampling bias may have exerted little effect on the results in this study. Second, the diagnostic accuracy of UGI-XR might be a problem. In this study, all subjects with a healthy gastric mucosa showed negative results in the serum or urine *H. pylori* antibody test, which seemed to reinforce the accuracy of UGI-XR diagnosis. Kamada et al. (2015) reported the prevalence of *H. pylori-associated* gastritis based on histological findings of biopsy specimens between the 1970s, 1990s, and 2010s. The prevalence of *H. pylori-associated* gastritis was the highest in the 1970s group and the lowest in the 2010s group. The proportion of participants with gastritis in the 1990s group using their biopsy specimens in the study were similar to that of our results using UGI-XR images. Thus, we think the diagnoses of a healthy mucosa and gastritis in our study made by UGI-XR may be valid.

Finally, additional endoscopic examination results or histological results of the biopsied samples were not used. Endoscopic examination, especially diagnosis of *H. pylori* infection using biopsy samples, does not necessarily have high sensitivity(Kato et al. 2019). Thus, we assert the accuracy of UGI-XR for assessing the gastric mucosal background.

In summary, our study assessed differences in the proportions of participants with a healthy mucosa using UGI-XR depending on birth years. The findings indicate that prevalence of a morphologically healthy gastric mucosa has been increasing in parallel with decreasing prevalence of *H. pylori* infection, which may make it necessary to reconsider screening procedures to account for the changes in the prevalence of *H. pylori* infection.

Declarations

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Data Transparency Statement

Data are available on request. Data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Asaka M, Kimura T, Kudo M, et al (1992). Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic Japanese population. *Gastroenterology*. 102:760-766. [https://doi.org/10.1016/0016-5085\(92\)90156-S](https://doi.org/10.1016/0016-5085(92)90156-S)
2. Asaka M, Sugiyama T, Nobuta A, et al (2001). Atrophic Gastritis and intestinal metaplasia in Japan: Results of a large multicenter study. *Helicobacter*; 6:294-299. <https://doi.org/10.1046/j.1523-5378.2001.00042.x>.
3. Brown LM (2000). *Helicobacter pylori*: epidemiology and routes of transmission. *Epidemiol Rev*. 20;22:283-297. <https://doi.org/10.1093/oxfordjournals.epirev.a018040>
4. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, Sobue T (2008). The Japanese guideline for gastric cancer screening. *Jpn J Clin Oncol*. 38:259-267. <https://doi.org/10.1093/jjco/hyn016>
<https://doi.org/10.1093/jjco/hyn017>
5. Hori M, Matsuda T, Shibata A, et al (2015). Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol*. 45:884-891. <https://doi.org/10.1093/jjco/hyv088>
6. Ito T, Saito M, Marugami N, et al (2015). Correlation between the ABC classification and radiological findings for assessing gastric cancer risk. *Jpn J Radiol*. 33:636-644. <https://doi.org/10.1007/s11604-015-0469-3>
7. Kamada T, Haruma K, Ito M, et al (2015). Time trends in *Helicobacter pylori* infection and atrophic gastritis over 40 years in Japan. *Helicobacter*. 20:192-198. <https://doi.org/10.1111/hel.12193>
8. Kanda Y (2013). Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant*. 48:452-458. <https://doi.org/10.1038/bmt.2012.244>
9. Kato M, Ota H, Okuda M, et al (2019). Guidelines for the management of *Helicobacter pylori* infection in Japan: 2016 Revised Edition. *Helicobacter*. 24; e12597. <https://doi.org/10.1111/hel.12597>
10. Kawai S, Wang C, Lin Y, et al (2021). Lifetime incidence risk for gastric cancer in the *Helicobacter pylori*-infected and uninfected population in Japan: A Monte Carlo simulation study. *Int. J. Cancer* 1-10. <https://onlinelibrary.wiley.com/doi/10.1002/ijc.33773>
11. Klein PD, Opekum AR, Smith EO, et al (1991). Water source as risk factor for *Helicobacter pylori* infection in Peruvian children. Gastrointestinal Physiology Working Group. *Lancet* 337:1503-1506. [https://doi.org/10.1016/0140-6736\(91\)93196-G](https://doi.org/10.1016/0140-6736(91)93196-G)
12. Matsuo T, Ito M, Takada S, et al (2011). Low prevalence of *Helicobacter pylori*-negative gastric cancer among Japanese. *Helicobacter* 16:415-419. <https://doi.org/10.1111/j.1523-5378.2011.00889.x>
13. Mendall M A, Goggin P M, Molineaux N, et al (1992). Childhood living conditions and *Helicobacter pylori* seropositivity in adult life. *Lancet* 339:896-897. [https://doi.org/10.1016/0140-6736\(92\)90931-R](https://doi.org/10.1016/0140-6736(92)90931-R)
14. Naito Y, Shimizu T, Haru H, et al (2008). Changes in the presence of urine *Helicobacter pylori* antibody in Japanese children in three different age groups. *Pediatr Int* 50:291-294. <https://doi.org/10.1111/j.1442-200X.2008.02587.x>
15. Nakajima S (2019). Diagnosis of background gastric mucosa with UGIS. In: Shiotani A (ed). *Gastric cancer*. Springer Nature Singapore Pte Ltd, Singapore, pp 106-12.
16. Okuda M, Miyashiro E, Booka M, et al (2007). *Helicobacter pylori* colonization in the first 3 years of life in Japanese children. *Helicobacter*. 12:324-327. <https://doi.org/10.1111/j.1523-5378.2007.00510.x>
17. Olmos JA, Rios H, Higa R (2000). Prevalence of *Helicobacter pylori* infection in Argentina: results of a nationwide epidemiologic study. Argentinean Hp Epidemiologic Study Group. *J Clin Gastroenterol* 31:33-37. <https://doi.org/10.1097/00004836-200007000-00008>
18. The Comprehensive R Archive Network. <http://cran.r-project.org/> (Accessed 5 August 2021).

19. Rowland M, Daly L, Vaughan M, et al (2006). Age-specific incidence of *Helicobacter pylori*. Gastroenterology 130:65-72. <https://doi.org/10.1053/j.gastro.2005.11.004>
20. Strickland RG, Mackay IR (1973). A reappraisal of the nature and significance of chronic atrophic gastritis. Am J Dig Dis 18:426-440. <https://doi.org/10.1007/BF01071995>
21. Uemura N, Okamoto S, Yamamoto S, et al (2001). *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 345:784-789. <https://doi.org/10.1056/NEJMoa001999>
22. Wang C, Weber A, Graham DY (2015). Age, period, and cohort effects on gastric cancer mortality. Dig Dis Sci 60:514-523. <https://doi.org/10.1007/s10620-014-3359-0>
23. Wang C, Nishiyama T, Kikuchi S, et al (2017). Changing trends in the prevalence of *H. pylori* infection in Japan (1908-2003): a systematic review and meta-regression analysis of 170,752 individuals. Sci Rep 7:15491.2. <https://doi.org/10.1038/s41598-017-15490-7>
24. Warren JR, Marchall BJ (1983). Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1:1273-1275. [https://doi.org/10.1016/S0140-6736\(83\)92719-8](https://doi.org/10.1016/S0140-6736(83)92719-8)
25. World Health Organization (1994). Schistomes, liver flukes and *Helicobacter pylori*; IARC working group on the evaluation of carcinogenic risks to humans. IARC Monographs on the Evaluation of Carcinogenetic Risks to Humans. IARC Scientific Publ. No. 61, IARC, Lyon. Monogr Eval Carcinogen Risks Hum 61:1-241.
26. Water supply rate in Japan (1950-2018) (in Japanese) (Accessed 29 April 2021) <https://www.mhlw.go.jp/content/000624219.pdf>
27. Water supply rate in Ibaraki prefecture in Japan p16 (1965-2013) (in Japanese) (Accessed 29 April 2021) <http://mobile.pref.ibaraki.jp/hokenfukushi/seiei/suido/seiei/suido/02abot/documents/h25ibarakikennosuidou.pdf>
28. Yamamichi N, Hirano C, Shimamoto T, et al (2014). Associates factors of atrophic gastritis diagnosed by double-contrast upper gastrointestinal barium X-ray radiography: a cross-sectional study analyzing 6,901 healthy subjects in Japan. PloS One 9:e111359. <https://doi.org/10.1371/journal.pone.0111359>

Figures

Figure 1

Study flow chart

Fig.2

Figure 2

Three representative frontal plane images of the stomach in the supine position obtained using double-contrast upper gastrointestinal barium radiography. (a) Healthy gastric mucosa without *Helicobacter pylori*-associated gastritis. (b) *Helicobacter pylori*-associated active gastritis. (c) *Helicobacter pylori*-associated inactive gastritis

Fig.3

Figure 3

Five representative images of the healthy gastric mucosa without *Helicobacter pylori*-associated gastritis obtained using double-contrast upper gastrointestinal barium radiography. (a) Right anterior oblique view in the near supine position. (b) Left anterior oblique view in the near supine position. (c) Frontal view in the prone position with the head down. (d) Right anterior oblique view in the supine standing position for upper body. (e) Anterior oblique view in the near supine position ("barium-divided" image)

Figure 4

Proportion of participants with a healthy gastric mucosa (%). The X-axis shows the birth year, and the Y-axis shows the proportion of participants with a healthy gastritic mucosa. Horizontal lines show point estimates of the proportion, and vertical lines represent their 95% confidence intervals. The proportion of individuals with a healthy gastric mucosa increased with birth year ($p < 0.001$)