Original Article

Increasing trend of *Helicobacter pylori*-uninfected gastric cancer without gastric atrophy

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The prevalence of *Helicobacter pylori* (*H. pylori*) has decreased during several decades due to improvements in the sanitary environment in Japan. Consequently, a relative increase in the incidence of *H. pylori*-uninfected gastric cancer is expected. We analyzed the trends in *H. pylori*-uninfected gastric cancer. Two hundred fifty-eight patients with gastric cancer were retrospectively analyzed. The study was divided into four periods: 2008–2011 (first period), 2012–2014 (second period), 2015–2017 (third period), and 2018–2021 (fourth period). The status of *H. pylori* infection was divided into four categories: uninfected, successful eradication, spontaneous eradication, and persistent infection. Gastric mucosal atrophy was divided into six grades according to the Kimura–Takemoto classification. The proportion of *H. pylori* infections significantly changed over the study period ($p = 0.007$). In particular, the rate of *H. pylori*-uninfected gastric cancer tended to increase over time (0%, 2.9%, 4.9%, and 13.4% in the first, second, third, and fourth periods, respectively; $p = 0.0013$). The rate of no atrophy (C-0) in gastric cancer tended to increase over time (0%, 2.9%, 4.9%, and 11.0% in the first, second, third, and fourth periods, respectively; $p = 0.0046$). In conclusion, the rate of *H. pylori*-uninfected gastric cancer without gastric atrophy tended to increase over time.

***Key Words*: *Helicobacter pylori*, uninfected, gastric cancer, trend**

Gastric cancer is firmly associated with *Helicobacter pylori* (*H. pylori*).[1] A prospective, long-term study showed that there were no cases of gastric cancer in *H. pylori* un-infected group.[2] However, in clinical practice, we occasionally encounter a small number of gastric cancers in *H. pylori* un-infected cases.[3] Besides *H. pylori*, there are other carcinogenic factors for gastric cancer such as *Epstein–Barr* virus infection, high salt intake, genetic factors and so on.[4–6]

The prevalence of *H. pylori* has decreased during several decades due to improvements in the sanitary environment and widespread eradication of *H. pylori* in Japan.[7,8] Therefore, a relative increase is expected in the incidence of *H. pylori*-uninfected gastric cancer. In this study, the trends in *H. pylori*-uninfected gastric cancer were analyzed.

Methods

Patients. Two hundred seventy-six patients with gastric cancer were retrospectively analyzed using an endoscopic database and clinical charts. Gastric cancers were diagnosed at the Toyoshima Endoscopy Clinic between January 2008 and July 2021. Patients underwent esophagogastroduodenoscopy for symptoms, surveillance for upper gastrointestinal disorders, abnormal findings on upper gastrointestinal Barium X-ray, or screening.[9] Biopsy specimens were taken from lesions suspected to be gastric cancer, and the final diagnosis of gastric cancer was pathologically confirmed.[10] Because the Toyoshima Endoscopic Clinic is an outpatient clinic, patients with gastric cancer were treated at other hospitals. The pathological reports of the resected specimens on patients treated for gastric cancer from other hospitals were also used in this study. The exclusion criteria are as follows: (1) esophagogastric junction carcinoma ($n = 11$) and (2) unknown *H. pylori* status ($n = 7$). Finally, 258 patients with gastric cancer were analyzed. The study was divided into four periods: 2008–2011 (first period), 2012–2014 (second period), 2015–2017 (third period), and 2018–2021 (fourth period).

Clinicopathological assessment. Clinicopathological findings, such as age, sex, gastric mucosal atrophy, and progression of early or advanced cancer, were reviewed. Gastric mucosal atrophy was divided into six grades (C-I, C-II, C-III, O-I, O-II, and O-III) according to the Kimura–Takemoto classification.[11–13] No atrophy was defined as C-0. Early gastric cancer was defined as adenocarcinoma confined to the mucosa and/or submucosa. Advanced gastric cancer was defined as gastric cancer that invaded deeper than the submucosal layer.

***H. pylori* infection status.** The *H. pylori* infection status was divided into four categories at the time of gastric cancer diagnosis. The four categories included uninfected, successful eradication, spontaneous eradication, and persistent infection.[14] *H. pylori* uninfected was defined as satisfying the following three criteria: (1) endoscopic findings showed C-0 or C-1 in the status of gastric mucosal atrophy; (2) clinical findings were negative for at least 1 of the 3 following tests: urea breath test, *H. pylori* stool antigen test, or serum *H. pylori* antibodies; and (3) no history of *H. pylori* eradication therapy. Successful eradication was confirmed by a ^{13}C-urea breath test after *H. pylori* eradication treatment.[15] Spontaneous eradication was defined as satisfying the following three criteria: (1) endoscopic findings showed gastric mucosal atrophy from C-2 to O-3 according to the Kimura–Takemoto Classification; (2) clinical findings were negative for at least 1 of the 3 following tests: ^{13}C-urea breath test, *H. pylori* stool antigen test, or *H. pylori*-specific

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immunoglobulin G antibodies in the serum; and (3) no history of *H. pylori* eradication therapy.[16] *H. pylori* infection was defined as *H. pylori*-positive infection, including eradication failure. *H. pylori* infection was defined when one of the following tests was positive: urea breath test, stool antigen test, or histology of the background mucosa. If there was a discrepancy in test results, urea breath test results were prioritized. Eradication failure was confirmed by a urea breath test.

Ethics. This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study was approved by the Certificated Review Board of Yoyogi Mental Clinic on July 16, 2021 (approval no. RKK227).

Statistical analysis. Categorical data were compared among the four groups using the χ^2 test. The Cochran-Armitage test was used to evaluate trends. We calculated with the Stat Mate IV software (ATOMS, Tokyo, Japan). A p value of less than 0.05 was considered to be statistically significant.

Results

The characteristics of the 258 patients included in this study are shown in Table 1. Among the 258 patients, 47, 68, 61, and 82 were diagnosed with gastric cancer between 2008–2011 (first period), 2012–2014 (second period), 2015–2017 (third period), and 2018–2021 (fourth period), respectively. There were no significant differences among the four groups in terms of age, sex, and the ratio of early gastric cancer to advanced gastric cancer.

Figure 1 shows the trend in *H. pylori* status in gastric cancer patients over time. The proportion of *H. pylori* infection significantly changed over the study period ($p = 0.007$). In particular, the rate of *H. pylori*-uninfected gastric cancer tended to increase over time (0%, 2.9%, 4.9%, and 13.4% in the first, second, third, and fourth periods, respectively; $p = 0.0013$).

Figure 2 shows the trend of the gastric atrophy status in gastric cancer over time. The proportion of patients with gastric atrophy also changed significantly over the study period ($p = 0.002$). Particularly, the rate of no atrophy (C-0) in gastric cancer tended to increase over time (0%, 2.9%, 4.9%, and 11.0% in the first, second, third, and fourth periods, respectively; $p = 0.0046$).

Table 2 shows clinicopathological features of *H. pylori*-uninfected gastric cancers. All *H. pylori*-uninfected gastric cancers were early gastric cancers and were treated by endoscopic resection. Histological types included signet ring cell carcinoma (12.5%), well-differentiated adenocarcinoma (37.5%), papillary adenocarcinoma (25%), and fundic gland type adenocarcinoma (25%).

Discussion

This study showed that the rates of *H. pylori*-uninfected gastric cancer and no atrophy in gastric cancer tended to increase over time. This is the first report on the increasing trend of *H. pylori*-uninfected gastric cancers without gastric atrophy.

This phenomenon is due to the decline in the *H. pylori* infection rate. A recent systematic review showed decreasing trends in the prevalence of *H. pylori* infection in Japan.[7] The predicted prevalence rates of *H. pylori* infection were 64.1%, 59.1%, 49.1%, 34.9%, 24.6%, 15.6%, and 6.6% among those born in 1940, 1950, 1960, 1970, 1980, 1990, and 2000, respectively. The prevalence of *H. pylori* infection is estimated to decrease by approximately 10% every 10 years across all age groups.

In another study, Kawai *et al.*[17] reported the cumulative incidence risks for gastric cancer during a lifetime. The risks were

Table 1. Characteristics of gastric cancer by period

Period	2008–2011	2012–2014	2015–2017	2018–2021
Patient number	47	68	61	82
Mean age ± SD	64.4 ± 12.6	65.5 ± 11.6	65.3 ± 13.4	68.2 ± 11.7
Male:Female	22:25	45:23	38:23	47:35
Early cancer:Advanced cancer	38:9	59:9	49:12	68:14

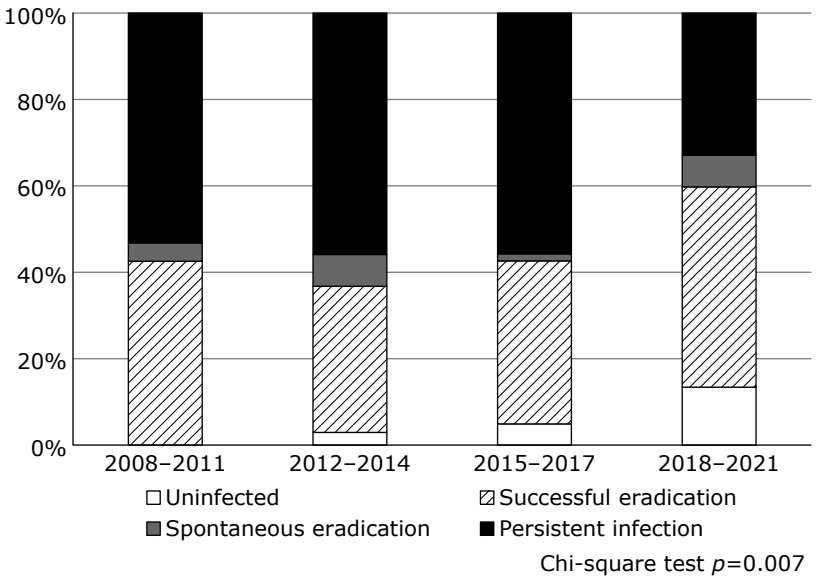

Fig. 1. Trend of *H. pylori* status in gastric cancer by period.

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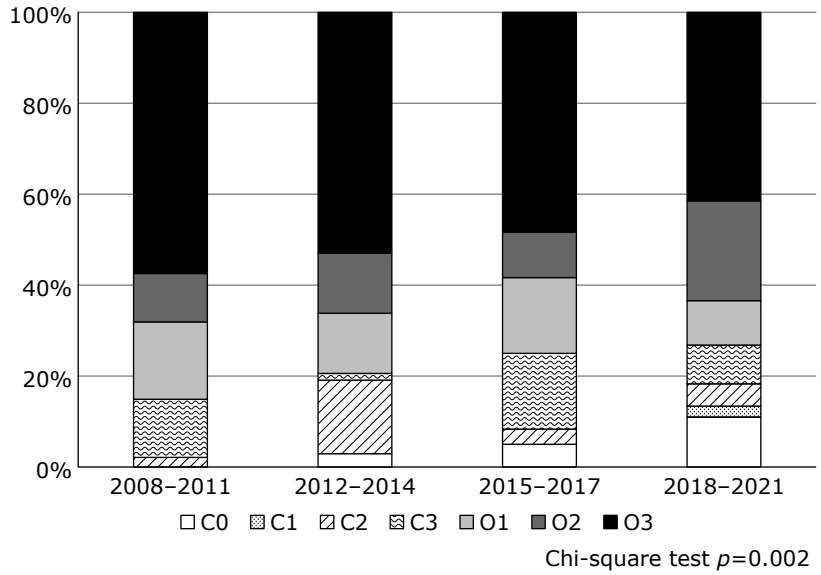

Fig. 2. Trend of gastric atrophy status in gastric cancer by period.

Table 2. Clinicopathological features of *H. pylori* un-infected gastric cancers (n = 16)

Location	
Upper part	5 (31.2%)
Middle part	7 (43.8%)
Lower part	4 (25%)
Tumor size (range; mm)	5.6 (2–14)
Morphology	
0-I (protruding)	2 (12.5%)
0-IIa (superficial elevated)	9 (56.2%)
0-IIb (superficial flat)	2 (12.5%)
0-IIc (superficial depressed)	3 (18.8%)
Depth of invasion	
M	12 (75%)
SM	4 (25%)
Histological type	
Signet ring cell carcinoma	2 (12.5%)
Well-differentiated adenocarcinoma	6 (37.5%)
Papillary adenocarcinoma	4 (25%)
Fundic gland type adenocarcinoma	4 (25%)

17.0% for males and 7.7% for females in the *H. pylori*-infected population, and 1.0% for males and 0.5% for females in the uninfected population. While the *H. pylori* infection rate changes dramatically, a change in the ratio of *H. pylori*-infected to uninfected gastric cancers would be natural.

The reported incidence of *H. pylori*-uninfected gastric cancer is in the range of 0.4–8.4%.[18–21] It ranged from 0.4–2.0% before the early 2010s and 1.2–8.4% after the late 2010s. Recent reports have indicated a relatively high incidence. Our study also showed an increasing trend in each period.

Histological types of *H. pylori*-uninfected gastric cancers included signet ring cell carcinoma (12.5%) and fundic gland-type adenocarcinoma (25%). The endoscopic features of signet ring cell carcinoma include pale-colored, superficial, flat or depressed lesions located in the lower-to-middle third of the stomach.[22] The endoscopic features of fundic gland type adenocarcinoma include flat elevated lesions similar to a submucosal tumor, with a whitish color, located in the middle-to-upper third of the stomach, and without atrophy in the background mucosa.[23] It is necessary to consider these characteristics during endoscopic screening.

A case of fundic gland type adenocarcinoma was reported in 2007.[24] Thereafter, 10 cases were reported by Ueyama *et al.*,[25] who proposed a novel disease concept based on endoscopic and immunohistochemical findings. Since then, reports on fundic gland type adenocarcinoma have been frequent.[26,27] This lesion has become well-recognized by endoscopists and may have contributed to an increase in the ratio of uninfected gastric cancer.

The present study had some limitations including a small sample size. Furthermore, this was a single-center, retrospective study, although the endoscopic database was well managed. Larger, multicenter studies are recommended for future studies.

In conclusion, the rate of *H. pylori*-uninfected gastric cancer without gastric atrophy tended to increase over time.

Author Contributions

Conceptualization: OT; Data curation: KS; Formal analysis: TN; Investigation: SY and TM; Writing: TN; Review & editing: AT, JK, HE, HS, MF, and OT.

Conflict of Interest

No potential conflicts of interest were disclosed.

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