Original Article

Efficacy evaluation of upper gastrointestinal endoscopy screening for secondary prevention of gastric cancer using the standardized detection ratio during a medical check-up in Japan

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We used standardized detection ratio to evaluate the quality of nasal upper gastrointestinal endoscopy screening for the secondary prevention of gastric cancer, and examined the gastric cancer risk in the era of total *Helicobacter pylori* (*H. pylori*) eradication. We performed 21,931 upper gastrointestinal endoscopies, 77 subjects were diagnosed with gastric cancer. Of these, 28 had gastric cancer after *H. pylori* eradication, 47 had gastric cancer with *H. pylori*-positive or others, and 2 had *H. pylori*-negative gastric cancer. The Standardized detection ratios for men and women were 5.33 and 4.82, respectively. Multivariable logistic regression analyses performed exclusively on first endoscopy subjects, excluding *H. pylori*-negative gastric cancer, revealed that smoking was a risk factor for developing gastric cancer (adjusted odds ratio, 3.31; 95% confidence interval, 1.65–6.64; $p = 0.001$). A statistically significant interaction was found between daily alcohol consumpption and *H. pylori* eradication on gastric cancer development ($p = 0.005$). In conclusion, relatively high standardized detection ratio values suggest that an appropriate endoscopic diagnosis of gastric cancer should be performed during a medical check-up. Smoking is a risk factor for developing gastric cancer, and continued alcohol consumption suggests a possible risk for developing gastric cancer after *H. pylori* eradication.

***Key Words*: gastric cancer, *H. pylori*, standardized detection ratio, alcohol, medical check-up**

According to the World Health Organization (WHO)/International Agency for Research on Cancer (IARC), *Helicobacter pylori* (*H. pylori*) infection causes approximately 90% of non-cardia cancers, and there was evidence of a 30–40% reduction in the incidence of gastric cancer (GC) among subjects after *H. pylori* eradication in 2013.(1) In Japan, *H. pylori*-infected gastritis has been covered by insurance for *H. pylori* eradication therapy since 2013, and all *H. pylori*-infected individuals should be offered *H. pylori* eradication therapy unless competing considerations exist. *H. pylori* eradication has been shown to reduce the risk of GC, and the degree of risk reduction depends on the presence, severity, and extent of atrophic damage at the time of *H. pylori* eradication, according to the Kyoto Global Consensus Report on *H. pylori* gastritis in 2014.(2)

Accumulating evidence suggests that endoscopic screening is effective in reducing mortality based on studies in Japan and Korea,(3–5) and the Japanese government has started a national program of endoscopic screening for GC since 2016. Following these trends, endoscopic screening is recommended equally as radiographic screening in the Japanese guidelines for GC screening.(6,7) Comparing endoscopic and radiographic screening, the detection rate of GC was previously reported to be 4.6 times higher with upper gastrointestinal (GI) endoscopy (0.123%) compared to gastric radiography (0.027%),(8) suggesting that upper GI endoscopy is useful in GC screening. Nevertheless, the incidence of GC cases in both sexes still remains high, resulting in 124,319 cases and ranked 3rd, based on the cancer incidence of Japan in 2019. Notably, GC remains a frequent cause of cancer-related deaths worldwide.(9,10)

Most previous studies have evaluated the accuracy of GC detection using the GC detection rate as the evaluation method. The detection rate evaluation methods cannot be standardized; however, the detection rate may be subject to bias owing to differences in the sex and age distributions of the subjects. Therefore, we focused on the standardized detection ratio (SDR), an evaluation method used in the field of lung cancer, to obtain a more accurate evaluation. The use of SDR corrects for differences due to sex and age distribution bias and is thought to enable more accurate medical check-up accuracy management. In this study, we aimed to conduct an actual survey to determine the quality of GC detection by screening upper GI endoscopy during a medical check-up using SDR and to examine the risk factors for carcinogenesis in the era of total *H. pylori* eradication.

Methods

Study design. This is a single-center, cross-sectional observational study.

Study population. Between April 2014 and March 2021, 41,277 participants underwent a medical check-up at the Osaka Metropolitan University-affiliated clinic, MedCity21 (Osaka, Japan), which provides medical examinations and health

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screening from the perspective of preventive medicine. All participants could choose screening programs using endoscopy or direct radiographic examinations as part of their general medical check-up. A total of 21,931 participants who voluntarily agreed to undergo endoscopic examination were consecutively enrolled in this study, and a web-based opt-out was organized. The clinical data of the participants were obtained from their medical records and general questionnaires that inquired about their lifestyle habits and symptoms during the medical check-up. Subjects with a history of multiple medical check-ups at our facility were analyzed based on questionnaires returned at the time of the first medical check-up. Cases in which endoscopy had to be interrupted for any reason and cases in which the subject could not be observed due to food residue were excluded.

Endoscopic examination. Screening of the upper GI tract was performed by several expert endoscopists in all subjects. We used a 5.4 mm-diameter endoscope (GIF-XP290N; Olympus Medical Systems Co., Ltd., Tokyo, Japan). The endoscopic procedure was performed without sedation, and the esophagus, stomach, and duodenum were observed using white-light imaging (WLI) with non-magnified narrow-band imaging (NBI) and indigo carmine, as required. The Kimura–Takemoto classification was used to evaluate the progression of atrophic gastritis.[11] We classified atrophic gastritis as none to mild (C-0, C-1), moderate (C-2, C-3), severe (O-1, O-2, and O-3), or others, including autoimmune gastritis, postoperative stomach, and cases in which atrophic gastritis could not be graded because the tumor occupied a large portion of the stomach.

Examinations of *H. pylori* infection. For a serological diagnosis of *H. pylori* infection, anti-*H. pylori* antibodies were used: from April 2014 to March 2020, E plate 'Eiken' *H. pylori* antibody II (Eiken Chemical Co., Ltd., Tochigi, Japan), from April 2020, L type Wako *H. pylori* antibody J (FUJIFILM Wako Pure Chemical Corporation Co., Ltd., Tokyo, Japan). Anti-*H. pylori* antibody titers were measured only when the participants requested for it.

Information on the *H. pylori* eradication history of subjects was obtained from their medical records or directly from them during a medical check-up. In this study, the *H. pylori* infection status was classified as follows: After *H. pylori* eradication: subjects with a history of *H. pylori* eradication. *H. pylori*-positive: subjects with anti-*H. pylori* antibodies ≥10 U/ml without a history of *H. pylori* eradication. The group that did not apply to either of the above was designated as "others", which include subjects with natural disappearance of *H. pylori* and those without a history of *H. pylori* eradication who did not request an anti-*H. pylori* antibody measurement.

Accessment of GC. GC identified by endoscopic biopsy screening was reported in the 2010 WHO classification, which recognizes the four major histologic patterns of GC: tubular, papillary, mucinous, poorly cohesive (including signet ring cell carcinoma), and uncommon histologic variants.[12] Subjects diagnosed with GC were divided into the early- and advanced-stage groups by the stage of cancer based on their final pathology report. Early GC was defined as an invasive cancer confined to the mucosa and/or submucosa, with or without lymph node metastases, irrespective of tumor size, and advanced GC was defined as a more deeply advanced GC.[13] *H. pylori*-negative GC (HpNGC) was defined as GC with no history of *H. pylori* eradication that was negative for anti-*H. pylori* antibodies or no endoscopic atrophy.

Caluculation of the SDR. SDR is an indicator of the degree to which GCs expected to be present in the examined population can be detected and is calculated using the following formula:

SDR = The number of cases of GC detected/Expected value of GC presence

Expected value of GC presence = Σ (incidence rate × the mean duration of disease × the number of subjects who underwent screening endoscopies)

The incidence rate was calculated by sex and 5-year age groups using the latest epidemiological survey data from the National Cancer Center in Japan in 2019.[14] The mean disease duration represents the period from the appearance of lesions that can be detected at a medical check-up to detection at a hospital with the appearance of symptoms, and the assumed value was set to one year. The number of subjects was defined as the number of subjects who underwent screening of the upper GI tract in each 5-year age group.

Outcome mesurement. The primary aim of this study was to examine the SDR and identify the risk factors for the development of GC based on the medical check-up data.

Ethical approval. This study was conducted in accordance with the Declaration of Helsinki, and a web-based opt-out was conducted. Opt-out informed consent protocol was used for use of participant data for research purposes. This concent procedure was reviewed and approved by the Ethics Committee of Osaka City University Graduate School of Medicine, approval number 3763, date of decision May 26, 2017. Information about this study was disclosed on the webpage of the institution, and the participants had the opportunity to opt out. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki for medical research involving human subjects and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Statistical analysis. The values are expressed as mean ± SD. Values in the two groups were determined by an unpaired *t* test for continuous variables, and the χ^2-test or Fisher's exact test were used for categorical data. For the multivariable logistic regression analysis, we performed a statistical analysis after selecting only subjects who underwent upper GI endoscopy for the first time at our facility. Multivariable logistic regression analysis in this study used a linear model to show the ORs that changed during 10-year age ranges. The clinical factors associated with GC were investigated using a multivariable logistic regression analysis, and odds ratios (OR) and 95% confidence intervals (CI) were calculated for each factor. Statistical calculations and analyses were performed using the R software, ver. 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria). *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics of subjects and comparison of those between subjects with and without GC. The baseline characteristics of the endoscopic screening are shown in Table 1. The mean age of the subjects (n = 21,931) was 51.5 years, 77 subjects (0.4%) were diagnosed with GC, and the mean age of the GC group was 66.3 years. For both men and women, the age group of 40–49 years had the highest number of participants, with 3,148 men (30.1%) and 3,728 women (32.5%) (Supplemental Table 1*). For men, the most common age group was 60–69 years in 2014, and the largest number of subjects was in the 40–49 years age group from 2015 to 2018, after which the largest number of subjects were in the 50–59 years age group. For women, the 40–49 years age group was the most common from 2014 to 2020, and only in 2021 did the 50–59 years age group slightly exceed the 40–49 years age group (Supplemental Table 2*). Regarding lifestyle habits, subjects drinking alcohol every day and having current smoking habit was significantly higher in the GC group than in the non-GC group (41.6% vs 27.3%; p = 0.007; 27.3% vs 15.5%; p = 0.007, respectively). Regarding the *H. pylori* infection status, subjects in the GC group were more likely to have anti-*H. pylori* antibody ≥10 U/ml without *H. pylori* eradication, and have *H. pylori* eradication history than those in the non-GC group (39.0% vs 14.8%, respectively, 29.3% vs 13.3%; p<0.001).

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Table 1. Baseline characteristics of study subjects

Variables	Total	GC	Non-GC	*p* value (GC vs non-GC)
Number of subjects	21,931	77	21,854	
Age (years), mean (SD)	51.5 (11.5)	66.3 (8.3)	51.5 (11.5)	<0.001
Age group				
<30	241 (1.1%)	0 (0.0%)	241 (1.1%)	1
30–39	3,052 (13.9%)	1 (1.3%)	3,051 (14.0%)	<0.001
40–49	6,876 (31.4%)	2 (2.6%)	6,874 (31.5%)	<0.001
50–59	6,058 (27.6%)	12 (15.6%)	6,046 (27.7%)	0.021
60–69	4,138 (18.9%)	30 (39.0%)	4,108 (18.8%)	<0.001
70–79	1,425 (6.5%)	30 (39.0%)	1,395 (6.4%)	<0.001
≥80	141 (0.6%)	2 (2.6%)	139 (0.6%)	0.088
Sex				<0.001
Men	10,461 (47.7%)	58 (75.3%)	10,403 (47.6%)	
Women	11,470 (52.3%)	19 (24.7%)	11,451 (52.4%)	
BMI (kg/m^2), mean (SD)	22.8 (3.6)	23.5 (3.1)	22.8 (3.6)	0.121
Drink alcohol everyday	5,992 (27.3%)	32 (41.6%)	5,960 (27.3%)	0.007
Smoking habit (current smoker)	3,410 (15.6%)	21 (27.3%)	3,389 (15.5%)	0.007
Brinkman index, mean (SD)	166.3 (302.4)	504.3 (573.3)	165.1 (300.4)	<0.001
H. pylori infection status				<0.001
H. pylori-positive	1,562 (14.9%)	16 (39.0%)	1,546 (14.8%)	
After *H. pylori* eradication	1,403 (13.4%)	12 (29.3%)	1,391 (13.3%)	
Others	7,526 (71.7%)	13 (31.7%)	7,513 (71.9%)	
Atrophic gastritis				<0.001
None to mild (C-0,1)	15,258 (69.6%)	3 (3.9%)	15,255 (69.8%)	
Moderate (C-2,3)	4,319 (19.7%)	25 (32.5%)	4,294 (19.6%)	
Severe (O-1,2,3)	2,269 (10.3%)	47 (61.0%)	2,222 (10.2%)	
Others	85 (0.4%)	2 (2.6%)	83 (0.4%)	
CEA, mean (SD)	2.1 (12.6)	2.5 (1.5)	2.1 (12.7)	0.823
CA19-9, mean (SD)	7.6 (43.6)	7.0 (6.7)	7.6 (43.6)	0.933

GC, gastric cancer; BMI, body mass index.

Table 2. Total assessment of standardized detection ratio of gastric cancer

	Total	Male	Female
Expected value of GC presence	14.83	10.89	3.94
Number of GC cases detected	77	58	19
SDR	5.19	5.33	4.82

GC, gastric cancer; SDR, standardized detection ratio.

Assessment of the SDR. The SDR of GC in men was 5.33. This was based on 58 GC cases detected, for a total expected value of 10.89 for the presence of GC in men. The SDR in women was 4.82. This is based on 19 GC cases detected for a total expected value of 3.94 for the presence of GC in women. The SDR for both sexes was 5.19, and the total expected value for the presence of GC was 14.83, with 77 GCs detected (Table 2). According to the SDR by age, men aged 50 years and older and women aged 45 years and older had higher SDRs than the younger age groups (Supplemental Table 3*). According to the SDR by year, the highest SDR was 8.49 in 2014, the year this study started, and the year Medcity21 was established, the SDR tended to decrease after 2014 (Supplemental Table 4*).

Comparison of the characteristics of GC cases after *H. pylori* eradication and those with *H. pylori*-positive or others. Comparison of the characteristics of patients with GC cases after *H. pylori* eradication and those with *H. pylori*-positive or others are shown in Table 3. Two subjects with HpNGC were excluded from this study regarding GC cases after *H. pylori* eradication and those with *H. pylori*-positive or others. We excluded HpNGC because it is considered different with respect to etiology, histology, and macroscopic features from the commonly observed *H. pylori*-associated GC.[15] There were 28 GC cases after *H. pylori* eradication and 47 GC cases with *H. pylori*-positive or others. Of these, 21 and 39 patients, respectively, had GC detected during the first endoscopy. A significantly higher proportion of GC cases after *H. pylori* eradication had daily drinking habits (60.7% vs 27.7%; $p = 0.007$). Endoscopically, a map-like redness was significantly more common in GC casas after *H. pylori* eradication (35.7% vs 8.7%; $p = 0.006$).

In 2018, the proportion of subjects after *H. pylori* eradication accounted for 27.2% of all endoscopic cases, the highest percentage during the study period. In 2015, 2017, 2019, and 2021, GC cases after *H. pylori* eradication will account for more than 50% of all GC cases annually (Supplemental Table 5*).

Comparison of the characteristics of GC lesions after *H. pylori* eradication and those with *H. pylori*-positive or others. Number of GC lesions after that *H. pylori* eradication was 33 and that with *H. pylori*-positive or others was 48. Macroscopically, type 0-IIc was more common in GC lesions after *H. pylori* eradication than those with *H. pylori*-positive or others (60.6% vs 31.2%, $p = 0.012$) (Table 4).

Risk factors for the development of GC. In this study, multivariable logistic regression analyses were performed on

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Table 3. Comparison of the characteristics of gastric cancer cases after *H. pylori* eradication and those with *H. pylori*-positive or others

Variables	GC cases after *H. pylori* eradication	GC cases with *H. pylori*-positive or others	*p* value
Number of subjects	28	47	
Age (years), mean (SD)	64.4 (8.0)	67.8 (9.0)	0.264
Age group			
<30	0 (0.0%)	0 (0.0%)	1
30–39	0 (0.0%)	1 (2.1%)	1
40–49	1 (3.6%)	1 (2.1%)	1
50–59	3 (10.7%)	8 (17.0%)	0.522
60–69	14 (50.0%)	15 (31.9%)	0.145
70–79	10 (35.7%)	20 (42.6%)	0.631
≥80	0 (0.0%)	2 (4.3%)	0.526
Sex			0.411
Men	19 (67.9%)	37 (78.7%)	
Women	9 (32.1%)	10 (21.3%)	
BMI (kg/m^2), mean (SD)	23.4 (2.9)	23.5 (3.2)	0.943
Drink alcohol everyday	17 (60.7%)	13 (27.7%)	0.007
Current smoking	6 (21.4%)	14 (29.8%)	0.59
Brinkman index, mean (SD)	500.2 (550.7)	504.0 (603.6)	0.978
Simultaneous occurrence GC	4 (14.3%)	1 (2.1%)	0.061
Anti-*H. pylori* antibody, mean (SD)	8.9 (7.3)	22.4 (23.2)	0.057
Atrophic gastritis type			0.645
None to mild (C-0,1)	0 (0.0%)	1 (2.1%)	
Moderate (C-2,3)	12 (42.9%)	13 (27.7%)	
Severe (O-1,2,3)	16 (57.1%)	31 (66.0%)	
Others	0 (0.0%)	2 (4.3%)	
Map-like redness	10 (35.7%)	4 (8.7%)	0.006
CEA, mean (SD)	2.4 (1.2)	2.5 (1.7)	0.784
CA19-9, mean (SD)	5.8 (6.8)	7.7 (6.8)	0.448

GC, gastric cancer; BMI, body mass index.

21,929 subjects who underwent first endoscopy, excluding HpNGC, and 60 of those who had GC detected during the first endoscopy. Multivariable logistic regression analysis adjusted for age, sex, smoking habits, and history of *H. pylori* eradication were performed (Table 5). It was identified that smoking was associated with development of GC (adjusted OR, 3.31; 95% CI, 1.65–6.64, $p = 0.001$). Assuming $p<0.2$ as an interaction, there was no statistical interaction between smoking and *H. pylori* eradication in the development of GC ($p = 0.569$) (Fig. 1).

Furthermore, multivariable logistic regression analysis adjusted for age, sex, alcohol consumption, and history of *H. pylori* eradication were performed (Table 6). Alcohol consumption was not a factor that caused the development of GC (adjusted OR, 0.65; 95% CI, 0.31–1.37; $p = 0.256$). Assuming $p<0.2$ as an interaction, there was a statistical interaction between daily alcohol consumption and *H. pylori* eradication for the development of GC ($p = 0.005$) (Fig. 2).

Discussion

This study examined the current status of GC screening in subjects undergoing upper GI endoscopy during a medical check-up and the characteristics of GC cases and lesions after *H. pylori* eradication and those with *H. pylori*-positive or others. Consistent with previous reports, the subjects in the GC group were significantly older, and more male subjects were included in the GC group than in the non-GC group.[16] Additionally, smoking habits and daily alcohol consumption were significantly higher in the GC group, suggesting a close relationship between lifestyle and GC. In the GC group, 93.5% of patients had moderate or severe atrophic gastritis, indicating that *H. pylori* infection had a significant influence on GC. In particular, the proportion of subjects with GC who were presumed to be currently *H. pylori*-infected was more than double that of those without GC who were presumed to be currently *H. pylori*-infected (39.0% vs 14.8%, respectively).

In general, GC is conventionally statistically evaluated using the incidence rate. Considering that the examination of GC incidence rates does not consider the sex or age distribution of subjects, a simple comparison of the incidence rates alone may not be sufficient as an evaluation measure for GC detection. Therefore in this study, we evaluated the GC detection system using SDR adjusted for sex and age distribution bias, and we found that the SDR was 5.33 for men and 4.82 for women, and 5.19 for the total of both sexes. This indicated that an appropriate endoscopic diagnosis was made for both men and women. In particular, the SDR was higher in the groups of men aged >50 years and women aged >45 years, suggesting that nasal endoscopy is useful for the detection of GC in these groups. The SDR calculated by year for all endoscopy subjects was the highest in 2014, the first year of this study, and the year Medcity21 was established and has been lower since then for both men and women. This may be due to the detection of GC during the initial GI endoscopy. Of the 77 patients with GC iden-

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Table 4. Comparison of the characteristics of gastric cancer lesions after *H. pylori* eradication and those with *H. pylori*-positive or others

Variables	GC lesions after *H. pylori* eradication	GC lesions with *H. pylori*-positive or others	*p* value
Number of lesions	33	48	
Location of lesions			0.937
Upper	6 (18.2%)	7 (15.2%)	
Middle	4 (12.1%)	6 (13.0%)	
Lower	23 (69.7%)	33 (71.7%)	
Others	0 (0.0%)	2 (4.2%)	
Macroscopic classification			
Type 0-I	0 (0.0%)	1 (2.1%)	1
Type 0-IIa	8 (24.2%)	19 (39.6%)	0.23
Type 0-IIb	5 (15.2%)	4 (8.3%)	0.475
Type 0-IIc	20 (60.6%)	15 (31.2%)	0.012
Type 1	0 (0.0%)	3 (6.2%)	0.267
Type 2	0 (0.0%)	0 (0.0%)	NA
Type 3	0 (0.0%)	4 (8.3%)	0.142
Type 4	0 (0.0%)	2 (4.2%)	0.511
Color tone of lesion			0.506
Same color tone	1 (3.0%)	6 (12.5%)	
Faded color	9 (27.3%)	14 (29.2%)	
Redness	16 (48.5%)	19 (39.6%)	
Others	7 (21.2%)	9 (18.8%)	
Therapy			0.037
ESD	23 (69.7%)	23 (47.9%)	
Surgery	8 (24.2%)	12 (25.0%)	
Others	2 (6.1%)	13 (27.1%)	
Pathological type			0.942
Tub1	23 (69.7%)	34 (70.8%)	
Tub2	6 (18.2%)	6 (12.5%)	
Por	3 (9.1%)	4 (8.3%)	
Sig	1 (3.0%)	3 (6.2%)	
Others	0 (0.0%)	1 (2.1%)	
Invasion depth			0.625
pT1a	25 (75.8%)	37 (77.1%)	
pT1b	8 (24.2%)	9 (18.8%)	
pT2	0 (0.0%)	0 (0.0%)	
pT3	0 (0.0%)	2 (4.2%)	

GC, gastric cancer; ESD, endoscopic submucosal dissection.

Table 5. Multivariable logistic regression analysis to assess the effect of smoking habit on the development of gastric cancer

Variables	Reference	Diff	Adjusted OR (95% CI)	*p* value
Age		10	3.31 (2.54–4.30)	<0.001
Men	Women		2.23 (1.24–4.01)	0.008
Smoking habit (current smoker)	Non smoker		3.31 (1.65–6.64)	0.001
After *H. pylori* eradication	*H. pylori*-positive or others		2.25 (1.2–4.23)	0.011

Diff, difference in the change by 10-year age; OR, odds ratio; CI, confidence interval.

tified in this study, 61 patients (79.2%) had GC detected on the first upper GI endoscopy, including two cases of HpNGC.

A comparison of the characteristics of GC cases and lesions after *H. pylori* eradication and those with *H. pylori*-positive or others, map-like redness in the stomach, and type 0-IIc were more common after *H. pylori* eradication, which is consistent with previous reports.[17] As it has been known that GC lesions after *H. pylori* eradication appear like gastritis,[18] GCs after *H. pylori* eradication are generally more difficult to be detected than GCs with *H. pylori*-positive or others. Although magnified NBI endoscopy shows significantly better diagnostic performance than WLI endoscopy in detecting red-depressed malignant lesions, such as type 0-IIc,[19] non-magnified WLI endoscopy is usually used for GC screening in a medical check-ups. Therefore,

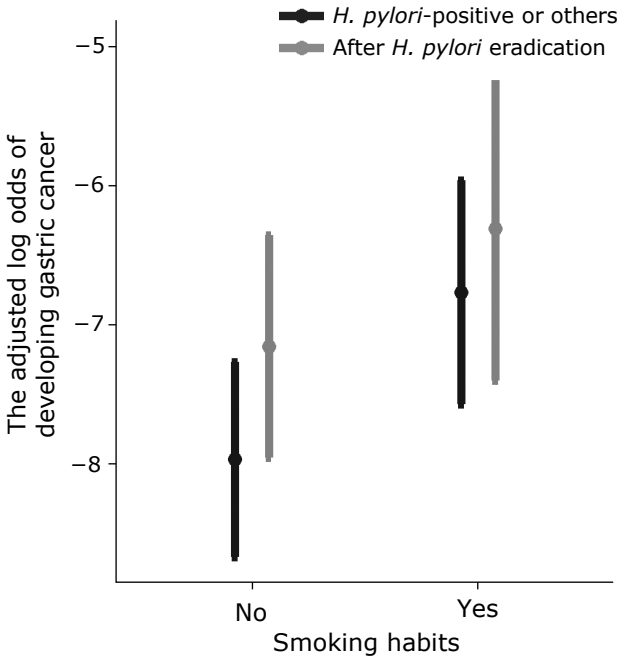

Fig. 1. The interaction between smoking and *H. pylori* eradication history in multivariable logistic regression analysis of risk factors associated with the development of gastric cancer.

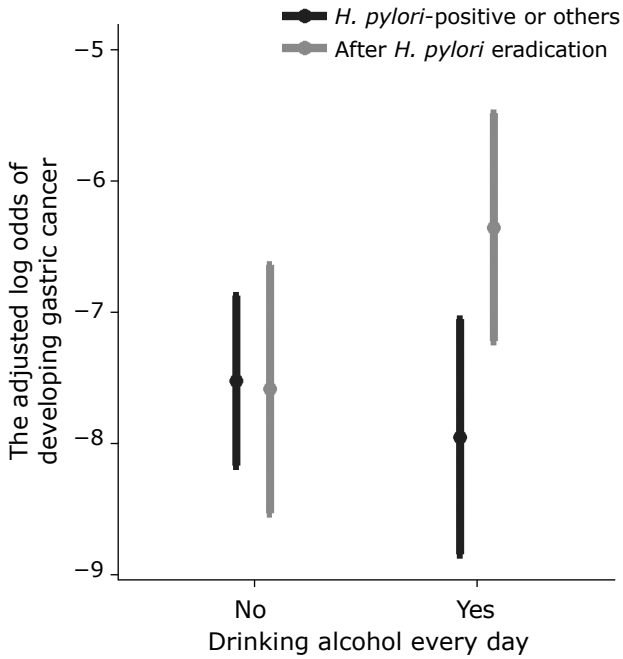

Fig. 2. The interaction between the daily alcohol consumption and history of *H. pylori* eradication in multivariable logistic regression analysis of risk factors associated with the development.

Table 6. Multivariable logistic regression analysis to assess the effect of alcohol consumption on the development of gastric cancer

Variables	Reference	Diff	Adjusted OR (95% CI)	*p* value
Age		10	3.04 (2.37–3.91)	<0.001
Men	Women		2.51 (1.37–4.59)	0.003
Drinking alcohol everyday	Opportunity drinking or not drinking alcohol		0.65 (0.31–1.37)	0.256
After *H. pylori* eradication	*H. pylori*-positive or others		0.94 (0.41–2.15)	0.879

Diff, difference in the change by 10-year age; OR, odds ratio; CI, confidence interval.

caution should be exercised when using WLI to screen subjects after *H. pylori* eradication. Most non-magnifying endoscopes used for GC screening are equipped with linked color imaging (LCI) or NBI. LCI can detect GC better than WLI using color contrast.[20] NBI has also been reported to be more effective than WLI for the borderline diagnosis of early GC.[21] The combined use of LCI or NBI with WLI in GC screening may be useful for detecting relatively difficult lesions, such as GCs, after *H. pylori* eradication.

We considered it necessary to identify the high-risk factors for developing GC after *H. pylori* eradication for more effective endoscopic examinations and to examine the lifestyle habits that are frequently observed during a medical check-up. Thus, multivariable logistic regression analyses were conducted to examine the risk of developing GC related to lifestyle habits and *H. pylori* eradication history. In a multivariable logistic regression analysis that evaluated the effect of smoking on GC development, *H. pylori* eradication inhibited the development of GC. In a multivariable logistic regression analysis that evaluated the effect of alcohol consumption, *H. pylori* eradication was not a significant factor in suppressing the development of GC. Although the results for *H. pylori* eradication were contradictory, it is reasonable to consider this a statistical error, since it is clear that *H. pylori* eradication reduces the incidence of GC, as we have discussed.

We found no interaction between smoking and history of *H. pylori* eradication on the development of GC in the interaction analysis, although smoking significantly increased the incidence of GC in the multivariable logistic regression analysis examining the effect of smoking on the development of GC. Smoking is known to increase the reactive oxygen species (ROS),[22–24] and increased levels of ROS are thought to cause oxidative deoxyribonucleic acid (DNA) damage and *de novo* synthesis, leading to oxidative DNA damage, DNA deamination, and alkylation.[25,26] This interferes with proper DNA repair and is thought to lead to carcinogenesis. In addition, *H. pylori* infection causes oxidative stress that results in elevated levels of ROS, leading to a variety of conditions that stimulate additional ROS production or decline in antioxidant defense.[27] It is reported that smoking history was a risk factor for the prevalence of GCs,[28] and a significant trend in the GC risk with increasing smoking duration was observed.[29,30] There are also reports that GC development shows an independent role of smoking from *H. pylori*.[31] The present study supports these results, showing that the effect of smoking on the development of GC does not change depending on whether the patient has had a history of *H. pylori* eradication.

In the multivariable logistic regression analysis examining the effect of alcohol consumption on the development of GC, alcohol consumption was not a factor causing the development of GC. In contrast, there was an interaction between daily alcohol consumption and a history of *H. pylori* eradication, suggesting that daily alcohol consumption after *H. pylori* eradication is asso-

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ciated with the development of GC. In this study, the daily alcohol consumption rates in GC cases with *H. pylori*-positive or others was similar to that in the non-GC group. However, the daily alcohol consumption rate was much higher in GC cases after *H. pylori* eradication than in the non-GC group. In other words, for subjects with current *H. pylori* infection, *H. pylori* infection is likely to be the sole condition for GC development; however, for subjects after *H. pylori* eradication, exposure to other GC risks, such as alcohol, may be necessary for GC development. Alcohol consumption has been reported as a risk factor for GC in previous studies,[32–34] particularly heavy alcohol consumption.[35] Alcohol dehydrogenase (ADH) metabolizes ethanol to acetaldehyde, which is then oxidized to acetic acid by aldehyde dehydrogenase. Acetaldehyde is classified as a Group 1 human carcinogen by the IARC[36] and is known to induce DNA damage in the digestive tract.[37] This study showed that daily alcohol consumption was a risk factor for GC development after *H. pylori* eradication. Since *H. pylori* infection significantly reduces the activity of class IV ADH in the stomach,[38] it is possible that subjects with *H. pylori*-positive who consumed alcohol daily had less aldehyde production; thus, drinking was less likely to contribute to GC development. However, continued alcohol consumption after *H. pylori* eradication causes chronic inflammation of the stomach, such as intestinal metaplasia.[39] In the gastric environment, after *H. pylori* eradication, gastric mucosal epithelial barrier damage occurs in acid-non-secreting areas, including the intestinal metaplasia, and chronic inflammation is involved in promoting gastric carcinogenesis,[40] which may explain the results of this study. The gastric microbiota is altered in atrophic gastritis,[41] and if dysbiosis of the gastric microbiota persists for a long time after *H. pylori* eradication, it is a risk factor for GC after *H. pylori* eradication.[42] The gastric microbiota in atrophic gastritis produces more acetaldehyde in the stomach due to ethanol metabolism[43] and may be more susceptible to GC formation due to alcohol consumption.

This study had several limitations. First, the study was based on a questionnaire administered during a medical check-up, which did not provide information on the type of alcohol consumed or duration of habitual drinking. Second, although the duration of disease in this study was set to one year for convenience, we cannot rule out the possibility that some of the subjects may have had GC for more than one year. Therefore, the expected value for the actual presence of GC is higher than that reported in this study. However, there is no realistic method to prove this, which is a limitation of the method. Third, the accurate *H. pylori* infection status is difficult to determine because of anti-*H. pylori* antibody levels were measured at a single medical check-up. Although anti-*H. pylori* antibody ≥10 U/ml without *H. pylori* eradication generally indicates current *H. pylori* infection, it is ideal to perform more than two types of examinations to increase the accuracy. Some subjects did not request measurement of anti-*H. pylori* antibodies, making it difficult to accurately determine *H. pylori* infection status. Although this study included 77 total GC cases, further accumulation of cases is expected in order to subdivide the study by *H. pylori* infection status.

In conclusion, the SDR in this study was 5.19 for men, 5.33 for women, and 4.82 for men and women combined, respectively. These results indicated that GC screening was appropriately performed using upper GI endoscopy. Smoking is a risk factor for GC development. Moreover, while the eradication of *H. pylori* for the prevention of GC is important, continued alcohol consumption after *H. pylori* eradication is a risk factor for GC development.

Author Contributions

CT and KO conceptualized and designed the study. CT, KO, MT, and HY contributed to statistical analysis. CT, KO, YN, TK, SFukumoto, and TW contributed to the collection of patient information. KO, MO, SFukunaga, SH, NK, FT, and KT contributed to the survey. CT and KO drafted the manuscript. TW and YF supervised the study.

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Data Availability Statement

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Abbreviations

ADH	alcohol dehydrogenase
CI	confidence interval
DNA	deoxyribonucleic acid
GC	gastric cancer
GI	gastrointestinal
HpNGC	*H. pylori*-negative gastric cancer
IARC	International Agency for Research on Cancer
LCI	linked color imaging
NBI	narrow-band imaging
OR	odds ratio
ROS	reactive oxygen species
SDR	standardized detection ratio
WHO	World Health Organization
WLI	white-light imaging

Conflict of Interest

No potential conflicts of interest were disclosed.

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