Analysis of Barrett’s Esophagus and Its Risk Factors: A Cross-Sectional Study of 10,122 Subjects at a Japanese Health Examination Center

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Keywords
Barrett’s esophagus · \textit{Helicobacter pylori} · \textit{Helicobacter pylori} eradication · Bile reflux

Abstract

\textbf{Introduction:} \textit{Helicobacter pylori} eradication is expected to significantly change the prevalence of Barrett’s esophagus (BE). However, few reports on this relationship exist. We analyzed the risk factors of BE using the current consensus on \textit{H. pylori} infection status. \textbf{Methods:} We analyzed 10,122 individuals (5,962 men; mean age = 52.9 ± 9.9 years) who had undergone esophagogastroduodenoscopy as part of a medical checkup. Correlations among factors including \textit{H. pylori} infectious status, endoscopic findings, and BE ≥1 cm were analyzed. \textbf{Results:} Prevalence of BE, long-segment BE, and esophageal adenocarcinoma was 22.5%, 0.014%, and 0%, respectively. Logistic regression analysis showed that the risk factors for BE were hiatal hernia (odds ratio [OR]: 2.89 [2.59–3.24]), female sex (OR: 0.52 [0.46–0.59]), social drinking (OR:0.77 [0.68–0.87]), \textit{H. pylori} eradication therapy (OR: 1.34 [1.19–1.51]), proton pump inhibitor (PPI) use (OR: 1.52 [1.18–1.96]), bile reflux (OR: 1.18 [1.04–1.33]), age ≥50 years (OR: 1.13 [1.02–1.26]), and nonsteroidal anti-inflammatory drug (NSAID) use (OR: 1.29 [1.02–1.62]). Although reflux esophagitis (RE) was more common in \textit{H. pylori}-negative patients (17.2%) than in those after \textit{H. pylori} eradication therapy (11.8%, \(p < 0.00001\)), the latter was correlated with BE, disputing RE as a strong risk factor for BE. Therefore, we conducted a subgroup analysis; most of the risk factors except for PPI use (\(p = 0.75\), H2-receptor antagonist use (\(p = 0.078\)), and atrrophic gastritis absence (\(p = 0.72\)) were positively correlated with BE after \textit{H. pylori} eradication therapy compared with \textit{H. pylori}-negative status. \textbf{Conclusions:} \textit{H. pylori} eradication, bile reflux, PPI use, and NSAID use were risk factors for BE along with hiatal hernia, male sex, and older age.

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Introduction

Esophageal adenocarcinoma (EAC) cases are rapidly increasing worldwide [1–3], with an estimated 5-year survival rate reported as <20% [4]. Hence, screening and surveillance for Barrett’s esophagus (BE), a precancerous lesion that can lead to EAC, are recommended [5–8]. In BE, chronic esophageal injury leads to replacement of the normal squamous epithelium of the distal esophagus with columnar epithelium [9]. The condition is classified into long-segment Barrett’s esophagus (LSBE) for lesions larger than 3 cm and short-segment Barrett’s esophagus (SSBE) for those smaller than 3 cm, and many studies have suggested that the risk for progression to high-grade dysplasia and EAC is higher in LSBE than in SSBE [10–12]. Thus, the British Society of Gastroenterology guidelines recommend separate surveillance intervals for LSBE (every 2–3 years) and SSBE (every 3–5 years) [7].

Many previous reports have discussed the risk factors for BE. Hiatal hernia and gastroesophageal reflux disease are reported to be the two strongest risk factors for BE, and other factors, such as age, sex, and race, have repeatedly been reported to be associated with BE [13]. Obesity, smoking, and alcohol consumption are also reported as risk factors for BE, whereas Helicobacter pylori infection, nonsteroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs) have been reported to have protective effects [9, 14]. However, other studies have reported contradictory results regarding the impact of the above-mentioned risk factors; thus, it has yet to be elucidated whether these are truly risk factors for BE [15, 16].

It is believed that there is a negative association between H. pylori infection and BE, and some posit that the decline in the H. pylori infection rate has played a role in the increase of EAC in developed countries [9]. In recent years, the number of H. pylori-positive individuals has been decreasing, partly due to the spread of eradication therapy, which has been widely reported to reduce the incidence of gastric cancer [17]. It is reported that the prevalence of BE is lower in H. pylori-positive individuals than in H. pylori-negative individuals, and it is assumed that H. pylori eradication negatively affects the prevalence of BE [18]. However, until now, there has been only one report measuring BE with and without H. pylori eradication therapy, and none have compared its presence among H. pylori-negative, H. pylori-positive, and H. pylori-eradicated individuals [19].

The definitions of BE differ across various guidelines, and this may have influenced the analysis of its risk factors in earlier studies [7, 8, 20–22]. Currently, the Asian-Pacific consensus on the definition of BE is columnar epithelium ≥1 cm from the esophagogastric junction (EGJ) [23]. In addition, the situation of H. pylori infection is changing, with an increase in the number of BE cases after H. pylori eradication therapy as described above, and there have been no large-scale studies taking these factors into account. Therefore, we conducted this large-scale cross-sectional study to investigate the prevalence of BE and its risk factors.

Materials and Methods

Participants

This study was performed prospectively for individuals who had visited Kameda Medical Center Makuhari (Chiba, Chiba, Japan) for a health checkup between January 1 and October 1, 2015. The inclusion criteria were as follows: esophagogastroduodenoscopy (EGD) and serum H. pylori IgG (E-plate “EIKEN” H. pylori antibody II, Eiken Chemical Co. Ltd., Tokyo, Japan) and pepsinogen (PG) (LZ test “EIKEN” pepsinogen I and II, Eiken Chemical Co. Ltd.). Exclusion criteria were individuals who (1) had a history of gastric surgery, (2) did not have EGD images of sufficient quality, and (3) had missing data for one or more of the following: age, sex, body mass index (BMI), serum PG, serum H. pylori IgG, smoking and drinking habits, H. pylori eradication history, or medication history. It is standard for subjects to undergo EGD during a health checkup in Japan, regardless of symptoms.

Definition of Endoscopic Findings

In this study, BE was defined as an “endoscopic finding of over 1 cm of continuous salmon pink-colored mucosa from the EGJ,” similar to that defined by Prague C & M Criteria – circumferential length (C) × maximal length (M) ≥1.0 – and in accordance with the Asian-Pacific consensus [23, 24]. BE length was evaluated retrospectively by optical measurement of the endoscopic images of EGI. A pathological diagnosis was not required for this study (online suppl. Fig. 1a–c; see www.karger.com/doi/10.1159/000526154 for all online suppl. material). EGJ was defined as the lower end of the palisading vessels, or the upper margin of the gastric folds if the palisading vessels were unclear [21]. Hiatal hernia was determined when the lumen of the stomach was seen from the esophagus or when the gastroesophageal flap valve was classified as III or IV via EGD [25] (online suppl. Fig. 2a–g). Reflux esophagitis (RE) was defined by modified Los Angeles classification grades A to D [26]. Kimura-Takemoto classification was used to classify atrophic gastritis [27]; C1 and C2 were classified as mild, C3 and O1 were classified as moderate, and O2 and O3 were classified as severe on the basis of endoscopic findings [28]. Bile reflux was defined using endoscopic findings of yellowish fluid storage or adhesions in the stomach or esophagus. These findings were retrospectively reviewed within the endoscopic images by two endoscopists (D.K. and M.M.).

H. pylori Infectious Status and Questionnaire Items

As described in previous reports, a detailed questionnaire was used to investigate social history and medications for this study [29]. Individuals identified by the questionnaire as having under-
Table 1. Comparison between individuals with and without Barrett’s esophagus

| Variables                        | Overall (n = 10,122) | Barrett’s esophagus (n = 2,279) | Non-Barrett’s esophagus (n = 7,843) | Odds ratio | 95% CI     | p value |
|----------------------------------|----------------------|----------------------------------|-------------------------------------|------------|------------|---------|
| Age, years                       | 24–88                | 54.0±10.1                        | 21–87                               | 52.6±9.8   |            | <0.0001*|
| 20–29                            | 17                   | 17.5%                            | 80                                  | 82.5%      | Reference  |         |
| 30–39                            | 168                  | 22.8%                            | 570                                 | 77.2%      | 1.39       | 0.80–2.41| 0.25    |
| 40–49                            | 575                  | 19.5%                            | 2,377                               | 80.5%      | 1.14       | 0.67–1.94| 0.63    |
| 50–59                            | 841                  | 22.3%                            | 2,931                               | 77.7%      | 1.35       | 0.80–2.29| 0.27    |
| 60–69                            | 542                  | 26.0%                            | 1,546                               | 74.0%      | 1.65       | 0.97–2.81| 0.065   |
| 70                               | 136                  | 28.6%                            | 339                                 | 71.4%      | 1.89       | 1.08–3.30| 0.026*  |
| Sex                              |                      |                                  |                                     |            |            |         |
| Male                             | 1,668                | 28.0%                            | 4,294                               | 72.0%      | Reference  |         |
| Female                           | 611                  | 14.7%                            | 3,549                               | 85.3%      | 0.44       | 0.40–0.49| <0.0001*|
| BMI (kg/m²)                      | 13.8–38.2            | 23.3±3.2                         | 11.6–48.1                           | 22.8±3.5   | Reference  | <0.0001*|
| Smoking                          |                      |                                  |                                     |            |            |         |
| Lifelong nonsmoker               | 1,178                | 19.9%                            | 4,756                               | 80.2%      | Reference  |         |
| Past habitual smoker             | 647                  | 25.6%                            | 1,883                               | 74.4%      | 1.39       | 1.24–1.55| <0.0001*|
| Current smoker                   | 454                  | 27.4%                            | 1,204                               | 72.6%      | 1.52       | 1.34–1.73| <0.0001*|
| Drinking                         |                      |                                  |                                     |            |            |         |
| Nondrinker                       | 629                  | 21.2%                            | 2,334                               | 78.8%      | Reference  |         |
| Social drinker                   | 715                  | 19.4%                            | 2,971                               | 80.6%      | 0.89       | 0.92–1.01| 0.065   |
| Current drinker                  | 935                  | 26.9%                            | 2,538                               | 73.1%      | 1.37       | 1.22–1.53| <0.0001*|
| PG I (ng/mL)                     | 2.8–684              | 59.4±41.7                        | 3–2,123                             | 55.0±40.1  | Reference  | <0.0001*|
| >70                              | 490                  | 28.1%                            | 1,257                               | 72.0%      | Reference  |         |
| ≤70                              | 1,789                | 21.4%                            | 6,586                               | 78.6%      | 0.70       | 0.62–0.78| <0.0001*|
| PG I/II ratio                    | 0.4–14.4             | 5.8±1.8                          | 0.2–24.6                            | 5.7±1.7    | Reference  | 0.0022*  |
| >3                               | 2,089                | 22.4%                            | 7,225                               | 77.6%      | Reference  |         |
| ≤3                               | 190                  | 23.5%                            | 618                                 | 76.5%      | 1.06       | 0.90–1.26| 0.48    |
| Helicobacter pylori infection     |                      |                                  |                                     |            |            |         |
| Negative                         | 1,288                | 20.6%                            | 4,956                               | 79.4%      | Reference  |         |
| Positive                         | 360                  | 23.5%                            | 1,170                               | 76.5%      | 1.18       | 1.04–1.35| 0.013*  |
| After eradication therapy        | 631                  | 26.9%                            | 1,717                               | 73.1%      | 1.41       | 1.26–1.57| <0.0001*|
| NSAID use                        |                      |                                  |                                     |            |            |         |
| No                               | 2,171                | 22.5%                            | 7,480                               | 77.5%      | Reference  |         |
| Yes                              | 108                  | 22.9%                            | 363                                 | 77.1%      | 1.03       | 0.82–1.28| 0.83    |
| PPI use                          |                      |                                  |                                     |            |            |         |
| No                               | 2,174                | 22.1%                            | 7,644                               | 77.9%      | Reference  |         |
| Yes                              | 105                  | 34.5%                            | 199                                 | 65.5%      | 1.86       | 1.46–2.36| <0.0001*|
| H2RA use                         |                      |                                  |                                     |            |            |         |
| No                               | 2,231                | 22.4%                            | 7,712                               | 77.6%      | Reference  |         |
| Yes                              | 48                   | 26.8%                            | 131                                 | 73.2%      | 1.27       | 0.91–1.77| 0.17    |
| Hiatal hernia                    |                      |                                  |                                     |            |            |         |
| Absence                          | 491                  | 11.8%                            | 3,658                               | 88.2%      | Reference  |         |
| Presence                         | 1,788                | 29.9%                            | 4,185                               | 70.1%      | 3.18       | 2.85–3.55| <0.0001*|
| RE                               |                      |                                  |                                     |            |            |         |
| Nonerosion (LA-N/M)              | 1,657                | 19.2%                            | 6,981                               | 80.8%      | Reference  |         |
| Erosion (LA-A/B/C/D)             | 622                  | 41.9%                            | 862                                 | 58.1%      | 3.04       | 2.71–3.41| <0.0001*|
| Atrophic gastritis               |                      |                                  |                                     |            |            |         |
| None                             | 1,282                | 20.4%                            | 5,001                               | 79.6%      | Reference  |         |
| Mild (C1/C2)                     | 341                  | 24.4%                            | 1,054                               | 75.6%      | 1.26       | 1.10–1.45| 0.0008* |
| Moderate (C3/O1)                 | 392                  | 27.0%                            | 1,058                               | 73.0%      | 1.45       | 1.27–1.65| <0.0001*|
| Severe (O2/O3)                   | 264                  | 26.6%                            | 730                                 | 73.4%      | 1.41       | 1.21–1.64| <0.0001*|
| Bile reflux                      |                      |                                  |                                     |            |            |         |
| Absence                          | 1,829                | 22.3%                            | 6,366                               | 77.7%      | Reference  |         |
| Presence                         | 450                  | 23.4%                            | 1,477                               | 76.7%      | 1.06       | 0.94–1.19| 0.33    |

CI, confidence interval; PG, pepsinogen; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; H2RA, H2-receptor antagonist. The level of significance was set at *p < 0.05.
gone *H. pylori* eradication therapy were classified as “after eradication therapy.” The period after eradication therapy was also checked. Individuals with no history of *H. pylori* eradication therapy were classified as “negative” or “positive,” according to the cutoff value of serum *H. pylori* IgG level, 3.0 U/mL, which was not according to the manufacturer’s instructions but a reliable measurement associated with *H. pylori* status [30, 31]. Individuals with a history of smoking were classified into three groups: lifelong nonsmokers, past habitual smokers, and current smokers, as per the questionnaire. Those who answered that they did not consume alcohol were classified as “nondrinkers,” those who rarely or sometimes consumed alcohol were classified as “social drinkers,” and those who consumed alcohol almost every day or every day were classified as “current drinkers.” In response to the question, “Do you use medications for stomach?,” a “yes” and the name of PPIs used was considered “PPI use.” Similarly, in response to the question, “Do you use pain killers?,” a “yes” and the name of NSAIDs were considered “NSAID use.”

This study was approved by the Ethics Committee of the University of Tokyo (10679) and was registered with UMIN Clinical Trials Registry (UMIN000016076), written informed consent was obtained from all participants, and the study was performed according to the 1964 Declaration of Helsinki including its later amendments.

**Statistical Analysis**

A univariate analysis was performed to evaluate background differences between participants with and without BE. Age, BMI, PG I, and PG I/II were evaluated using the Wilcoxon rank-sum test. Age grouped by 10 years; sex; smoking; alcohol consumption; *H. pylori* infection; use of medicine such as NSAIDs, PPI, or histamine H2-receptor antagonists (H2RA); hiatal hernia; RE; atrophic gastritis; and bile reflux were evaluated using the χ2 test. Next, a multivariate logistic regression analysis was performed for factors that showed significant differences in the univariate analysis. Standardized partial regression coefficients were calculated for each factor. In the subgroup analysis, the odds ratios of each factor after *H. pylori* eradication therapy and *H. pylori* negativity were calculated. In the multivariate logistic regression and subgroup analyses, the cutoff value for age was 50 years based on the risk factors for BE as specified by clinical guidelines [20, 32]; for BMI, the value was 25 kg/m² according to the definition of obesity described by Japanese guidelines [33]. Statistical significance was set at *p* < 0.05. All statistical analyses were performed using JMP® Pro 16.0 (SAS Institute Inc., Cary, NC, USA).

## Results

### Participants

A total of 10,454 participants met the inclusion criteria, with 332 excluded; 75 had EGD images that were of insufficient quality, 58 were postgastric surgery patients, and 199 had missing data.

### Participant Characteristics

The average age was 52.9 ± 9.9 years, 5,962 (58.9%) were male, and the average BMI was 22.9 ± 3.4 kg/m² (Table 1). The prevalence of BE and LSBE was 22.5% and 0.014%, respectively. The ratio of SSBE to total BE cases was 99.4%. There were 5,973 (59.0%) individuals with hiatal hernia and 1,484 (14.7%) with RE. The ratio of mild RE (LA-A or B) to total RE cases was 97.7%, and there were no cases of EAC.

### Univariate Analysis of Factors Correlated with Barrett’s Esophagus

As shown in Table 1, sex, age, BMI, smoking habits, drinking habits, *H. pylori* infection status, PG I, PPI use, hiatal hernia, RE, and atrophic gastritis showed statistically significant differences between the BE and non-BE groups. SSBE and LSBE were both positively correlated with RE (*p* = 0.0001 and *p* = 0.026, respectively). The prevalence of LSBE was positively correlated with the severity of RE (*p* = 0.008), whereas the prevalence of SSBE was not correlated with the severity of RE (*p* = 0.53). Excluding 22 participants who had missing data from after *H. pylori* eradication therapy, the final analysis of 2,326 participants after eradication therapy showed no correlation between the prevalence of BE and the period after *H. pylori* eradication therapy (Table 2).

### Multivariate Logistic Regression Analysis of Factors Correlated with BE

To avoid multicollinearity, atrophic gastritis, PG, and RE were excluded from the logistic regression analysis. This was because *H. pylori* infection was strongly corre-
lated with atrophic gastritis, PG I, PG II, and PG I/II (all \( p < 0.0001 \)). Additionally, RE was strongly correlated with hiatal hernia (\( p < 0.0001 \)). Although NSAIDs use and bile reflux were not correlated with BE in the univariate analysis, they are both reported to have correlation with BE, and thus we adopted these factors into the next logistic regression analysis [9, 14]. Finally, the factors of age \( \geq 50 \) years, sex, BMI \( \geq 25 \) kg/m\(^2\), drinking and smoking habits, \( H. \) pylori infection status, hiatal hernia, NSAID use, PPI use, and bile reflux were included in the logistic regression analysis. The logistic regression analysis showed that the factors with significant correlations with BE in the order of descending standardized coefficients were hiatal hernia, female sex, social drinking, after \( H. \) pylori eradication therapy, PPI use, bile reflux, age \( \geq 50 \) years, and NSAID use. Among these factors, female sex, and social drinking showed negative correlations with BE (Table 3).

**Table 3. Correlation between Barrett’s esophagus and selected background factors**

| Variables                                           | Standardized coefficients | Odds ratio | 95% CI     | \( p \) value |
|-----------------------------------------------------|---------------------------|------------|------------|---------------|
| Hiatal hernia: presence (reference: absence)         | 0.52                      | 2.89       | 2.59–3.24  | <0.0001*      |
| Female (reference: male)                            | −0.32                     | 0.52       | 0.46–0.59  | <0.0001*      |
| Social drinker (reference: nondrinker)              | −0.13                     | 0.77       | 0.68–0.87  | <0.0001*      |
| After an eradication therapy for \( H. \) pylori infection (reference: \( H. \) pylori infection negative) | 0.12                      | 1.34       | 1.19–1.51  | <0.0001*      |
| Use of PPI (reference: no)                          | 0.072                     | 1.52       | 1.18–1.96  | 0.001*        |
| Bile reflux presence (reference: absence)           | 0.064                     | 1.18       | 1.04–1.33  | 0.009*        |
| Age \( \geq 50 \) years old                        | 0.061                     | 1.13       | 1.02–1.26  | 0.019*        |
| Use of NSAID (reference: no)                        | 0.053                     | 1.29       | 1.02–1.62  | 0.033*        |
| \( H. \) pylori infection positive (reference: \( H. \) pylori infection negative) | 0.042                     | 1.12       | 0.98–1.29  | 0.98         |
| Past habitual smoker (reference: lifelong nonsmoker) | −0.039                    | 0.91       | 0.81–1.04  | 0.16          |
| Current smoker (reference: lifelong nonsmoker)      | 0.017                     | 1.05       | 0.91–1.20  | 0.52          |
| BMI \( \geq 25 \) kg/m\(^2\)                        | 0.0087                    | 1.02       | 0.91–1.14  | 0.72          |
| Current drinker (reference: nondrinker)             | −0.0039                   | 0.99       | 0.87–1.13  | 0.90          |

Multiple logistic regression analysis was applied to calculate the standardized coefficients and odds ratios for the selected 10 variables. CI, confidence interval; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; BMI, body mass index. The level of significance was set at \(^* p < 0.05\).

Subgroup Analysis between \( H. \) pylori-Negative Status and after \( H. \) pylori Eradication Therapy

As described above, compared with \( H. \) pylori-negative individuals, those who had undergone \( H. \) pylori eradication therapy in the past were at a higher risk for BE. Since this result was contrary to the fact that RE, one of the two major risk factors for BE, was more common in \( H. \) pylori-negative individuals (17.2%) than in those who had undergone \( H. \) pylori eradication therapy (11.8%), we decided to analyze the effect of each factor on BE in \( H. \) pylori-negative individuals and those who had undergone \( H. \) pylori eradication therapy. The odds ratios of BE in individuals in the after \( H. \) pylori eradication therapy group were higher than those of \( H. \) pylori-negative individuals for most factors, except for PPI use (\( p = 0.75 \)), H2RA use (\( p = 0.078 \), and atrophic gastritis absence (\( p = 0.72 \)) (Fig. 1). Notably, the prevalence of BE in \( H. \) pylori-negative patients differed between PPI users (67/188, 35.6%) and H2RA users (22/94, 23.4%) (\( p = 0.037 \)), whereas the prevalence of BE after \( H. \) pylori eradication therapy did not differ between PPI users (32/95, 33.7%) or H2RA users (22/60, 36.7%) (\( p = 0.70 \)). Furthermore, the prevalence of BE in \( H. \) pylori-negative patients was not different between patients with atrophic gastritis (159/560, 22.1%) or without atrophic gastritis (1,214/4,696, 20.5%) (\( p = 0.33 \)), whereas the prevalence of BE after \( H. \) pylori eradication therapy was different between patients with atrophic gastritis (573/1,480, 38.7%) and those without atrophic gastritis (58/237, 19.7%) (\( p = 0.0028 \)).

Discussion/Conclusion

In this retrospective cross-sectional study of 10,122 patients, \( H. \) pylori eradication, PPI use, bile reflux, and NSAID use were risk factors for BE along with hiatal her-
nia, male sex, and older age. It is recommended that patients who had undergone *H. pylori* eradication therapy take EGD for screening not only for gastric cancer but also for BE. We strictly defined BE based on endoscopic findings of continuous salmon pink-colored mucosa longer than 1 cm from the EGJ. The prevalence of BE was 22.5%; if BE was <1 cm long, the prevalence of BE was 51.0%.

A meta-analysis incorporating studies from multiple regions previously showed *H. pylori* infection to be negatively associated with the prevalence of BE [34]. The underlying mechanism is thought to be a decrease in acid secretion capacity due to *H. pylori* infection, leading to a decrease in the risks of RE and BE [34]. The rate of *H. pylori* infection in our institution showed a decreasing trend, from 49.8% in 1996 to 31.2% in 2010 [35], which further decreased to 15.1% in 2015. In this study, *H. pylori* infection status was also associated with the prevalence of RE, as previously reported [36], and the prevalence of RE was significantly higher in *H. pylori*-negative individuals (17.5%) and those with a history of *H. pylori* eradication therapy (11.8%) than in *H. pylori*-positive in-

| Subgroup                               | Odds ratio with 95% confidence interval | Odds ratio (95% confidence interval) |
|----------------------------------------|----------------------------------------|--------------------------------------|
| **Sex**                                |                                        |                                      |
| Male                                   |                                        | 1.34 (1.18–1.53)                     |
| Female                                 |                                        | 1.35 (1.10–1.66)                     |
| **Age**                                |                                        |                                      |
| <50 years old                          |                                        | 1.34 (1.07–1.68)                     |
| ≥50 years old                          |                                        | 1.36 (1.19–1.54)                     |
| **Body mass index**                    |                                        |                                      |
| <25 kg/m²                               |                                        | 1.38 (1.21–1.57)                     |
| ≥25 kg/m²                              |                                        | 1.48 (1.20–1.83)                     |
| **Smoking**                            |                                        |                                      |
| Lifelong nonsmoker                     |                                        | 1.27 (1.09–1.47)                     |
| Past habitual smoker                   |                                        | 1.60 (1.31–1.95)                     |
| Current smoker                         |                                        | 1.43 (1.09–1.87)                     |
| **Drinking**                           |                                        |                                      |
| Nondrinker                             |                                        | 1.38 (1.13–1.69)                     |
| Social drinker                         |                                        | 1.38 (1.13–1.67)                     |
| Current drinker                        |                                        | 1.41 (1.18–1.68)                     |
| **Non-steroidal anti-inflammatory drugs use** |                                      |                                      |
| No                                     |                                        | 1.36 (1.22–1.52)                     |
| Yes                                    |                                        | 2.74 (1.66–4.52)                     |
| **Proton pump inhibitor use**          |                                        |                                      |
| No                                     |                                        | 1.42 (1.27–1.59)                     |
| Yes                                    |                                        | 0.92 (0.55–1.54)                     |
| **H2-receptor antagonist use**         |                                        |                                      |
| No                                     |                                        | 1.39 (1.25–1.55)                     |
| Yes                                    |                                        | 1.89 (0.93–3.85)                     |
| **Hiatal hernia**                      |                                        |                                      |
| Absence                                |                                        | 1.36 (1.10–1.69)                     |
| Presence                               |                                        | 1.48 (1.30–1.69)                     |
| **Reflux esophagitis**                 |                                        |                                      |
| Absence                                |                                        | 1.57 (1.39–1.78)                     |
| Presence                               |                                        | 1.43 (1.10–1.86)                     |
| **Atrophic gastritis**                 |                                        |                                      |
| Absence                                |                                        | 0.95 (0.71–1.27)                     |
| Presence                               |                                        | 1.36 (1.12–1.67)                     |
| **Bile acid reflux**                   |                                        |                                      |
| Absence                                |                                        | 1.42 (1.26–1.60)                     |
| Presence                               |                                        | 1.35 (1.07–1.72)                     |
| **Overall**                            |                                        |                                      |
| Overall                                |                                        | 1.41 (1.27–1.58)                     |

Fig. 1. The forest plot shows the results of subgroup analysis between *Helicobacter pylori*-negative individuals and after *H. pylori* eradication therapy.
individuals (7.5%) ($p < 0.0001$). However, *H. pylori*-eradicated individuals and *H. pylori*-positive individuals had a higher correlation with BE than *H. pylori*-negative individuals, despite *H. pylori* infection reported to be a negative risk factor for BE in a previous meta-analysis [18]. We believe that this discrepancy in results is due to ethnic differences. In fact, in the meta-analysis, Asians and others were reported to have negative risk factors for BE, and the fact that the majority of the analyzed subjects were nonminority Americans may have influenced the analysis [37, 38]. Further, we believe that the most likely reason for the differing of our results to those of previous reports is that the subjects in this study were Japanese, but it is also possible that the strains of *H. pylori* were different. Further research is needed on the effect of race and *H. pylori* infection.

*H. pylori* eradication therapy is reported to be a risk factor for BE [19], and in this study, BE was more common in participants in the after *H. pylori* eradication therapy group than in those who were *H. pylori*-negative with or without RE, and more specifically, BE was more common after in the *H. pylori* eradication therapy group in most subgroups. There are some explanations for BE being more common in individuals who had undergone *H. pylori* eradication therapy than in those who were *H. pylori*-negative. One possible such explanation is that bile salts at intermediate pH are more threatening than those at low pH in the esophagus [39]. If acid output does not improve to the original level even after *H. pylori* eradication, bile reflux of intermediate pH occurs. In our study, we demonstrated that PPI users had a higher BE prevalence than did non-PPI users (Table 1). Furthermore, after *H. pylori* eradication therapy, the prevalence of BE was higher in H2RA users than in non-H2RA users. Similarly, the prevalence of BE was higher in the presence of atrophic gastritis than in the absence of atrophic gastritis. When atrophic gastritis was used as a variable instead of *H. pylori* infection status in the logistic regression analysis, it showed a positive correlation with BE (data not shown). The different effects of PPI and H2RA on BE in *H. pylori*-negative individuals may be related to the relatively weak inhibitory ability of H2RA on acid secretion [40]. These findings suggested that individuals with gastric acid suppression are more likely to have BE. Considering this, in *H. pylori*-positive individuals, the prevalence of RE should have decreased due to weakened gastric acid secretion; however, the increase in esophageal pH may have counteracted this, resulting in a lack of BE suppression. We believe that our findings provide some evidence that the prevalence of RE and BE differs depending on *H. pylori*-infection status. In this analysis, the number of after *H. pylori* eradication therapy individuals with LSBE was small, and it was difficult to assess the correlations between periods after *H. pylori* eradication therapy and the lesion length of BE. The prevalence of BE is not correlated with periods after *H. pylori* eradication therapy, and this is consistent with previous reports [19, 41]. These results indicate that *H. pylori* eradication therapy significantly altered the acid environment in the esophagus in a short period and contributed to the development of BE. Since it is also speculated that alterations in the microbiota may be involved in the development of BE, we cannot fully explain the association between RE and BE prevalence and *H. pylori*-infectious status; further research on this relationship is warranted.

In this analysis, a review of all EGD images showed a positive correlation between endoscopic findings of bile reflux and BE. The relationship between bile reflux and BE has previously been reported [14]. In mice, bile acids induce caudal-type homeobox 2 (CDX2) expression in esophageal squamous epithelial cells, which induces the production of mucin 2 and intestinal-type mucin, and causes intestinal metaplasia, eventually leading to adenocarcinoma [42, 43]. In humans, patients with BE also have severe bile acid reflux into the esophagus [44] and higher CDX2 expression [45]. To our knowledge, this is the first large-scale study to show a correlation between BE and bile reflux using endoscopic findings in humans. In this study, bile reflux was defined by endoscopic findings of yellowish fluid storage or adhesions in the stomach or esophagus. However, it is impossible to assess how often it occurs or to what extent it refluxes. Furthermore, we have not been able to evaluate the amount of bile acid. This is one of the limitations of this study. Ideally, rigorous evaluation of bile reflux in the esophagus via methods such as 24-h pH and bilirubin monitoring and quantitative evaluation of bile acid should be performed.

Chemoprevention agents against esophageal cancer have been desired, and there has been a protective association between NSAIDs, aspirin, statins, and PPIs and esophageal cancer [46–48]. Therefore, NSAIDs and aspirin are expected to be effective for BE suppression, but their effectiveness against BE formation is still undetermined [49, 50]. In this study, we demonstrated that NSAID use was weakly but positively correlated with BE development. NSAIDs have been reported to increase acid exposure in the esophagus and to contribute to gastroesophageal reflux disease formation [51]. We think that NSAIDs probably affect BE formation through a similar mechanism. Compared to previous studies, the pres-
ent study (1) lacked the separation between NSAIDs and aspirin use and quantitative data, (2) had a different definition of BE, and (3) had a larger sample size. This may explain the difference in results, but it also suggests that the use of NSAIDs alone is not likely to prevent BE. It will be necessary to conduct further research to determine what kind of individuals may achieve BE suppression by NSAIDs’ use.

In contrast to esophageal squamous cell carcinoma, alcohol consumption has not been considered associated with EAC and BE [52]. Some studies report that drinking small amounts of alcohol was a protective factor against BE, while others reported the opposite [15, 53–55]. In our study, social drinking was associated with a lower risk of BE than no drinking and current drinking in both univariate and multiple logistic regression analyses. There are still unknowns between these factors and BE – we await the results of a large-scale study of Asians.

This study has several limitations. First, there may have been some misclassification of individuals based on H. pylori infection status. Whether or not the individuals received H. pylori eradication therapy was determined by a questionnaire, and by use of the positive cutoff value of serum H. pylori IgG level ≥3.0 U/mL. However, we cannot exclude the possibility that individuals with coincidental eradication or H. pylori-negative individuals were somewhat mixed in with H. pylori positive individuals. However, confirmation of H. pylori eradication therapy using a questionnaire is reported to be quite reliable [56]. In recent years in Japan, the failure rate of H. pylori eradication up to secondary eradication is assumed to be about 5%, but even when this was 10%, it did not change the correlation between H. pylori infection status and BE [57]. We believe this to be robust evidence. Second, at the time of EGD, many individuals were administered analgesics and sedatives, and several different scopes were used, leading to possible variations in image quality. However, the EGD was recorded in at least 1–2 images in almost all cases; hence, determination of BE ≥1 cm and the presence of RE was available. Furthermore, this study was large-scale, with more than 10,000 cases; therefore, the results were probably not affected by any minor diagnostic errors. Third, the possibility cannot be ruled out that BE subjects tended to take PPI for the prevention of EAC development. However, in Japan, prophylactic PPI use in BE patients is not covered by National Health Insurance for EAC prevention; hence, it is assumed that this bias is unlikely to be present. Fourth, the durations of medication are unknown in this study. This study does not clarify whether the duration of medication use affects BE. Additional prospective studies with thorough imaging protocols, including standardization of the scopes used, evaluation for BE using Prague circumferential and maximal extent criteria, and avoidance of deep sedation, are necessary.

This was the first large-scale study to assess the risk factors for BE, which is strictly defined by endoscopic findings of continuous salmon-pink mucosa longer than 1 cm from the EGJ. BE was positively associated with hiatal hernia, after H. pylori eradication therapy, age ≥50 years, bile reflux, PPI use, and NSAID use, whereas it was negatively correlated with female sex and social drinking. BE was more common in individuals in whom gastric acid was somewhat suppressed, such as those who used PPIs or had atrophic gastritis, in addition to conditions wherein gastric acid was prone to reflux such as hiatal hernia. In future studies, we hope to analyze in detail the factors involved in the development of BE by measuring gastroesophageal pH and bile reflux along with H. pylori infection status and PPI use.

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Statement of Ethics

This study was approved by the Ethics Committee of the University of Tokyo (10679). Written informed consent was obtained from all participants.

Conflict of Interest Statement

All authors declare no conflicts of interest.

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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