Helicobacter pylori infection is associated with reduced risk of Barrett’s esophagus: a meta-analysis and systematic review

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Abstract

Background: Helicobacter pylori (Hp) is a class I carcinogen in gastric carcinogenesis, but its role in Barrett’s esophagus (BE) is unknown. Therefore, we aimed to explore the possible relationship.

Methods: We reviewed observational studies published in English until October 2019. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for included studies.

Results: 46 studies from 1505 potential citations were eligible for inclusion. A significant inverse relationship with considerable heterogeneity was found between Hp (OR = 0.70; 95% CI, 0.51–0.96; P = 0.03) and BE, especially the CagA-positive Hp strain (OR = 0.28; 95% CI, 0.15–0.54; P = 0.0002). However, Hp infection prevalence was not significantly different between patients with BE and the gastroesophageal reflux disease (GERD) control (OR = 0.99; 95% CI, 0.82–1.19; P = 0.92). Hp was negatively correlated with long-segment BE (OR = 0.47; 95% CI, 0.25–0.90; P = 0.02) and associated with a reduced risk of dysplasia. However, Hp had no correlated with short-segment BE (OR = 1.11; 95% CI, 0.78–1.56; P = 0.73). In the present infected subgroup, Hp infection prevalence in BE was significantly lower than that in controls (OR = 0.69; 95% CI, 0.54–0.89; P = 0.005); however, this disappeared in the infection history subgroup (OR = 0.88; 95% CI, 0.43–1.78; P = 0.73).

Conclusions: Hp, especially the CagA-positive Hp strain, and BE are inversely related with considerable heterogeneity, which is likely mediated by a decrease in GERD prevalence, although this is not observed in the absence of current Hp infection.

Keywords: Helicobacter pylori, Barrett’s esophagus, Gastroesophageal reflux disease

Background

Owing to improvements in hygiene and living conditions, the prevalence of Helicobacter pylori (Hp) has continued to fall in developed countries, along with the incidence of gastric cancer and peptic ulcer, although it remains high in some developing countries, such as 70.1% in Africa [1, 2]. Interestingly, in contrast to the decline in the rate of Hp infection, the incidence of esophageal adenocarcinomas (EAC) has increased significantly. Current epidemiological studies present a consistent, rapidly increasing incidence of EAC in the United States and most other western countries, especially among males, with an observed or estimated start between 1960 and 1990, while the incidence of esophageal squamous cell carcinoma is stable or declining in all racial groups [3, 4]. The etiology of EAC is multifactorial, and Barrett’s esophagus (BE) is a premalignant lesion that is observed in the majority of patients with EAC, and carries a risk of eventual development of EAC that is up to 30- to 125-fold higher than that in patients without this condition.
Previous studies have identified several risk factors for the development of BE, including male sex, older age, smoking, white race, obesity, hiatal hernia, and gastroesophageal reflux disease (GERD) [7, 8]. However, the possible role of Hp in BE is uncertain. Currently, Hp is classified by the World Health Organization as a class 1 carcinogen, since it promotes gastric cancer, and is also regarded as a commensal organism that confers some protection against asthma, allergies, and even obesity [9, 10]. Hp seems to have a protective influence on BE, however, the relationship between Hp and BE remains controversial.

Multiple studies have highlighted the relationship between Hp and BE [11–13]. Recently, Wang used individual-level data from six case–control studies to conduct analysis. Their study provided evidence that Hp infection was strongly inversely associated with BE, which was even stronger among individuals with cytotoxin-associated gene A (CagA) positive strain [14]. Another extensive meta-analysis also demonstrated that Hp infection was associated with a reduced risk of BE, and dysplastic, non-dysplastic, and long-segment BE (LSBE), and demonstrated that the risk reduction was not correlated with geographical location [15]. However, some researchers concluded that there was no clear association between Hp and BE, or demonstrated contrary conclusions in case–control studies and cohort studies [16, 17]. Fischbach's meta-analysis of 49 observational studies identified a protective effect of Hp on BE, and showed great heterogeneity between the majority of studies, which was potentially due to selection and information bias [18]. Consequently, it is understandable that different meta-analyses come to different conclusions.

Previous meta-analysis results are inconsistent, and the heterogeneity between them may derive from selection of the control group, the definition of BE, and the Hp detection method. To better understand this relationship, we performed meta-analysis and subgroup analysis based on the potential sources of heterogeneity. This study would contribute to the design of clinical studies and the decisions on whether to eradicate Hp.

Methods

Search strategy

PubMed, EMBASE, and COCHRANE databases were searched from inception to October 2019. We used the following MeSH terms or keywords as search terms: ("Barrett Esophagus"[Mesh]) OR (Barrett metaplasia) OR (Barrett metaplasias) OR (Barrett's Metaplasia) OR (Metaplasia, Barrett) OR (Metaplasias, Barrett) OR (Barrett's Syndrome) OR (Barretts syndrome) OR (Barrett Syndrome) OR (Barrett's Esophagus) OR (Barrett's oesophagus) OR (Barretts Esophagus) OR (Barrett's oesophagus) OR (Esophagus, Barrett's) OR (oesophagus, Barrett's) OR (oesophagus, Barrett) OR (Barrett Epithelium) OR (Epithelium, Barrett) OR (Barrett's) OR (Barrett) AND ("Helicobacter pylori"[Mesh]) OR (Helicobacter pylori) OR (H pylori) OR (H. pylori) OR (Helicobacter) OR (Campylobacter) AND (Humans).

Inclusion and exclusion criteria

All eligible studies satisfied the following inclusion criteria:

1. Observational studies: Case–control, cohort, or cross-sectional studies
2. Providing raw data on Hp infection in the BE and control groups
3. Studies conducted in adult populations

Studies with the following exclusion criteria were eliminated:

1. Full-text articles in languages other than English
2. Studies in which the data came from a review article or other non-full-text article
3. Less than five points in the Newcastle–Ottawa Scale (NOS)

When the same data appeared in different articles, only the study with the most complete relevant data was included.

Data extraction

Data were extracted by two independent investigators after reading each included study. When agreement was reached by discussion or with the help of third investigators, the data were recorded in a designed Excel 2019 sheet. We collected data on author, year of publication, journal, geographical location, study type, Hp infection testing methods, definition of cases and controls, number of cases and controls, number of Hp infections in cases and controls, and whether matched in sex, age, obesity, smoking, alcohol, and race. Data on dysplasia, segment length and infection of CagA-positive Hp strain were included when present. When the subjects of multiple reports are the same. Only one, the most complete, would be included.

Statistical analysis

Our primary objective was to compare the prevalence of Hp infection between BE groups and controls. The secondary objective was to conduct subgroup analysis according to the differences in definitions of the control group, the definitions of BE, and the Hp detection
methods, in order to clarify the impact of these aspects on the overall results. The correlation between \( H_p \) and BE was determined by calculating the odds ratios (ORs) and 95% confidence intervals (CIs) for risk. The results of the meta-analysis were displayed on a forest map, heterogeneity was assessed using Cochrane’s Q and I^2 statistics, and publication biases were checked by visual assessment of funnel plots. Heterogeneity was regarded as moderate, substantial, and considerable when the I^2 was between 30–60%, 50–90%, and 75–100%, respectively. All calculations were conducted by Review Manager 5.3.

**Results**

Searches initially generated 1505 potential citations after removing 546 duplicates from 2051 citations. A large sample study (n = 1445) was further excluded by screening titles, abstracts, and browsing full-text. A total of 62 studies remained for full-text review, and six studies without original data [19–24]. and seven studies with less than five points in NOS were additionally excluded [25–31]. Three studies were excluded because of repetitive research subjects [32–34]. Finally, Forty-five studies were included in this article; data from 36 of these were extracted to explore the relationship between \( H_p \) and BE, while others examined the correlation in \( H_p \) and BE dysplasia, lengths of BE, and the correlation between the CagA-positive \( H_p \) strain and BE. The study selection process is shown in Fig. 1.

**Prevalence of \( H_p \) infection in BE and controls**

The 36 included studies comprised a total of 90,895 BE patients and 430,846 controls [11–13, 35–67]. A summary of the characteristics of these studies is shown in Table 1. The prevalence of \( H_p \) infection in BE patients was significantly lower than that in controls (OR = 0.70; 95% CI, 0.51–0.96; \( P = 0.03 \)), with considerable heterogeneity observed between studies (I^2 = 98%, \( P < 0.00001 \)) (Fig. 2). Funnel plots suggested no obvious publication bias (Fig. 3). Subgroup analysis was conducted according to differences in definition of control group. Fourteen studies regarded patients with GERD as control group [37, 43, 49, 52, 54, 55, 58–60, 62, 63, 64, 66, 67]. There was no significant difference in the prevalence of \( H_p \) infection between BE and GERD controls (OR = 0.99; 95% CI, 0.82–1.20; \( P = 0.91 \); I^2 = 33%). In contrast, the negative relationship between \( H_p \) prevalence and BE was enhanced when defining subjects undergoing endoscopy in another 14 studies (OR = 0.55; 95% CI, 0.31–0.95;
| Authors               | Years | Journal                          | Hp testing method | Biopsy location | BE     | Control | Sex match | Age match | BMI/obesity match | Smoking match | Alcohol match | Race match |
|----------------------|-------|----------------------------------|-------------------|----------------|--------|---------|-----------|-----------|-------------------|---------------|--------------|-----------|
| Aghayeva et al.      | 2019  | Dis Esophagus                    | H, R             | Antrum         | IM†    | Endoscopy | Yes       | Yes       | Not clear         | Not clear     | Not clear     | Yes       |
| Chen et al.          | 2016  | PLoS One                         | R                | Antrum         | IM     | Primary care | Yes       | Yes       | Not clear         | Not clear     | Not clear     | Not clear |
| Chuang et al.        | 2019  | Kaohsiung Journal of Medical Sciences | H, R, U          | Not clear      | Not clear | Endoscopy, Primary care | No       | No       | Not clear         | Not clear     | Not clear     | Not clear |
| Corley et al.        | 2008  | Gut                              | S                | Antrum         | IM     | Population | Yes       | Yes       | Not clear         | Not clear     | Not clear     | Not clear |
| Csendes et al.       | 1997  | Dis Esophagus                    | H                | Antrum         | Gastric epithelium ≥ 3 cm or IM | Endoscopy, Primary care | No       | No       | Not clear         | Not clear     | Not clear     | Not clear |
| Dore et al. [63]     | 2016  | Scand J Gastroenterol            | H, R, 13C-UBT    | Antrum, Antrum, Corpus | IM     | GERD    | Not clear | Not clear | Not clear         | Not clear     | Not clear     | Not clear |
| Ferrández et al.     | 2006  | BMC Gastroenterol                | S                | H, R           | IM     | Blood donor | Yes       | Yes       | Not clear         | No            | No           | Not clear |
| Fischbach et al.     | 2014  | Am J Gastroenterol               | H, C            | Antrum, Corpus, Cardia | IM     | Endoscopy | Yes       | Yes       | Yes               | No            | Not clear     | No        |
| Hackelsbeiger et al. | 1998  | Gut                              | H, R            | Antrum, Corpus, Cardia | IM     | Endoscopic diagnosis | Not clear | Not clear | Not clear         | Not clear     | Not clear     | No        |
| Hirota et al.        | 1999  | Gastroenterology                 | H                | Antrum         | IM     | Endoscopy | Yes       | Yes       | Yes               | Yes           | Yes          | Not clear |
| Katsinelos et al.    | 2013  | Hippokratia                      | R                | Antrum         | IM     | Endoscopy | Yes       | Yes       | Yes               | Yes           | Not clear     | Not clear |
| Keyashian et al.     | 2013  | Dis Esophagus                    | H, S, stool antigen | Not clear      | IM     | GERD    | No        | No        | Yes               | Yes           | Not clear     | Not clear |
| Kiltz et al.         | 2002  | Eur J Gastroenterol Hepatol      | R, S            | Antrum, Corpus | IM     | Endoscopy | Not clear | Not clear | Not clear         | Not clear     | Not clear     | Not clear |
| Laheij et al.        | 2002  | Alimentary Pharmacology and Therapeutics | H, R, C | Antrum | CM**  | Endoscopy | Not clear | Not clear | Not clear         | Not clear     | Not clear     | Not clear |
| Loffeld et al.       | 2000  | Digestion                        | H, R, S, C      | Antrum         | CM     | Endoscopy | Not clear | Not clear | Not clear         | Not clear     | Not clear     | Not clear |
| Loffeld et al.       | 2004  | Netherlands Journal of Medicine  | H, C            | Antrum         | Not clear | Endoscopy | Not clear | No        | Not clear         | Not clear     | Not clear     | Not clear |
| Newton et al.        | 1997  | Gut                              | R                | Antrum         | GERD   | No        | No        | No        | Not clear         | Not clear     | Not clear     | Not clear |
| Authors                          | Years | Journal                                      | Hp testing method | Biopsy location | BE | Control | Sex match | Age match | BMI/obesity match | Smoking match | Alcohol match | Race match |
|---------------------------------|-------|----------------------------------------------|-------------------|-----------------|----|---------|-----------|-----------|-------------------|---------------|---------------|------------|
| Öberg et al. [43]               | 1999  | Archives of Surgery                          | H                 | Antrum, biopsies just below SCC | IM | GERD    | Not clear | Not clear | Not clear         | Not clear     | Not clear     | Not clear  |
| Park et al. [50]                | 2009  | J Clin Gastroenterol                         | H, R, S           | Not clear       | IM | Endoscopy | No        | No        | No                | No            | Yes           |           |
| Paull and Yardley [51]          | 1988  | Gastroenterology                             | H                 | Gastric biopsy  | Not clear | Endoscopy | Yes       | Yes       | Not clear         | Not clear     | Not clear     | Not clear  |
| Rajendra et al. [52]            | 2007  | Helicobacter                                  | H, R, S           | Antrum, Corpus, Cardia | IM | GERD    | Not clear | Not clear | Not clear         | Not clear     | Not clear     | Not clear  |
| Ronkainen et al. [53]           | 2005  | Gastroenterology                             | H, S              | Antrum, Corpus   | IM | Population | Not clear | Not clear | Not clear         | No            | No            | No         |
| Rubenstein et al. [54]          | 2014  | Clin Gastroenterol Hepatol                   | S                 | IM              | IM | GERD    | Yes       | Not clear | Not clear         | Not clear     | Not clear     | No         |
| Sharifi et al. [55]             | 2014  | Gastroenterol Res Pract                      | R                 | IM              | IM | GERD    | Yes       | No        | No                | Yes           | Yes           | Not clear  |
| Sonnenberg et al. [56]          | 2010  | Gastroenterology                             | H                 | Stomach         | IM | Endoscopy | No        | No        | Not clear         | Not clear     | Not clear     | No         |
| Sonnenberg et al. [11]          | 2017  | Aliment Pharmacol Ther                       | H                 | Stomach         | IM | Endoscopy | Not clear | Not clear | Not clear         | Not clear     | Not clear     | No         |
| Thrift et al. [57]              | 2012  | Int J Cancer                                 | S                 | IM              | IM | Population | Endoscopic diagnosis | Not clear | Not clear | Not clear         | Not clear     | Not clear     | No         |
| Usui et al. [35]                | 2019  | J Clin Gastroenterol                         | S                 | IM              | IM | Endoscopy | Not clear | Not clear | Not clear         | Not clear     | Not clear     | No         |
| Vaezi et al. [58]               | 2000  | Am J Gastroenterol                           | H, S              | Antrum, Corpus   | IM | GERD    | Not clear | Yes       | Not clear         | Not clear     | Not clear     | No         |
| Vicari et al. [59]              | 1998  | Gastroenterology                             | H, S              | Antrum, Fundus, Cardia | CM ≥ 3 cm or IM | GERD    | Not clear | Yes       | Not clear         | Not clear     | Yes           |           |
| Viet et al. [65]                | 2000  | Digestion                                    | H                 | Antrum, Corpus   | IM | NUD[1] | No        | No        | Not clear         | Not clear     | Not clear     | Yes        |
| Weston et al. [60]              | 2000  | Am J Gastroenterol                           | H                 | Stomach         | IM | GERD    | Yes       | Yes       | Not clear         | Yes           | Yes           | No         |
| White et al. [61]               | 2008  | Can J Gastroenterol                          | H                 | Not clear       | IM | Normal SCJ | No        | Yes       | Not clear         | Not clear     | Not clear     | No         |
| Wu et al. [66]                  | 2000  | Alimentary Pharmacology and Therapeutics     | H, R              | Antrum, Corpus   | IM | GERD    | Not clear | Not clear | Not clear         | Not clear     | Not clear     | No         |
| Zaninotto et al. [67]           | 2002  | Dig Liver Dis                                | H                 | Esophagus       | IM | GERD    | Not clear | Not clear | Not clear         | Not clear     | Not clear     | No         |
### Table 1 (continued)

| Authors         | Years | Journal                  | Hp testing meth od | Biopsy locat ion | BE | Control | Sex match | Age match | BMI/obesity match | Smoking match | Alcohol match | Race match |
|-----------------|-------|--------------------------|--------------------|------------------|----|---------|-----------|-----------|-------------------|---------------|--------------|------------|
| Zhang et al. [62] | 2004  | World J Gastroenterol    | H                  | Antrum           | IM | GERD    | Not clear | Not clear | Not clear          | Not clear     | Not clear     | Not clear  |

*: Histology, †: Rapid urease test, ‡: Intestinal metaplasia, §: Urea breath test, ¶: Serology, **: Culture, ††: Esophagogastric junction, ‡ ‡: Columnar metaplasia, §§: Squamous Columnar Junction, ¶¶: Non-ulcer dyspepsia
$P = 0.03; I^2 = 99\%$) or normal control (population or primary care people) in four studies (OR = 0.48; 95% CI, 0.38–0.61; $P < 0.00001; I^2 = 0\%$) as control groups (Fig. 4) [11, 13, 36, 38, 40–42, 44–48, 50, 51, 53, 56, 57]. When BE was defined as intestinal metaplasia (IM) in 26 studies, we found an increased negative correlation between $H. pylori$ prevalence and BE (OR = 0.64; 95% CI, 0.51–0.80; $P = 0.0011; I^2 = 90\%$) [11, 12, 13, 36, 39–44, 46–49, 51, 59]. However, the negative correlation disappeared (OR = 0.76; 95% CI, 0.51–1.14; $P = 0.18; I^2 = 92\%$) in the other subgroups, which diagnosed BE with columnar metaplasia (CM), endoscopic presentation, no clear definition, and gastric epithelium [35, 37, 39, 41, 46–49, 51, 59]. In addition, we divided the studies according to whether $H. pylori$ could be confirmed as a present infection, into the present infected subgroup ($H. pylori$ positive with rapid urease test, urea breath test, histology, or culture), infection history subgroup ($H. pylori$ positive with serological detection, treatment history, or infection history), and not clear subgroup. In the present infected group with 24 studies, the prevalence of $H. pylori$ infection in BE was significantly lower than that in controls (OR = 0.69; 95% CI, 0.54–0.89; $P = 0.005; I^2 = 92\%$) [11, 13, 36, 37, 39–44, 46–49, 51, 53, 55, 56, 60–63, 65–67], while the negative correlation disappeared again in the infection...
history subgroup (OR = 0.88; 95% CI, 0.43–1.78; P = 0.73; I² = 95%) (Fig. 5) [12, 35, 38, 54, 57].

**Correlation between *Hp* and length of BE**

We extracted data from 11 studies to explore the correlation between *Hp* and LSBE, and obtained a total of 669 BE patients and 31,243 controls [35, 42, 45, 58, 62, 67, 68–72]. We found that the risk of *Hp* infection in patients with LSBE was significantly lower than that in the controls (OR = 0.47; 95% CI, 0.25–0.90; P = 0.02; I² = 82%). In contrast, we extracted data from 12 studies to explore the correlation between *Hp* and short-segment BE (SSBE), and obtained a total of 7886 BE patients and 31,173 controls [35, 36, 42, 45, 58, 62, 67, 73, 70, 74–76]. There was no significant difference in the prevalence of *Hp* between the SSBE and controls (OR = 1.11; 95% CI, 0.78–1.56; P = 0.57; I² = 68%). Although the same *Hp* infection rate was observed in the ultra-short-segment BE (USBE) and GERD groups (22%, 2/9 vs. 22% 7/32) in Zaninotto’s study, such a small sample size might lead to bias [67]. Matsuzaki’s research suggested that the *Hp* infection rate in USBE was lower than that in controls, but the difference was not significant (66.3%, 57/86 vs 72.5%, 50/69; P > 0.05) [76].

**Correlation between *Hp* and BE dysplasia**

Only four previous studies have focused on whether *Hp* reduces the risk of BE dysplasia [11, 36, 5765]. Decades ago, Vieth found that patients with BE neoplasia (high-grade dysplasia or EAC) had significantly lower rates of *Hp* infection than patients with non-ulcer dyspepsia (P < 0.01), which was also lower than that observed in patients with simple BE [65]. This conclusion was further confirmed by two subsequent studies. In a population-based case–control study, Thrift determined that patients with BE had a lower likelihood of infection with *Hp* (OR = 0.37; 95% CI, 0.22–0.61) as was observed in many other studies. The BE group was then divided into two subgroups: BE without dysplasia and BE with dysplasia, and showed a reduced negative correlation (OR = 0.51; 95% CI, 0.30–0.86) and an increased negative correlation (OR = 0.10; 95% CI, 0.03–0.33) when compared to population control, respectively [57]. Another case–control study with many more research objects further verified this finding. When defining cases as BE with dysplasia or cancer, instead of simple BE, the negative correlation between *Hp* and the cases became stronger (OR = 0.31; 95% CI, 0.26–0.37 vs OR = 0.36; 95% CI, 0.34–0.38) [11].

However, a recent study in Azerbaijan, a high-prevalence area of *Hp* infection, directly compared BE with and without dysplasia, and found no significant difference in *Hp* infection between the two groups (OR = 0.42; 95% CI, 0.12–1.52; P > 0.05) [36]. Details of these studies are shown in Table 2.
Prevalence of CagA-positive H. pylori in BE and controls

In the ten studies that examined patients with BE, the prevalence of the CagA-positive H. pylori strain was significantly lower than that in controls (208/1080 [20.5%] vs 605/2070 [29.1%]) (OR = 0.28; 95% CI, 0.15–0.54, P = 0.0002; I² = 83%) (Fig. 6) [12, 38, 45, 47, 54, 58, 59, 69, 71, 72]. In a case–control study in 2008, Corley confirmed that the inverse association between H. pylori and BE...
5.1 Present infected subgroup

| Study                  | BE Events | Control Events | BE Total | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|------------------------|-----------|----------------|----------|---------------|--------|---------------------------------|
| Aghayeva 2019          | 53        | 83             | 103      | 167           | 3.0%   | 1.10 [0.64, 1.89]               |
| Chen 2016              | 42        | 148            | 261      | 588           | 3.1%   | 0.50 [0.34, 0.74]               |
| Chuang 2019            | 224       | 369            | 1548     | 2597          | 3.2%   | 1.05 [0.84, 1.31]               |
| Cséndes 1997           | 20        | 100            | 38       | 190           | 2.9%   | 1.00 [0.56, 1.83]               |
| Dore 2016              | 47        | 108            | 1251     | 2928          | 3.1%   | 1.03 [0.70, 1.52]               |
| Fischbach 2014         | 35        | 218            | 146      | 439           | 3.1%   | 0.38 [0.25, 0.58]               |
| Hackelberger 1998      | 43        | 108            | 156      | 315           | 3.1%   | 0.67 [0.43, 1.05]               |
| Horioka 1999           | 4         | 104            | 64       | 738           | 2.4%   | 0.42 [0.15, 1.18]               |
| Katsinelos 2013        | 14        | 75             | 414      | 1915          | 2.9%   | 0.63 [0.46, 1.50]               |
| Lahej 2002             | 6         | 23             | 281      | 528           | 2.5%   | 0.31 [0.12, 0.80]               |
| Lofield 2004           | 55        | 179            | 1550     | 3975          | 3.1%   | 0.69 [0.50, 0.96]               |
| Newton 1997            | 4         | 16             | 15       | 36            | 2.1%   | 0.47 [0.13, 1.73]               |
| Paul 1988              | 10        | 26             | 11       | 28            | 2.3%   | 0.85 [0.28, 2.58]               |
| Ronkainen 2005         | 5         | 16             | 383      | 984           | 2.4%   | 0.71 [0.26, 2.07]               |
| Sharif 2014            | 12        | 34             | 204      | 702           | 2.8%   | 1.33 [0.86, 2.07]               |
| Sonnenberg 2010        | 8         | 144            | 2510     | 9356          | 3.2%   | 0.44 [0.37, 0.52]               |
| Sonnenberg 2017        | 8         | 1972           | 7647     | 20683         | 3.2%   | 0.34 [0.32, 0.35]               |
| Viet 2000              | 5         | 463            | 1054     | 378           | 3.2%   | 0.69 [0.57, 0.84]               |
| Weston 2000            | 7         | 73             | 208      | 96            | 3.1%   | 0.68 [0.46, 1.01]               |
| White 2008             | 2         | 39             | 3        | 29            | 1.5%   | 0.47 [0.07, 3.00]               |
| Wu 2000                | 0         | 6              | 77       | 225           | 0.9%   | 0.15 [0.01, 2.65]               |
| Zanitchko 2002         | 6         | 34             | 7        | 32            | 2.2%   | 0.77 [0.23, 2.58]               |
| Zhang 2004             | 60        | 120            | 31       | 93            | 3.0%   | 2.00 [1.14, 3.50]               |
| Öberg 1999             | 5         | 40             | 8        | 69            | 2.2%   | 1.09 [0.33, 3.59]               |
| **Subtotal (95% CI)**  | **82093** | **378932**     | **64.8%**| **0.69 [0.54, 0.89]** |

Total events: 3299
Heterogeneity: Tau² = 0.27, Chi² = 282.30, df = 23 (P < 0.00001), I² = 92%
Test for overall effect: Z = 2.83 (P = 0.005)

5.2 Infection history subgroup

| Study                  | BE Events | Control Events | BE Total | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|------------------------|-----------|----------------|----------|---------------|--------|---------------------------------|
| Corley 2006            | 36        | 309            | 67       | 295           | 3.1%   | 0.45 [0.28, 0.70]               |
| Ferrández 2006         | 91        | 104            | 159      | 213           | 2.9%   | 2.38 [1.23, 4.59]               |
| Rubenstein 2014        | 25        | 150            | 86       | 375           | 3.0%   | 0.67 [0.41, 1.10]               |
| Thrift 2012            | 28        | 296            | 73       | 390           | 3.0%   | 0.45 [0.28, 0.72]               |
| Usui 2019              | 1764      | 7419           | 4596     | 29196         | 3.2%   | 1.67 [1.57, 1.78]               |
| **Subtotal (95% CI)**  | **8278**  | **30469**      | **15.2%**| **0.88 [0.43, 1.78]** |

Total events: 1944
Heterogeneity: Tau² = 0.59, Chi² = 75.10, df = 4 (P < 0.00001), I² = 95%
Test for overall effect: Z = 0.35 (P = 0.73)

5.3 Not clear subgroup

| Study                  | BE Events | Control Events | BE Total | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|------------------------|-----------|----------------|----------|---------------|--------|---------------------------------|
| Keyashian 2013         | 24        | 52             | 205      | 420           | 2.9%   | 0.90 [0.50, 1.60]               |
| Klitz 2002             | 8         | 35             | 175      | 545           | 2.7%   | 0.63 [0.28, 1.41]               |
| Lofield 2000           | 14        | 36             | 248      | 454           | 2.8%   | 0.53 [0.26, 1.06]               |
| Park 2009              | 39        | 215            | 12173    | 20154         | 3.1%   | 0.15 [0.10, 0.21]               |
| Rajendra 2007          | 29        | 55             | 37       | 80            | 2.8%   | 1.30 [0.65, 2.58]               |
| Vaezi 2000             | 41        | 230            | 151      | 434           | 3.1%   | 0.41 [0.27, 0.60]               |
| Vicari 1998            | 15        | 48             | 30       | 84            | 2.7%   | 0.82 [0.36, 1.74]               |
| **Subtotal (95% CI)**  | **671**   | **22171**      | **20.2%**| **0.86 [0.29, 1.05]** |

Total events: 170
Heterogeneity: Tau² = 0.66, Chi² = 56.92, df = 6 (P < 0.00001), I² = 89%
Test for overall effect: Z = 1.81 (P = 0.07)

Total (95% CI): 91042 431172 100.0% 0.68 [0.50, 0.94]

Fig. 5 Forest plot of subgroup analysis according to status of Hp infection. 5.1: Hp positive with rapid urease test, urea breath test, histology or culture; 5.2: Hp positive with serological detection, treatment history, or infection history; 5.3: not sure to status of Hp infection.
**Table 2.** Characteristics of the four studies about the correlation between *Hp* and BE dysplasia

| Authors                  | Years | Journal                  | *Hp* testing method | Biopsy location | BE                                      | Cases                                      | *Hp*+ | Total | Controls            | *Hp*+ | Total |
|--------------------------|-------|--------------------------|---------------------|-----------------|-----------------------------------------|--------------------------------------------|-------|-------|---------------------|-------|-------|
| Aghayeva et al. [36]     | 2019  | Dis Esophagus            | H*, R†              | Antrum          | IM‡                                     | BE with dysplasia                          | 5     | 11    | BE without dysplasia | 48    | 72    |
| Sonnenberg et al. [11]   | 2017  | Aliment Pharmacol Ther   | H                   | Stomach         | IM                                      | BE without dysplasia or cancer             | 1972  | 76,475| Endoscopy            | 20,683| 284,552|
|                         |       |                          |                     |                 | IM                                      | BE with dysplasia or cancer                | 138   | 6167  | Endoscopy            | 20,683| 284,552|
| Thrift et al. [57]       | 2012  | Int J.Cancer             | S§                  | IM              |                                        | BE                                         | 28    | 296   | Population           | 73    | 390   |
|                         |       |                          |                     |                 | IM                                      | BE without dysplasia                       | 25    | 208   | Population           | 73    | 390   |
|                         |       |                          |                     |                 | IM                                      | BE with dysplasia                          | 3     | 88    | Population           | 73    | 390   |
| Vieth et al. [65]        | 2000  | Digestion                | H                   | Antrum, Corpus  | IM‡                                     | BE                                         | 463   | 1054  | NUD                  | 378   | 712   |
|                         |       |                          |                     |                 | IM‡                                     | Barrett’s neoplasia (HGD|| or adenocarcinoma) | 54    | 138   | NUD                  | 378   | 712   |

*: Histology, †: Rapid ureas test, ‡: Intestinal metaplasia, §: Serology, ||: High dysplasia
was stronger in subjects with the CagA-positive strain, weaker but still present in those with CagA-negative strains [38]. Meanwhile, there were no substantial differences in the pattern of BE and the CagA-positive Hp strain after adjustment for GERD symptom severity or GERD symptom frequency, which was similar to Anderson’s conclusion [38, 69]. However, Anderson found a somewhat weaker pattern between the CagA-positive Hp strain and BE when analyzing for the CagA antigen only [69].

### Description of publication bias, heterogeneity, and sensitivity analysis

A visual inspection of the funnel plot was used to assess publication bias in the studies. There was no asymmetry in the funnel plots of the respective analyses and subgroup analyses. Considerable heterogeneity was noted in meta-analyses concerning the correlation between Hp prevalence and BE. Substantial heterogeneity was also noted when analyzing the relationship between Hp and lengths of BE, and that at between the CagA-positive Hp strain and BE. Through sensitivity analyses, we found that the significant heterogeneity could be attributed to factors other than a single study. We sometimes discovered decreased heterogeneity in the following subgroup meta-analyses. In the subgroup analysis of GERD, population and primary care people, the heterogeneity decreased considerably to 33% and 0%, respectively. This finding suggests that regarding subjects undergoing endoscopy as control might be the most potential sources of heterogeneity. There was also a significant decrease in heterogeneity when subgroup analysis was performed based on whether or not a match was made for sex and age. There were many factors closely related to Hp and BE, including sex, age, smoking, alcohol consumption, race, geographic location, definition of BE and control group, methods of Hp testing. It was hard to analyze and discuss each factor due to the limited number of publications and the heterogeneity of the description.

### Discussion

In accordance with recent studies, our meta-analysis showed an inverse relationship between the prevalence of Hp, especially the CagA-positive Hp strain, with BE. The conclusions of most of the previous studies are consistent with those of the current study [14, 15, 77], in that Hp is a protective factor for BE. It is generally recognized that Hp causes corpus-predominant gastritis with decreased acid secretion, which is associated with a decreased risk of GERD and BE [78, 79]. Meanwhile, Hp infection reduces the chance of regurgitation by promoting gastric emptying and reducing the incidence of obesity [79]. In subgroup analyses, Hp infection and BE were inversely related when compared with subjects undergoing endoscopy and normal control (population or primary care people), but not GERD control. Furthermore, the prevalence of Hp was not significantly different between patients with BE and those with GERD. Combined to previous studies, this protective effect of Hp is likely mediated by a decrease in prevalence of GERD in Hp-infected patients, since it disappears in patients with GERD [14]. However, there were no substantial differences in the relationship between BE and CagA-positive Hp strains after adjustment for GERD symptom severity or frequency [38, 71]. It suggested that CagA-positive Hp might reduce the risk of BE in some other ways.
Although *Hp* has been classified as a class 1 carcinogen, the majority of infected people had no symptoms associated with *Hp* infection actually [1]. Nowadays, the negative associations between *Hp* and asthma, allergies, GERD and inflammatory bowel disease are increasingly recognized [80]. The present study also revealed the protective effect of *Hp* on BE. Meanwhile, long-term use of proton pump inhibitors has been shown to increase the risk of gastric cancer after confounding factors, the HRs increased with cumulative duration, cumulative omeprazole equivalents and time since treatment initiation [81, 82]. Therefore, it would be important to explore new treatment options to alleviate BE symptoms and personalize *Hp* eradication.

The most likely protective mechanism of *Hp* to BE is the effect on gastric reflux by its influence on gastric acid secretion. Usually, antral-predominant gastritis is associated with increased acid secretion, whereas corpus-predominant gastritis, often accompanied by gastric atrophy, is associated with decreased acid secretion [83]. Ten previous studies only detected *Hp* infection with tissue from the antrum [13, 35, 36, 39, 44, 46–49, 55]; The meta-analysis of these articles showed *Hp* no protective impact to BE (OR = 0.80; 95% CI, 0.58–1.10; \( P = 0.17; \ I^2 = 66% \)) although with decreased heterogeneity. In contrast, studies that defined *Hp* exclusively from esophageal biopsies tended to find a positive association between *Hp* and BE [18]. *Hp* directly damages the esophageal mucosa with bacterial products, increases the production of prostaglandin, sensitizes the afferent nerve, reduces the pressure of the lower esophageal sphincter, and increases acidity via Gastrin, an oncogenic growth factor that contributes to esophageal carcinogenesis [84–88]. Due to the lack of classified discussion on the severity of gastric mucosal lesions after *Hp* infection in those included publications, our study is not able to prove the potential protective effect of *Hp* on BE might be explained by decreased acid secretion due to corpus-predominant gastritis. There are limited studies on the relationship between the duration, site, and severity of *Hp* infection and BE, and further discussions on classification are yet to be conducted.

In subgroup analyses based on different definitions of control and BE, we found that the inverse relationship disappeared when comparing BE with GERD control, and when BE was defined as a change other than IM. Conversely, the OR values of the other subgroups decreased to some extent. In particular, the prevalence of *Hp* infection in the normal control (population or primary care people) was much lower than that in patients with BE compared to the endoscopy subgroup. We also found that *Hp* was negatively correlated with LSBE, and that *Hp* infection could reduce BE dysplasia; however, there was no apparent correlation between *Hp* and SSBE. When it came to different detection methods for *Hp*, we found that the inverse relationship disappeared in the *Hp* infection history subgroup. Serological detection, treatment history, or infection history of *Hp* cannot reflect the current infection status of the study subjects, which will increase the uncertainty of information. In the present infected subgroup, our meta-analysis discovered a protective association between *Hp* and BE that was not present in the *Hp* infection history subgroup.

A few studies without obvious selection and information bias have reported a reduced risk of BE in people infected with *Hp* [18, 38, 53, 71]. The relationship between *Hp* infection and BE is controversial due to the considerable heterogeneity observed in most studies; indeed, significant heterogeneity was also noted in the current meta-analysis. A study by Fischbach et al. identified selection and information bias as potential sources of heterogeneity [71].

Subgroup analyses of the GERD and normal control (population or primary care people) showed a decrease of heterogeneity to 33% and 0%, respectively. The endoscopy subgroup might be one of the greatest sources of heterogeneity, since endoscopy might be associated with multiple gastrointestinal diseases. Applying subjects undergoing endoscopy, who were more likely to be colonized with *Hp* than the general population, as control, would lead to selection bias [38]; however, it also represents the most common and easiest control group. In the same way, blood donors cannot represent the population because they are likely to be healthier and younger [15]. Subject from the same geographical area as the BE patient would be the best choice of control.

A final, but no less important finding was that a significant decrease in overall heterogeneity was also observed when performing subgroup analyses based on whether or not a match was made for sex and age. Males and aging have been shown to be risk factors for *Hp* infection and BE, and in the current study, the protective effect of *Hp* infection wasn't presented when matching both sex and/or age (OR = 0.72; 95% CI, 0.50–1.05; \( P = 0.09; \ I^2 = 76% \)) [12, 13, 36, 38, 40, 44, 51, 60]. This result might be influenced by heterogeneity in definition of control group, definition of BE, *Hp* detection method, age, sex and so on. We collected information about whether or not the BE and control subjects were matched in sex, age, obesity, smoking, alcohol consumption, and race. However, it is unfortunate that, due to too many interfering factors, there were too few studies in single factor subgroups to perform additional
The heterogeneity of existing studies is great. To understand this, gastritis type, sex, age, obesity, smoking, alcohol, and HP attention to, but not only to, the definition of the control well-designed studies are needed. Researchers should pay attention to the inverse relationship between HP and BE disappeared in the SSBE. In addition, the inverse relationship between HP and BE disappeared in the HP infection history subgroup. The heterogeneity of existing studies is great. To understand the extent to which HP reduces the risk of BE, further well-designed studies are needed. Researchers should pay attention to, but not only to, the definition of the control group, the definition of BE, status of HP infection, sampling site, gastritis type, sex, age, obesity, smoking, alcohol, and race.

**Abbreviations**

HP: Helicobacter pylori; BE: Barrett's esophagus; OR: Odds ratio; CI: Confidence interval; GERD: Gastroesophageal reflux disease; LSBE: Long-segment BE; SSBE: Short-segment BE; USBE: Ultra-short-segment BE; EAC: Esophageal adenocarcinoma; CagA: Cytotoxin-associated gene A; NOS: Newcastle–Ottawa Scale; IM: Intestinal metaplasia; CM: Columnar metaplasia; S: Serology; R: Rapid urease test; U: Urea breath test; H: Histology; T: Treatment history; C: Culture; NUD: Non-ulcer dyspepsia; HGD: High grade dysplasia; SCJ: Squamous Columnar Junction; EGI: Esophagogastric junction.

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**Authors’ contributions**

Y-LD carried out the study selection and drafted the manuscript; Y-LD and R-QD contributed to extraction and analysis of the data; L-PD designed and supervised the study. All authors commented on drafts of the paper and approved the final manuscript.

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**Competing interests**

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