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## Effects of *Helicobacter pylori* infection in gastrointestinal tract malignant diseases: From the oral cavity to rectum

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### Abstract

*Helicobacter pylori* (*H. pylori*) has infected approximately fifty percent of humans for a long period of time. However, improvements in the public health environment have led to a decreased chance of *H. pylori* infection. However, a high infection rate is noted in populations with a high incidence rate of gastric cancer (GC). The worldwide fraction of GC attributable to *H. pylori* is greater than 85%, and a high *H. pylori* prevalence is noted in gastric mucosa-associated lymphoid tissue lymphoma patients. These results indicate that the majority of GC cases can be prevented if *H. pylori* infection is eliminated. Because *H. pylori* exhibits oral-oral or fecal-oral transmission, the relationship between this microorganism and other digestive tract malignant diseases has also attracted attention. This review article provides an overview of *H. pylori* and the condition of the whole gastrointestinal

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tract environment to further understand the correlation between the pathogen and the host, thus allowing improved realization of disease presentation.

**Key Words:** *Helicobacter pylori*; Gastrointestinal tract; Malignant disease

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**Core Tip:** *Helicobacter pylori* (*H. pylori*) has infected approximately fifty percent of humans for a long period of time. However, improvements in the public health environment have led to a decreased chance of *H. pylori* infection. This review article provides an overview of the correlation of *H. pylori* infection and gastrointestinal tract malignant diseases. Based on data on *H. pylori*, we believe that the digestive tract microenvironment and *H. pylori* motility affect the risk of cancer formation by *H. pylori* infection.

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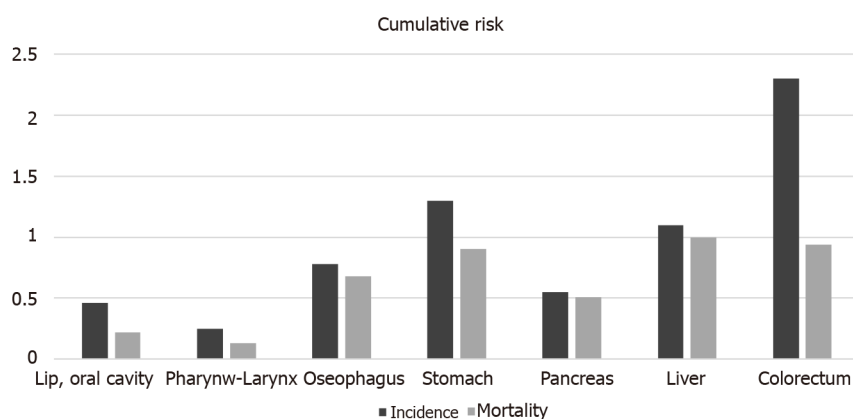
## INTRODUCTION

According to 2020 Global Cancer Observatory data, seven of the top twenty cancers with the highest cumulative risk of incidence affect the gastrointestinal system, including oral cavity, laryngeal-pharynx, esophagus, stomach, pancreas, liver and colorectal cancers (CRC). In 2020, gastrointestinal oncology diseases accounted for greater than 26% of all cancers worldwide. With the exception of pancreatic cancer and liver cancer, other cancer tracts were interlinked (Figure 1)[1]. Three major risk factors are thought to be related to cancers: Obesity, infection and ultraviolet radiation. Several infections are considered to be related to cancer formation, including infection by *Helicobacter pylori* (*H. pylori*), human papillomavirus (HPV), and hepatitis B and C viruses, and these different infectious agents account for greater than 90% of infection-related cancers worldwide[2]. *H. pylori* was identified as an origin of peptic ulcer disease and has become an important public health issue worldwide since 1982. With different geographic areas, ages, ethnicities and socioeconomic statuses, the prevalence rates of *H. pylori* infection are also different[3,4]. Approximately 50% of people worldwide are infected by this bacterium. At the beginning of the 21<sup>st</sup> century, the prevalence was reduced in highly industrialized countries of the Western world. In contrast, the prevalence remains high in developing and newly industrialized countries. The discrepancy in prevalence may result from the degree of urbanization, sanitation, access to clean water, and socioeconomic status[5].

According to the International Agency for Research on Cancer, *H. pylori* is a human carcinogen highly correlated with gastric cancer (GC)[6]. *H. pylori* also accounted for approximately 810000 infection-related cancer cases, which is greater than that reported for any other microorganism, in 2018[2].

Because *H. pylori* exhibits oral-oral or fecal-oral transmission and the whole gastrointestinal tract is connected, we further surveyed the role of *H. pylori* in different gastrointestinal malignant diseases to provide a better understanding of the relationship between *H. pylori* infection and malignant diseases. GC was highly correlated to *H. pylori* infection, but the relationship between *H. pylori* and cancer formation in other gastrointestinal tract malignant diseases, such as oral cavity cancer, laryngeal cancer, esophageal cancer, and colon cancer, has not been completely studied. Recent studies have shown some association between GC and *H. pylori* infection but lack a further overview of *H. pylori* infection and malignant diseases of the whole gastrointestinal tract. Past studies used the host viewpoint and examined which pathogen could cause disease in the host. This review article used the viewpoint of microorganisms and focused on the effects of *H. pylori* infection in gastrointestinal tract malignant diseases from the oral cavity to the rectum to further realize the





**Figure 1** Estimated cumulative risk of incidence and mortality of gastroenterology tract malignancy disease in 2020, both sexes, ages 0-74 (reproduced from <http://globocan.iarc.fr/>).

connection between infectious and malignant diseases.

## ORAL CANCER

### *Epidemiology of oral cancer*

Oral cancer represents approximately 3% of all cancers worldwide and is the 6<sup>th</sup> most common cancer globally. As a popular habit in Asian countries, betel quid chewing is associated with periodontal disease, oral submucous fibrosis, and oral cancer[7,8]. Compared with other tumors in the oral cavity, oral squamous cell carcinoma (OSCC) tends to exhibit local invasion and metastasis[9]. In addition, OSCC occurs more frequently in middle-aged and older populations, particularly in men[10].

### *Pathological differences in oral cancer*

Constituting 94% of oral malignancies, OSCC is far more common than the remaining malignancies, including salivary gland cancer, soft tissue sarcoma, jaw osteosarcoma, non-Hodgkin's lymphoma, melanomas and metastatic tumors, in the oral cavity[11, 12].

### *Role of *H. pylori* in oral cancer*

As a Class I carcinogen, the role of *H. pylori* in oral cancer is not yet clear. Whether the colonization of *H. pylori* is facilitated by betel chewing-related lesions or the resulting chemical changes in the oral cavity remains an important issue to be studied. By comparing the prevalence of *H. pylori* in patients with oral cancer and healthy controls with different betel chewing statuses (Table 1), Fernando *et al*[13] noticed a significantly higher rate of infection among betel chewers regardless of the cancer status. Thus, betel chewing, not oral cancer, is a potential contributing factor to *H. pylori* infection.

Few studies have shown the association between *H. pylori* and oral cancer. Grandis *et al*[14] reported a similar seroprevalence of *H. pylori* in 21 patients with oral cancer and 21 controls; thus, the association could not be proven. Another study adopted polymerase chain reaction (PCR) and culture techniques to identify the existence of *H. pylori* in serum and tissue samples and reported insignificant differences in the prevalence of *H. pylori* between patients with oral cancer and controls. Nevertheless, the odds ratio (OR) was 3.0 [95% confidence interval (CI): 0.34-26.4] by culture and 1.5 (95% CI: 0.28-8.0) by PCR[15]. Only a few studies have attempted to examine the presence of *H. pylori* in OSCC[16]. Due to conflicting results, the relationship between *H. pylori* and OSCC cannot be concluded. The variable results may be caused by differences in methodology, specifically the disparity in the sensitivity and specificity of diagnostic methods. Using the three detection methods [*H. pylori* immunoglobulin (Ig) G antibodies, PCR, and histochemical staining], Meng *et al*[17] suggested an inverse association between *H. pylori* infection and OSCC in the subgroup of individuals over 60 years of age according to the prevalence (35.3% *vs* 54.8%,  $P = 0.012$ ), stratification analysis ( $P = 0.037$ ) and Spearman's correlation (coef. = -0.191,  $P = 0.012$ ). Regardless of race, lifestyle and habitual risk factors, the absence of *H. pylori* in the available OSCC



**Table 1 Association with *Helicobacter pylori* infection and oral squamous cell carcinoma**

|                            | Prevalence of <i>H. pylori</i>                                   | Diagnostic tool of <i>H. pylori</i>        | Study design       | P value |
|----------------------------|--|--|--------------------|---------|
| Fernando <i>et al</i> [13] | Betel Chewers (20/104; 19.2%) and non-betel chewers (4/69; 5.8%) | Serology                                   | Case-control study | < 0.05  |
| Grandis <i>et al</i> [14]  | Case 57% <i>vs</i> controls 62%                                  | Serology                                   | Case-control study | > 0.05  |
| Dayama <i>et al</i> [15]   | OR: 3.0; 95%CI: 0.34-26.4  | Serum and tissue samples (PCR and culture) | Case-control study | NA      |
| Gupta <i>et al</i> [16]    | OR: 2.29; 95%CI: 0.61-8.68                                       | Serology, PCR, culture                     | Meta-analysis      | NA      |
| Meng <i>et al</i> [17]     | Case 35.3% <i>vs</i> controls 54.8%                              | Serology, PCR, histochemical staining      | Case-control study | 0.012   |

*H. pylori*: *Helicobacter pylori*; OR: Odds ratio; CI: Confidence interval; PCR: Polymerase chain reaction; NA: Not available.

cohorts indicates that *H. pylori* is unlikely to contribute to OSCC pathogenesis[18].

### Role of the host effect in oral cancer

It is well known that *H. pylori* modifies the host's immune response, resulting in GC. A similar mechanism might contribute to oral carcinoma; however, this relationship has not been revealed to date. To illustrate the potential relationship between *H. pylori* and oral cancer, a prospective cohort should be conducted in the future. Other risk factors, such as smoking, alcohol consumption, fungi (candidiasis) and viruses (Epstein-Barr virus and HPV), have already been extensively studied[19].

### Summary

According to currently available studies, the relationship between *H. pylori* and oral malignancy cannot be made at present (Tables 1 and 2). Results varied among the studies due to the use of different diagnostic methods (culture, immunohistochemistry, enzyme-linked immunosorbent assay, PCR) adopted for *H. pylori* identification. Overall, the meta-analysis revealed a nonsignificant association between the bacterium and OSCC.

## PHARYNGEAL-LARYNGEAL CANCER

### Epidemiology of pharyngeal-laryngeal cancer

Pharyngeal-laryngeal cancer is a common malignancy of the upper aerodigestive tract. The prevalence is greater in people over the age of 60 and in males (5.8 cases per 100000 in males *vs* 1.2 per 100000 in females)[20]. Pharyngeal-laryngeal cancer comprises 2%-3% of the malignancies of the whole body and constitutes 25% of head and neck cancers[21]. In addition, racial differences were noticed with a younger age and a higher incidence and mortality in African Americans than in Caucasians[22,23]. Moreover, the younger (< 40 years old) the patients were diagnosed, the more aggressive and the poorer the survival rate[24]. Major risk factors for pharyngeal-laryngeal cancer include cigarette smoking and alcohol consumption. A study examining the effect of alcohol consumption and smoking in laryngeal cancer reported that the adjusted odds ratios for nonsmoking heavy drinkers (defined as > 8 drinks per day) and for nondrinking smokers were 2.46 and 9.38, respectively[25]. Microbes, viruses, occupational exposures, gastroesophageal reflux, and genetic inheritance, for example, were also linked to malignancy[26].

### Pathological differences in pharyngeal-laryngeal cancer

Most of these cancers are squamous cell carcinoma, accounting for 85%-95% of pharyngeal-laryngeal malignancies[27].

### Role of *H. pylori* in pharyngeal-laryngeal cancer

*H. pylori* has been detected in tooth plaque, saliva, nasal sinuses, and the middle ear [28,29]. The association between *H. pylori* infection and pharyngeal-laryngeal cancer has been described by Zhou *et al*[30]. Eleven studies were included in a meta-analysis

**Table 2** *Helicobacter pylori* infection effect in whole gastroenterology tract malignant diseases

| Site            | Malignant cell type     | <i>H. pylori</i> effect     | Odds ratio | 95%CI     | P value | Gastrointestinal transit time |
|-----------------|-------------------------|-----------------------------|------------|-----------|---------|-------------------------------|
| Oral cavity     | Squamous cell carcinoma | Non related                 |            |           |         | 1 min                         |
| Pharynx-larynx  | Squamous cell carcinoma | Increased risk <sup>1</sup> | 2.87       | 1.71-4.84 | < 0.05  | 1 s                           |
| Oesophagus      | Squamous cell carcinoma | Non related                 |            |           |         | 4-8 s                         |
|                 | Adenocarcinoma          | Protected effect            | 0.56       | 0.46-0.68 | < 0.05  |                               |
| Stomach         | Adenocarcinoma          | Cause-effect                | 5.9        | 3.4-10.3  | < 0.05  | 2-4 h                         |
|                 | MALT lymphoma           | Cause-effect                | 1.96       | 1.0-3.9   | < 0.05  |                               |
| Small intestine | Lymphoma                | Non related                 |            |           |         | 6 h                           |
| Colorectum      | Adenocarcinoma          | Partial cause-effect        | 1.7        | 1.64-1.76 | < 0.05  | 10 h to days                  |
|                 | Lymphoma                | Non related                 |            |           |         |                               |

<sup>1</sup>Influence of smoking and alcohol consumption on *Helicobacter pylori* and laryngeal carcinoma was not removed from their study. CI: Confidence interval; MALT: Mucosa-associated lymphoid tissue; *H. pylori*: *Helicobacter pylori*.

that demonstrated a significantly higher rate of *H. pylori* infection in patients with pharyngeal-laryngeal cancer compared with healthy controls (OR = 2.87, 95%CI: 1.71-4.84;  $P < 0.0001$ ). Furthermore, the ORs for laryngeal carcinoma were greater than those for pharyngeal cancer [(OR: 3.28, 95%CI: 1.91-5.63) *vs* (OR: 1.35, 95%CI: 0.86-2.12), respectively]. On the basis of the study results, a relationship between *H. pylori* infection and laryngeal carcinoma but not pharyngeal cancer was suggested. This association may result from the direct exposure of the larynx to known carcinogens (*e.g.*, alcohol and tobacco), whereas mucosal and immune barriers were broken down after *H. pylori* infected the larynx. In patients with either benign or malignant laryngeal diseases, *H. pylori* was detected in greater than one-third (38.8%) of the biopsy samples from the larynx. The infection rate of *H. pylori* was highest in patients with laryngeal cancer (46.2%) and chronic laryngitis (45.5%) and was significantly lower in controls (9.1%)[31]. Based on the results of a meta-analysis, *H. pylori* infection increases the risk of laryngeal cancer by twofold compared to controls[32].

Burduk *et al*[33] showed a correlation of a high incidence of positivity for the *H. pylori* cytotoxin-associated gene A (*CagA*) gene in laryngeal cancer tissue (46.7% to 49.3%) and a reduced survival rate. However, several studies failed to demonstrate the direct correlation between *H. pylori* and laryngeal cancer. A study found a significantly higher frequency of *H. pylori* colonization at the antrum compared with the gastric body in patients with laryngeal cancer. It was hypothesized that *H. pylori* in the antrum reduces gastric acid when colonizing the body and increases by G cell hyperplasia, thus leading to laryngeal cancer through gastric reflux[34]. *H. pylori* has been identified in some laryngeal diseases. Given the lack of reliable research, the role of *H. pylori* in the larynx remains unclear.

In addition, acting as confounders, smoking cigarettes and alcohol consumption could mask the true relationship between laryngeal cancer and *H. pylori* infection, and well examined evidence supports the role of these confounders in the development of laryngeal cancer. Zhou *et al*[30] declared that no adjustment was made to eliminate the influence of tobacco and alcohol in their study. More concrete evidence is needed to determine whether *H. pylori* infection is simply associated with or has a causal relation with smoking and drinking among patients with laryngeal-pharyngeal cancer. Furthermore, given the lack of the temporality between laryngeal cancer and *H. pylori* infection, the causal relation cannot be defined by these studies. Finally, almost all these studies were case-control studies with potential recall and selection biases that potentially influenced the outcomes of the present research.

### Summary

Current studies demonstrate the existence of *H. pylori* in the laryngeal mucosa (Tables 2 and 3) and support a possible connection between *H. pylori* infection and laryngeal cancer, but this relationship is not noted in pharyngeal cancer. The etiological mechanism of *H. pylori*-induced laryngeal squamous cell carcinoma is unclear, and related studies are lacking. Further evaluation of the cause-effect of *H. pylori* infection

**Table 3 Association with *Helicobacter pylori* infection and pharyngeal-laryngeal cancer**

|                                 | Prevalence of <i>H. pylori</i>  | Diagnostic tool of <i>H. pylori</i>   | Study design        | P value             |
|---------------------------------|---|---------------------------------------|---------------------|---------------------|
| Zhou <i>et al</i> [30]          | Laryngeal CA: OR: 3.28; 95%CI: 1.91-5.63<br>Pharyngeal CA: OR: 1.35; 95%CI: 0.86-2.12 | Histochemical, PCR, rapid urease test | Meta-analysis       | < 0.0001<br>= 0.188 |
| Siupsinskiene <i>et al</i> [31] | Laryngeal CA: Case 46.2% and controls 9.1%  | Rapid urease test                     | Case- control study | < 0.05              |
| Zhou <i>et al</i> [32]          | Laryngeal CA: OR: 2.3 95%CI: 1.28-3.23  | Serology, histopathological methods   | Meta-analysis       | < 0.01              |
| Pirzadeh <i>et al</i> [34]      | Laryngeal CA: Case 49.2% and controls 40%   | Rapid urease test                     | Case- control study | NA                  |

OR: Odds ratio; CI: Confidence interval; PCR: Polymerase chain reaction; *H. pylori*: *Helicobacter pylori*; CA: Cancer; NA: Not available.

and pharyngeal-laryngeal cancer is required.

## ESOPHAGEAL CANCER

### *Epidemiology of esophageal cancer*

Esophageal cancer constitutes 5.3% of all global cancer deaths and affects greater than 570000 people worldwide. However, the incidence rate varies across regions and populations[35]. Esophageal cancer can be categorized into two main subtypes: Esophageal squamous-cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). In past years, ESCC accounted for 70% of all esophageal cancer cases, and EAC has observed a significant and sustained rise in Western industrialized countries[36]. ESCC exhibits severe geographic distribution differences: The incidence rate is highest in Eastern to Central Asia followed by the Indian Ocean coast and can exhibit greater than tenfold differences among countries. On the other hand, the prevalence of EAC increased in several regions, such as North America and Europe[36,37]. In addition, the global incidence of esophageal cancer in men is 70%, and the cumulative risk from birth to 74 years of age is also higher in men compared with women (1.15% *vs* 0.43%, respectively)[35]. Regarding subtypes, men have a higher risk for developing both ESCC and EAC than women with three- to fourfold and seven- to tenfold differences for each type[38]. The incidence of esophageal carcinoma increases with age, peaks in the seventh and eighth decades of life, and is rare in younger people[37].

### *Pathological and etiological differences in esophageal cancer*

ESCC and EAC exhibit very different biological presentations. ESCC is primarily found in the middle third of the esophagus, whereas EAC is located more often in the distal third of the esophagus[39]. Several dietary habits are related to both types of esophageal cancer. For example, a high intake of red meats, fats, and processed foods is linked to an increased risk, whereas a high intake of fiber, fresh fruits, and vegetables is associated with a lower risk[37]. Other major risk factors differ in these two types of esophageal cancer. ESCC is three to five times as likely to occur in people who consume alcohol (three or more drinks daily)[37]. Smoking or betel quid chewing also increase the risk of ESCC. In addition, the combination of alcohol intake and smoking has a synergistic effect in increasing ESCC risk[37,40]. The absolute risk of EAC developing in an individual 50 years of age or older is approximately 0.04% per year, and that risk is approximately twice as high among current smokers as it is among people who have never smoked[37,41]. The first risk factor reported for EAC was gastroesophageal reflux disease (GERD), which was identified in the 1990s[42]. Several significant associations between two of the common GERD symptoms, *i.e.*, heartburn sensation and acid regurgitation, and the risk of EAC have been demonstrated by several studies. When heartburn symptoms presented for at least 30 years, the risk of EAC was 6.2-fold greater than that in individuals without heartburn[43]. The increasing prevalence of GERD combined with the declining prevalence of *H. pylori* infection has been hypothesized to be related to the increasing incidence of EAC.

### *Role of *H. pylori* in esophageal cancer*

Rokkas *et al*[44] showed no consistent association between *H. pylori* infection and ESCC. Unlike ESCC, several studies have found that *H. pylori* infection is prevalent and leads to a reduced risk of EAC (OR: 0.50-0.57)[44-46]. Xie *et al*[47] showed that the

risk of adenocarcinoma decreased by 41% among persons with *H. pylori* infection. Since the middle of the twentieth century, the prevalence of *H. pylori* infection has decreased in Western populations, and an increasing incidence of EAC has occurred. Scientists have proposed that the elevated incidence of EAC might result from the decreased *H. pylori* infection rate in these populations[48,49]. The possible mechanism of this bacterial infection effect might involve *H. pylori* infection-induced host atrophic gastritis formation followed by reduced volume and acidity of gastric juice. Finally, this situation could counteract GERD and thereby reduce the risk of EAC[50]. Further meta-analysis studies also supported the notion of a decreased risk of EAC up to 40%-60% and an OR of 0.56 for *H. pylori* infection (95%CI: 0.46-0.68,  $P < 0.05$ )[46,47].

### **Role of host genetic effects in esophageal cancer**

Past studies have shown that esophageal cancer might not be associated with family history. However, in China, studies have demonstrated an approximately two-fold increased risk of ESCC in patients with first-degree relatives who have ESCC[51,52]. This situation might be explained by family members sharing some habitual factors, such as diet, obesity, alcohol and smoking. Several genetic disorders have been thought to be related to ESCC. For example, the concentrations of acetaldehyde after alcohol consumption are higher in persons with particular variants in the acetaldehyde dehydrogenase gene and the aldehyde dehydrogenase 2 family gene. If patients had these polymorphic variants, the risk of ESCC was increased up to 43- to 73-fold[53]. In all ESCC individuals, 83% had TP53 mutations, 76% exhibited EGFR overexpression, 46% harbored CCND1 mutations and 24% had CDK4/CDK6 mutations[40]. In EAC patients, 19% exhibited CCNE1 amplification, and 17% harbored cyclin E and MGST1 mutations[40]. These genetic studies might help us to detect esophageal cancer in earlier stages[54]. In addition to the above description, there are several known risk factors related to esophageal cancer. Excess intake of processed foods, hot foods and red meat was associated with an increased risk of both ESCC and EAC, and an increased intake of fresh fruits, vegetables and fiber was associated with a lower risk [37]. Obesity and increased body mass index (BMI) were also thought to be associated with EAC. In particular, if the increase in BMI began in childhood or adolescence, the EAC risk seemed to be stronger than if the increase in BMI began in adulthood[55].

### **Summary**

Unlike other gastrointestinal tract malignancy diseases, *H. pylori* infection might indicate a decreased risk of EAC and be unrelated to ESCC. The OR of EAC in *H. pylori*-infected participants was 0.56 (95%CI: 0.46-0.68,  $P < 0.05$ ) (Tables 2 and 4). *H. pylori* infection might increase atrophic gastritis in the host and decrease gastric acid formation, leading to a decrease in GERD and the probability of EAC. To prevent esophageal cancer, the elimination of smoking and alcohol and very hot food or drink consumption and the practice of healthy dietary habits are beneficial.

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## **GASTRIC ADENOCARCINOMA**

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### **Epidemiology and etiology of GC**

Although it is steadily decreasing in incidence, GC remains one of the most common malignant diseases worldwide[35]. According to GLOBOCAN 2020 data, GC is the sixth most commonly diagnosed cancer and the fifth leading cause of cancer mortality in the world, following lung, breast, colorectal and liver cancer. A Global Cancer Observatory report in 2018 noted that the cumulative risk of GC was higher in men than in women (1.87% and 0.79%)[1]. Compared to North and East Africa and North America, the incidence of GC was higher in East and Central Asia. In East Asia, the average incidence of GC for men and women is 3.21 and 1.32 per individual, respectively, whereas the incidence is 0.56 per million individuals in North America. The risk varies from six- to fifteen-fold between areas with the highest and the lowest incidence. The cause of this difference might be related to region and culture[56]. Ninety-five percent of GCs are adenocarcinomas followed by primary gastric lymphoma, and we focus on reviewing adenocarcinoma in this section. According to the anatomical site, gastric adenocarcinomas can be classified into cardia GCs and non-cardia GCs. The pathogenesis of cardia GCs might be related to GERD or EAC. Non-cardia GCs are caused by *H. pylori*-related atrophic gastritis and a variety of environmental factors, such as diet, alcohol, and smoking[57].

**Table 4 Association with *Helicobacter pylori* infection and Esophageal cancer**

|                          | Prevalence of <i>H. pylori</i>           | Diagnostic tool of <i>H. pylori</i>          | Study design  | P value          |
|--------------------------|--|--|---------------|------------------|
| Rokkas <i>et al</i> [44] | EAC: 0.52 (95%CI: 0.37-0.73)             | Serology and/or histology                    | Meta-analysis | EAC: $P < 0.001$ |
|                          | ESCC: 0.85 (95%CI: 0.55-1.33)            |  |               | ESCC: $P = 0.48$ |
| Islami <i>et al</i> [45] | EAC: 0.56 (95%CI: 0.46-0.68)             | Serology and/or histology                    | Meta-analysis | NA               |
|                          | ESCC: 1.10 (95%CI: 0.78-1.55)            |  |               |                  |
| Nie <i>et al</i> [46]    | EAC: 0.57 (95%CI: 0.44-0.73)             | Serology and/or histology; rapid urease test | Meta-analysis | NA               |
|                          | ESCC: 1.16 (95%CI: 0.8-1.60)             |  |               |                  |
| Xie <i>et al</i> [47]    | EAC: 0.59 (95%CI: 0.51-0.68)             | Serology and/or histology; rapid urease test | Meta-analysis | NA               |
|                          | ESCC: 0.97 (95%CI: 0.76-1.24)            |  |               |                  |
|                          | ESCC in Eastern: 0.66 (95%CI: 0.43-0.89) |  |               |                  |

CI: Confidence interval; *H. pylori*: *Helicobacter pylori*; EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous-cell carcinoma; NA: Not available.

In the past fifty years, the incidence of GC has steadily declined. This trend was more significant in East Asia and might be due to a successful reduction in the number of *H. pylori* infections. Approximately 90% of cases of non-cardia GCs are attributable to *H. pylori* infection. Given *H. pylori* eradication and reduced infection rates, the incidence of non-cardia GCs is also declining[58]. In addition to *H. pylori* eradication, improved food conservation, higher standards of hygiene, and high intake of fresh fruits and vegetables could explain the reduced incidence of GCs[59].

### Role of *H. pylori* in GC

In 1982, Warren and Marshall[60] found a connection between *H. pylori* and gastric ulcer disease, and since then, this bacterium has become a topic of study in the gastroenterology field. Twelve years later, the International Agency for Research on Cancer recognized *H. pylori* as a class I carcinogen[61]. For general microorganisms, the stomach environment is not suitable for survival because the gastric acid and pH level is less than 0.3-2.9[62]. However, with the assistance of urease-derived ammonia, *H. pylori* can buffer cytosolic, periplasmic and surface acidity in such an extreme environment of the stomach[63]. This environment might induce *H. pylori* to become the predominant microorganism in the stomach. In addition, the gastric transit time was greater than 2-4 h (Table 2), giving *H. pylori* more chances to attach to the stomach. When *H. pylori* strains carry the *cag* pathogenicity island (*cagPAI*), the risk of peptic ulcer disease or GC increases. With a size of 40 kb, *cagPAI* contains 30 genes, including *cagA*[64]. A previous study showed that *H. pylori*-infected people had an approximately sixfold increased risk of developing non-cardia GCs (OR: 5.9; 95%CI: 3.4-10.3) compared with uninfected individuals[65]. Furthermore, compared to infection with *cagA*-negative strains, a 1.64-fold (95%CI: 1.21-2.24) increased risk of GC was found for *cagA*-positive strains[66]. In gastric epithelial cells, a cell scattering effect caused by cytoskeletal modifications and proinflammatory responses triggered by the transcription factor NF- $\kappa$ B were observed when a functional *cagPAI* was present in *H. pylori*[67,68]. Activation of growth factor receptors, cell proliferation, inhibition of apoptosis, invasion and angiogenesis occurred through *cagA*[69].

The connection between *H. pylori* infection and GC was most significant in whole gastrointestinal tract cancer. *H. pylori* infection increases GC incidence, but GC incidence is decreased after *H. pylori* eradication. Lee *et al*[70] demonstrated an association of *H. pylori* infection eradication with a reduced incidence of GC in a meta-analysis study. After adjustment for baseline GC incidence, the pooled incidence rate for individuals receiving *H. pylori* eradication treatment was 0.53 (95%CI: 0.44-0.64). Recently, the long-term benefits of eradication were confirmed by Chiang *et al*[71], revealing a significant reduction in the occurrence of GC by 53% for a high-risk Taiwanese population. From 2004 to 2018, a mass eradication program was conducted in patients older than 30 years old on the Matsu Islands, where *H. pylori* infection was prevalent. After *H. pylori* eradication, the infection rates declined from 64% to 15%. GC incidence and mortality after the chemoprevention period were reduced to 53% (95%CI: 0.3-0.69) and 25% (95%CI: 0.14-0.51), respectively. The 2020 Taipei global consensus supported that "eradication therapy should be offered to all individuals



infected with *H. pylori*" and suggested that screen-and-treat is a cost-effective strategy for young adults in GC high incidence areas at the general population level[72].

### Role of host genetic effects in GC

In addition to *H. pylori* infection, dietary habits, lifestyle, family history and occupational exposure are also risk factors for GC. Fresh fruits and vegetables are protective against GC. Compared to individuals who intake less than one serving fruit and vegetable *per day*, participants who ate 2-5 servings had a hazard ratio (HR) of 0.56 (95% CI: 0.34-0.93)[73]. Some scientists have suggested that this might be related to an increase in vitamin C in fresh fruits and vegetables[74]. On the other hand, pickled vegetables, dried fish, and salted fish were associated with an increased incidence of GC[75]. High dietary salt intake was also associated with an increased risk of GC when salt intake was more than 10 g *per day*[76]. Regarding lifestyle, alcohol intake and smoking were thought to increase GC incidence. Duell *et al*[77] found that modest alcohol intake of greater 60 grams *per day* would increase the risk of GC to 1.65 (95% CI: 1.06-2.58). The meta-analysis conducted by Ladeiras-Lopes *et al*[78] included 42 studies from Asia, Europe and the United States and reported a relative risk of 1.53 for smokers (1.62 males and 1.2 females). Smoking not only increased GC risk but also affected GC recurrence and survival. As an independent risk factor, smokers had a significantly worse 5-year disease-free survival (HR: 1.46,  $P = 0.007$ ) and overall survival (HR: 1.48,  $P = 0.003$ ) than nonsmokers[79]. The GC risk was increased two- to threefold in first-degree relatives of patients with this disease. This finding might be due to the familial clustering trend of *H. pylori* infection[80]. Occupational exposures to dust and heat, such as those experienced by chefs, wood processing plant operators, food processing and related trade workers, and machine operators, was linked to a significantly raising risk of diffuse GC[67].

### Summary

In the whole gastrointestinal tract, GC was most related to *H. pylori* infection, especially in non-cardia GCs. The OR of GC in *H. pylori*-infected participants was 5.9 (95% CI: 3.4-10.3,  $P < 0.05$ ) (Tables 2 and 5). The host organ environment and pathogen characteristics might explain this result. The very low pH level in the stomach allows *H. pylori* to predominate in this niche, and adequate gastric transit time provides this bacterium with a greater chance of colonization in the stomach. *H. pylori* strains with a functional *cagPAI* further increased the risk for GC by 1.64-fold. Based on the 2020 Taipei global consensus, mass screening and eradication of *H. pylori* are necessary to prevent GC in high-risk populations.

## GASTROINTESTINAL TRACT LYMPHOMA

### Epidemiology of gastrointestinal tract lymphoma

As the most frequent location for extranodal lymphoma, the gastrointestinal tract represents 5%-20% of all cases[81]. However, primary gastrointestinal lymphoma is very rare. It only constitutes approximately 1%-4% of all gastrointestinal cancers. It is slightly male predominant with a men-women ratio of 3:2. Lymphoma incidence exhibits a double peak: One in patients younger than 10 years old and another in those with a mean age of 53 years[82].

The prevalence of lymphoma among different gastrointestinal locations is highest for the stomach (60%-75%) followed by the small intestine, ileocecal region and rectum [83]. With an elevated incidence worldwide, non-Hodgkin's lymphomas (NHLs) are the most common primary gastric lymphomas, accounting for 5% of gastric malignancies[84]. Primary small intestinal lymphoma occurrence is comparatively rare, constituting 19%-38% of small intestine cancers[85], 20%-30% of primary gut lymphomas[86], and 4%-12% of all NHLs[87]. The most frequent location of small intestine lymphoma involvement is the ileum (60%-65%) followed by the jejunum (20%-25%) and duodenum (6%-8%)[88].

Colorectal lymphoma constitutes 6%-12% of all gastrointestinal lymphomas. Simply contributing 0.2% of all cancers, it is very rare for primary colorectal lymphoma[89]. The most common sites of tumor growth are the cecum (71.5%), rectum (16.9%), and ascending colon (6.2%), whereas the sigmoid colon is rarely involved[90]. Primarily occurring from the fourth to the seventh decades of life, primary colorectal lymphomas are diagnosed at an average age of 50 years. Males are affected approximately twofold more frequently than females[91].

**Table 5 Association with *Helicobacter pylori* infection and gastric cancer**

|   | Prevalence of <i>H. pylori</i>                            | Diagnostic tool of <i>H. pylori</i>          | Study design      | P value   |
|---|---|--|-------------------|-----------|
| Helicobacter and Cancer Collaborative Group[68]                       | Non-cardia GC: OR: 5.9; 95%CI: 3.4-10.3                   | Serology and/or histology                    | Meta-analysis     | P = 0.002 |
| Huang <i>et al</i> [66]   | For cagA-positive OR: 1.64; 95%CI: 1.21-2.24 <sup>1</sup> | Serology and/or histology                    | Meta-analysis     | NA        |
| Gastric cancer incidence decreased after <i>H. pylori</i> eradication |   |  |                   |           |
| Lee <i>et al</i> [70]   | Incidence rate ratio = 0.53; 95%CI: 0.44-0.64             | Serology and/or histology; rapid urease test | Meta-analysis     | NA        |
| Chiang <i>et al</i> [71]  | Reducing GC incidence of 0.53; 95%CI :0.3-0.69            | Rapid urease test                            | Prospective study | P < 0.001 |

<sup>1</sup>In *Helicobacter pylori*-infected populations, cagA-positive strains further increased the risk for gastric cancer by 1.64-fold. GC: Gastric cancer; OR: Odds ratio; CI: Confidence interval; *H. pylori*: *Helicobacter pylori*; NA: Not available.

### Pathological differences in gastrointestinal tract lymphoma

Histopathologically, approximately 90% of primary gastrointestinal lymphomas are of the B cell lineage. Among them, over 90% are mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL). Notably, MALT lymphoma constitutes half of all primary lymphomas with gastric involvement[92].

Primary small intestine lymphomas that are more heterogeneous than those in the stomach include MALT lymphoma, DLBCL, enteropathy-associated T-cell lymphoma, mantle cell lymphoma (MCL), follicular lymphoma and immunoproliferative lymphoma[93].

Primary colorectal lymphomas include MALT-related low-grade B-cell lymphoma, MCL, and peripheral T-cell lymphoma. Manifesting as multiple polyps, MCL is aggressive. In contrast, low-grade B-cell lymphoma derived from MALT is indolent and occasionally appears as multiple polyps. Colonic peripheral T-cell lymphoma expresses as either a diffuse or a focal segmental lesion with extensive mucosal ulceration[94].

### Role of *H. pylori* in gastrointestinal tract lymphoma

A previous large population-based study, in which the seroprevalence of *H. pylori* was higher in patients with gastric lymphoma than in matched controls, confirmed the relationship between *H. pylori*-related chronic gastritis and MALT lymphoma[95]. Gastric MALT lymphoma is highly correlated with *H. pylori* in 72%-98% of low-grade cases[96]. In a retrospective study conducted by Parsonnet *et al*[95], *H. pylori* seropositivity preceded the diagnosis of gastric NHL for years (OR: 6.3; 95%CI: 2.0-19.9). MALT lymphoma was positively correlated with *H. pylori* infection (OR: 1.96; 95%CI: 1.0-3.9)[97]. The regression of low-grade gastric MALT lymphoma after the eradication of *H. pylori* has been described by some recent studies[98]. Epidemiological and experimental data support the hypothesis that *H. pylori* can serve as an antigenic stimulus supporting the growth of gastric lymphoma. Polymorphisms in host genes regulating the inflammatory response and antioxidative mechanisms in gastric MALT lymphoma patients suggest a correlation with the capacity to neutralize free radicals, and individual variations in the inflammatory response to *H. pylori* have been observed in recent research[99]. Expression of the CagA protein by *H. pylori* strains induced severe gastritis or even peptic ulcerations. The hypothesis that CagA+ *H. pylori* strains are linked to the development of gastric MALT lymphomas is observed in nearly all cases of patients in whom anti-CagA antibodies are present at a higher rate compared with inactive gastritis cases[100].

Parsonnet *et al*[95] failed to demonstrate a correlation between non-gastric NHL and prior *H. pylori* infection (OR: 1.2; 95%CI: 0.5-3.0). Several cases of colorectal MALT lymphoma that disappeared completely after *H. pylori* eradication were presented in 1998[101]. Unlike gastric MALT lymphomas, which can be successfully treated by *H. pylori* eradication alone, colorectal MALT lymphomas, which have different relationships with *H. pylori* infection, act and are viewed as a distinct clinical entity. However, antibiotic treatment against *H. pylori* is effective for colonic MALT lymphoma, and this treatment even influences *H. pylori*-negative patients[102].



### Role of the host effect in gastrointestinal tract lymphoma

Sixty-five percent of gastric MALT lymphomas present with chromosomal translocations, including the t(14;18)(q32;q21) translocation, which causes deregulation of MALT1; the t(11;18)(q21;q21) translocation, which causes the formation of the chimeric fusion gene AP12-MALT1; and the t(1;14)(p22;q32) translocation, which causes deregulation of BCL10. Through the regulation of different genes, these translocations are involved in immunity, inflammation and apoptosis[103].

Polymorphisms of specific cytokines have been researched in the context of MALT lymphoma. Upregulation of IL-1 production is typically noted in the presence of *H. pylori*[104]. High IL-1 levels favor a proinflammatory response. In combination with the inhibition of gastric acid, extensive *H. pylori* colonization is facilitated, and MALT growth is promoted[99].

Acting on the signaling pathway, tumor necrosis factor (TNF) and its receptors greatly influence the immune response. TNF may accelerate the growth of lymphoid cells *in vitro*, and high concentrations of TNF were detected in patients with malignant lymphoma[105].

A well-known oncogene, Bcl-6, which is located on the long arm of chromosome 3, is found in most extranodal high-grade lymphomas. Its overexpression was also reported in gastric DLBCL[106].

### Summary

Gastrointestinal lymphoma is a relatively rare disease with a diverse clinical presentation. The epidemiology and histopathologic subtypes as well as their relationship with *H. pylori* infection, are highlighted in this review. For gastric MALT lymphoma, a positive association with *H. pylori* infection was found (OR: 1.96; 95%CI: 1.0-3.9,  $P < 0.05$ ) (Tables 2 and 6). Other non-gastric MALT lymphomas did not show this association.

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## CRC

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### Epidemiology of CRC

CRC is the third most commonly diagnosed cancer in males and the second most commonly diagnosed cancer in females worldwide[107]. In the United States, CRC ranks as the second leading cause of cancer mortality in the population. This trend was similar in Europe, Australia and New Zealand, and these countries showed higher CRC incidence rates[108]. Japan, Thailand, Saudi Arabia and Iran have suffered rapid increases in CRC incidence over the past 30 years[109-111]. However, the age-standardized incidence rates vary in different countries. The country with the highest incidence rate was Hungary, which had 51.2 cases per 100000 persons per year, and the country with the lowest incidence rate was Gambia with 1.1 cases per 100000 persons per year. The cause of this variation might be due to several factors, such as lifestyle, genetics, economic status (for example, meat consumption) and life expectancy (for example, some underdeveloped countries had lower CRC incidence rates because fewer people reach ages over 65 years, when most CRC is diagnosed)[107,112]. It is worth noting that some countries had a low CRC risk regardless of a high prevalence of *H. pylori*. This finding challenges the connection between *H. pylori* and CRC development.

This result might be explained by the fact that CRC has multiple contributing factors and *H. pylori* infection is one of them. For example, together with hyperglycemia, *H. pylori* infection has a synergistic effect on the risk of colon adenoma[113]. Areas with a higher prevalence of *H. pylori* infection but lower incidence of CRC, including Asia, some eastern European countries, and specific countries in South America, exhibit a lower diabetes prevalence[114]. This finding indicates that if the DM prevalence increases, the CRC prevalence might be elevated, which leads to areas with a higher prevalence of *H. pylori* infection but lower CRC incidence rates.

### Pathological differences in CRC

There are three major pathologic pathways of CRC: The adenoma-carcinoma sequence, the serrated pathway and the inflammatory pathway. An estimated 85%-90% of sporadic CRC cases are derived from the adenoma-carcinoma sequence. In this pathway, several stepwise accumulations of genetic and epigenetic alterations drive the transformation of normal colon mucosal cells into an adenoma. First, the inactivated tumor suppressor gene *APC* is regarded as the gatekeeper against

**Table 6 Association with *Helicobacter pylori* infection and gastrointestinal tract lymphoma**

|   | Prevalence of <i>H. pylori</i> | Diagnostic tool for <i>H. pylori</i> | Study design        | P value   |
|---|--------------------------------|--------------------------------------|---------------------|-----------|
| Parsonnet <i>et al</i> [95] (Gastric NHL)             | OR: 6.3; 95%CI: 2.0-19.9       | Serology                             | Case- control study | NA        |
| Ishikura <i>et al</i> [97] (Gastric lymphoma overall) | OR: 2.14; 95%CI: 1.3-3.5       | Serology                             | Case- control study | P = 0.003 |
| Ishikura <i>et al</i> [97] (Gastric MALT)             | OR: 1.96; 95%CI: 1.0-3.9       | Serology                             | Case- control study | P = 0.051 |
| Ishikura <i>et al</i> [97] (Gastric DLBCL)            | OR: 1.92; 95%CI: 0.74-4.95     | Serology                             | Case- control study | P = 0.178 |
| Parsonnet <i>et al</i> [95] (Non-gastric NHL)         | OR: 1.2; 95%CI: 0.5-3.0        | Serology                             | Case- control study | NA        |

NHL: Non-Hodgkin's lymphomas; MALT: Mucosa-associated lymphoid tissue; DLBCL: Diffuse large B-cell lymphoma; OR: Odds ratio; CI: Confidence interval; *H. pylori*: *Helicobacter pylori*; NA: Not available.

**Table 7 Association with *Helicobacter pylori* infection and colorectal adenoma/ cancer**

|   | Prevalence of <i>H. pylori</i>      | Diagnostic tool of <i>H. pylori</i>                            | Study design         | P value   |
|---|-------------------------------------|--|----------------------|-----------|
| Hu <i>et al</i> [113]   | OR: 1.44; 95%CI: 1.2-1.73           | Rapid urease test  | Retrospective        | P < 0.001 |
| Sonnenberg <i>et al</i> [122]   | OR: 1.52; 95%CI: 1.46-1.57          | Histology  | Retrospective        | NA        |
| Liou <i>et al</i> [124]   | Case 14.2% <i>vs</i> controls 11.8% | <sup>13</sup> C-UBT  | Case-control study   | P = 0.513 |
| Choi <i>et al</i> [126]   | OR: 1.49; 95%CI: 1.37-1.62          | Serology, histology, rapid urease test and <sup>13</sup> C-UBT | Meta-analysis        | P < 0.001 |
| Zuo <i>et al</i> [127] <sup>1</sup>                                       | OR: 1.70; 95%CI: 1.64-1.76          | Serology, histology and rapid urease test                      | Meta-analysis        | NA        |
| Colorectal adenoma incidence decreased after <i>H. pylori</i> eradication |                                     |  |                      |           |
| Hu <i>et al</i> [133] <sup>2</sup>  | HR: 3.04; 95%CI: 1.754-5.280        | Rapid urease test  | Retrospective cohort | P < 0.001 |

<sup>1</sup>For colorectal cancer.

<sup>2</sup>Second rapid urease test (+) *vs* (-). <sup>13</sup>C-UBT: <sup>13</sup>C-urea breath test; OR: Odds ratio; CI: Confidence interval; *H. pylori*: *Helicobacter pylori*; HR: Hazard ratio; NA: Not available.

colorectal neoplasms. Second, *KRAS*, an oncogene mutation, facilitates adenoma growth. Then, inactivation of the tumor suppressor gene (*i.e.*, *TP53*) promotes CRC progression[115,116]. Approximately 10%-15% of sporadic CRC is caused by the serrated pathway. This pathway includes several gene mutations. Oncogene *BRAF* mutations induce uncontrolled cell proliferation and contribute to the formation of hyperplastic polyps through constitutive activation of the MAPK pathway[117]. Then, hypermethylation at repetitive CG dinucleotides CpG island methylator phenotype (CIMP) results in mutations in the promoter regions of tumor suppressor genes. CIMP presents cell progression to sessile serrated adenoma and CRC. Approximately 75% of sessile serrated adenomas and 90% of serrated adenocarcinomas had CIMP-positive presentations[118,119]. Less than 2% of all CRC is caused by the inflammatory pathway. In this path-way, normal colon mucosal cells progress from indefinite dysplasia to low-grade dysplasia, high-grade dysplasia and cancer due to chronic inflammation[107].

### Role of *H. pylori* in CRC

Since the 1990s, the connection between *H. pylori* and colorectal neoplasm formation has been widely discussed by scientists. Most reports demonstrated that *H. pylori* was linked to both benign and malignant colon lesions. For instance, *H. pylori* contributes to an elevated risk of 1.3- to 1.97-fold for colon adenoma with or without high-grade dysplasia[113,120-123]. Some scientists did not agree because their data revealed an insignificant increase in colon adenoma in combination with *H. pylori* infection[124, 125]. Nonetheless, two recent meta-analysis studies uncovered a significant and positive correlation between *H. pylori* infection and the risk of colorectal adenoma (OR: 1.49, 95%CI: 1.37-1.62)[126] and CRC (OR: 1.70; 95%CI: 1.64-1.76,  $P = 97\%$ )[127]. The potential mechanisms for *H. pylori*-induced colorectal neoplasms might include direct and/or indirect effects. However, a few studies have shown positive *H. pylori* PCR histology in colon tumors and found *H. pylori* in 22%-27% of colorectal polyps or

cancers[128,129]. Recent studies favored the associations between CRC and blood-stream infections caused by *Streptococcus gallolyticus* (*S. gallolyticus*), *Bacteroides fragilis* (*B. fragilis*) and *Fusobacterium nucleatum* (*F. nucleatum*)[130]. Thus, *S. gallolyticus*, *B. fragilis* and *F. nucleatum* could have direct effects on the formation of colon neoplasms or cancer.

*H. pylori* might affect colorectal tumors through indirect effects. In the whole gastrointestinal tract, the colonic transit time is the longest[131] (Table 2). The long transit time offers more opportunities for *H. pylori* to alter the colonization of the colon, in which other bacteria might promote the development of neoplasms. Additionally, *H. pylori* enhances the release of gastrin, which contributes to colorectal carcinogenesis, possibly through its mitogen activity. *H. pylori* also appears to be associated with metabolic diseases with established connections with CRC. Finally, systemic inflammatory responses triggered by *H. pylori*-induced chronic inflammation of the gastric epithelium may increase the risk of CRC[132]. Although the possible mechanism of *H. pylori*-induced CRC was indirect, our previous study demonstrated a reduced risk of colorectal adenoma after successful eradication therapy[133]. This result implies that *H. pylori* is related to colon neoplasm formation by being a “biomarker” or “indicator organism”, reflecting exposure to immune-stimulating carcinogenic bacteria or antigens.

### Role of the host effect in CRC

In addition to *H. pylori*, several host factors and other environmental factors potentially contribute to the pathogenesis of CRC. Risk factors for colorectal neoplasms included age 60 years or older, male sex, obesity, diet, dyslipidemia, impaired glucose tolerance, a family history of CRC, alcohol intake, tobacco use, and sedentary lifestyle[134-136]. Most of these risk factors were associated with metabolic syndrome. Compared with healthy individuals, patients with hyperglycemia have a higher prevalence of colonic neoplasms (26.6% vs 16.5%,  $P < 0.001$ )[137]. Waist circumference, one of the components of metabolic syndrome, was an independent risk factor for colorectal adenoma, and diabetes mellitus type 2 had an OR of 1.38 for CRC[138]. Compared to non- or occasional drinkers, people who consume four more drinks per day have a 72% increased risk of developing CRC. Cigarette smoking increased the risk of CRC approximately two- to threefold compared with nonsmokers[139].

### Summary

*H. pylori* infection might indicate an increased risk of CRC. The OR of CRC in *H. pylori*-infected participants was 1.70 (95%CI: 1.64-1.76,  $P < 0.05$ ) (Tables 2 and 7)[127]. Although *H. pylori* infection might have an indirect effect on the formation of CRC, the presence or absence of this bacterium could remind clinicians of the possibility of CRC. *H. pylori* eradication therapy benefits both gastric malignancies and colorectal neoplasms by reducing their occurrence.

## CONCLUSION

Given that *H. pylori* infection is an important infectious disease worldwide and affects human health through correlation with several diseases, such as gastric ulcers, GC and gastric MALT lymphoma, further realization of the effects of this bacterium in other gastrointestinal tract diseases is necessary. *H. pylori* infection induces chronic inflammatory changes in the human body and then increases GC, gastric MALT lymphoma and colorectal adenoma formation. In addition, an inverse relationship between *H. pylori* infection and EAC formation was observed due to atrophic gastritis and decreased gastric acid formation. From a microorganism viewpoint, the host gastroenterological microenvironment and motility status might play an important role in deciding which bacteria could colonize organs and subsequently induce chronic inflammatory and malignant changes in host organs. Further evaluation of human and bacterial interactions might allow us to better understand disease treatment.

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