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***Helicobacter pylori* and gastric cardia cancer: what do we know about their relationship?**

Yin JJ *et al.* *Helicobacter pylori* and gastric cardia cancer

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**Abstract**

The incidence of gastric cardia cancer is increasing around the world. Since the discovery of *Helicobacter pylori* (*H. pylori*), numerous studies have proved that it is a causative factor for many kinds of digestive system tumors. Although the literature on gastric cardia cancer and *H. pylori* is not scarce, there are still many controversies on the relationship between gastric cardia cancer and *H. pylori*. Many Western research results showed that there was a negative or no correlation between *H. pylori* infection and gastric cardia cancer, but in several studies in Asian countries, such as China, *H. pylori* was demonstrated to be a risk factor for gastric cardia cancer. Therefore, we intended to analyze the related studies to find out the relationship between *H. pylori* and gastric cardia cancer and find out the causes of the above controversies. We also conducted a meta-analysis of the relationship between cagA positive expression of *H. pylori* and gastric cardia cancer, to find out whether there is an effect between those two. The primary purpose of this paper was to explore the relationship between gastric cardia cancer and *H. pylori*. Through analysis, the study showed the reasons for the controversies mentioned above: (1) Geographical factors could affect the relationship between *H. pylori* and gastric cardia cancer; and (2) the definition of gastric cardia cancer in various studies is inconsistent. The result of a meta-analysis about the relationship between *H. pylori* virulence factor cagA and gastric cardia cancer showed that there was no relationship between these two.

**Key words**: Gastric cardia cancer; *Helicobacter pylori*; Cytotoxin-associated gene A; Relationship; Risk factors; Meta-analysis

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**Core tip:** The relationship between gastric cardia cancer and *Helicobacter pylori* (*H. pylori*) is unclear. Therefore, this article focuses on the relationship between gastric cardia cancer and *H. pylori* and the reasons for this relationship. This paper also discusses the relationship between cagA and gastric cardia cancer, as well as the influence of different colonization sites of *H. pylori* on gastric cardia cancer and the influence of *H. pylori* on the prognosis of gastric cardia cancer, and such.

**Introduction**

In modern society, cancer has become a significant cause of morbidity and mortality worldwide. At present, the incidence of gastric cardia cancer is increasing around the world[[1](#_ENREF_1),[2](#_ENREF_2)]. Gastric cardia cancer stands out distinctly and is different from gastric cancer and esophageal cancer[[3](#_ENREF_3),[4](#_ENREF_4)]. It is relatively insidious, and the degree of cancer cell differentiation is low. Gastric cardia cancer also has extensive invasion and rapid metastasis. Gastric cardia cancer has seriously endangered human health and has become a significant public health problem[[5](#_ENREF_5)]. This cancer occurs in the region of the gastric cardia, which is located at the junction of the stomach and esophagus. It is the transitional zone between the distal esophageal mucosa and the proximal gastric mucosa. Gastric cardia cancer always occurs on the lesser curvature side of the gastric cardia (~75%), followed by the posterior and anterior walls, and the greater curvature side is rarely affected.

Gastric cardia cancer is neither esophageal cancer nor gastric cancer. There are many differences among the three. Scholars have found that the incidence of esophageal cancer and gastric cardia cancer increased, while the incidence of distal gastric cancer decreased[[6-8](#_ENREF_6)]. Many epidemiological, histopathological, and molecular biological studies have showed that there are some similarities between gastric cardia cancer and distal esophageal adenocarcinoma, but gastric cardia cancer is different from distal gastric cancer and esophageal squamous cancer. Gastric cardia cancer and the other two cancers have not only different pathogenesis, but also have different prognostic factors. Besides, esophageal adenocarcinoma mainly spreads to the parastatal lymph nodes and the lower posterior mediastinum, while gastric cardia carcinoma has the characteristic of bilateral metastasis to the chest and abdominal cavity.

For the definition of gastric cardia cancer, there are few international definitions. Gastric cardia cancer is defined as cancer occurring at the anatomic site of the cardia, within 2 cm below the esophagogastric junction[[9](#_ENREF_9)]. The Siewert[[3](#_ENREF_3)] classification is another standard classification scheme. It differentiates the following three distinct tumor entities in the area of the esophagogastric junction: Esophageal tumor (type I), true cardia tumor (type II), and subcardial gastric carcinoma (types III). The World Health Organization (WHO) classification of tumors classified gastric cardia cancer as tumors of the esophagogastric junction in 2000. The literature states that “adenocarcinomas that cross the esophagogastric junction are called adenocarcinoma of the esophagogastric junction, regardless of where the bulk of the tumor lies.”

Some scholars believe that the formation of gastric cardia cancer has undergone multi-stage pathological processes such as cardia inflammation, intestinal metaplasia, intraepithelial neoplasia, carcinoma *in situ*, and invasive cancer[[10](#_ENREF_10)]. There are many reasons for the formation of gastric cardia cancer, and the development of gastric cardia cancer is the result of multiple factors interacting in various stages.

**EPIDEMIOLOGY OF GASTRIC CARDIA CANCER**

The age-standardized incidence of gastric cardia cancer (per 100000 cases) in different parts of the world was shown in the study of Colquhoun *et al*[[11](#_ENREF_11)]. It showed that Eastern/Southeastern Asia had a higher incidence of gastric cardia cancer than other regions in the world, at 8.7 per 100000 for males and 2.4 per 100000 for females. The incidence of gastric cardia cancer in Sub-Saharan Africa was lower than that in other regions, at 0.2 per 100000 for males and 0.1 per 100000 for females. Gastric cardia cancer was more common in males than in females.

China has a higher incidence of gastric cardia cancer in the world. Epidemiological data showed that the incidence of esophageal and gastric cardia cancer was consistent. China is a high incidence area of esophageal cancer, and many studies suggested that the incidence of gastric cardia cancer is also high in this area, where esophageal cancer has a high incidence. This phenomenon has been observed in China's Linxian (Henan Province)[[12](#_ENREF_12)], Cixian (Hebei Province)[[13](#_ENREF_13)], Chaoshan (Guangdong Province)[[14](#_ENREF_14)], and other areas with a high incidence of esophageal cancer.

**RELATIONSHIP BETWEEN *Helicobacter pylori* INFECTION AND GASTRIC CARDIA CANCER**

*Helicobacter pylori (H. pylori)*, which colonizes specifically in the human stomach, was first identified from patients with peptic ulcer disease by Barry Marshall and Robin Warren[[15](#_ENREF_15)]. The prevalence of *H. pylori* infection in most countries in the world remains high. According to Hooi *et al*[[16](#_ENREF_16)], there were 4.4 billion cases of *H. pylori* infection worldwide in 2015. Africa had the highest percentage of *H. pylori* infection (70.1%; 95% confidence interval [CI]: 62.6-77.7), while the lowest percentage was observed in Oceania (24.4%; 95%CI: 18.5-30.4). Nigeria had the highest *H. pylori* infection rate of any country (87.7%; 95%CI: 83.1-92.2). The prevalence of *H. pylori* in Latin America cannot be underestimated. A meta-analysis in a study by Curado *et al*[[17](#_ENREF_17)] suggested that *H. pylori* infection rates are high in all age groups in Latin America. Differences in social and economic conditions across different countries might also affect the infection rate of *H. pylori*[[18](#_ENREF_18)]. It was associated with many diseases[[19-21](#_ENREF_19)], especially gastric cancer[[22-24](#_ENREF_22)].

*H. pylori* colonizes uniquely in the human stomach. Severe diseases caused by *H. pylori* infection are related to the host, bacteria, and environment, such as some gastrointestinal disorders[[25](#_ENREF_25)]. There is also a link between gastric cardia cancer and *H. pylori*. Therefore, the purpose of this paper was to find out the relationship between them through literature review and meta-analysis (Supplementary Figure 1).

Data from GLOBOCAN 2018 showed that *H. pylori* infections account for 35.7% of cancers caused by infection-related factors worldwide, ranking first. It showed more details about the proportion of cancers caused by *H. pylori* infection in various regions of the world (Figure 1). The top three areas were: Central and Eastern Europe (49.3%), East Asia (47.6%), and West Asia (45.2%). These data showed the seriousness of the harm of *H. pylori* to humans.

***Relationship between H. pylori infection and gastric cardia cancer by region***

Table 1 shows the *H. pylori* infection rates and age-standardized incidence of gastric cardia cancer (per 100000 cases) in different parts of the world, based on the studies of Colquhoun *et al*[[11](#_ENREF_11)] and Hooi *et al*[[16](#_ENREF_16)]. The data showed that the infection rate of *H. pylori* was also high in several regions with a high incidence of gastric cardia cancer. However, although the infection rate of *H. pylori* was as high as 76.9% in Africa and Western Asia, the incidence of gastric cardia cancer was relatively low. Therefore, these data revealed a correlation between gastric cardia cancer and *H. pylori* to some extent.

Data from some Western countries showed that *H. pylori* was a protective factor for gastric cardia cancer, or there was no pathogenic relationship between these two. A nested case-control study of a Norwegian population by Hansen *et al*[[26](#_ENREF_26)] and others found that gastric cardia cancer was negatively associated with *H. pylori* (odds ratio [OR] = 0.27, 95%CI: 0.12-0.59). Ye *et al*[[27](#_ENREF_27)] found no correlation between gastric cardia cancer and *H. pylori* infection based on the native Swedish population who were younger than 80 years.

However, studies in China, Japan, and other Asian countries have shown that *H. pylori* was the pathogenic factor for gastric cardia cancer. A cohort study by Kamangar *et al*[[28](#_ENREF_28)] on 29584 residents in Linxian (Henan Province, China) suggested that *H. pylori* infection was a risk factor for gastric cardia cancer (hazard ratio [HR] = 1.64; 95%CI: 1.26-2.14). Yasuo *et al*[[29](#_ENREF_29)] also found that 75% of Japanese patients with gastric cardia cancer had *H. pylori* infection, and *H. pylori* infection was closely associated with gastric cardia cancer.

Marlene[[30](#_ENREF_30)] and others conducted a meta-analysis of the research on the relationship between *H. pylori* infection and gastric cardia cancer. The population of this study included people from all over the world. The results of the study showed that for gastric cardia cancer, thepooled relative risk (PRR) was 1.08 (95%CI: 0.83-1.40; *I2* = 52.8%), but the difference was not statistically significant. Subsequently, those authors divided the regions into high incidence areas and low incidence areas based on the incidence of gastric cancer. China, Japan, and South Korea were classified as high-risk settings, while Australia, Finland, Germany, United States, *etc*. were classified as low-risk Settings. The results showed that *H. pylori* infection was a risk factor for gastric cardia cancer in the high incidence areas of gastric cancer (RR = 0.78, 95%CI: 0.63-0.97; *I2* = 11.6%). This result suggested that geographical factors could affect the relationship between *H. pylori* and gastric cardia cancer.

Also, as mentioned above, although gastric cardia cancer was classified as a type of esophagogastric junction cancer by the WHO in 2000, there are still inconsistencies in the diagnostic criteria for gastric cardia cancer among many current studies. In the study of Hansen[[26](#_ENREF_26)] *et al*, the diagnosis of gastric cardia cancer was based on International Classification Atom of Diseases for Oncology (second edition). Inconsistencies in the diagnostic criteria for gastric cardia cancer may also lead to a wrong diagnosis, thus affecting the relationship between gastric cardia cancer and *H. pylori* and leading to inconsistent research results.

***Relationship between H. pylori virulence factor cagA and gastric cardia cancer: A meta-analysis***

The virulence factor genes of *H. pylori* include *vacA, cagA, cagE, oipA, babA2, babB*, and *iceA*, *etc*.[[31](#_ENREF_31),[32](#_ENREF_32)]. *H. pylori* virulence factors play an important role in the progression of gastric cardia cancer. Cytotoxin-associated gene A (cagA) is a virulence factor of *H. pylori* that has been studied most in the world. CagA is located at one end of the cag-PAI (a 40-kb piece of DNA) and is likely to be incorporated into the *H. pylori* genome through a horizontal transfer process[[33](#_ENREF_33)]. CagA was only found in *H. pylori* highly virulent strains. *H. pylori* cagA protein appears as a bacterial oncoprotein[[34](#_ENREF_34)]. Lee *et al*[[35](#_ENREF_35)] showed that people infected with *H. pylori* which contains the cagA protein produce more reactive oxygen species and have an increased risk of gastric cancer. CagA protein is the only bacterial oncoprotein identified to date. CagA contains two repeatable protein-binding motifs, the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif and the cagA multimerization (CM) motif. There are two major pathological and biochemical processes that contribute to *H. pylori* cagA-induced gastric cancer: Abnormal cancer-promoting signals caused by SHP2 imbalance *via* the EPIYA motif, and gastric epithelial destruction caused by CM-mediated PAR1 inhibition[[36](#_ENREF_36)]. EPIYA motifs are divided into four categories (EPIYA-A, -B, -C, and -D), depending on the amino acid sequence surrounding each EPIYA motif, and they have different characteristics[[37](#_ENREF_37)].

The current research results on the relationship between cagA and gastric cardia cancer are also controversial. In the study by Limburg *et al*[[38](#_ENREF_38)], the adjusted OR value of cagA positive gastric cardia cancer patients compared with cagA negative patients was 1.79 (95%CI: 1.05-3.06), indicating that cagA positivity was a risk factor for patients with gastric cardia cancer. Some other studies showed that there was a significant negative correlation between cagA positivity and the development of gastric cardia cancer. Ye *et al*’s[[27](#_ENREF_27)] study showed that cagA positivity was not associated with the risk for gastric cardia adenocarcinoma (OR = 1.00, 95%CI: 0.70-1.60). Therefore, we performed a meta-analysis of the relationship between *H. pylori* cagA and gastric cardia cancer.

The study was based on the guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE)[[39](#_ENREF_39)] and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[[40](#_ENREF_40)]. PubMed, Web of Science, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Wanfang (China) electronic databases were searched for relevant articles published up to December 2019. The search items were “gastric cardia cancer” and “*Helicobacter pylori* cagA”.

The quality of the eligible studies (Supplementary Table 1) was evaluated according to the Newcastle-Ottawa Scale (NOS)[[41](#_ENREF_41)] (Supplementary Table 2), and articles with a score higher than six were considered high-quality. The STATA (Version 13.1 MP, Stata Corp, College Station, TX, United States) was used to analyze the data. *P* < 0.05 or *I2* > 50.0% was considered to have significant heterogeneity. A fixed-effects model was used when there was no significant heterogeneity, otherwise a random-effect model was used. A sensitivity analysis was performed to evaluate the stability of the pooled results. Egger’s test[[42](#_ENREF_42)] and Begg’s test[[43](#_ENREF_43)] were used to assess the extent of publication bias. *P* < 0.05 was considered statistically significant, and all statistical tests were two-sided.

After screening, a total of 12 articles were included in the study[[27](#_ENREF_27),[38](#_ENREF_38),[44-53](#_ENREF_44)]. The random-effects model (*I2* = 42.2%, *P* = 0.099) and fixed-effects ~~s~~model (*I2* = 42.2%, *P* = 0.060) were used for heterogeneity testing, respectively. The results of the heterogeneity test showed no significant difference. The sensitivity analysis showed that the combined OR did not change significantly, indicating that the combined OR was fairly stable. The *P*-values of Egger’s and Begg’s tests were 0.277 and 0.244, respectively. Detailed results are shown in the Supplementary Materials. The fixed-effect model was eventually selected for use (Figure 2). The pooled OR of this study was 1.03 (95%CI: 0.84-1.26). The results could not indicate that *H. pylori* cagA positivity is a risk factor for gastric cardia cancer (Supplementary Figures 2-4).

***Other relationships between H. pylori and gastric cardia cancer***

*H. pylori* infection in different parts of the gastric cardia mucosa is different, which is consistent with the difference in the incidence of gastric cardia cancer in different regions. The distribution of *H. pylori* infection in the cardia mucosa is characterized by the invasion of both sides of the root of mucosal fold in the cardia. The high incidence area of gastric cardia cancer overlap with the high infection area of *H. pylori*. In the course of gastric cardia cancer, *H. pylori* infection in the cardia and gastric antrum mainly promotes the occurrence of the tumor. *H. pylori* infection also affects the prognosis of patients with gastric cardia cancer. *H. pylori* may be related to the prediction of gastric cardia cancer, but it is not an independent factor.

**OTHER RISK FACTORS FOR GASTRIC CARDIA CANCER**

Gastric cardia cancer is a multi-factorial ailment, which is the result of the interaction of multiple factors, including genetic factors, environmental factors, *etc*.

Demographic characteristics such as age, gender, and ethnicity are all factors influencing gastric cardia cancer. The incidence of gastric cardia cancer increases in the elderly, and the research by Chen *et al*[[14](#_ENREF_14)] showed that the population of 50-80 years had a high incidence of gastric cardia cancer. Several other studies suggested that gastric cardia cancer is more prevalent in males. Colquhoun[[11](#_ENREF_11)] and others showed that the incidence of gastric cardia cancer was significantly higher in males than in females (male: female = 3:1). Kubo *et al*[[54](#_ENREF_54)] and others, through the analysis of five groups of cancer registration data (1992-1998), also found a high incidence of gastric cardia cancer in males.

Current studies have found that many tumors have a family genetic predisposition, and studies on the relationship between gastric cardia cancer and family history have found a correlation between these two. Yang *et al*[[55](#_ENREF_55)] investigated 16605 patients with gastric cardia cancer and 26053 patients with non-cardia cancer through questionnaires. And after a long period of follow-up of 2000 patients, they found that positive family history significantly increased the risk of gastric cardia cancer.

Yang *et al*[[55](#_ENREF_55)] found that smoking significantly increased the risk of gastric cardia cancer (OR = 1.98, 95%CI: 1.79-2.19). The results of the study by Zendehdel *et al*[[56](#_ENREF_56)] also showed that compared to never-users of any tobacco, smokers had an increased risk for gastric cardia cancer (RR = 2.10, 95%CI: 1.50–3.00). Obese subjects (BMI ≥ 30 kg/m2) had a higher risk of gastric cardia cancer than the average population (RR = 2.73, 95%CI: 1.56-4.79), according to the results of a prospective cohort study in the Netherlands[[57](#_ENREF_57)]. Also, Jansson *et al*'s[[58](#_ENREF_58)] study showed a correlation between covert coping strategies when maltreated at work and the risk of gastric cardia cancer.

Genetic risk factors, epigenetic risk factors, long noncoding RNAs, and microRNAs are all in the field of molecular biology. For example, a tumor suppressor protein encoded by the *p53* gene often mutates in many kinds of cancers and is related to cell proliferation and tumor growth[[59](#_ENREF_59)]. Shao’s[[60](#_ENREF_60)] study showed that after Bonferroni correction, the association between TP53BP1 rs560191 G4C and gastric cardia cancer remained significant. The advent of multiple genome-wide association studies has led to the successful identification of many single nucleotide polymorphisms (SNPs), including those associated with gastric cardia cancer. Xiao *et al*’s[[61](#_ENREF_61)] study also showed that the interaction between SNPs and *H. pylori* infection is related to the increased risk of gastric cardia cancer. In Abdi *et al*’s[[62](#_ENREF_62)] study, the factors of molecular biology of gastric cardia cancer were studied more specifically, including not only SNPs~~d~~ but also long noncoding RNAs and microRNAs.

**CONCLUSION**

This article discusses the relationship between *H. pylori* and gastric cardia cancer; however, the relationship between *H. pylori* and gastric cardia cancer could not be analyzed generally. Accurate classification of gastric cardia cancer and patients' geographic factors can influence the relationship between *H. pylori* and gastric cardia cancer. Also, *H. pylori* has a large number of different virulence factors. In this study, only the relationship between the positive expression of cagA and gastric cardia cancer was meta-analyzed, but no correlation between these two was found. The effects of other virulence factors on gastric cardia cancer need to be further studied. Both *H. pylori* related hosts and the environment may have an impact on cardia cancer, which has not been discussed in depth in our research. In addition, the impact of family history on the relationship between *H. pylori* and gastric cardia cancer, and even the relationship between eradication of *H. pylori* and gastric cardia cancer were not included in this study, which need further research.

**References**

1 **Kusano C**, Gotoda T, Khor CJ, Katai H, Kato H, Taniguchi H, Shimoda T. Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center in Japan. *J Gastroenterol Hepatol* 2008; **23**: 1662-1665 [PMID: 19120859 DOI: 10.1111/j.1440-1746.2008.05572.x]

2 **Carr JS**, Zafar SF, Saba N, Khuri FR, El-Rayes BF. Risk factors for rising incidence of esophageal and gastric cardia adenocarcinoma. *J Gastrointest Cancer* 2013; **44**: 143-151 [PMID: 23435833 DOI: 10.1007/s12029-013-9480-z]

3 **Siewert JR**, Stein HJ, Sendler A, Fink U. Surgical resection for cancer of the cardia. *Semin Surg Oncol* 1999; **17**: 125-131 [PMID: 10449684 DOI: 10.1002/(sici)1098-2388(199909)17:2<125::aid-ssu7>3.0.co;2-9]

4 **Kim JY**, Lee HS, Kim N, Shin CM, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Park DJ, Kim HH, Jung HC. Prevalence and clinicopathologic characteristics of gastric cardia cancer in South Korea. *Helicobacter* 2012; **17**: 358-368 [PMID: 22967119 DOI: 10.1111/j.1523-5378.2012.00958.x]

5 **da Costa DM**, Dos Santos Pereira E, de Lima Silva-Fernandes IJ, Ferreira MV, Rabenhorst SH. Characterization of Gastric Cardia Tumors: Differences in Helicobacter pylori Strains and Genetic Polymorphisms. *Dig Dis Sci* 2015; **60**: 2712-2717 [PMID: 25902748 DOI: 10.1007/s10620-015-3666-0]

6 **Ang TL**, Fock KM. Clinical epidemiology of gastric cancer. *Singapore Med J* 2014; **55**: 621-628 [PMID: 25630323 DOI: 10.11622/smedj.2014174]

7 **Abrams JA**, Gonsalves L, Neugut AI. Diverging trends in the incidence of reflux-related and Helicobacter pylori-related gastric cardia cancer. *J Clin Gastroenterol* 2013; **47**: 322-327 [PMID: 22914345 DOI: 10.1097/MCG.0b013e318260177a]

8 **Vial M**, Grande L, Pera M. Epidemiology of adenocarcinoma of the esophagus, gastric cardia, and upper gastric third. *Recent Results Cancer Res* 2010; **182**: 1-17 [PMID: 20676867 DOI: 10.1007/978-3-540-70579-6\_1]

9 **Wijnhoven BP**, Siersema PD, Hop WC, van Dekken H, Tilanus HW. Adenocarcinomas of the distal oesophagus and gastric cardia are one clinical entity. Rotterdam Oesophageal Tumour Study Group. *Br J Surg* 1999; **86**: 529-535 [PMID: 10215831 DOI: 10.1046/j.1365-2168.1999.01082.x]

10 **Wang LD**, Zheng S, Zheng ZY, Casson AG. Primary adenocarcinomas of lower esophagus, esophagogastric junction and gastric cardia: in special reference to China. *World J Gastroenterol* 2003; **9**: 1156-1164 [PMID: 12800215 DOI: 10.3748/wjg.v9.i6.1156]

11 **Colquhoun A**, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 2015; **64**: 1881-1888 [PMID: 25748648 DOI: 10.1136/gutjnl-2014-308915]

12 **Wang LD,** Zheng S. Cancer mechanisms of esophagus and cardia in populations with high incidence of esophageal cancer in Henan. *Zhengzhou Daxue Xuebao* (Yixue Ban) 2002; **37**: 717-729 [DOI: 10.3969/j.issn.1671-6825.2002.06.001]

13 **He YT**, Hou J, Chen ZF, Qiao CY, Song GH, Meng FS, Jin HX, Chen C. Trends in incidence of esophageal and gastric cardia cancer in high-risk areas in China. *Eur J Cancer Prev* 2008; **17**: 71-76 [PMID: 18287862 DOI: 10.1097/CEJ.0b013e3282b6fd97]

14 **Chen GC,** Liu SH, Hong LL. Analysis of 575 cases of gastric cardia pathological changes in Chaoshan gastric cardia cancer high risk area. *Zhongguo JIceng Yiyao* 2017; **24**: 801-804 [DOI: 10.3760/cma.j.issn.1008-6706.2017.06.001]

15 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023 DOI: 10.1016/s0140-6736(84)91816-6]

16 **Hooi JKY**, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology* 2017; **153**: 420-429 [PMID: 28456631 DOI: 10.1053/j.gastro.2017.04.022]

17 **Curado MP**, de Oliveira MM, de Araújo Fagundes M. Prevalence of Helicobacter pylori infection in Latin America and the Caribbean populations: A systematic review and meta-analysis. *Cancer Epidemiol* 2019; **60**: 141-148 [PMID: 31009922 DOI: 10.1016/j.canep.2019.04.003]

18 **Zamani M**, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, Derakhshan MH. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2018; **47**: 868-876 [PMID: 29430669 DOI: 10.1111/apt.14561]

19 **Kyburz A**, Müller A. Helicobacter pylori and Extragastric Diseases. *Curr Top Microbiol Immunol* 2017; **400**: 325-347 [PMID: 28124160 DOI: 10.1007/978-3-319-50520-6\_14]

20 **Xie SH**, Lagergren J. Risk factors for oesophageal cancer. *Best Pract Res Clin Gastroenterol* 2018; **36-37**: 3-8 [PMID: 30551854 DOI: 10.1016/j.bpg.2018.11.008]

21 **Kucukazman M**, Yeniova O, Dal K, Yavuz B. Helicobacter pylori and cardiovascular disease. *Eur Rev Med Pharmacol Sci* 2015; **19**: 3731-3741 [PMID: 26502864]

22 **Amieva M**, Peek RM Jr. Pathobiology of Helicobacter pylori-Induced Gastric Cancer. *Gastroenterology* 2016; **150**: 64-78 [PMID: 26385073 DOI: 10.1053/j.gastro.2015.09.004]

23 **Polk DB**, Peek RM Jr. Helicobacter pylori: gastric cancer and beyond. *Nat Rev Cancer* 2010; **10**: 403-414 [PMID: 20495574 DOI: 10.1038/nrc2857]

24 **Cover TL**. Helicobacter pylori Diversity and Gastric Cancer Risk. *mBio* 2016; **7**: e01869-e01815 [PMID: 26814181 DOI: 10.1128/mBio.01869-15]

25 **Passaro DJ**, Chosy EJ, Parsonnet J. Helicobacter pylori: consensus and controversy. *Clin Infect Dis* 2002; **35**: 298-304 [PMID: 12115096 DOI: 10.1086/341245]

26 **Hansen S**, Vollset SE, Derakhshan MH, Fyfe V, Melby KK, Aase S, Jellum E, McColl KE. Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status. *Gut* 2007; **56**: 918-925 [PMID: 17317788 DOI: 10.1136/gut.2006.114504]

27 **Ye W**, Held M, Lagergren J, Engstrand L, Blot WJ, McLaughlin JK, Nyrén O. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004; **96**: 388-396 [PMID: 14996860 DOI: 10.1093/jnci/djh057]

28 **Kamangar F**, Qiao YL, Blaser MJ, Sun XD, Katki H, Fan JH, Perez-Perez GI, Abnet CC, Zhao P, Mark SD, Taylor PR, Dawsey SM. Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China. *Br J Cancer* 2007; **96**: 172-176 [PMID: 17179990 DOI: 10.1038/sj.bjc.6603517]

29 **Egi Y**, Ito M, Tanaka S, Imagawa S, Takata S, Yoshihara M, Haruma K, Chayama K. Role of Helicobacter pylori infection and chronic inflammation in gastric cancer in the cardia. *Jpn J Clin Oncol* 2007; **37**: 365-369 [PMID: 17578895 DOI: 10.1093/jjco/hym029]

30 **Cavaleiro-Pinto M**, Peleteiro B, Lunet N, Barros H. Helicobacter pylori infection and gastric cardia cancer: systematic review and meta-analysis. *Cancer Causes Control* 2011; **22**: 375-387 [PMID: 21184266 DOI: 10.1007/s10552-010-9707-2]

31 **Chang WL**, Yeh YC, Sheu BS. The impacts of H. pylori virulence factors on the development of gastroduodenal diseases. *J Biomed Sci* 2018; **25**: 68 [PMID: 30205817 DOI: 10.1186/s12929-018-0466-9]

32 **Dabiri H**, Jafari F, Baghaei K, Shokrzadeh L, Abdi S, Pourhoseingholi MA, Mohammadzadeh A. Prevalence of Helicobacter pylori vacA, cagA, cagE, oipA, iceA, babA2 and babB genotypes in Iranian dyspeptic patients. *Microb Pathog* 2017; **105**: 226-230 [PMID: 28215588 DOI: 10.1016/j.micpath.2017.02.018]

33 **Hatakeyama M**, Higashi H. Helicobacter pylori CagA: a new paradigm for bacterial carcinogenesis. *Cancer Sci* 2005; **96**: 835-843 [PMID: 16367902 DOI: 10.1111/j.1349-7006.2005.00130.x]

34 **Hayashi T**, Senda M, Morohashi H, Higashi H, Horio M, Kashiba Y, Nagase L, Sasaya D, Shimizu T, Venugopalan N, Kumeta H, Noda NN, Inagaki F, Senda T, Hatakeyama M. Tertiary structure-function analysis reveals the pathogenic signaling potentiation mechanism of Helicobacter pylori oncogenic effector CagA. *Cell Host Microbe* 2012; **12**: 20-33 [PMID: 22817985 DOI: 10.1016/j.chom.2012.05.010]

35 **Lee DY**, Jung DE, Yu SS, Lee YS, Choi BK, Lee YC. Regulation of SIRT3 signal related metabolic reprogramming in gastric cancer by *Helicobacter pylori* oncoprotein CagA. *Oncotarget* 2017; **8**: 78365-78378 [PMID: 29108235 DOI: 10.18632/oncotarget.18695]

36 **Nishikawa H**, Hatakeyama M. Sequence Polymorphism and Intrinsic Structural Disorder as Related to Pathobiological Performance of the Helicobacter pylori CagA Oncoprotein. *Toxins (Basel)* 2017; **9**: [PMID: 28406453 DOI: 10.3390/toxins9040136]

37 **Chen SY**, Zhang RG, Duan GC. Pathogenic mechanisms of the oncoprotein CagA in H. pylori-induced gastric cancer (Review). *Oncol Rep* 2016; **36**: 3087-3094 [PMID: 27748858 DOI: 10.3892/or.2016.5145]

38 **Limburg P**, Qiao Y, Mark S, Wang G, Perez-Perez G, Blaser M, Wu Y, Zou X, Dong Z, Taylor P, Dawsey S. Helicobacter pylori seropositivity and subsite-specific gastric cancer risks in Linxian, China. *J Natl Cancer Inst* 2001; **93**: 226-233 [PMID: 11158192 DOI: 10.1093/jnci/93.3.226]

39 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]

40 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**: 1006-1012 [PMID: 19631508 DOI: 10.1016/j.jclinepi.2009.06.005]

41 **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

42 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563 DOI: 10.1136/bmj.315.7109.629]

43 **Begg CB**, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088-1101 [PMID: 7786990]

44 **Peleteiro B**, Cavaleiro-Pinto M, Barros R, Barros H, Lunet N. Is cardia cancer aetiologically different from distal stomach cancer? *Eur J Cancer Prev* 2011; **20**: 96-101 [PMID: 21150780 DOI: 10.1097/CEJ.0b013e3283429e77]

45 **Nomura AM**, Kolonel LN, Miki K, Stemmermann GN, Wilkens LR, Goodman MT, Perez-Perez GI, Blaser MJ. Helicobacter pylori, pepsinogen, and gastric adenocarcinoma in Hawaii. *J Infect Dis* 2005; **191**: 2075-2081 [PMID: 15897993 DOI: 10.1086/430353]

46 **Fernández de Larrea-Baz N**, Pérez-Gómez B, Michel A, Romero B, Lope V, Pawlita M, Fernández-Villa T, Moreno V, Martín V, Willhauck-Fleckenstein M, López-Abente G, Castilla J, Fernández-Tardón G, Dierssen-Sotos T, Santibáñez M, Peiró R, Jiménez-Moleón JJ, Navarro C, Castaño-Vinyals G, Kogevinas M, Pollán M, de Sanjosé S, Del Campo R, Waterboer T, Aragonés N. Helicobacter pylori serological biomarkers of gastric cancer risk in the MCC-Spain case-control Study. *Cancer Epidemiol* 2017; **50**: 76-84 [PMID: 28888185 DOI: 10.1016/j.canep.2017.08.002]

47 **Simán JH**, Engstrand L, Berglund G, Forsgren A, Florén CH. Helicobacter pylori and CagA seropositivity and its association with gastric and oesophageal carcinoma. *Scand J Gastroenterol* 2007; **42**: 933-940 [PMID: 17613922 DOI: 10.1080/00365520601173863]

48 **Persson C**, Jia Y, Pettersson H, Dillner J, Nyrén O, Ye W. H. pylori seropositivity before age 40 and subsequent risk of stomach cancer: a glimpse of the true relationship? *PLoS One* 2011; **6**: e17404 [PMID: 21399687 DOI: 10.1371/journal.pone.0017404]

49 **Palli D**, Masala G, Del Giudice G, Plebani M, Basso D, Berti D, Numans ME, Ceroti M, Peeters PH, Bueno de Mesquita HB, Buchner FL, Clavel-Chapelon F, Boutron-Ruault MC, Krogh V, Saieva C, Vineis P, Panico S, Tumino R, Nyrén O, Simán H, Berglund G, Hallmans G, Sanchez MJ, Larrãnaga N, Barricarte A, Navarro C, Quiros JR, Key T, Allen N, Bingham S, Khaw KT, Boeing H, Weikert C, Linseisen J, Nagel G, Overvad K, Thomsen RW, Tjonneland A, Olsen A, Trichoupoulou A, Trichopoulos D, Arvaniti A, Pera G, Kaaks R, Jenab M, Ferrari P, Nesi G, Carneiro F, Riboli E, Gonzalez CA. CagA+ Helicobacter pylori infection and gastric cancer risk in the EPIC-EURGAST study. *Int J Cancer* 2007; **120**: 859-867 [PMID: 17131317 DOI: 10.1002/ijc.22435]

50 **Bakhti SZ**, Latifi-Navid S, Zahri S, Bakhti FS, Hajavi N, Yazdanbod A. Are Helicobacter pylori highly cytotoxic genotypes and cardia gastric adenocarcinoma linked? Lessons from Iran. *Cancer Biomark* 2017; **21**: 235-246 [PMID: 29036792 DOI: 10.3233/CBM-170701]

51 **Xu XF**. Infection of CagA-positive Helicobacter pylor and the risk for cardia and non-cardia gastric cancer in high-risk area of China. Fuzhou: Fujian Yike Daxue 2004

52 **Ekström AM**, Held M, Hansson LE, Engstrand L, Nyrén O. Helicobacter pylori in gastric cancer established by CagA immunoblot as a marker of past infection. *Gastroenterology* 2001; **121**: 784-791 [PMID: 11606491 DOI: 10.1053/gast.2001.27999]

53 **Song H**, Michel A, Nyrén O, Ekström AM, Pawlita M, Ye W. A CagA-independent cluster of antigens related to the risk of noncardia gastric cancer: associations between Helicobacter pylori antibodies and gastric adenocarcinoma explored by multiplex serology. *Int J Cancer* 2014; **134**: 2942-2950 [PMID: 24259284 DOI: 10.1002/ijc.28621]

54 **Kubo A**, Corley DA. Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. *Am J Gastroenterol* 2004; **99**: 582-588 [PMID: 15089886 DOI: 10.1111/j.1572-0241.2004.04131.x]

55 **Yang X,** Wang JP, Cui JL, Lin HL, Hou ZC, Zhu WL, Song X, Li XM, Wang XD, Li JL, Wang LD. Influence of family history, BMI, smoking, and alcohol drinking on risk and prognosis of gastric cardia cancer. *Zhengzhou Daxue Xuebao* (Yixue Ban) 2013; **48**: 124-127 [DOI: 10.3969/j.issn.1671-6825.2013.01.035]

56 **Zendehdel K**, Nyrén O, Luo J, Dickman PW, Boffetta P, Englund A, Ye W. Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. *Int J Cancer* 2008; **122**: 1095-1099 [PMID: 17973262 DOI: 10.1002/ijc.23076]

57 **Merry AH**, Schouten LJ, Goldbohm RA, van den Brandt PA. Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. *Gut* 2007; **56**: 1503-1511 [PMID: 17337464 DOI: 10.1136/gut.2006.116665]

58 **Jansson C**, Johansson AL, Jeding K, Dickman PW, Nyrén O, Lagergren J. Psychosocial working conditions and the risk of esophageal and gastric cardia cancers. *Eur J Epidemiol* 2004; **19**: 631-641 [PMID: 15461194 DOI: 10.1023/b:ejep.0000036806.51918.40]

59 **Soussi T**, Béroud C. Assessing TP53 status in human tumours to evaluate clinical outcome. *Nat Rev Cancer* 2001; **1**: 233-240 [PMID: 11902578 DOI: 10.1038/35106009]

60 **Shao A**, Zheng L, Chen S, Gu H, Jing H. p21, p53, TP53BP1 and p73 polymorphisms and the risk of gastric cardia adenocarcinoma in a Chinese population. *Biomarkers* 2015; **20**: 109-115 [PMID: 25532599 DOI: 10.3109/1354750X.2014.996607]

61 **Xiao FK**, Yang JX, Li XM, Zhao XK, Zheng PY, Wang LD. Interaction of 22 risk SNPs with *Helicobacter pylori* infection and risk of gastric cardia adenocarcinoma. *Future Oncol* 2019; **15**: 3579-3585 [PMID: 31650851 DOI: 10.2217/fon-2019-0319]

62 **Abdi E**, Latifi-Navid S, Zahri S, Yazdanbod A, Pourfarzi F. Risk factors predisposing to cardia gastric adenocarcinoma: Insights and new perspectives. *Cancer Med* 2019; **8**: 6114-6126 [PMID: 31448582 DOI: 10.1002/cam4.2497]

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**Figure Legends**



**Figure 1 Proportions of cancer cases among both sexes attributable to infections in 2012 (by region).**



**Figure 2 Forest plot of studies evaluating the odds ratios of *Helicobacter pylori* cagA positive expression for gastric cardia cancer.**

**Table 1 Gastric cardia cancer age-standardized incidence rates (per 100000) and *Helicobacter pylori* infection rates**

|  |  |  |  |
| --- | --- | --- | --- |
| **Region1** | **Gastric cardia cancer** |  | ***H. pylori* infection rate (%)** |
| **Males** | **Females** |  | **General population** |
| Eastern/Southeastern Asia | 8.7 | 2.4 |  | 58.1 |
| Eastern Europe | 4.7 | 1.4 |  | 62.8 |
| Central/Southern America & Caribbean | 4.0 | 1.3 |  | 63.4 |
| Central Asia | 3.8 | 1.7 |  | 79.5 |
| Northern & Western Europe | 3.7 | 1.0 |  | 37.2 |
| Oceania | 3.4 | 1.1 |  | 24.4 |
| Southern Europe | 3.3 | 0.9 |  | 55.0 |
| Northern American | 2.7 | 0.7 |  | 37.1 |
| Northern Africa & Western Asia | 2.5 | 1.2 |  |  76.92 |
| Sub-Saharan Africa | 0.2 | 0.1 |  |

1Regions were based on the following UN geographical regions: Sub-Saharan Africa (including Eastern, Middle, Southern and Western Africa), Northern Africa and Western Asia, Central Asia (including India), Eastern and South-Eastern Asia (including China), Central/Southern America and the Caribbean, Northern America, Eastern Europe, Northern and Western Europe, Southern Europe and Oceania. 2Total *H. pylori* infection rate of Northern Africa, Western Asia, and Sub-Saharan Africa. *H. pylori*: *Helicobacter pylori*.