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Epidemiology and risk of colorectal cancer in patients with a history of *Helicobacter pylori* infection: a population-based study

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Abstract

Background Numerous modifiable risk factors have been associated with colon cancer. *Helicobacter pylori* (*H. pylori*) is the most common bacterial infection worldwide and the strongest known risk factor for gastric cancer. We aim to assess whether the risk of colorectal cancer (CRC) is higher in patients with a history of *H. pylori* infection.

Methods A validated multicenter and research platform database of more than 360 hospitals was queried. Patients aged 18-65 years were included in our cohort. We excluded all patients who had previously had a diagnosis of inflammatory bowel disease or celiac disease. Univariate and multivariate regression analyses were used to calculate CRC risk.

Results A total of 47,714,750 patients were selected after application of the inclusion and exclusion criteria. The 20-year-period prevalence rate of CRC in the United States population from 1999 to September 2022 was 370 of 100,000 individuals (0.37%). According to multivariate analysis, the risk of CRC was higher in smokers (odds ratio [OR] 2.52, 95% confidence interval [CI] 2.47-2.57), obese patients (OR 2.26, 95%CI 2.22-2.30), those with irritable bowel syndrome (OR 2.02, 95%CI 1.94-2.09), or type 2 diabetes mellitus (OR 2.89, 95%CI 2.84-2.95), and patients who had a diagnosis of *H. pylori* infection (OR 1.89, 95%CI 1.69-2.10).

Conclusion We provide the first evidence from a large population-based study demonstrating an independent association between a history of *H. pylori* infection and CRC risk.

Keywords Colon adenoma, colorectal cancer, gastric cancer, *Helicobacter pylori*

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Introduction

The prevalence of colon cancer is rising in the developing countries and it is the third leading type of cancer in the world [1]. In the United States (US), it is the second most common cause of cancer-related death [2]. Numerous modifiable risk factors have been associated with the disease, including alcohol consumption, obesity, smoking history, and a diet rich in processed and red meat [3]. A history of inflammatory bowel disease, a family history of colorectal cancer (CRC), and age are non-modifiable risk factors that have also been associated with colon cancer. Some evidence of an association of CRC with pathogenic bacterial infection, including *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides gragilis*, *and Salmonella enterica,* have been described in the literature [4].

Helicobacter pylori (*H. pylori*) is the most common bacterial infection worldwide and the strongest known risk factor for gastric cancer [5]. There is sparse evidence in the literature for the association of CRC with *H. pylori* infection [1,6-9]. Only one population-based study illustrated the increased risk of colorectal adenoma in patients with *H. pylori*-related gastritis [10]. Therefore, we aimed to assess whether the risk of CRC is greater in patients with a history of *H. pylori* infection.

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Conflict of Interest: None

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Materials and methods

Database

Explorys Inc., Cleveland, OH, USA is a validated multicenter and research platform database encompassing more than 360 hospitals from 26 different healthcare systems across the US and containing data accumulated from 1999 to September 2022. It was developed and has been prospectively maintained by IBM Corporation, Watson Health [11]. It contains the electronic health records of more than 60 million unique patients and covers a broad regional distribution of the US, representing approximately 15% of the population. The Explorys database was used to construct a retrospective cohort analysis. A Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) hierarchy [12] was used to select diagnoses, findings, and procedures. Prescription drug orders are mapped into SNOMED and RxNorm [13]. Institutional Review Board approval was not required as the source data are de-identified. To protect patient confidentiality, The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Access to the database is granted to participating healthcare systems. Use of the Explorys platform has been validated in multiple fields, including gastroenterology [14,15].

Patient selection

Patients aged 18 years and above were included. We excluded the senior population aged 65 years and above to avoid any misinterpretation of our results, since the risk of CRC increases with age. In addition, we excluded all patients who had a diagnosis of inflammatory bowel disease or celiac disease. A subgroup of patients diagnosed with CRC was later selected and used in the analysis. The control group was identified as patients who did not have a diagnosis of CRC.

Statistical analysis

Patients who developed CRC were compared to those who did not. The prevalence of CRC in the US population was calculated. The prevalence rates of CRC in Caucasian, African America, Hispanic and Asian patients were also calculated for different age groups. A univariate regression model was used to calculate the risk of CRC. A multivariate regression analysis was performed to account for potential cofounders, including male sex, smoking, obesity, alcoholism, irritable bowel syndrome (IBS), type 2 diabetes mellitus (T2DM), and patients who had a history of *H. pylori* infection based on positive serological testing. A 2-sided P-value <0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Results

Descriptive epidemiology

A total of 80,749,290 individuals were screened and of these 47,714,750 were selected after application of the inclusion and exclusion criteria. The baseline characteristics of our cohort are displayed in Table 1. The 20-year-period prevalence rate of CRC in the US population from 1999 to September 2022 was 370 per 100,000 individuals (0.37%). When the prevalence of CRC was compared among different ethnic and age groups, it was found to increase with age in all ethnic groups. Interestingly, Hispanic and Asian patients had a peak in CRC prevalence earlier in life (30- to 40-year group age category), as illustrated in Fig. 1.

Caucasian (70.31%) and Asian race (2.98%), T2DM (17.04%), hyperlipidemia (30.61%), obesity (21.23%), a positive serological test for *H. pylori* infection (0.34%), IBS (3.40%), smoking (16.32%), and alcohol use (2.74%) were more common in patients with CRC compared to controls.

Risk and predictors of CRC using univariate regression analysis

The risk of being diagnosed with CRC was greater in smokers (odds ratio [OR] 3.65, 95% confidence interval [CI] 3.30-3.42), obese patients (OR 3.70, 95%CI 3.63-3.76), those with IBS (OR 3.19, 95%CI 3.07-3.32), or T2DM (OR 4.60, 95%CI 4.52-4.69), and patients who had a history of *H. pylori* infection (OR 3.92, 95%CI 3.52-4.36) (Table 2).

Risk and predictors of CRC using a multivariate regression analysis

In order to adjust for confounding variables, a multivariate regression analysis was performed. The risk of CRC was greater in smokers (OR 2.52, 95%CI 2.47-2.57), obese patients (OR 2.26, 95%CI 2.22-2.30), those with IBS (OR 2.02, 95%CI 1.94-2.09), or T2DM (OR 2.89, 95%CI 2.84-2.95), and patients who had a history of *H. pylori* infection (OR 1.89, 95%CI 1.69-2.10) (Fig. 2).

Discussion

H. pylori plays an important role in the development of gastric cancer [16]. However, most of the people infected with the bacteria will not develop cancer. The risk of gastric cancer secondary to *H. pylori* is altered by the polymorphic nature of the bacterial population in the host, the host genotype, and environmental exposures [17]. A number of factors, including cytotoxin-associated antigen A (CagA) proteins, HP-NAP, oipA and dupA, play a role in the virulence of the bacteria and determine the pattern of the disease [18]. Infection with *H. pylori* leads to chronic inflammation of the stomach lining, predisposing infected individuals to gastric malignancy.

Table 1 Baseline characteristics of patients with colorectal cancer (CRC) and controls

Characteristics	Total	CRC (%)	No CRC (%)
		n=82,420	n=47,632,330
Sex	Male	35,410 (42.96)	21,354,920 (44.83)
	Female	46,840 (56.83)	25,954,180 (54.48)
Race	Caucasian	57,950 (70.31)	24,364,530 (51.15)
	African American	10,770 (13.06)	5,392,410 (11.32)
	Hispanic	1110 (1.34)	744,570 (1.56)
	Asian	2460 (2.98)	798,890 (1.67)
Comorbidities	Type 2 diabetes mellitus	14,050 (17.04)	2,179,130 (4.57)
	Hyperlipidemia	25,230 (30.61)	4,548,180 (9.55)
	Obesity	17,500 (21.23)	3,456,560 (7.26)
	Helicobacter pylori	280 (0.34)	52,980 (0.11)
	Irritable bowel syndrome	2810 (3.40)	578,560 (1.21)
Substance abuse	Smoking	13,450 (16.32)	2,765,380 (5.80)
	Cannabis	1560 (1.89)	485,860 (1.02)
	Alcohol	2260 (2.74)	413,340 (0.86)

Data are presented as n (%)

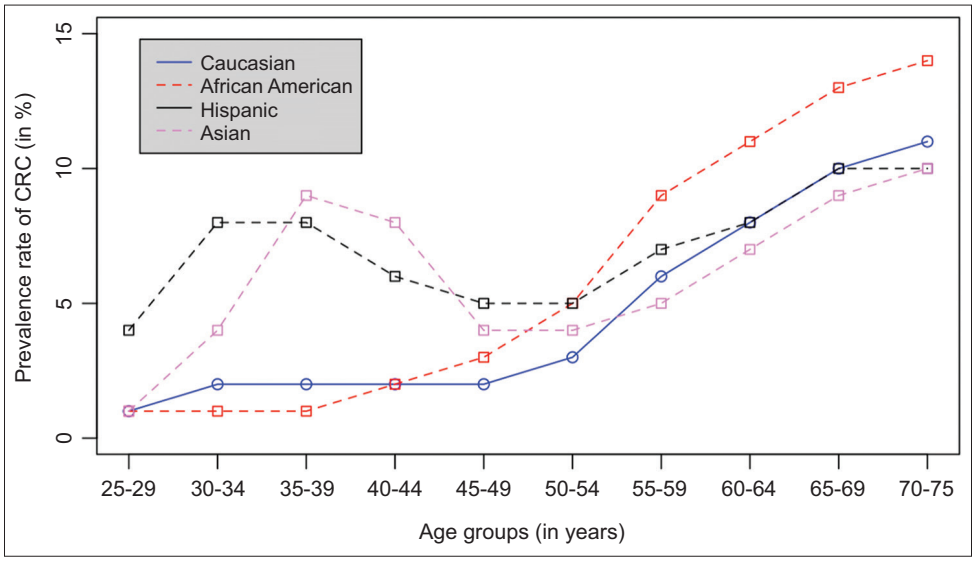

Figure 1 Prevalence of colorectal cancer (CRC) among different age and ethnic groups

H. pylori infection has also been associated in some studies with the development of colorectal adenoma [7,10] and carcinoma [7,10,19,20]. One study showed significant numbers of *H. pylori* in tubular and tubulovillous adenoma [19]. The presence of *H. pylori* is associated with gastrin secretion [7]. There is some evidence demonstrating that it might play a role in the development of CRC [21,22]. In one study, hypergastrinemia has been associated with a statistically significantly greater risk of colorectal malignancy [23]. In fact, gastrin could contribute to CRC by inducing a higher proliferation of colonic mucosal cells [24]. Other studies suggested that gastrin antagonism inhibits the growth of CRC cells *in vitro* [25,26]. Another potential mechanism involves changes in the colonization of the gut by *H. pylori* infection, which could contribute to CRC [27]. However, the association of gastrin with the development of CRC is still controversial [24]. One study showed that there was no difference in the seroprevalence of *H. pylori* in patients with colon polyp or cancer compared to the control group [16]. Other cohorts demonstrated that neither hypergastrinemia nor a seroprevalence of *H. pylori* was associated with an elevated risk of recurrence of colon adenoma [28,29].

One abstract reported a study that used a nationwide inpatient sample database and found an increased risk of CRC in patients

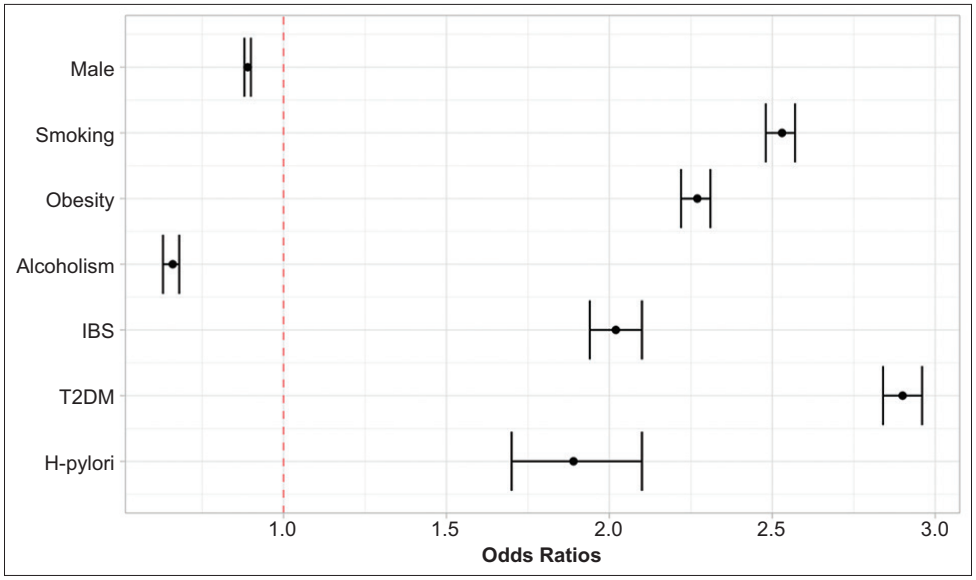

Figure 2 Forest plot for risk of developing colorectal cancer
IBS, irritable bowel syndrome; T2DM, type 2 diabetes mellitus

Table 2 Risk of developing CRC according to a univariate regression analysis model

Variables	CRC	
	OR (95%CI)	P-value
Male sex	0.81 (0.80-0.83)	<0.001
Smoking	3.65 (3.30-3.42)	<0.001
Obesity	3.70 (3.63-3.76)	<0.001
Alcoholism	0.59 (0.57-0.61)	<0.001
IBS	3.19 (3.07-3.32)	<0.001
T2DM	4.60 (4.52-4.69)	<0.001
H. pylori	3.92 (3.52-4.36)	<0.001

CRC, colorectal cancer; OR, odds ratio, CI, confidence interval; IBS, irritable bowel syndrome; T2DM, type 2 diabetes mellitus

with *H. pylori* infection [30]. However, only univariate regression analysis was used. Therefore, we considered that conducting a multicenter national study to assess the risk of CRC in patients with a history of *H. pylori* infection would be of high clinical value if confounding variables were held constant. To the best of our knowledge, we are reporting the first and largest population-based cohort demonstrating an independent risk of CRC in patients with a history of *H. pylori* infection based on positive serological testing. It is important to note that our results only illustrate a positive correlation between a history of *H. pylori* infection and the development of CRC and do not establish any direct causality. Moreover, despite the fact that the risk of developing CRC in patients with IBS is still controversial in the current literature [31,32], it is important to note that our study demonstrated a significantly elevated OR of 3.19 (95%CI 3.07-3.32).

Our article also shows a different age distribution of the prevalence of CRC among different ethnic groups (Fig. 1): Asian and Hispanic populations had an earlier peak of CRC prevalence. One study found that Japanese Americans and African American women are at higher risk of CRC relative to whites [33]. Another population-based study found that the specific CRC incidence rates were higher in Blacks and lowest in Latinos [34]. Differences in CRC epidemiology among ethnic groups could be explained in part by genetics, environmental exposure and access to health care services [33,35]. In fact, further studies would be needed to evaluate the effect of socioeconomic status on the risk of developing CRC in patients who have an active or past history of *H. pylori* infection. Furthermore, it would be interesting to compare the risk of developing CRC in patients who have received treatment for *H. pylori* infection vs. those who did not.

Nevertheless, our study has several limitations. First, it was limited by the use of a large research database that could lead to overpowering and overestimation of the measured outcomes. However, the Explorys database has been validated in multiple fields, including gastroenterology [14,15]. Second, some variables were not accessible; therefore, we could not control for patients who had a history of radiation therapy or a history of CRC, or those who had been using aspirin. Third, the diagnosis of *H. pylori* infection is based on serological studies, which cannot differentiate between active and past infection. Therefore, care must be taken in interpreting the results of this study, as it is limited by the fact that the risk of CRC was higher in patients who had either an active or a past history of *H. pylori* infection. In other words, no temporal association between the development of CRC and the time of *H. pylori* infection can be inferred from this study.

In conclusion, we have reported the first and largest population-based study demonstrating an independent positive association between the risk of CRC and a history of *H. pylori* infection. An increasing amount of evidence for this association exists in the literature, but it has not yet been established on a large scale.

Summary Box

What is already known:

- Some evidence of an association between colon cancer and pathogenic bacterial infection has been described in the literature
- *Helicobacter pylori* (*H. pylori*) is the most common bacterial infection worldwide and the strongest known risk factor for gastric cancer

What the new findings are:

- This is the first and largest population-based study demonstrating an independent positive association between the risk of colorectal cancer (CRC) and a history of *H. pylori* infection
- We found differences in the age distribution of the prevalence of CRC among different ethnic groups, with Asian and Hispanic patients having an earlier peak of CRC prevalence

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