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Long-term effect of *Helicobacter pylori* eradication on colorectal cancer incidences

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Chuan-Guo Guo, Feifei Zhang, Fang Jiang, Lingling Wang, Yijun Chen, Wenxue Zhang, Anni Zhou, Shutian Zhang and Wai K. Leung

Abstract

Background: There is evidence supporting the association between *Helicobacter pylori* infection and colorectal cancer (CRC), but whether *H. pylori* eradication reduces the risk of CRC is still unknown.

Objectives: To compare the incidence of CRC in subjects who had received *H. pylori* eradication therapy with general population.

Design: A population-based retrospective cohort study.

Methods: This study included all *H. pylori*-infected subjects who had received their first course of clarithromycin-containing triple therapy in 2003–2015 in Hong Kong. We compared the observed incidences of CRC in this *H. pylori* eradicated cohort with the expected incidences in the age- and sex-matched general population. The standardized incidence ratio (SIR) with 95% confidence interval (CI) was computed.

Results: Among 96,572 *H. pylori*-eradicated subjects with a median follow-up of 9.7 years, 1417 (1.5%) developed CRC. Primary analysis showed no significant difference in the observed and expected incidences of CRC (SIR: 1.03, 95% CI: 0.97–1.09). However, when stratified according to the follow-up period, higher incidence of CRC was only observed in the first 5 years after eradication (SIR: 1.47, 95% CI: 1.39–1.55), but it was lower (SIR: 0.85, 95% CI: 0.74–0.99) than general population after 11 years. When stratified by tumor location, the observed incidence was higher for colon (SIR: 1.20, 95% CI: 1.12–1.29) but lower for rectal cancer (SIR: 0.90, 95% CI: 0.81–0.999) among *H. pylori*-eradicated subjects.

Conclusions: *H. pylori*-infected subjects appeared to have a higher incidence of CRC initially, which declined progressively to a level lower than general population 10 years after *H. pylori* eradication, particularly for rectal cancer.

Keywords: clarithromycin-containing triple therapy, colorectal cancer, epidemiology, *Helicobacter pylori*, standardized incidence ratio

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Correspondence to:
Wai K. Leung
Department of Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong 999077, China
waikleung@hku.hk

Chuan-Guo Guo
Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Department of Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

Feifei Zhang
National Institute of Health Data Science at Peking University, Beijing, China

Fang Jiang
Department of Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

Lingling Wang
Department of Gastroenterology, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Yijun Chen
Wenxue Zhang
Anni Zhou
Shutian Zhang
Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Introduction

Helicobacter pylori (*H. pylori*) infection is the major etiologic factor for chronic gastritis, peptic ulcer disease, and gastric cancer. Although the prevalence of *H. pylori* infection is declining in many regions, the disease burden, particularly in mid- and low-income countries with high background prevalence of infection, remains substantial.[1] While the stomach is the usual habitat of *H. pylori* and is considered as the primary target organ, there is emerging evidence suggesting the putative association between *H. pylori* infection and other extra-gastric diseases including colorectal cancer (CRC).[2,3] The association between *H. pylori* infection and CRC as well as colorectal adenoma had been recently suggested.[4] Two meta-analyses showed that *H. pylori* infection was associated with a higher risk of colorectal adenoma and CRC, with the pooled odds ratio of 1.51 and 1.70, respectively.[5,6] As yet, most of

these data were based on case–control or cross-sectional studies, and *H. pylori* infection was mainly defined by positive serological tests.[6]

Although the benefits of *H. pylori* eradication in prevention of gastric cancer development have been widely demonstrated,[7] it remains uncertain whether *H. pylori* eradication has any effects on the risk of subsequent CRC development to further strengthen the putative link between *H. pylori* infection and CRC. There is so far no study which addresses the role of *H. pylori* eradication on CRC development.

In this study, using a large population-based cohort of *H. pylori*-infected subjects who had received clarithromycin-containing triple therapy for *H. pylori* in Hong Kong, we aimed to compare the incidence of CRC in *H. pylori*-eradicated subjects with matched local general population to determine the potential effects of *H. pylori* eradication on subsequent risk of CRC.

Methods

Data source

We used the Clinical Data Analysis and Reporting System (CDARS), an electronic healthcare database of the Hong Kong Hospital Authority which is the only public healthcare provider serving the 7 million local population, to identify subjects who had previously received *H. pylori* eradication. The CDARS included patient's demographics, diagnoses, out-patient attendance and hospitalization, drug prescriptions, and dispensing records from all public hospitals and clinics.[8–10] All data from this database are anonymized and deidentified.

For incidences of CRC in the general population, we retrieved the number of new cases of CRC from the Hong Kong Cancer Registry.[11] The corresponding population demographics of that period were obtained from Hong Kong Annual Digest of Statistics with the mid-year population by 5-year age groups and sex over the study period.[12]

Subjects

This is a retrospective population-based cohort study involving all subjects who had received their first course of clarithromycin-containing triple therapy for *H. pylori* eradication in Hong Kong between January 2003 and December 2015. Clarithromycin-containing triple therapy was identified by the co-prescription of proton pump inhibitor, clarithromycin and amoxicillin, or metronidazole with the same prescription start date and an overlapping prescription duration of 7, 10, or 14 days.[13] Subjects who received only a single course of clarithromycin-containing triple therapy were regarded as eradication success, while those who received retreatment for *H. pylori* were treated as retreatment group.[13] Retreatments after failure of the initial treatment included the repeated prescription of clarithromycin-containing triple therapy, subsequent prescription of the second-line or third-line therapy. We excluded subjects who had ever received resection of any gastrointestinal tract segment, those who had been diagnosed with CRC before the eradication, and those who developed CRC or died within 1 year after the eradication (Figure 1).

CRC incidences in matched general population

We computed the CRC incidences in the local general population using the number of new CRC cases from the Hong Kong Cancer Registry and the mid-year population by 5-year age group and sex from 2003 to 2019 (the latest available year). This cancer registry is a population-based registry committed to collecting data from all cancer cases and covering the entire local population in Hong Kong. Cancers from different sites were identified according to International Classification of Diseases (ICD)-9 and/or ICD-10 codes. The expected CRC cancer incidence of the age- and sex-matched local population was estimated based on the age- and sex-specific CRC incidence.

Outcome

The primary outcome was the observed incidence of CRC, including colon cancer and rectal cancer, which developed more than 1 year after eradication therapy in *H. pylori*-eradicated subjects *versus* the expected incidence in the matched general population. The date of diagnosis of CRC for *H. pylori*-eradicated subjects was the first date of inpatient or outpatient records for CRC workup or treatment, or death date when it was only identified from death certificate. The incident CRC was retrieved using ICD-9 (CRC: 153–154, colon cancer: 153; rectal cancer: 154) or ICD-10 (CRC: C18–21; colon cancer: C18; rectal cancer: C19–21).

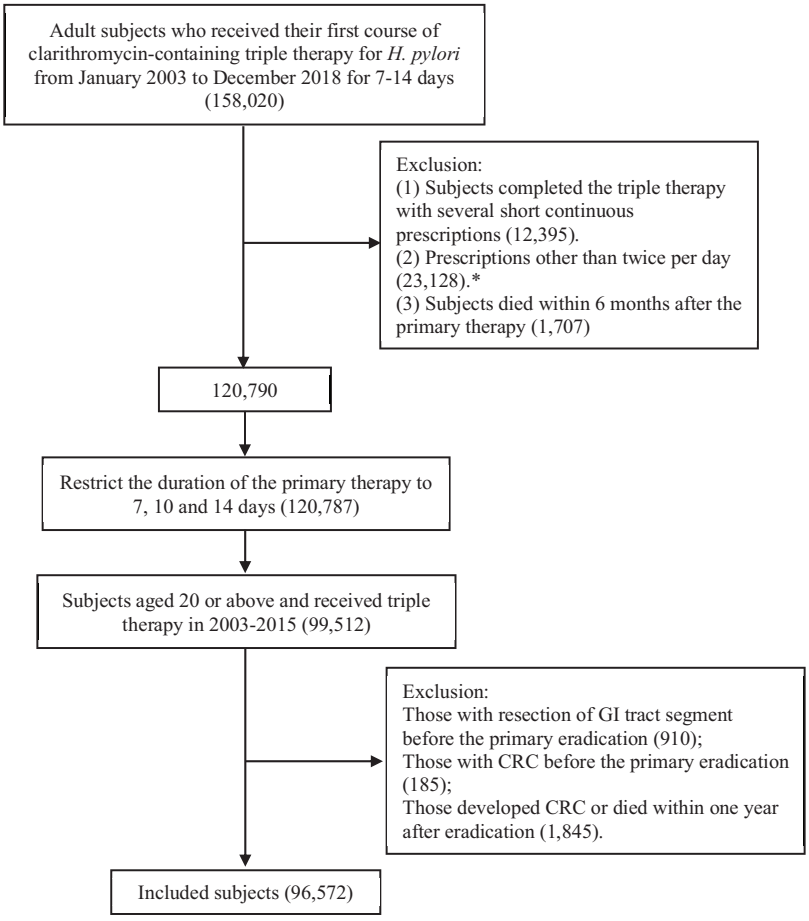

Figure 1. Flow chart of patient selection.
*For metronidazole, prescriptions with frequency of three or four times per day were also included.

Statistical analyses

Subjects were followed up from 1 year after *H. pylori* eradication until the date of diagnosis of CRC, death, or the end of follow-up on 31 December 2020, whichever came first. The observed incidence of CRC in *H. pylori*-eradicated subjects was compared with the expected incidence in the age- and sex-matched general population. The expected cumulative incidence and Kaplan–Meier survival curve for the matched general population were estimated using the methods from Finkelstein *et al.*,[14] which was raised to compare the survival of a single sample to that of a defined reference population and had been used in previous studies.[8,15] To estimate the expected CRC cases in the matched general population with specific age and sex, the probability of observing an incident CRC during the same follow-up period as that for the matched subjects in our cohort was calculated, based on local CRC incidence. Thus, the mean age- and sex-specific incidences in 2003–2019 in Hong Kong were used. In the sensitivity analysis, the mean incidences in 2003–2012 or 2010–2019 were used due to the potential changes in cancer incidences in the general population during the study period. The one-sample log-rank test and the standardized incidence ratio (SIR) with an exact 95% confidence interval (CI) were used to test the difference between the observed incidence of CRC in *H. pylori*-eradicated subjects and the expected incidence in the matched general population. Subcategory analyses by colon or rectal cancer were also performed. A sensitivity analysis using CRC from inpatient diagnosis or death record in *H. pylori*-eradicated subjects was performed.

To demonstrate the time trend of cancer incidence after *H. pylori* eradication, we compared the observed and the expected CRC incidences in different periods after eradication. The

cumulative incidences and the corresponding SIRs in different periods (1–5, 6–10, and ⩾11 years) after eradication were computed. Furthermore, subgroup analyses were performed according to the age group (<40, 40–59, and ⩾60 years old), treatment outcome (eradication success and retreatment), and history of prior lower endoscopy before *H. pylori* eradication (yes/no). Tests with a two-sided p value <0.05 were considered statistically significant. All statistical analyses were performed using the R software, version 4.2.0 (Vienna, Austria).

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[16]

Results

Patient characteristics

We included 96,572 *H. pylori*-infected subjects, aged 20 or above [median age: 54 years, interquartile range (IQR): 45–65; male: 46.8%], who had received clarithromycin-containing triple therapy for *H. pylori* in this study. Among them, 9781 (10.1%) subjects required retreatment for *H. pylori* and was treated as eradication failure. At baseline, there were 13,106 (13.6%) subjects who had received prior lower endoscopy.

CRC after H. pylori *eradication* versus *matched general population*

After a median follow-up of 9.7 (IQR: 6.4–13.2) years, 1417 *H. pylori*-eradicated subjects developed CRC with an incidence of 1.51 (95% CI: 1.43–1.59) per 1000 person-years. The expected incidence of CRC in the corresponding age- and sex-matched general population was 1.47 (95% CI: 1.39–1.55) per 1000 person-years, and there was no significant difference between the observed and expected CRC incidences with an SIR of 1.03 (95% CI: 0.97–1.09).

When considering CRC incidences according to different follow-up intervals after *H. pylori* eradication, higher incidence of CRC was observed in *H. pylori*-eradicated subjects than matched general population in the first 5 years (SIR: 1.14, 95% CI: 1.04–1.24). However, a lower incidence of CRC was observed after 11 years (SIR: 0.85, 95% CI: 0.74–0.99; Figure 2(a) and (b), Tables 1 and 2).

Separate analysis was performed for colon and rectal cancer. The observed incidence of colon cancer in *H. pylori*-eradicated subjects was significantly higher than the general population (SIR: 1.20, 95% CI: 1.12–1.29). However, analysis according to different follow-up durations showed significant difference in the first 5 years only (SIR: 1.34, 95% CI: 1.22–1.48), and the risk decreased with time to a level comparable to the general population afterwards (Figure 2(c) and (d), Table 2). For rectal cancer, *H. pylori*-eradicated subjects had an overall lower incidence rate than the general population (SIR: 0.90, 95% CI: 0.81–0.999). Notably, the incidence of rectal cancer in *H. pylori*-eradicated subjects was comparable to the matched general population in first 10 years but declined after 11 years of eradication (Figure 2(e) and (f), Table 2).

The results were consistent when using either the mean cancer incidences in 2003–2012 or 2010–2019 to estimate the expected cancer incidences (Supplemental Tables 1 and 2). When using CRC from inpatient diagnosis or death record in *H. pylori*-eradicated subjects, the result was also consistent (Supplemental Table 3).

Subgroup analyses by subjects' characteristics

Further subgroup analyses were performed according to patient's age, *H. pylori* eradication success and prior colonoscopy at baseline. The results were consistent among subjects aged 60 or above, in which higher incidences of all CRC, and colon cancer, were observed in the first 5 years after eradication among *H. pylori*-eradicated subjects (SIR for CRC: 1.19, 95% CI: 1.08–1.31; SIR for colon cancer: 1.39, 95% CI: 1.24–1.56). For rectal cancer, the incidence was lower in *H. pylori*-eradicated subjects, aged 60 or above, after 11 years of the eradication (SIR: 0.64, 95% CI: 0.43–0.97). However, the incidences of CRC were comparable to the age-matched general population among *H. pylori*-eradicated subjects <40 years and 40–59 years throughout the follow-up period (Table 3).

Consistent results were observed in subgroups of subjects with *H. pylori* eradication success (Table 3). There was no decreasing trend of the incidence of CRC among subjects with initial eradication failure who received retreatment for *H. pylori*.

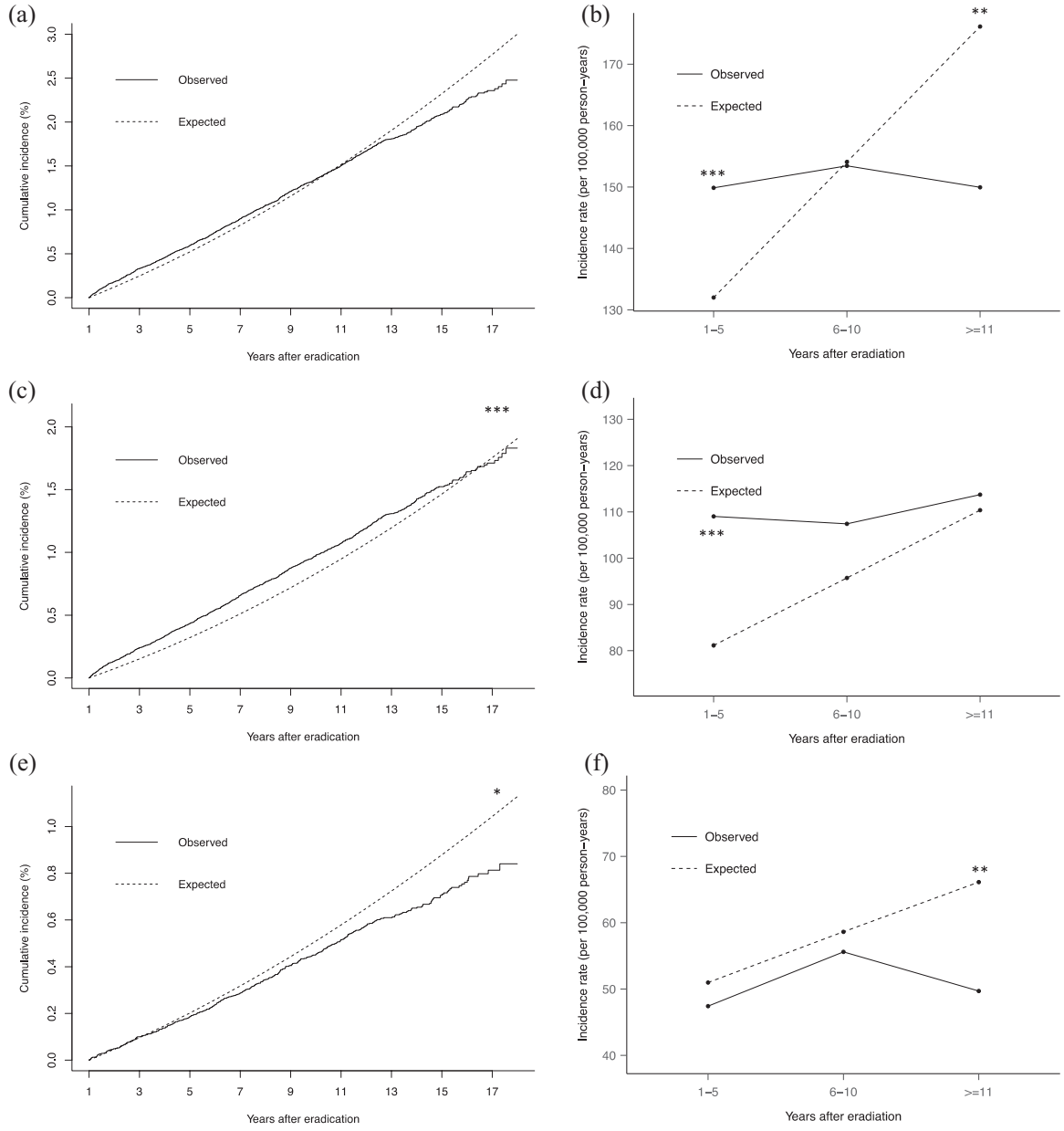

Figure 2. Observed CRC incidence after *H. pylori* eradication compared with the expected incidence in the matched general population. (a) Cumulative incidence of CRC; (b) incidence rates of CRC according to follow-up duration; (c) cumulative incidence of colon cancer; (d) incidence rates of colon cancer according to follow-up duration; (e) cumulative incidence of rectal cancer; and (f) incidence rates of rectal cancer according to follow-up duration.
*$p < 0.05$. **$p < 0.02$. ***$p < 0.001$. CRC, colorectal cancer.

In subgroup of subjects who had prior lower endoscopy at baseline, the incidences of CRC, including colon cancer and rectal cancer, were lower than matched general population (Table 3). Furthermore, the incidence of CRC in *H. pylori*-eradicated subjects who had prior lower endoscopy showed a progressive decreasing trend during the extended follow-up period when compared to the matched general population (SIR in 1–5 years: 0.76, 95% CI: 0.59–0.98; SIR in 6–10 years: 0.56, 95% CI: 0.40–0.80; SIR after 11 years: 0.50, 95% CI: 0.28–0.88).

Discussion

In this population-based study with a median follow-up of 9.7 years, we found that *H. pylori*-eradicated subjects had an overall higher incidence of CRC, colon cancer in particular, when compared with matched general population, which was mainly observed in the first 5 years after treatment for *H. pylori*. This finding was in line with previous studies that *H. pylori*-infected subjects was associated with a higher risk of CRC.[4,6] However, with lengthening of the follow-up duration after treatment for *H. pylori*, the CRC incidence declined to a level comparable with, and even lower than, the general population in the long term. Furthermore, apart from testifying the cancer prevention effects of colonoscopy, the risk of CRC further declined with time after *H. pylori* eradication suggesting the potential additional benefits of *H. pylori* eradication.

Table 1. Baseline characteristics of subjects.

Characteristic	Value
N	96,572
Age, median (IQR)	54.0 (45.0, 65.0)
Age group (%)	
⩾60 years	35,086 (36.3)
40–59 years	48,213 (49.9)
<40 years	13,273 (13.7)
Male (%)	45,200 (46.8)
Retreatment	9,781 (10.1)
Prior lower endoscopy[a]	13,106 (13.6)

[a]Including any colonoscopy and sigmoidoscopy before the primary eradication.
IQR, interquartile range.

The positive association between *H. pylori* infection and CRC has been reported in previous studies.[4] To date, majority of previous studies were case–control or cross-sectional in design, which failed to demonstrate the potential causality between *H. pylori* infection and CRC.[4] Although *H. pylori* infection and its related complications may increase patients' visits to physicians and the chance of receiving CRC screening, we found that the increase in risk was mainly observed for colon cancer but not rectal cancer, which could not be explained by simple health seeking and screening effects. A retrospective population-based cohort study showed that *H. pylori* infection was associated with a significantly higher risk of CRC with an adjusted HR of 1.87.[17] A recent large nested case–control study based on 10 prospective cohorts found that seropositivity to 4 out of 13 *H. pylori* proteins was associated with a 10–11% increased risk of CRC.[18] This was however disputed by others.[19,20] In our study involving all *H. pylori*-eradicated subjects, we found that *H. pylori*-eradicated subjects had a higher incidence of CRC, particularly in the first 5 years after treatment. This finding supports that *H. pylori*-infected subjects have an increased risk of CRC. However, after treatment for *H. pylori*, the incidence declined to a level comparable to general population, indicating that *H. pylori*

Table 2. CRC incidences after *H. pylori* eradication compared with the expected incidences in the matched general population.

	CRC			Colon cancer			Rectal cancer		
Observation period	Person-years	Observed/expected number of cases	SIR (95% CI)	Person-years	Observed/expected number of cases	SIR (95% CI)	Person-years	Observed/expected number of cases	SIR (95% CI)
Overall	937738.5	1417/1377.5	1.03 (0.97–1.09)	939113.2	1026/854.6	1.20 (1.12–1.29)	940742.9	476/528.0	0.90 (0.81–0.999)
Years after eradication									
1–5 years	461084.4	691/608.7	1.14 (1.04–1.24)	461410.3	503/374.4	1.34 (1.22–1.48)	461883.5	219/235.5	0.93 (0.80–1.08)
6–10 years	320616.2	492/494.0	1.00 (0.90–1.10)	321182.3	345/307.4	1.12 (0.99–1.27)	321898.6	179/188.7	0.95 (0.80–1.12)
⩾11 years	156037.9	234/274.8	0.85 (0.74–0.99)	156520.6	178/172.7	1.03 (0.87–1.22)	156960.8	78/103.8	0.75 (0.58–0.97)

CI, confidence interval; CRC, colorectal cancer; SIR, standardized incidence ratio.

Table 3. Subgroup analyses of CRC incidences after *H. pylori* eradication compared with the expected incidence in the matched general population.

Subgroups	CRC			Colon cancer			Rectal cancer		
	Person-years	Observed/expected number of cases	SIR (95% CI)	Person-years	Observed/expected number of cases	SIR (95% CI)	Person-years	Observed/expected number of cases	SIR (95% CI)
Age ⩾60	294452.7	934/874.0	1.09 (0.99–1.15)	295195.5	701/565.4	1.24 (1.14–1.35)	296329.4	290/312.5	0.93 (0.81–1.06)
1–5 years	159423.9	516/434.7	1.19 (1.08–1.31)	159628.0	386/277.4	1.39 (1.24–1.56)	160011.0	153/158.4	0.97 (0.81–1.16)
6–10 years	96417.6	302/303.3	1.00 (0.88–1.13)	96735.0	217/197.5	1.10 (0.94–1.28)	97234.0	107/107.5	1.00 (0.80–1.24)
⩾11 years	38611.2	116/135.9	0.85 (0.69–1.05)	38832.5	98/90.5	1.08 (0.86–1.36)	39084.4	30/46.6	0.64 (0.43–0.97)
Age 40–59	497280.6	457/479.5	0.95 (0.85–1.06)	497876.9	309/276.4	1.12 (0.98–1.27)	498349.6	175/204.2	0.86 (0.72–1.02)
1–5 years	235894.7	165/167.8	0.98 (0.83–1.17)	236006.0	111/93.8	1.18 (0.96–1.46)	236097.4	61/74.2	0.82 (0.62–1.09)
6–10 years	173226.1	179/182.0	0.98 (0.83–1.16)	173462.4	121/105.3	1.15 (0.94–1.41)	173668.6	68/77.1	0.97 (0.81–1.16)
⩾11 years	88159.8	113/129.7	0.87 (0.71–1.08)	88408.5	77/77.3	1.00 (0.77–1.28)	88583.7	46/52.9	0.87 (0.63–1.21)
Age <40	146005.2	26/24.1	1.08 (0.70–1.67)	146040.8	16/12.7	1.26 (0.72–2.18)	146064.0	11/11.3	0.97 (0.50–1.89)
1–5 years	65765.8	10/6.2	1.62 (0.81–3.25)	65776.3	6/3.2	1.87 (0.77–4.53)	65775.2	5/3.0	1.69 (0.64–4.43)
6–10 years	50972.5	11/8.7	1.26 (0.65–2.45)	50984.8	7/4.6	1.52 (0.67–3.46)	50996.1	4/4.1	0.97 (0.33–2.84)
⩾11 years	29267.0	5/9.2	0.55 (0.21–1.43)	29279.7	3/4.9	0.61 (0.18–2.06)	29292.7	2/4.3	0.47 (0.11–2.01)
Retreatment	95437.9	152 / 127.2	1.20 (1.00–1.43)	95611.0	110 / 78.6	1.40 (1.13–1.73)	95736.5	54 / 49.1	1.10 (0.81–1.49)
1–5 years	47312.9	70/55.8	1.25 (0.96–1.64)	47351.5	45/34.1	1.32 (0.95–1.84)	47375.7	28/21.8	1.29 (0.84–1.96)
6–10 years	32578.8	53/46.1	1.15 (0.85–1.56)	32656.7	41/28.6	1.43 (1.01–2.03)	32710.3	17/17.7	0.96 (0.56–1.64)
⩾11 years	15546.2	29/25.3	1.15 (0.76–1.74)	15602.8	24/15.8	1.52 (0.96–2.39)	15650.4	9/9.6	0.94 (0.45–1.95)
Eradication success	842300.6	1265/1250.4	1.01 (0.95–1.08)	843502.2	916/776.0	1.18 (1.10–1.27)	845006.4	422/478.9	0.88 (0.79–0.98)
1–5 years	413771.5	621/552.9	1.12 (1.03–1.23)	414058.7	458/340.3	1.35 (1.21–1.49)	414507.8	191/213.7	0.89 (0.76–1.05)
6–10 years	288037.4	439/447.9	0.98 (0.88–1.09)	288525.6	304/278.8	1.09 (0.96–1.24)	289188.3	162/171.0	0.95 (0.79–1.13)
⩾11 years	140491.7	205/249.6	0.82 (0.70–0.96)	140917.9	154/156.9	0.98 (0.82–1.18)	141310.4	69/94.2	0.73 (0.56–0.96)
Prior lower endoscopy[a]	115713.0	130/200.0	0.65 (0.53–0.79)	115840.4	90/124.7	0.72 (0.57–0.91)	115977.8	45/75.8	0.59 (0.43–0.83)
1–5 years	62404.1	75/98.7	0.76 (0.59–0.98)	62443.9	50/61.0	0.82 (0.60–1.12)	62498.9	27/37.9	0.71 (0.46–1.09)
6–10 years	38659.7	40/71.1	0.56 (0.40–0.80)	38710.8	29/44.6	0.65 (0.43–0.98)	38774.3	13/26.7	0.49 (0.26–0.90)
⩾11 years	14649.1	15/30.2	0.50 (0.28–0.88)	14685.7	11/19.2	0.57 (0.30–1.11)	14704.6	5/11.2	0.45 (0.17–1.18)
No prior lower endoscopy	822025.6	1287/1177.5	1.09 (1.03–1.16)	823272.8	936/729.9	1.28 (1.19–1.38)	824765.1	431/452.2	0.95 (0.86–1.06)
1–5 years	398680.3	616/510.0	1.21 (1.10–1.32)	398966.3	453/313.4	1.45 (1.30–1.61)	399384.6	192/197.6	0.97 (0.83 1.14)
6–10 years	281956.5	452/422.9	1.07 (0.96–1.19)	282471.5	316/262.9	1.20 (1.06–1.36)	283124.3	166/162.0	1.02 (0.86–1.22)
⩾11 years	141388.8	219/244.6	0.90 (0.77–1.04)	141835.0	167/153.6	1.09 (0.91–1.29)	142256.2	73/92.6	0.79 (0.61–1.02)

[a]Including any colonoscopy, sigmoidoscopy, or polypectomy before the primary eradication.
CI, confidence interval; CRC, colorectal cancer; SIR, standardized incidence ratio.

eradication may have long-term protective effect on CRC development. In a secondary analysis of a randomized controlled trial on *H. pylori* treatment and gastric cancer, *H. pylori* treatment was also associated with a lower long-term risk of CRC specific death after controlling baseline gastric histology (hazard ratio: 0.25, 95% CI: 0.07–0.89), and a protective trend was also observed in the multivariate model.[21]

The association between *H. pylori* and the site of colorectal neoplasia had also been evaluated previously. Hong *et al.*[22] reported that positive association between *H. pylori* infection and colonic adenoma or advanced adenoma was confined to proximal adenoma. In contrast, Zhang *et al.*[23] found that *H. pylori* infection may be associated with the increased risk of CRC in the left colon. Further studies are needed to confirm and evaluate the potential different effects of *H. pylori* infection on colon and rectal cancer.

Despite the reported association between *H. pylori* infection and CRC, the underlying mechanism remains unclear.[4,24] *H. pylori* could have direct and/or indirect effects on colorectal carcinogenesis.[4] Although colon is not the usual habitat of *H. pylori*, the bacterium could traverse the colon and rectum and it was also detected in colorectal lesions.[25,26] Studies have reported that components of *H. pylori* or specific strains may promote DNA synthesis and cell proliferation in small intestinal epithelial cell line.[27,28] *H. pylori* may also promote colorectal carcinogenesis in an indirect manner. First, colorectal carcinogenesis might be caused by dysbiosis of the gut microbiota induced by *H. pylori* infection.[29,30] *H. pylori* infection may result in changes in gut microbiota by altering gastric acidity and host–microbe interactions.[29] Studies have shown that treatments for *H. pylori* with antibiotics significantly reduced the alpha-diversity of the gut microbiota transiently.[29] After *H. pylori* eradication, short-chain fatty acids-producing bacteria were enriched,[31,32] which has been shown to have anticancer effect on CRC.[33,34] Guo *et al.*[31] reported that the *Bifidobacterium*-related taxa was enriched after successful eradication, which is a well-known probiotic and has potential CRC prevention effect.[35] Several studies have also reported increased abundance of putative CRC-associated gut bacteria in *H. pylori*-positive patients.[32,36] Whether *H. pylori* eradication therapy could reduce presumed CRC-associated bacteria in the long term remains unknown. Second, *H. pylori* infection-related gastric and systemic inflammation may promote colorectal carcinogenesis. *H. pylori* infection was reported to modulate the production and activity of cyclooxygenase 2 and consequently prostaglandin E2,[37] that have been associated with CRC risk.[38,39] *H. pylori* infection induces different signal transduction processes with the production of pro-inflammatory cytokines like tumor necrosis factor alpha, interferon gamma, interleukin (IL)-1, IL-6, IL-8, leading to the development and progression of gastric inflammation and carcinogenesis,[40] which may also promote colorectal carcinogenesis.[41] Third, *H. pylori* infection and related gastritis increase the secretion of gastrin, which can act as a promoter of gastric and colorectal carcinogenesis.[42,43] Several studies reported that elevated serum gastrin level was associated with an increased risk of colorectal adenoma and CRC.[44,45] However, CRC tumor cells themselves have been shown to secrete gastrin in an autocrine manner.[46,47]

Our study has several strengths. First, this is a large population-based cohort study involving subjects that had received eradication therapy for *H. pylori* infection with long-term follow-up period, allowing us to evaluate the temporal trend of CRC risk after treatment for *H. pylori*. Second, this study is based on a comprehensive healthcare database in Hong Kong, where the majority of local residents received medical attention due to the easy availability of high-quality medical care at heavily subsided cost. Therefore, almost all diagnosed cancers are recorded in this system.

This study has limitations. First, *H. pylori*-infected subjects who had never received treatment should be ideally included. Nevertheless, due to the high background incidence of gastric cancer and peptic ulcer disease, *H. pylori* is generally eradicated once detected in local practice. As *H. pylori* test result is not recorded in the electronic system, we were unable to identify any untreated *H. pylori*-infected cohort in this database. However, we have included subjects who required retreatment or failure of *H. pylori* eradication as an internal control. The accuracy of the retreatment-inferred eradication failure had been validated previously with a sensitivity of 91.3% and a specificity of 98.7%.[13] Second, we only included *H. pylori*-eradicated subjects who had received clarithromycin-containing triple therapy as the primary

therapy. It was the most commonly prescribed first-line eradication therapy in Hong Kong, due to a relatively low prevalence of clarithromycin resistance, approximately 10%.[48] Third, the association between *H. pylori* and CRC might also be altered by genetic heterogeneity of *H. pylori* strains,[18] which was not evaluated in our study. Serum-based tests for *H. pylori* infection, test for specific *H. pylori* antigen in particular, were not generally conducted in the local clinical practice in a population with predominant *cagA*-positive strains.[49]

Conclusion

H. pylori-eradicated subjects had a higher incidence of CRC, colon cancer in particular, compared with the matched general population, which was mainly observed in the first 5 years after treatment for *H. pylori*. Importantly, the CRC incidence progressively declined to a level comparable to the general population after treatment for *H. pylori*, and the rectal cancer incidence was found to be lower than general population after more than 10 years of eradication.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (Reference Number: UW 21-431). As deidentified data from the healthcare system and public data were used, patient consent was not required by the Institutional Review Board.

Consent for publication

Not applicable.

Author contribution(s)

Chuan-Guo Guo: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Software; Validation; Visualization; Writing – original draft.

Feifei Zhang: Formal analysis; Investigation; Methodology; Software; Visualization; Writing – review & editing.

Fang Jiang: Data curation; Investigation; Validation; Writing – review & editing.

Lingling Wang: Investigation; Writing – review & editing.

Yijun Chen: Investigation; Writing – review & editing.

Wenxue Zhang: Investigation; Writing – review & editing.

Anni Zhou: Investigation; Writing – review & editing.

Shutian Zhang: Investigation; Resources; Supervision; Writing – review & editing.

Wai K. Leung: Conceptualization; Funding acquisition; Investigation; Project administration; Resources; Supervision; Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The clinical data that support the findings of this study were from the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority, which were used under license for this study. The cancer statistics are openly available from the Hong Kong Cancer Registry at https://www3.ha.org.hk/cancereg/.

ORCID iD

Chuan-Guo Guo https://orcid.org/0000-0002-0657-473X

Supplemental material

Supplemental material for this article is available online.

References

1. Hooi JKY, Lai WY, Ng WK, *et al.* Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology* 2017; 153: 420–429.

2. Franceschi F, Covino M and Roubaud Baudron C. Review: *Helicobacter pylori* and extragastric diseases. *Helicobacter* 2019; 24: e12636.

3. Venerito M, Vasapolli R, Rokkas T, *et al*. *Helicobacter pylori*, gastric cancer and other gastrointestinal malignancies. *Helicobacter* 2017; 22: e12413.

4. Butt J and Epplein M. *Helicobacter pylori* and colorectal cancer-A bacterium going abroad? *PLoS Pathog* 2019; 15: e1007861.

5. Ko HJ, Lin YC, Chen CC, *et al*. *Helicobacter pylori* infection and increased diabetes prevalence were the risks of colorectal adenoma for adults: a systematic review and meta-analysis (PRISMA-compliant article). *Medicine (Baltimore)* 2021; 100: e28156.

6. Zuo Y, Jing Z, Bie M, *et al*. Association between *Helicobacter pylori* infection and the risk of colorectal cancer: a systematic review and meta-analysis. *Medicine (Baltimore)* 2020; 99: e21832.

7. Ford AC, Yuan Y and Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut* 2020; 69: 2113–2121.

8. Leung WK, Wong IOL, Cheung KS, *et al*. Effects of *Helicobacter pylori* treatment on incidence of gastric cancer in older individuals. *Gastroenterology* 2018; 155: 67–75.

9. Guo CG, Cheung KS, Zhang F, *et al*. Incidences, temporal trends and risks of hospitalisation for gastrointestinal bleeding in new or chronic low-dose aspirin users after treatment for *Helicobacter pylori*: a territory-wide cohort study. *Gut* 2020; 69: 445–452.

10. Guo CG, Cheung KS, Zhang F, *et al*. Delay in retreatment of *Helicobacter pylori* infection increases risk of upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2021; 19: 314–322. e312.

11. Hong Kong Hospital Authority. Hong Kong cancer registry (HKCaR), https://www3.ha.org.hk/cancereg/ (2022, accessed 17 May 2022).

12. Census and Statistics Department Hong Kong Special Administrative Region. Hong Kong annual digest of statistics, https://www.censtatd.gov.hk/en/ (2022, accessed 17 May 2022).

13. Guo CG, Jiang F, Cheung KS, *et al*. Timing of prior exposure to antibiotics and failure of *Helicobacter pylori* eradication: a population-based study. *J Antimicrob Chemother* 2022; 77: 517–523.

14. Finkelstein DM, Muzikansky A and Schoenfeld DA. Comparing survival of a sample to that of a standard population. *J Natl Cancer Inst* 2003; 95: 1434–1439.

15. Spector LG, Menk JS, Knight JH, *et al*. Trends in long-term mortality after congenital heart surgery. *J Am Coll Cardiol* 2018; 71: 2434–2446.

16. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.

17. Liu IL, Tsai CH, Hsu CH, *et al*. *Helicobacter pylori* infection and the risk of colorectal cancer: a nationwide population-based cohort study. *QJM* 2019; 112: 787–792.

18. Butt J, Varga MG, Blot WJ, *et al*. Serologic response to *Helicobacter pylori* proteins associated with risk of colorectal cancer among diverse populations in the United States. *Gastroenterology* 2019; 156: 175–186.e172.

19. Chen XZ, Schottker B, Castro FA, *et al*. Association of *Helicobacter pylori* infection and chronic atrophic gastritis with risk of colonic, pancreatic and gastric cancer: a ten-year follow-up of the ESTHER cohort study. *Oncotarget* 2016; 7: 17182–17193.

20. Blase JL, Campbell PT, Gapstur SM, *et al*. Prediagnostic *Helicobacter pylori* antibodies and colorectal cancer risk in an elderly, caucasian population. *Helicobacter* 2016; 21: 488–492.

21. Li WQ, Zhang JY, Ma JL, *et al*. Effects of *Helicobacter pylori* treatment and vitamin and garlic supplementation on gastric cancer incidence and mortality: follow-up of a randomized intervention trial. *BMJ* 2019; 366: l5016.

22. Hong SN, Lee SM, Kim JH, *et al*. *Helicobacter pylori* infection increases the risk of colorectal adenomas: cross-sectional study and meta-analysis. *Dig Dis Sci* 2012; 57: 2184–2194.

23. Zhang Y, Hoffmeister M, Weck MN, *et al*. *Helicobacter pylori* infection and colorectal cancer risk: evidence from a large population-based case-control study in Germany. *Am J Epidemiol* 2012; 175: 441–450.

24. Papastergiou V, Karatapanis S and Georgopoulos SD. *Helicobacter pylori* and colorectal neoplasia: is there a causal link? *World J Gastroenterol* 2016; 22: 649–658.

25. Jones M, Helliwell P, Pritchard C, *et al*. *Helicobacter pylori* in colorectal neoplasms: is there an aetiological relationship? *World J Surg Oncol* 2007; 5: 51.

26. Soylu A, Ozkara S, Alis H, *et al.* Immunohistochemical testing for *Helicobacter pylori* existence in neoplasms of the colon. *BMC Gastroenterol* 2008; 8: 35.
27. Bark J, Enroth H, Engstrand L, *et al.* Cancer-associated strains of *Helicobacter pylori* stimulate DNA synthesis in IEC-6 cells. *Eur J Gastroenterol Hepatol* 1998; 10: 837–841.
28. Brannstrom J, Zachrisson K, Hulten K, *et al.* *Helicobacter pylori* stimulates DNA synthesis in a small intestinal cell line in vitro. *Digestion* 1998; 59: 33–39.
29. Chen CC, Liou JM, Lee YC, *et al.* The interplay between *Helicobacter pylori* and gastrointestinal microbiota. *Gut Microbes* 2021; 13: 1–22.
30. Song M, Chan AT and Sun J. Influence of the gut microbiome, diet, and environment on risk of colorectal cancer. *Gastroenterology* 2020; 158: 322–340.
31. Guo Y, Zhang Y, Gerhard M, *et al.* Effect of *Helicobacter pylori* on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer. *Gut* 2020; 69: 1598–1607.
32. Dash NR, Khoder G, Nada AM, *et al.* Exploring the impact of *Helicobacter pylori* on gut microbiome composition. *PLoS One* 2019; 14: e0218274.
33. Liu NN, Jiao N, Tan JC, *et al.* Multi-kingdom microbiota analyses identify bacterial-fungal interactions and biomarkers of colorectal cancer across cohorts. *Nat Microbiol* 2022; 7: 238–250.
34. Hou H, Chen D, Zhang K, *et al.* Gut microbiota-derived short-chain fatty acids and colorectal cancer: ready for clinical translation? *Cancer Lett* 2022; 526: 225–235.
35. Hidalgo-Cantabrana C, Delgado S, Ruiz L, *et al.* Bifidobacteria and their health-promoting effects. *Microbiol Spectr* 2017; 5: 1–19.
36. Iino C, Shimoyama T, Chinda D, *et al.* Influence of *Helicobacter pylori* infection and atrophic gastritis on the gut microbiota in a Japanese population. *Digestion* 2020; 101: 422–432.
37. Zhao J, Wen S, Wang X, *et al.* *Helicobacter pylori* modulates cyclooxygenase-2 and 15-hydroxy prostaglandin dehydrogenase in gastric cancer. *Oncol Lett* 2017; 14: 5519–5525.
38. Davenport JR, Cai Q, Ness RM, *et al.* Evaluation of pro-inflammatory markers plasma C-reactive protein and urinary prostaglandin-E2 metabolite in colorectal adenoma risk. *Mol Carcinog* 2016; 55: 1251–1261.
39. Konturek PC, Kania J, Burnat G, *et al.* Prostaglandins as mediators of COX-2 derived carcinogenesis in gastrointestinal tract. *J Physiol Pharmacol* 2005; 56: 57–73.
40. Wessler S, Krisch LM, Elmer DP, *et al.* From inflammation to gastric cancer–the importance of Hedgehog/GLI signaling in *Helicobacter pylori*-induced chronic inflammatory and neoplastic diseases. *Cell Commun Signal* 2017; 15: 15.
41. Muthusami S, Ramachandran IK, Babu KN, *et al.* Role of inflammation in the development of colorectal cancer. *Endocr Metab Immune Disord Drug Targets* 2021; 21: 77–90.
42. Renga M, Brandi G, Paganelli GM, *et al.* Rectal cell proliferation and colon cancer risk in patients with hypergastrinaemia. *Gut* 1997; 41: 330–332.
43. Hartwich A, Konturek SJ, Pierzchalski P, *et al.* *Helicobacter pylori* infection, gastrin, cyclooxygenase-2, and apoptosis in colorectal cancer. *Int J Colorectal Dis* 2001; 16: 202–210.
44. Thorburn CM, Friedman GD, Dickinson CJ, *et al.* Gastrin and colorectal cancer: a prospective study. *Gastroenterology* 1998; 115: 275–280.
45. Selgrad M, Bornschein J, Kandulski A, *et al.* *Helicobacter pylori* but not gastrin is associated with the development of colonic neoplasms. *Int J Cancer* 2014; 135: 1127–1131.
46. Charnley RM, Thomas WM, Stanley J, *et al.* Serum gastrin concentrations in colorectal cancer patients. *Ann R Coll Surg Engl* 1992; 74: 138–140.
47. Bombski G, Gasiorowska A, Orszulak-Michalak D, *et al.* Elevated plasma gastrin, CEA, and CA 19-9 levels decrease after colorectal cancer resection. *Int J Colorectal Dis* 2003; 18: 148–152.
48. Kuo YT, Liou JM, El-Omar EM, *et al.* Primary antibiotic resistance in Helicobacter pylori in the Asia-Pacific region: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2017; 2: 707–715.
49. Wong BC, Lam SK, Ching CK, *et al.* Seroprevalence of cytotoxin-associated gene A positive *Helicobacter pylori* strains in Changle, an area with very high prevalence of gastric cancer in South China. *Aliment Pharmacol Ther* 1999; 13: 1295–1302.