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TOPIC HIGHLIGHT

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Helicobacter pylori-related chronic gastritis as a risk factor for colonic neoplasms

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Abstract

To summarize the current views and insights on associations between *Helicobacter pylori* (*H. pylori*)-related chronic gastritis and colorectal neoplasm, we reviewed recent studies to clarify whether *H. pylori* infection/*H. pylori*-related chronic gastritis is associated with an elevated risk of colorectal neoplasm. Recent studies based on large databases with careful control for confounding variables have clearly demonstrated an increased risk of colorectal neoplasm associated with *H. pylori* infection. The correlation between *H. pylori*-related chronic atrophic gastritis (CAG) and colorectal neoplasm has only been examined in a limited number of studies. A recent large study using a national histopathological database, and our study based on the stage of *H. pylori*-related chronic gastritis as determined by serum levels of *H. pylori* antibody titer and pepsinogen, indicated that *H. pylori*-related CAG confers an increased risk of colorectal neoplasm, and more extensive atrophic gastritis will probably be associated with even higher risk of neoplasm. In addition, our study suggested that the activity of *H. pylori*-related chronic gastritis is correlated with colorectal neoplasm risk. *H. pylori*-related chronic gastritis could be involved in an increased risk of colorectal neoplasm that appears to be enhanced by the progression of gastric atrophy and the presence of active inflammation.

Key words: Colorectal neoplasm; Cancer risk; Pepsinogen; *Helicobacter pylori* antibody; Atrophic gastritis

Core tip: This review revealed that *Helicobacter pylori* (*H. pylori*)-related chronic gastritis plays a role in risk enhancement of colorectal neoplasm, and that this risk could be further enhanced by the progression of atrophy and the presence of active inflammation. These findings may be useful for selecting groups at high risk for colorectal neoplasm that warrant colonoscopic surveillance, particularly in areas where *H. pylori* infection is highly prevalent.

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INTRODUCTION

Infection with *Helicobacter pylori* (*H. pylori*) induces chronic inflammation in the stomach of both humans and ani-

mals, and *H. pylori*-related gastritis is closely associated with the development of gastric cancer[1]. Promotion of tumor development by *H. pylori* infection in extragastric target organs has recently been reported[2]. The majority of previous studies concerning correlations between colorectal neoplasm and *H. pylori* infection/*H. pylori*-related chronic gastritis have been hospital-based, showing several weaknesses in terms of limited sample size and incomplete control of confounding variables, including former colonoscopy[3-14]. In addition, results have been inconsistent, with some studies indicating a positive correlation and others finding no correlation[3-14]. Two meta-analyses combining the results of 11 and 13 case-control studies with summary OR of 1.4 (95%CI: 1.1-1.8) and 1.5 (95%CI: 1.2-1.9), respectively[15,16], have suggested modest increases in colorectal neoplasm risk due to *H. pylori* infection. However, the evidence remains limited because of significant heterogeneity among included studies and potential publication bias. A large-scale study is thus needed to confirm the increased risk of colorectal neoplasm by *H. pylori* infection owing to the relatively small OR. Several studies based on larger databases with adequate control for confounding factors were published from 2010 onward[17-20] and have demonstrated that *H. pylori* infection correlates with a moderately increased risk of colorectal neoplasm.

On the other hand, the mechanism by which *H. pylori* infection increases the risk of colorectal neoplasm is currently unclear. Progressive chronic gastritis induced by persistent *H. pylori* infection (*H. pylori*-related chronic gastritis) leads to extensive glandular atrophy and reduced acid secretion, in turn inducing hypergastrinemia, a putative trophic factor for large bowel mucosa[21]. Gastric acid reduction also alters the gastrointestinal microenvironment composed of bacterial flora[22], and thus may contribute to colorectal carcinogenesis. However, whether *H. pylori*-related chronic gastritis is associated with an increased risk of colorectal neoplasm remains inconclusive because of the limited number of epidemiological studies. This review summarizes recent findings and insights into the association between *H. pylori* infection/*H. pylori*-related chronic gastritis and colorectal neoplasm.

CORRELATION BETWEEN *H. PYLORI* INFECTION AND RISK OF COLORECTAL NEOPLASM

Since 2010, various studies have examined the correlation between *H. pylori* infection and colorectal neoplasm based on large databases with careful controls for confounding variables (Table 1). Two cross-sectional studies using the health check-up databases of Korea and Taiwan[19,20] showed that *H. pylori* infection was significantly associated with an increased risk of colorectal adenoma, with adjusted OR of 1.36 (95%CI: 1.10-1.68) and 1.37 (95%CI: 1.23-1.52), respectively. Our population-based case-control study, which investigated 478 asymptomatic male Japanese factory workers, identified *H. pylori* infection as a risk factor for colorectal adenoma (OR = 2.52; 95%CI: 1.57-4.05)[17]. In addition, a large population-based case-control study in Germany suggested a positive association between *H. pylori* infection and risk of colorectal cancer using *H. pylori* immunoglobulin (Ig)G (OR = 1.30; 95%CI: 1.14-1.50) and cytotoxin-associated gene A protein (CagA) (OR = 1.35; 95%CI: 1.15-1.59)[18]. These results clearly demonstrated an increased risk of colorectal neoplasm among patients with *H. pylori* infection.

CORRELATION BETWEEN *H. PYLORI*-RELATED CHRONIC ATROPHIC GASTRITIS DIAGNOSED ON THE BASIS OF PEPSINOGEN TEST RESULTS AND RISK OF COLORECTAL NEOPLASM

The pepsinogen method is a reliable screening method for precancerous lesions of the stomach. In addition, serum pepsinogen (PG) I and the PG I / Ⅱ ratio are also valuable markers for gastric acid secretion and the extent of resultant chronic atrophic gastritis (CAG) caused by chronic gastritis. The combination of these two serum markers is the one most widely used for the detection of CAG in Japan.

Table 2 shows the correlation between CAG determined on the basis of PG test results and colorectal neoplasm. A previous hospital-based case-control study of 113 cases and 226 controls[14] and our population-based case-control study[17] in Japan showed that CAG based on the criteria of PG I $\leqslant$ 70 ng/mL and PG I / Ⅱ $\leqslant$ 3.0 were not associated with a significantly increased risk of colorectal neoplasm. Since the prevalence of autoimmune gastritis is extremely low in Japan[23], the possible inclusion of autoimmune gastritis among the analyzed cases of CAG and subsequent underestimation of the risk was considered negligible. Meanwhile, subjects identified as CAG-negative based on the above-mentioned PG test criteria included not only those subjects with a *H. pylori*-free healthy stomach, but also *H. pylori*-infected subjects without CAG, which may have resulted in underestimation of colorectal neoplasm risk in CAG. A case-control study consisting of subjects with similar clinical indications for colonoscopy in Italy indicated that hypergastrinemic CAG (diagnosed by histological evaluation, fasting hypergastrinemia and low PG I levels) was not associated with an increased risk of colorectal neoplasm compared to normogastrinemic controls with healthy gastric mucosa[24]. However, in this study, most cases of hypergastrinemic CAG did not include active *H. pylori* infection and were positive for anti-parietal cell antibodies. Hypergastrinemic CAG in this study therefore may not have been equivalent to CAG resulting from *H. pylori* infection. Interestingly, a recent study indicated that other gastric pathologies likely unrelated to *H. pylori* infection, such as *H. pylori*-negative gastritis, showed

Table 1 Studies investigating correlations between *Helicobacter pylori* infection and risk of colorectal neoplasm

Ref.	Country	Year of publication	Type of study design	No. of subjects	Measure of *H. pylori* status	Outcome	Crude OR (95%CI)	Adjusted OR (95%CI)
[20]	Taiwan	2010	Cross-sectional	9311	Urease test	Adenoma	-	1.37 (1.23-1.52)
[19]	South Korea	2012	Cross-sectional	2195	IgG	Adenoma	1.35 (1.10-1.66)	1.36 (1.10-1.68)
						Advanced adenoma	2.19 (1.40-3.42)	2.21 (1.41-3.48)
[17]	Japan	2011	Population-based Case-control	478	IgG	Adenoma	2.26 (1.44-3.55)	2.52 (1.57-4.05)
[18]	Germany	2012	Population-based Case-control	3381	IgG	Cancer	-	1.3 (1.14-1.50)
					CagA	Cancer	-	1.35 (1.15-1.59)

H. pylori: *Helicobacter pylori*; IgG: Immunoglobulin G; CagA: Cytotoxin-associated gene A.

Table 2 Studies investigating correlations between *Helicobacter pylori*-related chronic atrophic gastritis diagnosed on the basis of pepsinogen tests and risk of colorectal neoplasm

Ref.	Country	Year of publication	Type of study design	No. of subjects	Measure of CAG status	Outcome	Crude OR or HR (95%CI)	Adjusted OR or HR (95%CI)
[14]	Japan	2007	Case-control	339	PG test	Cancer	-	OR = 1.56 (0.86-2.85)
[17]	Japan	2011	Population-based Case-control	478	PG test	Adenoma	OR 1.31 (0.89-1.93)	OR = 1.45 (0.97-2.17)
[24]	Italy	2012	Case-control	320	PG test + histopathology	Adenoma	-	OR = 0.59 (0.23-1.48)
						Cancer	-	OR = 1.03 (0.34-3.16)
[26]	Finland	2010	Cohort	20269	PG test + histopathology	Cancer	HR 1.00 (0.65-1.55)	HR = 0.98 (0.61-1.58)
[27]	Japan	2013	Cohort	99	PG test	Adenoma + Cancer	HR 2.02 (1.05-3.91)	HR = 2.72 (1.33-5.57)

CAG: Chronic atrophic gastritis; PG: Pepsinogen; OR: Odds ratio; HR: Hazard ratio.

no or only weak associations with the risk of colorectal neoplasm[25]. Considering these results, CAG determined by PG test results might not correlate with the risk of colorectal neoplasm. However, the heterogeneity of CAG criteria and differences in the selection of controls and other limitations of these studies, such as relatively small sample size, inadequate consideration of potential confounding variables including prescribed medication or previous history (use of proton pump inhibitors (PPIs), gastric resection, *H. pylori* eradication therapy, renal failure, *etc.*) that might affect PG test results might have influenced and distorted the results. The necessity for large studies examining the effects of *H. pylori*-related CAG on colorectal neoplasm compared to healthy gastric mucosa with adequate control of confounders should be emphasized to obtain valid results.

As for the correlation between the incidence of colorectal neoplasm and CAG diagnosed by the PG test, two relevant studies are as follows. A long-term cohort study among Finnish participants (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) did not indicate an increased risk of colorectal cancer by CAG based on histological findings and low PG I levels, although the investigators did not include any information on PPI therapy that might have affected serum PG levels[26]. Our study showed that CAG (diagnosed based on criteria of PG I $\leqslant$ 70 ng/mL and PG I / II $\leqslant$ 3.0) was associated with an increased risk of recurrent colorectal neoplasm after first endoscopic resection in a hospital-based cohort study, with an adjusted HR of 2.72 (95%CI: 1.33-5.57)[27]. The difference in the results of these two studies may be attributable to differences in the carcinogenic potential of the colorectal mucosa between study subjects. Subjects subsequent to colorectal neoplasm removal are considered to be at higher risk of future neoplasm, and risk enhancement with the establishment of CAG leads to the development of recurrent neoplasm; on the other hand, subjects without colorectal neoplasm on initial colonoscopy are at lower risk, and some additional factors other than CAG are required for the development of a neoplastic lesion[28,29]. The inconsistent findings between these studies might also be due to differences in study methodologies, such as differences in CAG criteria, selection of subjects, sample size, and follow-up period.

PROGRESSION OF *H. PYLORI*-RELATED CHRONIC GASTRITIS AND RISK OF COLORECTAL NEOPLASM

Once established in the stomach mucosa, *H. pylori*-related chronic gastritis is generally believed to trigger a series of events involved in stomach carcinogenesis, represented as the gastritis-atrophy-metaplasia-dysplasia-cancer sequence[30]. In addition, gastric atrophy and intestinal metaplasia, an end stage of *H. pylori*-related chronic gastritis, subsequently induce hypochlorhydria that may contribute to colorectal carcinogenesis.

Table 3 shows the correlation between the progression of *H. pylori*-related chronic gastritis and colorectal neoplasm. A recent large study using a national histopathological database in the United States indicated that

Table 3 Studies investigating correlations between progression of *Helicobacter pylori* -related chronic gatritis and risk of colorectal neoplasm

Ref.	Country	Year of publication	Type of study design	No. of subjects	Measure of *H. pylori*-related gastritis	Outcome	Crude OR (95%CI)	Adjusted OR (95%CI)
[17]	Japan	2011	Population-based Case-control	478	*H. pylori* IgG and PG test [mild CAG (Group B)]	Adenoma	2.61 (1.54-4.11)	2.81 (1.64-4.81)
[17]	Japan	2011	Population-based Case-control	478	*H. pylori* IgG and PG test [extensive CAG (Group C)]	Adenoma	2.3 (1.38-3.83)	2.7 (1.58-4.62)
					H. pylori IgG and stricter CAG criteria [more extensive CAG (Group C)]	Adenoma	3.75 (1.70-8.23)	4.2 (1.88-9.40)
[25]	United States	2012	Cross-sectional	100296	Histopathology (*H. pylori*-related gastritis)	Adenoma	1.52 (1.46-1.57)	-
				57820		Advanced adenoma	1.8 (1.69-1.92)	-
				51067		Cancer	2.35 (1.98-2.80)	-
[25]	United States	2012	Cross-sectional	90953	Histopathology (intestinal metaplasia)	Adenoma	1.82 (1.71-1.94)	-
				52802		Advanced adenoma	2.02 (1.82-2.24)	-
				46882		Cancer	2.55 (1.93-3.37)	-

H. pylori: *Helicobacter pylori;* IgG: Immunoglobulin G; PG: Pepsinogen; CAG: Chronic atrophic gastritis; OR: Odds ratio.

H. pylori-related chronic gastritis conferred increased risks of colorectal adenoma (OR = 1.52; 95%CI: 1.46-1.57) and cancer (OR = 2.35; 95%CI: 1.98-2.80) compared to normogastrinemic controls. In addition, a similar risk was found in intestinal metaplasia, a more easily recognizable form of mucosal alteration and the advanced stage of gastric atrophy most frequently associated with *H. pylori* infection[25]. However, those investigators had access only to histopathological information, so the possibility of uncontrolled confounders remains.

We stratified study subjects based on the stage of *H. pylori*-related chronic gastritis as determined by 2 serum tests (*H. pylori* antibody titer and PG)[31], then evaluated colorectal adenoma risk in each stage. The classification reflects each stage of a serial change in stomach mucosa induced by chronic *H. pylori* infection. There were 3 groups: Group A, *H. pylori*-negative and PG test-negative; Group B, *H. pylori*-positive and PG test-negative; and Group C, PG test-positive. Group A corresponds to a *H. pylori*-free healthy stomach, Group B to *H. pylori*-related non-atrophic gastritis, and Group C to the presence of extensive CAG. The presence of *H. pylori*-related chronic gastritis significantly increased the risk of colorectal adenoma as a whole (Group B: adjusted OR = 2.81; 95%CI: 1.64-4.81; Group C: adjusted OR = 2.70; 95%CI: 1.58-4.62) compared to the *H. pylori*-free healthy stomach (Group A). However, no significant difference in risk existed between Groups B and C; that is, the establishment of CAG did not show any additional increase in the risk of adenoma[17]. On the other hand, stricter criteria for positive PG I ($\leqslant$ 30 ng/mL) and PG I / II ratio ($\leqslant$ 2.0) were used to detect subjects with more extensive and severe CAG[32]. These advanced-stage CAG subjects were at even higher risk for adenoma (adjusted OR = 4.20; 95%CI: 1.88-9.40) compared to CAG-positive subjects diagnosed using the less strict criteria (PG I $\leqslant$ 70 ng/mL and PG I / II $\leqslant$ 3.0) (Tables 3 and 4).

MECHANISMS BY WHICH *H. PYLORI*-RELATED CHRONIC GASTRITIS INCREASES THE RISK OF COLORECTAL NEOPLASM

Various mechanisms have been suggested to underlie the correlation between *H. pylori* infection and colorectal neoplasm. First, *H. pylori* infection increases gastrin secretion, which could contribute to colorectal carcinogenesis by inducing mucosal cell proliferation in the colon[21]. An epidemiological study of patients with *H. pylori* infection showed that mild hypergastrinemia was associated with about a 4-fold increase in the risk of colorectal neoplasm[11]. As for the correlation between colorectal neoplasm and gastrin, a limited number of epidemiological studies have been conducted with inconsistent results; some have indicated positive correlations[11,33], while others found no correlation[4,8]. The differences in these results might be attributable to non-amidated gastrins, such as progastrin or glycine-extended gastrin, acting as more important promoters of colorectal carcinogenesis than the fully amidated form of the hormone measured by most commercially available assays[21,34].

Second, *H. pylori* infection seems likely to adversely impact the intestinal flora, contributing to colorectal carcinogenesis[35-37], as a result of the hypochlorhydria caused by *H. pylori*-related chronic gastritis. Several studies have indicated that the presence of enteric infection and overgrowth of intestinal bacteria are directly correlated with hypochlorhydria[38-40]. Our previous study demonstrated that CAG-positive asymptomatic middle-aged subjects (diagnosed on the basis of serum PG levels of PG I $\leqslant$ 70 ng/mL and PG I / II ratio $\leqslant$ 3.0) had a larger population of colonic microflora than CAG-negative subjects[22]. Hypochlorhydria was also reported to lead to an increase in unabsorbed nutrients in the lower

Table 4 Correlation between stage of *Helicobacter pylori*-related chronic gatritis and risk of colorectal neoplasm

	H. pylori CAG	Controls (*n* = 239)	Total adenoma cases (*n* =239)	Proximal adenoma (*n* = 38)	Bilateral adenoma (*n* = 78)	Distal adenoma (*n* = 123)
Group A	(-) (-)	71	35	4	15	16
Group B	(+) (-)	105	127	18	41	68
	B1 (PG1/2 > 3)	92	103	14	34	55
	B2 (PG1/2 ≤ 3)	13	24	4	7	13
Group C	(+)	63	77	16	22	39
	C1 (PG1/2 > 2, PGI > 30)	50	53	11	15	27
	C2 (PG1/2 ≤ 2, PGI ≤ 30)	13	24	5	7	12
Adjusted OR[1]	(A:B) (95%CI)	1	2.81 (1.64-4.81)	3.06 (0.99-9.42)	1.85 (0.94-3.62)	3.05 (1.62-5.73)
	(A:B1) (95%CI)	1	2.36 (1.43-3.88)	2.73 (0.86-8.65)	1.74 (0.87-3.47)	2.86 (1.50-5.47)
	(A:B2) (95%CI)	1	3.78 (1.71-8.38)	5.32 (1.17-24.1)	2.66 (0.89-7.98)	4.36 (1.68-11.3)
Adjusted OR[1]	(A:C) (95%CI)	1	2.7 (1.58-4.62)	4.51 (1.43-14.2)	1.76 (0.83-3.74)	3.05 (1.54-6.07)
	(A:C1) (95%CI)	1	2.27 (1.29-3.99)	3.88 (1.17-12.9)	1.52 (0.67-3.45)	2.59 (1.25-5.35)
	(A:C2) (95%CI)	1	4.2 (1.88-9.40)	6.95 (1.63-29.6)	2.65 (0.87-8.05)	5.09 (1.89-13.7)

[1]Adjusted for current smoking and total cholesterol by conditional logistic regression analysis. B1: Group αβ, subgroup based on less-strict criteria for PG Ⅰ (≤ 70 ng/mL) and PG Ⅰ / Ⅱ ratio (> 3.0) or PG Ⅰ (> 70 ng/mL) and PG Ⅰ / Ⅱ ratio (> 3.0) to detect mild inflammation; B2: Group γ, subgroup based on stricter criteria for PG Ⅰ (> 70 ng/mL) and PG Ⅰ / Ⅱ ratio (≤ 3.0) to detect severe active inflammation; C1: Subgroup based on less strict criteria for PG Ⅰ (≤ 70 ng/mL) and PG Ⅰ / Ⅱ ratio (≤ 3.0) to detect extensive CAG; C2: Subgroup based on stricter criteria for positive PG Ⅰ (≤ 30 ng/mL) and PG Ⅰ / Ⅱ ratio (≤ 2.0) to detect more extensive and severe CAG; *H. pylori*: *Helicobacter pylori*; CAG: Chronic atrophic gastritis.

intestine due to impaired gastric protein digestion[41], so some metabolites derived from bacterial fermentation of malabsorbed proteins are likely to play a role in the etiopathogenesis of colonic disorders[42,43].

Third, *H. pylori* infection might result in damage to the colorectal epithelium through inflammatory responses, such as those mediated by interleukin (IL)-8, which is associated colorectal cancer[44]. Shmuely *et al*[5] reported a 10-fold increase in colorectal cancer risk with CagA-positive strains (known to cause enhanced inflammatory response) compared to CagA-negative strains. A recent cross-sectional study showed that *H. pylori* infection-concomitant metabolic syndrome might further increase the risk of colorectal neoplasm[20] and proposed that such concomitant effects might occur secondary to common inflammatory pathways through inflammation-related factors such as tumor necrosis factor-alpha (TNF-α)[20]. Therefore, we further classified former study subjects[17] in Group B into three subgroups based on the activity of *H. pylori*-related chronic gastritis determined by serum PG levels, as described previously[32]: Group α, PG Ⅰ ≤ 70 ng/mL and PG Ⅰ / Ⅱ > 3.0; Group β, PG Ⅰ > 70 ng/mL and PG Ⅰ / Ⅱ > 3.0; and Group γ, PG Ⅰ > 70 ng/mL and PG Ⅰ / Ⅱ ≤ 3.0. The activity of *H. pylori*-related chronic gastritis is considered to be higher in the order γ, β, α, and we evaluated colorectal adenoma risk at each stage. The severe active inflammation group (γ) showed an increased risk of colorectal adenoma (adjusted OR = 3.78; 95%CI: 1.71-8.38) compared to the mild inflammation groups (α and β) (adjusted OR = 2.36; 95%CI: 1.43-3.88) (Table 4), suggesting that the activity of *H. pylori*-related chronic gastritis correlates with colorectal neoplasm risk. In general, the concentrations of IL-1β and TNF-α (*i.e.*, proinflammatory cytokines that mediate host inflammatory response) have been shown to be elevated in stomach mucosa showing active inflammation[45,46]. Since both cytokines potently inhibit gastric acid secretion[47], they appear to represent an additional link between *H. pylori*-related active inflammation and colorectal neoplasm.

Correlation between location and risk of colorectal neoplasm

Accumulating evidence suggests that the risk of colorectal neoplasm associated with various environmental and genetic factors differs for proximal and distal neoplasm, probably reflecting two recently proposed tumorigenic pathways based on the molecular features of CpG island methylator phenotype (CIMP+) and microsatellite instability (MSI+) occurring predominantly in the proximal colon, and chromosomal instability (CIN) occurring in the distal colon[48]. Animal models suggest that the mitogenic action of gastrin is selective for the distal colon[49,50]. On the other hand, chronic inflammation is known to induce aberrant DNA methylation in normal tissues, and alterations in DNA methylation have been proposed to be involved in the carcinogenic process of the proximal colon[51]. In addition, colonic bacterial overgrowth is considered to lead to enhanced production of secondary bile acids, which are reported to cause DNA damage and activation of the carcinogenic pathway involving DNA methylation, particularly in the proximal colonic mucosa[52,53], thereby increasing the risk of proximal colon cancer[54].

Previous studies have classified colorectal neoplasms according to location, and examined the correlation between colorectal neoplasm and *H. pylori* infection in each group. However, the results of those studies were inconclusive, because of insufficient sample sizes to detect site-selective effects on associations; some studies indicated that the increased risk associated with *H. pylori* infection was limited to patients with proximal neoplasms[19], while other studies found the same for distal neoplasms[18]. Furthermore, the significantly increased

risk of colorectal neoplasm with *H. pylori*-related chronic gastritis has been reported to be similar for different locations of colorectal neoplasm[17,25]. Our reanalysis of previous data using serum PG levels as indices of the activity of *H. pylori*-related chronic gastritis or the resulting gastric atrophy revealed that colonic neoplasm risk in both proximal and distal regions increases with the enhancement of active inflammation or the progression of gastric atrophy (Table 4).

CONCLUSION

This review has shown that relatively few studies are available in this field, and the current evidence remains limited. Larger studies with adequate controls for confounders and that compare against normogastrinemic controls with *H. pylori*-free healthy gastric mucosa are necessary to clarify the role of *H. pylori*-related chronic gastritis in carcinogenesis of the colorectum.

In conclusion, based on critical analyses of previous studies, including our own, *H. pylori*-related chronic gastritis may well be associated with an increased risk of colorectal neoplasm. This risk appears to be further enhanced by the progression of atrophy or active inflammation. In areas where *H. pylori* infection is highly prevalent, the stage of *H. pylori*-related chronic gastritis could contribute to the identification of individuals at high risk of colorectal neoplasm. In addition, whether eradication therapy for *H. pylori*-infected subjects reduces the risk of colorectal neoplasm is a problem for future study.

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