REVIEW

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Helicobacter pylori and colorectal neoplasms: a concise review

Luiz Gonzaga Vaz **COELHO**[1] and Maria Clara Freitas **COELHO**[2]

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ABSTRACT – *Helicobacter pylori* is the main etiological agent of all malignant tumors caused by an infectious disease. It is a major, at times dominant, factor in the pathogenesis of a large spectrum of diseases such as acute and chronic gastritis, gastric and duodenal ulcers, gastric carcinoma, and lymphoma. Epidemiological and experimental studies suggest that *H. pylori* chronic infection may be related to different extragastric diseases, including colorectal neoplasms. This concise review aims to explore the association of *H. pylori* infection with colorectal cancer and adenoma, including the recent epidemiological findings, the diagnostic methods employed to detect *H. pylori* and virulent factors, and the potentially involved mechanisms. Furthermore, is attempted to establish the current data integration for causal inference using the Bradford-Hill causality criteria. The weak, although global, strength of the epidemiological positive association between *H. pylori* infection and colonic neoplasms associated to new mechanisms postulated to explain this interaction, including intestinal dysbiosis, should stimulate future studies. Prospective confirmatory studies to establish the role of *H. pylori* eradication in the process of carcinogenic transformation of the colonic epithelium may define its eventual role in the treatment and prevention of colonic neoplasms.

HEADINGS – *Helicobacter* infections. Colorectal neoplasms. Adenoma. Epidemiologic factors.

INTRODUCTION

It is estimated today that at least 13% of all malignant tumors are caused by an infectious agent, and *Helicobacter pylori* (*H. pylori*) is the main etiological agent and responsible for approximately 810,000 cases of gastric cancer worldwide each year[1]. After *H. pylori* was identified by Marshall and Warren in 1983 in Australia, this microorganism has been found in at least 50% of the world´s population[2]. It is a major, at times dominant, acquired environmental factor in the pathogenesis of a large spectrum of diseases such as acute and chronic gastritis, gastric and duodenal ulcers, gastric carcinoma, and lymphoma. Epidemiological and experimental studies suggest that *H. pylori* chronic infection may be related to different extragastric diseases, including colorectal cancer (CRC) and precancerous lesions[3,4] (FIGURE 1).

CRC is a multifactorial disease of global concern, being the third most commonly diagnosed cancer with nearly 1.4 million new cases in 2018[5]. A majority of CRC is sporadic; both genetic and environmental factors like nutritional practices, cigarette smoking, physical activity, obesity, and heavy alcohol consumption play an important part in the etiology of CRC[6]. Besides, increasing evidence has established a role for the intestinal microbiota in the development of colorectal cancer[7].

This paper aims to make a concise review of the association of *H. pylori* infection with colorectal cancer and adenoma, including the main epidemiological findings and potentially involved mechanisms. For these purposes, a PubMed search up to May 2020 was performed using a combination of the following keywords: *Helicobacter pylori*, colorectal cancer, colon cancer, adenoma, and colonic polyps. Also, the reference lists of all relevant articles were reviewed.

Potential associations among *H. pylori* infection and colorectal neoplasms

Four recent meta-analyses demonstrated a positive association between *H. pylori* infection and the risk of CRC and colorectal adenoma, presenting OR (95%CI) varying from 1.27 (1.17–1.37) to 1.44 (1.26–1.65) regarding CRC and 1.49 (1.37–1.62) to 1.66 (1.39–1.97) to colorectal adenoma[8-11] (TABLE 1). The studies involved in these meta-analyses came from 16 countries situated in Asia (38%), Europe (33%), America (mostly the USA) (20%), Middle-East (7%), and Oceania (2%).

H. pylori infection

H. pylori can be detected in the gastric mucosa by different methods, either in fragments removed during endoscopy and used for histopathological, microbiological, biochemical and molecular studies or by non-invasive tests that include searching for *H. pylori* anti-antibodies in a blood sample, breath tests using carbon-13 labeled urea or investigating fecal antigens[12].

Although most studies analyzed mainly the presence of serum antibodies to *H. pylori*, it is important to consider some factors that may contribute to the heterogeneity among the studies results and their relationship with CRC. Among them, the presence of current or previous infection and the presence or absence of bacterial virulence factors such as the cag pathogenicity island, which encodes the oncogenic effector protein cagA and the allelic variation in the vacuolating cytotoxin A (vacA) were not mentioned[13]. Likewise, studies didn´t inform the presence or absence of chronic sequelae of *H. pylori* infection in gastric epithelium inducing premalignant changes (atrophic gastritis and intestinal metaplasia), the increased level of serum gastrin promoting epithelial cell

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[1] Universidade Federal de Minas Gerais, Instituto Alfa de Gastroenterologia, Belo Horizonte, MG, Brasil. [2] Faculdade de Ciências Médicas de Minas Gerais, Belo Horizonte, MG, Brasil.
Corresponding author: Luiz Gonzaga Vaz Coelho. E-mail: lcoelho22@gmail.com

Extragastric digestive diseases: NAFLD, NASH, autoimune pancreatitis, pancreatic cancer, and colorectal neoplams.
Cardiovascular diseases: coronary atherosclerotic disease and myocardial infarction.
Neurological diseases: stroke, Alzheimer's disease, Parkinson's disease, Guillain-Barré syndrome, and migraine.
Dermatological diseases: rosacea and chronic urticaria.
Hematologic diseases: iron deficiency anemia, pernicious anemia, and primary immune thrombocytopenia.
Ophthalmological diseases: open-angle glaucoma, central serous chorioretinitis, and neuromyelitis optica.
Otorhinolaryngological diseases: chronic rhinosinusitis.
Endocrinology disorders: metabolic syndrome, type 2 diabetes.

FIGURE 1. *Helicobacter pylori* infection and potentially linked extragastric diseases.
NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis.

TABLE 1. Studies included on the meta-analyses about the association between *H. pylori* and colorectal cancer and colorectal adenoma.

Meta-analysis Author (year)	Number of studies	Colorectal cancer OR (95% CI)	Colorectal adenoma OR (95% CI)
Wu (2013)[8]	27	1.39 (1.18–1.64)	1.66 (1.39–1.97)
Zhao (2016)[9]	14	1.33 (1.01–1.77)	
Yang (2019)[10]	27	1.27 (1.17–1.37)	
Choi (2020)[11]	48	1.44 (1.26–1.65)	1.49 (1.37–1.62)

growth and proliferation, and hypochlorhydria that might lead to bacterial overgrowth in the gastrointestinal tract and alterations in the colonic microenvironment of the bacterial flora[14,15]. All these factors may contribute to colonic carcinogenesis.

As the serological test is not able to discriminate current from past infections, one study suggests that such a distinction may be crucial because only current *H. pylori* infection would induce humoral and cellular immune responses that provoke or perpetuate chronic inflammatory processes in the gastrointestinal tract with potential oncogenic sequelae including metastases and mortality. The authors also suggest that *H. pylori* eradication might inhibit the development or delay progression of CRC and recommend large-scale studies[16].

H. pylori virulence factors expressed by different bacterial strains can modulate gastric adenocarcinoma risk[17]. To assess whether such effects may also exist in the CRC, three recent studies were carried out in Europe[18,19] and USA[20] using *H. pylori* multiplex serology, a recently developed technique able to quantify seroreactivity immune response to several different *H. pylori* proteins. Fernández de Larrea-Baz N et al., in Spain, in a case-control study, analyzed 1488 CRC cases and 2495 controls and found that neither *H. pylori* seropositivity, nor seropositivity to the virulence factor cagA is associated with higher CRC risk[18]. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort measured antibody responses to 13 *H. pylori* proteins in pre-diagnostic serum samples from 485 CRC cases and 485 matched controls[19]. Specifically, *Helicobacter* cysteine-rich protein C (HcpC) (OR: 1.66, 95%CI: 1.19–2.30) and vacA (OR: 1.34, 95%CI: 0.99–1.82), were associated with an increased risk of developing CRC. In the study from USA, serum samples were analyzed from 4063 incident cases of CRC and 4063 controls and found serologic responses to *H. pylori* vacA associated with increased risk of CRC risk, particularly for African Americans (OR: 1.45, 95%CI: 1.08–1.95)[20]. These two studies suggest that antibody responses to different *H. pylori* virulence factors, mainly vacA and cagA, were significantly associated with increased risk of developing CRC and the association could vary by race/ethnicity. Further studies are needed to investigate causality among this association and the underlying biological mechanisms involved (see below).

The sequence infection by *H. pylori* → chronic gastritis → glandular atrophy → intestinal metaplasia → dysplasia → gastric cancer constitutes a set of associated alterations that are very frequently observed in the development of gastric cancer since *H. pylori* is recognized as a class I carcinogen[21]. The risk of gastric adenocarcinoma increases significantly with premalignant progression[22,23]. To investigate the relationship between gastric mucosa histological changes induced by the bacterium and colonic neoplasms, Sonnenberg and Genta conducted a large study including 156,000 patients undergoing both colonoscopy e gastroscopy, with histological assessment of the gastric mucosa and the colon[24]. *H. pylori* status was performed by a polyclonal anti-*H. pylori* immunohistochemical stain. Compared with normal gastric mucosa, *H. pylori* gastritis occurred more frequently among patients with hyperplastic polyps, adenomatous polyps, advanced adenomas, villous adenomas, or adenomas with high-grade dysplasia, and adenocarcinomas. Other gastric conditions etiologically associated with *H. pylori*, such as intestinal metaplasia, adenoma, lymphoma, and adenocarcinoma, were also significantly associated with an increased risk of colonic neoplasm. Similar results were also observed in a Chinese study involving 233 patients[25]. To explore whether *H. pylori* atrophic gastritis, a pre-malignant condition, plays some role in the relation between *H. pylori* infection and advanced colonic neoplasms, Lee JY et al. in a cross-sectional study investigated the relationship between the presence of serum anti-*H. pylori* IgG antibodies, atrophic gastritis endoscopically-diagnosed, and advanced colonic neoplasms in 6,351 consecutive asymptomatic subjects who underwent a screening colonoscopy[26]. A total of 316 (5.0%) participants had advanced colonic neoplasm. The results showed that advanced colonic neoplasms occurred more frequently in *H. pylori*-infected patients with atrophic gastritis than without atrophic gastritis (7.3% vs 4.4%, $P<0.001$). A large recent study also investigated the association of gastric *H. pylori* presence with the risk of colorectal polyps and CRC[27]. The results confirmed that patients with *H. pylori* infection were 2.19 and 3.05 times more likely to develop colorectal polyps and CRC, respectively, than those without *H. pylori* active infection. Additionally, they found that the incidence of *H. pylori* infection coexisting with atrophic gastritis or intestinal metaplasia was higher in patients with colorectal polyps and CRC than in the control group. These findings reproduced Sonnenberg & Genta's study which showed that the *H. pylori*-positive gastritis and intestinal metaplasia, a more easily recognizable pre-malignant lesion, increased risk for colonic neoplasms while *H. pylori*-negative gastritis did not[24].

Potential mechanisms for causality

H. pylori is a pathogen restricted to primates (natural infection restricted to humans and monkeys) and, in humans, binds exclusively to the surface of the mucus-secreting cells of the stomach. In vivo, only 2–20% of the bacterial population exhibits adherence to the epithelial surface, the rest of the microorganisms remaining protected in the gastric mucus layer[28]. This specific tissue tropism is partly explained by the existence of specific adhesin molecules on the bacterial surface that acts as ligands in gastric epithelium receptors. The challenge is to account any action at a distance from this unique bacteria on colonic neoplasms risks. *H. pylori* direct and/or indirect effects on colorectal carcinogenesis have been considered trying to explain causality[28].

Regarding direct effects, studies evaluating the presence of *H. pylori* in the colorectal neoplastic epithelium are still scarce. Three pilot studies, two using immunohistochemical methods and a PCR technique identified *H. pylori* between 22–27% in samples of polyps or CRC fragments[29-31]. Greek authors, using immunohistochemical staining technique to identify *H. pylori* in 50 patients with CRC, 25 patients with colorectal adenomas and 10 controls described a significantly higher prevalence of *H. pylori* in the adenoma (68%) and CRC (84%) groups when compared to the control group (30%)[32]. As almost everything present in the stomach can be found in the stools, *H. pylori* is eliminated via this route and, although difficult, has been cultured in the stools since 1992[33]. Although *H. pylori* or its DNA have already been identified in the colonic epithelium, it is important to note that *H. pylori* infects only the gastric type mucosa and, in vivo, it has never been described adhered to the colonic epithelium. Bacterial adherence to a cell can trigger a cascade of events where adhesins can act as biological effector molecules[34]. One study showed that some components of the cell wall of *H. pylori* itself can be carcinogenic to the colorectal epithelial cell lining[30]. Studies are still needed to assess whether *H. pylori* acting directly on the colonic epithelium is capable of causing carcinogenic effects on the colon and rectum as observed in the gastric mucosa.

The mechanisms by which *H. pylori* virulence factors are involved in increasing the risk of developing colorectal neoplasms remain unclear. One of the major *H. pylori* virulent factors is the multifunctional vacA toxin. Considered a gastric cancer virulence factor, it has been speculated that it would be able to exert, outside the stomach, its effects on cellular vacuolation, cellular permeability, interference with cellular pathways, in addition to immunomodulatory and pro-inflammatory properties[35,36]. One recent suggestion is that vacA forms chloride channels that become inserted into the cell and mitochondrial membranes thereby reducing the membrane potential and mitochondrial energy production, interfering on cell proliferation control. Therefore, it would be biologically plausible that the vacA toxin of *H. pylori* could increase the risk of colon cancer, by chronically altering ionic equilibrium enterocytes exposed to the toxin[37]. Regarding the virulent factor cagA, which requires direct contact between bacteria and host cells, a Japanese study[38] suggested that exosomes containing cagA were detectable in the blood of cagA-positive *H. pylori*-infected individuals and could facilitate the development of multiple extragastric diseases. Because cagA is a bacterial oncoprotein, exosome-mediated cagA delivery may also be involved in the development of neoplasias outside the stomach and further studies are required in this area.

Indirect mechanisms have been also hypothesized involving *H. pylori* infection and increased risk of colorectal neoplasms such as gastrin-17 levels and *H. pylori* and microbiota interactions. Gastrin-17 belongs to a subgroup of gastrin composed of 17 amino acids, being produced by G cells of the gastric antrum and indicative of the glandular integrity of the antral mucosa. Their levels are closely related to the stomach's intraluminal pH, that is, they are reduced in acidic medium and abnormally high in case the patient has hypo or achlorhydria[39]. The rationale for exploring the association between gastrin and colorectal neoplasms is the putaitve role of the hormone in epithelial cell growth and to prevent apoptosis[40]. Experimental, in vitro, and human studies have shown discrepant results about the gastrin role to stimulate the growth of normal colonic epithelium and colorectal neoplasms[41-45]. A large nested case-control study of CRC and gastrin evaluated gastrin levels in subjects before cancer development[40]. The results support the hypothesis that, for a subset of CRC patients, hypergastrinemia may play a small role in tumor development, accounting for 8.6% of the CRC cases. However, these results have not been reproduced by other studies[46-49]. In addition to *H. pylori* (the most common cause of hypergastrinemia), three other conditions can increase gastrin expression: use of proton pump inhibitor (PPI), autoimmune gastritis, and Zollinger-Ellison syndrome (gastrinoma). A meta-analysis performed in 2012 found no association between PPI use and the risk of CRC[50]. A recent nationwide cohort study performed in Taiwan involving 45,382 elegible PPI users suggests that PPIs use might increase the risk of CRC in a dose-dependent manner[51] while another USA recent nested case-control study in a large community-based integrated healthcare setting involving 18,595 CRC patients suggests that PPI use for at least two years was not associated with CRC risk (OR: 1.05, 95%CI: 0.99–1.12)[52]. A systematic review with meta-analysis was performed to evaluate the incidence of cancer (other than gastric cancer) in pernicious anemia (PA), a late sequel of autoimmune gastritis where hypergastrinemia is secondary to damaged oxyntic mucosa and impaired gastric secretion[53]. It was found that PA patients had a lower RR (0.14, 95%CI: 0.01–0.19) for CRC compared to the general population. Likewise, the long-term hypergastrinemia secondary to Zollinger-Ellison syndrome has shown no effect on colonic adenomas or CRC development[54]. Some other studies included investigations related to an eventual autocrine production of gastrin by colorectal neoplasms[55], other forms of gastrin serum determinations and not only amidated forms[56], the real status of *H. pylori* infection[57], and previous information about PPI use and surgeries in the patients[48], but even though, more studies to clarify the conflicting studies of hypergastrinemia and colonic neoplasms in humans are needed.

H. pylori relation to the intestinal microbiota has also been investigated. CRC results from a combination of inherited and acquired mutations in the colon's epithelial cells and associated with different factors including the intestinal microbiota[58]. Increasing evidence shows that specific bacteria and bacterial dysbiosis can potentiate the initiation or progression of CRC. The speculated mechanisms involve damaging DNA, activating oncogenic signaling pathways, producing tumor-promoting metabolites such as secondary bile acids, and suppressing antitumor immunity[59,60]. *H. pylori* infection seems to span beyond gastric microbiota and affects downstream gastrointestinal microbiota[15]. Experimental studies with atrophic gastritis patients demonstrate that acid secretion reduction induces colorectal microbiota changes, intestinal bacterial overgrowth, and may favor carcinogenesis[61-63]. The enhanced

production of secondary bile acids by colonic bacterial overgrowth can also increase the risk for CRC, especially proximal colon cancer[26,64]. It is still unclear whether there are specific microbes that are particularly pathogenic and directly cause colorectal carcinogenesis, or whether the process requires specific interactions between host tissues and microbes[58].

Association or causation?

As the main human cancer-associated bacteria, studies continue to search for other *Helicobacter* species with oncogenic potential[65] as well as for other non-gastric tumors where it could have a causal role, such as CRC and adenomas (TABLE 1). The Bradford Hill criteria[66] (FIGURE 2), described in 1965 to establish a causal relationship between an agent and a disease, are still useful tools in establishing causation and also in proposing other necessary researches to confirm a potentially causal association[67] and will be briefly discussed here.

- ✓ Strength of association
- ✓ Consistency of observation
- ✓ Specificity
- ✓ Temporality
- ✓ Biological gradient
- ✓ Biological plausibility
- ✓ Coherence
- ✓ Experiment
- ✓ Analogy

FIGURE 2. Bradford-Hill causality criteria[66].

Strength and consistency: the positive association demonstrated between *H. pylori* and colorectal neoplasms is evidenced mainly by case-control studies and some prospective studies. Such observation has been consistently confirmed in different regions of the world, with some predominance in Asian countries. However, the OR found always ranges below 2, considered a weak association to the assessment of potentially causal relationships[8-11]. Specificity: needless to point out that *H. pylori* and colorectal neoplasm association is not specific given the well-known relationship between *H. pylori* and gastroduodenal diseases. However, this is not uncommon in the infectious diseases field where an individual may harbor a microorganism as an asymptomatic carrier while others, in the presence of genetic or environmental factors, will develop associated diseases. In other words, the presence of *H. pylori* could be necessary, but not sufficient for the development of colorectal neoplasms. Temporality: the concept that an agent´s exposure must precede disease´s onset, seems to be observed in the association, since infection by *H. pylori* uses to be acquired in childhood, before 10 years of age, in most patients[17]. The positivity of the association also observed in prospective studies excludes the possibility of reverse causality[8,40]. Biological gradient: the presence of a dose-response effect traditionally supports a causal relationship between an agent and the effect. Some studies suggest that patients infected with *H. pylori* strains expressing gastric cancer virulence factors such as cagA and vacA, or presenting premalignant gastric lesions have higher odds of association with CRC[19,20,27,57]. Biological plausibility and coherence: these criteria seek to analyze whether the relationship between the agent and the disease is consistent with current knowledge concerning the etiology and mechanism of the disease. Although the pathophysiological mechanisms underlying the association between *H. pylori* and colonic neoplasms remain unclear, important progress has been recently observed in the direct and/or indirect potential actions of *H. pylori* infection, or even associated with intestinal dysbiosis, in colonic carcinogenesis process[4,24,26,61]. Experiment: considered by Hill[67] as the strongest support for causal inference, the intervention through which can be demonstrated that disease´s risk declines after a treatment or exposition cessation, still lacks definite proof in studies about the association between *H. pylori* and colorectal neoplasms. To assess the development of colorectal adenoma, a recent retrospective study followed 615 patients for nine years with no history of colorectal adenoma or cancer at baseline[68]. Patients underwent upper digestive endoscopy and colonoscopy and were classified into three groups: individuals with no *H. pylori* infection, successful *H. pylori* eradication, and persistent *H. pylori* infection. During follow-up, the incidence rates of colorectal adenoma progression in participants uninfected with *H. pylori* were similar to the eradication group while the risk seen in the persistent infection group was 3-fold higher (HR: 3.04, 95%CI: 1.905.86. Despite retrospective study limitations, the results might support a causal relationship. Analogy: the situation where for analogous exposures and outcomes an effect has already been shown, would be sometimes acceptable to "judge by analogy". The tools diversity available today allowing the search for specific analogies such as the pattern of CRC progression, common risk factors, confounders and disease mechanisms, the modern value of the analogy seems more relevant in proposing and testing mechanistic hypotheses that confirm a causal inference[67].

CONCLUSION

Although the strength of the positive association between *H. pylori* infection and colonic neoplasms is considered weak from an epidemiological point of view, new mechanisms have been postulated trying to explain how a bacterium acting far from its ecological niche − the gastric milieu – could directly or indirectly interfere in colonic carcinogenesis, either through its virulence factors and/or metabolites or by promoting intestinal dysbiosis. A preliminary study suggests that the colorectal adenoma ratio might decrease after successful eradication of *H. pylori*. Several further studies are still necessary to establish a causal relationship in a disease with complex multifactorial etiology as colorectal neoplasms. Well-designed studies to better understand the changing incidence of colorectal cancer, the prevalence of *H. pylori* infection, and ethnic and environmental aspects involved in CRC are warranted. Prospective confirmatory studies to establish the role of *H. pylori* eradication in the process of carcinogenic transformation of the colonic epithelium may define its eventual role in the treatment and prevention of colonic neoplasms.

Authors' contribution

Coelho LGV contributed to the conception, design, and writing the paper; Coelho MCF contributed for reviewing the literature and writing the paper.

Orcid

Luiz Gonzaga Vaz Coelho: 0000-0002-8721-7696.
Maria Clara Freitas Coelho: 0000-0001-8028-6114.

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RESUMO – *Helicobacter pylori* é o principal agente etiológico dos tumores malignos causados por doenças infecciosas. Constitui fator importante, às vezes dominante, na patogênese de um amplo espectro de doenças como gastrite aguda e crônica, úlceras gástricas e duodenais, carcinoma gástrico e linfoma. Estudos epidemiológicos e experimentais sugerem que a infecção crônica por *H. pylori* pode estar relacionada a diferentes doenças extragástricas, incluindo neoplasias colorretais. Esta concisa revisão tem como objetivo explorar a associação da infecção por *H. pylori* com câncer colorretal e adenoma, incluindo os recentes achados epidemiológicos, os métodos de diagnóstico empregados para detectar *H. pylori* e seus fatores de virulência com os mecanismos potencialmente envolvidos nesta relação. Além disso, procura-se estabelecer a integração dos dados atuais na busca de inferência causal com o emprego dos critérios de causalidade de Bradford-Hill. A associação epidemiológica positiva entre infecção por *H. pylori* e neoplasias do cólon embora classificada como fraca – porém global – do ponto de vista epidemiológico, quando associada a mecanismos recentemente postulados para explicar essa interação, incluindo disbiose intestinal, deverá estimular a realização de investigações futuras. Estudos prospectivos confirmatórios para estabelecer o papel da erradicação do *H. pylori* no processo de transformação carcinogênica do epitélio do cólon são aguardados para definir seu eventual papel no tratamento e prevenção de neoplasias do cólon.

DESCRITORES – Infecções por *Helicobacter*. Neoplasias colorretais. Adenoma. Fatores epidemiológicos.

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