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REVIEW

Helicobacter pylori and Colorectal Cancer: Meeting Sir Austin Bradford Hill's Causality Criteria

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ABSTRACT

Introduction: Epidemiological and experimental studies have suggested that chronic *H. pylori* infection may be associated with colorectal cancer (CRC), a topic of growing interest. The Bradford-Hill criteria are the mainstay of the epidemiological approach to causal inference. We aim to evaluate the epidemiological evidence based on the Bradford-Hill causality criteria and the association between *H. pylori* and CRC.

Methodology: A literature review of the databases search: Pubmed, ScienceDirect, Embase, SciELO, Cochrane, and Medline. There are no limits in a period. Information sources that were coherent with the objectives set were selected.

Results: Applying the Bradford Hill criteria, we can conclude that *H. pylori* is positively associated with CRC. The current epidemiological findings should stimulate future studies to explain how *H. pylori* interacts with intestinal dysbiosis and the role of *H. pylori* eradication in the treatment and prevention of CRC.

Conclusions: *H. pylori* reasonably meets the Bradford Hill criteria for causality. Further studies are required to consolidate the data and generate strategies to determine whether *H. pylori* eradication translates into decreased CRC incidence and mortality in large populations.

1 | Introduction

Helicobacter pylori (*H. pylori*) is the primary etiological factor of chronic gastritis, gastric and duodenal ulcers, gastric mucosa associated lymphoid tissue (MALT) lymphoma, and non-cardia gastric cancer (nCGC) [1]. It is considered responsible for 90%–95% of gastric cancers (GC) (intestinal type), of which more than 800,000 cases occur worldwide each year [2]. It was identified by Marshall and Warren in 1983 and currently affects 44% of the world's population [3]. Colorectal cancer (CRC) is the second cause of cancer death and the third most common cancer worldwide, with 2.19 million new cases in 2021, ranking as the most common gastrointestinal cancer [4]. Likewise, 70%–80% of CRCs are sporadic, and 10%–20% have a hereditary component such as Lynch syndrome (3%–4%) or familial adenomatous polyposis (1%), and 1%–2% come from inflammatory bowel disease [5]. Sporadic cases have a very complex, multifactorial origin, with various risk factors, such as genetic predisposition, environmental

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factors, metabolic alterations, microbiome composition, alteration of the integrity of the intestinal barrier, smoking, alcohol consumption, fatty liver associated with metabolic dysfunction (MASLD) and consumption of processed meat [6–10]. Other factors have also been found, such as ferropenic anemia, obesity, gastrectomy, and low physical activity [9]. Recently, it has been determined that it is positively associated with a new indicator, which is "sociodemographic index (SDI)," varying from 7.39 to 40.52 cases per 105 people if the SDI is low or high, respectively [8]. The SDI combines several indicators, including total fertility rate, average education in individuals over 15 years of age, and per capita income [8]. This indicator is related to factors such as obesity, metabolic dysfunction-associated fatty liver disease (MASLD), and processed meat consumption. In the last two decades, *H. pylori* has been implicated as a risk factor for both CRC [11–16] and its precursor lesions, such as adenomatosis polyps [17, 18]. The causal link is considered to be related to alterations in the microbiota and immunology in these microenvironments [10, 19]. Taking into account the increasingly frequent research on the possible relationship between *H. pylori* and CRC, it was decided to carry out the present work with the aim of analyzing whether *H. pylori* meets the Bradford-Hill causality (BHC) criteria [11] for CRC. BHCs are a set of epidemiological principles proposed by epidemiologist Sir Austin Bradford Hill in 1965 to assess the causal relationship between risk factor and disease [11]. They are considered especially useful in epidemiological studies where controlled experiments are not always possible, as is the case with chronic infections involved in the development of complex diseases such as cancer [11]. In the context of *H. pylori* infection and its possible causal relationship with CRC, BHCs can provide a structured framework to critically and scientifically assess that causal relationship. BHCs and their interpretation are shown in Figure 1.

2 | Methods

2.1 | Aim and Search Criteria

A literature review on causality between *H. pylori* infection and CRC was conducted. The stages of the review were as follows: articles search, selection of articles, and review of the references of the selected studies. In addition, some of the articles included in the references of the selected publications were added to the final selection if they provided information for causality analysis. During the first phase of this review, the initial search was conducted from February 2015 to April 2024 under the following parameters: Metasearch engines and databases were: Pubmed, ScienceDirect, Embase, SciELO, Cochrane, and Medline. The search keywords were *Helicobacter pylori*, causality, colonic neoplasms, and with period: unlimited. Languages: English and Spanish. Type of studies: analytical observational studies

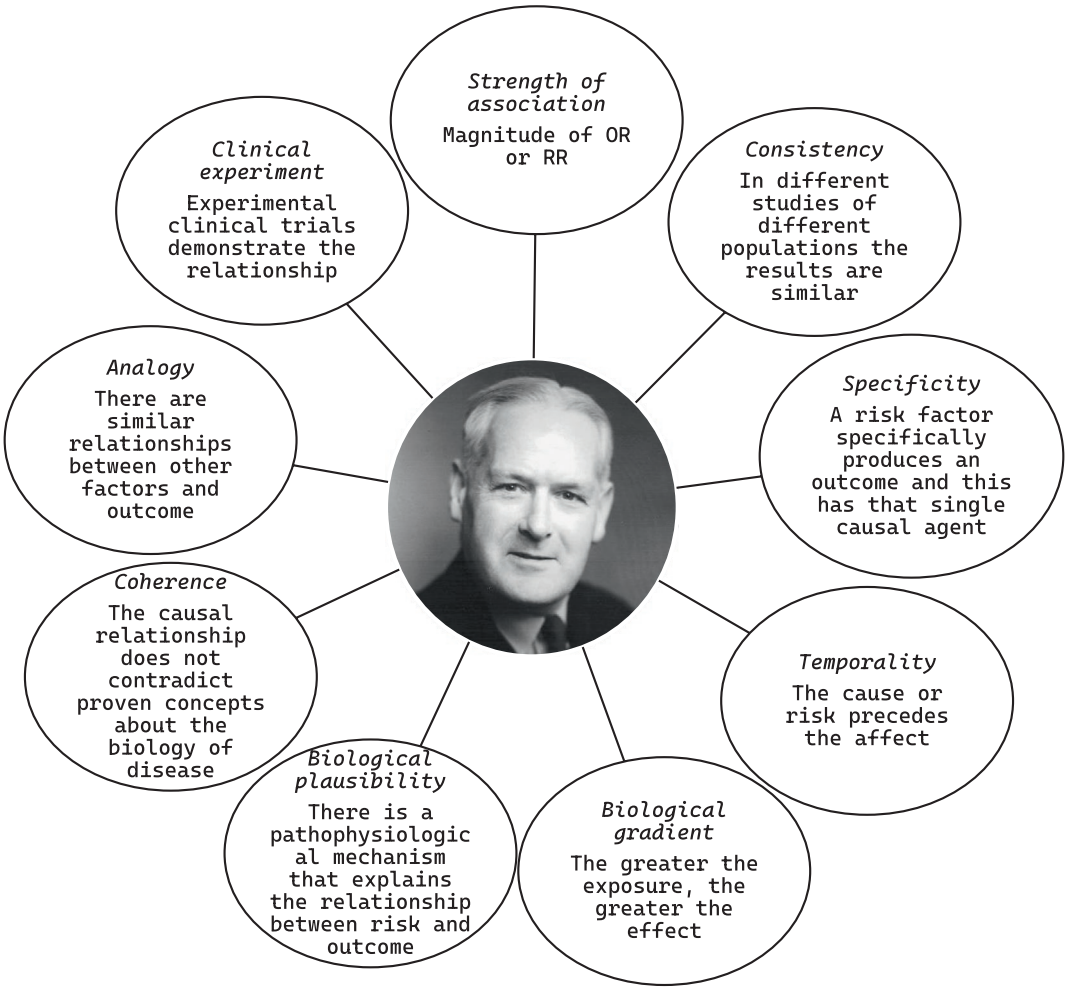

FIGURE 1 | Bradford-Hill criteria. *Source:* Authors.

(case–control, cohort, cross-sectional), randomized controlled clinical trials, and systematic reviews and/or meta-analyses.

2.2 | Eligibility Criteria

The use of scales of evidence and grading of recommendations have been published by authors affiliated with world-renowned institutions. Articles were included that, after the initial search, upon reading their titles and abstracts individually, met the eligibility criteria described and were consistent with the objective of this review article.

3 | Results

3.1 | Strength of Association

Epidemiologically, the strength of the association is measured by the change in the frequency of a disease when introducing a specific factor in the community, expressed in absolute or relative terms [12]. The strength of the association is measured based on the magnitude of the association in terms of OR (odds ratio) or RR (relative risk) [12]. Different meta-analyses have found an association between *H. pylori* and CRC with an OR of less than 2 [13–17]. Table 1 shows the most recent meta-analyses on this topic (see Table 1).

These different meta-analyses show an association ranging from 1.27 to 1.8, which is "weak." Classically, strong associations have been considered to be more likely to be causal than weak ones (cohort RR between 0.5 to 2, cases and controls OR between 0.33 to 3) [20]. According to the "GRADE Working Group," an association is considered strong when the RR ranges from 2 to 5 or from 0.2 to 0.5 [21]. Globally, when it is less than 3, there are often hidden or confounding variables, not controlled, that participate in the final magnitude of association with the disease or outcome [20]. In contrast, when a strong association is found, the possibility of an uncontrolled confounder or other biases can be excluded [20]. So far, the strength of the association found between *H. pylori* and CRC is less than 2. However, a weak association per se, does not exclude a causal relationship, as recognized initially by Hill [21]. Weak associations exist when the disease being studied is relatively common [12, 22]. A recurrent example is the causal relationship between smoking and cardiovascular disease [22]. Despite the low magnitude of the risk, based on multiple investigations, nowadays, no one would doubt that cigarette smoking is a risk factor for cardiovascular disease [22]. Likewise, passive smokers have an RR for lung cancer of 1.2–1.3. A relatively recent case–control study found an OR 1.9 (IC: 1.05–3.56) for CRC in patients infected with *H. pylori*, which is higher than other known risk factors for CRC, such as smoking, alcohol, and obesity [23]. Recently, Shah et al. [24] conducted a retrospective cohort study with a population sample of over 800,000 individuals to evaluate the impact of successful treatment of *H. pylori* on the incidence and mortality of CRC. Treatment versus no treatment was associated with lower incidence and mortality from CRC at 15 years of follow-up (absolute risk reduction 0.23%–0.25%). *H. pylori* (+) versus *H. pylori* (−) patients had an 18% higher risk for CRC (adjusted hazard ratio 1.18 95% CI 1.12–1.24) and 12% higher (adjusted hazard ratio 1.12 95% CI: 1.13–1.34) CRC mortality. The comparison between untreated versus treated individuals for *H. pylori* had a 23% higher incidence of CRC (adjusted HR 1.23 95% CI 1.13–1.34) and 40% higher mortality (adjusted HR 1.40 95% CI 1.24–1.58). Based on these results, the authors concluded that positive-*H. pylori* may be associated with a small but statistically significant higher incidence and mortality from CRC. A population-based study that included 47,714,750 patients with a follow-up 20 years-period demonstrated that the risk of CRC was OR 1.89 (95% CI 1.69–2.10) in the patients who had a diagnosis of *H. pylori* infection [25].

3.2 | Consistency

This is interpreted as the replicability of the results [26]. It refers to the fact that the results are similar in different studies, as well as in different populations and under different circumstances [21, 27]. Epidemiologically, a single study is not considered definitive for medicine evidence-based decision making and concluded for a hypothesis. The potential of the epidemiological approach in the study of specific causal relationships lies in the systematic observation of similar findings derived from a large set of different studies [28]. The basis of this criterion is that the possible cause-effect relationship remains constant. At the same time, other factors may vary, which is related to the a priori probability but can also be seen in terms of confounding variables [21, 27]. If numerous studies carried out in different places and under different conditions show the same association between a variable and a disease, this provides evidence that a confounding variable is not responsible for the demonstrated association [28, 29]. The consistency between *H. pylori* and CRC has been shown from observational

TABLE 1 | Association between *H. pylori* and CRC.

Author/year	OR (CI: 95%)	References	Heterogeneity I^2
Xu H/2024	1.80 (1.31–2.47)	[13]	95%
Ma L/2023	1.48 (1.10–1.99)	[14]	70%
Zuo Y/2020	1.70 (1.64–1.76)	[16]	97%
Choi DS/2020	1.50 (1.28–1.75)	[17]	58%
Yang F/2019	1.27 (1.17–1.37)	[18]	45%

Note: Meta-analysis results.
Source: The authors.

studies and, more recently, based on systematic reviews and meta-analyses that confirm their weakly positive association [17, 18, 30, 31]. Currently, it has been found that, like GC, the *H. pylori* eradication decreases the risk of CRC [24]. Based on this latest and engaging study, it could be considered that *H. pylori* eradication can reduce the risk of CRC to the same extent as GC. It is a topic of great interest nowadays due to its significant epidemiological impact since, in terms of primary prevention of CRC, it could be a future strategy for simultaneous screening programs for GC and CRC. However, a recent study carried out in Sweden did not find a decrease in the incidence of CRC with *H. pylori* eradication [32]. With a single strategy, such as *H. pylori* eradication, benefits could be obtained for these two types of cancer, which have high mortality worldwide.

3.3 | Specificity

Specificity refers to whether a cause produces a single effect [21]. In this sense, a relationship is specific if it is associated with the outcome being studied and not with others, and conversely, if that outcome is only due to the factor being studied and not to others [27, 33]. Specificity originated in Robert Koch's postulates to evaluate causality in infectious diseases when the outcome is based on the state of exposure, such as, for example, by the presence of the tuberculosis bacillus [28]; but actually, in epidemiology, it is uncommon since exposure can cause different outcomes; likewise, an outcome can be the result of different causes [32, 34]. In the case of the tuberculous bacillus, the disease "*tuberculosis*" will occur if there are other simultaneous exposures, such as overcrowding, malnutrition, or alcoholism [34]. In this example, the relationship with alcohol is also nonspecific in TB because this substance, likewise, has different outcomes or consequences. Thus, when exposure can produce multiple outcomes and the outcome can be due to different exposures, the concept of specificity, as it was initially proposed, has limited utility and would be an invalid or obsolete concept [28]; since knowledge has advanced, many diseases have different causal factors, which are not specific, as occurs for example with cirrhosis secondary to alcohol, a substance that also has other effects such as dilated cardiomyopathy and this, in turn, has other causes as does chronic pancreatitis. Thus, there is no longer specificity in the causal agent nor the outcome; therefore, specificity, according to its initial conception, is a weak and irrelevant criterion from the epidemiological point of view [35]. However, by going deeper and analyzing the concept, it can have new implications on interpretations in the context of a broader integration according to the current conception that diseases, in addition to exposure to the causal agent, must also exist in susceptibility and the concurrence of various factors, since pathological conditions are actually multifactorial. Although there are necessary causes, these are usually insufficient [32–34]. This was conceived in Rothman's approach when he stated that a sufficient cause could be made up of multiple components and causes so that an outcome occurs. In this way, there may be more than one accurate cause so that the result can occur through various pathways [33]. In this sense, specificity refers to how a vital component is in relation to others, also known as rate difference etiological fraction or attributable risk [36].

H. pylori is mainly known for its causal role in GC and other gastroduodenal diseases [1]. GC has many risk factors, including genetic predisposition, salt consumption, low consumption of vegetables and fruits, smoking, and chronic gastritis-mediated *H. pylori*. Among the different risk factors involved, *H. pylori* has an attributable risk of 90%–95%; that is, it is responsible for that number of gastric cancers [1, 3]. Although a relationship with CRC has been found, the specificity of this association is low because *H. pylori* can cause other gastroduodenal pathologies [1]. However, its ability to induce chronic inflammation in the stomach, alter acid secretion, induce increased gastrin, and modify the microbiota in the lower digestive tract could be considered a key causal agent in the pathogenesis of CRC [37–40]. In this way, *H. pylori* infection, like other infectious diseases, can cause an individual to harbor a microorganism as an asymptomatic carrier. In contrast, the presence of genetic, epigenetic, and environmental factors can develop specific diseases. In other words, the presence of *H. pylori* could be a non-sufficient cause for the development of CRC [12]. For GC, it is a necessary but not sufficient cause since less than 4% of those infected develop that tumor [1].

Also, there are other factors that may interact with H. pylori to generate CRC. The interaction between diabetes mellitus, smoking, body mass index (BMI), and *H. pylori* infection in the context of CRC risk is complex and multifactorial. Diabetes mellitus and H. pylori are among the best described. The study by Hu et al. [41] found that individuals with both elevated hemoglobin A1c (HbA1c) levels and *H. pylori* infection had a significantly higher risk of developing colorectal adenomas compared to those with only one of these conditions. This suggests that hyperglycemia may exacerbate the carcinogenic potential of *H. pylori*. Smoking has been shown to modify the risk of advanced colorectal neoplasia associated with *H. pylori* infection. Specifically, younger individuals (< 50 years) with a history of smoking and *H. pylori* infection have an increased risk of advanced colorectal neoplasia compared to non-smokers. This indicates that smoking may potentiate the carcinogenic effects of *H. pylori*, possibly through mechanisms involving increased DNA damage and altered immune responses [42, 43]. While the direct interaction between BMI and *H. pylori* in the context of CRC is less clear, BMI is a known risk factor for various cancers, including CRC. The literature suggests that both low and high BMI can be associated with increased cancer risk, although this has been more extensively studied in the context of gastric cancer. The role of BMI in CRC risk in the presence of *H. pylori* infection remains to be fully elucidated [44].

3.4 | Temporality

This is one of the most important criteria for establishing causality: exposure must precede the development of the disease [28]. It is particularly relevant in slow-developing diseases, as exposure must precede the disease [39]. In studies investigating the relationship between *H. pylori* and CRC, it is essential to demonstrate that chronic infection by this bacterium occurs before the development of cancer. Temporality is key to supporting the hypothesis that *H. pylori* contributes to a chronic inflammatory environment that could favor carcinogenesis in the colon and rectum. *H. pylori* infection is usually acquired in childhood, before 10 years of age [45], and CRC appears in the 5th or 6th decade, so there would be no doubt

about temporality. This positive association has been proven in different epidemiological studies, primarily prospective, excluding the possibility of reverse causality [30, 38–40]. This type of causality is also known as the direction fallacy, such as that argued by tobacco companies, who argued that tobacco did not cause lung cancer but rather induced patients to smoke to reduce pain [43, 46].

3.5 | Biological Gradient

This refers to the fact that with greater exposure, there will be a greater risk of presenting the outcome or disease with a unidirectional dose–response curve [21]. In this regard, Hill considered that "if a response to the dose is documented, it is more likely that there is a causal relationship" [21, 27]. Exposure should be measured in terms of duration of exposure, average intensity of exposure, and integration of these two factors, which will give a measure of total exposure [22, 27]. However, associations that do not show a monotonic trend in the frequency of the disease with increasing levels of exposure do not necessarily invalidate causality since more complex "dose–response" relationships may exist, and studies in recent decades have shown that a "monotonic dose–response" curve is too simplistic for most causal relationships [28]. For example, innate immune responses can repair, eliminate, or reverse molecular changes produced by low levels of exposure [28]. Likewise, with such exposures, adaptive epigenetic changes may occur with greater or lesser expression of a disease [34]. Conversely, confounding factors may generate a monotonic relationship between a non-causal risk factor and the disease if the confounding factor per se demonstrates a biological gradient in its relationship with the disease [4, 28, 35, 45]. The exposure, in conjunction with its temporal precedence, is expected to show a latent period curve, as would be appropriate in a circumstance in which a single brief exposure is responsible for a disease [37]. The presence of a response dose effect traditionally supports a causal relationship between an agent and effect. Some studies suggest that patients infected with *H. pylori* strains that express virulence factors, such as cytotoxin-associated protein (cagA) and Vacuolating cytotoxin A (VacA), or who present premalignant gastric lesions have a higher probability of association with CRC [40, 42, 43, 46].

3.6 | Biological Plausibility

Biological plausibility examines whether there is a pathophysiological mechanism that explains how the causal agent could induce the disease [21, 34]. It consists of being able to infer the causal relationship based on these mechanisms, and as such, it will depend on the knowledge available on the subject at a given time; therefore, the lack of plausibility does not rule out causality since scientific knowledge may be incomplete [47]. Although the pathophysiological mechanisms underlying the association between *H. pylori* and colonic neoplasia are not precise [47, 48], it has recently been found that the infection has indirect actions in the process of colonic carcinogenesis through the modulation of the intestinal microbiota, the immune response of the host, and activation of oncogenic genes, producing changes in the composition of the microbiome, which favors tumor development [19, 49, 50] (Figure 2).

Experimentally, it has been shown that *H. pylori* infection affects the intercellular tight junctions, thereby weakening the integrity of the mucosal barrier and also interfering with the differentiation of mucus-producing goblet cells and overstimulation of the activator of transcription 3 (STAT3) (Figure 3) [51–56]. In addition, it induces a pro-inflammatory response with loss of Treg lymphocytes (LTreg), which then differentiate into forkhead box protein 3 gene (FOXP3) and Interleukin-17A (IL-17A) [51]. *H. pylori* produced changes in the microbiota, favoring the appearance of mucolytic bacteria, pro-inflammatory bacteria, and other pro-carcinogenic bacteria [51]. The changes induced in the microbiota and the immune system, together with the alteration of the mucosal barrier, are changes also observed among the mechanisms of colon carcinogenesis in humans [54–56]. *H. pylori*, through CagA, is the main oncogenic factor in gastric carcinogenesis and can activate multiple canonical and non-canonical constitutive signaling pathways (Figure 4). In this regard, modulation of the phosphoinositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway (PI3K/AKT/mTOR), Janus kinase-signal transduction and activation of transcription (JAK–STAT) pathway, Mitogen-activated protein kinase (MAPK), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Rat Sarcoma (RAS), proto-oncogene B-Raf (BRAF), Wnt/β-catenin signaling pathway, and Hippo pathways through phosphorylation and non-phosphorylation has been described [57]. The alteration of these fundamental pathways results in decreased cell polarity and adhesion and changes in morphology, proliferation, and motility [58]. In the colonic carcinogenesis model, several of these pathways are altered, mainly PI3K/AKT/mTOR, Transforming growth factor (TGF)-β, WNT/β-catenin, and RAS/proto-oncogene, serine/threonine kinase (RAF)/mitogen-activated extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK signaling pathway (RAS/RAF/MERK/ERK) have been described [59] (Figure 3). Although it is not clear whether these pathways are activated simultaneously under chronic inflammation by *H. pylori*, they are shared in carcinogenesis for both the colon and the stomach. These circuits form an intricate and complex network of cellular signaling that dictates the malignant phenotype, the immune response, and the tumor microenvironment (TME), which influences the efficacy of therapeutic options [59].

On the other hand, in gastric carcinogenesis, genetic alterations such as chromosomal aneuploidies, mutation of the P53 gene (38%–45%), deletion of p53 (60%), microsatellite instability (27%), and mitochondrial microsatellite instability (33%) have been observed [51]. *H. pylori* can produce genetic changes through reactive oxygen species (ROS). Similarly, the bacteria induce aberrant expression of activating cytidine dismutase (AID), which is renowned as the DNA and RNA editor, a crucial protein in antibody-mediated immunity due to the variation in affinity for antigens, allowing high-affinity B cells to differentiate into plasma cells and produce antibodies in the germinal centers of B cells through a mechanism known as somatic hypermutation that produces changes in the DNA of genes associated with the regulation of Ig in B cells [51]. In this scenario, AID is involved in mutations of the *P53* and *APC* (Adenomatous Polyposis Coli) genes in gastric epithelial cells, which means a relevant phenomenon in the development of adenocarcinoma [51]. APC is a tumor suppressor that includes functions in the regulation of chromosome segregation and

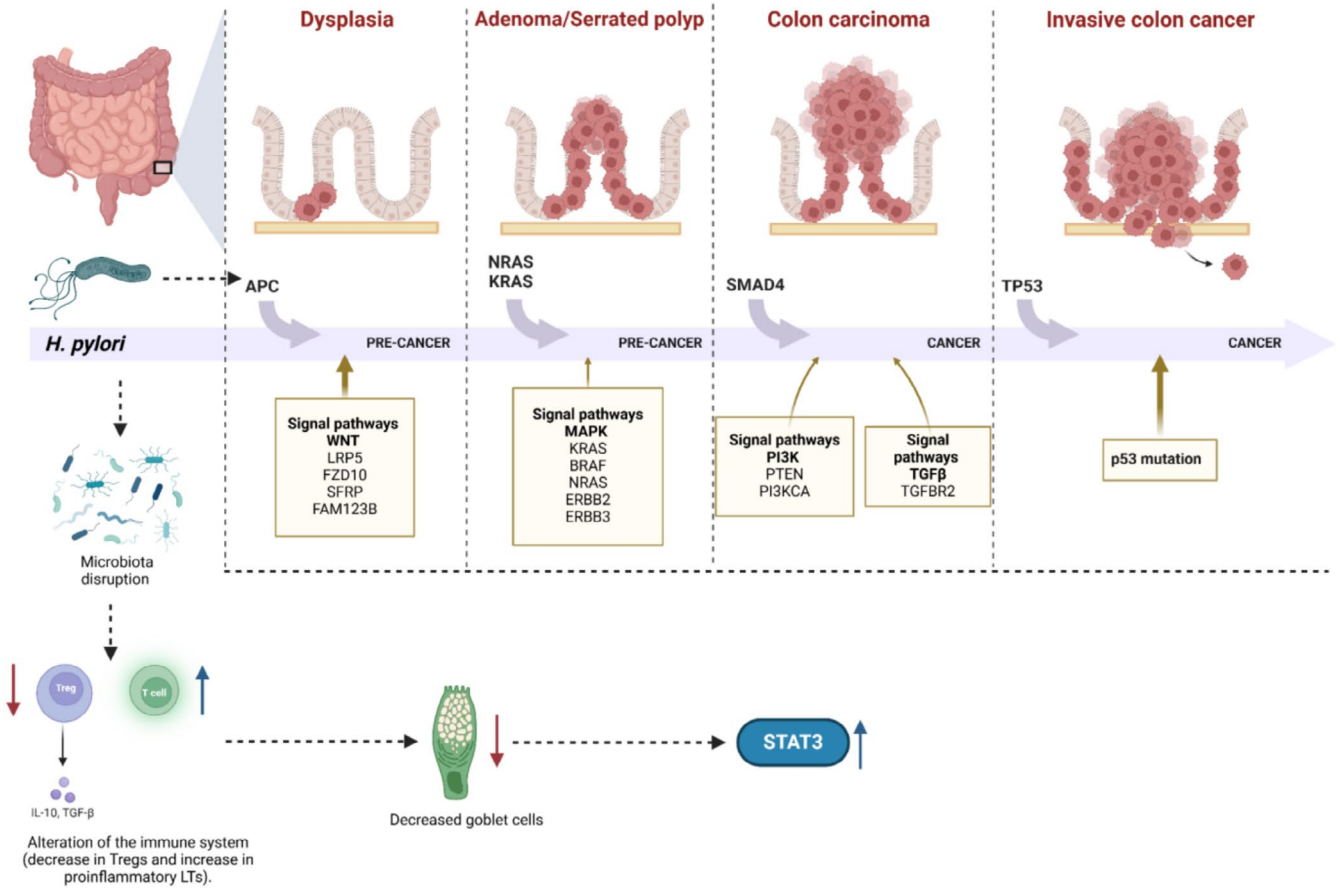

FIGURE 2 | Possible mechanism of colonic carcinogenesis mediated by *H. pylori*. *Source:* The authors.

cell division, migration, adhesion, and apoptosis; in addition, its primary function is defined as the negative control of the WNT signaling pathway [52]. In colon carcinogenesis, it has been described that the mutation in the *APC* gene is considered critical for its initiation and progression in CRC [53]. Its participation in the WNT/β-catenin pathway has been widely described since it is part of the canonical constitutive pathway in the formation of the β-catenin destruction complex composed of the proteins AXIN, PI-4,5-P2-sensitive casein kinase Iα (CKIα), APC, and glycogen synthase kinase-3 beta (GSK-3 beta) that prevents its translocation to the nucleus and exerts the transduction of significant genes in the carcinogenic process [52].

In the same sense, GC it has been seen that aberrant DNA methylation accompanies global hypomethylation and local hypermethylation, which are associated with genomic instability and inactivation of tumor suppressor genes [54]. *H. pylori* infection increases CpG island methylator phenotype (CIMP) positivity [55], which leads to *H. pylori* causing aberrant DNA hypermethylation of specific genes, followed by CIMP induction during gastric carcinogenesis [51]. This finding is interesting, given that in CRC, there is also high microsatellite instability (MSI) in 15% [55] and genomic instability whose mutations in fundamental genes in the control of mitosis, DNA damage repair, centrosome structure and function, and other processes in DNA replication have catastrophic consequences in colorectal carcinogenesis [60]. *H. pylori* has been shown to have an influence on MSI in GC by reducing the level of MutL (hMLH1 and hPMS2) and MutS (hMSH2 and hMSH6)/dMMR (deficiency mismatch repair) proteins responsible for DNA repair [61]. CRC also has elevated MSI [62], and it would be interesting to explore in future studies whether this is generated by *H. pylori* infection. On the other hand, in the survey conducted by Jia et al. [59], they have shown that *H. pylori* infection is an unfavorable factor for immunotherapy in CRC and esophageal squamous cell cancer with microsatellite instability-high/mismatch repair deficient (MSI/Dmmr) phenotype with deficiency for DNA repair. Other studies showed that *H. pylori* infection affects the immunotherapy in CRC [49, 63]. The possible mechanism of action is to decrease cancer's sensibility and reactivity to ICIs, which is the result of the low anti-CTLA-4 and anti-PDL-1 therapy [49, 63].

Also, studies have shown that serologic responses to certain *H. pylori* proteins, such as VacA and CagA, are associated with an increased risk of CRC. For instance, Butt et al. found that seropositivity to *H. pylori* VacA was associated with an increased risk of CRC, particularly among African Americans. This suggests that specific antibody responses could reflect exposure to more virulent strains of *H. pylori*, which may contribute to colorectal carcinogenesis [42].

Some authors suggest that *H. pylori* infection has linked antigen levels to colonic carcinogenesis. In this sense, the study conducted by Genua et al. [64] demonstrated that the association between levels of *H. pylori* antigens and CRC risk is gradually decreased with adenoma progression, which reveals

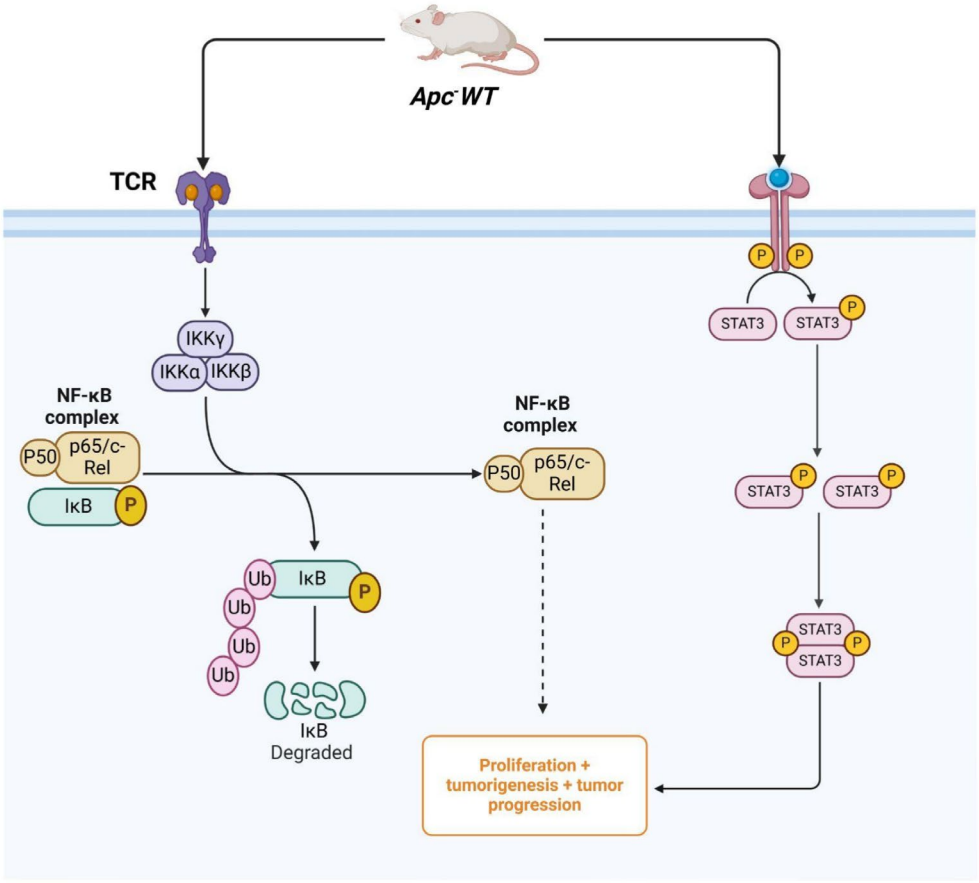

FIGURE 3 | Signaling pathways involved in a possible model of colonic carcinogenesis. *Source:* The authors.

the role of the early detection of the immune response and its repercussions in the polyp stage. In this context, the immune response with antibody levels to specific bacterial antigens is essential for the development of biomarkers that detect early stage neoplasia. As hypothesized, the chronic inflammation from sustained infection by microorganisms (*Streptococcus gallolyticus* subsp. and *Fusobacterium nucleatum*) favors the progression of CRC, which is associated with advanced stages (CRC and adenoma) [64, 65]. This novel evidence allowed an approach for early detection of antibody response to the bacterium, which provided a landscape and timeline of microbial exposures in colorectal carcinogenesis and benefited the identification of patients with increased CRC risk for diagnosis in the early stages of CRC. On the other hand, it is interesting that *H. pylori*, with its metabolites, influences and increases the likelihood of developing polyps [64]. Some mechanisms have been described; *H. pylori* can induce mucosal and systemic antibody responses, leading to pro-carcinogenic effects, although genotoxic and enterotoxic factors by *Escherichia coli* and *Bacteroides fragilis* microorganisms [66]. A recent study has demonstrated that *H. pylori* CagA+ modulates CRC through intestinal flora. In this murine model, the *H. pylori* CagA+ infection produces loss of resident cells and infiltration of immune cells in colorectal mucosa. Moreover, MHC-II-positive in *H. pylori* CagA+ colorectal cells and highlevels of TNF-α, IL-6, IL-8, and IL-10 serum. Finally, gut microbiota alteration in the distribution reduction in Front-to-Back (F/B ratio) decreased the α-diversity metric (Chao1 and Shannon). In β-diversity, gut microbiota in control and HP CagA+ groups showed a significant distance based on UniFrac distance. The CagA+ group was enriched with a higher abundance of *Staphylococcus* and *Corynebacterium*, while control subjects were enriched in *Marinifilaceae* and *Odoribacter*, which were also observed [67].

Other relevant evidence supports that *H. pylori* CagA+ strains are associated with the onset and progression of colorectal lesions. Consistent with this idea, Guo et al. [68] showed that *H. pylori* CagA+ strains could increase Claudin-2, although the CDX2-dependent pathwayis implicated in the disruption of the intestinal epithelial barrier during chronic colitis. Likewise, Ghayemi et al. [69] concluded that CagA expression in colorectal cells increased the risk of CRC, and Zhang et al. found high levels of CagA+ serum in patients with colorectal adenoma. In addition, adenoma patients with *H. pylori* CagA+ infection showed high Ki67 expression compared with adenoma patients with *H. pylori* CagA− infection [70]. CagA+ increases the levels of the pro-survival factor phosphorylated ERK signal pathway and the anti-apoptotic protein called MCL1; therefore, it dampens gut epithelial self-renewal by inhibiting apoptosis [49, 71]. This is very important because CagA+ is considered an oncoprotein that is the most critical in gastric carcinogenesis, and this scenario could play a key role in CRC. CagA+ oncoprotein triggered multiple signal pathways, both canonical and non-canonical, in both GC and CRC. Also, VacA (VacA virulence factor) enters cells and mitochondrial membranes through the formation of chloride (Cl-) channels, resulting in loss of mitochondrial membrane

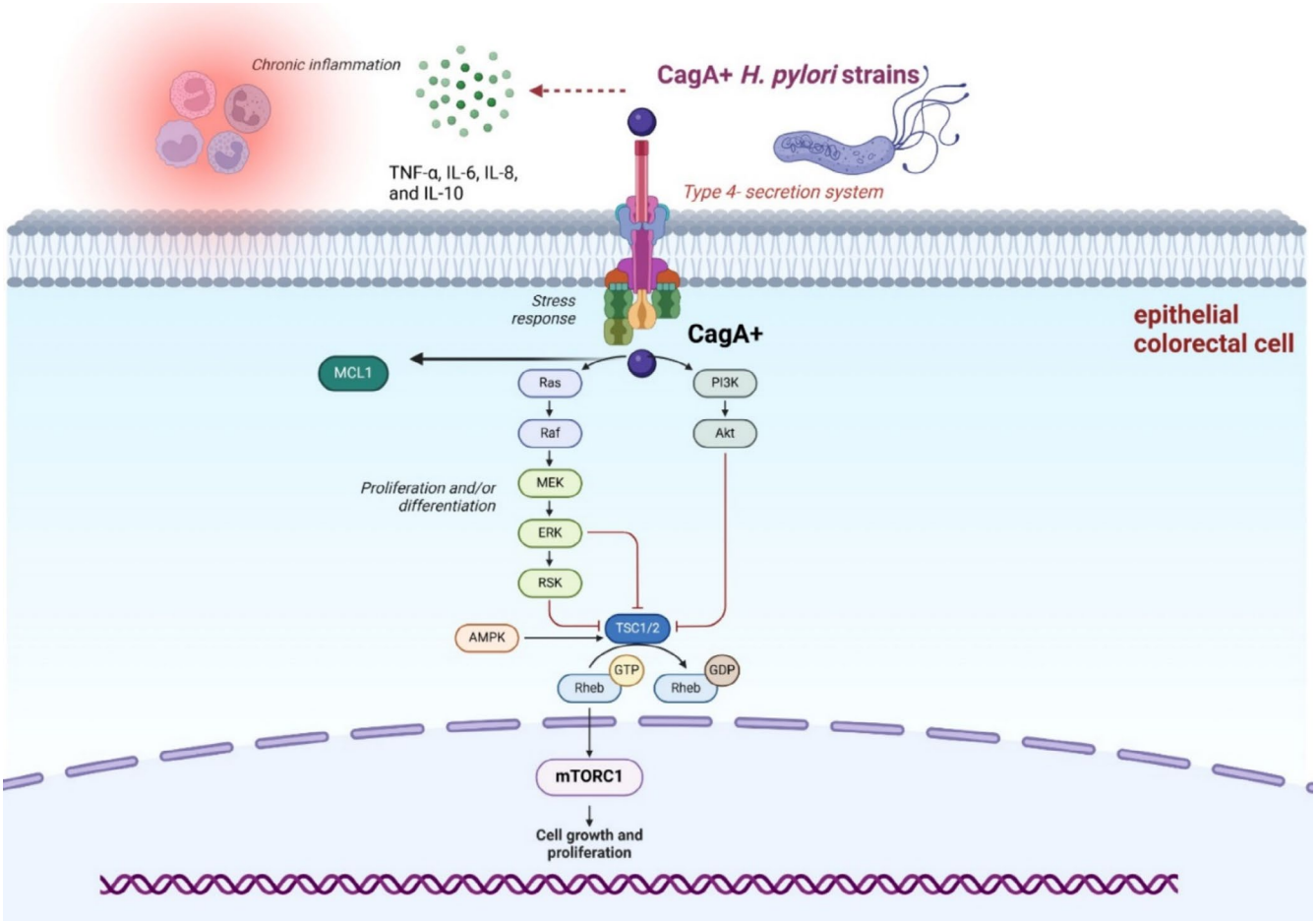

FIGURE 4 | Colonization of tumor cells by *H. pylori* and expression of Cag A, which activates the mTORC1 signaling pathway and increases the expression of the anti-apoptotic protein MCL1, and the release of proinflammatory cytokines TNF, IL-6, IL-1. *Source:* The authors.

potential, mitochondrial fragmentation, reactive oxygen species formation, autophagy [72].

There is evidence of *H. pylori* infection in the TME of the CRC, which was identified for molecular assessment. The study carried out by Grahn et al. detected the presence of *H. pylori* DNA in 77 CRC samples. The samples were tested by a *Helicobacter* species-specific 16S rDNA PCR assay and real-time DNA pyroseq of the 16S rDNA variable V3 region, which found *H. pylori* in 27% of the CRC samples [73].

3.7 | Coherence

The association should not contradict existing and previously demonstrated knowledge about the natural history and biology of the disease [21, 22]. This criterion assesses whether the proposed causal relationship is consistent with existing knowledge about the biology of the disease [22]. Chronic inflammation is known to be a well-established risk factor for CRC. If *H. pylori* is associated with chronic intestinal inflammation, then the hypothesis of a possible causal relationship between the bacteria and CRC would be consistent with this knowledge. Coherence assesses whether the proposed causal relationship is consistent with other knowledge about the biology of the disease. Chronic inflammation is known to be a well-established risk factor for CRC. Although *H. pylori* is associated with chronic intestinal inflammation, the hypothesis of a possible causal relationship between the bacteria and CRC would be consistent with this knowledge.

It implies that a cause-and-effect interpretation of an association does not conflict with what is known about the natural history and biology of the disease; it may become redundant with biological plausibility. However, contrary to biological plausibility, the inferences will deny the possibility that there is a contradiction of association [47]. Similar to biological plausibility, the mechanisms are still not precise and include the participation of the intestinal microbiota, the effects of *H. pylori* directly and indirectly, and the induction of growth in cells of the colonic mucosa [74].

3.8 | Experiment

This criterion is considered the most substantial evidence and the best way to assess causality [28]. The relationship between *H. pylori* and CRC is very complex, and although there is important information, the mechanisms and verification of these have not been extensively studied. However, a recent experimental study in a murine model of *APC* gene mutants (adenomatous polyposis coli) (*Apc+/min* and *Apc+/1638N*) and *Apc+ C57BL/6* mice, as a

surrogate model for CRC in humans [75] since mutations in the gene encoding APCs are one of the most critical mutations that lead to sporadic CRC along with mutations in TP53 and kirsten rat sarcoma viral oncogene (KRAS) [75, 76]. The study conducted by Ralser et al. [75] showed that *H. pylori* infection produced an almost 2-fold increase in the appearance of CRC, which coincides with published analytical studies. Underlying this risk, *H. pylori* induced significant changes in the immune response and the epithelial structure of the intestine with a decrease in Treg and an increase in pro-inflammatory T cells, as well as the activation of the pro-carcinogenic STAT3 signaling pathway, which promotes tumor development. When *H. pylori* was eradicated, a decrease and normalization of STAT3 levels were found [75]. In infected animals compared to uninfected animals, there was a marked decrease in mucus-producing goblet cells, reflecting a reduction in the integrity of the colonic mucosal barrier. Furthermore, these alterations indicate that *H. pylori* induces carcinogenesis signaling pathways and also diminishes the mucosal barrier by decreasing goblet cells and mucus production [75]. Likewise, in infected mice, alterations in the composition of the microbiota were found, with the appearance of mucus-degrading bacteria (*Akkermansia* spp. and *Ruminococcus* spp.) and others that have been linked to colon carcinogenesis [77]. In this respect, *H. pylori* produced changes in the microbiota, favoring the appearance of mucolytic bacteria, pro-inflammatory bacteria, and other pro-carcinogenic bacteria [75].

Additionally, the *H. pylori* eradication prevented the CRC-promoting effects. Infected mice received treatment with clarithromycin, metronidazole, and omeprazole. Changes in the microbiota and immune system, as well as disruption of the mucosal barrier, have also been observed among the mechanisms of colon carcinogenesis in humans [54–56]. A key finding of this research was that *H. pylori* eradication normalized the tumor phenotype in these murine models, suggesting that the adverse effects of infection are potentially reversible. This reversibility would have important public health implications since *H. pylori* eradication therapy would not only be beneficial in preventing gastric cancer but also in reducing the risk of CRC and, in the future, could be part of CRC prevention strategies, similar to what is currently done with GC [78].

3.9 | Analogy

This criterion is linked to the criteria of plausibility and coherence. According to this criterion, there must be a similarity between the mechanisms considered in the causal relationship with other situations in which the same outcome also occurs when exposed to different risk factors [11]. Recently, Ralser et al. [51] confirmed that *H. pylori* infection in murine models with mutations in the *APC* gene produces alterations in the intestinal microbiota, which trigger molecular mechanisms that activate proinflammatory and carcinogenic pathways, promoting the accelerated development of CRC. Proliferative factors such as STAT3, NF-κB, and WNT signaling pathways are activated by signals from epithelial cells and immune cells, triggering chronic inflammation, a mechanism classically known in the genesis of sporadic CRC [79] and

TABLE 2A | Bradford Hill criteria in the relationship between *H. pylori* and CRC.

Criteria	Fulfilled	Comments
Strength of Association	Yes. OR and RR 1.4–1.9	Although the magnitude of the association is weak (less than 3), this does not exclude causality because in diseases that are frequent and multifactorial, the strength of the association is usually weak, as is the case with smoking and lung cancer
Consistency	Yes	In different studies, with different methodologies and different places, an association between *H. pylori* and CRC is found. These similar results could exclude hidden and uncontrolled confounding variables
Specificity	No	Today, specificity, that is, that an agent causes a single effect and vice versa, is obsolete since an agent can cause various diseases and these, in turn, are multifactorial. *H. pylori* induces changes in the microbiota, which would be a risk factor that, together with others, leads to CRC. Specificity is currently irrelevant
Temporality	Yes	*H. pylori* infection is acquired before the age of ten, and CRC appears in the 5th or 6th decade, so there would be no doubt about temporality
Biological Gradient	Yes	Some studies suggest that patients infected with *H. pylori* strains expressing virulence factors, such as CagA and VacA, or who have premalignant gastric lesions are more likely to be associated with CRC. The more frequently infected with CagA and VacA-positive strains, the higher the risk of CRC
Biological Plausibility	Yes	*H. pylori* induce changes in the microbiota and activation of immune system signaling pathways, as well as deterioration of the mucosal barrier with a decrease in goblet cells. These changes in an inflammatory environment constantly activate carcinogenic pathways like those found in patients with sporadic CRC. CagA+ increases the levels of the pro-survival factor phosphorylated ERK signal pathway and the anti-apoptotic protein (MCL1), therefore dampening gut epithelial self-renewal by inhibiting apoptosis. Therefore, eradication of *H. pylori* decreases the incidence and mortality from CRC

Source: The authors.

TABLE 2B | Bradford Hill criteria in the relationship between *H. pylori* and CRC (Contin).

Criteria	Fulfilled	Comments
Coherence	Yes	The published evidence from experimental findings on the mechanisms by which *H. pylori* infects CRC does not contradict accepted evidence on the mechanisms operating in the carcinogenesis of sporadic CRC in humans
Experiment	Yes	In a murine model featuring the APC knockout gene, *H. pylori* infection expedited the onset of CRC. The immunological responses were marked by a decline in regulatory T lymphocytes and a rise in pro-inflammatory T cells, alongside the activation of carcinogenic signaling pathways (STAT3) and a decrease in goblet cells. Eradicating *H. pylori* in infected subjects halted these developments and, in some cases, even reversed them. Conversely, *H. pylori* CagA+ strains induce gut microbiota dysbiosis, resulting in the degradation of the intestinal barrier, which contributes to CRC by promoting the colonization of *Staphylococcus* and *Corynebacterium*. Changes in microbiota composition were observed, including the emergence of mucus-degrading bacteria (*Akkermansia* spp and *Ruminococcus* spp) and other species correlated with colon carcinogenesis. *H. pylori*-induced shifts in microbiota, favoring the growth of mucolytic bacteria, pro-inflammatory bacteria, and other pro-carcinogenic microorganisms. *H. pylori* infection was confirmed through molecular testing in the TME of CRC in 77 samples
Analogy	Yes	The changes produced by *H. pylori* in the colonic microbiota, as well as inflammation and carcinogenic pathways, are like those found in CRC sporadic and are related to other risk factors (obesity, metabolic syndrome, and others)

Source: The authors.

also that which occurs with inflammatory bowel disease [80, 81], that associated with metabolic syndrome and fatty liver associated with metabolic dysfunction [82]. GC also appears in an environment of chronic inflammation that progresses to precursor conditions such as atrophy, intestinal metaplasia, and alterations in the microbiota [1], In a multifactorial process with inflammatory and procarcinogenic immune alterations, as has been found experimentally in CRC [67, 75].

For decades, it has been shown that *H. pylori* treatment decreases the incidence and mortality of GC by stopping or attenuating the inflammatory cascade [83–86]. Similarly, *H. pylori* infection promotes the appearance of adenomatous polyps in the colon and CRC [64, 87]; therefore, its eradication reduces the incidence and mortality of CRC [24] by decreasing the proinflammatory immune response, microbiota disruption, and carcinogenic signaling pathways [20, 51], as recently demonstrated by Ralser [75].

4 | Summary and Conclusions

Based on different publications from the last two decades, we consider that *H. pylori* is positively associated with CRC and reasonably meets the current conception of the BHCs [32, 34]. Further studies are required to consolidate the information and generate strategies to determine whether the eradication of *H. pylori* translates into a decrease in the incidence and mortality from CRC in large populations. Table 2A and Table 2B summarize the evidence on the causal role of *H. pylori* as a promoter of CRC.

Author Contributions

W.O.R. conceived the study's idea and edited and supplemented the initial version of the paper with J.S.F.-O., A.R., H.M.-F., L.O.-P., J.A.U., J.D.P.-M., and E.O.-R. All authors contributed to all steps of the preparation of the paper and gave final approval of the version presented. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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