REVIEW
Gastroenterology & Hepatology Research 2022;4(4):22. https://doi.org/10.53388/ghr2022-12-064

Research progress in gastric cancer caused by Helicobacter pylori

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Author contributions
Zhao-Chun Chi was responsible for reviewing academic papers in gastric cancer field and writing manuscripts.
Competing interests
The authors declare no conflicts of interest.
Acknowledgments
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Peer review information
Gastroenterology & Hepatology Research thanks all anonymous reviewers for their contribution to the peer review of this paper.
Abbreviations
H. pylori, helicobacter pylori; GC, gastrointestinal cancer; CI, confidence interval; VacA, vacuolating cytotoxin A; CagA, cytotoxin-associated A; OR, odds ratio; Ig, immunoglobulin; NOD, nucleotide-binding oligomerization domain; NFκB, nuclear factor kappa-B; TLRs, toll-like receptors; IL, interleukin; MAPK, mitogen-activated protein kinase; IDA, iron deficiency anemia;
Citation
ZC Chi. Research progress in gastric cancer caused by Helicobacter pylori. Gastroenterol Hepatol Res. 2022;4(4):22. doi: 10.53388/ghr2022-12-064.

Executive editor: Miao Peng.
Received: 13 September 2022; **Accepted:** 27 December 2022; **Available online:** 30 December 2022.

Abstract
Helicobacter pylori (*H. pylori*) infection is the most prevalent cause of gastric cancer. According to recent studies, the likelihood of developing gastric cancer can be significantly increased by subtle microbial differences and has hereditary traits. *H. pylori* and gastric mucosal begetter cells have a complex relationship because of their ability to recombine epithelial cells and activate stem cells. Gastric antecedent and stem cells can be directly influenced by cell-associated *H. pylori*, which can colonize gastric organs. The balance between *H. pylori's* activities as a symbiont or pathogen can be changed by external and natural factors, such as calories count and gastrointestinal microbiota, which provides information for determining its full carcinogenic potential.

Keywords: helicobacter pylori; gastric cancer; pathogenesis; H. pylori virulence

Background

Gastrointestinal cancer (GC) is the fifth most common malignant tumor and the most common cause of cancer-related deaths worldwide, and its incidence is increasing [1]. According to statistics, there are about 1 million new GC cases and more than 720,000 GC-related deaths annually, accounting for 7.0% of all new cancer cases and 9.0% of total cancer-related deaths. From the new cases of GC occurring throughout the world, approximately 74% occur in Asia, and almost half of the global cases stem from China. Different countries, such as those in Latin America and Eastern Europe, have relatively high rates of GC. Despite substantial improvements in the care of malignancies, the 5-year survival rate for GC remains less than 30%. GC is associated with *Helicobacter pylori* (*H. pylori*) infection. The incidence of GC is very low in patients without *H. pylori* infection, and the relationship between *H. pylori* infection and the prevalence of GC has been thoroughly investigated.

The World Health Organization has classified *H. pylori* as a class 1 carcinogen, and approximately 74.7–89.0% of GCs are related to *H. pylori* infection. A meta-analysis of 12 prospective studies showed that the risk of GC in *H. pylori*-positive patients was 2.4 [95% confidence

interval (CI), 2.0–2.8] [2]. *H. pylori* infects the stomach lining during childhood and causes chronic inflammation that can persist for decades, if left untreated. This persistent gastric mucosal inflammation leads to GC in < 3.0% of the infected individuals.

H. pylori infection is widespread, with a prevalence approaching 100% in some regions of the world; Alternatively, 97–99% of people with the infection never develop GC [3]. In general, a high incidence of GC is associated with a high frequency of *H. pylori* infections. However, in other areas of the world, the incidence of GC is low, even while the frequency of *H. pylori* infection is high [4]. This association is uncommon worldwide. The incidence of GC in these locations is quite low, which is related to the inheritance of *H. pylori*, despite the fact that the prevalence of *H. pylori* infection is high in Africa (nearly 100% of the African population carries the *H. pylori* strain) and South Asia [5].

The pathogenesis of GC caused by H. pylori

Relationship between *H. pylori* virulence factors and GC risk

Many studies have reported substantial differences in the prevalence of vacuolating cytotoxin A (VacA) alleles among patients with different clinical benefits. Therefore, the precise genotype of *H. pylori* may be related to the severity of gastrointestinal disease [6]. Many different *H. pylori* pathogenic factors, including VacA, cytotoxin-associated A (CagA), bloodstream-group antigen-presenting adhesin, *H. pylori* exterior membrane protein, outer other protein A, and sialic acid-binding adhesion, are expected to be predictors of gastric atrophy, intestinal metaplasia, and other gastric conditions. The CagA and VacA family genes play a key role in inducing *H. pylori* disease, which in turn is mainly linked to chronic gastric pain and epithelial cell damage caused by GC. *H. pylori* CagA and VacA carcinogenic proteins cause GC through a multistep process [7].

The role of VacA genotype in the pathogenesis of GC

The well-known *H. pylori* virulence factor can cause damage to gastric mucosal cells. VacA toxin also causes cell functional changes, such as vacuolation, disruption of lysosomal function, and promotion of immune regulation. The mosaic recombination of s1, s2, i1, i2, m1, and m2 alleles lead to an increased risk pathogenic ability of VacA [8].

VacA protein is the key causative agent first identified in *H. pylori*. Although all *H. pylori* strains carry the VacA gene, each strain differs significantly in terms of vacuole activity. The key difference is mainly related to the gene structure of the central and signal regions. These regions are composed of s1 (s1a, s1b, and s1c), s2, i1, i2, m1, and m2 subtypes. Region is the key region for vacuole formation. Recently, a loss of 81 bp was found between zones M and I, referred to as zone D (D1 or D2). In another study on 3′VacA gene, a new polymorphic area named VacA c (c1:15 bp is missing) was discovered, and the VacA c1 type was found to be associated with a significant risk for GC [9].

The role of the CagA genotype in the pathogenesis of GC

The CagA protein is associated with gastric diseases, has a variety of buildings, and is immunogenic. Epiya strains in East Asia differ from those in the West in that they have a specific Glutamate-Proline-Isoleucine-Tyrosine-Alanine (EPIYA)-D sequence rather than a repetitive alanine sequence (EPIYA motif), which may be associated with the prevalence of gastric tumors in East Asia [10]. CagA affects endoplasmic reticulum stress, mitochondrial dysfunction, and irritation in a manner similar to that of VacA. In particular, fragile vacuolation and strong CagA phosphorylation have been suggested to be functionally related through increasing evidence [11]. Through the type IV secretion system, the CagA protein enters *H. pylori*-adhered gastrointestinal epithelial cells, and tyrosine phosphorylates its C-terminus. Phosphorylated CagA can cause cytoskeletal rearrangement, induce morphological changes in cells, enhance cell motility, cause abnormal cell movement and proliferation, and eventually lead to cancer development.

Large epidemiological studies have shown that the presence of CagA is strongly correlated with the occurrence of precancerous gastric lesions. This is particularly evident in East Asia (90%), whereas the *H. pylori* strain CagA +, prevalent in Western countries, accounts for 50–70%. The odds ratio (OR) also increased with GC severity. Four, five, or six specific *H. pylori* antigens seroprevalence more than quadrupled the risk estimate. However, when both Omp and HP0305 were seropositive, the risk increased to 7.43. This suggests that these serological biomarkers are more predictive of the risk of advanced gastric lesions than CagA seropositivity in East Asia [12].

Interactions and coevolution between *H. pylori* and host genetic ancestors may be major determinants of GC

The approach known as multilocus sequence typing is frequently employed to assess and contrast the genetic diversity across *H. pylori* strains. According to previous studies, *H. pylori* became less virulent over time. The breakdown of the coevolution between *H. pylori* and humans may play a role in the pathogenesis of GC caused by *H. pylori*; however, this microbe is still the most potent known risk factor for the disease [13, 14, 15].

Studies have shown that in Western countries, the risk of GC is positively correlated with CagA. However, in East Asia, CagA positivity does not indicate a risk of GC, although it indicates the EPIYA-D fragment [16]. In view of this, no correlation between the VacA genotype and clinical outcome and histopathological changes in GC was found in the survey report of East Asia. It has been suggested that the interaction between bacteria and host genetic ancestors might be the cause of this difference.

Some researchers have studied the evolution of *H. pylori* in the American population. There are significant differences in the prevalence of *H. pylori* strains of African and European origins in the United States. However, bottlenecks and extensive gene flow between Colombian and Nicaraguan isolates have led to the dramatic expansion of new *H. pylori* subgroups. Three outer membrane proteins were identified in the American strains, which were significantly different from those prevalent in Asia. However, almost completely fixed alleles were found in the South American isolates. Therefore, ethnic composition of the host may be crucial for the expansion of exotic strains [17].

Differences in genotypes showing different risks to the host, such as proinflammatory cytokine polymorphisms associated with infection with *H. pylori* strains, are associated with differential GC risk in many populations. Therefore, genetic variation in *H. pylori* strains and hosts may contribute to differences in the risk of GC [18].

H. pylori strain variation and risk of GC

CagA and Cag pathogenicity islands

According to previous studies, the CagA protein is not present in all *H. pylori* strains, and its mucosal immunoglobulin (Ig) A response is related to peptic ulcer disease. The activity, characterized by increased infiltration of neutrophils in the gastric epithelium, is significantly associated with gastritis [7]. CagA was identified as a product of the type IV secretion system, toxin-associated gene pathogenicity island (Cag-PAI). CagA is an oncoprotein that translocates to gastric epithelial cells via the type IV secretion system of pathogens and induces a variety of signaling cascades [19]. Cag-PAI also transports peptidoglycan breakdown products to gastric epithelial cells, activating the intracellular nucleotide-binding oligomerization domain (NOD) -like receptor 1 (NOD1) and nuclear factor kappa-B (NF κ B), thereby promoting an enhanced CXC chemokine response and active gastritis in Cag-PAI-positive infection [7].

Recent studies have demonstrated that the Cag type IV release system, which is carried to epithelial cells, also mediates bacterial heptose-1, 7-diphosphate (HDP), a metabolic precursor for lipopolysaccharide biosynthesis, in addition to the NOD1 service [20]. Without the aid of NOD1, HDP activates fork head-interacting proteins (TIFA) and cytosolic tumor necrosis element receptor-associated factor (TRAF)-interacting proteins, activating NF κ B and CXC chemokines early. Therefore, an innate immune system inflammatory reaction is triggered by two independent *H. pylori* components that are delivered through the Cag type IV secretion system to activate epithelial NOD1 and TRAF-interacting proteins with a TIFA-associated domain.

CagA serology and atrophic gastritis

CagA is an immunodominant protein that was initially identified by gastric mucosal IgA and serum IgG responses following infection with *H. pylori* CagA-positive strains. The relationship between CagA IgG seropositivity and endoscopic pathological diagnosis of atrophic gastritis has been investigated in several studies [21]. Therefore, patients with CagA-positive *H. pylori* infection have a higher risk of developing atrophic gastritis than those with CagA-negative *H. pylori* infection [22].

Within the Eurogast research, all CagA-IgG seropositive assays revealed that patients who had been administered the medication had substantially lower pepsinogen A/C ratios than those who did not. These studies support a link between gastrointestinal corpus atrophy and CagA-positive strains in several European nations [23].

H. pylori DNA promotes GC cell proliferation, migration, and invasion by activating toll-like receptor 9

Toll-like receptors (TLRs) are single-transmembrane, noncatalytic proteins that may identify compounds originating from microorganisms with conserved structures. TLRs may identify pathogens that pass the body's physical defenses, such as the skin and mucous membranes, and trigger the immune system to create an immune cell response [24]. Recent research has demonstrated that TLR9 plays a key role in the initiation and progression of several malignancies, including breast, prostate, and lung cancers. Additionally, research has indicated that TLR9 upregulation may have encouraging effects on the development of GC [25]. Human gastric adenocarcinoma cell line GC cells were found to be more prone to invasion by the *H. pylori* DNA; however, this invasion could be inhibited by chloroquine, a nonspecific TLR9 [26]. Current studies, however, do not conclusively show that TLR9 is the pathway via which these effects are mediated. According to previous studies, *H. pylori* DNA upregulates TLR9 expression and promotes proliferation, migration, and invasion of human GC cells. Additionally, TLR9 knockdown markedly reduced cell motility, invasion, and proliferation. According to the studies mentioned above, TLR9 may play a role in the development of GC [27].

TLR9 has been found to be exironed in human gastric epithelial cells [28]. Moreover, it can recognize *H. pylori* DNA and induce the expression of inflammatory factors [29]. For example, the interaction of *H. pylori* DNA with TLR9 significantly increases the expression of interleukin (IL) -8. IL-8 mRNA expression is related to the degree of gastric wall lesions [30, 31]. Studies have shown that TLR2/TLR9 signaling activates mitogen-activated protein kinase (MAPK) and promotes the binding of a group of transcription factors to the Cyclic Adenosine monophosphate(cAMP) response element and activin 1 in the Cyclooxygenase (COX)-2 promoter. Prostaglandin E2 release promotes GC invasion and angiogenesis [32]. Other studies have also shown that stimulation of TLR9 with agonists can increase Recombinant Matrix Metalloproteinase (MMP)13 expression in GC cells [29]. Therefore, *H. pylori* DNA proliferation, migration, and invasion can be promoted by TLR9 activation in GC.

Iron, salt, and *H. pylori* virulence

Iron and *H. pylori* virulence

Iron and the virulence of *H. pylori* are related from two significant clinical viewpoints. First, both adults and children with *H. pylori* infection may develop iron deficiency anemia (IDA). This is frequently true in population-level iron deficiency frailty, and signs of iron deficiency are linked to a higher risk of GC [33]. Subsequently, *H. pylori* may lead to low iron status and aggravate *H. pylori* infection. Hepcidin, the primary regulator of iron metabolism, is also upregulated by inflammation; this initiates the iron reduction response in pathogens by preventing iron absorption in the small intestine [34].

Amid *H. pylori* disease, hepcidin may diminish press accessibility, causing IDA. If antimicrobials are not utilized to kill the microbes, *H. pylori*-related iron insufficiency does not react to verbal iron treatment. Verbal iron treatment in *H. pylori*-infected children with IDA did not diminish serum hepcidin levels, suggesting that disease destruction is required to reestablish normal iron levels. Hepcidin is locally exironed within the parietal cells of the gastric organ, and gastric hepcidin increases in *H. pylori* disease, but returns to normal after disease clearance [35]. Ponders have suggested that *H. pylori* not only employed iron in food but also within the body to pass the epithelial boundary disconnected from iron stores. Iron-deficient Mongolian gerbils contaminated with CagA+ *H. pylori* created more extreme aggravation and quickened premalignant and harmful injuries than those nourished with iron-rich count calories [33]. In conclusion, recent studies on the pathogenic factors involved in iron ingestion have proposed a connection between *H. pylori* destructiveness and GC hazard.

Salt and *H. pylori* virulence

An expansive number of human studies have detailed the affiliation between tall salt admissions and the expanded chance of GC. Quality exironion in a few bacterial pathogens, including *H. pylori*, can be affected by salt concentration. Transcriptional and proteomic ponders have revealed the expanded exironion of CagA under high-salt conditions [36]. A study suggested that *H. pylori* contamination in gerbils and a high-salt count calories autonomously initiated atrophic gastritis and intestinal metaplasia, while another suggested that *H. pylori* disease and an increased salt diet were synergistic with the advancement of GC [37].

Gaddy et al examined the impact of a high-salt diet on microbial-induced cancer in gerbils using a special strain of carcinogenic *H. pylori*. Gastric adenocarcinomas were recognized at a significantly higher rate within the infected creatures that bolstered a high-salt diet than in those encouraged to eat normally. Gastric juice, deletion of parietal cells, and high levels of gastric mucosal IL-1B were identified in the creatures that developed cancer. Creatures tainted with an agA-negative isogenic mutant and encouraged to eat a high-salt diet appeared to have lower levels of gastric irritation and did not create hypochloremia or GC. Moreover, high-salt count calories do not cause GC in uninfected animals [38].

The effect of H. pylori on gastric stem cells

To investigate the processes by which an inflammatory response caused by *H. pylori* infection causes long-lived cells to multiply in a dysregulated manner eventually leading to cancer, a number of possible models have been constructed. As *H. pylori* dwells within the shallow bodily fluid layer over the gastric lumen and follow bodily fluid pit cells, these terminally separated cells may be the targets for oncogenic change. These include dedifferentiation into duplicating cells, securing oncogenic transformations, and cancer stem cell characteristics. Various studies suggested that CagA has the reconstructing potential to convert physical epithelial cells into a pluripotent stem cell-like state [39, 40]. For example, cells exironing CagA or contaminated with CagA-positive microscopic organisms lose the key highlights of epithelial separation and experience phenotypic and atomic changes related to stemness and epithelial-mesenchymal transition [41].

It is generally recognized that precancerous metaplastic lesions, which lose parietal and other differentiated cells, occur before multifocal atrophic gastritis. The development of immature proliferating cells is another characteristic of chronic atrophic gastritis in a mouse model in which parietal cells undergo genetic modifications [42]. These studies are among the first to show that a portion of *H. pylori* may exist in adult gastric stem cells as a safe niche, for avoiding eradication.

Stem and begetter cells are candidate tumor-initiating cells in GC and are a source of GC stem cells. Mouse tests have shown that the tumor supironor-quality adenomatous polyposis coli (APC) is erased from leucine-rich rehash unit G protein-coupled receptor 5 (LGR5+) stem cells and causes rapid growth of adenomas [43]. Moreover, inactivation of the tumor supironor quality KLF4 in villin-positive gastric begetter cells expanded gastric tumorigenesis and movement in mice [44]. Several studies have linked stem cell number and damage to GC progression. A study found an enlarged pool of LGR5+ stem

cells in the gastric antrum of patients with GC and *H. pylori* infection and higher amounts of DNA oxidative damage [45].

The bacterium *H. pylori* appears to have developed particular ways to interact with and impact stem and progenitor cells in the stomach glands, regardless of whether the infection results in human cancers. *H. pylori* can reach the stomach surface, connect to epithelial cells, and develop directly at epithelial junctions deep into the gastric glands as attached microcolonies that escape the gastrointestinal cavity [46]. This gland-associated *H. pylori* population, which is rich in mitotic progenitors and emerges early during mouse colonization and in asymptomatic individuals before the onset of atrophic gastritis, is more prevalent in the isthmus [47, 48]. Green fluorescent protein can be used to mark LGR5+ stem cells in mice, allowing researchers to study how *H. pylori* infection affects these cells [39, 40]. Since mutant *H. pylori* are unable to colonize the glands, stem cells are not activated, which suggests that bacteria and stem cells interact directly. Stem cells are spatially connected to the glands when gland-associated *H. pylori* is present. Hyperproliferation was aided by this activity.

H. pylori autophagy and GC

There are two types of autophagy: canonical and atypical autophagies. Signal induction, membrane nucleation, cargo targeting, phagosome lengthening, formation of new autophagy, fusion of two, degradation of cargo, nutrient cycling, and other processes are all included in the term “autophagy”. In eukaryotic cells, autophagy is a common physiological process that is highly conserved and primarily responsible for removing misfolded proteins and damaged organelles. The main function of autophagy is to degrade specific cellular components and provide energy. The body engulfs diseased organelles or damaged cytoplasmic proteins to create autophagosomes when cells are under stress, such as starvation and hypoxia. To maintain cellular homeostasis, it collaborates with lysosomes to create autolysis. The degenerated cells are recycled, reused, and degraded as part of this process. By preventing the buildup of toxins or metabolites, autophagy can help tumor cells survive and clear damaged cells when stimulated by unfavorable external factors. Autophagy, which is advantageous for *H. pylori* survival, can be induced by acute parasite infection. Autophagy can be inhibited by chronic *H. pylori* infection, which can result in the dysfunction of autophagosome-related proteins. Inhibition of autophagy can result in ongoing infection [49]. As a result, autophagy has two sides and can either help or hinder cell survival. Autophagy appears to be one of the pathophysiological pathways involved in GC and is crucial for the occurrence, growth, metastasis, and survival of gastric tumors [50, 51].

The type, stage, and genetic background of cancer are related to autophagy, which appears to play a dual role in tumorigenesis. To prevent further cell deterioration and the growth of malignant tumors, autophagy serves as a tumor suppressor by reducing the oncogenic protein p62. It also helps remove damaged organelles and DNA. Autophagy can then enhance tumor immune escape, metabolism, and growth, leading to drug resistance by shielding tumors from harm caused by nutritional deficiencies, radiotherapy, and chemotherapy [52, 53].

For the most part, it is accepted that the pathogenesis of GC is closely related to the downstream signaling pathway involving autophagosome arrangement initiated by *H. pylori* infection. Autophagy is involved in *H. pylori* infection and plays a critical role in the pathogenesis of GC [54]. The process by which *H. pylori* disease activates GC remains unclear [55]. In expansion, *H. pylori* can initiate the unusual enactment of cell signaling pathways, such as the Nod1 NF-κB/MAPK-ERK/FOXO4 pathway, permitting cells to elude autophagy and drive GC [56].

In conclusion, new mechanistic insights are offered by the connection between autophagy and DNA damage response in *H. pylori*-associated gastric carcinogenesis. Autophagy is lost as a result of chronic *H. pylori* infection, which is followed by the build-up of substrate P62. By directly interacting with the E1-activating enzyme during ubiquitination with Rad51, accumulated p62 inhibits the DNA damage repair capacity [53]. Double-strand breaks and genomic instability are increased by *H. pylori* as a result of these cellular events, which may help cause GC.

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