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# Literature Review on *Helicobacter pylori* as a Major Risk Factor for Stomach Cancer

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ABSTRACT: *Helicobacter pylori (H. pylori)* is a prevalent bacterium that infects approximately 50% of the world's population. *H. pylori* colonization of the gastric mucosa with the help of its motility organ, the flagella, triggers immune responses, and important toxins are released, which play a role in the disease. These virulence factors and molecular mechanisms of *H. pylori* could lead to the development of gastric cancer. Important virulence factors of *H. pylori* include the cytotoxin-associated gene A (CagA), vacuolating cytotoxin (VacA), and outer inflammatory protein A (OipA). H. pylori is a major pathogenic contributor to gastric diseases. Therefore, further research into these virulence factors can help develop effective prevention of gastric cancer. Eradication methods of *H. pylori* infection related to the flagella reveal promising treatment methods worldwide despite antibiotic resistance. This review paper discusses the importance of *H. pylori* flagella and virulence factors as possible anticancer targets.

KEYWORDS: Behavioral and Social Sciences, Psychology, Psychological Safety, Student Management Systems.

## Introduction

Gastric cancer is the fifth most common cancer worldwide, accounting for 5.6% of all cancer cases. It is more prevalent in East Asia, Central Asia, and South and Central America, with around 75% of all new stomach cancer cases and deaths reported from Asia. It also accounts for 7.7% of all cancer deaths. In the US, the disease occurs more frequently among Black, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native individuals, with increasing rates in younger females.[1] One major risk factor is *Helicobacter Pylori*, which is responsible for 70% of all gastric cancer cases. In addition, stomach cancer remains a major health problem due to its aggressive nature and diverse characteristics, such as its role in pathogenicity.[1]

*H. pylori* is a spiral-shaped, gram-negative bacterium that lives in the mucus layer of the human stomach. Its survival in the hostile, acidic environment of the stomach is aided by adaptation mechanisms such as neutralizing the stomach acid and attaching itself to the mucus layer.[2] Although the exact route of transmission of *H. pylori* and how it gets into the stomach is still under investigation, studies suggest infections occur due to either human-to-human transmission or environmental contamination. They indicated that human-to-human transmission occurs within families due to close contact and shared genetics. Infections are often acquired in childhood, typically through gastric fluids or saliva transmission, where *H. pylori* can colonize the mouth. Oral-to-oral transmission may be the primary route, but *H. pylori* can sometimes be passed from mother to child through contaminated oral secretions. Poor hygiene increases the risk, as contaminated water can carry *H. pylori* and spread infections.[3] The majority of infected individuals remain asymptomatic, and usually remain chronic unless treated with antibiotics. Over time, about 10%-15% of infected individuals develop duodenal ulcers, and around 1% develop gastric cancer. In fact, *H. pylori* infection is a significant risk factor for the development of gastric cancer.[4] The current prevalence of chronic *H. pylori* infections in the U.S. population is estimated to be around 36%.[5]

Chronic *H. pylori* infections develop slowly and persist over time, while acute *H. pylori* infections are very rare and clearance of such infections is extremely rare. Many acute *H. pylori* infections tend to turn into chronic infections because they are asymptomatic, and although they do activate the immune system, its response is not effective in clearing the infection.[6] Although the reason behind *H. pylori's* asymptomatic behavior is unclear, it is believed that some people may be born with resistance against *H. pylori*.[7] Persisting *H. pylori* infections cause chronic inflammation by manipulating the host immune system, which leads to chronic gastritis.[8]

The infection's outcome of chronic gastritis can increase the risk of stomach cancer by 0.1%. In addition, specific host genetic mutations can affect the intensity of the inflammation of the gastric tissue, which also influences the risk of subsequent development of stomach cancer.[6]

A causal relationship between *H. pylori* infection and gastric cancer was first proposed in the 1980s through the work of Australian scientists Barry Marshall and Robin Warren. Their research included isolating *H. pylori* and showing how stomach ulcers are caused. This led to further studies on the association between chronic *H. pylori* infections and the development of gastric cancer. In 2005, Marshall and Warren were awarded the Nobel Prize in Physiology for discovering *H. pylori* and its role in gastric diseases.[9]

*H. pylori* pathogenesis is related to several mechanisms. First, *H. pylori* produces urease to neutralize the stomach acid to survive and colonize. *H. pylori* uses its flagella for motility, allowing it to reach the gastric cells, where it attaches to host



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receptors through bacterial adhesins. This leads to successful colonization and infection. Lastly, *H. pylori* can produce the cytotoxins, CagA and VacA, both of which are associated with a higher chance of developing stomach cancer.[2]

*H. pylori* flagella are a motility organ composed of protein subunits, primarily the flagellin. The pathogenesis of *H. pylori* depends on colonization, with the flagella playing a major role in allowing *H. pylori* to navigate the gastric mucosal layer. Flagellar motility is essential for colonization.[10]

This review discusses the role of *H. pylori* flagella in colonization and inflammation, and the mechanisms associated with increased risk of gastric cancer following *H. pylori* infection.

## Discussion

### *Roles of H. pylori Flagella in Colonization:*

*H. pylori* has a helical motility organ of four to eight unipolar and distinct flagella that are composed of multiple protein subunits, including FlaA, FlaB, and FliD as shown in Figure 1.[10]

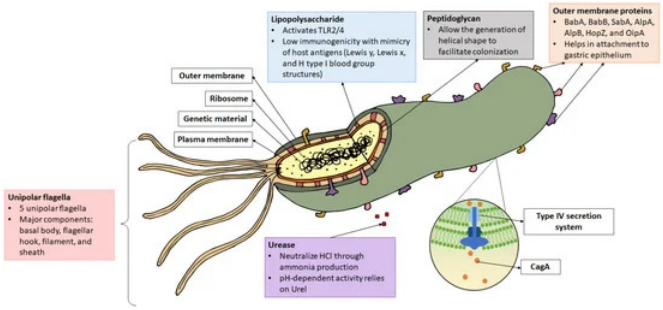


**Figure 1:** *H. pylori* morphology. Important outer membrane proteins, urease production, CagA, and structural composition of *H. pylori* are indicated. These important features allow for successful bacterial colonization.

Its helical shape helps its invasion into the mucous layer of gastric epithelial cells.[6] Once *H. pylori*, with the help of the flagella, reaches the gastric epithelium cells, it attaches firmly and establishes permanent colonization. In addition, the helical shape helps the bacteria to swim through the mucus gel present in the stomach. Its helical shape helps the bacteria to create a screw-like rotation while the flagella produce the force needed to move forward.[11]

The flagella are crucial for successfully colonizing the gastrointestinal mucosa.[10] The flagellar filament's structural proteins play an important role in bacterial motility to drive the bacterium through the mucus layer. The FaaA protein is found in the flagellar sheath, which protects the flagella from the effects of acid. Optimal flagellar function enables efficient colonization.[10]

Another role of the flagella is to protect *H. pylori* from the stomach's acidic environment. The pH within the stomach can reach pH 1-2, which is essential for digesting food. Without specialized mechanisms, this acidity harms most organisms by disrupting cellular homeostasis and damaging membranes and proteins. However, the mucus layer that lines the stomach has a pH 6-7 gradient, allowing the bacteria to survive near the stomach lining.[12] *H. pylori* can thrive in the stomach by protecting itself from the harmful stomach acid with the help of specialized systems. One such system is the presence of a flagellar sheath, which protects the flagellar filaments from damage. The structure of the flagella, with its outer sheath to protect against the acid, ultimately results in enhanced motility of *H. pylori*.[12]

Motility allows *H. pylori* to survive and thrive in the hostile environment of the stomach. *H. pylori* possesses 4-8 flagella. Motility plays a crucial role in the bacteria's ability to survive in harsh gastric conditions, thus enabling stable colonization of the gut.[14]

*H. pylori* senses acid, and flagellar motility is essential in enabling the bacteria to swim away from acid and reach the gastric mucus layer, where the pH is close to neutral. Thus, bacterial motility, particularly its flagella, is critical in enabling the bacteria to persist under these extreme conditions. In addition, bacterial urease production is also essential for acid resistance.

Once *H. pylori* colonizes the stomach, it triggers an inflammatory response.[6] Flagella in *H. pylori* are involved in both *H. pylori*-induced inflammation and immune evasion. Specific flagellin proteins that compose the flagella, such as FlaA and FlaB, can promote humoral immunity and trigger the immune system to produce antibodies that target *H. pylori* infection.[15]

*H. pylori* inflammation can evolve into chronic gastritis, a lifelong illness that causes inflammation and potentially progresses to atrophic gastritis. Chronic inflammation results from the inability to effectively clear the bacteria from the stomach. This leads to prolonged infection and continuous immune cell recruitment.[16]

Though the exact transmission route of *H. pylori* to the stomach is still being studied, research indicates that infections are the result of human-to-human transmission within families due to close contact and shared genetics.[3] Since *H. pylori* infections are often asymptomatic, infected patients are unaware of the ongoing infection until severe tissue damage occurs. Therefore, infections are usually diagnosed when chronic.[16] Some potential therapeutic vaccines have been used to target urease subunits; however, few have demonstrated protection against the infection. Thus, it is important to study the early stages of *H. pylori* infections by targeting certain pathways, such as NF-kB, which are one of the pathways *H. pylori* activates during the onset of gastric cancer.[16]

### *H. Pylori Motility and Survival in the Stomach and Links to Stomach Cancer:*

Outer membrane proteins (OMPs) act as a barrier to help *H. pylori* bacteria withstand their harsh environment.[16] Three *H. pylori* outer membrane proteins are linked to gastric cancer: OipA, HomB, and HopQ. The host cell JAK/STAT signaling pathway functions as a signaling mechanism from the cell membrane to the nucleus and also triggers various mediators of cancer and inflammation.[24] When *H. pylori* adheres to gastric epithelial cells, OipA stimulates the JAK/STAT signaling pathway by triggering JAKs (a non-receptor tyrosine kinase) to phosphorylate STAT (Signal Transducers and Activators of Transcription). This causes STAT to translocate to the nucleus to bind to specific DNA sequences called GAS (Interferon γ-Activated Sequence), leading to inflammatory gene expression.[25] Dysregulation of these pathways by OipA can disrupt

normal cell functions, which may ultimately contribute to the development of gastric cancer.[6]

HomB is another outer membrane protein of *H. pylori* that binds to gastric epithelial cells and initiates inflammation in the gastric mucosa. HopQ facilitates the transfer of CagA protein into gastric epithelial cells through a cell surface receptor called CEACAM (carcinoembryonic antigen-related cell adhesion molecule). However, the exact mechanism by which HopQ's interaction with CEACAm facilitates CagA transfer is unclear. Once inside gastric epithelial cells, CagA alters normal cell signaling and promotes inflammation. This also causes DNA damage, which increases the risk of gastric cancer.[25]

*H. pylori* produces intracellular urease, around 10% of the total protein produced, indicating that it's crucial to the bacteria's survival. Urease is also found extracellularly and contributes to the external neutralization of stomach acid. Urease-catalyzed urea hydrolysis into ammonia (NH3) and carbon dioxide ($CO_2$). Ammonia neutralizes the stomach acidity around the bacteria, while carbon dioxide helps maintain a balanced pH around the bacteria. $NH_3$ and $CO_2$ production are necessary for creating an environment for *H. pylori*'s survival. Ammonia production can disrupt cell junctions and damage the gastric epithelium.[14] Urease was recently found to contribute to tumor growth by promoting angiogenesis.[17] *H. pylori* urease can also activate the PI3K-AKT-mTOR, a major signaling pathway in regulating cell growth and cell cycle in gastric cells. Increased mTOR activity increases the level of a protein called HIF-1α, and urease was found to trigger the differentiation of endothelial cells by generating reactive oxygen species and activating lipoxygenase, an inflammatory pathway.[14] These mechanisms aid *H. pylori*'s survival in the stomach's acidic environment while simultaneously increasing the risk of gastric cancer.

*H. pylori* is a spiral organism, but coccoid forms can be found, depending on environmental conditions, including pH. *H. pylori* exists in its spiral form, known as spiral viable culturable form (SVCF), only under favorable conditions; it is capable of causing infections. However, under harsh conditions, *H. pylori* can transform into its coccoid form known as coccoid viable non-culturable form (CVNCF), which can persist for a prolonged time, enabling it to survive under unfavorable conditions. Due to this unique mechanism, the spiral/helical shape promotes motility through the corkscrew mechanism. This mechanism and flagellar motility allow *H. pylori* to migrate quickly to the gastric epithelial surface.[28]

The flagellum of *H. pylori* allows the bacterium to move efficiently through the basal layer of the gastric epithelium. In this context, the flagellum is a virulence factor because its increased motility enables initial colonization. In addition, once *H. pylori* moves through the basal layer of the stomach, it can obtain nutrients and metabolic substrates from the host's cells and release toxins to damage the host cells, contributing to gastric cancer.[19]

***H. Pylori Virulence and Links to Stomach Cancer:***

Virulence factors are molecules or structures produced by pathogens, such as bacteria, viruses, or fungi, enabling them to infect and cause disease in a host. *H. pylori*'s virulence factors trigger several mechanisms that allow it to invade, colonize, and stimulate inflammation within the gastric mucosa. The severity of *H. pylori* infections is associated with the type of virulence factors expressed since they control and regulate inflammatory responses, promoting immune evasion. The sequence of events that occur in *H. pylori* colonization and infection is shown in Figure 2.[15]

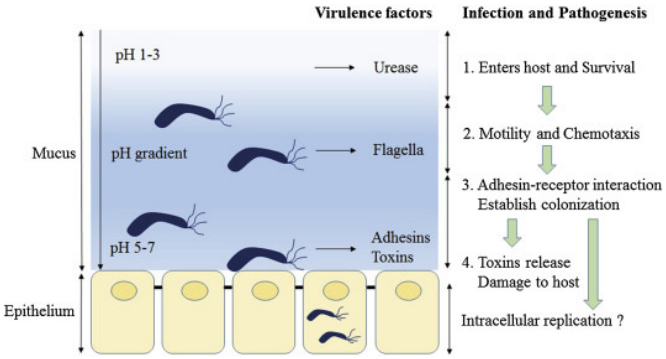


**Figure 2:** *H. pylori* infection and pathogenesis. Flagella-mediated motility, adhesions, toxins, and urease production contribute to successful bacterial colonization, which leads to the survival of *H. pylori* in the stomach.

Major toxins that *H. pylori* releases are cytotoxin-associated gene product A (CagA), vacuolating cytotoxin A (VacA), and high-temperature requirement A (HtrA). Important adhesions that mediate binding of *H. pylori* to gastric cells are blood group antigen-binding adhesion (BabA), outer inflammatory protein (OipA), outer membrane protein (OMP), outer membrane vesicles (OMV), neutrophil-activating protein A (NapA), and sialic acid-binding adhesins (SabA), as shown in Figure 3.[18]

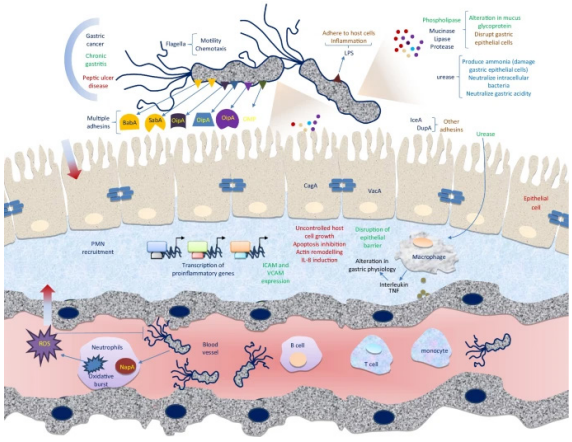

**Figure 3:** Pathogenic mechanisms of *H. pylori*. Four key stages are involved in H· pylori colonization: adapting to the stomach's acidic environment, moving to the epithelial cells, penetrating and attaching to the epithelial cell barrier, and causing tissue damage.

Once *H. pylori* successfully colonizes the gastric epithelium, the toxins produced by *H. pylori* damage host tissues. The damage triggers the immune system to release signaling molecules called chemokines. Chemokines recruit neutrophils to the infection area, which causes inflammation.[18] They are also involved in promoting angiogenesis and influencing tumor growth.[26]


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Bacterial colonization triggers humoral and cellular responses by recruiting immunoinflammatory cells such as lymphocytes, neutrophils, etc. This damages the stomach's epithelial cells. In addition, *H. pylori* causes NF-kB activation, which leads to long-term chronic infection. NF-kB is a proinflammatory pathway activated to release various proinflammatory cytokines and chemokines, playing a role in evading apoptosis.[27]

CagA (cytotoxin-associated gene A) protein is highly immunogenic and is present in around 50 to 70% of *H. pylori* strains. The CagA protein is part of a larger genomic element called the cag pathogenicity island (PAI). The PAI encodes components of the Cag T4SS, which is required for the translocation of CagA from the bacteria into host cells. It was found that patients with CagA+ strains have an increased inflammatory response, leading to a higher risk of developing gastric cancer.[21] The CagType 4 secretion system (-T4SS) is encoded for genes on the cag PAI, and it functions to inject the CagA protein directly into the gastric epithelial cells.[25]

CagA is then phosphorylated at a specific motif (EPIYA), enabling it to bind to the SHP-2 protein. This activates oncogenic signaling processes, which cause abnormal changes to cell polarity, cell proliferation, proinflammatory responses, etc., which is shown in Figure 4.[16]

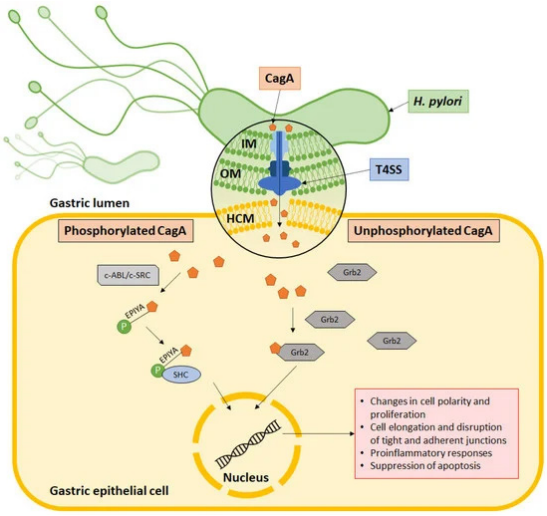


**Figure 4:** Bacterial virulence factor, CagA. Cag PAI influences *H. pylori*'s pathogenicity by facilitating the transfer of virulence factors, including CagA, into the host cells.

The Cag PAI influences *H. pylori*'s pathogenicity by facilitating the transfer of virulence factors into cells. Non-phosphorylated CagA from *H. pylori* can manipulate cell signaling by disrupting E-cadherin (a cell adhesion protein) and β-catenin interactions. Non-phosphorylated CagA binds to E-cadherin, which results in the dissociation of the E-cadherin-β-catenin complex.[16] The E-cadherin-β-catenin complex is important for maintaining epithelial integrity.[23] B-catenin accumulates in the cytoplasm and moves to the nucleus to form a complex with Tcf (T cell factor). This activates the transcription of genes, including Cyclin D1 and c-Myc, which promote cell growth and division. Non-phosphorylated CagA also interacts with SOS (guanine nucleotide exchange factor) to activate the Ras/MEK/ERK pathway. The Ras/MEK/ERK pathway is a signaling cascade that regulates cellular functions, but dysregulation can lead to cancer.[25] Overall, this leads to loss of cell polarity, mitogenic responses, and proinflammatory signaling involved with gastric cancer development. CagA protein was also found to promote DNA double-stranded breaks and activate Hippo signaling (a pathway that regulates cell proliferation and apoptosis), contributing to genome instability, and is involved in cancer development. CagA was further observed to induce epithelial-mesenchymal transition (EMT), a cellular process that increases tumor invasiveness and metastatic activity.[22] Along with the activation of YAP (Yes-associated protein) signaling, this accelerates carcinogenesis and the spread of cancer.[16]

Once CagA is injected inside the cell, it can be phosphorylated and bind to a phosphatase known as SHP-2. This binding can influence cell adhesion, spread, and migration. In addition, CagA can affect host cell behavior by inducing cytoskeleton rearrangements and cell proliferation. Nonphosphorylated CagA can activate the phosphatidylinositol 3-kinase/Akt pathway, which promotes gastric cell proliferation and leads to the development of chronic gastritis and eventually, gastric cancer.[19]

VacA causes vacuolization (formation of vacuoles that disrupts cell function), necrosis (induces cell death), and apoptosis. VacA can integrate into the host cell membrane and act as an anionic selection channel to release bicarbonate and organic anions into the cytoplasm. As a result, it can help *H. pylori* colonization by providing metabolic substrates for growth. VacA can also target various organelles within the host cells; for example, it can enter the endosome to release cytochrome C and trigger apoptosis. In addition, it was observed that VacA can cause stress in the endoplasmic reticulum (ER). This further promotes apoptosis in gastric epithelial cells, which can influence gastric atrophy and cancer development.[19] Furthermore, another virulence protein called OipA is known to adhere to gastric epithelial cells, causing mucosal damage and host cell apoptosis. It was also found that OipA-positive strains improved CagA's translocation, contributing to cell proliferation and damage.[14]

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***H. pylori*-Induced Prolonged Inflammation and Its Link to Stomach Cancer:**

Prolonged inflammation of the gastric tissue due to *H. pylori* generates large amounts of nitric oxide, which can damage the gastric epithelial cells.[6] In addition, *H. pylori* secretes a bacterial protein called *H. pylori* neutrophil-activating protein (HP-NAP), which can activate neutrophils (a type of white blood cell) and influence immune responses that contribute to tissue damage and cancer development. Once HP-NAP activates neutrophils, it generates reactive oxygen species (ROS) and reactive nitrogen species (RNS) to adhere to endothelial cells. ROS and RNS induced by *H. pylori* can cause DNA damage and mutations, which can lead to gastric cancer.

*H. pylori* infections can trigger DNA damage in host cells, negatively affecting how DNA repair processes work, resulting in genetic instability and chromosomal abnormalities.[19] The *H. pylori* protein HP-NAP activates neutrophils, which produce ROS and RNS.[20] Overproduction of ROS and RNS induces several types of DNA damage, including point mutations, DNA adducts, 8-OHdG, and DSB (single or double-strand DNA breaks). APE1 is a crucial protein that helps cells respond to oxidative stress by repairing damaged DNA. However, *H. pylori* can alter normal APE1 functions, including DNA repair and gene regulation, in various ways. Although increased oxidative stress from *H. pylori* infection can increase APE1 levels to repair DNA damage, a chronic *H. pylori* infection can eventually reduce APE1 expression, which results in genetic instability. In addition, genetic and epigenetic changes can impact the repair of DNA. Altogether, these changes cause inaccurate DNA repair, genomic instability, and chromosomal aberrations, which promote gastric cancer.

## Conclusion

This review depicts the importance of *H. pylori* motility, virulence factors, and inflammatory response and their links to stomach cancer. About 50% of the world's population and approximately 30-40% of the population in the US are infected with *H. pylori*. Recent improvements in *H. pylori* infection rates are largely due to improved hygiene and reduced transmission. However, novel treatment mechanisms are necessary to combat resistance, and much remains unknown about *H. pylori*'s pathogenicity and its link to stomach cancer. In this respect, the flagella's structure may be a crucial target for successful bacterial eradication. Associated mechanisms such as urease production and inflammatory responses or toxins (CagA, VacA, etc.), differences in shapes, and DNA damage influence the severity of *H. pylori* infections and thus, cancer formation. Therefore, further research on *H. pylori*'s pathogenic mechanisms, including the role of flagella, can allow for more effective personalized treatment methods and prevention.

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