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Helicobacter Pylori and Gastric Carcinogenesis: Mechanisms, Clinical Implications, and Preventive Strategies

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Abstract. Helicobacter pylori is a spiral shaped Gram-negative bacterium that colonizes the human stomach and persists for decades when untreated. Infection is common worldwide, especially in East Asia and parts of South America, and it is the strongest established risk factor for non-cardia gastric adenocarcinoma. In 1994 the International Agency for Research on Cancer classified the organism as a Group I carcinogen, which placed a common bacterial infection at the center of cancer prevention. The pathway from infection to carcinoma proceeds along Correa's cascade, beginning with chronic active gastritis and advancing through atrophic gastritis, intestinal metaplasia, dysplasia, and invasive cancer. Carcinogenesis reflects an interplay between virulence factors such as CagA and VacA, persistent inflammation with immune evasion, and durable epigenetic and genomic injury that remodels transcriptional programs in the gastric epithelium. Clinical evidence indicates that eradication therapy reduces cancer incidence, although benefit declines once advanced precancerous changes are established. This review synthesizes mechanistic and clinical data, outlines the epidemiology and pathology of infection associated with cancer, assesses the impact of eradication at individual and population levels, and evaluates diagnostics and risk markers that can focus surveillance. It also considers challenges that include antibiotic resistance and microbiome consequences, and it discusses future directions such as precision prevention, biomarker-based triage, and vaccine development. A coherent strategy that integrates molecular understanding with public health practice can reduce the global burden of gastric cancer in diverse settings.

Keywords: helicobacter pylori, gastric garcinogenesis, mechanisms, clinical implications, preventive Strategies

1. Introduction

Gastric cancer remains a major global health challenge. It ranks among the top causes of cancer related death and continues to impose disproportionate mortality in East Asia, Eastern Europe, and selected regions of South America. More than one million new cases are diagnosed annually worldwide. Many patients are present at advanced stages because early disease is often silent or nonspecific, which limits curative options. Prevention and early interception therefore carry unusual importance compared with many other solid tumors. Within the spectrum of risk factors that include

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tobacco use, high salt intake, nitrosamine exposure, and hereditary syndromes, Helicobacter pylori stands apart because it is both common and causally linked to most non-cardia gastric cancers.

Infection is typically acquired in childhood through fecal oral oral oral transmission, and in the absence of therapy the organism persists. Prevalence exceeds seventy percent in many low- and middle-income countries and remains high in older birth charts even in wealthy nations where cohort effects and improved sanitation have lowered incidence in younger people. The geographical overlap between infection and cancer is striking. Countries with high prevalence often display higher background rates of non-cardia cancer, and within countries the burden is greater in communities with crowding and limited access to clean water. These features make the organism a compelling target for prevention because a single course of therapy can extinguish a decades long inflammatory stimulus. At the same time, the benefit of eradication depends on the timing of intervention and on the extent of preneoplastic change at the time of cure. Once intestinal metaplasia or dysplasia has taken hold, the mucosa carries an epigenetic scar that attenuates risk reduction even when the organism is cleared. These realities push prevention upstream toward earlier stages and motivate risk stratification to identify individuals who will gain the most from treatment and from endoscopic surveillance.

2. Mechanistic insights into Hp-driven carcinogenesis

2.1. Virulence determinants and epithelial signaling

The organism’s capacity to transform the gastric mucosa depends heavily on virulence factors that reprogram epithelial behavior [1]. The cytotoxin associated gene A protein is the best studied example [2]. It is delivered into epithelial cells by a type IV secretion system and becomes tyrosine phosphorylated by Src and Abl kinases [3]. Phosphorylated CagA binds the SHP2 phosphatase and drives Ras ERK activation, leading to increased proliferation and motility. CagA also perturbs the Wnt beta catenin pathway and promotes nuclear accumulation of beta catenin, which enhances transcription of genes such as cyclin D1 and c-MYC. It influences the JAK STAT and PI3K AKT axes and interferes with polarity complexes, which contributes to loss of junctional integrity. Even in the absence of phosphorylation, CagA interacts with junctional proteins and receptor tyrosine kinases in ways that disrupt orderly architecture. The vacuolating cytotoxin A provides complementary functions. It forms anion selective channels in endosomal membranes, triggers vacuolation, and induces mitochondrial dysfunction that can release cytochrome c. It suppresses T cell proliferation and interferes with antigen presentation. It also inhibits autophagy, which leads to intracellular accumulation and stabilization of CagA, thereby amplifying its signaling footprint. Adhesins such as BabA, OipA, and SabA complete this picture by anchoring the organism to mucosal glycoconjugates, increasing dwell time, and focusing inflammatory signaling at sites of contact. OipA stimulates interleukin 8 production by epithelial cells, which recruits neutrophils and sustains a pro inflammatory milieu.

2.2. Chronic inflammation, immune evasion, and DNA damage

Persistent colonization generates chronic active gastritis, the initiating lesion of Correa’s cascade, and decades of cohort studies confirm this sequence [4]. The inflamed mucosa contains neutrophils and macrophages that release reactive oxygen and nitrogen species, including superoxide, hydrogen peroxide, and nitric oxide [5]. These species generate oxidative lesions such as 8 oxo deoxyguanosine and produce single and double strand breaks. Inflammatory cytokines such as

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interleukin 1 beta and tumor necrosis factor alpha reduce gastric acidity and alter mucus properties, which facilitates colonization and deepens injury [6]. Repeated cycles of cell death and regeneration expand the pool of proliferating cells that can acquire and fix mutations. In parallel, the organism reshapes the immune microenvironment to permit persistence. Regulatory T cells expand and dampen effector responses. Programmed death ligand 1 is upregulated on epithelial and immune cells, which inhibits cytotoxic T cell function and resembles the immune checkpoint engagement observed in neoplasia. Dendritic cell maturation is skewed in a way that lowers bactericidal capacity. The result is an equilibrium in which inflammation persists, but clearance fails, and the cost of that equilibrium is cumulative genomic damage [7].

2.3. Epigenetic remodeling and the persistence of risk

Beyond direct DNA lesions, infection imprints long lasting epigenetic changes in the gastric epithelium. Promoter hypermethylation silences tumor suppressor genes including CDH1, p16, and RUNX3. Interleukin 1 beta and downstream pathways upregulate DNA methyltransferase 1 [8], creating a mechanistic link between inflammatory tone and methylation load. Histone modifications alter chromatin accessibility, which reshapes the transcriptional response to injury. Noncoding RNAs add a post transcriptional layer of regulation. MicroRNAs such as miR 21 and miR 155 increase and repress apoptosis and immune regulatory targets, while miR 375 falls and removes restraint on proliferation. These epigenetic signatures persist even after eradication and likely underline the observation that risk reduction is incomplete when therapy follows the establishment of intestinal metaplasia. The epithelium, in other words, remembers infection in its chromatin and noncoding RNA landscape.

3. Mechanistic insights into Hp-driven carcinogenesis

The infection’s clinical imprint is clearest in intestinal type gastric adenocarcinoma. This subtype follows the Correa sequence and often arises on a background of atrophy and intestinal metaplasia in older adults [9]. It predominates in regions with high prevalence and displays a more stepwise evolution that yields a window for prevention and surveillance. Diffuse type gastric carcinoma is less tightly linked to infection and is frequently associated with disruption of the CDH1 locus that encodes E cadherin [10]. Loss of adhesion produces poorly cohesive cells that infiltrate the stomach wall, which leads to linitis plastica and a worse prognosis. This subtype can arise in younger individuals and in some families in whom germline mutations define hereditary diffuse gastric cancer. The distinction matters because intestinal type disease provides an opportunity for microbe targeted prevention, while diffuse type tumors may not be preceded by an extended phase of metaplasia that lends itself to surveillance [11].

Risk is concentrated in identifiable populations. A first-degree family history of gastric cancer confers additional risk that compounds with active infection [12]. Diet modifies biology in accessible ways. High salt intake impairs mucus and increases epithelial permeability; it also raises expression of certain virulent determinants in the organism [13]. Low intake of fruits and vegetables remove antioxidant defenses against reactive species generated during inflammation. Tobacco smoke and heavy alcohol cause worsening oxidative stress and impair mucosal repair. Genetic polymorphisms in inflammatory pathways, including variants in IL1B, heighten the severity of gastritis and increase the likelihood of progression along Correa’s cascade. These modifiers interact with virulence to explain why outcomes vary so widely across and within populations that share exposure.

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A minority of gastric cancers follow alternative oncogenic routes. Epstein–Barr virus positive tumors account for roughly ten percent of cases and often occur without evidence of active colonization, and they show CpG island methylator phenotype with distinct immune profiles. They are enriched in the proximal stomach, display extensive CpG island methylation, and show high programmed death ligand 1 expression with a lymphoid stroma. Their immunobiology and therapeutic sensitivities differ from infection associated with intestinal cancers and illustrate that gastric cancer is a family of diseases rather than a single entity. Recognizing these subtypes clarifies why universal policies may need tailoring and why biomarker-based classification can guide therapy and surveillance.

4. Evidence for eradication and prevention strategies

Intervention trials and meta-analyses provide the strongest support for prevention. In patients who underwent endoscopic resection for early gastric cancer [14], randomized studies showed that post resection eradication reduced the incidence of metachronous cancers by about half over several years of follow up [15]. Community and workplace chores have demonstrated that eradication lowers incidence at the population level, with relative risk reductions on the order of forty to fifty percent. Absolute benefit varies with background incidence, adherence, and duration of observation. Importantly, the degree of risk reduction depends on histological context. When atrophy and intestinal metaplasia are absent or limited at the time of treatment, benefit is substantial. When extensive metaplasia or dysplasia is present, benefit diminishes, which supports the concept of a point of no return in which epigenetic scarring and clonal evolution blunt the impact of cure [16]. These findings compel early detection and treatment. They also justify continued surveillance in selected patients after eradication, particularly in high-risk regions and in individuals with a family history or with advanced preneoplastic change.

Population strategies align with regional burdens and resources. Japan and the Republic of Korea have integrated testing and treatment into organized screening frameworks that also include endoscopy. Some programs combine pepsinogen testing with questionnaire-based risk scoring to triage individuals into endoscopic evaluation. These approaches have contributed to declining mortality by shifting diagnosis earlier and by removing the inflammatory driver of field cancerization. In North America and much of Western Europe, where background incidence is lower and organized endoscopic screening is uncommon, guidance favors a targeted test and treatment strategy [17]. Priority groups include patients with dyspepsia who test positive, individuals with a first-degree family history, immigrants from high prevalence regions, and patients with gastric premalignant lesions. This calibrated approach aims to concentrate resources where the yield is greatest while limiting unnecessary antibiotic exposure.

The concept of precision prevention is gaining momentum. Bacterial genotyping that captures CagA serostatus and VacA alleles, combined with host genetic markers and serologic or tissue-based indicators of atrophy, can be assembled into multivariate risk tools. These tools can identify people who merit early eradication and continued surveillance. They can also identify low risk individuals who can be safely managed with treatment alone. As simple and scalable biomarkers become available, prevention programs can move beyond binary infection status to a more nuanced triage that delivers the right intervention at the right time.

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5. Diagnostics and emerging biomarkers

Rational prevention depends on accurate diagnosis and informative risk stratification. Invasive diagnosis with endoscopic biopsy enables histology and rapid urease testing and allows cultures that reveal antibiotic susceptibility. Culture directed therapy improves outcomes in refractory cases but requires laboratory infrastructure that is not always available. Noninvasive testing supports primary care and public health programs. The urea breath test offers high sensitivity and specificity for active infection and is preferred for post treatment confirmation when medications that suppress urease activity are withheld for an adequate interval. Stool antigen testing provides a practical alternative that fits existing clinical workflows and is useful in children. Serology can be informative in epidemiologic surveys or when pretest probability is high, but it cannot distinguish active from past infection, and it performs poorly for confirming cure.

Risk biomarkers extend diagnosis into prognosis. Serum pepsinogen I and II concentrations, and their ratio, reflect corpus atrophy and correlate with cancer risk. Gastrin levels capture antral physiology and, in combination with pepsinogens, can refine estimates of mucosal status. Tissue based methylation panels that include E cadherin and p16 measure epigenetic burden and may identify high risk mucosa after cure. Circulating microRNAs such as miR 21 and miR 106a, and assays of cell free DNA methylation patterns, are being explored as noninvasive markers that can flag dangerous field effects before lesions are visible endoscopically. In high incidence regions, combinations of these markers could triage individuals into surveillance endoscopy at intervals tailored to risk. In lower incidence settings, they could sharpen the selectivity of endoscopy and improve the efficiency of limited resources.

6. Challenges and future directions

Antibiotic resistance is the most immediate obstacle to translating trial efficacy into real world effectiveness. Clarithromycin resistance now exceeds thresholds that make empirical triple therapy unacceptable in many regions, and levofloxacin resistance has risen with widespread use. Bismuth based quadruple therapy achieves higher cure rates in resistant settings. Regimens that include potassium competitive acid blockers such as vonoprazan raise intragastric pH more effectively than proton pump inhibitors and can improve eradication rates. Wider access to susceptibility testing, either through culture or molecular assays that detect resistance mutations, would enable rational regimen selection. Stewardship that reduces unnecessary macrolide exposure for unrelated infections can slow resistance growth. Investment in new therapeutics that target virulence rather than viability may reduce selection pressure while disarming carcinogenic mechanisms.

Changes in the microbiome represent a more subtle challenge. Eradication alters gastric acidity and microbial communities in the stomach and intestine. Most shifts appear transient and the reduction in cancer risk outweighs potential dysbiosis. Nonetheless, research continues to examine links between eradication and reflux disease, small intestinal bacterial overgrowth, and metabolic outcomes. Probiotic adjuncts have been studied with mixed results. Narrower spectrum regimens, if validated, could minimize collateral effects on commensals. A deeper understanding of how the gastric ecosystem recovers after cure may reveal ways to support mucosal resilience and to consolidate the preventive benefit of therapy.

Precision prevention will likely define the next decade. A risk algorithm might consider bacterial genotype, host genetic polymorphisms, family history, serologic evidence of atrophy, tissue methylation load, diet, and regional incidence. Such a model could produce actionable tires. A young adult with a high virulence strain, a low pepsinogen ratio, and a family history would receive

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prompt eradication and scheduled endoscopy, while an older adult in a low incidence region with infection but no biomarkers of atrophy could be treated and discharged without surveillance. As biomarker assays mature and costs fall, these individualized plans can be delivered at scale.

Vaccination remains an appealing long-term strategy. Recombinant urease-based vaccines and multicomponent formulations that target CagA and VacA have entered early clinical testing. The hurdles include eliciting durable mucosal immunity and designing trials that can demonstrate long term cancer prevention. Even partial efficacy could shift prevalence downward if delivered in childhood in high incidence regions. Combined with improved sanitation and targeted eradication, vaccination could reshape the epidemiology of infection and reduce the pool of adults at risk decades later.

An additional frontier is the intersection with immune oncology. Infection induces programmed death ligand 1 and creates an immune landscape that shares features with the tumor microenvironment. While checkpoint blockade therapy is established for a subset of advanced gastric cancers, its integration with prevention remains speculative. Nevertheless, understanding how eradication changes immune tone and antigen presentation might inform adjuvant strategies in patients after resection of early tumors or in those with high-risk lesions. EBV positive disease, with its strong immune signature, already illustrates how biomarker defined subtypes can guide the choice of systemic therapy and surveillance.

7. Conclusion

Helicobacter pylori is a common exposure that becomes a powerful carcinogenic driver in the right biological and environmental context. Virulence proteins rewire epithelial signaling, chronic inflammation produces persistent DNA injury, and epigenetic remodeling locks in transcriptional programs that outlast the organism. Clinical trials and population studies converge on the same conclusion that eradication reduces gastric cancer incidence, and that benefit is greatest when delivered before advanced preneoplastic change. The practical tasks are to detect infection accurately, to treat with regimens that overcome resistance, to stratify risk with biomarkers that capture mucosal status and epigenetic burden, and to enroll high risk individuals into surveillance programs that can intercept disease at a curable stage. Policy must adapt to regional circumstances. High incidence countries can integrate testing, treatment, and endoscopy into organized frameworks that have already shown value. Lower incidence countries can pursue targeted test and treat strategies that prioritize families with a history of cancer, immigrants from endemic regions, and patients with preneoplastic lesions. Over the long term, vaccines that blunt acquisition and reduce colonization promise to shift cohort risk. If prevention is guided by evidence and tailored to risk, the burden of gastric cancer can be reduced substantially across diverse populations.

References

[1] Abdullah, M., Greenfield, L. K., Bronte-Tinkew, D., Capurro, M. I., Rizzuti, D., & Jones, N. L. (2019). VacA promotes CagA accumulation in gastric epithelial cells during Helicobacter pylori infection. Scientific reports, 9(1), 38..

[2] Yao, Y., Ding, Y., Bai, Y., Zhou, Q., Lee, H., Li, X., & Teng, L. (2021). Identification of Serum Circulating MicroRNAs as Novel Diagnostic Biomarkers of Gastric Cancer. Frontiers in genetics, 11, 591515.

[3] Kanizaj, T. F., & Kunac, N. (2014). Helicobacter pylori: future perspectives in therapy reflecting three decades of experience. World journal of gastroenterology, 20(3), 699–705.

[4] Correa P. (1988). A human model of gastric carcinogenesis. Cancer research, 48(13), 3554–3560.

[5] Song, J. H., Yang, S. Y., Lim, J. H., Choi, J. M., & Kim, S. G. (2017). The Effect of Helicobacter pylori Eradication on the Metachronous Neoplasm after Endoscopic Resection for Gastric Dysplasia. The Korean journal of

DOI: 10.54254/2753-8818/2025.AU27174

gastroenterology = Taehan Sohwagi Hakhoe chi, 70(1), 27–32.
[6] Ford, A. C., Yuan, Y., & Moayyedi, P. (2020). Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut, 69(12), 2113–2121.
[7] Walduck, A. K., & Raghavan, S. (2019). Immunity and Vaccine Development Against Helicobacter pylori. Advances in experimental medicine and biology, 1149, 257–275.
[8] Hatakeyama M. (2014). Helicobacter pylori CagA and gastric cancer: a paradigm for hit-and-run carcinogenesis. Cell host & microbe, 15(3), 306–316.
[9] Tay, S. W., Li, J. W., & Fock, K. M. (2021). Diet and cancer of the esophagus and stomach. Current opinion in gastroenterology, 37(2), 158–163.
[10] Wang, F., Meng, W., Wang, B., & Qiao, L. (2014). Helicobacter pylori-induced gastric inflammation and gastric cancer. Cancer letters, 345(2), 196–202.
[11] LAUREN P. (1965). THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. AN ATTEMPT AT A HISTO-CLINICAL CLASSIFICATION. Acta pathologica et microbiologica Scandinavica, 64, 31–49.
[12] Kim, H. J., Kim, Y. J., Seo, S. I., Shin, W. G., & Park, C. H. (2020). Impact of the timing of Helicobacter pylori eradication on the risk of development of metachronous lesions after treatment of early gastric cancer: a population-based cohort study. Gastrointestinal endoscopy, 92(3), 613–622.e1.
[13] Malfertheiner, P., Megraud, F., O'Morain, C. A., Gisbert, J. P., Kuipers, E. J., Axon, A. T., Bazzoli, F., Gasbarrini, A., Atherton, J., Graham, D. Y., Hunt, R., Moayyedi, P., Rokkas, T., Rugge, M., Selgrad, M., Suerbaum, S., Sugano, K., El-Omar, E. M., & European Helicobacter and Microbiota Study Group and Consensus panel (2017). Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut, 66(1), 6–30.
[14] Maekita, T., Nakazawa, K., Mihara, M., Nakajima, T., Yanaoka, K., Iguchi, M., Arii, K., Kaneda, A., Tsukamoto, T., Tatematsu, M., Tamura, G., Saito, D., Sugimura, T., Ichinose, M., & Ushijima, T. (2006). High levels of aberrant DNA methylation in Helicobacter pylori-infected gastric mucosae and its possible association with gastric cancer risk. Clinical cancer research : an official journal of the American Association for Cancer Research, 12(3 Pt 1), 989–995.
[15] Megraud, F., Bruyndonckx, R., Coenen, S., Wittkop, L., Huang, T. D., Hoebeke, M., Bénéjat, L., Lehours, P., Goossens, H., Glupczynski, Y., & European Helicobacter pylori Antimicrobial Susceptibility Testing Working Group (2021). Helicobacter pylori resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. Gut, 70(10), 1815–1822.
[16] Yang, J., Liu, Z., Zeng, B., Hu, G., & Gan, R. (2020). Epstein-Barr virus-associated gastric cancer: A distinct subtype. Cancer letters, 495, 191–199.
[17] Wang, H., Wang, L., Wu, Z., Sun, R., Jin, H., Ma, J., Liu, L., Ling, R., Yi, J., Wang, L., Bian, J., Chen, J., Li, N., Yuan, S., & Yun, J. (2014). Three dysregulated microRNAs in serum as novel biomarkers for gastric cancer screening. Medical oncology (Northwood, London, England), 31(12), 298.