SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 9
Issue: 5
Page N. 309-315
Year: 2025

Original Article www.wjahr.com

GASTRIC CANCER UNDER THE MICROSCOPE: FROM SILENT RISK TO STRATEGIC MANAGEMENT

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Article Received date: 20 March 2025 **Article Revised date:** 10 April 2025 **Article Accepted date:** 30 April 2025

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ABSTRACT

The etiology of gastric cancer is complex and multifactorial, involving environmental and host-related factors, as well as genetic and epigenetic changes. Helicobacter pylori infection is necessary but not sufficient for the development of gastric cancer. The annual incidence of gastric cancer is 0.1% in patients with chronic atrophic gastritis, 0.25% in those with gastric intestinal metaplasia, 0.6% in those with mild to moderate gastric epithelial dysplasia, and 6.0% in those with severe gastric epithelial dysplasia within 5 years of diagnosis. The most widely used histological classification of gastric cancer is the Lauren classification, which identifies three subtypes: diffuse (33%, arising from normal gastric mucosa), intestinal (53%, glandular origin and associated with chronic atrophic gastritis and intestinal metaplasia), and mixed (14%). Eradicating H. pylori infection and early detection of precancerous gastric lesions in the general population, along with appropriate treatment and monitoring, are key strategies for prevention, early diagnosis, reduced mortality, improved survival, and enhanced quality of life. Nevertheless, precancerous gastric lesions are frequently overlooked in clinical practice, resulting in variable surveillance and treatment practices and suboptimal risk stratification.

KEYWORDS: gastric adenocarcinoma, gastric cancer, risk factors, Helicobacter pylori, epidemiology, classification, management.

INTRODUCTION

Over the past century, the incidence of gastric cancer (GC) has steadily and significantly declined by 2–3% annually, especially in Western countries. This trend is attributed to improved hygiene standards, healthier dietary habits, effective eradication and reduced prevalence of *Helicobacter pylori* (HP) infection, and GC screening, particularly in younger cohorts. However, the disease remains a significant global health burden and one of the leading causes of cancer-related death worldwide.[1–8]

It is estimated that the absolute number of new GC cases will continue to rise due to global population growth and aging, increased prevalence of risk factors (RFs)—particularly among individuals under 50—and population expansion in developing countries with high GC incidence.[9] In this context, a significant increase in GC incidence has been reported among individuals aged 25–39 years.[4]

According to the latest global statistics, GC ranks among the most common cancers, with marked worldwide variability, accounting for 5.5% of all new cancer cases. Moreover, it is the fourth most common malignancy and the second leading cause of cancer-related death, contributing to 7.7% of all cancer deaths globally. The highest incidence is seen in older men, although rising rates have been reported in younger patients (<50 years) in recent years.[1, 6, 10–12]

Given this background, this article aims to provide a narrative synthesis of current studies, reviewing contemporary concepts regarding the epidemiology, classification, diagnosis, and management of patients with gastric adenocarcinoma, with the goal of outlining effective prevention strategies.

MATERIALS AND METHODS

To meet the objective, a comprehensive search was conducted using Google Search and databases such as PubMed, Hinari (Health Internet Work Access to Research Initiative), SpringerLink, the National Center

for Biotechnology Information, and Medline. The inclusion criteria focused on contemporary data concerning the epidemiology, classification, diagnosis, and management of patients with gastric adenocarcinoma. Keywords included: "gastric adenocarcinoma" and "gastric cancer," combined with "epidemiology," "clinical picture," "risk factors," "classification," "diagnosis," and "management" to maximize search yield.

Filters applied to refine the selection included: full-text availability, English language, and publication years between 1990 and 2024. After an initial title review, original articles, editorials, narrative and systematic reviews, and meta-analyses relevant to the scope of the study were selected. References from the identified articles were also reviewed to find additional relevant publications not retrieved in the initial database search.

The information from included publications was collected, classified, evaluated, and synthesized, highlighting the main aspects of current perspectives on the epidemiology, clinical features, risk factors, classification, diagnosis, and management of gastric adenocarcinoma. To minimize the risk of systematic errors (bias), comprehensive searches were performed, only valid studies were considered, and strict exclusion criteria were applied.

Additional sources were consulted as needed for clarification of specific concepts. Duplicate publications, articles irrelevant to the topic, and those not available for full review either through HINARI or the university's scientific medical library were excluded.

RESULTS AND DISCUSSION

Data Processing and Article Selection

Following the processing of information identified through the Google Search engine and databases such as PubMed, Hinari, SpringerLink, the National Center for Biotechnology Information, and Medline, based on defined search criteria, a total of 315 articles addressing the epidemiology, clinical presentation, risk factors, classification, diagnosis, and management of patients with gastric cancer (GC) were found.

After an initial review of titles, 52 articles were deemed potentially relevant for the current synthesis. Upon further detailed examination, 40 publications were ultimately selected as relevant to the proposed aim. These 40 articles were included in the final bibliography and considered representative of the materials published on the topic of this review article.

Publications whose content did not reflect the selected topic, although initially retrieved by the search engines, as well as articles that were not accessible either freely or through the HINARI database or available at the scientific medical library of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, were excluded from the final list.

Definition

Gastric cancer is a malignant epithelial neoplasm with glandular differentiation arising from the gastric mucosa. It represents a biologically heterogeneous group of tumors with respect to etiology, histogenesis, morphology, and molecular characteristics. Overall, gastric adenocarcinoma accounts for 90–95% of all gastric malignancies.[13, 14, 15]

Epidemiology

The disease is often asymptomatic in its early stages, when survival rates can exceed 90% with surgical or minimally invasive endoscopic intervention.[12]

The vast majority of GC cases (approximately 75% of all new GC cases and 80–90% of non-cardia GC cases) are associated with Helicobacter pylori (HP) infection.[4, 7, 12, 13, 16] Moreover, over 70% of all GC cases occur in developing countries.[7]

The incidence of GC shows significant global variation, with the highest rates observed in East Asia**,** Central and Eastern Europe**,** and South America. Over the last 60 years, a gradual decline in GC incidence has been observed in **Western Europe** and **North America**, with more recent declines also reported in **high-risk countries**.[10, 17]

Globally, approximately **990,000 people** are diagnosed with GC annually, and about **738,000** die from the disease. The incidence rate is **about twice as high in men** compared to women and increases progressively with age — the average age at diagnosis being **60–70 years**. However, approximately **10%** of gastric carcinomas are detected in individuals under **45 years old**.[7, 10]

The **5-year survival rate** is relatively good **only in Japan**, where it reaches up to **90%**, likely due to early detection through endoscopic examinations and prompt tumor resection. In **European countries**, survival rates range between **10% and 30%**.[1,10] The recent epidemiological changes in GC highlight the need for further cancer control efforts, with **primary and secondary prevention** being the main focus, given the poor prognosis in many parts of the world.[6]

The **annual incidence** of gastric cancer (GC) was **0.1%** among patients with **chronic atrophic gastritis (CAG)**, **0.25%** in those with **gastric intestinal metaplasia (GIM)**, **0.6%** in patients with **mild to moderate gastric epithelial dysplasia (GED)**, and **6.0%** in those with **severe GED**, within **five years** after diagnosis.[18]

A **nationwide Dutch cohort study** found that the **10-year risk** of GC in patients with mild to moderate and severe GED was **3.9%** and **32.7%**, respectively.[2, 18]

In a **rural Chinese cohort** from a high-risk area for GC, the progression rates of **precancerous gastric lesions (PGLs)** were assessed: among patients with mild or moderate-to-severe GED, the **5-year risk** of GC was **2.8%** and **7.0%**, respectively.[2]

These data suggest that **gastric cancer is strongly associated** with **severe epithelial dysplasia** of the gastric mucosa compared to mild-grade dysplasia, and such patients represent the **ideal target population for GC surveillance programs**.[2, 19]

Risk Factors. Gastric cancer (GC) is one of the most common and aggressive types of cancer worldwide, and the molecular mechanisms remain largely elusive. In the past two decades, there has been a broad paradigm shift in the understanding of GC and its pre-malignant states, moving from histological models to increasingly precise molecular descriptions. Both **precancerous gastric lesions (PGL)** and GC are associated with a spectrum of genetic and epigenetic abnormalities. Genetic factors mainly refer to cancer susceptibility genes, which are involved in multiple genetic and epigenetic modifications of oncogenes, tumor suppressor genes, cell cycle regulators, and DNA repair genes.[14, 20, 21, 22, 23, 24, 25]

Although the carcinogenic mechanisms of Helicobacter pylori (HP) infection are not fully understood, two distinct mechanisms are involved. HP infection induces persistent inflammation, accompanied by **hyperproliferation of gastric epithelial cells**, progression of pre-neoplastic gastric conditions, and DNA damage (indirect mechanism). The second pathway involves the direct action of HP **cytotoxins** on gastric epithelial cells. Two virulence factors extensively studied are **CagA** and **VacA cytotoxins**, which play a crucial role in the pathogenicity of HP infection. These virulent strains contribute to gastric carcinogenesis through **immunosuppressive activities**, promoting bacterial survival and maintaining inflammation in the stomach, and are associated with **PGL** and progression to a malignant phenotype.[15, 26]

Intestinal-type gastric adenocarcinoma represents the final stage of a prolonged precancerous process, called **Correa's cascade of gastric carcinogenesis in multiple stages**. The pathogenesis of GC includes a sequence of events that begins with **superficial chronic gastritis** (non-atrophic), induced by HP, progressing to **chronic atrophic gastritis** (initially limited to the body or antrum, later multifocal), **gastric intestinal metaplasia** (initially "complete" and then "incomplete"), **gastric epithelial dysplasia** or **intraepithelial neoplasia** (initially mild and then severe), and GC. It is believed that progression to gastric epithelial dysplasia and GC are processes that no longer require the presence of HP.[3, 15]

However, HP infection alone is not sufficient to cause GC, which develops only in a minority of infected individuals. Gastric adenocarcinoma is a multifactorial condition and results from the complex interaction between an individual's genetic susceptibility and environmental factors.[7, 15, 27, 28, 29] The major risk factors (RF) for GC and PGL have been classified into three main categories:

1. **Genetic RF**. Single nucleotide polymorphisms (SNPs) in interleukin genes (IL-1β-511T, IL-1β-31C, IL-1β-3954, IL-1-RN2, IL-4-R-398, IL-8-251, IL-10T-819C, IL-18RAP917997, IL-22-rs1179251, and IL-32-rs2015620 (AA or AT)) are genetic susceptibility factors associated with individual or familial susceptibility to carcinogenesis mediated by HP infection (PGL and GC). However, the underlying mechanisms of tumorigenesis are largely unknown. Current data suggest that **IL-1β gene polymorphisms** may promote GC through their involvement in PGL and **hypochlorhydria**.
2. **Environmental RF**. Exposure to **radiation**, **toxins**, **cigarette smoke**, lifestyle habits, and dietary patterns (high intake of **salt-preserved**, **smoked foods**, **red and processed meats**, and low intake of **fresh fruits and vegetables**) are the most important environmental RFs.
3. **Biological RF**. **HP infection** and a family history of GC are the most significant biological RFs for GC. It is estimated that approximately **75%** of the global burden of GC is attributed to HP-induced inflammation. Based on strong evidence supporting the **etiological role** of HP infection in GC, in 1994, **HP** was classified by the **World Health Organization (WHO)** as a **Class I carcinogen** (a definite cause of human GC). Compared to other risk factors, **CAG** and **GIM** exponentially increase the risk of GC.[2, 4, 5, 21, 22, 26, 27, 28, 29]

Furthermore, recent advances demonstrate that **Helicobacter pylori (HP) infection** induces **IL-1β expression**, which, in turn, promotes gastric carcinogenesis by affecting both inflammatory and epithelial cells. HP infection has a **synergistic effect** with **IL-1β gene polymorphisms**.[27] **Antibiotic resistance** to HP infection, non-adherence, and failure to follow the treatment regimen are two common reasons for the failure to eradicate the infection. However, **IL-1β polymorphisms**, which are associated with a **lower gastric acid suppression** due to reduced IL-1β expression, despite confirmed antibiotic sensitivity and patient adherence to treatment, have been associated with a significantly higher probability of **HP infection eradication failure** (1.72 times).[30]

Both HP infection and **chronic atrophic gastritis (CAG)** have been significantly associated with GC. The progression of CAG tends to reduce the prevalence of HP but leads to a **constant increase in gastric cancer development**.[31]

Although the majority of gastric cancers are **sporadic**, up to **10%** are familial, and **1-3%** of all GC cases are hereditary.[5, 13, 14, 15, 32]

The genomic alterations involved in the **multi-step process of intestinal-type GC carcinogenesis** result from both genetic and epigenetic abnormalities, including:

1. **Silencing of tumor suppressor genes** (TP53, APC) and activation of **oncogenes** (HER2, EGFR);
2. **Genomic instability** through two distinct pathways: **microsatellite instability** and **chromosomal instability**; and
3. **Epigenetic alterations**.[3, 6, 14, 21, 22, 23, 24, 25]

It has been demonstrated that **HP infection** induces **promoter methylation** and silencing of the **E-cadherin gene** in **neoplastic gastric mucosa** and **GC**. **Methylation of neoplastic gastric mucosa** can be reversed after successful HP eradication. **Somatic mutations** of **E-cadherin** have been identified in **50-70%** of sporadic cases.[3] IL-1β expression decreases after **HP eradication**, followed by an increase in **gastric acidity**.[27]

The **genetic predisposition** for **non-hereditary GC** is difficult to assess because neither the actual prevalence of **precancerous gastric lesions (PGL)** in different populations nor the **environmental risk factors (RF)** for GC progression are clearly defined. The risk of GC increases with the severity of **PGL**. Early detection, appropriate treatment, and surveillance of precancerous changes in gastric mucosa are important for early detection and prevention of GC, leading to a significant reduction in the incidence of this disease.[4, 5, 17, 18] HP infection and **PGL** are increasingly recognized as **key targets** for GC prevention strategies.[4, 18, 26]

Classification. Depending on the depth of invasion into the gastric wall, gastric cancer (GC) is classified as **early** or **advanced**. **Early gastric cancer** is defined as a carcinoma limited to the mucosa or mucosa and submucosa, regardless of tumor size or the presence of lymph node metastasis. Gastric adenocarcinomas that invade the muscular layer and beyond are defined as **advanced**.[3, 13]

Over the years, numerous morphological and molecular classifications of GC have been proposed. Despite these efforts, the complexity of the disease has not led to the development of a unifying classification for GC. Two of the most widely accepted classifications of gastric adenocarcinoma are the **Lauren classification (1965)** and the **WHO classification (2010)**. Traditionally, the **WHO classification**, the most detailed among all classification systems, divides GC into 5 subtypes:

1. **Papillary** (features papillary architecture resembling fingers, sometimes mixed with glandular structures - **tubulo-papillary phenotype**);
2. **Tubular** (composed of tubular, glandular, or acinar structures of variable diameter and different degrees of differentiation);
3. **Mucinous** (defined by the presence of mucin pools representing >50% of the tumor);
4. **Poorly cohesive** (composed of isolated tumor cells or small groups with no cellular cohesion);
5. **Mixed** (features both distinct tubulo-papillary and poorly cohesive components).[1, 3, 4, 11, 13, 20, 28]

The most popular and frequently used classification for GC is the **Lauren classification**, which histologically divides GC into three subtypes:

1. **Diffuse** (33%, arises from normal gastric mucosa);
2. **Intestinal** (53%, originates from glands and is associated with **chronic atrophic gastritis (CAG)** and **intestinal metaplasia (IM)**);
3. **Mixed** (14%).

The **intestinal type** of GC is primarily caused by **environmental (exogenous)** factors. The **diffuse type** is primarily due to **hereditary and genetic (endogenous)** factors, caused by mutations in the **E-cadherin gene (CDH1)**, and is less associated with environmental factors and the inflammatory cascade. These classification systems are based on morphology. There are also other classifications based on molecular and genetic aspects.[1, 3, 4, 11, 13, 20, 28]

Diagnosis. Most **early gastric cancers** are asymptomatic at diagnosis. **Endoscopic examination** with biopsies is the standard method for diagnosing GC. The introduction of new endoscopic techniques has significantly facilitated the early detection of GC, increasing diagnostic yield. However, up to **10% of GC cases** are missed during **upper gastrointestinal endoscopy**.[7, 13, 33]

Early gastric cancer is limited to the mucosa or submucosa, regardless of lymph node status, and has an excellent prognosis with a 5-year survival rate of over **90%**. Even though early detection and treatment are possible, due to the asymptomatic progression and molecular and histological heterogeneity, the majority of GC cases are diagnosed at an **advanced stage**, leading to an overall **5-year survival rate** of around **20-30%** in most countries worldwide (an average survival of approximately **24 months**) and around **5%** for advanced disease.[2, 4, 5, 10, 20]

At the advanced stage of the disease, common signs and symptoms include **dyspepsia**, **epigastric pain**, **abdominal mass**, and **alarm symptoms** (dysphagia, significant weight loss, signs and symptoms of gastrointestinal bleeding, and vomiting).[13]

Management. Gastric cancer (GC) results from a combination of **environmental risk factors (ERFs)** and the accumulation of specific genetic changes.[1, 4, 5] Although managing environmental risk factors is the main way to reduce the incidence of GC, early detection

can improve the overall survival rate. For **early-stage GC**, **surgical resection** (endoscopic mucosal resection for lesions ≤10 mm in size, endoscopic submucosal dissection for lesions >10 mm in size) remains the cornerstone of curative treatment, reducing the need for invasive surgery. Treatment for advanced GC (a combination of surgery, chemotherapy, and radiotherapy) is palliative, improving quality of life and survival. Despite global trends showing a decline, prevention of GC remains a priority. Prevention of **Helicobacter pylori (HP) infection** and its timely eradication (before the development of extensive atrophic changes) are the most effective strategies to prevent the development of **gastric precancerous lesions (LGP)** and provide primary prophylaxis for GC. An attractive proposal to reduce the incidence of the disease is the identification of high-risk individuals who can benefit from screening, preventive, and therapeutic measures to prevent the onset of malignancy.[1, 2, 4, 5, 10, 17, 32, 33]

On the other hand, new therapeutic methods such as **immunotherapy**, alongside conventional methods (surgery, radiotherapy, chemotherapy, and hormone therapy), are included in the strategy for managing advanced GC, although the benefit of these approaches remains undetermined.[6, 17, 34, 35]

The current option for reducing the incidence and mortality caused by GC is based on the **eradication of HP infection**, maintaining a balanced diet, moderate alcohol consumption, smoking cessation, and maintaining a normal weight, diagnosing at a stage suitable for curative therapy, and timely and early treatment and monitoring of patients with **LGP** (gastric atrophic gastritis [GCA], intestinal metaplasia [IM], dysplastic epithelial changes [DEG]). Complex pathogenesis-based treatment of patients with **GCA** significantly reduces the risk and incidence of GC, may help detect GC at an early stage when surgery or chemotherapy offers a better prognosis, with 5-year survival rates exceeding **90-95%**. Therefore, identifying risk groups for GC development (patients with LGP), effective treatment, and careful monitoring of these patients is a priority for prevention, increasing the rate of early detection, and, implicitly, reducing morbidity and mortality from GC.[5, 10, 11, 13, 19, 29]

There is substantial evidence from high-quality international studies supporting both **primary prevention** (eradication of HP) and **secondary prevention** (GC screening), which contribute to reducing the incidence and mortality from GC. Population-based endoscopic screening for asymptomatic individuals is recommended only in regions with very high GC incidence.[8, 9, 11, 17, 29]

There is consistent evidence that **HP eradication** significantly reduces (by 41%) the risk of histological progression of LGP, which significantly contributes to a 39% reduction in the incidence of GC in healthy individuals, patients with GCA, and those with a family history of GC. A similar but statistically insignificant reduction in GC mortality has also been observed. These results suggest that HP eradication is effective in preventing GC.[5, 8, 9, 17, 31]

The risk of GC was 55% lower in first-degree relatives of GC patients who received treatment for HP eradication compared to those who were given a placebo during a 9.2-year follow-up. The risk of GC was 73% lower in those for whom HP eradication was successful than in those with persistent infection.[36]

A meta-analysis found that **HP eradication** halts the progression of precancerous conditions even after the onset of **intestinal metaplasia (IM)**. Two meta-analyses confirmed that HP eradication significantly reduces the risk of GC in patients with GCA or **chronic non-atrophic gastritis**, but not in patients with IM or DEG. Thus, the benefit is maximized when eradication is applied in the early stages of HP infection.[5]

There is evidence among asymptomatic healthy individuals infected with HP showing that HP eradication reduces the incidence of GC. A systematic review and meta-analysis of 6 international randomized controlled trials, published in 2014, compared the risk of developing GC in adults who tested positive for HP and underwent eradication therapy, placebo, or no therapy. The relative risk of developing GC was 34% lower among the 3,294 individuals who received eradication treatment compared to the 3,203 control subjects. Thus, to prevent 1 case of GC, **124 patients** need to be treated.[37]

Over 5 years after the publication of this systematic review, an update published in 2020 found that HP eradication therapy was superior to placebo or no treatment in preventing the development of subsequent GC. HP eradication reduced **GC mortality**. The risk of subsequent GC with HP eradication therapy was reduced by 46%, and **72 patients** needed to be treated to prevent one case of GC.[37]

A recent prospective, randomized, placebo-controlled study with 26.5 years of follow-up provided strong evidence that HP eradication therapy may offer long-term protection against GC in high-risk populations, particularly in individuals infected without advanced gastric lesions at baseline.[38]

Thus, there is consistent evidence suggesting that **HP eradication** is extremely beneficial for patients with **chronic non-atrophic gastritis** and GCA, both histologically and in reducing the risk of GC. In the later stages of gastritis (establishment of IM), weaker evidence suggests that HP eradication has beneficial histological effects (reduces inflammation and atrophy),

but no conclusive effect on reducing the risk of GC.[5, 8, 32, 39]

Although **HP eradication** is a feasible, effective, and potentially cost-effective method (especially in areas with high GC levels) for reducing the risk of developing subsequent gastric adenocarcinoma, its use has not yet been universally adopted. Furthermore, HP eradication has become a challenge due to the development of antibiotic resistance in this bacterium. Some studies have reported that approximately **1.0%** of patients still developed GC even after successful HP eradication. Thus, there remains a need for the development of new and effective treatments for HP infection, considering antimicrobial resistance in various regions of the world.[39, 40]

CONCLUSIONS

1. **The etiology of gastric cancer is complex and multifactorial**, involving environmental factors, host factors, as well as genetic and epigenetic changes. **Helicobacter pylori infection** is necessary but not sufficient for the development of gastric cancer.
2. The **annual incidence of gastric cancer** was 0.1% for patients with **chronic atrophic gastritis**, 0.25% for patients with **gastric intestinal metaplasia**, 0.6% for patients with **mild to moderate gastric epithelial dysplasia**, and 6.0% for patients with **severe gastric epithelial dysplasia** within 5 years of diagnosis.
3. The most popular and widely used classification of gastric cancer is **Lauren's classification**, which histologically divides gastric cancer into three subtypes: **diffuse** (33%, originating from normal gastric mucosa), **intestinal** (53%, originating from glands and associated with chronic atrophic gastritis and gastric intestinal metaplasia), and **mixed** (14%).
4. **Eradication of Helicobacter pylori infection** and early diagnosis of **precancerous gastric lesions** in the general population, along with treatment and monitoring of these patients, are crucial considerations for the **prevention**, **early identification**, and **reduction of gastric cancer mortality**, as well as for improving survival rates and the quality of life of patients. However, at present, **precancerous gastric lesions** are often neglected in clinical practice, resulting in a variable frequency of monitoring or treatment with suboptimal risk stratification.

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