Gastric Cancer Risk in Patients with *Helicobacter pylori* Infection and Following Its Eradication

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KEYWORDS

• *H pylori* • Gastric cancer risk • Gastric cancer prevention • Pepsinogens
• OLGA staging • Atrophic gastritis

KEY POINTS

- *Helicobacter pylori* is a first-class carcinogen; the eradication of the infection is a primary cancer-prevention strategy.
- In gastric mucosa, *H pylori* infection results in both (1) inflammation (ie, gastritis) and (2) structural modifications of the native anatomy/function (ie, precancerous lesions: atrophy/metaplasia, intraepithelial neoplasia [synonym dysplasia]).
- Anatomic changes are assessable by endoscopy/biopsy. Pepsinogen serology mirrors gastric mucosa atrophy with a high negative predictive value.
- Following *H pylori* eradication, the rate of reversion of the histology lesions decreases along with their increasing severity.
- Successful eradication invariably results in eliminating the *H pylori*–associated mucosal inflammation (ie, the inflammatory component of the mucosal damage).
- Mucosal atrophy and intestinal metaplasia may (at least partially) be reversed by *H pylori* eradication (the higher the gastritis stage, the lower/slower the reversion rate).
- Contradictory information is available on the benefit achievable by eradicating patients with advanced precancerous lesions (ie, intraepithelial neoplasia); beneficial effects have been reported only in association with low-grade lesions.
- In patients (endoscopically/surgically) treated for early gastric cancer, *H pylori* eradication delays/lowers the risk of metachronous cancers.
- The choice of eradicating is independent from both the severity of the mucosal damage and the (expected) rate of its reversibility; the mucosal status at eradication time only affects the timing/strategy of posteradication interventions (follow-up, ablation, surgical therapy).

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INTRODUCTION

The so-called epidemic or intestinal-type gastric cancer (GC) is the most frequent gastric neoplasia, and the fact that its (race-independent) incidence is declining throughout all developed countries supports the hypothesis that environmental factors play a major role in its cause. A second clinico-biological variant of GC is hereditary (ie, syndromic), and it is associated with specific mutational profiles; the epidemiologic impact of this variant is negligible.[1]

Irrespective of its morphologic/epidemiologic variants, GC is associated with a poor prognosis, with a 5-year overall survival rate lower than 30%.

The onset of intestinal-type GC is definitively associated with age (older than 50 years), which is consistent with the most accepted theory concerning the long natural history of GC. Chronic gastritis (mostly caused by *H pylori* infection) may represent the earliest phase of gastric oncogenesis. After several decades, long-standing inflammation extensively modifies the native gastric mucosa, creating a microenvironment prone to cancer development. This "cancerization field" consists of 2 main types of lesions: (1) inflammation of the gastric mucosa and (2) gastric mucosal atrophy characterized by both an absolute loss of resident glandular units and/or a metaplastic transformation (eg, intestinalization) of native glandular structures.[2] The metaplastic epithelium may further undergo dedifferentiation, acquiring most of the biological characteristics of neoplastic cells but still lacking invasion capability (intraepithelial neoplasia [IEN], formerly defined as dysplasia).[3] By acquiring stromal invasion capability, IEN ultimately progresses to invasive cancer.

GC's natural history, known as Correa oncogenic cascade, provides a biological rationale behind the multidisciplinary approach for primary and secondary prevention strategies.[4]

HELICOBACTER PYLORI INFECTION IS THE MOST IMPORTANT DETERMINANT OF GASTRIC CANCER RISK

As with most neoplastic diseases, GC is a multifactorial neoplasia. In most cases, environmental factors are the main cancer-promoting agents, but even in nonsyndromic (ie, sporadic) cancers, host-related factors are involved in cancer promotion.

Among all possible environmental factors, *H pylori* is consistently recognized as the leading etiologic agent of GC.[5] In 1994, *H pylori* was recognized as a type I carcinogen; it is currently considered the most common etiologic agent linked to infection-related cancers, which represent 5.5% of the global cancer burden.[6] **Fig. 1** outlines the most relevant etio-pathogenetic factors involved in sporadic GCs.

Globally, about 3.5 billion people have the *H pylori* infection, and solid evidence supports a fecal-oral and/or gastric-oral transmission pattern that takes place early in life.[7] The rates of *H pylori* infection vary considerably by geographic area, with a generally higher prevalence in developing countries.[8] A large percentage of those who are infected develop non–self-limiting gastric inflammation; approximately 10% develop peptic (duodenal or gastric) ulcers; 3% develop gastric adenocarcinoma, with less than 0.5% developing mucosa-associated lymphoid tissue lymphoma.

The variable outcome of the infection probably depends on the infection's bacterial properties, on environmental cofactors, as well as on host-related immune response modulation.[9] All these variables must be taken into consideration when GC risk following *H pylori* eradication is being assessed.[10]