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Atrophic gastritis of distinct etiologies: malignant potential in *Helicobacter pylori*-associated and autoimmune forms

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Abstract

Atrophic gastritis is an important step in the Correa cascading pathway. It forms a pivotal period between chronic inflammation and a biologically-disrupted mucosal epithelial phenotype leading to gastric neoplasia. From a more than superficial perspective, both *Helicobacter pylori* (*H. pylori*)-associated atrophic gastritis and autoimmune atrophic gastritis converge on glandular loss and metaplastic reprogramming, but their etiologic pathways, molecular mediators, topographic distribution and neoplastic characteristics differ drastically. *H. pylori* infection induces multifocal atrophy and incomplete intestinal metaplasia and is the typical path to intestinal-type gastric adenocarcinoma, while autoimmune gastritis results in corpus-restricted oxyntic destruction, severe hypochlorhydria, hypergastrinemia, and a distinctive predisposition to type I gastric neuroendocrine neoplasms. Despite *H. pylori* eradication, the epigenetic landscape of metaplastic mucosa often persists, requiring risk-adapted surveillance approaches underpinned by histologic systems such as OLGA and OLGIM. This narrative review aggregates mechanistic, epidemiologic and clinical evidence establishing malignant potentials for both etiologies of atrophic gastritis, and offers an integrated framework for surveillance and prevention.

Keywords Atrophic gastritis, *Helicobacter pylori*, autoimmune gastritis, gastric cancer, intestinal metaplasia

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Introduction

Gastric cancer still ranks among the top causes of cancer-related mortality worldwide, with incidence rates declining in certain parts of the world; however, the condition remains a major burden in East Asia, Latin America and some areas of Eastern Europe [1-4]. Histologic transformations are likely to occur in the progression from chronic gastritis to gastric neoplasia, including intestinal metaplasia (IM), dysplasia and eventually invasive cancer [1,2] (Fig. 1). Atrophic gastritis sits at the intersection of this cascade, as it represents the permanent loss of native gastric glands and the generation of metaplastic lineages that are prone to malignant evolution. Two main causes underlie most atrophic gastritis globally: i.e., *Helicobacter pylori* (*H. pylori*)-related chronic atrophic gastritis (CAG) and autoimmune atrophic gastritis (AIG), characterized by autoimmune-mediated destruction of oxyntic mucosa. Both lead to glandular atrophy, but their biological mechanisms are distinct. Specifically, in *H. pylori*-associated atrophic gastritis, pathogenic factors (*CagA* and *VacA*) that disturb epithelial architecture lead to the generation of chronic inflammation, oxidative stress and DNA damage [5-12]. Autoimmune gastritis, however, is defined by T-cell targeting of parietal cell H^+/K^+-ATPase, and leads to loss of acid output, hypergastrinemia and enterochromaffin-like (ECL) cell hyperplasia [13-16]. For clinical practice, the distinction and study of these differences in processes is critical, as the nature, degree and molecular phenotype of atrophy determine both the magnitude and the pattern of cancer risk. Thus, the aim of this review is to synthesize data from cohort studies, meta-analyses and mechanistic studies to delineate the malignant potential of both forms.

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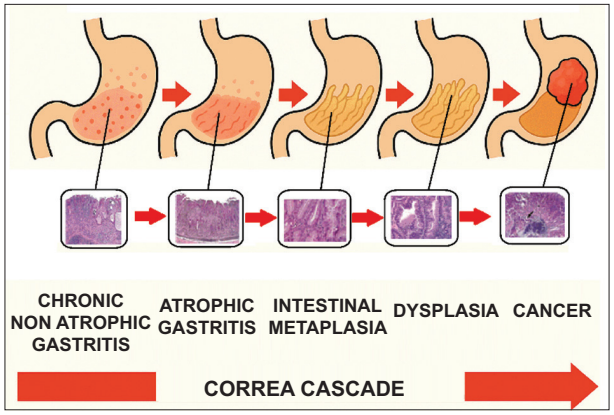

Figure 1 The Correa cascade leading to intestinal-type gastric cancer

Epidemiology, characteristics and natural history

Atrophic gastritis is a common global diagnosis, with geographic, ethnic and environmental exposures varying drastically in prevalence. In high-prevalence *H. pylori* regions, for example East Asia, Latin America and Eastern European countries, *H. pylori*-associated atrophic gastritis is the predominant route toward gastric precancerous lesions [4,17,18]. In this setting, infection is acquired in early childhood; chronic inflammation often progresses for several decades, and this has a predisposing effect on the risk of progression to atrophy and intestinal metaplasia. Population-based studies have shown that the risk of non-cardia gastric cancer in people with atrophic gastritis has increased significantly, and the severity and breadth of topographic atrophy correlate with higher risk [17-20]. AIG shows a different epidemiological pattern. It is more common in Northern Europe and North America and is closely related to other autoimmune diseases, such as autoimmune thyroiditis, type 1 diabetes and vitiligo [21]. Pernicious anemia is the most common late manifestation of autoimmune gastritis; the condition develops after many years' progression of continuous autoimmune-mediated destruction of the oxyntic mucosa in autoimmune patients [22]. While the risk of chronic autoimmune gastritis is markedly higher for type 1 gastric neuroendocrine neoplasms (gNEN), pernicious anemia is associated with a greater risk of gastric cancer [23-26] (Fig. 2).

The natural history of atrophic gastritis is shaped by the interplay between environmental exposures and host factors. High-salt diets, smoking, alcohol and nitrosamine exposures increase the carcinogenic potential of chronic gastritis, particularly when *H. pylori* infection is present [27,28]. Genetic polymorphisms that affect inflammatory cytokines, including interleukin-1β and tumor necrosis factor-α, modify susceptibility to glandular loss and neoplastic progression in the individual [29,30]. Incomplete intestinal metaplasia has long been established as a potent prognostic marker of progression to dysplasia, with long-term data demonstrating significantly higher cancer rates in patients who have incomplete vs. complete metaplasia [31,32].

Notably, the features and natural history of these 2 forms differ depending on their etiology (Fig. 3). In *H. pylori*-associated disease, the atrophic process is initiated in the antrum and, in time, spreads proximally to the incisura and corpus [33]. In comparison, autoimmune gastritis is commonly corpus-restricted, sparing the antrum unless prior *H. pylori* infection has developed a mixed pattern [23,24]. This difference in distribution has important implications for cancer risk and surveillance strategies.

Atrophic gastritis and malignancy

Mechanisms of gastric carcinogenesis

Stomach carcinogenesis proceeds from a combination of chronic inflammation, metaplastic lineage reprogramming, microbial factors, host immunity and epigenetic remodeling [34-37] (Fig. 4). Chronic *H. pylori* infection is a leading cause of atrophic gastritis and cancer worldwide. A bacterium that attaches to the gastric epithelium injects *CagA* into host cells, and then induces SHP2, ERK and NF-κB in host cells, while *VacA* induces mitochondrial damage as well as immune dysregulation [38-40]. The end result is constant mucosal harm, rapid epithelial turnover, and gene and epigenetic disorder accumulation. Among the first and most striking changes is parietal cell loss, which leads to the appearance of spasmolytic polypeptide-expressing metaplasia (SPEM). SPEM is marked by mucous cell phenotypic changes and developed on the basis of transdifferentiation of mature chief cells under the influence of inflammatory cytokines. Adaptable at first, SPEM becomes vulnerable to neoplastic transformation under long-term inflammatory stress. With the expansion of SPEM, IM frequently forms in the margins of SPEM, and forms a patchwork of metaplastic lineages with different, but convergent, oncogenic potential [41-43]. IM comes in 2 forms, complete and incomplete. The immature, colonic-type phenotype, associated with disordered mucin expression, increased proliferative indices and genomic instability, is the most substantial hallmark of incomplete IM [31,32,44-48]. Incomplete IM has a higher level of promoter methylation and abnormal Wnt/β-catenin signaling than complete IM [49-51]. These molecular features help explain how incompleteness of IM leads to dysplasia and early gastric cancer.

AIG tracks a different carcinogenic pathway. Immune-mediated destruction of parietal cells leads to massive hypochlorhydria with remarkable hypergastrinemia. Gastrin is a powerful trophic hormone that activates ECL cells, which undergo progressive hyperplasia, dysplasia, and in some instances progress to type I gastric neuroendocrine tumors [15,16,52,53]. In addition, hypochlorhydria modifies the gastric microbiome, leading to colonization by bacteria capable of producing nitrosating agents and improving the chemical environment of carcinogenesis [54,55]. Metagenomic comparative studies (Table 1) demonstrate a common hypochlorhydria-facilitated dysbiosis state in *H. pylori*-acquired

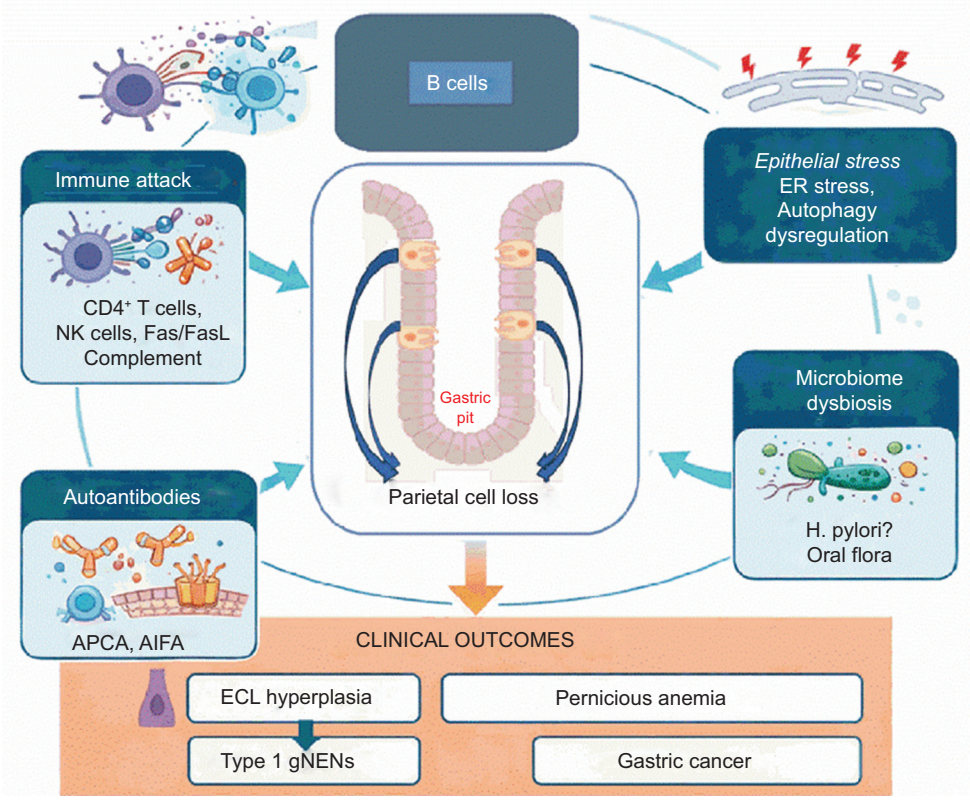

Figure 2 Mechanisms of autoimmune-mediated parietal cell injury and loss
ER, endoplasmic reticulum; NK, natural killer; APCA, anti-parietal cell antibodies; AIFA, anti-intrinsic factor antibodies; ECL, enterochromaffin-like; gNENs, gastric neuroendocrine neoplasms

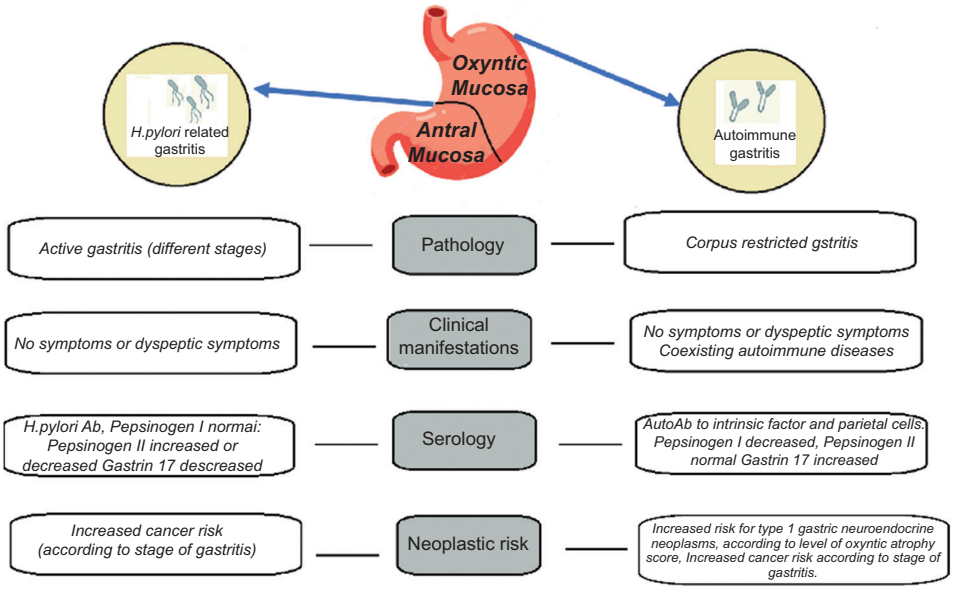

Figure 3 Major characteristics of *Helicobacter pylori* (*H. pylori*)-related vs. autoimmune gastritis

atrophic gastritis and AIG, but differences in cancer-associated microbiome mechanisms [56]. In *H. pylori*-associated atrophy, the microbiome is initially *Helicobacter*-dominant and minimized in diversity, with progression permitting secondary colonization by non-*Helicobacter* taxa. In contrast, AIG is characterized by profound achlorhydria,

Table 1 Cancer-relevant metagenomic mechanisms in *Helicobacter pylori* (*H. pylori*)-related vs. autoimmune atrophic gastritis (AIG)

Mechanistic axis	*H. pylori*-related atrophic gastritis	AIG	Cancer relevance
Nitrosation potential (NOC generation)	Increased after progression to atrophy and hypochlorhydria; persistent inflammation + dysbiosis may favor nitrate-reducing bacteria	Markedly increased due to profound achlorhydria enabling colonization by nitrate-reducing oral taxa	Promotes endogenous carcinogen formation (NOCs), DNA damage, and gastric carcinogenesis
Lactate-producing bacteria	Variable; often suppressed during active *H. pylori* dominance, but increase after atrophy/eradication	Enrichment of *Streptococcus, Lactobacillus* and other fermentative taxa in hypochlorhydric environment	Lactate fuels tumor metabolism, angiogenesis, and epithelial proliferation
Oralization of gastric microbiome	Partial oralization after atrophy and *H. pylori* decline	Pronounced "oral-type microbiome" shift (e.g., *Streptococcus, Veillonella, Prevotella*) due to loss of acid barrier	Oral commensals linked to carcinogenic metabolic pathways and chronic inflammation
Bile-tolerant / intestinal-type taxa	May emerge with intestinal metaplasia and altered gastric ecology	More frequent in long-standing achlorhydria and metaplastic mucosa	Supports metaplasia–dysplasia microenvironment
Microbial diversity & biomass	Often reduced during active *H. pylori* infection (ecologic dominance)	Higher diversity and bacterial load in achlorhydric AIG stomach	Increased metabolic crosstalk and carcinogenic metabolite production
Inflammation-driven microbial synergy	Direct virulence (*CagA/VacA*) + dysbiosis	Immune-mediated atrophy + secondary dysbiosis (no direct bacterial oncogenic virulence)	Convergent pro-carcinogenic inflammatory signaling
Functional metagenomic pathways (inferred)	Enrichment of inflammation-associated and virulence-related pathways	Distinct metabolic enzyme profiles and functional shifts in hypochlorhydric microbiome	Different routes to a similar carcinogenic niche

NOC, N-nitroso compound

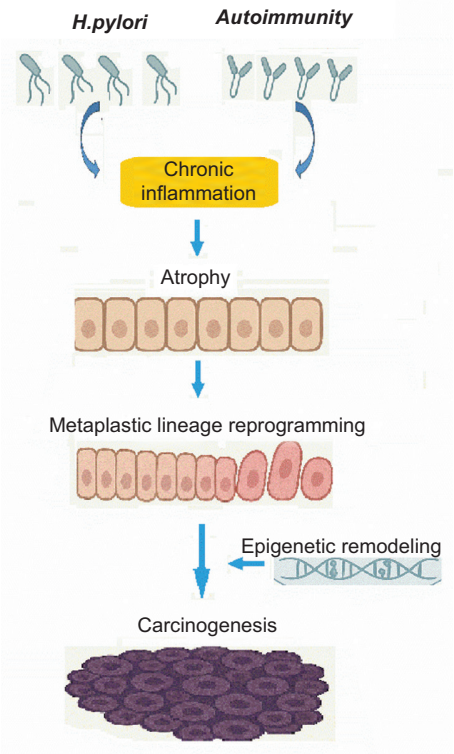

Figure 4 Mechanisms of gastric carcinogenesis

low *Helicobacter* abundance, and higher bacterial load and diversity, with enrichment of oral-type and fermentative taxa (e.g., *Streptococcus*, *Lactobacillus*). This oralization in AIG could promote carcinogenesis via more nitrosation and N-nitroso formation, as well as lactate-dependent epithelial proliferation and metabolic reprogramming. Metagenomic functional data also suggest differences in unique metabolic pathways between AIG and *H. pylori*-induced atrophy, despite histologic convergence towards atrophy and intestinal metaplasia. Accordingly, both conditions result in a similar pro-carcinogenic, hypochlorhydric niche, but with different paths: infection-driven inflammation and dysbiosis in *H. pylori* gastritis, vs. immune-mediated atrophy with achlorhydria-mediated microbial rearrangement in AIG. Whatever the cause, the pivotal transition that delivers the risk of malignant progression is stable metaplastic lineages. These lineages exhibit epigenetic fixation, altered differentiation, and susceptibility to extra genetic attack, creating a "field cancerization" effect throughout the stomach [37,38].

The natural history is different in each of these 2 etiologies. In *H. pylori*-associated disease, the atrophic process will begin in the antrum itself, and over time spread proximally to the incisura and the corpus [49]. By contrast, AIG is characteristically corpus-restricted, sparing the antrum unless prior *H. pylori* infection has created a mixed pattern [23,49,57,58]. This distributional difference is significant in relation to cancer risk and surveillance. Some cases of *H. pylori* infection—with no serological markers of autoimmunity—develop chronic gastric acid hyposecretion and corpus-typical atrophic modifications that are most similar to AIG. In a study by El-Omar *et al*, *H. pylori*-associated hypochlorhydria could be induced by inflammation-mediated parietal cell dysfunction followed by loss [59], with subsequent structural irregularities, including corpus-predominant atrophy and intestinal metaplasia. These alterations mimic

the morphological profile of AIG, and likewise increase the propensity for gastric adenocarcinoma.

Malignant potential

Atrophic gastritis presents a significantly higher risk of gastric neoplasia, but the extent and type of risk vary significantly between etiologies and histologic phenotypes (Fig. 5). *H. pylori*-associated atrophic gastritis leads to intestinal-type gastric adenocarcinoma as the main neoplastic outcome. The chronic inflammation promotes oxidative stress, DNA damage and epigenetic changes that favor malignant transformation. As atrophy progresses, intestinal metaplasia develops, initially in complete form, but often transitioning to the incomplete subtype, which carries the highest malignant potential [31,43-49]. Incomplete intestinal metaplasia is characterized by the expression of colonic-type mucins, absence of a brush border, expanded proliferation zones, and a tendency to exhibit early dysplastic changes. These lesions display genomic instability, TP53 abnormalities, and aberrant Wnt signaling, making them a key biomarker for future neoplastic progression [49-51]. Population-based cohort studies consistently show that extensive or multifocal intestinal metaplasia, particularly when involving both antrum and corpus, is associated with a several-fold increased risk of gastric cancer [17,18]. Autoimmune gastritis has a different, but no less important, tumor potential. Corpus-restricted oxyntic atrophy, leading to profound hypochlorhydria, encourages bacterial overgrowth and nitrosamine production [55]. At the same time, hypergastrinemia promotes proliferation of ECL cells, resulting over time in linear and also micronodular hyperplasia, dysplastic nodules and type 1 gNEN [15,16,52,53]. Though these tumors generally confer low metastatic potential, their presence indicates significant endocrine and structural remodeling. Additionally, studies have shown that patients with autoimmune gastritis carry a 3- to 6-fold higher risk of gastric adenocarcinoma, similar to that observed in *H. pylori*-associated disease [60]. This suggests that although the initiating triggers—i.e., autoimmune-mediated parietal cell destruction vs. infection-driven chronic inflammation, and certain mechanistic pathways—differ between AIG and *H. pylori* gastritis, both conditions may converge into a similar hypochlorhydric, atrophic, and metaplastic mucosal phenotype. At this stage, the magnitude of gastric adenocarcinoma risk appears broadly comparable, with reported 3- to 6-fold increases in AIG that fall within the range observed in advanced *H. pylori*-associated atrophic gastritis.

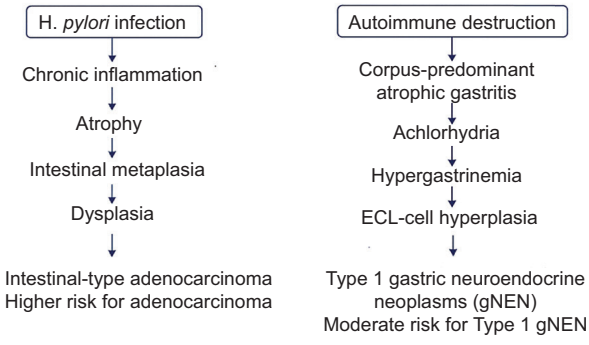

Figure 5 Comparative malignant potential of *Helicobacter pylori* (*H. pylori*)-associated and autoimmune gastritis

A particularly high-risk phenotype has been described in patients with "mixed-etiology" gastritis, and several experts [61,62] suggest that, in this subgroup, *H. pylori* may directly induce gastric autoimmunity through mechanisms of molecular mimicry in genetically predisposed individuals. These individuals have serologic or histologic evidence of past *H. pylori* infection combined with autoimmune markers and corpus-restricted atrophy. In such cases, antral changes reflect prior bacterial injury, while corpus changes reflect autoimmune destruction. This dual pathology creates an environment with increased inflammatory signaling, endocrine stimulation, and widespread epigenetic remodeling, markedly elevating the risk of both adenocarcinoma and neuroendocrine tumors [53,54].

This subgroup warrants a structured diagnostic approach: i.e., (i) systematic evaluation for current or past *H. pylori* infection (histology with or without noninvasive testing), with eradication if positive; and (ii) parallel confirmation of an autoimmune phenotype (corpus predominant atrophy, anti-parietal cell and/or intrinsic factor antibodies, hypergastrinemia, and/or a clinical context of pernicious anemia), followed by standardized staging (OLGA/OLGIM and/or endoscopic staging). With regard to cumulative risk, there are only limited robust prospective data quantifying whether mixed-etiology disease confers additive or synergistic neoplastic risk beyond each condition alone. Although the recent literature supports biological plausibility and reports gastric neoplasia in coexistence states, the current evidence is insufficient to justify a universal 1–2-year surveillance interval for all mixed cases. Therefore, a pragmatic and guideline-consistent strategy is to manage patients with mixed etiology according to the highest-risk feature present (extent of atrophy or intestinal metaplasia, incomplete intestinal metaplasia, dysplasia, family history, or endoscopic severity). Intensified surveillance (e.g., every 1-2 years) should be reserved for patients who meet high-risk criteria based on contemporary risk-stratification algorithms, whereas autoimmune gastritis without additional high-risk features is generally monitored at longer intervals (e.g., approximately 3 years, as suggested in MAPS III) [63].

These clinical observations are confirmed by molecular studies. Epigenetic studies of the gastric mucosa indicate that atrophic gastritis is defined by extensive promoter hypermethylation of the tumor suppressor genes, particularly coupled with intestinal metaplasia. Even after *H. pylori* eradication, these methylation signatures persist, consistent with a process of "epigenetic memory" in which the risk of cancer remains high despite the removal of microorganisms. Collectively they will help us understand why atrophic gastritis acts not only as a marker of risk but as a potent contributor to neoplastic transformation [61,62,64].

Comparative neoplasia risk: *H. pylori*-associated vs AIG

Although both *H. pylori*-associated atrophic gastritis and AIG converge phenotypically on glandular loss and intestinal metaplasia, they diverge in terms of topographic patterns, molecular signatures, endocrine milieu and neoplastic outcomes. These differences directly affect cancer risk stratification and surveillance recommendations. Atrophic change is most commonly first localized in the antrum, and advances proximally to the incisura and corpus in *H. pylori*-associated disease over time as infection progresses. The pattern of atrophy and intestinal metaplasia are usually multifocal. This multifocality is clinically relevant, as involvement of both antrum and corpus, especially in patients with incomplete intestinal metaplasia, is associated with a markedly higher cancer risk [24,46]. The molecular milieu of *H. pylori*-related carcinogenesis is defined by chronic inflammation, interleukin-1β-mediated acid inhibition, DNA methylation drift, oxidative DNA damage, and activation of pro-oncogenic signaling pathways via *CagA* [5,9-16]. Together, these changes propel the classic pathway to intestinal-type gastric adenocarcinoma [24,48,58,65-70].

AIG, on the other hand, begins from and goes on to predominantly inhabit the oxyntic mucosa of the corpus and fundus. This anatomic restriction results from targeted immune injury of the parietal cells by autoreactive T cells, as well as autoantibodies. The functional consequences are severe hypochlorhydria, loss of intrinsic factor secretion and progressive hypergastrinemia. The latter causes slowly progressive enterochromaffin-like-cell hyperplasia that could progress over time to type 1 gNENs. The neoplastic profile thus markedly differs from that of *H. pylori* gastritis: *H. pylori* disease mainly tends to predispose to adenocarcinoma, while autoimmune gastritis also affords a predisposition to adenocarcinoma and type 1 gNENs, with the latter being almost absent in *H. pylori*-associated disease [24,48,58].

Mixed patterns of gastritis—where autoimmune markers also coexist with evidence for previously seen *H. pylori* exposure—may be particularly concerning. In these patients there is the potential for the presence of exogenous antral injury that is typical of a past infection, as well as corpus-restricted autoimmune damage. This hybrid status has an additive synergy between inflammatory signaling from the antrum and endocrine hyperplasia from the corpus, and exacerbates cancer processes. In a number of studies, mixed-etiology patients demonstrated relatively more incomplete intestinal metaplasia, a higher OLGA and OLGIM stage risk, and a greater risk of adenocarcinoma and neuroendocrine tumors compared with either etiology alone [59-61].

The functional effects of these diseases also illustrate the disparities between them. Acid suppression in *H. pylori*-associated atrophic gastritis can occur gradually, and gastrin levels rise moderately following parietal cell loss. In autoimmune gastritis, acute acid decline is sudden and strong, resulting in marked increases in gastrin level that lead to a proliferation of ECL cells. Hypochlorhydria also changes the gastric microbiome, promoting bacterial overgrowth and luminal nitrosation reactions. These chemical mechanisms yield N-nitroso compounds that have reliable carcinogenic potential, strengthening the adenocarcinoma risk linked to immune-mediated oxyntic atrophy [52-55].

Collectively, these mechanistic and clinical differences suggest that the malignant potential of atrophic gastritis should be understood through an etiologic lens. *H. pylori* infection and autoimmunity both present risk, but via divergent pathways through target tissues, molecular effects and neoplastic endpoints.

Impact of *H. pylori* eradication

Eradication of *H. pylori* is one of the most efficacious therapies designed to reduce the occurrence of gastric cancer. Whether such improvements translate into an actual reduction in the rate of gastric cancer can depend largely on the state of mucosal injury at which therapy first begins.

In high-risk populations, eradication may reduce gastric cancer incidence by 40-60% if done early, before atrophy or intestinal metaplasia [71,72]. Randomized trials and long-term cohort studies in Japan, Korea and China consistently demonstrated that the elimination of the organism prior to the onset of irreversible mucosal changes inhibits the activation of chronic inflammatory pathways, and minimizes accumulation of alterations in methylation. These observations provide support for early screening and treatment programs in countries with a high prevalence of gastric cancer. However, once atrophy/intestinal metaplasia is evident, the ability to reverse the process is limited. Partial regression of the antral atrophy could develop after eradication of *H. pylori*, especially in younger patients. However, corpus atrophy and intestinal metaplasia rarely regress meaningfully following eradication, particularly in the setting of incomplete intestinal metaplasia. Moreover, the metaplastic epithelium exhibits stable epigenetic changes—including elevated promoter methylation of tumor suppressor genes—many years after microbial clearance [73]. This "epigenetic memory" may explain why the risk for cancer decreases but does not normalize after eradication in patients with known precancerous alterations [74,75]. Eradication of *H. pylori* alone does not reverse autoimmune gastritis, but it may improve gastric inflammation when autoimmune gastritis coexists with *H. pylori*-associated gastritis. O.K.In these cases, eradication decreases inflammation signaling, may reduce some gastrin by restoring somatostatin tone in the antrum, and may also ameliorate a synergistic carcinogenic situation of mixed-etiology gastritis [76]. Crucially, the eradication of *H. pylori* following endoscopic resection of early gastric cancer or high-grade dysplasia significantly decreases the risk of metachronous cancer [77]. This effect will occur with the intestinal metaplasia, and illustrates that microbial elimination favorably alters the biological environment, despite already obvious, irreversible changes. Consequently, the efficacy of eradication lies on a stage-dependent gradient, with its impact being highly preventive if it occurs early, risk-modifying but not completely restorative when it is performed following

metaplasia development, and, indirectly, beneficial for mixed or autoimmune-modified mucosa.

Surveillance strategies

Surveillance of atrophic gastritis seeks to detect dysplasia or early neoplasia at a stage when endoscopic therapy is most effective (Table 2). Risk-adapted surveillance integrates histologic severity, distribution of atrophy and metaplasia, etiologic factors, and patient-specific risk modifiers such as family history. High-quality endoscopy is essential. Modern practice incorporates high-definition white light endoscopy and image-enhanced modalities, such as narrow-band imaging, blue laser imaging and linked-color imaging, to improve the visualization of metaplastic and subtle dysplastic lesions [78-82]. Systematic biopsy acquisition using the updated Sydney protocol enhances diagnostic accuracy and allows for histologic staging using OLGA and OLGIM systems [83,84]. These staging systems categorize patients by the severity and topographic extent of atrophy or intestinal metaplasia and correlate strongly with gastric cancer risk. In addition to histologic staging systems like OLGA and OLGIM, emerging noninvasive biomarkers are increasingly being explored as adjunctive tools for gastric cancer risk stratification. Recent studies suggest that serological microbial protein panels (e.g., Omp, HP0305 and other similar antigens) and liquid biopsy strategies (circulating cell-free DNA methylation profiles and signatures of non-coding RNA) can inform the identification of persons who continue to be at high risk despite suppression of *H. pylori*. These molecular and serologic markers may reflect the remaining carcinogenic aspects associated with epigenetic alterations and continued mucosal instability beyond what histology can adequately demonstrate [85-87]. While OLGA/OLGIM staging is the current reference standard for the allocation of surveillance in international guidelines, the introduction of validated noninvasive biomarkers would improve the risk stratification paradigms, especially in patients presenting at low-risk OLGIM stages, where they may gradually minimize recurrent invasive endoscopy. At present though, these approaches should be viewed as adjunct mechanisms to histologic assessment, needing further prospective validation to demonstrate clinical and economic utility.

Table 2 Suggested surveillance according to risk category/lesion

Risk category / lesion	Suggested interval	Notes
OLGA/OLGIM 0-II without IM	No routine surveillance	If strong family history, consider individualized follow up
Extensive IM (antrum + corpus) or OLGA/OLGIM III-IV	Every 3 years	Based on MAPS III and ESGE guidelines
Autoimmune AG without type 1 gNENs	Every 3-5 years	Risk-stratified approach according to AGA suggestions
Autoimmune AG with ECL hyperplasia / micro-gNENs	Every 1-2 years	Consider polypectomy, biopsy mapping
Low-grade gastric dysplasia	6-12 months	European and Asian practice varies
High-grade dysplasia / intramucosal carcinoma	Endoscopic resection + close follow up	ESGE/ESD guidelines

IM, intestinal metaplasia, AG, atrophic gastritis; gNENs, gastric neuroendocrine neoplasms; AGA, American Gastroenterological Association; ESGE, European Society of Gastrointestinal Endoscopy; ESD, endoscopic submucosal dissection

Surveillance frequency is structured by international guidelines. Endoscopic surveillance should happen every 3 years for patients with extensive intestinal metaplasia involving both antrum and corpus, with shorter intervals for incomplete metaplasia, high OLGA or OLGIM stages, or a strong family history of gastric cancer [63]. It is also vital that virtual chromoendoscopy-guided biopsies are recommended as a standard for first-time gastroscopy risk assessment. The American Gastroenterological Association (AGA), with its recognition of the lower background incidence rates experienced in the USA, endorsed shared decision-making, yet supported selective endoscopy every 3 to 5 years for high-risk individuals [88]. In Eastern Asia some of the national screening programs include surveillance of atrophic gastritis and intestinal metaplasia as part of population-level cancer prevention activities [89]. Autoimmune gastritis needs special emphasis, given its specific risk of being associated with gastric neuroendocrine tumors. People with hypergastrinemia or enterochromaffin-like cell hyperplasia need to be monitored more often, maybe annually or every 2 years, particularly if a resection of prior type 1 gNENs has been made [15,16,53,54]. Corpus-restricted incomplete intestinal metaplasia or high OLGA stages warrant endoscopic surveillance approximately every 3 years. Innovative technologies may continue to hone risk stratification. Using artificial intelligence (AI) in endoscopic imaging to detect the presence of minor lesions is likely to facilitate the detection of fine lesions, and may be used to aid in better classification of intestinal metaplasia and early dysplasia [90-92]. In the future, molecular biomarker panels of methylation signatures or transcriptomic profiles may be used to identify which patients suffering from atrophic gastritis are particularly more prone to developing gastric cancer [93,94].

Concluding remarks

Atrophic gastritis represents a pivotal turning point in the natural history of gastric carcinogenesis. Whether arising from chronic *H. pylori* infection or the autoimmune devastation of the oxyntic mucosa, atrophy marks a point of transition to a biologically modified state with glandular loss, lineage reprogramming and durable epigenetic modifications. These alterations provide an amenable environment for intestinal metaplasia, dysplasia and ultimately gastric neoplasia. While these commonalities exist amongst the main etiologies, they are distinguished fundamentally by their mechanistic basis,

phenotypic expression and neoplastic endpoints. *H. pylori*-associated atrophic gastritis continues to be the hallmark global predictor of intestinal-type gastric adenocarcinoma, attributable to chronic inflammation, virulence factor-induced epithelial injury and persistent molecular instability. In contrast, AIG represents the specific destruction of oxyntic glands, and features significant hypochlorhydria with marked hypergastrinemia and associated risk for type 1 gNENs in addition to adenocarcinoma.

The malignant potential of atrophic gastritis is neither a uniform nor a binary pattern, but rather ranges over a continuum shaped by the severity and distribution of atrophy, accompanied by the presence and subtype of intestinal metaplasia, in addition to patient-specific influences such as family history and comorbid autoimmune disease. Incomplete intestinal metaplasia is a consistent high-risk histologic phenotype, and OLGA and OLGIM stages III and IV are robust predictors of risk across diverse populations. Mixed-etiology gastritis represents a significant challenge, as the coexistence of molecular instability from prior *H. pylori*-related injury and the endocrine stimulation and chemical carcinogenesis associated with autoimmune oxyntic atrophy may render the gastric mucosa particularly susceptible to neoplastic progression O.K. As the molecular and microbiome-mediated basis for carcinogenesis in these patients is further elucidated, it is becoming more and more evident that management needs to support the specific risks associated with this hybrid phenotype.

Elimination of *H. pylori* has always been the most effective treatment for the prevention of gastric cancer, if it is implemented before the onset of irreversible mucosal changes. When intestinal metaplasia emerges, however, the mucosa remains in an epigenetic state of memory of previous injury for long after the bacterium has been cleared. Metaplastic lineages, and particularly incomplete intestinal metaplasia, indicate a mucosal milieu leading to the accumulation of genetic and epigenetic aberrations. This rationalizes why cancer risk decreases but never fully returns to baseline after eradication in patients with preexisting precancerous lesions. For autoimmune gastritis, the early recognition and management of nutritional deficiencies and endocrine abnormalities, in parallel with appropriate surveillance for neuroendocrine tumors, are key strategies to reduce risk and improve patient outcomes.

The key areas of surveillance for treating atrophic gastritis are as follows. Developments in endoscopic technology (e.g., high-definition imaging, narrow-band imaging and AI-assisted detection) improved detection of early neoplastic alterations that were previously unnoticed. Together with systematic biopsy and histologic staging systems, these approaches enable the possibility of better risk stratification by the clinician, with improving accuracy. Global structured guidelines, such as MAPS III, the AGA updates and established East Asian screening programs, are able to ensure a comprehensive monitoring system that considers regional disparities in gastric cancer epidemiology. These recommendations highlight the need to identify individuals at high risk—patients with generalized or incomplete intestinal metaplasia, corpus involvement, significant OLGA/OLGIM status, mixed-etiology gastritis, or autoimmune-driven hypergastrinemia—and provide them with routine endoscopy. In personalized risk assessment, one important part of the future of gastric cancer prevention will be the combination of molecular pathology, microbiome science and advanced imaging. However, DNA methylation markers, transcriptional signatures and microbial taxa related to carcinogenesis provide tantalizing avenues to improve surveillance intervals and prevention efforts. AI in general is likely to contribute increasingly to the standardization of detection in different clinical scenarios, and to the reduction in interobserver variation.

In conclusion, atrophic gastritis is a multi-dimensional biological condition characterized by prolonged injury, lineage plasticity, immune dysregulation, microbial interactions and molecular instability, leading to an increased likelihood of gastric neoplasia. Its malignant potential is significant; however, it is modifiable. Acknowledging etiologic differences, identifying at-risk histologic features, eliminating *H. pylori* early, monitoring autoimmune sequelae, performing evidence-based surveillance, and recognizing the pathogenesis of chronic gastritis to developing gastric cancer, can allow clinicians to substantially intervene in the disease progression. Such a deep integration, based on robust mechanistic knowledge and enhanced by new technologies, presents the best avenue to alleviate the worldwide burden of gastric cancer due to atrophic gastritis.

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