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LETTER TO THE EDITOR

Autoimmune gastritis studies and gastric cancer: True renaissance or bibliometric illusion

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Abstract

A bibliometric analysis of studies dedicated to autoimmune gastritis (AIG) recently published demonstrated a noteworthy surge in publications over the last three years. This can be explained by numerous publications from different regions of the world reporting the results of several studies that stimulated reassessment of our view of AIG as a precancerous condition. Follow-up studies and retrospective analyses showed that the risk of gastric cancer (GC) in AIG patients is much lower than expected if the patients ever being infected with *Helicobacter pylori* (*H. pylori*) were excluded. The low prevalence of precancerous lesions, such as the incomplete type of intestinal metaplasia, may explain the low risk of GC in AIG patients because the spasmolytic polypeptide-expressing metaplasia commonly observed in AIG does not involve clonal reprogramming of the gastric gland and can be considered as an adaptive change rather than a true precancerous lesion. However, changes in gastric secretion due to the progression of gastric atrophy during the course of AIG cause changes in the gastric microbiome, stimulating the growth of bacterial species such as streptococci, which may promote the development of precancerous lesions and GC. Thus, *Streptococcus anginosus* exhibited a robust proinflammatory response and induced the gastritis-atrophy-metaplasia-dysplasia sequence in mice, reproducing the well-established process for carcinogenesis associated with *H. pylori*. Prospective studies in *H. pylori*-naïve patients evaluating gastric microbiome changes during the long-term course of AIG might provide an explanation for the enigmatic increase in GC incidence in the last decades in younger cohorts, which has been reported in economically developed countries.

Key Words: Autoimmune gastritis; Gastric cancer; Type 1 neuroendocrine tumors; *Helicobacter pylori*; *Streptococcus anginosus*; Intestinal metaplasia

Core Tip: Autoimmune gastritis (AIG) is associated with a lower risk of gastric cancer than expected due to the low prevalence of precancerous lesions. In contrast, the risk of type 1 neuroendocrine tumors (Type1-NETs) is high and always co-exists with anti-parietal cell antibodies and extensive oxyntic atrophy. Endoscopic surveillance is needed for the early diagnosis and curative treatment of Type1-NETs. The progression of gastric atrophy during the course of AIG leads to hypochlorhydria and subsequent changes in the gastric microbiome. Among the numerous species harboring the stomach in patients with atrophic AIG, *Streptococcus anginosus* is one of the key candidates to be a driver of gastric carcinogenesis in post- *Helicobacter pylori* era.

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TO THE EDITOR

A timely bibliometric analysis of the studies dedicated to autoimmune gastritis (AIG) published recently in the *World Journal of Gastroenterology*[1] serves as a poignant reminder that a disease first described in 1849 by Thomas Addison as a "very remarkable form of general anaemia''[2] continues to persist and capture the attention of researchers even after 175 years. During the initial hundred years of AIG research, significant progress has been made in understanding its pivotal role in the pathogenesis of pernicious anemia. This progress culminated in the development of an effective substitutive treatment with vitamin B_{12}, a breakthrough recognized with Nobel Prizes in 1934 and 1964. However, the fundamental question of why autoantibodies against parietal cells and intrinsic factor emerge remains to be answered. Furthermore, the widespread use of endoscopy has provided comprehensive insights into the topography of atrophic gastritis, revealing a higher prevalence of antral gastritis than fundal gastritis, the latter being associated with autoimmunity. These findings underscore the notion that gastric atrophy may not result solely from autoimmune mechanisms.

The discovery of *Helicobacter pylori* (*H. pylori*) in 1982 marked a paradigm shift in gastritis research. This discovery established the bacterial etiology of antral gastritis and promoted a myriad of studies dedicated to its long-term progression to atrophic gastritis, a significant risk factor for gastric cancer (GC). Over the past four decades, research on AIG has been overshadowed by extensive investigations into *H. pylori*-associated gastritis and its consequences. Bibliometric analysis indicated that until 2019, the number of publications dedicated to AIG did not exceed 15 per year[1], while hundreds of full-text papers and numerous abstracts concerning *H. pylori*-associated gastritis were published. Even in the most recent year, a PubMed database search using the MESH term "*Helicobacter*" yielded ten times more full-text papers on *H. pylori* than those dedicated to AIG. However, the noteworthy surge in AIG publications over the past three years, as indicated by the bibliometric analysis, warrants further explanation.

The first and most important point that has attracted interest from the scientific community during the last few years was the results of several recently published studies that stimulated reassessment of our vision of AIG as a precancerous condition. The most exciting study was published by Rugge *et al*[3], who reported a long-term follow-up study of a group of AIG patients who were negative for *H. pylori*. This long-term histological follow-up of patients with AIG consistently showed oxyntic-predominant-mononuclear inflammation with no significant changes in the prevalence of atrophic AIG over time. The prevalence of pseudopyloric metaplasia was greater than that of intestinal metaplasia (IM) at both time points, and IM scores increased by the end of follow-up. The prevalence of OLGA-III stage was less than 5%, and no OLGA-IV stage occurred. The ECL cell status progressed from diffuse to adenomatoid hyperplasia/dysplasia. Type 1 neuroendocrine tumors (Type1-NETs) always coexisted with extensive oxyntic atrophy and ECL adenomatoid hyperplasia or dysplasia. The prevalence of atrophic lesions in the distal stomach (antrum) was negligible, with both non-metaplastic and IM atrophic changes involving less than 30% of biopsy specimens. Cancer risk in patients with AIG was assessed through record linkage with the regional cancer registry, and no excess risk of gastric or other malignancies was found, except for a marginally significant increase in thyroid cancer risk. Their findings suggest that neuroendocrine neoplasia, rather than secondary prevention of gastric cancer (GC), should prioritize AIG surveillance in naïve *H. pylori*-negative patients[3]. This publication promoted intensive discussion arguing for[4-6] and against[7,8] the authors' conclusions, which included an editorial published in *Gut* with the notable title "No *H. pylori*, no adenocarcinoma for patients with autoimmune gastritis"[9]. These findings were supported by the results of numerous well-planned retrospective studies published during the last three years. Thus, in a nested case-control study based on the Finnish Cancer Registry, to identify cases of invasive stomach cancers during the period–1983-2016 in young Finnish women, the role of *H. pylori* and AIG as risk factors for gastric malignancies was evaluated[10]. A total of 507 stomach cancer cases and 907 age-matched controls were identified, from which multiplex serology for *H. pylori* and AIG was performed. In this study, seropositivity to *H. pylori* and AIG was associated with higher odds of developing gastric malignancies both in young women (< 50 years old) and in those older than 50 years. Histological subtype analyses revealed that *H. pylori* seropositivity was associated with higher odds of adenocarcinomas, including the diffuse type, whereas AIG was mostly associated with carcinoid tumors. In a retrospective case-control study from German centers, AIG was found only in 4.9% of all GC cases; however, 35% of them were also *H. pylori*-positive according to histology and/or patient history[11], decreasing the true association of AIG with GC to 3%. Interestingly, patients with AIG demonstrated better survival

compared to non-AIG-associated GC patients, possibly due to early diagnosis as patients with pernicious anemia prompt endoscopy surveillance. A similar distribution of AIG in GC patients and better survival was demonstrated in a Japanese cohort of 261 GC patients, in which only 8 (3%) had a pure AIG confirmed by anti-parietal cell antibodies, high blood gastrin level, oxyntic mucosa atrophy, and never being positive for *H. pylori*[12]. Compared to non-AIG-related GC patients with AIG demonstrated lower cancer recurrence rate and better survival. It has been speculated that the presence of an autoimmune response in patients with AIG might cause unknown molecular changes in the atrophic and metaplastic glands, which makes AIG less susceptible to cancer development than *H. pylori*-related gastritis. Indeed, the authors demonstrated that precancerous lesions adjacent to cancerous lesions showed greater intraepithelial infiltration of CD3 positive cells and lower positivity for dysplastic transition TROP2 in AIG-associated GC than in *H. pylori*-associated GC cases[6]. Recently published meta-analysis based on 13 eligible publications reported a low incidence rate of GC in patients with AIG calculated from the pooled data (0.14% per person-year) in both single-center studies and national registration studies[13]. However, the calculated pooled incidence rate for Type1-NETs in AIG patients was six times higher (0.83% per person-year) than that for GC.

Explanation of the low incidence of GC in AIG patients in comparison to *H. pylori*-associated gastritis is provided in part by the studies dedicated to the genesis and course of the precancerous lesions in different types of atrophic gastritis, which have also been published in recent years. Atrophic gastritis is characterized by metaplastic changes in the gastric mucosa, specifically the development of different types of metaplasia involving reprogramming of stem/progenitor cells, resulting in clonal changes in the entire gland[14]. This process, known as transcommitment, leads to conversion of the gastric gland into an intestinal phenotype[15]. According to a systematic review of 24 studies, type III incomplete IM is associated with a 4- to 11-fold higher relative risk of GC than complete type IM or the absence of incomplete IM[16]. Prospective studies in different ethnic populations also showed that the incomplete subtype of IM carries an increased risk of developing GC[17,18]. However, the incomplete type of IM rarely occurs in AIG in comparison to *H. pylori*-associated gastritis (8.3% *vs* 37.7%)[19] or occurs at a similar rate (4%) as in the general population[20], which explains the low risk of GC in AIG. Moreover, the metaplastic glands in AIG patients demonstrated a significantly lower level of epithelial proliferation compared to non-AIG patients, as well as a lower number of CD68-expressing macrophages clustered around metaplastic glands, indicating that AIG patients lacked prominent macrophage infiltrates that may drive the evolution of proliferative metaplasia and lead to dysplasia[21]. It is not surprising that the most common type of metaplasia in AIG is spasmolytic polypeptide-expressing metaplasia (SPEM) because it appears as a glandular response to the elimination of parietal cells through autoimmune injury, in which lost cells are substituted by metaplastic ones. They express a spasmolytic polypeptide, which is normally expressed by the chief progenitor mucous neck cells[22]. SPEM is easily induced in rodents by the elimination of parietal cells by cell-specific toxic drugs or tamoxifen[23-25], but it is fully reversible and does not lead to the development of dysplasia or neoplasia[23]. It seems that the SPEM commonly observed in AIG may not be a true example of metaplasia, as it does not involve clonal reprogramming of the gastric gland; therefore, it can be considered an adaptive change that can revert to its original phenotype, but not as a true precancerous lesion.

AIG was considered a precancerous condition for many years because earlier registry-based retrospective studies evaluating GC risk in patients with AIG/pernicious anemia did not take into account the rate of concomitant *H. pylori* infection[26,27], which obviously has to be high, as it was prevalent in the general population in economically developed countries decades ago and is still prevalent in the developing world. Recently published studies have confirmed that the rate of *H. pylori* infection in AIG patients varies from 15% to 79.9%[12,28-31] depending on the population in which the study was performed. However, in some *H. pylori*-negative AIG patients pangastritis was found considering this pangastritis may not be the consequence of AIG, as in AIG patients antral mucosa is rarely involved into the inflammatory process[3,32] and atrophy and incomplete IM occurs also rare[19]. This means that many years ago, these patients with pangastritis were infected with *H. pylori*, in whom classical antral gastritis progressed to atrophic and *H. pylori* had disappeared due to hypochlorhydria ("alkaline suicide"). Even if *H. pylori* is eradicated at the early stages of atrophy in the antrum, it may not guarantee the absence of its progression[18,33]. This scenario is also partly confirmed by the location of adenocarcinomas that were found in AIG patients with pangastritis, most of which were located in the distal part of the stomach or at the border between the antrum and the body[34], but not in the body of the stomach, as is typical for AIG Type1-NETs.

However, in addition to the study published by Rugge *et al*[3], in which they could not demonstrate any increased risk for GC during the 7 years follow-up of AIG patients naïve to *H. pylori*, several other studies with carefully selected patients with AIG have been published. Thus, in a retrospective study of 135 patients with AIG from China, 31.1% of patients did not have any neoplasia, 37% had multiple Type1-NETs, 31.9% had multiple gastric hyperplastic polyps including 1/3 with neoplastic transformation, 3.7% had single gastric low-grade dysplasia or adenoma, and 5.9% had single or double gastric high-grade dysplasia or adenocarcinoma[32]. All patients with adenocarcinoma were *H. pylori*-negative, and severe atrophy in the corpus and body of the stomach with IM was observed in all patients. In all patients, ECL cell hyperplasia was also observed, and there was no atrophy in the antrum. All eight adenocarcinomas were well-differentiated, 5 located in the corpus and 3 in the antrum and 7/8 were associated with hyperplastic polyps. In a Japanese cohort of 76 GC patients with anti-parietal cell antibodies, only 8 patients were *H. pylori* naïve, and severe atrophy was found in the fundus and body of the stomach[12]. In a recently published prospective study with a median follow-up of 5 years among 275 patients with corpus-restricted atrophic gastritis, 6 GC/1 high-grade intraepithelial dysplasia, and 42 Type 1-NETs have been reported with a crude incidence of 2.5% and 15.3%, respectively[35]. The prevalence of *H. pylori* in the study cohort was 36.7% which was determined by histology, serology, or a previous history of eradication therapy. All GC cases were *H. pylori*-negative, but 71.2% (4 GCs and 1 high-grade dysplasia) were positive for anti-parietal antibodies. On the contrary 95.8% of patients with Type1-NETs were anti-parietal antibody-positive and 21.4% were *H. pylori*-positive. All GC lesions were classified as intestinal-type adenocarcinomas and were located in the

body (2), incisura angulus (2), and antrum (3). All Type1-NETs except 1 located in the body of the stomach. In all GC cases, IM was found, and its score significantly increased during the follow-up; however, in Type1-NETs patients gastric atrophy score was higher at baseline than in patients without any neoplastic lesions but remained stable during the follow-up. During the last decades, progress in endoscopic diagnostic techniques, such as magnifying endoscopy and narrow-band imaging, has allowed the effective diagnosis and classification of AIG and Type1-NETs[36-38]. These advanced diagnostic techniques lead to better surveillance of AIG patients and undoubtedly increase the number of Type1-NETs diagnosed at early stages, allowing the treatment and follow-up of large cohorts of patients for many years and the evaluation of the risk of tumor recurrence and mucosal atrophy progression[31,35,39,40].

Besides IM, patient age and pernicious anemia were strong predictors of GC in body-restricted atrophic gastritis. Summarizing the results of retrospective and prospective studies, it is clear that GC is quite rare in compare to Type1-NETs in patients with AIG, and in some GC cases, the participation of *H. pylori* in the development of gastric atrophy may be considered. The absence of *H. pylori* or anti-*H. pylori* antibodies in older persons does not rule out its participation in the early stages of gastritis development and progression. The majority of patients with GC and severe AIG from the cited studies were older (70+ years), and it is difficult to imagine that they were never infected by *H. pylori*, as the prevalence of the infection clearly demonstrates the cohort phenomenon[41]. However, the mechanisms of carcinogenesis in *H. pylori*-naïve patients with AIG remain unclear. Pernicious anemia is considered a major risk factor for GC in registry-based studies[26,27], as well as in prospective cohort studies of AIG[35]. Patients with pernicious anemia lack parietal cells and consequently develop severe hypochlorhydria, which dramatically changes the stomach environment. As a result of hypochlorhydria, gastrin secretion increases, which can promote the development of GC[42]; however, changes in the stomach microbiome may be more important.

Changes in gastric secretion during the progression of gastric atrophy play a major role in the changes in the gastric microbiome. Thus, in the normal stomach and under treatment with a typical dose of proton-pump inhibitors, microbial diversity is high and very few alterations in microbiome composition have been found[43]. In contrast, in *H. pylori*-associated gastritis, microbial diversity decreased, but in atrophic AIG, it increased with several specific alterations of the microbiome[29,43-45]. In several studies, *Streptococcaceae* was found to be the most dominant group in atrophic AIG patients[43,44,46] and may be one of the key candidates for participating in the carcinogenic cascade in these patients[47]. Interestingly, women with AIG demonstrated higher microbial diversity than men[47], which may make them more susceptible to carcinogenesis in AIG. Among *Streptococcaceae Streptococcus anginosus (S. anginosus)* was recently shown to be an important candidate for a major gastric carcinogenesis trigger beyond *H. pylori*. Using a murine model, *S. anginosus* was demonstrated for the first time as a trigger of gastric tumorigenesis and a mechanism through which *S. anginosus* communicates with gastric epithelial cells to drive oncogenesis[48]. Consistent with its tumor-promoting effect, *S. anginosus* infection drives increased cell proliferation in the gastric mucosa and tumors. Moreover, it was found that *S. anginosus* infection impaired gastric barrier function, as indicated by the time-dependent reduction in the expression of tight junction markers, which can enhance the effects of food carcinogens. The most important result of the study was that *S. anginosus* induced the gastritis-atrophy-metaplasia-dysplasia sequence in mice, finely reproducing the well-established process for GC associated with *H. pylori*. Interestingly, macrophages infected with *S. anginosus*, but not with other streptococci, exhibited a robust proinflammatory response characterized by significantly increased levels of inflammatory cytokines and mediators, including TNF, IL-6, IL-1β, NOS2, and COX2, accompanied by enhanced NF-κB activation[49]. This unique ability of *S. anginosus* may induce macrophage infiltration to drive the evolution of proliferative metaplasia and lead to dysplasia, as in *H. pylori*-associated atrophic gastritis[21]. Taken together, it seems that *S. anginosus* is a second bacterium after *H. pylori*, which is casually implicated in the pathology of GC[50] and a new possible scenario for the development of GC (Table 1).

A multidisciplinary consensus was recently published by Real-world gastritis initiative (RE.GA.IN), which reported a high level of agreement between experts that gastric microbiota may play a pathogenetic role in gastritis, particularly once gastric atrophy and achlorhydria develop, and that gastric microbiota may impact on different stages of gastric carcinogenesis initiated by *H. pylori* infection, but further studies to identify microbiota-driven carcinogenic pathways are needed[51]. The number of studies on gastric microbiota beyond *H. pylori* as a carcinogenic factor has been growing during the last 5 years[52], showing sometimes conflicting results, but it is clear that patients with AIG are the best group for such studies due to lifelong disease, hypochlorhydria, which provides a friendly environment for the wide spectrum of pathogens, and the fact that many of them (especially younger cohorts) have never been infected with *H. pylori*. Such studies may be extremely important, as the eradication of *H. pylori* strengthens the long-term trend for a decrease in the incidence of GC worldwide, and in many countries, it becomes a rare disease up to 2035 when the incidence reaches less than 6/100000 according to predictive modelling[53].

A strict decline in GC incidence will continue in many countries in which the prevalence of *H. pylori* and GC is high, as in Japan or in many Eastern European countries; however, in countries with low or moderate prevalence of *H. pylori*, the incidence of GC may increase[53], and this increase will not be related to *H. pylori* infection. In countries with multi-ethnic populations, such as the United States, several trends exist simultaneously. First, in many countries, the incidence of GC decreased in the older population (over 50 years old)[54], mainly due to the continuing trend from the middle of the last century as well as active *H. pylori* treatment started 25 years ago. Recently, it was shown that the eradication of *H. pylori* in a large (0.71 mLn) diverse population in the USA reduced GC risk substantially after 7-10 years of follow-up[55]. However, no decrease in GC incidence was noted in young cohorts (less than 50 years old)[54], and the estimated annual percentage change in GC incidence among non-Hispanic whites rose by 1.3% for persons younger than 50 years and fell by 2.6% for older individuals. These converging trends manifested a birth cohort effect that was more pronounced among women than men, with incidence among women born in 1983 twofold greater than those born in 1951[56]. The authors speculate that if this trend continues, CG incidence in females may exceed that in males in the United States by 2030.

Table 1 Etiology of chronic gastritis and risk of gastric neoplasia

Etiology	Initial gastritis topography	Topography of atrophic gastritis	Typical pre-neoplastic lesions/risk markers	Risk of the neoplasia	Typical age at presentation
Autoimmune	Parietal cells zone (fundus and partly body of the stomach)	Fundus and body of the stomach	Gastrin induced ECL-cells hyperplasia /dysplasia	Type 1 NETs[1]–high; GC-very low	70+
Autoimmune + *H. pylori*	Parietal cells zone + antrum	Pangastritis	Mixed	Type 1 NETs[1]-high; GC- low; Rarely both tumors in the same patient[13]	70+
H. pylori	Antrum	Antrum predominant	OLGA-III-IV atrophy, incomplete IM, dysplasia	GC-highest possible risk with trend to decline in countries with high prevalence	50-70+ (varies due to the prevalence of *H. pylori*)
Autoimmune + bacterial (*Streptococcus anginosus*)?	Pangastritis?	No data	No data	GC-very low with trend to increase	< 50, predominantly in women

[1]Usually two-third of Type 1 neuroendocrine tumors classified as Grade 1 during the diagnosis, however grade 2 or grade 3 gastric neuroendocrine tumors are associated with a larger size, deeper invasion, and extragastric recurrence, which require active treatment.
GC: Gastric cancer; IM: Intestinal metaplasia; ECL-cell: Enterochromaffine like cell; Type 1 NET: Type 1 neuroendocrine tumor; *H. pylori: Helicobacter pylori.*

The reasons for these trends are unclear, as the role of *H. pylori* as a major driver of gastritis progression in younger generations in developed countries diminishes owing to a decrease in the prevalence of infection in every younger cohort. Autoimmunity may be a good candidate, as the prevalence of autoimmune diseases increases in developed countries, and women are more predisposed to autoimmune diseases than men. However, it is difficult to induce carcinogenesis in the stomach without atrophic gastritis and changes in the gastric gland phenotype as a key event in this process; however, pernicious anemia as a marker of severe gastric atrophy is extremely rare in young or middle-aged women, as it requires many decades to develop. However, recent studies have demonstrated various levels of anti-parietal cell antibodies in children with diabetes or autoimmune thyroiditis at an early age, and some with the highest levels of autoantibodies demonstrated normocytic anemia[57,58]. It means that it is a lot of time for the atrophic gastritis to develop before the age of 50 years. Moreover, it is not known what level of decrease in gastric acid production is sufficient or necessary for changes in the gastric microbiome, which may be related to carcinogenesis, possibly severe gastric body mucosa atrophy associated with pernicious anemia is not an obligatory condition for such changes.

To date, no specific treatment has been developed for AIG. Micronutrient supplementation for deficiencies (iron and vitamin B_{12}) and symptomatic treatment of dyspepsia are the only universally accepted options[59,60]. Patients' diet may enhance postprandial symptoms like fullness and bloating if it contains a lot of fat and protein; however, fruits, vegetables, and dietary fibers are considered to be useful as alternative treatments for gastritis[61], but its efficacy has not been proven in controlled studies. Interestingly, some food components, such as wheat and barley protein and fucoidan, were found to alleviate symptoms and promote specific changes in the microbiome in patients with different types of atrophic gastritis[62,63].

Therefore, to evaluate the true risk of GC in AIG-specific cohorts, prospective studies must be selected. It should include patients with anti-parietal/anti-intrinsic factor antibodies, *H. pylori*-naïve, with atrophy in the body of the stomach, and preserved antral mucosa. Among the recently published studies, the cohort in the study published by Rugge *et al*[3] was very close to this description, except for the sex and age of the patients. It will be important to enroll in such prospective studies groups of women in the fourth decade of life, as they represent the only population in which the growth of GC incidence was predicted by epidemiological data[56]. Simultaneously, gastric microbiome changes need to be investigated during the progression of gastric atrophy with special attention to bacterial diversity and *S. anginosus* prevalence over time. To do that, we need the renaissance of AIG studies by joining the efforts of gastroenterologists, pathologists, and microbiologists, as at the beginning of the *Helicobacter* era 30 years ago.

FOOTNOTES

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