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Review

Gastritis and Gastric Cancer: Time for gastric cancer prevention

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SUMMARY

Gastric cancer represents a major clinical problem, associated with significant morbidity and mortality. Work over several decades has identified multiple risk factors for gastric cancer, which can be best classified as environmental and host-related factors. Gastric cancer is divided into intestinal-type and diffuse type. Precursor lesions for intestinal–type cancer are atrophic gastritis, intestinal metaplasia and dysplasia, while for diffuse type, that are less common, is the lack of intracellular adhesions (loss of E-cadherin protein). Currently, there are neither surveillance strategies nor clear-cut estimates of the benefits and risks of endoscopic surveillance. Thus gastroenterologists must individualize their approach to each patient, which may include frequent endoscopy, topographic mapping of the entire stomach, chromoendoscopy and magnifying endoscopy. In all cases of course the wishes of the patient must be factored in, but a frank discussion with patients and their relatives can be immensely helpful. Unlike colon cancer, for which clear and generally accepted guidelines have been developed over the years, the situation for gastric cancer remains still incompletely developed, reflecting, no doubt, our still limited understanding of gastric cancer pathogenesis. More work is needed to develop a rational and effective approach to the prevention of gastric cancer, mainly in the areas of the detection of early lesions and optimal allocation of limited resources to an effective screening program.

Key words: Gastric cancer, chronic gastritis, atrophic gastritis, intestinal metaplasia, gastric epithelial dysplasia, gastric cancer prevention.

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Gastric cancer represents a major clinical problem, associated with significant morbidity and mortality. The magnitude of this problem persists despite the recent fall in the incidence of non-cardiac gastric cancer, because of the unfortunate increase in recent years of the incidence of the cardiac type of gastric cancer, more specifically that which develops in association with Barrett's esophagus. This worrisome trend suggests the need for even greater vigilance concerning the early detection of gastric cancer, and more importantly, its prevention. One recent study from The Netherlands supports that patients with premalignant gastric lesions are at considerable risk for gastric cancer.[1] Here, we review the development of gastric cancer in the context of atrophic gastritis, present data on its prevention and discuss future directions.

GASTRIC CANCER: A BRIEF OVERVIEW

Despite the decline in its incidence in the West, gastric cancer still remains the most frequent type of cancer in Asia, the third in Eastern and South Europe and South America, and the fourth most common cancer worldwide. Ninety percent of gastric malignacies are adenocarcinomas and the rest are non-Hodgkin lymphomas and leiomyosarcomas (Table 1).

Work over several decades has identified multiple risk factors for gastric cancer, which can be best classified as environmental and host-related. Environmental factors include the subject's socioeconomic status and dietary factors, such as nitroso compounds, salt, folate, smoking and alcohol. Host-related factors include prior gastric surgery, infection with the Epstein-Barr virus or *Helicobacter pylori* and factors such as blood group, familial predisposition, genetic polymorphisms, gastric polyps, hypertrophic gastropathy and immunodeficiency syndromes, gastric ulcer, pernicious anemia. As often is the case, here too the interplay between host and environmental factors has assumed a critical role.

Table 1. Anatomical and histological features of gastric cancer

Gastric cancer by site
Gastroesophageal junction
Proximal stomach
Distal stomach
Body
Antrum
Gastric cancer by morphologic type
Intestinal type
Diffuse type

GASTRITIS AND ITS RELATIONSHIP TO GASTRIC CANCER

Gastritis is the inflammation of the gastric mucosa. Associated with mucosal injury, gastritis is classified as *acute,* characterized histologically by neutrophilic infiltration, and *chronic*, whose histological hallmark is infiltration of the mucosa by mononuclear cells such as lymphocytes, plasma cells and macrophages (Table 2).

Chronic gastritis is sub-divided into non-atrophic and atrophic.[2] When the anatomical distribution of chronic gastritis is taken into account, further subclassifications have been used to discribe th eseemingly protean variations of this entity. Thus, the non-atrophic type is further classified as antral-predominant gastritis (superficial gastritis, diffuse antral gastritis, chronic active gastritis) and pangastritis (nonulcer pangastritis). In a similar manner, the atrophic type is also subclassified as multifocal atrophic gastritis (progressive intestinalized pangastritis, metaplastic atrophic gastritis) and corpus-predominant gastritis (autoimmune gastritis, diffuse corporal gastritis, type A gastritis).

The discovery of *H. pylori* as an aetiolgical agents of gastritis has been a step in the right direction. *H. pylori* has altered in a major way our understanding of this rather diverse group of nosological entities, unifying and elucidating sevral apparently disparate entities. Infection with *H. pylori* is a major cause of non-atrophic chronic gastritis and is associated with gastric ulcer disease and distal gastric carcinoma. Multifocal atrophic gastritis is also caused by *H. pylori* but other environmental and/or genetic factors are also causative. For corpus-predominant gastritis autoimmune response to parietal cell antigen and a familial predisposition are important factors. This type of chronic gastritis is associated with pernicious anemia, gastric carcinoma and other autoimmune diseases (Hashimoto's thyroiditis, Insulin-Dependent Diabetes Mellitus, Addison's disease).

Table 2. Classification of gastritis

Definition of gastritis: Inflammation of the gastric mucosa that is associated with mucosal injury.	
Acute:	Neutrophilic infiltration
Chronic:	Infiltration by mononuclear cells (lymphocytes, plasma cells and macrophages)
	Non-atrophic types (inflammation)
	Antral predominant
	Pangastritis
	Atrophic types (loss of glands, intestinal metaplasia)
	Multifocal atrophic
	Corpus predominant

Histologically, atrophic gastritis is characterized by progressive atrophy of the glandular epithelium with loss of parietal cells, chief cells and also endocrine cells. Glandular atrophy results in hypochlorhydria with the consequent increase of gastric pH; decrease in luminal ascorbic acid; increase in serum gastrin; and finally microbial colonization and nitrosation. The loss of endocrine cells is not inconsequential; in fact, it leads to two important changes: decreased levels of epidermal and transforming growth factors and decreased regeneration of damaged tissue.

In one study of patients with atrophic gastritis, the risk of development gastric cancer during 4.4 years average follow up was 5.7.[3] Another study showed that in patients with fundic atrophic gastritis, the risk of development gastric cancer was 5.76.[4]

It is evident from what mentioned above that the world of gastritis is characterized by multiple, often redundant terminology and seemingly endless sub-classifications. That multiple terms for each category encountered in the literature reflects years of research and the difficulty of gastroenterologists and pathologists in reaching concensus. The deeper reason for the extensive sub-classification of gastritis lies perhaps in the lack of a unifying mechanistic understanding of gastritis that may reflect either our limited grasp of what is really essential or the widely ranging contributing factors. The latter should not be surprising, given the strategic location of the stomach in the communication in terms of exposure of the gastrointestinal tract to the outside world.

INTESTINAL METAPLASIA AND THE INCREASED RISK OF GASTRIC CANCER

Gastric cancer is classified as being of the intestinal-

type and of the diffuse type. Precursor lesions for intestinal–type cancer are atrophic gastritis, intestinal metaplasia and dysplasia, while for diffuse type, that is less common, lack of intracellular adhesions (loss of E-cadherin protein) are considered precursor lesions.

Intestinal metaplasia represents the replacement of the surface, foveolar and grandular epithelium in the oxyntic or antral mucosa by intestinal epithelium, which is recognized by the presence of goblet cells. In multifocal atrophic gastritis, intestinal metaplasia is patchy and progresses with time. It begins in the lesser curvature, often at the angularis, from which it spreads proximally and distally. In corpus-predominant gastritis, intestinal metaplasia is marked in the body, while the antrum is spared. Intestinal metaplasia is classified as: complete or type I (small intestinal epithelium with absorptive, Paneth's and goblet cells that secrete acidic sialomucins) and incomplete type (it resembles colonic mucosa, with fewer goblet cells that secrete acidic and sulfomucins). Depending on the type of mucins that are present, incomplete intestinal metaplasia is subclassified as type II, in which acidic sialomucins predominate, and type III with sulfomucins predominating.[5]

Remarkably, the increased risk for gastric cancer correlates primarily with the presence and extent of intestinal metaplasia type III. Age seems to be an important factor, as the occurrence and extent of type III intestinal metaplasia increased with advancing age; the underlying mechanism is obscure. The crucial point here is that patients with intestinal metaplasia have a >10 fold increased risk of developing gastric cancer, which may be even higher in some countries (e.g. Japan) or in patients with *H. pylori* infection.[6] An 11% risk of gastric cancer is reported in patients with gastric atrophy or intestinal metaplasia over a 10-year follow-up period.[7] One recent study from Japan supports that *H. pylori* eradication does not reduce the histologic gastric intestinal metaplasia score, but changes its the cellular phenotype, and this may be an important factor in the reduction of gastric cancer incidence.[8]

ASPECTS OF GASTRIC CANCER PREVENTION

Currently, there are neither surveillance strategies nor clear-cut estimates of the benefits and risks of endoscopic surveillance. Thus gastroenterologists must individualize their approach to each patient, which may include frequent endoscopy, chromoendoscopy and magnifying endoscopy. In all cases of course the wishes of the patient must be factored in (and respected), but in our experience a frank discussion with patients and their relatives can be immensely helpful.

Endoscopic surveillance

Biopsy mapping of the stomach (according to the updated Sydney system) requires at least five biopsy specimens: two from the antrum within 2-3 cm from the pylorus (one from the distal lesser curvature and the other from the distal greater curvature); two from the corpus about 8 cm from the cardia (one from the lesser and the other from the greater curvature); and one from the incisura angularis. Biopsy specimens should also be obtained from any visually suspicious areas. More extensive biopsy mapping of the gastric mucosa may be required in high-risk individuals.[9]

The low incidence of gastric cancer in developed countries seems to make a surveillance program impractical. Despite the association with cancer, the presence of intestinal metaplasia is neither sufficiently sensitive nor specific enough to guide surveillance strategies. In one recent review of the management of patients with intestinal metaplasia in the US, it is reported that for most USA patients the risk of progression to cancer is low and surveillance is not clinically indicated for the "average risk" patient.[10]

Endoscopic surveillance must be individualized and must take into consideration several relevant parameters, including the extent and severity of gastric atrophy, the extent and type of intestinal metaplasia, the family history and ethnic background, and the findings of careful topographic mapping of the entire stomach which must also include additional biopsies from any endoscopically visible abnormalities. Endoscopic surveillance must be seriously considered in the presence of high risk gastritis (corpus gastritis, intestinal metaplasia, gastric atrophy). We believe that if multifocal atrophic gastritis is present, surveillance every 1-3 years should be considered.

Gastric epithelial dysplasia

Gastric epithelial dysplasia is a neoplastic epithelial proliferation characterized by variable cellular and architectural atypia, and like dysplasia in other organs, it is classified as low-grade dysplasia (LGD) and high-grade dysplasia (HGD). Gastric epithelial dysplasia is most commonly found in multifocal atrophic gastritis, particullary in the antrum or the incisura and in close anatomical proximity to the cancer in 40-100% of early gastric cancers and 5-80% of advanced adenocarcinomas.[11] Often the presence of gastric epithelial dysplasia is associated with cancer elsewhere in the stomach. In many cases there are no endoscopic abnormalities in the surrounding mucosa that would make a strong case for the underlying deterioration towards neoplasia. Various endoscopic patterns may

be seen, including mucosal abnormalities in a background of atrophic gastritis, erosions, ulcers, mucosal scars, diffuse inflammatory changes, plaques and polyps, but none is diagnostic although they should raise our threshold of diagnostic suspicion. This notion is reinforced by the findings of a series of 1900 cases from Japan which examined the context in which early gastric cancers developed. In this series, 94.8% of the cancers arose an area of irregularity within atrophic gastritis, and only 2.5% were seen in association within an adenoma.[6]

A well-appreciated problem in the identification and grading of gastric epithelial dysplasia is the significant intra-observer and inter-observer variability. For this reason, it is recommended that before management decisions are made, two expert pathologists should agree on a diagnosis of HGD[12]. Patients with confirmed HGD are at significant risk for harboring a prevalent or incident cancer. Both retrospective and prospective European studies of patients with HGD report alarmingly that the incidence of cancer detection with endoscopic surveillance ranges from 33-85%[12-17]. LGD regresses in 38-75% of cases but it persists in 19-50%. HGD regresses in only 0-16% of cases and persists in 14-58%[11,13]. LGD progresses to adenocarcinoma in 0-23% of cases within a mean interval of 10 months to 4 years. In HGD the rate of malignant transformation ranges from 60-85% over a median interval of 4 to 48 months[13,14,16,18]. Chromoendoscopy and EUS are used to evaluate the extent and depth of the lesions. Complete excision of mucosal lesions must be performed by endoscopic mucosal resection (EMR), in many cases obviating the need for surgical resection. Mucosal lesions not amenable to endoscopic resection and those with a submucosal component are managed best with surgical resection.[19]

If LGD is detected in a patient with intestinal metaplasia, surveillance endoscopy with a topographic mapping biopsy strategy should be performed every 3 months, at least for the first year. Such arduous surveillance should be suspended when two consecutive endoscopies show completely negative results. Because of the high probability of coexisting invasive adenocarcinoma, patients with confirmed HGD should undergo surgical or endoscopic resection[20]. Regarding the follow-up surveillance there are not standard data and each case must be individualized. However, after successful resection of a dysplastic lesion, endoscopic surveillance every 1-2 years appears reasonable. Patients with confirmed HGD should be considered for gastrectomy or local endoscopic mucosal resection. If *H. pylori* infection is identified, eradication therapy should be considered. Usually by the time the epithelium is dysplastic, the changes are irreversible, but even late eradication, may arrest progression of the carcinogenenic process by eliminating the stimulus provided by persistent chronic inflammation[21].

ASGE guidelines

The ASGE guideline for gastric intestinal metaplasia and dysplasia[22] include the following:

- Endoscopic surveillance for gastric intestinal metaplasia cannot be uniformly recommended as this entity has not been extensively studied in the US.
- Patients at increased risk for gastric cancer due to ethnic background or family history may benefit from surveillance.
- Endoscopic surveillance should incorporate topographic mapping of the entire stomach.
- Patients with confirmed HGD are at significant risk for progressing to cancer and should be considered for gastrectomy or local (eg, endoscopic) resection.

CONCLUCIONS

Unlike colon cancer, for which clear and generally accepted guidelines have been developed over the years, the situation for gastric cancer remains still incompletely developed, reflecting, no doubt, our still limited understanding of gastric cancer pathogenesis. While significant progress has been made in the last two decades, reflected in evolving classifications of gastritis, mush remains to be accomplished. Evidenced by seemingly endless sub-classification schemes, our understanding of gastritis is still incomplete and we lack a unifying mechanistic insight into this common disease. The appreciation of the role of *H. pylori* in the pathogenesis of gastritis and gastric cancer has brought a level of clarity for a sizable fraction of the cases of gastritis, but it is clear that much remains to be accomplished.[23]

The most frightening clinical consequence of gastritis is its ability to transition to the various grades of dysplasia and eventually to gastric cancer that, sadly, remains a significant source of cancer mortality worldwide. It is this often lethal possibility that concerns us physicians the most and dictates a level of vigilance when dealing with such patients. This concern is exacerbated by the absence of clear guidelines for screening and surveillance of these patients.

Two developments hold significant promise. The ability to endoscopically remove premalignant and even some of the malignant gastric mucosa without resorting to drastic surgery (gastrectomy) will make a real difference in the care of these patients. When simplified and widespread,

the impact of endoscopic mucosal resection on gastric cancer and the quality of life of these patients will be real and immediate. The second area where significant progress is expected is in the development of methods for the noninvasive detection of genetic abnormalities associated with early stages of gastric carcinogenesis. Methods to detect such changes in, for example, gastric cells detected in stool, could revolutionize gastric cancer screening and surveillance. Many laboratories around the world are in pursuit of such approaches and the next decade should bring some welcome (and badly needed) progress. In between, however, optimization of the use of the available endoscopic methods should be a fruitful area of investigation.

It is clear that the problem of gastric cancer demands significant attention. Gastric cancer is clinically very important because of a) its attendant morbidity, mortality and worldwide incidence and b) the gaps in our knowledge that preclude the development of cost-effective and widely applicable methods for its prevention or cure. As often is the case in medicine, more work is needed, but we should also acknowledge the tremendous progress that has been made. Indeed, we have good reasons to be optimistic.

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