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Gastric cancer: pathogenesis, risks, and prevention

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Intestinal (IGCA) and diffuse (DGCA) gastric adenocarcinomas, the two main microscopic subtypes, are dissimilar regarding their epidemiological and demographic characteristics. Both tumor types comprise approximately 40% of all gastric adenocarcinomas. The DGCAs more often occur in young age groups, more often affect the corpus, and are less infrequently associated with atrophic gastritis and intestinal metaplasia than the IGCAs. The risk of both DGCA and IGCA is increased in the presence of *Helicobacter pylori* infection, and the risk rises with increases in grade and extent of atrophic gastritis and intestinal metaplasia. It is likely that the development of up to 80% of the DGCAs and IGCAs can be prevented with early eradication of the *H. pylori* infection. The pathogenesis and morphogenesis of DGCAs are unknown, but the morphogenesis of IGCAs includes identifiable precancerous conditions such as atrophic gastritis and intestinal metaplasia as well as identifiable precancerous lesions (adenomas, dysplasias). Atrophic gastritis is a direct result of the *H. pylori* infestation. Atrophic gastritis, for unknown reasons, appears in more than half of the infected subjects during their lifetime. *H. pylori* gastritis triggers a variety of reactions, with the reaction cascades resulting in errors of the cell genome and ending up as neoplastic tumors.

Key words: gastric cancer, chronic gastritis, *Helicobacter pylori*, atrophic gastritis, carcinogenesis

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Introduction

Up to 80% of gastric adenocarcinomas (GCAs) are related to *Helicobacter pylori* infection and subsequent gastritis. Most of the gastritis is atrophic and exhibits intestinal metaplasia in the underlying mucosa.[1] Autoimmune, corpus-limited atrophic gastritis, which may or may not be related to a preceding *H. pylori* infection, is a definite risk condition for gastric cancer. These autoimmunity-related cases comprise approximately 10% of all gastric cancers in northern Europe[2] but may be less frequent in other parts of the world.

Although *H. pylori* infection is a key phenomenon in triggering gastritis-related carcinogenic events in most cases, the relation between gastric cancer and atrophic gastritis of the autoimmune type suggests that the presence of *H. pylori* organisms is not a necessity, and the requirement for the development of gastric carcinoma is atrophic gastritis. In *H. pylori*-related chronic gastritis, it is conceivable that the cascade of events initially triggered by the infection result in errors in the cell genome. These cascades are obviously manifold and merely relate to acute and chronic inflammation, sequelae of atrophic gastritis, intestinal metaplasia, or hypochlorhydria than primarily to the *H. pylori* organisms themselves.[3]

In Western and other parts of the world, the incidence of GCA has markedly decreased over the past decades.[4] This decrease is a global event, suggesting that one or more globally and generally common factors play a critical role in the pathogenesis of GCA; and, moreover, that this factor or factors have decreased in influence worldwide during the past few decades. These etiopathogenetic factors are hardly exotic differences in local habits of eating or drinking alone. Such exotic and local factors cannot explain the striking consistency of the global epidemiology of GCA. Regarding *H. pylori* infection as a key factor in the pathogenesis of gastric cancer, however, the requirements of globality are fulfilled.

Atrophic gastritis

Helicobacter pylori-related atrophic gastritis may occur as an antral- or corpus-limited infection, but it is most often multifocal (multifocal atrophic gastritis, MAG), affecting both the antrum and corpus of the stomach to a varying extent and grade.[2,5] In *H. pylori*-infected subjects, atrophic gastritis and intestinal metaplasia increase in prevalence with increasing age, but these changes are rare before the age of 30 in Western populations.[5–7] Direct long-term follow-up studies of patients with *H. pylori* gastritis show that more than half of the infected patients suffer from atrophic gastritis during their lifetime.[8,9] In a 32-year follow-up study, 20 (30%) of 66 patients with nonatrophic *H. pylori* gastritis in the corpus mucosa did get atrophic gastritis.[8] In a population-based endoscopic series from Finland during the 1970s,[6] 60% of subjects > age 65 with chronic gastritis had atrophic gastritis in the antrum or corpus, and 49% had intestinal metaplasia in the biopsy specimens, indicating that the lifetime risk of atrophic gastritis is high among *H. pylori*-infected individuals. Among Finnish centenarians,[10] advanced atrophic gastritis (serum pepsinogen I below 28 μg/l) was found in 36% of 173 subjects and positive *H. pylori* serology in 66%.

Progression of *H. pylori* infection into atrophic gastritis may be based, for example, on differences in the cytotoxicity of the *H. pylori* strains; differences in genetic liability of the host to atrophy; differences in diet; the presence or absence of vitamins, micronutrients, or salt in the dietary environment; or differences in smoking habits.[2,11–14] All these factors have been implicated as playing a role in the pathogenesis of gastric cancer and possibly in the pathogenesis of atrophic gastritis. A possibility exists that environmental factors not only contribute to the development of atrophic gastritis or gastric cancer but may also play a role in the risk of acquiring the *H. pylori* infection.[2,14]

Gastric cancer

Morphogenesis

The intestinal (IGCA) and diffuse (DGCA) subtypes of gastric adenocarcinomas are markedly different entities regarding their epidemiology and biological background.[15] DGCA tumors occur more often in young age groups (< age 50 years) than the IGCA tumors. In contrast to IGCA, the DGCA tumors are equally frequent in males and females and appear at sites in the corpus and fundus more often than the IGCAs.[15] Morphogenetically and microscopically, the IGCAs resemble ordinary adenocarcinomas of the gastrointestinal tract, and their precursor lesions show morphogenetic steps from mature intestinal epithelium (intestinal metaplasia) to overt cancers.[14,16–20] The DGCAs appear as scattered single mucous cells (signet-ring cells, mucocellular cells) without differentiation to form glandular or ductular structures. The morphogenesis of gastric cancer is presented in Fig. 1.

The dissimilar morphogenesis of IGCA and DGCA may result from differences in the type of genetic errors that appear during carcinogenesis. These errors may occur in genes that regulate synthesis of the cell adhesion molecules. Down-regulation of the expression of the cell adhesion molecules may contribute to the development of gastric cancers that are of the DGCA

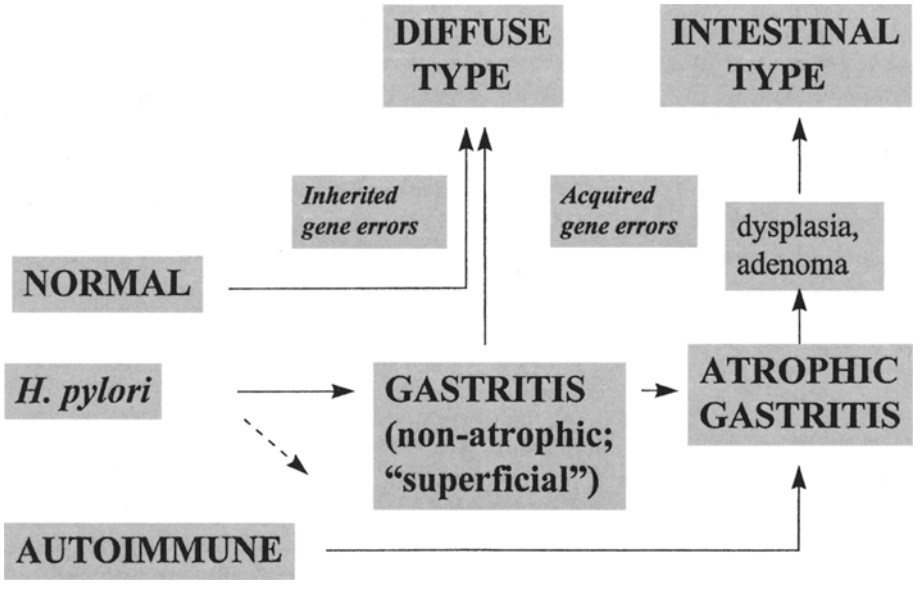

Fig. 1. Known pathogenetic steps in the morphogenesis of gastric cancer of intestinal and diffuse subtypes

type.[21,22] Expression of the cell adhesion molecules may, on the other hand, be required for formation of tumors of the IGCA type.[22]

Sex-related differences: protective influence of estrogen?

Gastric cancer is known to occur approximately twice as often in males as in females. This is due to the IGCA tumors, which strongly predominate in males, whereas the DGCA tumors occur equally often in males and females. The male predominance of gastric cancer cannot be explained with *H. pylori* infection or its sequelae. A proper analysis of the male/female (M/F) ratio of the incidence of gastric cancer provides some new views.[23] The M/F ratio of the GCA incidences rises with increasing age and reaches a peak at age 60, after which the ratio decreases. The form and magnitude of this "bell shaped form" of the age-specific curve of the M/F ratio is independent of the incidence of gastric cancer or of the prevalence of *H. pylori* gastritis in the population. The reason for the high M/F ratio is that the IGCA tumors begin to appear in males at an earlier age (age before 60) than in females, and that there is a delay of 10–15 years between males and females before IGCAs appear. Among women, the IGCA tumors begin to increase progressively in prevalence at and after age 60 (menopause), resulting in a decrease in the M/F ratio of cancer incidence. The most logical explanation for this gender-related difference is that the sex hormones, obviously estrogen somehow protect women from IGCA. Hence this type of gastric tumor begins to be common in women only after menopause. In an early Italian study of 339 female GCA patients after menopause[24] the GCA risk was found to be inversely related to the duration of fertility and to the late age of menopause, suggesting that female sex hormones are protective.

Atrophic gastritis–gastric cancer relation

Different topographical phenotypes of nonatrophic and atrophic gastritis show dissimilarities concerning the risk of gastric cancer (Fig. 1) and of other gastric disorders (Fig. 2). The cancer risk is highest in patients with advanced severe atrophic gastritis, particularly among those in whom advanced atrophy occurs in both the antrum and the corpus. In these cases the relative risk of GCA may even be 90-fold compared to the cancer risk for subjects with a normal, healthy stomach.[25] Correspondingly, the risk of peptic ulcer disease is emphasized in those with gastritis that is nonatrophic and predominantly antral (Fig. 2).

Compared to the cancer risk in normal, healthy stomach, the presence of nonatrophic *H. pylori* gastritis raises the cancer risk approximately twofold.[25] Correspondingly, even though the gastric cancer risk is low in patients with duodenal ulcer disease and with nonatrophic *H. pylori* gastritis, this cancer risk may be higher than the risk of cancer in subjects with healthy, normal stomach. This means that duodenal ulcer disease does not protect from gastric cancer, although the cancer risk in duodenal ulcer patients is lower than expected (i.e., lower than the cancer risk for the general population).

Gastritis (atrophic gastritis in particular) results in functional failure of the gastric mucosa. Atrophy means a loss of normal glands that subsequently results in failure of the antral and corpus mucosa to secrete gastrin, hydrochloric acid, intrinsic factor, and pepsinogens. Serum levels of pepsinogens (pepsinogen groups I and II)

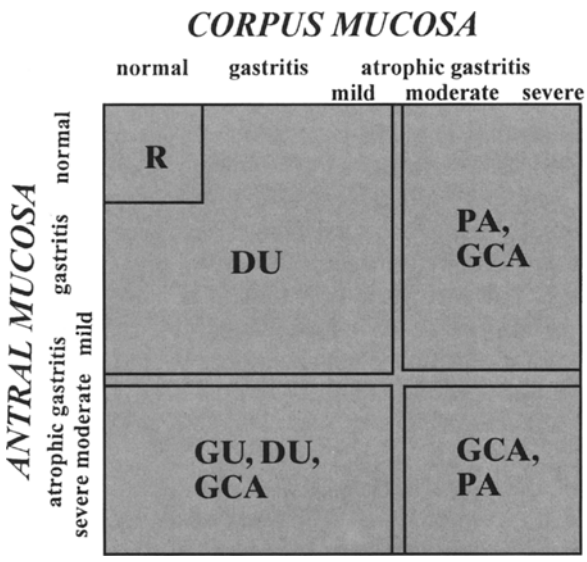

Fig. 2. Increased risks of gastric cancer and other gastric disorders in various topographic phenotypes of atrophic gastritis (i.e., in relation to the presence or absence of atrophic gastritis in the antrum, corpus, or both)

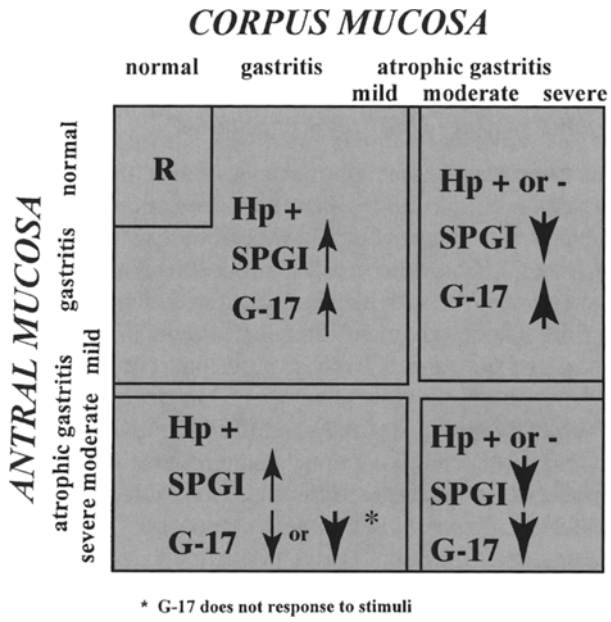

Fig. 3. Expected results in assays of *H. pylori* antibodies, serum levels of pepsinogen I and gastrin-17, and response of antral mucosa to secrete gastrin-17 into the circulation after a meal stimulus for various topographic phenotypes of atrophic gastritis

and gastrin-17, as well as the response of antral G cells to secrete gastrin-17 after a dietary protein stimulus, are tools that could be used as indirect, noninvasive measures of topography and extent of atrophic gastritis in the stomach. Examples of the use of these laboratory measures concerning the risk conditions of GCA and other gastric disorders are presented in Figs. 2 and 3.

Gastric cancer in atrophic gastritis of autoimmune origin

Corpus-limited autoimmune-type atrophic gastritis is a condition in which the cancer risk is three- to fivefold higher than the risk in subjects with a normal, healthy stomach.[25,26] The cancers are of the IGCA type in these patients and occur most often in the corpus and fundus, although occasionally in the antrum.

In a meta-analysis of six follow-up studies (follow-up 9–15 years) including more than 600 patients with pernicious anaemia and severe atrophic corpus gastritis,[26] the annual incidence of cancer varied from 0 to 1% (median 0.6%), and the proportion of cancers associating with the autoimmune atrophic gastritis varied from 0 to 14.8% (median 6.0%) among all cancer patients. In a more recent endoscopic follow-up of 105 pernicious anemia patients in Finland for 7 years on average, the cumulative lifetime prevalence of gastric cancer was 3% and that of carcinoid tumors 4%.[27]

Errors in cell genome

Studies on cancer itself or on precancerous lesions indicate a large variety of mutations in the tumor cell genome, unexpected expression of oncogenes, and changes in gene stability.[28] These changes may appear at quite early stages of *H. pylori* gastritis, much before the appearance of overt precancerous and neoplastic lesions. This is demonstrated, for example, by the occurrence of abnormal synthesis of mucus glycoproteins [e.g., Lewis blood groups, Ca 19-9, sialyl Le(x)] and unexpected expression of abnormal gene products (K-*ras*) in gastritic stomach or intestinal metaplasia with no evidence of coexisting, overt precancerous lesions such as dysplasia or adenoma.[29–37] It seems plausible that an array of various genotoxic affections are triggered by the *H. pylori* gastritis, and that the resulting genetic errors may play a role as effector mechanisms modulating the further course and outcomes of the *H. pylori* gastritis. Correspondingly, it is possible that even atrophic gastritis and intestinal metaplasia may result from unknown mutations in epithelial cell genes and thus may be due to an imbalance between proliferation and death (apoptosis) of the epithelial cells.[38]

There are no studies so far showing that *H. pylori* itself produces mutagenic or carcinogenic substances. The molecular mechanisms of the carcinogenesis of gastric carcinoma are, correspondingly, largely unknown. There is, however, no doubt that these lesions of the genes in epithelial cell genes are manifold, or that these changes are of ultimate importance and final events in the pathogenesis of gastric cancer, possibly in the pathogenesis of atrophic gastritis and intestinal metaplasia as well.[39]

None of the genetic errors identified so far in gastric cancer are specific or unique.[28] The prevalence and type of genetic errors vary between intestinal- and diffuse-

type cancers and between individual cancers with the same cancer subtype. Some of the cancers may show expression of a specific abnormal gene, whereas others of similar microscopic type do not,[37,39] indicating that gastric cancer may not be a monomorphic entity but varies in genotype.

Mutations of the *p53* gene are the most common genetic changes found in human cancers so far, occurring in more than 60% of all cancers.[40–43] These mutations lead to errors in the expression of cell cycle inhibitory genes such as *pic1* and result in overexpression, for example, of cyclin E and finally in dysregulation of cell growth. There is a high prevalence of single base-related alterations in the *p53* gene, particularly including conversions of G:C to A:T.[42] The base mutations of this type are considered to be especially induced by *N*-nitroso compounds, thereby providing evidence that cellular genes are molecular targets of the environmental mutagens that are thought to play a role in gastric carcinogenesis and that appear in atrophic, hypochlorhydric stomach.

Allelic deletions of the *APC* (adenomatosis polyposis coli) and *MCC* (mutated in colon cancer) genes on chromosome 5q are found in 64% of gastric cancers but seem never to occur without the loss of the p53 allele.[44] Activation of K-*ras* and c-*erb* and abnormal transcription of CD44 are common events in gastric cancer but seem to vary in frequency between intestinal- and diffuse-type cancers.[28]

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