GASTRITIS AND GASTRIC CANCER Western Countries

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Western Countries

Pentti Sipponen [1] **MD, PhD**
Barry J. Marshall [2] **MBBS, FRACP, FAA, FRS**

[1] Department of Pathology, Jorvi Hospital, Espoo; and Biohit, Ltd., Helsinki, Finland (PS)
[2] The NHMRC Helicobacter pylori Research Laboratory, Queen Elizabeth II Medical Centre, Nedlands, Western Australia (BJM)

Address reprint requests to
Pentti Sipponen, MD
Department of Pathology
Jorvi Hospital
02740 Espoo
Finland
e-mail: pentti.sipponen@jorvi.ushp.fi

Atrophic gastritis and intestinal metaplasia are well-accepted precancerous conditions for gastric cancer, excluding cancers at the gastrointestinal junction and lower esophagus. [6] [46] Of gastric carcinomas, 80% are related to *Helicobacter pylori* gastritis; most of this gastritis is atrophic in the microscopic phenotype and exhibits intestinal metaplasia as an underlying mucosal lesion, in addition to the loss of mucosal glands. [33] *H. pylori* gastritis progresses gradually, within years to decades, from the nonatrophic form into the atrophic form. Atrophic gastritis is the morphologic phenotype of *H. pylori* gastritis in more than half of infected individuals. In 1994, the International Agency for Research on Cancer, Lyon, France (IARC) classified *H. pylori* infection as a carcinogenic agent (class 1) that triggers cascades that, on a multifactorial basis, may lead to the appearance of gastric malignancies in a percentage of affected subjects. [33]

Autoimmune, corpus-limited atrophic gastritis is a relatively common disease in Europe (in Nordic Europe in particular), and it is often expressed with a concomitant pernicious anemia and neurologic damage caused by deficiency of vitamin B_{12} . In addition to *H. pylori* gastritis, atrophic gastritis of the autoimmune type is a definite risk factor for gastric cancer and is related on average to nearly 10% of all gastric cancers in endemic areas. [51]

The relationship between gastric cancer and atrophic gastritis of the autoimmune type suggests that the presence of *H. pylori* organisms is not necessary for the development of gastric malignancy in atrophic gastritis, although *H. pylori* is the key phenomenon in the triggering of the gastritis-related processes and the subsequent carcinogenic events. It seems likely that the eradication of *H. pylori* nullifies and prevents the influences of other carcinogenic mechanisms that play a role in the pathogenesis of gastric cancer--the early eradication of *H. pylori* prevents the triggering of the reaction cascades that later end up as cancers in some infected subjects. Concerning *H. pylori*-related chronic gastritis, it is conceivable that the cascades of events, which are initially triggered by the infection, result in errors of the cell genome and that these final cascades in gastric carcinogenesis are manifold and related more to acute and chronic inflammation, atrophic gastritis, intestinal metaplasia, or hypochlorhydria than to the presence of *H. pylori* organisms by themselves. [6] There is an inverse relationship between the degree of *H. pylori* colonization in the stomach and cancer risk. The cancer risk tends to be highest in severe atrophic gastritis and in hypochlorhydric stomachs, in which cases the colonization of the gastric mucosa with *H. pylori*

organisms often is low and scanty. Correspondingly the cancer risk is low, even though increased, in nonatrophic gastritis in which the *H. pylori* colonization is highest and most intense in degree.

In the developed Western world, the incidence of gastric carcinoma has decreased markedly. [11] In developed countries, gastric carcinoma is no longer the most prevalent cancer type, as it tended to be some decades earlier. From an epidemiologic viewpoint, the decrease of gastric carcinoma incidence seems to be a similar, general, and global event throughout the Western world, suggesting that one or more globally and generally common factors play a critical role in the pathogenesis of gastric carcinoma and that these factors have decreased in influence worldwide. [37] These etiopathogenetic factors cannot be exotic, and they cannot be differences in local habits of eating or drinking only. Such exotic and local factors hardly can explain the striking consistency of the global epidemiology of gastric carcinoma, particularly the similarity in the decrease of the gastric carcinoma incidence worldwide. Regarding *H. pylori* infection as a global cancer-promoting factor, the requirements of the globality are fulfilled-- *H. pylori*-related gastritis and the subsequent atrophic gastritis and intestinal metaplasia are lesions that affect humans globally.

Changes in the epidemiology of gastric carcinoma should be associated with similar changes in the epidemiology of chronic gastritis, atrophic gastritis, and intestinal metaplasia if it is assumed that *H. pylori* infection is the initial cause of the events that lead to cancer. This seems to be the case: A decrease of gastric carcinoma incidence is associated with a corresponding decrease in the prevalence rate of *H. pylori* and atrophic gastritis in Western populations. [37] Although incidence of gastritis and atrophic gastritis is decreasing in many populations, atrophic gastritis and intestinal metaplasia, when acquired, are similar premalignant conditions at the individual level as they were the risk conditions at the individual level for gastric carcinoma several decades earlier. At the population level, the prevalence of atrophic gastritis largely depends on the incidence rate of *H. pylori* acquisition. [33] Among individuals infected with *H. pylori*, the proportional share of people who progress to atrophic gastritis may vary among the populations. It is possible that the pathogenesis of atrophic gastritis in *H. pylori*-infected subjects is multifactorial, and the likelihood of acquiring atrophic gastritis can depend on genetic factors and on the interplay of many other environmental factors than *H. pylori* alone. [6] [7] [8] [9] [32] [56] In general and on average, however, the prevalence of atrophic gastritis is high in populations in which *H. pylori* infection rate is high and low in countries or populations in which *H. pylori* infection rate is low.

ATROPHIC GASTRITIS

Atrophy means a loss of normal mucosal glands. This atrophy results in loss of normal physiologic functions of the gastric mucosa; these dysfunctions, correspondingly, contribute to the appearance of various gastric disorders and increase in severity with increasing grade and extent of the atrophy. [14] In corpus, atrophic gastritis is associated with a reduction of the acid output; this reduction ends up, along the progression and extension of atrophic gastritis, in achlorhydria in subjects with severe atrophic gastritis. Correspondingly, atrophic gastritis in the antrum is reflected by an impairment of the antral G cell function. This impairment is reflected as a poor serum gastrin response to various stimuli. In severe atrophic antral gastritis, all G cells are practically absent, and the gastrin-17 fraction is null or minimal in the blood, even in the presence of achlorhydria or protein stimulus. [44]

Atrophic gastritis may occur as antral or corpus limited but is most often multifocal *(multifocal atrophic gastritis)*, affecting antrum and corpus in varying extent and grade. [3] [45] In chronic gastritides of *H. pylori* origin, the atrophic changes first appear in the antral mucosa and in its small curvature in particular and gradually show a pylorocardial extension with time and increasing age. [21] In autoimmune atrophic gastritis, the antral mucosa is normal, unaffected, resulting in a high serum gastrin-17 level because of a normal number of antral G cells, which maximally secrete gastrin in the achlorhydric stomach.

It is likely that *H. pylori*-related chronic gastritis occasionally ends up as severe corpus-predominant or corpus-limited atrophic gastritis, resembling the corpus-limited atrophic gastritis of autoimmune origin, in which cases the progression of atrophic lesions in corpus is associated with a healing of the antral mucosa. [1] [20] [53] This healing may result from emphasis of the colonization of *H. pylori* in the corpus and on the absence of bacteria in the antrum in subjects in whom the acid output is endogenously low and decreases further with the progression of atrophic gastritis in the corpus. [26] The progression of hypochlorhydria that follows the extension of atrophic gastritis is associated with a shift of the infection from antrum to corpus.

GEOGRAPHIC DIFFERENCES IN THE TYPE AND PREVALENCE OF ATROPHIC GASTRITIS

A few studies indicate that some racial differences occur in the prevalence of *H. pylori*-related atrophic gastritis among different populations and countries. An old study using methylene blue-spraying endoscopy showed that atrophic gastritis was more severe and extensive in all age groups of Japanese outpatients compared with Canadian outpatients. [23] Based on comparison of the serum levels of pepsinogen I (SPGI) (pepsinogen A), [35] advanced atrophic corpus gastritis (SPGI <17 mug/L) was found to be more prevalent among Japanese (4.4%) than Dutch people (1.6%). In a more recent unpublished endoscopic and bioptic investigation of Japanese and Swedish patients with peptic ulcer disease, atrophic antral gastritis was found to be significantly more frequent and severe in Japan than in Sweden. Duodenal ulcer disease was the prevailing peptic ulcer type in Sweden, whereas gastric ulcer predominated in Japan, and this ulcer type was associated with the atrophic gastritis in particular. Among duodenal ulcer patients, no differences occurred in the grade or extent of atrophic gastritis between the two patient populations.

The dissimilarities in the progression of *H. pylori* gastritis into atrophic gastritis may be based on differences in cytotoxicity of the *H. pylori* strains between different populations; on differences in the genetic liability of the host to acquire atrophic gastritis; on differences in the diet; on the presence or absence of vitamins, micronutrients, or salt in the dietary environment; or on differences in smoking habits. [2] [4] [5] [6] [7] [55] All of these factors have been implicated in the pathogenesis of atrophic gastritis as well as in the pathogenesis of gastric cancer.

All subjects with *H. pylori* infection do not acquire atrophic gastritis, and the gastritis remains nonatrophic throughout life in at least in 20% to 30% of infected subjects. [50] In general, the factors that are considered to predispose to atrophic gastritis are common in the developing countries where *H. pylori* infection also is frequent. A possibility exists that environmental factors not only contribute to the development of atrophic gastritis, but also they may play a role in the rate of acquiring *H. pylori* infection. [2] [3]

The incidence and prevalence rates of *H. pylori* acquisition and chronic gastritis are bound strongly to the birth cohorts (Fig. 1) . Most *H. pylori* infections occur in childhood and adolescence. [29] This is the case in the developed and developing countries and populations. Also in the developed populations in which *H. pylori* infection is infrequent at present, a high infection rate was present in childhood of cohorts that were born in the beginning of the twentieth century. The infection rate is low in cohorts that were born in the 1970s and 1980s, and the rate is expected to be low in future birth cohorts (see Fig. 1) .

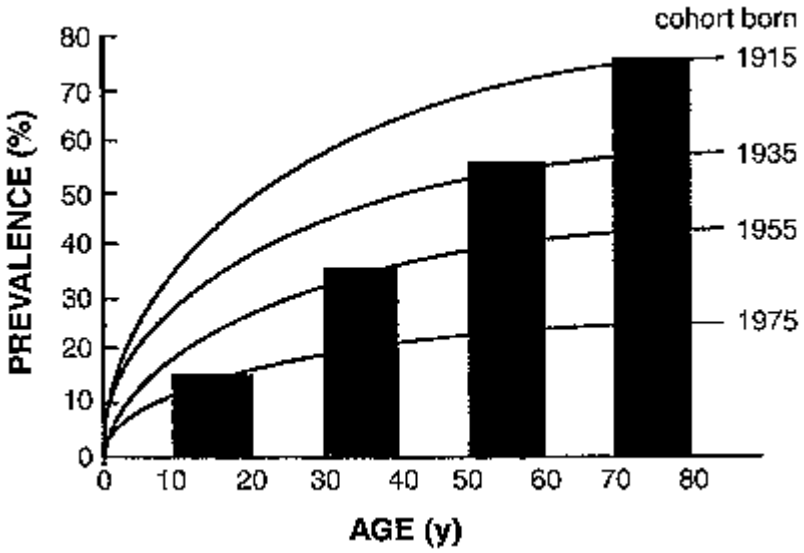

Figure 1. The *cohort phenomenon*, and the birth cohort-specific prevalence rates of chronic *H. pylori* gastritis in different age groups in a Western outpatient population (Finland) in the late 1980s. The increase of the prevalence of gastritis with age can be converted to estimate the birth cohort-specific prevalence rates of the *H. pylori* acquisition in different age groups.

In *H. pylori*-infected subjects, the prevalence of atrophic gastritis and intestinal metaplasia increases with increasing age, but intestinal metaplasia and atrophy are rare findings before age 30 years in Western populations. [14] [31] [45] Direct long-term follow-up studies in patients with *H. pylori* gastritis show that more than half of infected patients acquire

atrophic gastritis during their lifetime. [12] [50] In a 32-year follow-up, 20 (30%) of 66 patients with nonatrophic *H. pylori* developed atrophic corpus gastritis. [50] In a population-based endoscopic series from Finland in the 1970s, [14] 60% of subjects older than age 65 with chronic gastritis showed atrophic gastritis in the antrum or corpus, and 49% showed intestinal metaplasia in biopsy specimens from the antrum or corpus, indicating that the lifetime risk of atrophic gastritis is high in *H. pylori*-infected individuals in developed populations.

No differences in the prevalence or grade of atrophic gastritis have been observed between the sexes. [14] The estimated progression of gastritis into atrophic gastritis is similar in men and women; the risk of acquiring atrophic gastritis was 2.1% per year in an endoscopic study of the Finnish population sample. [18]

GASTRIC CANCER

The most successful classification of the gastric carcinoma is that of Lauren. [25] This classification is based on differentiation of gastric carcinomas of intestinal (IGCA) and diffuse (DGCA) type. [15] Both of these types constitute approximately 40% of all gastric carcinomas, the rest being cases that cannot be classified reliably microscopically (unclassified, mixed carcinomas). [25] The IGCA and DGCA tumors are remarkably different entities regarding the epidemiology and biologic background in particular. [15] [41] DGCA tumors occur more often in younger age groups than IGCA tumors. In contrast to IGCA, DGCA tumors are equally frequent in men and women but occupy the corpus and fundus more often than IGCA tumors. [41] Morphogenetically and microscopically, IGCA tumors resemble ordinary adenocarcinomas of the gastrointestinal tract, and their precursor lesions show morphogenetic steps from mature intestinal epithelium (intestinal metaplasia) to overt cancer. [15] DGCA tumors appear as scattered single mucinous cells (signet-ring cells) without differentiation to form glandular or ductular structures.

The morphogenesis of DGCA is uncertain, and no comprehensive precancerous lesions are known. The morphogenesis of IGCA includes identifiable precancerous conditions, such as atrophic gastritis and intestinal metaplasia, and is associated with the appearance of dysplastic precancerous lesions [16] [17] [30] [32] [52] and finally with the appearance of overt cancers. The dissimilar morphogenesis of IGCA and DGCA may result from differences in type of gene errors that appear during carcinogenesis. These errors may occur in the genes that regulate the synthesis of cell adhesion molecules. Down-regulation in the expression of adhesion molecules may contribute to the development of gastric cancers that are of the DGCA type. [48] [49] The expression of the cell adhesion molecules may be a requirement for the formation of tumors of the IGCA type. [48]

Sex Differences

Gastric cancer is known to be approximately twice as common in men as in women. This difference is due to IGCA tumors, which strongly predominate in men, whereas DGCA tumors occur equally often in men and women (Fig. 2) . The male predominance of gastric cancer cannot be explained with *H. pylori* infection, chronic gastritis, atrophic gastritis, or intestinal metaplasia, which all occur equally often in men as in women. Analysis of the male-to-female ratio of the incidences of gastric cancer provides new insight to the gender-related differences regarding the pathogenesis of IGCA and DGCA. [37] The male-to-female ratio of gastric cancer incidence rises with increasing age and reaches a peak at age 60, after which the ratio decreases. The form and magnitude of this *reversed V shape* of the age-specific curve of the male-to-female ratio are independent of the incidence of gastric cancer and of the prevalence of *H. pylori* gastritis in the world populations. The curve is similar in shape and magnitude in countries with a low (e.g., developed countries) and a high (e.g., Japan and developing countries) gastric cancer incidence. The high male-to-female ratio of cancer incidence at age 60 concerns tumors of the IGCA type but not those of the DGCA type. The incidence of IGCA begins to rise in men at an earlier age (<55 years) than in women, and, correspondingly, there is a delay of 10 to 15 years between men and women in acquiring IGCA tumors (see Fig. 2) . Among women, IGCA tumors begin to increase progressively in prevalence at and after age 60 (i.e., menopause), resulting in a decrease of the male-to-female ratio of cancer incidence. The most logical explanation for this gender-related difference is that the sex hormones (i.e., estrogens) protect women somehow from IGCA tumors, and these gastric tumors begin to be common in women only after menopause; alternatively the male sex hormones may promote the pathogenesis of IGCA tumors in men.

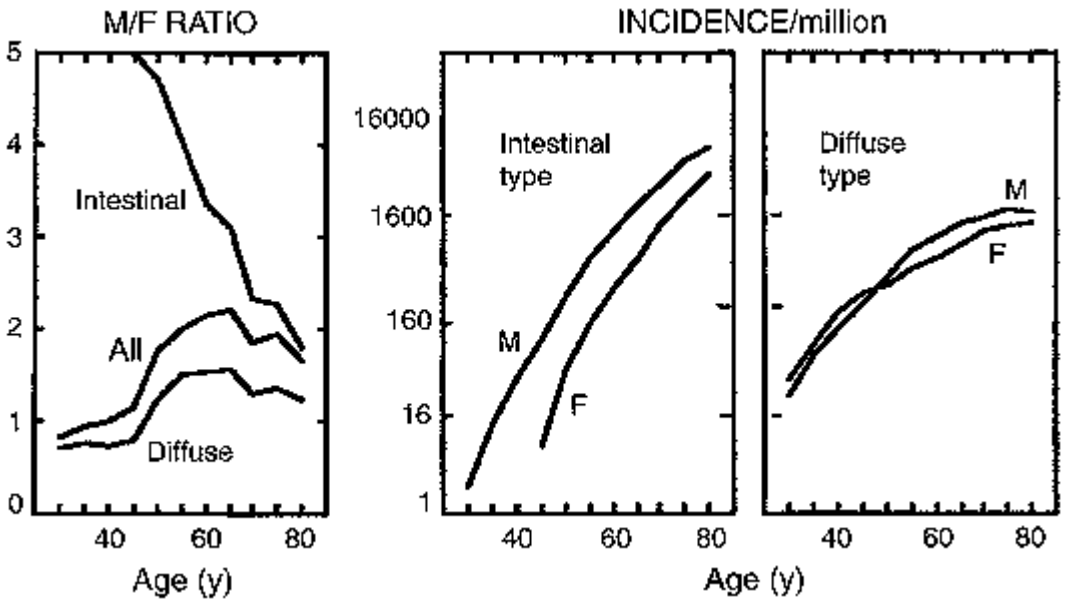

Figure 2. Epidemiology of gastric cancer in Finland in the late 1980s. Note the difference between gastric cancer of the intestinal and the diffuse types regarding the age-specific incidence and regarding the male to female (M/F) ratio of the incidences of the different subtypes of gastric cancer in different age groups. The data are extrapolated from the registry data of the Finnish Cancer Registry for 1985-1989.

Because the male-to-female ratio of gastric carcinoma incidence seems to be consistent throughout the world, it can be assumed that the overall pathogenesis of gastric carcinoma is similar worldwide. Correspondingly, it is conceivable that the morphogenesis of gastric carcinoma--of IGCA and DGCA--is similar in developed and developing countries. The global consistency in gastric carcinoma epidemiology indicates that the proportion of IGCA and DGCA tumors among all gastric tumors is similar in developed and developing counties (i.e., the percentage share of the IGCA and DGCA subclasses among gastric tumors is equal in the populations with a high gastric carcinoma incidence compared with those with a low gastric carcinoma incidence. The consistency further may mean that the decrease of gastric carcinoma incidence in the developed countries equally involves IGCA and DGCA tumors. [17]

Precancerous Lesions

Precancerous gastric lesions are adenomas and dysplastic changes of various cross-morphologic type and form. [30] Both are local, intramucosal, noninvasive lesions, and their proper diagnosis requires biopsy sampling of the endoscopically visible mucosal lesions, such as tumors, polyps, ulcers, folds, erosions, and discolored spots of the mucosa. [52] Adenomas and dysplastic lesions are precursors for gastric carcinoma of the intestinal type mainly, and they are morphologically graded as low-grade or high-grade lesions. [27] High-grade lesions are considered intramucosal, noninvasive cancers by Japanese pathologists [34] ; these lesions progress to invasive carcinomas in a few years. [24]

Dysplastic lesions rarely are diagnosed by random biopsy sampling of the stomach. In an analysis of 63 cases with gastric cancer or definite dysplasia (low or high grade) among 1344 patients with advanced atrophic gastritis (SPGI $\leq$ 25 mug/L) in Finland, all but one of the neoplastic-dysplastic lesions were found to occur in visible mucosal alterations. [52]

GASTRITIS-ATROPHIC GASTRITIS-GASTRIC CANCER RELATIONSHIP

The risk for gastric cancer and precursor lesions increases exponentially with increasing grade and extent of atrophic gastritis and intestinal metaplasia in the stomach, the risk for cancer being about 90 times higher in patients with multifocal severe atrophic gastritis affecting the gastric antrum and corpus than in subjects with a normal, healthy gastric mucosa (Fig. 3) . [39] In an endoscopic cross-sectional survey of approximately 1344 middle-aged men with advanced atrophic gastritis (SPGI <25 mug/L), 63 (4.7%) cancers or definite dysplasias of low or high grade were discovered. [52] The lifetime follow-ups of patients with severe corpus atrophy and pernicious anemia have indicated that 10% of these patients get gastric cancer. [46] [47] [51] Corresponding high prevalence rates of gastric carcinoma have been reported in Japan from endoscopic surveys of patients with advanced atrophic gastritis, screened with low SPGI levels. [22] [28] [54] The cancers or precursor lesions that develop in these patients are usually of IGCA subtype.

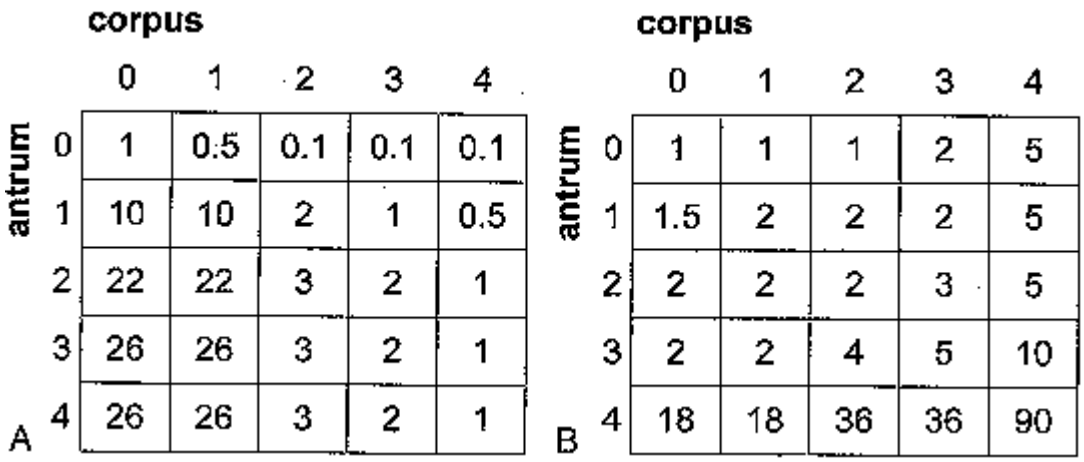

Figure 3. Relative risk for peptic ulcer (duodenal or gastric) *(A)* and gastric cancer *(B)* in different topographical phenotypes of chronic gastritis and atrophic gastritis. The reference group indicates subjects with a normal, healthy stomach (antrum and corpus mucosa are histologically normal--OR is 1; the left upper corner). 0 = normal; 1 = nonatrophic gastritis; 2-4 = mild, moderate, or severe atrophic gastritis.

The association of gastric cancer of IGCA subtype with atrophic gastritis provides some possibilities to identify and diagnose the cancer cases at an early, curable stage or to screen subjects with an increased cancer risk. SPGI is a direct measure and *serum biopsy* of multifocal atrophic gastritis and of atrophic gastritis that affects the gastric corpus in particular. The SPGI level decreases linearly with increasing grade of atrophy and loss of oxyntic glands and is low ($\leq$ 25 mug/L) typically in subjects with advanced atrophic corpus gastritis and hypochlorhydria or achlorhydria. [52]

A Finnish study [52] included approximately 22,000 elderly (55 to 69 years old) men who at first were screened with SPGI. Approximately 2000 men were found who fulfilled the screening criterion (SPGI $\leq$ 25 mug/L) and of whom 1344 subsequently were endoscopically examined. Of the 63 cases with cancer or definite dysplasia found on endoscopy, 18 (29%) were asymptomatic men with cancer (11 cases) or dysplasia (7 cases) of high grade. Of the 11 cancer cases, 7 were *early cancers* (invasion of the cancer limited to the submucosa). Another analysis of approximately 80 consecutive gastric cancer patients revealed that a low SPGI level (SPGI $\leq$ 25 mug/L) occurred in 23% of cancer cases, indicating that one fourth of all gastric carcinomas can be disclosed with the SPGI-endoscopy procedure at an early, curable stage in Finland. The diagnosis of 18 subjects with cancer or high-grade dysplasia in the Finnish project indicates that the SPGI-endoscopy procedure improves the cancer diagnosis at least 3 to 5 fold (this is because the expected annual incidence of new gastric cancers among 22,000 men at age 65 is 20, of which 5 are have a low SPGI level and can be identified with the SPGI-endoscopy procedure). This improvement of cancer diagnosis is based on the diagnosis of the cancers and the precancerous lesions at an asymptomatic phase--3 to 5 years earlier than the case is with tumors diagnosed with routine clinical diagnostic procedures at a symptomatic stage.

As compared with the cancer risk in the normal, healthy stomach, the presence of nonatrophic *H. pylori* gastritis raises the cancer risk approximately twofold. [39] Correspondingly, even though the gastric cancer risk is low in patients with duodenal ulcer disease and nonatrophic *H. pylori* gastritis, it is conceivable that the cancer risk is higher in these patients than the risk of cancer in subjects with healthy, normal stomach. The 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 in the general population).

The investigations on the seroprevalence of *H. pylori* antibodies show that IGCA and DGCA tumors are related to coexisting and preceding *H. pylori* infection in Western developed countries (Fig. 4) . [33] Early direct endoscopic studies of the occurrence of chronic gastritis in the families of gastric cancer patients support this view. In an old Finnish study, chronic gastritis in antrum and corpus was more common in cancer patients than in controls, and the gastritis was significantly more prevalent among 100 first-degree relatives of the DGCA patients than in the 108 first-degree relatives of control probands who were matched by age, sex, and place of residence to the cancer probands. [13] [18] No such family accumulation of gastritis occurred in the IGCA families even though the IGCA patients themselves had gastritis, atrophic gastritis, and intestinal metaplasia significantly more frequently than the age-matched control subjects representing the general population. [18]

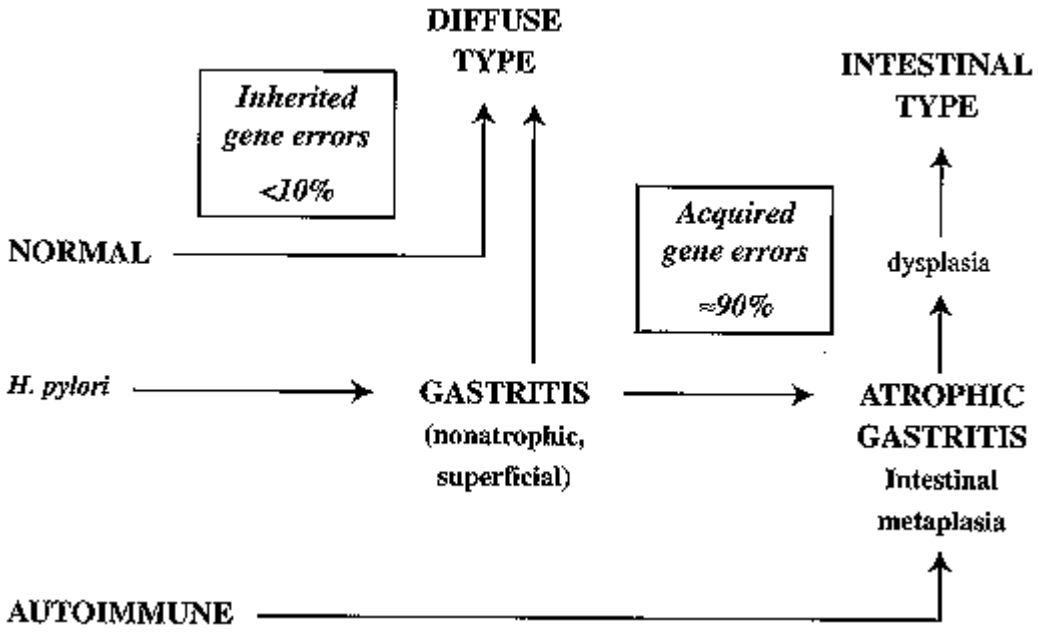

Figure 4. Scheme on the pathogenesis of gastric carcinoma of diffuse and intestinal type.

The Finnish studies among the first-degree relatives of gastric cancer patients indicate that not only gastritis in general, but also atrophic gastritis and intestinal metaplasia are more prevalent lesions in DGCA family members than in members of the control families, [13] whereas no such associations were found between IGCA families and their control families. Among the DGCA relatives, the mean maximal acid output also was found to be significantly lower and basal serum gastrin significantly higher than those in the controls.

Studies intended to compare the topographic associations between the site of cancer and the site of gastritis-related lesions in the stomach have generated positive results. [16] [19] [40] [42] [43] In IGCA and DGCA tumors, the age-adjusted grades of gastritis and intestinal metaplasia in the tumor site (antrum versus corpus) are significantly higher than in the tumor-free parts of the stomach. However, this is the case in the IGCA cases in particular, and the difference is less clear or nonexistant in the DGCA cases.

GASTRIC CANCER IN ATROPHIC GASTRITIS OF AUTOIMMUNE ORIGIN

Corpus-limited autoimmune-type atrophic gastritis is a condition in which the cancer risk is 3 to 5 times higher than the cancer risk in subjects with a normal, healthy stomach. [39] [51] The cancers are of the IGCA type in these patients and occur most often in the corpus and fundus but may occur occasionally in the antrum. In an old meta-analysis of six follow-up studies (follow-up time, 9 to 15 years) including more than 600 patients with pernicious anemia and severe atrophic corpus gastritis, [51] the annual incidence of cancer varied from 0% to 1% (median, 0.6%), and the proportion of cancers associated with autoimmune atrophic gastritis varied from 0% to 14.8% (median, 6.0%) among all cancer patients. [51] In a more recent endoscopic follow-up of 105 pernicious anemia patients in Finland (average follow-up, 7 years), the cumulative prevalence of gastric cancer was 3% and that of carcinoid tumors 4%. [28]

TIME TRENDS

The incidence of gastric cancer has decreased progressively in most developed countries. [11] In Finland, the decrease has been 60% to 70% since the 1950s and is proportionally similar to the decrease of cancer incidence in other Nordic countries. [10] The extrapolations of the birth group-specific and the age group-specific prevalence of gastritis indicate that gastritis prevalence has decreased similarly to the gastric cancer incidence. [36] The decline of cancer incidence among Finnish men at age 50 and the corresponding decrease of gastritis prevalence in the same age group in different birth cohorts are presented in Figure 5 . The decrease in the prevalence of gastritis appears to be associated with the exponential decrease in the incidence of gastric cancer.

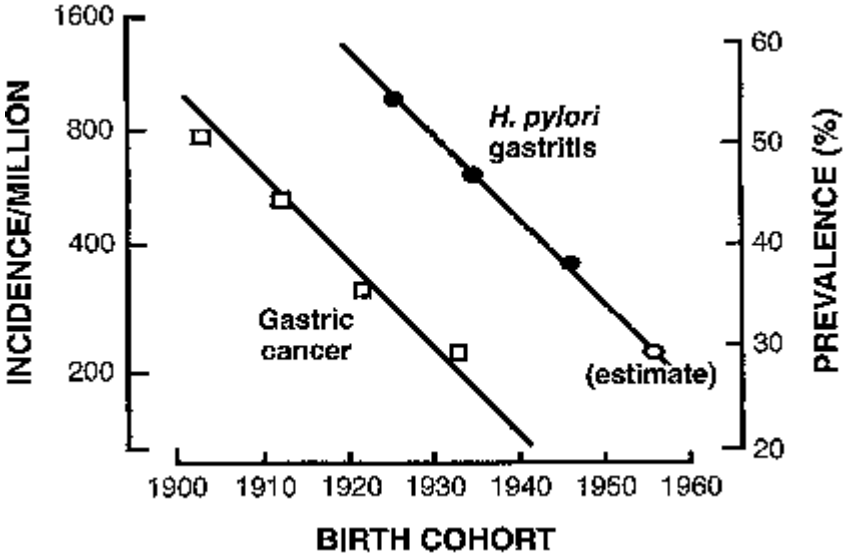

Figure 5. Association between the decrease of the gastric cancer incidence in Finland among men at age 50 (data of Finnish Cancer registry) and the decrease of the prevalence of *H. pylori* gastritis at age 50 *(data from estimations as shown in Fig. 4)* in different birth cohorts. Note that a linear decrease in the prevalence of gastritis is associated with an exponential decrease of the incidence of cancer.

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