

POLYPS AND OTHER PRECURSORS OF GASTRIC (NON-CARDIA) CARCINOMAS

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BULLET POINTS

- The rate of gastric carcinoma has been declining over the past 70 years, but gastric cancer still remains the fourth most common cancer and the second most common cause of cancer deaths worldwide.
- Most gastric carcinomas are intestinal-type, and the intestinal type accounts for most of the marked geographic variation in stomach cancer. While intestinal-type carcinomas are decreasing, the rate of diffuse-type gastric carcinoma is steady or increasing.
- Environmental risk factors for intestinal-type adenocarcinomas include *H. pylori* infection, salted/preserved foods, and tobacco use. These carcinomas progress through a sequence as follows: superficial non-atrophic gastritis (corpus-predominant) → chronic atrophic gastritis → intestinal metaplasia (complete→incomplete) → dysplasia (low→high-grade) → carcinoma.
- Approximately 10% of gastric cancers show familial clustering. Known genetic syndromes with an autosomal dominant pattern of inheritance (but varying penetrance rates for gastric cancer) are: 1) Li Fraumeni syndrome, 2) Peutz-Jeghers syndrome, 3) hereditary non-polyposis colorectal cancer (HNPCC), 4) familial adenomatous polyposis, 5) juvenile polyposis, and 6) hereditary diffuse gastric carcinoma.
- Hereditary diffuse gastric carcinoma (HDGC) is the only syndrome with stomach cancer as the predominant manifestation. ~30-50% of HDGC are due to germline mutations in the *CDH1* (E-cadherin) gene. Carriers have a high lifetime risk for symptomatic or clinically evident gastric signet ring cell carcinomas (67% for men, 83% for women).
- Studies of prophylactic total gastrectomies in *CDH1* mutation carriers reveal that almost all harbor small (mean size <1 mm), and usually multiple, foci of signet ring cell carcinoma in the superficial lamina propria. At this stage there has never been a reported metastasis and patients are cured by the gastrectomy procedure. *In situ* signet ring cell carcinomas are less frequently detected in these gastrectomies.

EPIDEMIOLOGY OF GASTRIC CARCINOMA

There is a nearly 10-fold variation in gastric carcinoma rates worldwide, with the highest incidences in Japan and Korea, other East Asian countries, Eastern Europe, and Central and South America.¹ Low incidences are found in North America, South Asia, Australia, and New Zealand. Seventy years ago, gastric cancer constituted the most common cause of cancer deaths in the US and in Europe, but in these countries gastric cancer mortality has markedly declined, primarily due to a decrease in adenocarcinomas of the antrum and body (while proximal cardia and GE junction tumors have increased). Still, the worldwide rate of gastric cancer remains

high, overall constituting the 4th commonest cancer and the second leading cause of cancer mortality.^{1,2} Gastric cancer accounts for >10% of all cancer deaths worldwide.³

CLASSIFICATION OF GASTRIC ADENOCARCINOMAS

The Lauren classification, proposed in 1965 and still the major classification system in use, divides gastric adenocarcinomas into intestinal and diffuse types.⁴ Signet ring cell carcinomas are a subtype of diffuse carcinomas. Of 1,344 Finnish cases reviewed by Lauren, 915 were intestinal-type, 441 were diffuse, and 188 had overlapping patterns or could not be classified for other reasons.⁴ Stomachs harboring intestinal-type adenocarcinomas were also more likely to show intestinalization of the surrounding mucosa, supporting Lauren's earlier hypothesis that these carcinomas originated from heterotopic islands of intestinal mucosa, which in turn originated in a background of chronic gastritis.⁵

Intestinal-type carcinomas are more common in men (male:female ratio ~2:1), blacks, high-risk geographic regions, and older patients (with a peak incidence in the 50-70 yr range). In contrast, diffuse-type carcinomas have a more equal male:female ratio and tend to occur in younger patients. It is the intestinal-type that accounts for much of the worldwide, geographic variation in gastric cancer rates; and the decline in gastric cancers in Western countries over the past several decades mostly reflects a decline in intestinal-type cancers. Diffuse carcinomas are more uniformly distributed throughout the world and their incidence has remained steady or increased.¹

RISK FACTORS

Environmental

Diet, tobacco, and *H. pylori* infection are the major environmental risks, particularly for intestinal-type cancers. In particular, diets rich in salt or salt-preserved foods, high in nitrites used for meat preservation, and low in fresh fruits and vegetables are associated with greater risk. Smokers have ~2-fold elevated risk for distal gastric cancer.¹

In 1994, *H. pylori* was declared a class I carcinogen (group 1: sufficient evidence of carcinogenicity to humans) by the International Agency for Research on Cancer (IARC).⁶ Both case-control and prospective studies have shown a significant association between *H. pylori* infection and gastric cancer. The risk is higher in individuals who are infected by a more virulent *H. pylori* strain which carries the *cagA* gene (cytotoxin-associated gene A) predisposing to more severe atrophic gastritis and distal cancers; nearly all strains of *H. pylori* in Japan are *cagA*+, whereas *cagA* positivity is found in only ~60% of *H. pylori* strains in the West.¹

Genetic

Approximately 10% of gastric cancers show familial aggregation, but only 1-3% are attributable to known genes that are inherited in an autosomal dominant fashion.⁷ Genetic syndromes associated with increased risk of gastric cancer include: 1) hereditary diffuse gastric cancer (discussed below), 2) hereditary nonpolyposis colorectal cancer (HNPCC/Lynch syndrome), 3)

Peutz-Jeghers, 4) some families with Li Fraumeni syndrome, 5) some juvenile polyposis families, and 6) FAP (in Asian countries). Among these syndromes, hereditary diffuse gastric cancer is the only one that is dominated by gastric cancer.

Other

Gastric radiation, autoimmune atrophic gastritis (a risk factor for both adenocarcinoma and carcinoid tumors), and prior surgery with Billroth-II anastomosis are other risk factors.

PRECURSOR LESIONS IN INTESTINAL-TYPE (*H. PYLORI*) ADENOCARCINOMA

Gastric adenocarcinomas can arise in polypoid lesions including adenomas, hamartomas, hyperplastic/inflammatory polyps (rarely), and dysplastic fundic gland polyps (extremely rarely) in the setting of FAP. However, unlike colorectal cancers, most gastric adenocarcinomas do not arise through an adenoma/polyp → cancer sequence but rather through a flat or sessile dysplasia → cancer sequence that is in turn preceded by chronic gastritis, atrophy, and intestinal metaplasia as precursor lesions.

In the setting of *H. pylori* infection, Correa⁵ has proposed the following stepwise progression (this sequence would also apply to autoimmune gastritis):

Active chronic gastritis → Glandular atrophy → Intestinal metaplasia → Dysplasia → AdenoCA
 (nonatrophic) (multifocal) (complete→incomplete) (low→high grade)

This is a dynamic process in which lesions (or at least their detection by biopsy) can regress as well as progress, and in which multiple stages can coexist in the same stomach. In a study by Correa *et al.*⁸ that evaluated sequential biopsy specimens in 1,422 residents from a high-risk region in Columbia, there was a net gain of 1.7% individuals/year for atrophic gastritis, 0.9% for intestinal metaplasia, 0.7% for dysplasia, and 0.03% for carcinoma. Together this represents a net loss of 3.3% individuals/year from the group that began with normal stomach histology or superficial nonatrophic gastritis. Despite the net overall forward movement through the sequence over time, individuals could also regress (e.g., from dysplasia to intestinal metaplasia).

PRECURSOR LESIONS IN SIGNET RING CELL CARCINOMA

In two reports from the 1980s and 1990s, Liu described “globoid dysplasia” as a precursor to invasive signet ring cell carcinoma.^{9,10} Earlier in 1975, Grundmann had reported “signet ring cell drippings” in the lower tubule necks as the initial form of signet ring cell carcinoma.¹¹ However, unlike the situation for intestinal-type adenocarcinomas, the morphologic precursor(s) of gastric signet ring carcinomas are relatively unknown. Over the past decade, the identification of families at high risk for signet ring carcinomas and the morphologic study of prophylactic gastrectomy specimens in these individuals has provided an opportunity to study early (intramucosal) signet ring cell carcinomas and to identify signet ring cells in an in-situ phase.

Hereditary Diffuse Gastric Carcinoma - Definition

Hereditary diffuse gastric cancer (HDGC) was defined by the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 as any family meeting one of the following criteria: 1) 2 or more documented cases of diffuse cancer in 1st or 2nd degree relatives, at least one diagnosed before age 50, or 2) 3 or more cases of documented diffuse cancer in 1st or 2nd degree relatives, independent of age.¹² Lobular breast carcinoma and rare signet ring cell carcinomas of the colorectum also appear to be part of HDGC in some families, but are not currently part of the inclusion criteria.

The IGCLC also recognized an autosomal dominant syndrome of diffuse gastric cancer and hyperplastic gastric polyps, not linked to mutations in the *E-cadherin/CDH1* gene.

CDH1 Mutations

In 1998, Guilford *et al.*¹³ first identified three different truncating germline mutations in the *CDH1* gene among three Maori kindreds with HDGC. *CDH1* encodes for E-cadherin, a transmembrane protein that is mainly expressed at the basolateral membranes of epithelial cells and plays a critical role in cell–cell adhesion. E-cadherin also indirectly influences organization of the actin cytoskeleton of epithelial cells through the interaction of its cytoplasmic domain with the α , β , and γ catenins.¹⁴

Since 1998, at least 68 families with germline *CDH1* mutations have been identified worldwide.¹⁴ A few studies have also found germline *CDH1* mutations in apparently sporadic cases of early-onset diffuse gastric cancer, and one study identified a germline *CDH1* mutation in one of 23 families with lobular breast cancer (but not gastric cancer) who had tested negative for *BRCA1/2* mutations.¹⁵ The *CDH1* gene spans 16 exons and mutations have been found throughout the gene without apparent hot-spots.¹⁴ Most (nearly 80%) of these mutations result in premature truncation of E-cadherin protein (i.e., nonsense, frameshift, or splice-site mutations). The functional significance of missense mutations can be predicted by *in vitro* assays.

Since *CDH1* is a tumor suppressor gene, cancers in individuals with germline *CDH1* mutations should harbor somatic, “second hit” *CDH1* alterations; some have been found to have intragenic deletions or hypermethylation of the wild-type *CDH1* promoter. These cancers show absent or reduced expression of E-cadherin by immunostaining (as do sporadic signet ring cell carcinomas and sporadic lobular breast carcinomas).

Only 30-50% of families meeting the criteria for HDGC have identifiable *CDH1* mutations,^{14,16} implying that there is genetic heterogeneity in HDGC. This also means that there will be a significant number of HDGC families in whom carrier status of individual members can not be assessed.

Risk and Therapy

The clinical penetrance of *CDH1* mutations is high but not complete. For unclear reasons, female carriers of *CDH1* mutations are at greater risk of gastric cancer than are male carriers of the same mutations. It is estimated that the risk of clinically significant diffuse gastric cancer reaches 83% in women and 67% in men by the age of 80.¹⁷ The risk of lobular breast cancer in women is 40%.

Age of onset of gastric cancer is difficult to predict and varies widely, even within families. Gastric cancer has been reported in a 14-year-old boy who died of the disease,¹⁸ and in a 15-year-old.¹⁹ Another 15-year-old Maori girl who did not have clinically evident gastric cancer but underwent prophylactic gastrectomy was found to harbor 318 separate foci of intramucosal signet ring cell carcinoma ranging from 0.1 to 10mm.²⁰ However, overall risk of advanced gastric cancer is thought to be <1% at age 20 and 4% by age 30.¹⁸

Surveillance upper endoscopies are often performed in mutation carriers, but even with chromoendoscopy and MRI examinations the negative predictive value is low. Random mucosal biopsies typically fail to detect carcinomas in these patients. Therefore, the recommended treatment is prophylactic total gastrectomy between the ages of 20 – 30 years; the quoted operative mortality for the procedure is ~1%, which would exceed the risk of clinically significant gastric cancer before the age of 20.¹⁸ It is important that all gastric mucosa be removed during the surgery, and to ensure this the proximal and distal gastric margins are usually examined by frozen section intraoperatively. As an illustration of the importance of total removal of the stomach, Huntsman *et al.*²¹ described a mutation carrier who underwent prophylactic subtotal gastrectomy at age 32; she died of metastatic signet ring cell carcinoma arising in the unresected cardia at age 56.

It is also recommended that female *CDH1* mutation carriers be referred to high-risk breast cancer screening programs. MRI examinations may be more sensitive than mammography in this population at risk for lobular rather than ductal carcinomas.

Precursor Lesions in *CDH1* Mutation Carriers

Essentially, all prophylactic gastrectomies that are embedded in toto and carefully examined will contain one or more foci of superficial signet ring cell carcinoma, even when the stomach is endoscopically and macroscopically normal.^{14,20-25} The number of separate foci has varied from 1 to hundreds per stomach, with published means ranging from 10.9²² to 40²⁴ to 145²⁰ in different series. Most foci are <1 mm in size, implying that the “true” number of carcinomas in each stomach is likely to be higher than the number reported at sign-out of the specimen since tissue blocks are usually 2-3 mm thick. In almost all prophylactic gastrectomies, signet ring cell carcinomas are invasive only into the upper half of the lamina propria, although occasional cases with invasion into the deep lamina propria^{22,24} or even previously undetected superficial submucosal invasion have been reported. Carcinomas limited to the mucosa have never been associated with observable lymphovascular invasion nor lymph node metastases.

In many foci of early carcinomas from these patients, an interesting polarity is seen in the morphology of the intramucosally-invasive cells. Humar *et al.*²⁵ have shown that the most superficial cells, which appear as classic signet ring cells with abundant intracytoplasmic mucin, stain for MUC5A, a marker of gastric pit cells. In contrast, cells at the base of the carcinoma foci are smaller, with less mucin; these cells stain for MUC6, a marker of mucous neck cells. These cells coincide with the upper neck region where gastric progenitor cells reside. Based on their topographic distribution, MUC6 staining, and Ki-67 labeling studies showing predominant expression of Ki-67 in these basal rather than superficial cells, Humar *et al.* concluded that early

diffuse carcinomas in *CDH1* mutation carriers originate in upper neck region of the gastric glands.²⁵

Carniero *et al.*²⁴ have proposed a progression model of early diffuse carcinomas in these patients:

In situ signet ring cells → Overt pagetoid spread and early invasion → Invasive carcinoma (upper neck and/or gastric pits)

Interestingly, in situ/pagetoid signet ring cells are not identified in all prophylactic gastrectomies, and when they are detected they are less numerous than the invasive foci. Thus, the in situ phase may not persist for long, it may be geographically limited, or there may be in situ signet ring cells that are not recognizable by H&E stain.

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