Risk factors for gastric cancer

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INTRODUCTION

Gastric cancer has significant geographic, ethnic, and socioeconomic differences in distribution. This topic review will discuss risk factors for gastric cancer. Epidemiologic aspects are presented separately. (See "Epidemiology of gastric cancer".)

There are two main histologic variants of gastric adenocarcinoma. The most frequent is the "intestinal type," so called because of its morphologic similarity to adenocarcinomas arising in the intestinal tract. The less common "diffuse type" gastric cancers are characterized by a lack of intercellular adhesions, which leaves them unable to form glandular structures. In patients with the inherited form of diffuse type gastric cancer, the absence of intercellular adhesions is caused by a germline mutation in the cell adhesion protein E-cadherin (CDH1). (See 'Hereditary diffuse gastric cancer' below.)

Although several risk factors are described, *Helicobacter pylori* infection and family history of gastric cancer are the two main risk factors for gastric cancer. This topic will review the major risk factors for gastric cancer. A more in-depth discussion on the link between *H. pylori* and gastrointestinal tract malignancy is provided elsewhere. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy".)

PRECURSOR LESIONS

The sequence of molecular events that underlies intestinal type gastric cancer and its well-defined precursor lesions is incompletely understood. In comparison, much more is known about the molecular pathogenesis of diffuse type gastric cancers, which display a prominent molecular abnormality in the cell adhesion protein E-cadherin (CDH1). (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'The preneoplastic cascade' and "Gastric cancer: Pathology and molecular pathogenesis", section on 'Hereditary diffuse gastric cancer'.)

Intestinal-type cancer — One model for intestinal type gastric cancer describes a progression from chronic gastritis to chronic atrophic gastritis, to intestinal metaplasia, to dysplasia, and eventually, to adenocarcinoma [1,2].

- Longstanding chronic superficial gastritis caused by chronic *H. pylori* infection, pernicious anemia, or possibly, a high-salt diet leads eventually to chronic atrophic gastritis and intestinal metaplasia.

- Gastric atrophy is accompanied by a loss of parietal cell mass and therefore a reduction in acid production (hypochlorhydria or achlorhydria), a decrease in luminal ascorbic acid (vitamin C) levels, and a compensatory increase in serum gastrin, a potent inducer of gastric epithelial cell proliferation.

  Similarly, gastric resection results in hypochlorhydria or achlorhydria, secondary hypergastrinemia, and bile reflux, especially after a Billroth II anastomosis. The increase in gastric pH would permit colonization of bacteria capable of converting dietary nitrates into potent mutagenic N-nitroso compounds.

- Chronic inflammation results in epithelial cell damage with increased free radical generation, a further reduction in luminal ascorbic acid levels, and increased cell turnover.

Atrophic gastritis — Atrophic gastritis is an autoimmune disorder that is characterized by progressive atrophy of the glandular epithelium with loss of parietal and chief cells. The loss of the normal exocrine glands of the gastric mucosa causes hypochlorhydria (a decrease in hydrochloric acid) and a resultant increase in gastric pH. An abnormally high pH in the stomach permits microbial colonization, some of which possess nitrate reductase, allowing nitrosation that is genotoxic. In addition, there is a loss of endocrine cells, which normally secrete epidermal and transforming growth factors, thereby aiding the stomach in regenerating damaged tissue. Populations with a high prevalence of atrophic gastritis also have a high prevalence of gastric cancer and vice versa [3].

Atrophic gastritis and other conditions that cause gastric atrophy are associated with an increased risk of both cardia and noncardia gastric adenocarcinomas (figure 1). The

magnitude of the risk is variable in the literature, with estimates ranging from 3 to 18 times greater than an age-matched population. This subject is discussed in detail elsewhere. (See "Metaplastic (chronic) atrophic gastritis", section on 'Gastric adenocarcinomas'.)

Intestinal metaplasia and dysplasia — Metaplasia is a potentially reversible change from one fully differentiated cell type to another, a process of adaptation to environmental stimuli. The most common form of metaplasia in the stomach is the intestinal type (picture 1). It occurs as a result of *H. pylori* infection or bile reflux, or it can be induced experimentally with irradiation [4,5]. Intestinal metaplasia is more frequent in countries with a higher incidence of gastric carcinoma [6], and at least in experimental animal models, it precedes the development of gastric carcinoma [7]. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'Intestinal metaplasia' and "Gastric cancer: Pathology and molecular pathogenesis", section on 'Gastric dysplasia'.)

An approach to patients with intestinal metaplasia is presented separately. (See "Metaplastic (chronic) atrophic gastritis".)

Data from humans also provide support for the concept of intestinal metaplasia as a precursor lesion for intestinal type gastric cancer. A study from Japan found that the presence of intestinal metaplasia was the only criterion associated with the development of intestinal type gastric cancer [8]. In China, intestinal metaplasia was found in 33 percent of the population in a high-prevalence area of gastric cancer, and dysplasia, common in the lesser curvature of the body and in the incisura, was found in 20 percent [9].

Most patients diagnosed with high-grade dysplasia of the gastric mucosa either already have or will soon develop gastric cancer. In gastrectomy specimens for gastric cancer, 20 to 40 percent of patients have associated dysplasia [10]. Rates of progression from dysplasia to gastric cancer have been estimated at 21, 33, and 57 percent of cases of mild, moderate, and severe dysplasia, respectively [10].

The absolute magnitude of risk conferred by intestinal metaplasia and dysplasia was addressed in a report from Sweden that included 405,172 patients with gastric biopsy samples taken for a non-malignant indication between 1979 and 2011 [11]. The risk of gastric cancer was significantly increased in the presence of intestinal metaplasia (hazard ratio [HR] 6.2, 95% CI 4.7-8.2) and dysplasia (HR 10.9, 95% CI 7.7-15.4). It was estimated that approximately 1 in 39 patients with intestinal metaplasia and 1 in 19 with dysplasia would develop gastric cancer within 20 years.

Diffuse-type cancers — In contrast to intestinal type gastric cancers, diffuse type gastric cancers have no clearly defined precancerous lesion. Diffuse type gastric cancer is discussed

elsewhere. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'Intestinal versus diffuse types'.)

ENVIRONMENTAL RISK FACTORS

There are geographic and ethnic differences in the incidence of gastric cancer around the world, as well as trends in each population over time. Emigrants from high-incidence to low-incidence countries often experience a decreased risk of developing gastric carcinoma. Such findings strongly suggest that environmental factors have an important role in the etiology of gastric cancer and that exposure to risk factors occurs early in life. (See "Epidemiology of gastric cancer".)

Helicobacter pylori — The World Health Organization's International Agency for Research on Cancer (IARC) classified *H. pylori* as a group 1 or definite carcinogen [12]. As noted above, intestinal-type gastric carcinoma is believed to evolve as a progression from atrophy to metaplasia, to dysplasia, and then to carcinoma. The most common cause of gastritis is *H. pylori* (picture 2).

Four sources of evidence support an association between *H. pylori* infection and gastric cancer: epidemiologic studies comparing prevalence rates of gastric cancer and *H. pylori* infection, cross-sectional studies evaluating *H. pylori* infection in patients with gastric cancer, prospective studies associating *H. pylori* infection with gastric cancer, and clinical trials demonstrating a significantly reduced incidence of gastric cancer after eradication of *H. pylori*. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy".)

It is thought that *H. pylori* infection triggers inflammation at the corpus mucosa, which results in atrophy and intestinal metaplasia. *H. pylori* infection has been associated with an approximately sixfold increase in the risk of adenocarcinomas distal to the cardia, including both the intestinal and diffuse types. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy" and "Gastric cancer: Pathology and molecular pathogenesis", section on 'Helicobacter pylori'.)

A paradox in *H. pylori* infection is that divergent clinical outcomes occur: some patients develop a duodenal ulcer or gastric cancer, while the majority have no significant clinical symptoms. Bacterial virulence factors alone have not adequately explained why the ulcer or the gastric cancer phenotype develops. Ongoing studies are helping to elucidate the basis for these varying outcomes. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy".)

Diet

Salt and salt-preserved foods — Substantial evidence from ecologic, case-control, and cohort studies strongly suggests that the risk of gastric cancer increases with a high intake of salt and various traditional salt-preserved foods, such as salted fish, cured meat, and salted vegetables [13-18]. In 2007, salt and salted/salty foods were classified as probable risk factors for gastric cancer [19].

A potential synergistic effect of salt and *H. pylori* has also been described [17,20], although not in all studies [18]. High salt intake damages stomach mucosa and increases the susceptibility to carcinogenesis in rodents [21-23]. The induced proliferative change may act to promote the effect of food-derived carcinogens.

The declining incidence of gastric cancer worldwide over the last 50 years has been attributed, at least in part, to the spread of refrigeration [24], the use of which would inversely correlate with salting and other salt-based methods of preservation, such as curing and smoking, and with the overall volume of salt in the diet. (See "Epidemiology of gastric cancer".)

Nitroso compounds — Humans are exposed to N-nitroso compounds (compounds containing an -NO group) from diet, tobacco smoke, and other environmental sources, as well as from endogenous synthesis, which contributes to 40 to 75 percent of total exposure [25]. N-nitroso compounds are generated after consumption of nitrates, which are natural components of foods like vegetables and potatoes and are used as a food additive in some cheeses and cured meats. Dietary nitrates are absorbed in the stomach and secreted in saliva in a concentrated form, where they are reduced to nitrites by oral bacteria. Nitrites can also react with nitrosatable compounds, such as amines, amides, and amino acids, to form N-nitroso compounds.

The evidence linking N-nitroso compounds to gastric cancer is as follows:

- Elevated levels of gastric nitrite, particularly in a high-pH environment, have been linked to advanced precancerous gastric lesions [26].

- The risk of gastric cancer associated with dietary intake of nitrites and nitrosodimethylamine (NDMA), and endogenous formation of nitroso compounds was investigated in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [27]. While there was no association between intake of nitrites/NMDA and gastric cancer risk, endogenous production of N-nitroso compounds was significantly associated with noncardia cancer risk (hazard ratio [HR] 1.42, 95% CI 1.14-1.78).

- Diets that are high in fried food, processed meat, fish, and alcohol (and low in vegetables, fruits, milk, and vitamin A) have been associated with an increased risk of gastric carcinoma in several epidemiologic studies [16,28,29]. A meta-analysis estimated that the relative risk of gastric cancer associated with consumption of 30 g of processed meat per day (approximately one-half of an average serving) was 1.15 (95% CI 1.04-1.27) [30]. The risk of noncardia gastric cancer was particularly increased by red and processed meat consumption among *H. pylori*-positive individuals in a large, prospective nutrition survey [28].

  In 2015, the World Health Organization's IARC reviewed the evidence linking intake of processed meat with a variety of cancer sites and concluded that there was a positive association between consumption of processed meat and stomach cancer [31]. A majority of the working group concluded that there was sufficient evidence in human beings for the carcinogenicity of consuming processed meat. Processed meats (eg, sausages, bacon, ham, beef jerky, corned beef, and other smoked, salted, fermented, or cured meats) were classified as group 1 carcinogens, placing these foods in the same risk category for cancer as asbestos, cigarettes, and alcohol (although the amount of increased risk is nowhere near the same).

Low folate levels — A meta-analysis of epidemiology studies found an inconsistent association between low levels of folate and the risk of gastric cancer [32].

Obesity — Excess body weight is associated with an increased risk of gastric cancer [33-35]. In a meta-analysis of cohort studies identifying 9492 gastric cancer cases, excess body weight (defined as a body mass index [BMI] ≥25 kg/m^2) was associated with an increased risk of gastric cancer (odds ratio [OR] 1.22, 95% CI 1.06-1.41) [33]. The strength of the association increased with increasing BMI. Whether this risk extends to all stomach sites is not clear. An updated 2016 analysis of observational studies on cancer risk and excess body fat conducted by a working group of the IARC concluded that the data were sufficient for gastric cardia cancers (relative risk for the highest BMI category evaluated versus a normal BMI 1.8, 95% CI 1.3-2.5) but not for gastric noncardia cancers [35].

Smoking — Several studies have examined the relationship between tobacco smoking and gastric cancer. A meta-analysis of 42 studies estimated that the risk was increased approximately 1.53-fold and was higher in men [36]. A prospective study from Europe (EPIC) found a similar magnitude of risk, which diminished after 10 years of smoking cessation [37]. Approximately 18 percent of gastric cancer cases were attributed to smoking.

Occupational exposures — There is some evidence that occupations in coal and tin mining, metal processing (particularly steel and iron), and rubber manufacturing industries lead to an increased risk of gastric cancer; however, the data are disparate [38-41].

Influence of salt and intake of salted foods — As noted above, there is a link between intake of salt and highly salted foods and gastric cancer risk; high salt intake damages stomach mucosa and increases the susceptibility to carcinogenesis.

The consumption of salted food appears to increase the possibility of persistent infection with *H. pylori* [42,43]. In addition, a synergistic interaction between *H. pylori* infection and salted food intake that increases the risk of gastric cancer has also been reported in some [17,44,45], but not all [18], case-control studies. (See "Bacteriology and epidemiology of Helicobacter pylori infection".)

There may be a protective effect of nonsteroidal anti-inflammatory drug (NSAID) use. (See 'NSAIDs' below.)

Epstein-Barr virus — Infection with Epstein-Barr virus (EBV) is associated with a number of malignancies, especially nasopharyngeal carcinoma. (See "Epidemiology, etiology, and diagnosis of nasopharyngeal carcinoma", section on 'Epstein-Barr virus' and "Epidemiology, etiology, and diagnosis of nasopharyngeal carcinoma", section on 'Etiology and risk factors'.)

A possible role in gastric cancer was initially suggested in a study from Korea in which evidence of EBV was found in the tumor cells of 12 of 89 (13 percent) gastric carcinoma patients compared with none of 27 controls with a benign ulcer or any of the benign tissues from the cases [46]. Some of the tumor cells had a histologic appearance similar to that of nasopharyngeal carcinoma.

Since then, it has been estimated that between 5 and 10 percent of gastric cancers worldwide are associated with EBV [47,48]. EBV-associated gastric cancers are characterized by DNA methylation of the promoter region of various cancer-associated genes, which silences the expression of these genes [49-54]. How this leads to gastric cancer is unclear, but silencing the expression of certain genes may modulate the latent-lytic switch of EBV infection, allowing the virus to escape immune detection and remain dormant within the host cells [55].

EBV-associated gastric cancers have distinct clinicopathologic characteristics, including male predominance, preferential location in the gastric cardia or postsurgical gastric stump, lymphocytic infiltration, a lower frequency of lymph node metastasis, perhaps a more favorable prognosis [49,51,56-59], and a diffuse type of histology in most [49,51,52,59,60], but not all [55-

57], series. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'Epstein-Barr virus-associated gastric cancer'.)

Alcohol — A consistent association between alcohol consumption and the risk of gastric cancer has not been demonstrated [61-64]. At least one European study suggests that daily intake of wine may be protective [61].

Socioeconomic status — The risk of distal gastric cancer is increased by approximately twofold in populations with low socioeconomic status [65-68]. By contrast, proximal gastric cancers have been associated with higher socioeconomic class [69].

Gastric surgery — There is an increased risk of gastric cancer after gastric surgery, with both the risk and the interval between initial gastric surgery and the development of remnant gastric cancer depending on the reason for the initial surgery and the type of reconstruction [70-73]:

- The Billroth II procedure (gastrojejunostomy) carries a higher risk than the Billroth I procedure (gastroduodenostomy) [71,73-75]. Although the exact cause of the increased risk is unknown, it is thought to be due to regurgitation of alkaline bile and pancreatic juice (which is greater after a Billroth II procedure compared with a Billroth I procedure). (See "Partial gastrectomy and gastrointestinal reconstruction", section on 'Gastrointestinal reconstruction'.)

- The risk also increases with longer duration of follow-up after gastric surgery [71,73-75].

- The interval between initial gastric surgery and the development of remnant gastric cancer is longer if the original surgery was done for benign disease versus gastric cancer (mean 30 versus 12 years in one series [73]) and if the gastric reconstruction is a Billroth II versus a Billroth I procedure (mean 32 versus 12 years in the same series).

Cancer survivors who received abdominal irradiation — An elevated risk of gastric cancer has been reported in adult survivors of testicular cancer and Hodgkin lymphoma and in childhood cancer survivors who received abdominal radiation therapy [76]. An especially high risk has been noted in Hodgkin lymphoma survivors who received both subdiaphragmatic radiation therapy and high-dose procarbazine (OR 77.5, 95% CI 14.7-1452) [77]. (See "Second malignancies after treatment of classic Hodgkin lymphoma", section on 'Gastrointestinal cancers'.)

Possible protective factors

Fruits, vegetables, and fiber — Consumption of fruits and vegetables (particularly fruit) is probably protective against gastric cancer [13]. Case-control studies from Europe, Asia, and

North America and a pooled analysis of multiple such studies have consistently found intake of fruits and vegetables to be protective against gastric cancer, reducing the risk by approximately 30 to 40 percent for both fruits and vegetables for the highest versus lowest categories of intake [78-82]. Some studies suggest that diets low in citrus fruit show the strongest association with gastric carcinoma [83].

Cohort studies have been less consistent. A meta-analysis of 17 studies found a weaker overall association in the reduction of gastric cancer risk from high intake of fruits (summary relative risk 0.90, 95% CI 0.83-0.98), but there was no discernible protective effect from vegetables (summary relative risk 0.96, 95% CI 0.88-1.06) [84].

The protection afforded by vegetables and fruits is most likely related to their vitamin C content, which is thought to reduce the formation of carcinogenic N-nitroso compounds inside the stomach. Cooked vegetables do not show the same protective effect as uncooked vegetables [85].

Dietary fiber may reduce the risk of gastric cancer. In a meta-analysis, the summary OR for the highest versus lowest intake of dietary fiber was 0.58 (95% CI 0.49-0.67) [86]. The association was similar for different fiber sources and types, and for diffuse type (OR 0.62, 95% CI 0.42-0.92) and intestinal type gastric cancer (OR 0.63, 95% CI 0.45-0.89). In contrast to these results, the prospective EPIC-EURGAST study found that cereal fiber (but not other types of fiber) had a strong protective role for diffuse type gastric cancer but not intestinal type gastric cancer [87]. Further study on different food sources of fiber in relation to gastric cancer risk is warranted to confirm these relationships.

NSAIDs — Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been inversely associated with the risk of distal gastric adenocarcinoma [88,89], and there may be an interaction between NSAID use and *H. pylori* infection. (See 'Helicobacter pylori' above.)

A retrospective study looked at 52,161 patients who had been hospitalized with peptic ulcer disease [88]. On multivariate analysis, regular NSAID use was an independent protective factor against the development of gastric cancer (HR 0.79 for each year of NSAID use), and the protective effect was most pronounced in patients with a history of *H. pylori* infection (HR 0.52 for each incremental year).

Reproductive hormones — Gastric cancer incidence rates are consistently lower in women than in men in both high- and low-risk regions worldwide. There are data that support the hypothesis that reproductive hormones may have a protective role in gastric cancer risk in women [90-92]. One study found that there were associations between age of menopause (HR 0.80 per five-year increase in menopausal age, 95% CI 0.66-0.97), years of fertility (participants

with less than 30 years of fertility were at increased risk compared with those with 30 to 36 years of fertility, HR 1.90, 95% CI 1.25-2.90), years since menopause (HR 1.26 per each five years, 95% CI 1.03-1.53), and intrauterine device use (HR for users 1.61, 95% CI 1.08-2.39) [90].

HOST-RELATED FACTORS

Familial predisposition — Although most gastric cancers are sporadic, aggregation within families occurs in approximately 10 percent of cases. Truly hereditary (familial) gastric cancer accounts for 1 to 3 percent of the global burden of gastric cancer and comprises at least three major syndromes: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC). The risk of developing gastric cancer is high in these families, but only HDGC is genetically explained. A summary of clinical features, recommendations for genetic screening, and the genetic alterations described for these three syndromes is outlined in the table (table 1) [93]. (See 'Hereditary diffuse gastric cancer' below.)

Hereditary diffuse gastric cancer — HDGC is an inherited form of diffuse type gastric cancer, a highly invasive tumor that is characterized by late presentation and a poor prognosis.

Germline truncating mutations in the cadherin 1 (*CDH1*) gene, which encodes the cell adhesion protein E-cadherin, have been identified in approximately 19 to 50 percent of affected kindreds who meet the clinical criteria for HDGC as described by the International Gastric Cancer Linkage Consortium (IGCLC). These mutations are not concentrated in a single hotspot, but rather they are evenly distributed along the *CDH1* gene in several different exons. The trigger and molecular mechanism by which the second allele of E-cadherin is inactivated appear to be diverse and include promoter hypermethylation, mutation, and loss of heterozygosity. The end result is loss of expression of the cell adhesion molecule E-cadherin. (See "Hereditary diffuse gastric cancer", section on 'Criteria for genetic testing' and "Gastric cancer: Pathology and molecular pathogenesis", section on 'Hereditary diffuse gastric cancer'.)

HDGC is inherited as an autosomal dominant trait with high penetrance. The cumulative risk for gastric cancer by age 80 for *CDH1* mutation carriers is up to 70 percent in men and up to 56 percent in women [94]. Affected patients generally are diagnosed with gastric cancer at an early age (average age 38). (See "Hereditary diffuse gastric cancer", section on 'Risk of cancer in carriers of a pathogenic or likely pathogenic CDH1 variant'.)

The risk of gastric cancer in asymptomatic carriers of a pathogenetic *CDH1* mutation who belong to families with highly penetrant HDGC is sufficiently high to warrant prophylactic

gastrectomy. Surgery is usually recommended between the age of 20 and 30, although factors other than age, including fertility considerations, the family phenotype (especially the age of onset of clinical cancer in probands), physical fitness, and preexisting nutritional disorders, should also be taken into account. (See "Surgical management of hereditary diffuse gastric cancer".)

Women in these affected families are also at high risk of developing breast cancer, predominantly lobular. The cumulative risk of breast cancer by age 80 for *CDH1* mutation carriers is approximately 42 percent, and similar to gastric cancers, the increased relative risk starts early (before age 30) [94]. (See "Hereditary diffuse gastric cancer", section on 'Breast cancer' and "Hereditary diffuse gastric cancer", section on 'Surveillance for breast cancer'.)

Referral for genetic testing — Guidelines from the International Gastric Cancer Linkage Consortium and others recommend referral for genetic counseling and DNA testing for *CDH1* mutations and large rearrangements in patients with diffuse gastric cancer who have one or more of the following [94,95] (see "Hereditary diffuse gastric cancer", section on 'Criteria for genetic testing'):

- Family history of two gastric cancers, at any age, with at least one confirmed diffuse gastric cancer
- Diffuse gastric cancer diagnosed at age <40 years, regardless of family history
- Personal or family history of diffuse gastric cancer and lobular breast cancer, with at least one diagnosed at <50 years of age

In addition, families in whom testing could be considered include the following:

- Bilateral lobular breast cancer or family history (first- or second-degree relative) of two or more cases of lobular breast cancer <50 years
- A personal or family history (first- or second-degree relative) of cleft lip/palate in a patient with diffuse gastric cancer
- An individual with in situ signet ring cells and/or pagetoid spread of signet ring cells on a gastric biopsy

GAPPS — Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) was initially identified in 2012 and is characterized by the autosomal dominant transmission of fundic gland polyposis (including dysplastic lesions, intestinal type gastric adenocarcinoma, or both) that is restricted to the proximal stomach, with no evidence of duodenal or colorectal polyposis or another hereditary gastrointestinal cancer syndrome [96,97]. It is characterized by incomplete penetrance. The finding of inherited point mutations in exon 1B of the adenomatous polyposis coli (*APC*) gene reveals this to be a variant of familial adenomatous polyposis (FAP) [98]. (See

"Gastric cancer: Pathology and molecular pathogenesis", section on 'Gastric adenocarcinoma and proximal polyposis of the stomach' and "Clinical manifestations and diagnosis of familial adenomatous polyposis".)

Familial intestinal gastric cancer — FIGC should be considered a potential diagnosis when histopathologic reports denote intestinal type gastric cancers that segregate within families without gastric polyposis. An autosomal dominant inheritance pattern has been noted in many such families [99]. The genetic cause is unknown, and few recommendations are available for the clinical management of these patients [100].

Other hereditary cancer syndromes — Gastric cancer has also been described in association with certain other inherited cancer syndrome, such as:

- **Lynch syndrome (hereditary nonpolyposis colorectal cancer)** (see "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Extracolonic manifestations')
- **Familial adenomatous polyposis (FAP)** (see "Clinical manifestations and diagnosis of familial adenomatous polyposis", section on 'Extracolonic manifestations')
- **Li-Fraumeni syndrome** (see "Li-Fraumeni syndrome", section on 'Spectrum of malignancies and age at onset')
- **Peutz-Jeghers syndrome** (see "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management", section on 'Gastrointestinal cancers')
- **Juvenile polyposis syndrome** (see "Juvenile polyposis syndrome", section on 'Gastrointestinal cancer risk')
- **Hereditary breast and ovarian cancer syndrome** (see "Overview of hereditary breast and ovarian cancer syndromes" and "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Other solid tumors')
- **Phosphatase and tensin homolog (PTEN) hamartoma tumor (Cowden) syndrome** (see "PTEN hamartoma tumor syndromes, including Cowden syndrome", section on 'Gastrointestinal')
- **Ataxia-telangiectasia** (see "Ataxia-telangiectasia")

These inherited cancer syndromes are rare causes of gastric cancer. However, there is an increased risk of gastric cancer among people with pathogenic variants associated with specific inherited cancer syndromes who are also infected with *H. pylori* [101]. In an observational

cohort study of over 10,000 patients with gastric cancer in Japan, germline pathogenic variants in certain cancer-predisposing genes were associated with an increased risk of gastric cancer [101]; these genes and associated syndromes included *APC* (FAP), *ATM* (ataxia-telangiectasia), *BRCA1*, *BRCA2*, and *PALB2* (hereditary breast and ovarian cancer syndrome), *CDH1* (hereditary diffuse gastric cancer), and *MLH1*, *MSH2*, and *MSH6* (Lynch syndrome). *H. pylori* infection also significantly modified the association between these pathogenic variants and the risk of gastric cancer, both for these specific cancer-predisposing genes overall (relative excess risk due to interaction 14.22) and the homologous-recombination genes (*ATM*, *BRCA1*, *BRCA2*, and *PALB2;* relative excess risk due to interaction 16.01). Carriers of these pathogenic variants who were also infected with *H. pylori* had a higher lifetime risk of gastric cancer (46 percent) compared with non-carriers infected with *H. pylori* (14 percent) and carriers not infected with *H. pylori* (less than 5 percent).

These data suggest that individuals with these pathogenic variants should be tested for H. pylori infection and offered eradication treatment if present. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults".)

Other associations — In some families who appear to have a familial aggregation of gastric cancers but no identifiable inherited syndrome, certain risk factors may explain the association:

- Some of the observed familial risk may be due to clustering of *H. pylori* infection within families [102]. However, a case-control study found that a family history increased the risk of gastric cancer independently of *H. pylori* infection [103]. Another case-control study found that a positive history of gastric cancer in one or more first-degree relatives was associated with an increased risk of gastric cancer in women (odds ratio [OR] 5.1) but not in men after controlling for *H. pylori* infection and other confounding variables [104].

- A genetic predisposition for chronic atrophic gastritis, a precursor of gastric carcinoma, has been described and may account for at least some cases of familial gastric cancer [105]. The genetic segregation analysis showed Mendelian transmission of a recessive autosomal gene, with penetrance dependent on age and the status of chronic atrophic gastritis in the mother. Significantly more patients were affected whose mothers were also affected (48 versus 7 percent).

Importance of Helicobacter pylori infection — There may be a role for screening selected asymptomatic individuals for *H. pylori* (eg, individuals who are both first-generation immigrants from areas of high gastric cancer incidence and have a first-degree relative with gastric cancer). However, further studies are needed before it can be recommended.

Infection with *H. pylori* is an important and potentially modifiable risk factor for gastric cancer. (See 'Helicobacter pylori' above.)

In several regions of high gastric cancer incidence, routine screening and eradication of *H. pylori* has been implemented or is being evaluated to decrease rates of gastric cancer. Limited data suggest that screening for *H. pylori* in asymptomatic, healthy individuals in areas of high gastric cancer incidence may decrease the risk of gastric cancer. (See "Gastric cancer screening".)

Successful eradication of *H. pylori* infection in first-degree relatives with gastric cancer has been demonstrated to significantly reduce the risk of a subsequent gastric cancer in areas of high cancer incidence [106]. This was illustrated in a randomized trial in South Korea in which 1838 individuals with *H. pylori* infection and a first-degree relative with gastric cancer were assigned to receive either eradication therapy or placebo. During a median follow-up of 9.2 years, gastric cancer developed in significantly fewer patients in the *H. pylori* treatment group as compared with the placebo group, although the overall incidence of gastric cancer in both groups was low (2.7 versus 1.2 percent; hazard ratio [HR] 0.45). Trial participants were not evaluated for genetic susceptibility to gastric cancer or the bacterial virulence of the *H. pylori*.

In general, in areas of low gastric cancer incidence, there is no role for routine screening of asymptomatic, average-risk, healthy individuals for *H. pylori* in order to decrease the risk of gastric cancer. There might be a role for screening individuals who are both first-generation immigrants from areas of high gastric cancer incidence and have a first-degree relative with gastric cancer, but additional data are needed. This subject is discussed in more detail elsewhere. (See "Gastric cancer screening", section on 'Helicobacter pylori eradication'.)

Genetic polymorphisms — Certain polymorphisms have been associated with gastric cancer:

- The human interleukin 1 beta (*IL-1B*) gene is the most important candidate gene in the host that could affect the clinical outcome of *H. pylori* infection because it is upregulated by infection, profoundly proinflammatory, and the most powerful acid inhibitor known. Polymorphisms in the *IL-1B* gene (carriers of IL-1B-511*T) and in the IL-1 receptor antagonist gene (IL-1RN*2/*2) have been associated with an increased risk of gastric cancer [107]. Another study showed that polymorphisms (IL-1B-511*T carriers [IL-1B-511*T/*T or IL-1B-511*T/*C]) and *H. pylori* virulence factors (*vacAs1*, *vacAm1*, and *cagA* positive) were additive in increasing the risk of gastric cancer [108].

- Interferon gamma (IFN-gamma) signaling has an essential role in human *H. pylori* infection. The *IFNGR1* gene encodes chain 1 of the IFN-gamma receptor. Sequencing of *IFNGR1* revealed a close association between the 56C>T, H318P, and L450P variants and high *H. pylori* antibody concentrations [109]. These variants were more prevalent among

Africans than in White subjects in a cohort of families from Northern Senegal, which might in part explain why *H. pylori* infection is highly prevalent in Africa but is relatively less pathogenic.

- Polymorphisms of methylenetetrahydrofolate reductase (MTHFR) have been associated with gastric cancer, mainly in Eastern Asian subjects [110].

Gastric polyps — Gastric polyps are typically found incidentally when an upper gastrointestinal endoscopy is performed for an unrelated indication; only rarely do they cause symptoms or other clinical signs. Nevertheless, their discovery can be important since many polyps have malignant potential. (See "Gastric polyps".)

Blood group — The role of genetic factors was first suggested by the study of blood groups and determinants of chronic gastritis [111]. Individuals of blood group A have been known for decades to show an approximately 20 percent excess of gastric cancer compared with those of group O, B, or AB [112-114]. They also show a similar increase in the rate of pernicious anemia. Some data suggest that group A may be particularly associated with diffuse-type gastric cancer [111]. It is possible that the observed associations are not due to the blood group antigens themselves but to the effects of genes closely associated with them.

Hypertrophic gastropathy and immunodeficiency syndromes — Hypertrophic gastropathy (including Ménétrier's disease) [75] and various immunodeficiency syndromes [115,116] have been linked with gastric cancer. However, the strength of these associations remains undefined. (See "Approach to the patient with large gastric folds".)

Gastric ulcer — An association between benign gastric ulcers and gastric cancers probably reflects common risk factors (ie, mainly *H. pylori* infection) [117-120]. The largest cohort study followed (for an average of nine years) almost 60,000 Swedish patients who had been hospitalized for a gastric or duodenal ulcer [121]. The risk of gastric cancer was increased among patients with benign gastric ulcers (incidence ratio 1.8), was unchanged among patients with prepyloric ulcers, and was decreased among patients with benign duodenal ulcers (incidence ratio 0.6).

In a study from Japan, 1120 patients with peptic ulcer disease who had *H. pylori* eradication therapy were followed for a mean of 3.4 years [122]. Gastric cancer developed only in patients with a gastric ulcer but not in patients with duodenal ulcers. Patients who developed gastric cancer were significantly more likely to have persistent *H. pylori* infection (HR 3.4). A follow-up study from the same group showed that in patients with peptic ulcer diseases, the risk of gastric cancer was significantly increased with persistent *H. pylori* infection, a higher grade of baseline gastric mucosal atrophy, and older age [123].

Pernicious anemia — Pernicious anemia, a sequela of autoimmune chronic atrophic gastritis directed against hydrogen-potassium ATPase in the gastric parietal cells, is associated with an increased risk of intestinal type gastric cancer. A two- to sixfold excess risk has been reported [124-128], but as with other predisposing conditions, the actual degree of risk varies with the duration of disease and geographic location. Pernicious anemia is also associated with an increased risk of gastric neuroendocrine tumors, presumably due to prolonged achlorhydria resulting from parietal cell loss, compensatory hypergastrinemia, and argyrophilic cell hyperplasia [129]. (See "Metaplastic (chronic) atrophic gastritis", section on 'Gastric neuroendocrine (carcinoid) tumors' and "Metaplastic (chronic) atrophic gastritis", section on 'Gastric adenocarcinomas' and "Causes and pathophysiology of vitamin B12 and folate deficiencies", section on 'Pernicious anemia'.)

On the other hand, "iatrogenic" achlorhydria induced by long-term use of histamine 2 receptor antagonists or proton pump inhibitors has not been associated with an increased risk of either gastric adenocarcinomas or neuroendocrine tumors [130-134]. An association between maintenance therapy with omeprazole and the development of atrophic gastritis in individuals with *H. pylori* infection has been suggested, but the data are inconclusive. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Atrophic gastritis'.)

Although the benefit of screening or surveillance endoscopy in patients with pernicious anemia has not been established, a guideline issued by the American Society for Gastrointestinal Endoscopy (ASGE) recommends the following [135]:

- A single endoscopy should be performed to identify prevalent lesions (carcinoid tumors and gastric cancer).
- There are insufficient data to support subsequent surveillance endoscopy in patients without these findings.

Despite these recommendations, the cost-effectiveness of initial screening endoscopy in patients with pernicious anemia is uncertain. This subject is addressed in detail elsewhere. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency", section on 'Determining the underlying cause of vitamin B12 deficiency'.)

INTERPLAY BETWEEN HOST AND ENVIRONMENTAL FACTORS

Several observations have described interplay between host and environmental factors.

- As noted above, higher salt intake correlates with a higher prevalence of persistent *H. pylori* infection and with a higher risk of gastric cancer in those infected with *H. pylori*. A possible explanation is that mucosal damage caused by high salt intake facilitates *H. pylori* infection. The resultant hypochlorhydria and bacterial overgrowth, with the subsequent conversion of nitrites into the mutagenic N-nitrosamines, may then lead to metaplasia, dysplasia, and cancer. (See 'Influence of salt and intake of salted foods' above.)

- The gastric juice of *H. pylori*-positive individuals had a lower concentration of vitamin C than that of *H. pylori*-negative individuals, but the concentration returned to normal when the *H. pylori* was eradicated [136]. As a result, vitamin C may have an important role in preventing the damage caused by *H. pylori* through its antioxidant effect [136].

- Beta-carotene and ascorbic acid are believed to interfere with progression to cancer through their antinitrosation and antioxidant effects, and thus act as protective factors [137].

- A model of gastric carcinogenesis recognizes the interplay between exogenous risk factors (such as *H. pylori* or nitroso compounds), endogenous protective factors (such as the ability to repair DNA damage), and exogenous protective factors (such as antioxidants). *H. pylori* infection in early life leads to chronic inflammation. The resulting cellular proliferation increases the likelihood of mitotic error. Dietary mutagens may also increase the risk of mutation while dietary antioxidants act as protective factors. Because some DNA damage can be self-corrected, *H. pylori*-related mutations only rarely lead to malignant transformation. Thus, a longer duration of infection, especially infection acquired during childhood and continuing until old age, increases the risk of significant DNA damage with subsequent malignant transformation [137].

- The *H. pylori* genotype and host genetic polymorphisms have a role in determining the clinical consequences of *H. pylori* infection and thus the risk of developing gastric cancer. It has been suggested that combined bacterial/host genotyping may provide an important tool in defining disease risk and targeting *H. pylori* eradication to high-risk individuals.

SCREENING GUIDELINES

Approaches to screening patients for gastric cancer are discussed elsewhere. (See "Gastric cancer screening".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastric cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Stomach polyps (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Several risk factors for gastric cancer have been identified, the most important of which are infection with *H. pylori* and family history. (See 'Introduction' above.)

- The sequence of molecular events that underlies intestinal-type gastric cancer and its precursor lesions is incompletely understood. In comparison, much more is known about the molecular pathogenesis of diffuse-type gastric cancers, which display a prominent molecular abnormality in the cell adhesion protein E-cadherin (CDH1). (See 'Precursor lesions' above.)

- Gastric cancer developing in patients considered to be at average risk involves an interplay of bacterial, host, and environmental factors. Dietary (nitroso compounds, high-salt diet with few vegetables) and lifestyle factors (smoking and alcohol consumption) probably account for one-third to one-half of all gastric cancers. *Helicobacter pylor*i infection, especially certain genotypes (*vacAs1*, *vacAm1*, and *cagA* positive), remains an important risk factor. The risk is increased further in hosts who possess specific types of cytokine

polymorphisms (IL-1B-511*T/*T or IL-1B-511*T/*C). (See 'Interplay between host and environmental factors' above.)

- Although most gastric cancers are sporadic, aggregation within families occurs in approximately 10 percent of cases. Truly hereditary (familial) gastric cancer accounts for 1 to 3 percent of the global burden of gastric cancer and comprises at least three major syndromes: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC). The risk of developing gastric cancer is high in these families, but only HDGC is genetically explained (germline mutations in the *CDH1* gene encoding E-cadherin in up to 50 percent of HDGC patients). (See "Hereditary diffuse gastric cancer".)

  Gastric cancer has also been described in association with certain other inherited cancer syndromes, including Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, juvenile polyposis, hereditary breast and ovarian cancer syndrome, and possibly, phosphatase and tensin homolog (PTEN) hamartoma tumor (Cowden) syndrome, but these are all fairly rare causes of gastric cancer. Nevertheless, guidelines for management of individuals affected by these syndromes generally recommend screening for gastric cancer. (See 'Familial predisposition' above.)

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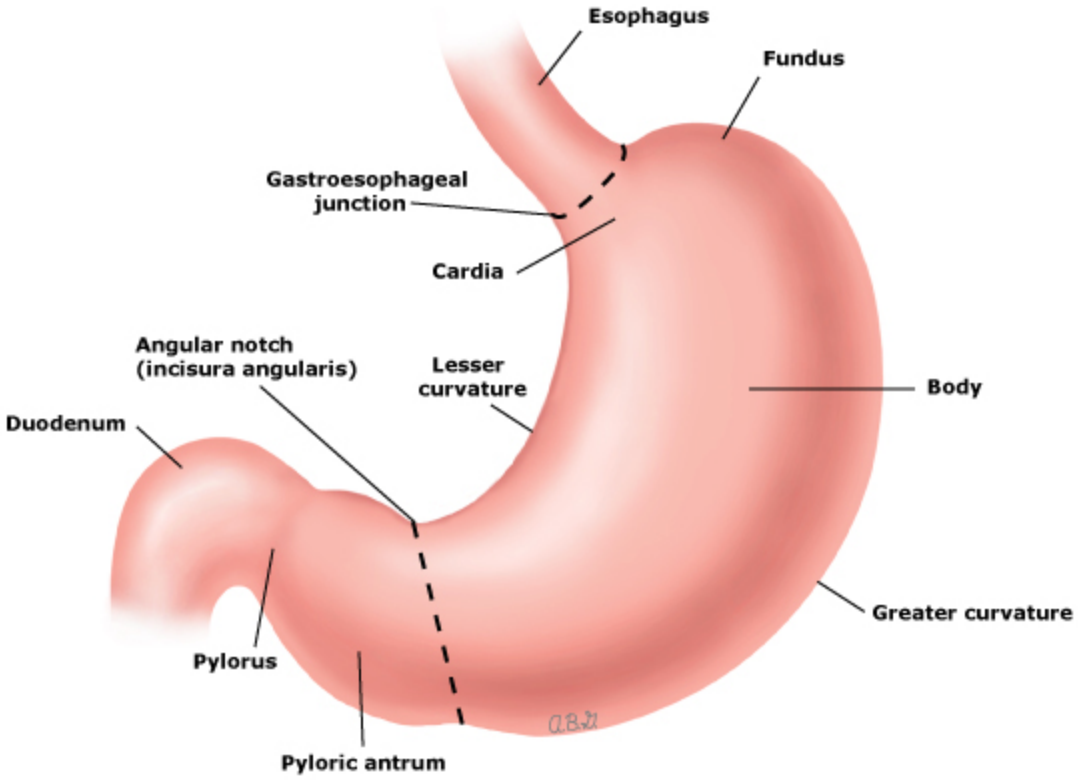
Topic 2617 Version 57.0

GRAPHICS

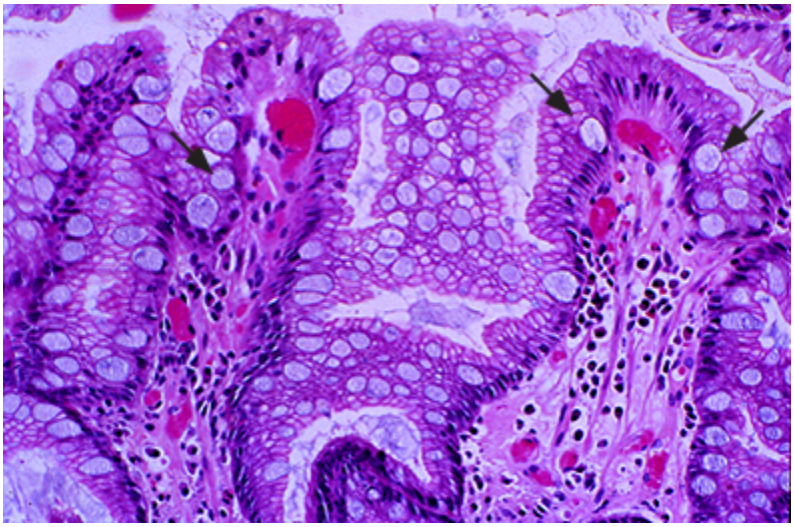
Parts of the stomach



This drawing shows the parts of the anterior surface of the stomach. The body of the stomach is separated from the pyloric part by an oblique line that extends from the angular notch (incisura angularis) on the lesser curvature to the greater curvature.

Graphic 79793 Version 4.0

Incomplete intestinal metaplasia

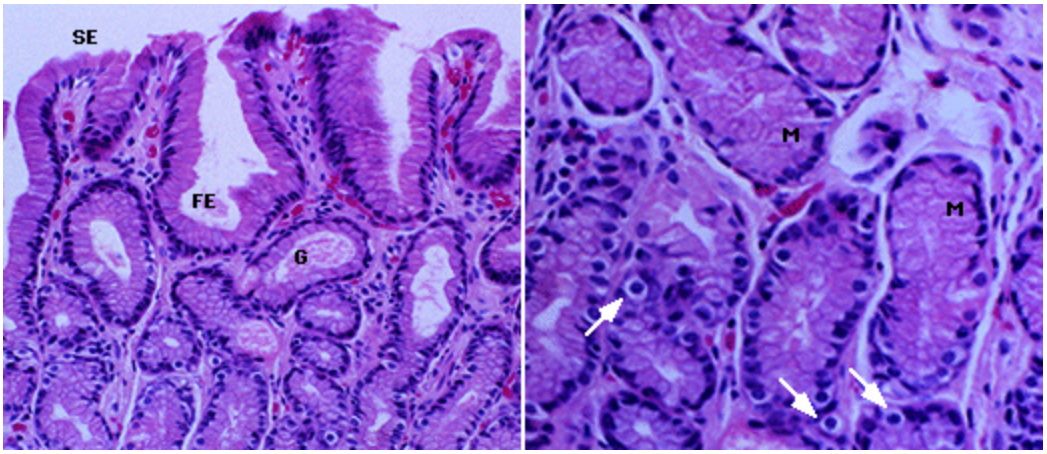


High power view (H&E stain) of chronic atrophic gastritis with incomplete intestinal metaplasia showing metaplastic goblet cells in the surface and foveolar epithelium (arrows).

Courtesy of Robert Odze, MD.

Graphic 64199 Version 3.0

Normal gastric antrum

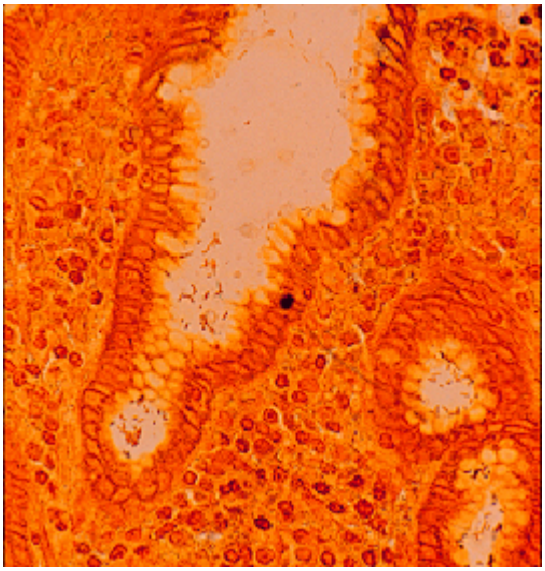


Left panel: Normal surface (SE) and foveolar epithelium (FE) and glands (G). Right panel: Higher power view of the glands shows mucous cells (M) and gastrin-secreting endocrine cells (arrows).

Courtesy of Robert Odze, MD

Graphic 79895 Version 1.0

Helicobacter pylori in gastric pits



Dieterle's silver strain (x200).

Courtesy of Paul C Schroy III, MD.

Graphic 51050 Version 1.0

Clinical criteria, recommended screening, and inherited alterations of familial gastric cancer syndromes

	Clinical criteria	Genetic screening	Alterations described
Hereditary diffuse gastric cancer	Two or more cases of gastric cancer, one confirmed case of diffuse gastric cancer in someone younger than 50 years Three or more confirmed diffuse gastric cancer cases in first-degree or second-degree relatives, independent of age of onset Diffuse gastric cancer before age 40 years without a family history	Sequencing of *CDH1* coding sequences Multiplex ligation-dependent probe amplification (large *CDH1* rearrangements)	Mutations throughout the *CDH1* gene and deletions mainly implicating flanking untranslated regions
	Personal or family history of diffuse gastric cancer and lobular breast cancer, one of which must be diagnosed before age 50 years	Sequencing of *CTNNA1* coding sequences	One germline truncating mutation in *CTNNA1*
Gastric adenocarcinoma and proximal polyposis of the stomach	Gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis More than 100 polyps carpeting the proximal stomach in the index case or more than 30 polyps in a first-degree relative of another case Mainly fundic gastric polyps, some with regions of dysplasia (or a family member with either dysplastic fundic gastric polyps or gastric adenocarcinoma) Autosomal dominant pattern of inheritance Exclusions include other heritable gastric polyposis syndromes and use of proton pump inhibitors*	No screening available	No inherited mutations so far
Familial intestinal gastric cancer	Two or more cases of gastric cancer in first-degree or second-degree relatives, with at least one confirmed case of intestinal	No screening available	No inherited mutations so far

	histology in someone younger than 50 years Three or more confirmed cases of intestinal gastric cancer in first-degree or second-degree relatives, independent of age		

* Proton pump inhibitors can induce a proximal polyposis of the stomach that may mimic a gastric adenocarcinoma. Patients taking these drugs should undergo a repeat endoscopy off-therapy to confirm the diagnosis of gastric adenocarcinoma versus proximal polyposis of the stomach.

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Contributor Disclosures

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