Genetic Testing by Cancer Site
Stomach

Nicki Chun, MS, CGC and James M. Ford, MD

Abstract: Gastric cancer is a global public health concern, ranking as the fourth leading cause of cancer mortality, with a 5-year survival of only 20%. Approximately 10% of gastric cancers appear to have a familial predisposition, and about half of these can be attributed to hereditary germline mutations. We review the genetic syndromes and current standards for genetic counseling, testing, and medical management for screening and treatment of gastric cancer. Recently, germline mutations in the E-cadherin/*CDH1* gene have been identified in families with an autosomal dominant inherited predisposition to gastric cancer of the diffuse type. The cumulative lifetime risk of developing gastric cancer in *CDH1* mutation carriers is up to 80%, and women from these families also have an increased risk for developing lobular breast cancer. Prophylactic gastrectomies are recommended in unaffected *CDH1* mutation carriers, because screening endoscopic examinations and blind biopsies have proven inadequate for surveillance. In addition to this syndrome, gastric cancer risk is elevated in Lynch syndrome associated with germline mutations in DNA mismatch repair genes and microsatellite instability, in hereditary breast and ovarian cancer syndrome due to germline *BRCA1* and *BRCA2* mutations, in familial adenomatous polyposis caused by germline APC mutations, in Li-Fraumeni syndrome due to germline p53 mutations, in Peutz-Jeghers syndrome associated with germline *STK11* mutations, and in juvenile polyposis syndrome associated with germline mutations in the *SMAD4* and *BMPR1A* genes. Guidelines for genetic testing, counseling, and management of individuals with hereditary diffuse gastric cancer are suggested. A raised awareness among the physician and genetic counseling communities regarding these syndromes may allow for increased detection and prevention of gastric cancers in these high-risk individuals.

Key Words: Gastric cancer, familial predisposition, hereditary germline mutations, genetic counseling

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Gastric cancer encompasses a heterogeneous collection of etiological and histological subtypes associated with a variety of known and unknown environmental and genetic factors. It is a global public health concern, accounting for 700,000 annual deaths worldwide and currently ranking as the fourth leading cause of cancer mortality, with a 5-year survival of only 20%. The incidence and prevalence of gastric cancer vary widely with Asian/Pacific regions bearing the highest rates of disease.

Recent and rapid advances in molecular genetics have provided an understanding of the cause for many inherited cancer syndromes, offering possibilities for individual genetic testing, family counseling, and preventive approaches. For most cancer syndromes, however, not every individual tested is found to have inherited a germline mutation in a candidate gene, suggesting additional uncharacterized alterations in other genes that result in similar outcomes. Nevertheless, the ability to genetically define many individuals and families with inherited cancer syndromes allows for a multidisciplinary approach to their management, often including consideration of surgical and medical preventive measures. Without question, such complex management and decision making should be centered in the high-risk cancer genetics clinic, where physicians, genetic counselors, and other health professionals jointly consider optimal management for patients and families at high risk for developing cancer.

Approximately 3% to 5% of gastric cancers are associated with a hereditary predisposition, including a variety of Mendelian genetic conditions and complex genetic traits. Identifying those gastric cancers associated with an inherited cancer risk syndrome is the purview of cancer genetics clinics. The keystone to any cancer genetics evaluation is a complete, 3-generation family history. Pedigree analyses suggesting an inherited gastric cancer risk include familiar features such as multiple affected relatives tracking along 1 branch of the family in an autosomal dominant pattern, young ages at onset, and additional associated malignancies related to an identified syndrome. It is imperative to document the histology of the gastric tumors and other familial cancers as this is the initial node in the decision tree of an inherited gastric cancer syndrome differential. Finally, there are clinical criteria for recognized gastric cancer syndromes published by expert consensus panels that assist genetic practitioners in assessing both the likelihood of identifying an underlying germline DNA mutation and guide management in the absence of a molecular confirmation. Herein, we review the literature regarding incidence, recurrence risks, and defined gastric cancer genetic syndromes to assist in providing genetic counseling for families affected by gastric cancer.

HISTOLOGICAL DEFINITIONS AND DESCRIPTIONS

Gastric cancer has traditionally been subtyped pathologically according to Lauren's[1] classification published in 1965 and revised by Carneiro et al[2] in 1995. The 4 histological categories include (1) glandular/intestinal, (2) border foveal hyperplasia, (3) mixed intestinal/diffuse, and (4) solid/undifferentiated.

More clinically relevant, the majority of gastric cancers can be subdivided into intestinal type or diffuse type. Diffuse tumors exhibit isolated cells, typically developing below the mucosal lining, often spreading and thickening until the stomach appears hardened into the morphological designation called "linitis plastica." Diffuse gastric tumors frequently feature "signet ring cells," named for the marginalization of the nucleus to the cell periphery due to high mucin content. Intestinal-type gastric tumors more often present as solid masses with atrophic gastritis and intestinal metaplasia at the periphery. The intestinal subtype is seen more commonly in older patients, whereas the diffuse type affects younger patients and has a more aggressive clinical course. The relative proportions of gastric cancer subtypes worldwide are 74% intestinal versus 16% diffuse and 10%

From the Program for Clinical Cancer Genetics, Division of Oncology, Departments of Medicine, Pediatrics and Genetics, Stanford University School of Medicine, Stanford, CA.

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Reprints: James M. Ford, MD, Program for Clinical Cancer Genetics, Division of Oncology, Departments of Medicine, Pediatrics and Genetics, Stanford University School of Medicine, Stanford, CA 94305. E-mail: jmf@stanford.edu.

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other,[3] although diffuse gastric cancer is becoming relatively more common in the Western countries. The importance of distinguishing these 2 main histopathologic types of gastric cancer is highlighted by finding specific genetic changes associated with the different types. For the purposes of genetic counseling, E-cadherin (*CDH1*) mutations are found exclusively in the diffuse type.[4–8] Whereas intestinal-type hereditary gastric cancer families have been identified clinically, no genetic associations have yet been discovered.

As individual molecular profiling of solid tumors becomes more common in the future, we expect classification systems will evolve based on tumor biology more than histology. Advances in deciphering the mechanisms of gene alterations that lead to gastric cancer include gene mutation, amplification, deletion, and epigenetic methylation.[9] For example, 2 recent studies have performed whole-exome sequencing of human gastric tumors and identified a number of known (eg, *p53, PTEN*, *PIK3CA*), but also previously unreported somatic gene mutations and pathway alterations. Both found *ARID1A* inactivating gene mutations in the majority of microsatellite-instable tumors, a member of the SWI-SNF chromatin remodeling family.[10,11] However, whether any of these somatic gene alterations are found to confer cancer risk when mutated in the germline remains to be determined.

ETIOLOGY

Analogous to other common cancers, a host of factors are implicated as causes of gastric cancer. Widely diverse geographical disparities suggest both environmental and genetic contributions. Furthermore, a strong association with endemic *Helicobacter pylori* carrier rates implicates infection as a major risk factor. There are likely to be a host of factors contributing to the development of most gastric cancers.

Environmental Risk Factors

Geographic variations in gastric cancer rates have prompted investigations of shared diet and lifestyle variables. Gastric cancer is correlated with the chronic ingestion of pickled vegetables, salted fish, excessive dietary salt, and smoked meats and with smoking.[12–16] Fruits and vegetables may have a protective effect. The influence of environmental factors as causes of gastric cancer is highlighted by declining rates of intestinal gastric cancer among immigrants from high-incident countries to low-incident countries.

Infectious Risk Factors

Helicobacter pylori infection is endemic in the Asian-Pacific basin.[17] Transmission routinely occurs through family contacts in childhood and leads to atrophic gastritis.[18,19] As evidenced by high indigenous infection rates, *H. pylori* is insufficient to singularly cause gastric cancer, suggesting complex interactions between virus and host genetic backgrounds. However, *H. pylori* species are consistently implicated as a major risk factor primarily associated with intestinal-type gastric cancer. Studies in a variety of high- and low-risk populations have found odds ratios ranging from 2.56 to 6.0 for noncardia gastric cancer.[20]

Epstein-Barr virus has recently been implicated in about 10% of gastric carcinoma worldwide or an estimated 80,000 cases annually. Epstein-Barr virus–associated gastric cancer shows some distinct clinicopathologic characteristics, such as male predominance, predisposition to the proximal stomach, and a high proportion in diffuse-type gastric carcinomas. Mechanistically, Epstein-Barr virus gastric tumors display epigenetic promoter methylation of many cancer-related genes, causing downregulation of their expression.[21]

Genetics

Five percent to 10% of gastric cancer is associated with strong familial clustering and attributable to genetic factors. Shared environmental factors account for the majority of familial clustering of the intestinal type; however, approximately 5% of the total gastric cancer burden is thought to be due to germline mutations in genes causing highly penetrant, autosomal dominant gastric cancer risk of both intestinal and diffuse subtypes. We review the definitions of hereditary gastric cancer families and recognize genetic syndromes associated with increased gastric cancer risk.

EPIDEMIOLOGY OF GASTRIC CANCER

Gastric cancer is now the fourth most common malignancy worldwide, with rates having fallen steadily since 1975 when global statistics were first compared. The incidence and prevalence of gastric cancer vary widely among world populations. High-risk countries (reported incidence × 100,000 per year) include Korea (41.4), China (41.3), Japan (31.1), Portugal (34.4), and Colombia (20.3). Intermediate-risk countries include Malaysia, Singapore, and Taiwan (11–19), whereas low-risk areas include Thailand (8), Northern Europe (5.6), Australia (5.4), India (5.3), and North America (4.3). More than 70% of cases occur in developing countries, and men have roughly twice the risk of women.[22] In 2008, estimates of gastric cancer burden in the United States were 21,500 cases (13,190 men and 8310 women) and 10,880 deaths.[23] The median age at diagnosis for gastric cancer is 71 years, and 5-year survival is approximately 25%.[24] Only 24% of stomach cancers are localized at the time of diagnosis, 30% have lymph node involvement, and another 30% have metastatic disease. Survival rates are predictably higher for those with localized disease, with corresponding 5-year survival rates of 60%.

The worldwide decline in the incidence of gastric cancer has been attributed to modifications in diet, improved food storage and preservation, and decreased *H. pylori* infection. Fresh fruit and vegetable consumption, refrigeration, decreased urban crowding, and improved living conditions have reduced *H. pylori* exposure and carrier rates. By contrast, the incidence of diffuse-type gastric cancer is stable, and in North America, it may even be increasing.[16,25–27]

FAMILIAL GASTRIC CANCER

Shared environmental factors, such as diet and *H. pylori* infection, account for the majority of familial clustering of the intestinal type of gastric cancer, with no known causative germline variants. However, few nongenetic risks for diffuse gastric cancer have been identified, supporting a larger role for hereditary factors. Approximately 5% of the total gastric cancer burden is thought to be due to germline mutations in genes causing a highly penetrant, autosomal dominant predisposition. The International Gastric Cancer Linkage Consortium (IGCLC) has redefined genetic classification of familial intestinal gastric cancer to reflect the background incidence rate in a population (Table 1).

Thus, countries with high incidence of intestinal-type gastric cancer (China, Korea, Japan, Portugal) use criteria analogous to the Amsterdam criteria invoked for Lynch syndrome:

(1) at least 3 relatives with intestinal gastric cancer, one a first-degree relative of the other two,
(2) at least 2 successive generations affected, and
(3) gastric cancer diagnosed before the age of 50 years in at least 1 individual.

In countries with a low incidence of intestinal-type gastric cancer (United States, United Kingdom):

TABLE 1. Clinical Criteria for *CDH1* Testing Defined by IGCLC[44] 2010

(1) Two gastric cancer cases in the family: one confirmed diffuse type, one diagnosed at age <50 y
(2) Three confirmed diffuse gastric cancers in first- or second-degree relatives independent of age
(3) Diffuse gastric cancer diagnosed at age <40 y (no additional family history needed)
(4) Personal or family history (first- or second-degree) of diffuse gastric cancer and lobular breast cancer, one diagnosed at age <50 y

(1) at least 2 first-/second-degree relatives affected by intestinal gastric cancer, one diagnosed before the age of 50 years; or
(2) 3 or more relatives with intestinal gastric cancer at any age.

Familial intestinal gastric cancer families are similarly prevalent as familial diffuse gastric cancer families, yet a germline genetic defect underlying the disease remains yet to be identified.[28] Hemminki et al[29] reported Swedish data on all available types of cancer in first-degree relatives by both parent and sibling probands. The relative risks (RRs) for gastric cancer were greater than 3 for siblings with any relative with gastric cancer and greater than 5 when a sibling was younger than 50 years. Shin et al[30] assessed 428 gastric cancer subjects and 368 controls in Korea for the risk of gastric cancer in first-degree relatives and found an RR of 2.85 with 1 first-degree relative and greater than 5 in a first-degree relative with *H. pylori* and a positive family history. Therefore, in the high-incident countries of Japan and Taiwan, population screening for gastric cancer has greatly enhanced early detection, leading to 5-year survival rates of greater than 90%.[31]

HEREDITARY DIFFUSE GASTRIC CANCER

In 1999, the first IGCLC defined hereditary diffuse gastric cancer (HDGC) as families with (1) 2 cases diffuse gastric cancer in first-/second-degree relatives with 1 younger than 50 years, and (2) 3 cases diffuse gastric cancer at any age.[32] The first clear evidence for a gastric cancer susceptibility genetic locus was the identification in 1998 of a germline inactivating mutation in the gene encoding for E-cadherin (*CDH1*), in a large, 5-generation Maori family from New Zealand with 25 kindred with early-onset diffuse gastric cancer.[33] The age at diagnosis of gastric cancer ranged upward from 14 years, with the majority occurring in individuals younger than 40 years. The pattern of inheritance of gastric cancer was consistent with an autosomal dominant susceptibility gene with incomplete penetrance. Similar reports of *CDH1* mutations in widely diverse HDGC cohorts from Asia, Europe, and North America followed soon thereafter.[34–39] Germline *CDH1* mutations have been found to be associated with approximately 30% of families with HDGC, with a lifetime risk for gastric cancer of greater than 80%, and up to 60% risk for female carriers developing lobular breast cancer.[40] To date, *CDH1* is the only gene implicated in HDGC. Worldwide, about 100 *CDH1* mutation–positive families have been reported.[41]

E-CADHERIN MUTATIONS AND GASTRIC CANCER

The E-cadherin gene coding sequence gives rise to a mature protein consisting of 3 major domains, a large extracellular domain (exons 4–13) and smaller transmembrane (exons 13–14) and cytoplasmic domains (exons 14–16). As in other autosomal dominant cancer predisposing genes, only 1 *CDH1* allele is mutated in the germline, and the majority of genetic changes lead to truncation of the protein, with mutations distributed throughout the gene's 2.6 kb of coding sequence and 16 exons without any apparent hotspots. Somatic *CDH1* mutations have been identified in about half of sporadic diffuse gastric cancers, but occur rarely in intestinal gastric cancer. CDH1 encodes the calcium-dependent cell-adhesion glycoprotein E-cadherin. E-cadherin is a transmembrane protein that connects to the actin cytoskeleton through a complex with catenin proteins.[5,42] Functionally, E-cadherin impacts maintenance of normal tissue morphology and cellular differentiation. With regard to HDGC, it is believed that CDH1 acts as a tumor suppressor gene, with mutation of CDH1 leading to loss of cell adhesion, proliferation, invasion, and metastasis.[43]

GENETIC TESTING FOR HDGC

At the second meeting of the IGCLC in 2010, HDGC guidelines[44] were extended to recommend *CDH1* genetic testing to families with

(1) 2 cases of gastric cancer in which 1 case is histopathologically confirmed as diffuse and younger than 50 years,
(2) families with both lobular breast cancer and diffuse gastric cancer, with 1 diagnosed younger than 50 years, and
(3) probands diagnosed with diffuse gastric cancer younger than 40 years, with no family history of gastric cancer.

Using the initial IGCLC criteria for HDGC, *CDH1* mutation testing yielded a detection rate of 30% to 50%.[45] Interestingly, a pattern began to emerge of lower *CDH1* mutation rates among HDGC families in high gastric cancer incidence populations and higher rates in low-incident countries.[46,47] Other reports suggest that the rate of *CDH1* mutations in isolated cases of diffuse gastric cancer younger than 35 years is similar in both low- and high-risk countries hovering at around 20%.[48]

Approximately 50% to 70% of clinically diagnosed HDGC families have no identifiable genetic mutation. Multiple candidate loci have been investigated without identifying causative mutations that would account for the large number of non-*CDH1* HDGC families.[49–51] Huntsman's group has published a report of multiplex ligation-dependant probe amplification-based exon duplication/deletion studies performed on 93 non-*CDH1* families and found 6.5% carried large genomic deletions bringing the detection rate up to 45.6% in their cohort of 160 families.[52]

As *CDH1* mutation families were identified, data on these families provided the foundation for genetic counseling information. Initially, the cumulative risk of gastric cancer by age 80 years in HDGC families was initially estimated as 67% for men and 83% for women. The age at onset shows marked variation between and within families. The median age at onset in the 30 Maori *CDH1* mutation carriers who developed gastric cancer was 32 years, significantly younger than the median age of 43 years in individuals with gastric cancer from other ethnicities.[53] More recent reports of the lifetime risks of diffuse gastric cancer suggest greater than 80% in both men and women by age 80 years.[48,54]

The lifetime risk for lobular breast cancer among female *CDH1* carriers, originally estimated to be in the range of 20% to 40% now approaches 60% with an average age of 53 years at time of diagnosis.[36,54,55] Of note, *CDH1* mutations have been seen in up to 50% of sporadic lobular breast cancer. Pathological similarities between diffuse gastric and lobular breast carcinomas such as high mucin content with associated signet ring features and loss of E-cadherin on immunohistochemistry hint at a common molecular mechanism.[56,57] To evaluate the *CDH1* carrier rate in women with lobular breast cancer without a family history of diffuse gastric cancer, a multicenter study of 318 women with lobular type breast cancer diagnosed before

age 45 years and known to be *BRCA1/2*-negative were sequenced for *CDH1* mutations. Only 4 possibly pathogenic mutations were identified for a rate of 1.3%, suggesting *CDH1* is a rare cause of early lobular cancer without associated gastric cancer family history.[58]

Signet ring colon cancer has been reported in 2 families with germline *CDH1*, but no screening guidelines have been suggested.[45,59] Nonsyndromic cleft lip and/or palate was reported in 7 individuals from 3 families in the Netherlands and in 4 individuals from 2 families in France. There is speculation that defects in the cell-adhesion role of E-cadherin may contribute to this developmental anomaly, although no association can be drawn from these scant case reports.[40,60]

Like other familial cancer syndromes with an autosomal dominant inheritance pattern, high penetrance for heterozygotes, and significant mortality unless diagnosed early, genetic counseling and testing should occur early, and a comprehensive screening plan developed, as well as consideration of prophylactic surgery. Pretest and posttest genetic counseling should be provided to individuals from HDGC kindred who are undergoing genetic testing for germline *CDH1* mutations. Because cases of gastric cancer in HDGC families have been reported in individuals as young as 14 years, HDGC may be considered one of the sets of hereditary cancer syndromes, such as MEN2 associated medullary thyroid cancer, Li-Fraumeni syndrome (LFS), and familial adenomatous polyposis (FAP), in which genetic testing is potentially clinically useful in children.

SCREENING AND MANAGEMENT OF CANCER RISK IN HDGC

Diagnosing gastric cancer in its early stages provides the best chance for curative resection but is a difficult task. Symptoms due to gastric cancer do not appear until the disease is more advanced and are generally nonspecific. The survival of early gastric cancer (eg, not beyond the mucosa or submucosa) is much better than advanced lesions, so identifying these lesions at the earliest of stages is imperative for optimal survival. Endoscopy is generally considered to be the best method to screen for gastric cancer, but diagnosing diffuse gastric carcinoma is most difficult, as these lesions tend not to form a grossly visible exophytic mass, but rather spread submucosally as single cells or clustered islands of cells. Improved chromoendoscopic-aided methods for directed biopsies to diagnose these early diffuse lesions may prove beneficial, but so far all approaches at screening, including computed tomography and positron emission tomography imaging, have proven disappointing.[61]

Given the inadequacy of clinical screening in HDGC, prophylactic total gastrectomy is offered to carriers of germline *CDH1* mutations.[62,63] In every published series of this approach, nearly all specimens contain multiple foci of intramucosal diffuse signet ring cell cancer. Currently, there is information available from 96 total gastrectomies in the setting of HDGC,[44] approximately 3 quarters of which were performed in asymptomatic *CDH1* carriers following negative screening endoscopy and biopsies. Only 3 cases did not show evidence for early invasive carcinoma, and in 2 of these, tiny foci of *in situ* signet ring cell carcinoma were observed observations.[44] Although malignant foci are generally localized to the proximal one third of the stomach,[64] lesions may be distributed throughout the entire stomach, necessitating a total gastrectomy for comprehensive prevention. The optimal timing of prophylactic gastrectomy is unknown but is generally recommended when the unaffected carrier is 5 years younger than the youngest family member who has developed clinical symptoms of HDGC. Clinical management and screening strategies remain uncertain for families who meet criteria for HDGC but are negative for *CDH1* mutations or variants of unknown significance, although screening endoscopy is often suggested.

The impact and long-term outcomes of prophylactic gastrectomy on carriers' lifestyle and health are significant, particularly because 20% to 30% of carriers may never develop invasive gastric cancer. Certainly, all patients experience some level of morbidity, including diarrhea, weight loss, and difficulty eating. Mortality due to this indication for a gastrectomy has not been reported. Early evidence suggests that women can successfully carry healthy pregnancies after gastrectomy.[65] Most importantly, to date, there have been no reports of gastric cancer recurrence in a member of a HDGC family after prophylactic total gastrectomy.

Women with HDGC also exhibit an up to 60% lifetime risk for developing breast cancer, primarily of the lobular type, and as more women are prevented from developing diffuse gastric cancer, breast cancer screening is of great relevance. The correct approach to screening for lobular breast cancer in women with HDGC is not known, but based on approaches used in other hereditary breast cancer susceptibility syndromes. Although prophylactic mastectomy has been shown to effectively prevent the development of breast cancer and to result in improved long-term survival in *BRCA1/2* mutation carriers, such an approach remains completely investigational for women in HDGC families. The prognosis of lobular cancers that develop in HDGC patients is currently unknown, and given the relatively late onset compared with breast cancers in *BRCA1/2* carriers, prophylactic mastectomies may not be appropriate. Standard screening recommendations therefore include annual breast magnetic resonance imaging and mammogram starting at age 35 years.[66,67] An open question is whether chemoprevention with tamoxifen may benefit women with HDGC, given its role in reducing breast cancer risk in half in women at elevated risk because of age, family history, or history of biopsy-proven lobular carcinoma in situ.[68]

In summary, individuals from HDGC families with inherited germline mutations in the *CDH1* gene face up to an 80% likelihood of developing gastric cancer and for women an additional 60% chance of developing lobular breast cancer during their lifetime, with significant risk beginning at relatively young ages. Such levels of overall cancer risk are similar to that of developing breast or colon cancer for carriers of *BRCA1* or 2 gene mutations, or mismatch repair gene mutations, respectively. Therefore, rigorous surveillance and consideration of prophylactic surgery are important for the management of these individuals. At the very least, regular endoscopic examination with random biopsy of the stomach should be performed every 6 to 12 months, probably starting 10 years earlier than the youngest affected patient in the family, or by age 25 years. Because mucosal abnormalities tend to occur late in diffuse gastric cancer and delay the endoscopic diagnosis, prophylactic gastrectomy should be seriously considered as a means of preventing gastric carcinoma, although it clearly comes with high morbidity. It is somewhat less clear as to the correct approach for screening and prevention of lobular breast cancer in women with HDGC. Adherence to standard recommendations for screening mammography for breast cancer should be followed. Consideration of investigative approaches to screening with magnetic resonance imaging and chemoprevention with tamoxifen or other agents are appropriate. The decision to perform prophylactic gastrectomy should be balanced with age-based risk, based on age-specific penetrance data, as well as many other personal factors. Therefore, it is essential that patients carrying the gene have the opportunity for extensive counseling, discussion, and

reflection with knowledgeable clinicians, geneticists, and counselors before making the decision to proceed.

OTHER HEREDITARY CANCER SUSCEPTIBILITY SYNDROMES WITH INCREASED GASTRIC CANCER RISK

Lynch Syndrome

The seminal report of a family with dominantly inherited colon and gastrointestinal (GI) cancers in 1979 by Lynch and Lynch[69] began decades of defining and refining this hereditary syndrome. Lynch syndrome is caused by a germline mutation in a mismatch DNA repair gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) and is thus associated with tumors exhibiting microsatellite instability (MSI). It is estimated that 2% to 4% of all diagnosed colorectal cancers[70] and 2% to 5% of all diagnosed endometrial cancers[71] are due to Lynch syndrome. With a frequency estimated at 1/440 in the US,[72] it is similar to the BRCA carriage rate. The life time risks for Lynch syndrome associated cancers are highest for colorectal cancer at 52% to 82% (mean age at diagnosis 44–61 years), followed by an endometrial cancer risk of 25 to 60% in women (mean age at diagnosis 48–62 years), a 6% to 13% risk for gastric cancer (mean age at diagnosis 56 years), and 4% to 12% for ovarian cancer (mean age at diagnosis 42.5 years).[70–78]

Lynch-associated gastric cancers show predominantly intestinal histology (more than 90% of the cases). This correlation echoes the strong association between MSI tumor phenotype and intestinal gastric cancer. The International Collaborative Group on HNPCC developed the original Amsterdam Criteria in 1991. Revisions followed with Bethesda criteria outlined in 1997 and revised in 2004 with the inclusion of extra-colonic tumor risks including gastric cancer.[79,80]

Microsatellite instability screening by molecular and/or immunohistochemistry for the 4 common Lynch protein products (MSH2, MSH6, MLH1, and PMS2) should be considered in families who meet the Bethesda criteria. As 15% of all gastric tumors exhibit MSI histology, the majority of these have acquired this mutator phenotype through sporadic mutations, and further germline testing of individuals with MSI-positive tumors is necessary to confirm a molecular diagnosis of Lynch syndrome.

Hereditary Breast/Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer due to germline *BRCA1* and *BRCA2* mutations is perhaps the most well-defined and recognized inherited cancer syndrome. With a prevalence of 1/300 to 1/400 in most populations and up to 1/40 in select groups with founder mutations, most notably those with Ashkenazi Jewish ancestry, it represents the most common of the hereditary disorders due to high-risk mutations. Carriers face a fivefold to sixfold increased risk of generally early-onset breast cancer and 10- to 20-fold increased risk for ovarian, fallopian, and primary peritoneal malignancies. Male carriers have a recognized increased risk for prostate cancer and male breast cancer. *BRCA1* and *BRCA2* have been implicated in multiple cellular functions but serve primary roles as tumor suppressor genes recruited to maintain genomic stability through DNA double-strand break repair. Following the cloning of the *BRCA1* and *BRCA2* genes in 1994 and 1995,[81,82] the Breast Cancer Linkage Consortium convened to pool data and generate a body clinical information to assist in counseling and management of BRCA carriers, resulting in a seminal publication outlining the spectrum of *BRCA* mutation–associated cancer risks. In 173 breast-ovarian cancer families with *BRCA2* mutations from 20 centers in Europe and North America, the RR of gastric cancer was 2.59 (95% confidence interval [CI], 1.46–4.61).[83] Carriers of the 6174 delT *BRCA2* Ashkenazi Jewish founder mutation in Israel found gastric cancer to be the most common malignancy after breast and ovarian. Conversely, 5.7% of patients with gastric cancer in Israel were found to carry this *BRCA2* mutation[84]; 20.7% of a Polish cohort of families with both gastric and breast malignancies were attributable to mutations in *BRCA2*. A *BRCA2* mutation was also found in 23.5% of women with ovarian cancer and a family history of stomach cancer in this population.[85,86]

Several studies have implicated *BRCA1* mutations as a risk factor for gastric cancer. A large Swedish population-based study published in 1999 involving 150 malignant tumors from 1145 relatives in *BRCA1* found an RR = 5.86 (95% CI, 1.60–15.01) and observed that gastric cancer diagnosed before age 70 years was twice as common in carrier families compared with the general population. They did not observe the same risk with *BRCA2*.[87,88]

Brose et al[89] observed the highest RR for gastric cancer (6.9) in 147 families with *BRCA1* mutations in Pennsylvania. Risch et al[90] also observed an RR = 6.2 in first-degree relatives of 39 *BRCA1* mutation carrier families and to a lesser extent in 21 *BRCA2* families in Ontario, Canada.

More recently, a meta-analysis of more than 30 studies of tumor risk in *BRCA1* and *BRCA2* carriers found an RR of 1.69 (95% CI, 1.21–2.38) for gastric cancer, the highest risk after breast, ovarian, and prostate, followed closely by pancreatic cancer, with RR = 1.62 (1.31–2.00).[91] No pathology details were included in these studies, and it is unknown if one of the histological subtypes of gastric cancer predominates in BRCA-associated tumors.

Familial Adenomatous Polyposis

Familial adenomatous polyposis is a rare colon cancer syndrome associated with the striking presentation of early-onset multiple colonic adenomas and, in classic form, a near-complete certainty of early colon cancer without prophylactic surgical intervention. Incidence estimates for FAP range from 1/10,000 to 1/20,000, and almost one third of those diagnosed carry a de novo mutation, making family history unreliable for ascertainment of many cases. Extracolonic findings include upper GI adenomas, fundic gland polyps, and desmoids tumors. A wide spectrum of extracolonic tumors can occur including relatively rare cancers such as hepatoblastomas, duodenal adenocarcinomas, and adrenal, pancreatic, thyroid, biliary tract, and brain tumors. Additional diagnostic aids can include the finding of congenital hypertrophy of the retinal pigment epithelium, supernumerary teeth, osteomas, cutaneous lipomas, and cysts.

It is estimated that the lifetime risk for upper GI cancer in FAP is approximately 4% to 12%, of which only 0.5% to 2% are gastric cancers, although this risk has been reported as sevenfold to 10-fold higher in Asia.[75,92,93] Approximately 50% of individuals with FAP have gastric fundus polyps, and 10% have adenomas of the stomach. Although gastric fundus polyps are unlikely to have malignant potential, gastric adenomas can occasionally develop into invasive disease.[94] Prophylactic gastrectomy is even discussed for diffuse fundic gland polyps showing high-grade dysplasia or large polyps.[95] Attenuated FAP is a muted form of classic FAP characterized by fewer than 100 colonic adenoma, a later median age and lower overall risk of colon cancer, and a high proportion of fundic gland polyps, suggesting a measurable risk for gastric cancer.[96–99]

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is a devastating cancer syndrome with an extremely high risk for a multitude of tumor types. The most common malignancies are early-onset breast cancers and

sarcomas followed by brain tumors, leukemia, and lung and then gastric cancer.[100] Four families were originally described by Drs Li and Fraumeni[101] in 1969. The risk of an initial primary cancer is 50% by age 30 years and 90% by age 70 years,[102] with sex-specific differences in lifetime cancer risk of 73% in males and close to 100% in females primarily accounted for by an excess high breast cancer risk.[103] There are high risks for multiple primary cancers, with 60% of carriers developing a second tumor and 4% a third malignancy.[104] Previously thought to be extraordinarily rare with an incidence of 1/50,000 to 1/100,000, recently relaxed testing criteria suggest the actual carrier rate may be several times higher. Seventy percent of individuals who meet classic LFS clinical criteria are found to carry a TP53 germline mutation. The de novo mutation rate is now estimated at 7% to 20%.[105] A negative family history can no longer exclude consideration of LFS, and clinical criteria have been updated to recommend P53 testing for single cases of adrenal cortical carcinoma, choroid plexus carcinoma, and breast cancer under age 30 years.

Although not one of the hallmark tumors of LFS, the International Agency for Research on Cancer database reports that gastric cancer frequency is up to 2.8% of LFS families.[106] Somatic TP53 alterations are associated with both the intestinal and diffuse forms of gastric cancer in equal frequency. However, TP53 constitutional mutations are very rarely documented in the overall gastric cancer mutational spectrum. Among 62 TP53 mutant LFS families seen at the Dana-Farber Cancer Institute in Boston and the National Cancer Institute, gastric cancer was diagnosed in 4.9% of affected members.[107] The mean and median ages at gastric cancer diagnosis were 43 and 36 years, respectively (range, 24–74 years), compared with the median age of 71 years in the general population based on Surveillance Epidemiology and End Results data. Five families (8.1%) reported 2 or more cases of gastric cancer. Pathology review of the available tumors revealed both intestinal and diffuse histologies. A study of 180 families with LFS in the Netherlands found a concordant rate of gastric cancer among carriers with an RR = 2.6 (95% CI, 0.5–7.7).[108]

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare inherited disorder of GI hamartomas, polyposis, and, most strikingly, early development of pigmented lesions on the lips, oral mucosa, and fingers. Incidence rates are estimated in the range of 1/25,000 to 1/250,000. Initially described by Peutz[109] in 1921 and subsequently by Jeghers et al[110] in 1949, PJS is characterized by both hamartomatous and adenomatous polyposis throughout the GI tract and high predisposition to GI malignancies. The clinic diagnosis of PJS is made on the basis of histologically confirmed hamartomatous polyps and 2 of the following: positive family history, hyperpigmentation of the digits and mucosa of the external genitalia, and small bowel polyposis.[111] The mucocutaneous hyperpigmentation characteristically occurs on the buccal mucosa or near the eyes, nose, mouth, axilla, or fingertips. Typically noticeable by age 5 years, they frequently fade by puberty. Classic pigmented lesions in a first-degree relative of a diagnosed individual are sufficient to meet criteria for PJS.

Chronic GI bleeds, anemia, and recurrent obstruction due to intussusception are frequent complications and often require surgical intervention. Among GI cancers, gastric cancer was found to be the third most frequent tumor in PJS, after small intestine and colorectal carcinoma. The cumulative cancer risk is 47% at the age of 65 years.[112] Relative risks reported for colon, stomach, and small intestine neoplasms have been as high as 84, 213, and over 500, respectively.[113] Increased risk is also present for other GI cancers (pancreatic, esophageal), as well as neoplasms outside the GI tract (lung, breast, ovarian, and endometrial). Other tumors associated with PJS are benign ovarian tumors called sex cord tumors with annular tubules, calcifying Sertoli tumors of the testes, and adenoma malignum of the cervix.

A Dutch team reviewed 20 PJS cohort studies, and 1 meta-analysis published between 1975 and 2007 with a total of 1644 patients.[114,115] They found the cumulative lifetime risks of GI cancers of 38% to 66%, and for all cancers, a lifetime risk range of 37% to 93%. Specifically, the gastric cancer risks were 29%, the third most common malignancy after colorectal and breast. Understandably, this prompted a call for screening upper endoscopy every 2 to 5 years starting at age 20 years, whereas others suggest initiating endoscopy at age 8 years with addition of colonoscopy at age 20 years and breast screening at age 25 years.

STK11/LKB1 is the only gene identified to cause PJS, and mutations are found in 70% of those who meet clinical criteria.[116] Fifty percent of affected individuals have a family history of PJS, and 50% may represent de novo mutations, although the penetrance of PJS has yet to be confirmed. The absence of a mutation in *STK11* does not preclude a diagnosis of PJS in individuals meeting the clinical diagnostic criteria.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is another very rare, hereditary cancer syndrome with a broadly defined incidence rate between 1 in 16,000 and 1 in 100,000.[117–120] The diagnosis is based on the presence of multiple hamartomatous polyps with a distinct morphology termed "juvenile," although not restricted to development in childhood. Solitary juvenile polyps occur in 1% to 2% of the general population.

The diagnosis of JPS requires more than 5 juvenile polyps in the colorectum, multiple juvenile polyps throughout the GI tract, or a number of juvenile polyps in an individual with a known family history of juvenile polyps. There is wide interfamilial and intrafamilial variability in number and distribution

TABLE 2. Inherited Cancer Syndromes With Associated Gastric Cancer (GC) Risks

Cancer Syndrome	Gene(s)	Frequency	Gastric Cancer Risk	Reference
HDGC	*CDH1*	Vary rare	>80%	Fitzgerald et al[44]
Hereditary breast/ovarian cancer	*BRCA1/2*	1/40–1/400	2.6%–5.5%	Brose et al[89]
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *Epcam*	1/440	6%–13%	Chen et al,[72] Watson et al[77]
Li-Fraumeni syndrome	*P53*	1/5000	2.8%	Gonzalez et al[105]
FAP	*APC*	1/10–20,000	0.5%–2.0%	Garrean et al[92]
Juvenile polyposis	*SMAD4*, *BMPR1A*	1/16–100,000	21%	Howe et al[121]
PJS	*STK11*	1/25–250,000	29%	Giardiello et al[113], van Lier et al[114]

of polyps. Juvenile polyps are commonly benign, but the risk of malignant transformation is present. Larger polyps have been noted to contain adenomatous regions resulting in a high lifetime risk of colorectal cancer approaching 20% by age 35 years and 68% by age 60 years. Gastric cancer has been found in 21% of JPS patients affected with gastric polyps, and increased incidence of pancreatic and small bowel cancers has also been reported (Table 2).[121]

Approximately 75% of JPS cases are familial, and 25% of JPS cases appear to be de novo. Two genes have been implicated as the cause of JPS in 40% of affected individuals: *SMAD4* (or *MADH4*) and *BMPR1A*, with an approximate equal frequency.[121,122] The majority of JPS is due to as yet unidentified gene(s). Mutations in *SMAD4* are also associated with hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome. Hereditary hemorrhagic telangiectasia is associated with visceral bleeding, telangiectasias, or arteriovenous malformations. Currently, 15% to 22% of *SMAD4* mutation carriers are suspected of having combined JPS/HHT.[123]

Surveillance recommendations for screening individuals with JPS include monitoring for rectal bleeding, anemia, and GI symptoms from infancy and additional complete blood count, upper endoscopy, and colonoscopy at age 15 years, or when symptoms are present. Endoscopy is repeated every 1 to 3 years, depending on polyp load. In families with *SMAD4* mutations, HHT surveillance begins in early childhood.

CONCLUSIONS

Hereditary gastric cancer is a relatively unusual disease. Given the very poor prognosis for most gastric cancer patients once diagnosed, every effort should be made to identify lesions early when they are still curable. Genetic testing for gastric cancer susceptibility allows for identification of families with elevated risk for this and other tumors and development of rational surveillance strategies for early detection. Unfortunately, reliable screening tools for gastric cancer are not available, and prophylactic surgical gastrectomy has proven beneficial in certain autosomal dominant, high-penetrance genetic syndromes, including HDGC caused by germline *CDH1* mutations. Genetic testing for other gastric cancer risk genes may also be warranted as reviewed here. Major goals for clinical cancer genetics include identifying additional risk alleles to explain cancer susceptibility in families without known germline variants and to develop more robust tools for clinical screening for gastric cancer in high-risk individuals. Finally, the advent of whole genome sequencing of germline DNA and tumor genomes will lead to the rapid identification of novel variants and risk alleles of various penetrance. A challenge for the next generation of cancer genetics professionals will be the interpretation of multiple rare variants found in personal genomes and integration with schemes for prevention and early detection of gastric cancer.

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