

## REVIEW

## Historical Perspective on Familial Gastric Cancer

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## SUMMARY

Most gastric cancer is acquired as a consequence of chronic inflammation due to infection by *Helicobacter pylori*. Rarely, familial clusters of gastric cancer are caused by germline mutations in a few genes. The principal familial gastric cancer syndrome is hereditary diffuse gastric cancer caused by germline mutations in the *E-cadherin* gene. There are also a few, rare highly penetrant familial gastric cancer genes, and several other familial cancer syndromes for which gastric cancer is a low penetrance feature.

**Gastric cancer is a common disease worldwide, typically associated with acquired chronic inflammation in the stomach, related in most instances to infection by *Helicobacter pylori*. A small percentage of cases occurs in familial clusters, and some of these can be linked to specific germline mutations. This article reviews the historical background to the current understanding of familial gastric cancer, focuses on the entity of hereditary diffuse gastric cancer, and also reviews the risks for gastric cancer related to a number of other familial genetic diseases. (Cell Mol Gastroenterol Hepatol 2017;3:192-200; <http://dx.doi.org/10.1016/j.jcmgh.2016.12.003>)**

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All cancers are fundamentally genetic diseases characterized by a widely variable number of somatic mutations in the tumors.<sup>1,2</sup> However, the fact that cancers are genetic diseases is not equivalent to the concept that they are necessarily based on heritable genetic factors. The population incidence of many cancers reflects a critical role of extrinsic environmental factors, such as the role of ultraviolet light in skin cancers or smoking in most lung cancers. When multiple members of a family share a common exposure to these DNA-damaging stimuli, certain tumors might cluster within a family. Alternatively, some DNA sequence variations in the germline can predispose individuals to a high incidence of early onset tumors in specific organs that overwhelm the effects of external exposures; in these instances, certain tumors will cluster in those who carry the sequence variants. Consequently, it can be challenging to sort out genetic (intrinsic) vs environmental (extrinsic) factors when trying to understand the basis of familial clusters of cancer, particularly for common

cancers. This confusion ruled early in attempts to understand the etiologic factors in gastric cancer.

Gastric adenocarcinoma is one of the most common cancers worldwide, and is among the top 3 cancers for incidence and mortality outside of the United States. More than 70% of new cases and deaths occur in developing countries, which provides some clue to its causation.<sup>3</sup> A century ago, gastric cancer was the most common malignancy in the United States and internationally. However, the incidence of this disease decreased dramatically in the United States during the 20th century, and has decreased in other countries over a slightly later time frame.<sup>4</sup> This pattern suggests the influence of some noninherited factor that has changed over time, because the changes in our genome do not occur so quickly. Nonetheless, the presence of geographic and familial clusters of gastric cancer presented a conundrum until the most common cause of this disease—chronic infection by *Helicobacter pylori*—was discovered by Marshall and Windsor.<sup>5</sup> All of this suggests that most, probably more than 90% of, gastric cancer is determined by environmental rather than genetic causes.

Jackson et al<sup>6</sup> noted in 1980 that the incidence of gastric cancer was very high in the tiny Republic of San Marino (within Italy), where more than 9% of all deaths were attributed to this malignancy, and genetic factors were suspected. A subsequent study in Northern Italy suggested that approximately 8% of gastric cancers were related to familial factors.<sup>7</sup> Even as late as 2006, an Italian study found that nearly 20% of patients undergoing surgery for gastric cancer had a family history of the disease, a familial risk that was greater than that for the comparative cancers in the study.<sup>8</sup> A study from Japan reported a positive family history of gastric cancer in nearly half of their cases, together with an earlier age at onset of the disease in this setting.<sup>9</sup>

However, it subsequently was noted that infection with *H pylori* was most likely a key factor for gastric cancer in the San Marino region.<sup>10</sup> In Japan, where gastric cancer is the most prevalent malignancy by incidence and mortality,

**Abbreviations used in this paper:** DGC, diffuse gastric cancer; FAP, familial adenomatous polyposis; GAPPs, gastric adenocarcinoma and proximal polyposis of the stomach; HDGC, hereditary diffuse gastric cancer; LBC, lobular breast cancer.

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the prevalence of *H pylori* infection among those born before 1950 was 80%–90%, but has decreased to approximately 10% among those born after 1990.<sup>11</sup> Making the link between *H pylori*, chronic gastric inflammation, and gastric cancer helped untangle some confusing and misleading epidemiology.<sup>5</sup>

Even with our understanding of the role of *H pylori* in the genesis of chronic inflammation and cancer in the stomach, there is a possibility that some intrinsic genetic factors play a role in determining which *H pylori*-infected individuals will progress to cancer, because most do not. Certain polymorphisms in the *interleukin 1 $\beta$*  promoter reportedly influence the inflammatory response to *H pylori* infection in gastric mucosa and play a role in the risk for gastric cancer, but this relationship has not been reproduced robustly in all populations.<sup>12,13</sup> This underscores the complex relationship between genetic and environmental factors in disease causation. These sequence variants do not appear to be responsible for high-penetrance familial gastric cancer clusters.

## Hereditary Diffuse Gastric Cancer

For most organs, a small, single-digit percentage of the cases is caused by strong, inherited, single-gene effects. In some instances, the inherited forms of the cancer have specific pathologic features. Slightly more than half of all gastric cancers have an “intestinal” pathology, approximately a third have “diffuse” pathology, and a small number are “indeterminate.”<sup>14</sup> *H pylori* infection may be linked more closely with intestinal-type gastric cancer because it was found in nearly 90% of the noncancerous gastric mucosa in this setting compared with fewer than one third of the diffuse-type cases.<sup>15</sup> Consequently, one could speculate that these 2 pathologic variants might be associated with different causes. The first major inherited form of gastric cancer was found in cases of diffuse gastric cancer (DGC).

## Discovery of Hereditary DGC and Mutations in *CDH1*

In 1994, a family was reported at the annual American Gastroenterological Association Institute meeting in which there were 8 related members who had gastric cancer that occurred at uncharacteristically early ages (ages, 31–65 y), over 4 generations, and the pedigree suggested autosomal-dominant inheritance.<sup>16</sup> The family included a pair of identical twins, both of whom died of gastric cancer. Tissue was available from 3 family members, which showed diffuse gastric cancer characterized by multiple isolated nests of signet ring cancer cells in the gastric mucosa. At least one member of the family had a linitis plastica tumor that extended from the proximal stomach well into the small intestine. This was a report of a high-penetrance, familial gastric cancer family that included some novel features, but the genetic basis of this clinical syndrome was unknown at that time.

In 1998, a large indigenous (Maori) kindred from New Zealand was identified with multiple cases of early onset, histologically poorly differentiated, high-grade diffuse

gastric cancer. The pedigree analysis suggested autosomal-dominant inheritance. Genetic linkage analysis showed significant linkage to the *E-cadherin* (*CDH1*) gene on chromosome 16q22.1, and a damaging splice site mutation was found that led to the production of a truncated E-cadherin protein. Two more families were found with familial clusters of diffuse gastric cancer. One family had a single base-pair insertion mutation (creating a frameshift and premature stop codon downstream in *CDH1*), and the other family had a nonsense mutation in the gene. Somatic mutations in *CDH1* had been reported previously in both diffuse gastric cancers and lobular breast cancers (LBCs) that were not necessarily familial. This was a report of a hereditary diffuse gastric cancer (HDGC) and its linkage to a causative germline mutation.<sup>17</sup>

This initial report was followed up the next year in 6 more families that were dominated by DGC and LBC. Heterozygous inactivating mutations were found in *CDH1* in all of these families and confirmatory mutations were reported by additional groups. The mutations were scattered throughout the gene.<sup>18</sup>

Subsequent reports have confirmed that inactivating germline mutations in *CDH1* underlie an autosomal-dominant, highly penetrant predisposition to DGC and LBC. Moreover, the original family reported in abstract form at a national meeting<sup>16</sup> subsequently was found to have a germline *CDH1* mutation.<sup>19,20</sup> Affected patients typically are asymptomatic until the time of diagnosis, develop early gastric cancer characterized by diffuse spreading of individual signet ring cells throughout the mucosa, and these malignant cells usually are not associated with a visible mucosal abnormality under direct visualization.

## Diagnosis and Features of HDGC

The suspicion of HDGC may come from the identification of a familial cluster of gastric cancer or through the recognition of an individual with a DGC or LBC. The diagnosis can be made by finding a deleterious germline mutation in *CDH1*. A consortium of collaborating groups has developed the following clinical criteria to suggest this diagnosis and determine who should undergo germline *CDH1* testing<sup>21,22</sup>: (1) families with 2 or more individuals with gastric cancer at any age, 1 with confirmed DGC; (2) individuals with DGC before age 40; and (3) families with both DGC and LBC, with 1 diagnosis before age 50. In addition, the disease should be considered in the following patients: (1) individuals with bilateral or familial LBC before age 50, (2) individuals with gastric cancer and cleft lip or cleft palate,<sup>23</sup> and individuals with precursor lesions for signet ring carcinoma of the stomach.

Such criteria have been shown to have almost 90% sensitivity for detecting germline *CDH1* mutations within a Dutch national registry,<sup>22</sup> although some of these criteria are more predictive than others. For example, in a report by Hansford et al,<sup>24</sup> among families that met criteria 1 ( $\geq 2$  cases of gastric cancer, at least 1 DGC, 1 before age 50), 26% of 84 index cases were found to have pathogenic germline mutations in *CDH1*. However, in this study, only 2 of 38

(5%) isolated individuals with DGC before age 40 had a germline mutation in *CDH1*. This is probably a reflection of ascertainment bias because the registry was based on familial clusters of gastric cancer. When there was a personal or family history of both DGC and LBC with 1 affected individual younger than 50 years of age, 10 of 60 (17%) had deleterious mutations in *CDH1*. In this collaborative registry of 183 families, only 1 family comprised 3 confirmed cases of DGC at any age.<sup>24</sup> For individuals and families that fulfill these criteria but in whom germline analysis is unrevealing, it is unclear whether the observed cancers are caused by other genetic factors, shared environmental exposures, or perhaps even poorly understood interactions between germline and environmental risk factors.

### Mutations in *CDH1*

A Dutch registry consisting of 578 individuals who had undergone genetic testing for a suspicion of HDGC from 499 families reported 15 different pathogenic *CDH1* mutations in 18 different families.<sup>22</sup> Three of the 18 families had likely pathogenic missense mutations. Therefore, slightly less than 4% in this registry had a likely diagnosis of HDGC linked to a germline mutation in *CDH1*. In addition, 11 other silent missense mutations or mutations near a splice site were found that were considered less likely to be pathogenic. Half of the pathogenic mutations were missense, which can be challenging to interpret when found outside of the context of a familial cluster of DGC. No deleterious mutations in *CDH1* were found in any of 67 families whose members had only intestinal-type gastric cancers, or in any of 22 families with only LBC. This latter finding should be taken with caution because ascertainment for the registry was based on the presence of gastric cancer. Only 1 pathogenic germline mutation was found in *CDH1* in a family that did not meet the clinical criteria for HDGC. Broadening the criteria for inclusion in the HDGC registry to include DGC patients younger than age 40 without a family history and with only LBC is likely to identify *CDH1* mutations in these individuals and challenge the initial impressions about this disease.<sup>25</sup> The prevalence of germline *CDH1* mutations among all individuals with gastric cancer, regardless of histology, age, and family history, is not well understood, although it is presumed to be rare.

The germline mutations reported to date include nonsense mutations, missense mutations, splicing defects, insertion/deletions, and large deletions or rearrangements.<sup>24,26</sup> As mentioned, the germline mutations do not cluster in the *CDH1* gene,<sup>24</sup> unlike the cluster of somatic mutations that occurs in the extracellular domain of *CDH1* in sporadic diffuse or mixed gastric carcinomas. At present, there are no specific germline mutations that predict different clinical phenotypes.

In all of the autosomal-dominant familial cancer diseases, the patient inherits a mutation in 1 allele of the affected gene, but the allele from the unaffected parent is usually wild-type. A second hit is required in the wild-type allele for the neoplastic process to begin. In a careful study of 16 primary HDGC lesions and 12 metastatic lesions from

17 patients drawn from 15 families, somatic alterations in *CDH1* were found in 75% of all cancers. Promoter hypermethylation of *CDH1* was found in 32%, loss of heterozygosity was found in 25%, both alterations were found in 18%, and neither was present in 25%. Therefore, epigenetic inactivation of the second allele is an important factor in the pathogenesis of this disease. Interestingly, 2 different mechanisms for the second hit were found in 2 separate lesions from individual patients, and even in different portions of an individual tumor.<sup>27</sup> Somatic point mutations also are found in these tumors, and the presence of a second hit correlates well with loss of E-cadherin protein expression in the tumor.<sup>28</sup>

### Penetrance for Cancer in HDGC

When a relatively rare hereditary disease such as HDGC is first identified, the registries initially are over-represented with highly penetrant and the most severely affected families. That said, the cumulative incidence of cancer in patients with germline mutations in the *CDH1* gene initially was reported to be 67%–70% for advanced gastric cancer in men and 56%–83% for advanced gastric cancer in women (by age 80), depending on the registry consulted.<sup>24,29</sup> The disease begins with isolated clusters of signet ring cells in multiple loci throughout the gastric mucosa, but the biologic mechanisms that lead to such clusters progressing to advanced cancer remain unknown. It is possible that many or most of these clusters do not progress. Understanding factors that contribute to the progression of these lesions may be key to devising novel strategies for cancer risk reduction.

### Other Genes Possibly Related To HDGC

Only 25%–30% of families fulfilling the criteria for HDGC have germline mutations in the *CDH1* gene.<sup>25</sup> A family with HDGC was identified in which 6 affected members had a truncating germline mutation in the *CTNNA1* gene.<sup>30</sup> This protein is in the same functional network as the E-cadherin protein, making it a reasonable addition to the HDGC saga. Other catenin gene family members (*CTNNA1*, *JUP*, and *CTNND1*) were not found to have germline mutations in 22 HDGC families who did not have *CDH1* mutations.<sup>31</sup> However, many of the HDGC families who do not have germline mutations in *CDH1* have reduced expression of CDH1 protein and *CDH1* allele-specific expression imbalance in the tumor tissue, implicating *CDH1* even in those families without detectable germline mutations.<sup>32</sup> Studies in mice have suggested that sequences in intron 2 of *CDH1* may be important for gene expression, and this represents an area for future research into novel mechanisms of gene regulation and inactivation.<sup>33</sup>

Likely deleterious germline mutations have been found in the *MAP3K6* gene in multiple HDGC families that do not have mutations in *CDH1*. At least 1 large kindred and 4 other unrelated individuals harbored germline mutations in this setting, and convincing second hits were found in the tumor tissue.<sup>34</sup>

Another study using total exome sequencing in families with HDGC and no germline mutation in *CDH1* showed 3 new candidate genetic causes of the disease. One candidate was a missense mutation (p.E1313K) in the *INSR* gene, the second a missense mutation (p.R81P) in the *FBX024* gene, and the third a missense mutation (p.P1146L) in the *DOT1L* gene.<sup>35</sup> These sequence variants were not found in databases of controls, and were not found in 26 other suspected cases of HDGC. The actual role of these sequence variants in the causation of HDGC remains to be confirmed.

### Management of HDGC

The risk of gastric cancer before age 20 in HDGC is less than 1%, suggesting that genetic diagnosis and treatment can wait until at least that age.<sup>29</sup> Because the penetrance is very high for DGC and LBC in HDGC, for individuals with confirmed deleterious germline mutations in *CDH1*, prophylactic complete gastrectomy should be offered, despite the obvious morbidity of this procedure.<sup>21</sup> Careful pathologic examination of the entire stomach should be undertaken by a pathologist with expertise in this disease. Surveillance endoscopy can be attempted, but the sensitivity of this approach is uncertain and thought to be poor for the detection of early disease. Chromoendoscopy using Congo Red or methylene blue dyes has been recommended to help identify subtle alterations in the mucosa,<sup>29</sup> but the sensitivity of this approach is unknown. Careful inspection at conventional endoscopy with targeted and random biopsies can identify at least some early signet ring cancers, helping to determine the optimal timing of surgery.<sup>36</sup> The technical requirements of optimal surgery for HDGC suggest the use of centers and surgeons with expertise in this disease.<sup>25</sup>

Breast cancer surveillance with annual magnetic resonance imaging should be offered beginning at age 35 or 30.<sup>25,37</sup> It is not known whether annual imaging of the breasts is sufficient to prevent cancer deaths, or whether prophylactic surgery is more reliable in this regard.

### Familial Intestinal Gastric Cancer

Familial intestinal gastric cancer, in which there are 2 or more cases of intestinal-type gastric cancer in first- or second-degree relatives with at least 1 younger than age 50, or in families with 3 or more cases of intestinal-type gastric cancer reported, but in which there are no germline mutations known to cause this (with the exception of the gastric adenocarcinoma and proximal polyposis of the stomach [GAPPS] syndrome, described later).<sup>26</sup>

### Familial Adenomatous Polyposis and Gastric Adenocarcinoma

Familial adenomatous polyposis (FAP) is the autosomal-dominant inherited predisposition to adenomatous polyps caused by germline mutations in the *APC* gene. In the classic-type of FAP, probands develop hundreds to thousands of adenomatous polyps in the colon and rectum, typically beginning in the second or third decades of life, and mutation carriers classically have a near-100% lifetime

risk of colorectal cancer unless they undergo prophylactic colectomy. Extracolonic manifestations of FAP can include gastric polyps and cancers, duodenal and peri-ampullary adenomas and adenocarcinomas, thyroid cancer, desmoid tumors, hepatoblastomas, medulloblastomas, osteomas, congenital hypertrophy of the retinal pigment epithelium, and supernumerary teeth. The prevalence of germline *APC* mutations among unselected gastric cancer patients is unknown, although presumed to be very rare.

The first known association between gastric cancer and FAP came in 1962<sup>38</sup> with a case report of a Mexican boy who underwent a total colectomy at age 15 in the setting of approximately 100 polyps in his sigmoid colon and rectum, followed by a diagnosis of metastatic gastric carcinoma within the following year. There was a family history of colorectal polyposis in 2 cousins as well as a grandfather who died of gastric cancer, although additional details on this family's history were not presented, and thus it was not confirmed genetically that this family had autosomal-dominant FAP vs another form of hereditary polyposis.

It is well recognized that FAP patients frequently develop fundic gland polyps of the stomach and, less commonly, gastric adenomas. Initial case series from Japan published in the 1970s described that two thirds of patients with FAP had some type of gastric abnormality, including fundic gland polyps and adenomas. However, gastric carcinomas occurred in only a small number of patients (the youngest of whom was diagnosed at age 17).<sup>39,40</sup> It initially was speculated that gastric neoplasia in FAP might be limited to Japanese individuals, given the high incidence of chronic gastric inflammation, adenomatous polyps, and gastric cancer in the Japanese population generally.<sup>40</sup>

In 1983, however, a registry series of 34 Finnish individuals with FAP described gastric fundic gland polyps in 53% of individuals and gastric adenomas (all occurring within the antrum) in 12% of individuals; none had gastric cancer.<sup>41</sup> Likewise, a study of 100 patients from the Cleveland Clinic's Familial Polyposis Registry was published in 1987 describing the findings from prospective surveillance with upper endoscopy, and found that 26% of individuals had gastric fundic gland polyps, 2% had gastric adenomas, but none had gastric cancer.<sup>42</sup>

From more recent data, the lifetime risk of gastric cancer in FAP patients has been estimated to be less than 1% in Western populations, although the risk is significantly higher in Japanese and Korean probands.<sup>43-46</sup> Although it is speculated that both gastric adenomas and fundic gland polyps can be precursor lesions to FAP-associated gastric carcinomas, the vast majority of fundic gland polyps have essentially no malignant potential, even those in which low-grade dysplasia is identified.<sup>47,48</sup> Likewise, endoscopic polypectomy and surveillance is sufficient management for most FAP-associated gastric adenomas.<sup>49</sup> For the rare FAP patients with fundic gland polyps containing high-grade dysplasia, referral to a specialty center is warranted because the role of gastrectomy in such situations is debatable and is associated with unique challenges in FAP patients, many of whom previously may have undergone total colectomy and be at risk for intra-abdominal desmoid disease.

## GAPPS

Emerging data have shown that the gastric cancer predisposition syndrome known as GAPPS is actually a phenotypic variant of FAP.<sup>50</sup> GAPPS initially was described in a 2012 series of 3 families showing an autosomal-dominant pattern of gastric fundic gland polyposis, often with dysplasia, sparing the antrum and occasionally including adenomatous or hyperplastic polyps.<sup>51</sup> Several probands from this original case series developed gastric adenocarcinoma, the youngest of whom was diagnosed at age 33 years, and none of the patients in this report had phenotypes of colorectal polyposis.<sup>51</sup> A recent analysis of 6 GAPPS families identified germline point mutations in the *APC* 1B promoter region, which segregated with the fundic gland polyposis phenotype in these families.<sup>50</sup> Some members of this family had a fundic gland polyposis phenotype, while others did not. This study<sup>50</sup> demonstrated that those individuals within the family with this phenotype had the germline mutations, whereas those who lacked the phenotype did not have the mutation. In the field of hereditary syndromes, this is commonly referred to as a mutation segregating with a particular phenotype. Interestingly, large deletions of this same *APC* 1B promoter region previously have been observed in families with more classic FAP phenotypes, but who also developed gastric fundic gland polyps and gastric cancers, showing that this region of the *APC* promoter is of particular importance in gastric neoplasia.<sup>50</sup> The lifetime risk of gastric cancer in patients with the GAPPS syndrome remains undefined.

## Lynch syndrome

Lynch syndrome is the most common inherited gastrointestinal cancer syndrome, and is caused by germline mutations in the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) or *EPCAM* (germline deletions that induce constitutional methylation of the *MSH2* promoter, leading to epigenetic silencing of *MSH2*). Colorectal, endometrial, and ovarian cancers are the most common malignancies to develop in individuals with Lynch syndrome, although probands are at increased lifetime risk for a wide array of malignancies, including gastric cancer, urothelial cancer, small-bowel cancer, pancreatic cancer, hepatobiliary cancers, and others.<sup>46</sup>

Aldred S. Warthin, a pathologist from the University of Michigan, is credited with publishing one of the earliest descriptions of a family with what is now known as Lynch syndrome in 1913.<sup>52–54</sup> Of the 9 siblings described in this initial family (known as Family G), 2 died of advanced gastric cancer in their 60s, and more recent analyses of this family now spanning 929 individuals over 7 generations showed gastric cancer to be the third most common malignancy in this family.<sup>53</sup> Interestingly, gastric cancer within this family has become much less common in more recent generations, mirroring the overall decrease in sporadic gastric cancer in the United States and suggesting that environmental effects may influence the risk of gastric cancer within Lynch syndrome families.<sup>53,54</sup> Current estimates of the lifetime risk of gastric cancer in individuals with Lynch syndrome range from less than 1% to 13%, with data suggesting that the

gastric cancer risks may be higher in males, those with *MLH1* or *MSH2* mutations, and those of Asian ancestry.<sup>46,55,56</sup> In contrast with FAP, there does not seem to be an increased incidence of gastric polyps in Lynch syndrome mutation carriers and, in contrast with HDGC, Lynch syndrome-associated gastric cancers tend to show intestinal-type histology. There are no proven strategies to reduce the risk of gastric cancer in Lynch syndrome probands, although published guidelines are mixed regarding the use of screening upper endoscopy, sometimes recommending this,<sup>46</sup> some recommending a 1-time upper-endoscopic visualization, and testing for infection with *H pylori*,<sup>57</sup> or, in some instances, not recommending any intervention.<sup>58,59</sup> Similar to FAP, it is unknown what fraction of unselected gastric cancers arise as a result of Lynch syndrome, but this is assumed to account for an overall very small percentage of the overall burden of gastric cancer in the United States and worldwide.

## Li-Fraumeni Syndrome

Li-Fraumeni syndrome originally was described in 1969 as an autosomal-dominant cancer predisposition syndrome linked to risks of soft-tissue sarcomas, breast cancers, lung cancers, and other malignancies, often occurring in children and young adults.<sup>60</sup> Li-Fraumeni syndrome is caused by germline mutations in the *TP53* tumor-suppressor gene, and data since have shown risks for a wide array of cancers, including leukemias, choroid plexus carcinomas and other brain tumors, adrenocortical carcinomas, colorectal cancer, and gastric cancer, among others.<sup>61</sup> A large case series<sup>62</sup> of 429 individuals from 62 families with germline *TP53* mutations evaluated through the Dana-Farber/National Cancer Institute Li-Fraumeni syndrome registry reported that 5% of probands carried a diagnosis of gastric cancer, with the median age at diagnosis of 36 years. Overall, 23% of Li-Fraumeni families in this study had at least 1 diagnosis of gastric cancer. Gastric cancers with both diffuse-type and intestinal-type histology were described in this case series.<sup>62</sup> Similar to FAP and Lynch syndrome, Li-Fraumeni syndrome patients of Asian ancestry may have particularly increased risks of gastric cancer.<sup>63</sup> There are currently no consensus guidelines for gastric cancer screening in individuals with germline *TP53* mutations and the prevalence of such mutations among unselected gastric cancer patients is unknown, although presumably quite rare.

## Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is a rare, autosomal-dominant cancer predisposition syndrome caused by germline mutations in *STK11* (or *LKB1*). Patients with Peutz-Jeghers syndrome are at markedly increased lifetime risks for cancers of the breast, colorectum, pancreas, lung, small intestine, ovaries, testes, as well as the stomach. Classic nonmalignant phenotypic features of Peutz-Jeghers syndrome include childhood freckling of the lips, fingers, and oral mucosa, as well as hamartomatous polyps of the gastrointestinal tract, particularly the small bowel.<sup>64</sup> Such hamartomatous polyps have long been recognized to occur in the stomach in

**Table 1.** Hereditary Cancer Syndromes With Increased Risks of Gastric Cancer

Syndrome	Associated gene(s)	Lifetime gastric cancer risk	Other associated cancers	Nonmalignant phenotypic features
HDGC	<i>CDH1</i> ; possibly <i>CTNNA1</i> , <i>MAP3K6</i> , and others	67%–70% (males), 56%–83% (females)	Lobular breast carcinoma	Cleft lip/palate in some families
FAP	<i>APC</i>	<1% <sup>a</sup>	Colorectal duodenal/ampullary, thyroid, desmoid tumors, hepatoblastoma, medulloblastoma	Colorectal (and duodenal and gastric) adenomas, gastric fundic gland polyps, osteomas, CHRPE, supernumerary teeth
GAPPS	<i>APC</i> (promoter 1B region)	Undefined, but likely higher than FAP	None known	Fundic gland polyps of the proximal stomach
Lynch syndrome	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>EPCAM</i>	<1% to 13% <sup>a</sup>	Colorectal, endometrial, ovarian, urothelial, pancreatic, small-bowel, and hepatobiliary	Cutaneous sebaceous adenomas and keratoacanthomas
Li–Fraumeni syndrome	<i>TP53</i>	~5% <sup>a</sup>	Breast, sarcomas, lung, adrenocortical, brain (choroid plexus), leukemias, colorectal, many others	None
Peutz–Jeghers syndrome	<i>STK11</i>	~29%	Breast, pancreatic, lung, colorectal, small intestine, ovaries, testes	Hyperpigmentation of oral/genital mucosa, lips, fingers; hamartomatous polyps of GI tract, especially small bowel
Juvenile polyposis syndrome	<i>BMPR1A</i> , <i>SMAD4</i>	~21%	Colorectal and duodenal cancers	Juvenile polyps of the GI tract

CHRPE, congenital hypertrophy of the retinal pigment epithelium; GI, gastrointestinal.

<sup>a</sup>Risks may be higher in Asian patients.

Peutz–Jeghers syndrome patients as well, and initial descriptions of gastric cancer occurring in Peutz–Jeghers syndrome, including 1 patient diagnosed at age 13 years, were published in case reports in the 1960s.<sup>65</sup> In 2000, a meta-analysis including data on 210 Peutz–Jeghers patients calculated a relative risk of gastric cancer of 213 with a median age at diagnosis of 30 years and a 29% cumulative risk of gastric cancer up to age 64 years.<sup>66</sup> Consensus guidelines recommend that Peutz–Jeghers patients undergo initial upper endoscopy at age 8 years to screen for upper gastrointestinal tract cancers and polyps.<sup>46,67</sup> Given the rarity of Peutz–Jeghers syndrome, it is assumed that this accounts for a minute fraction of all gastric cancer cases.

## Juvenile Polyposis

Juvenile polyposis syndrome is another rare, autosomal-dominant syndrome characterized by unique hamartomatous polyps (juvenile polyps) of the gastrointestinal tract. Most patients and families with juvenile polyposis harbor germline mutations in the *BMPRIA* or *SMAD4* genes, and mutation carriers are at increased lifetime risk for developing cancer of the colorectum, stomach, and duodenum.<sup>46,64,68,69</sup> Juvenile polyposis initially was described in 1964 by investigators from St. Mark's Hospital as an entity clinically distinct from FAP.<sup>70–72</sup> In these initial descriptions, it was noted that, similar to FAP, families with juvenile polyposis had a preponderance of intestinal cancers, and attention was drawn to the striking gross and microscopic differences between juvenile polyps vs the adenomatous polyps seen in FAP.<sup>70</sup>

The first report linking gastric cancer to juvenile polyposis came from the University of Iowa in 1975 when a family was published in which a clear autosomal-dominant pattern of gastrointestinal cancer and gastrointestinal juvenile polyposis was seen.<sup>73</sup> Across 3 generations, 21 individuals within this family had juvenile polyps and/or invasive cancer of the gastrointestinal tract, including 4 with juvenile polyps of the stomach and 2 with invasive gastric cancer.<sup>73</sup> Data on this same family were updated in 1998, including 117 individuals across 6 generations.<sup>74</sup> Of the 29 family members with histories of juvenile polyposis, 16 (55%) developed gastrointestinal cancer, including 4 (14%) with gastric cancer. Although data remain limited because of the rarity of this syndrome and likely ascertainment biases, the lifetime risk of gastric cancer in individuals with juvenile polyposis currently is estimated to be 21%, and guidelines recommend initiation of endoscopic screening of the upper gastrointestinal tract at age 12–15 years.<sup>46,64,72,75</sup> As with the other syndromes discussed, juvenile polyposis is presumed to account for a very small fraction of all gastric cancer cases, although the precise prevalence has not been defined.

## Summary

Gastric cancer is quite common, and usually is not related to highly penetrant inherited genetic factors. Hereditary diffuse gastric cancer is the one highly penetrant, single-gene disease in which the major manifestation

is a very high risk for DGC. The penetrance for gastric cancer in this instance is 67%–83% (depending on sex) by age 80. GAPPs is a variant of FAP caused by specific mutations in the promoter 1B of *APC* that causes a high risk for proximal gastric adenomas and gastric adenocarcinoma. Increased risks for gastric cancer also are found in Lynch syndrome, Li–Fraumeni syndrome, Peutz–Jeghers syndrome, and Juvenile polyposis syndrome. The incidence of gastric cancer in Lynch syndrome families may be decreasing (in parallel with decreasing incidences in the United States and elsewhere), and the risk of gastric cancer within each of these rare syndromes appears to be particularly pronounced in Asian countries, all of which suggest an interplay between genetic risk and environmental factors, such as *H pylori*. Each syndrome has its own unique management recommendations, but there are no prospective trials to assist in the assessment of these strategies.

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