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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.[1,2] 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.[3] 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.[4] 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 Warren.[5] All of this suggests that most, probably more than 90% of, gastric cancer is determined by environmental rather than genetic causes.

Jackson et al[6] 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.[7] 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.[8] 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.[9]

However, it subsequently was noted that infection with *H pylori* was most likely a key factor for gastric cancer in the San Marino region.[10] 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.[11] Making the link between *H pylori*, chronic gastric inflammation, and gastric cancer helped untangle some confusing and misleading epidemiology.[5]

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 1β* 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.[12,13] 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."[14] *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.[15] 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 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.[16] 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 plastic 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.[17]

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.[18]

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[16] subsequently was found to have a germline *CDH1* mutation.[19,20] 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[21,22]: (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,[23] 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,[22] although some of these criteria are more predictive than others. For example, in a report by Hansford et al,[24] 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