Hereditary Gastric Cancer Syndromes

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KEYWORDS

- Hereditary gastric cancer syndromes • Diagnosis • Management
- Genetic counseling • Gastrectomy • Hereditary diffuse gastric cancer
- Familial intestinal gastric cancer
- Gastric adenocarcinoma and proximal polyposis of the stomach

KEY POINTS

- Hereditary gastric cancer syndromes are responsible for a small but distinct group of gastric cancers, which can be associated with a high penetrance of early-onset and aggressive gastric cancer.
- Endoscopy is used for disease surveillance, but clinicians must be wary that early cancers can be missed.
- For some individuals with hereditary gastric cancer syndromes, prophylactic total gastrectomy offers the only option for preventing the development of gastric cancer.
- Mutations of CDH1 is currently the only genetic marker of prognostic value, but is present in only a minority of families with hereditary diffuse gastric cancer.
- Significant opportunities for optimizing the management of individuals affected by hereditary gastric cancer syndromes exist, emphasizing the importance of continuing to manage affected families under research settings.

INTRODUCTION

Gastric cancer is one of the leading causes of global cancer mortality, causing more than 700,000 deaths per annum worldwide.[1–3] In most cases, environmental factors, including *Helicobacter pylori* infection,[4] smoking,[5,6] and diet,[7] account for much of the etiology of the disease. This article is dedicated to the small but distinct group of gastric cancers (1%–3%) that result from hereditary gastric cancer syndromes.[8]

There are 3 recognized syndromes that confer heritable predisposition to cancers primarily of the stomach. These syndromes are segregated according to their

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histologic types or their macroscopic morphology and are (1) hereditary diffuse gastric cancer (HDGC), (2) familial intestinal gastric cancer (FIGC), and (3) gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). Of these syndromes, the genetic cause is known only in individuals with HDGC, and even then in a minority of this subgroup.[8]

Particularly in individuals affected by HDGC with pathologic mutations of cadherin-1 (CDH1), the seriousness of the condition is underlined by a high penetrance of early-onset and aggressive disease that is not always possible to detect by endoscopic surveillance; most individuals are therefore advised to undergo prophylactic total gastrectomy as a means of eliminating the risk of developing advanced-stage and incurable gastric cancer.[9,10] We discuss the nature of each of the hereditary gastric cancer syndromes and their management. These and other inherited syndromes associated with gastric cancers are summarized in **Table 1**.

IDENTIFICATION OF THOSE AT RISK

A thorough family history and the documentation of gastric and other relevant cancers occurring frequently and/or at young ages in a family is central to the identification of hereditary gastric cancer syndromes. The diagnosis of hereditary gastric cancer syndrome is based on the family history and information concerning the histologic subtype of gastric cancers that have occurred in the family. The positive diagnosis of hereditary gastric cancer syndrome in turn can allow other family members to be screened with the aim of identifying disease before progression to advanced and incurable stages. Given the potential for very early age of onset of hereditary gastric cancer, the importance of securing accurate cancer family history information as early as the pediatric age group is noted.

HEREDITARY DIFFUSE GASTRIC CANCER

Clinical Features

HDGC is an autosomal dominant syndrome, characterized by the development of highly aggressive diffuse type gastric cancer.[22–24] Fifteen percent to 50% of the families affected by HDGC have been identified to harbor germline mutations in the E-cadherin gene, CDH1.[11,12] In individual members of HDGC families who are carriers of pathogenic CDH1 mutations, the largest study to date has estimated the risk of developing gastric cancer to be 70% in men and 56% in women by the age of 80.[13] Individuals without previous knowledge of being at risk often present with advanced cancers that are associated with dismal prognosis.[22] The median age of invasive gastric cancer diagnosis for mutation carriers is 38, which is approximately 3 decades earlier than sporadic cases of gastric cancer[25]; however, diagnosis has been reported to occur over a wide range of ages from 14 to 82 years.[26,27]

Clinicians should be aware that women affected by HDGC associated with mutant CDH1 are also at significantly increased risk of developing lobular breast carcinoma,[28–32] with cases arising mostly after 40 years of age, and the lifetime cumulative risk being approximately 40% by the age of 80 years.[13,27] In some families affected by HDGC, there may also be an increased risk of developing colon cancers.[10]

Genetics

The earliest report of germline mutations of CDH1 in HDGC was made by Guilford and colleagues[22] in 1998 in Maori families in New Zealand. CDH1 is located on chromosome 16q22.1 and encodes E-cadherin, a cell adhesion protein that plays an important role in the maintenance of cellular polarity and epithelial tissue