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# Preemptive Total Gastrectomy for Hereditary Gastric Cancer

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**Abstract** Hereditary gastric cancer is a recently described clinical syndrome, associated with truncating mutation of the E-cadherin gene, named *CDH1*. It is characterized by autosomal dominant transmission, presentation at an early age, and with diffuse type of gastric adenocarcinoma. Clinical management of these patients is challenging and includes intense endoscopic surveillance or prophylactic gastrectomy, which is associated with short- and long-term morbidity. We report four patients submitted to a prophylactic gastrectomy performed in members of three families with hereditary gastric cancer in a tertiary referral center in Mexico City. These are the first Hispanic families with hereditary gastric cancer reported in the literature.

**Keywords** Hereditary gastric cancer · E-cadherin mutation · Prophylactic gastrectomy

Genetically defined inherited forms of cancer are relatively uncommon, representing 5 to 10% of many types of adult-onset malignancies, although familial clustering of cancer often constitutes another 20% or more of cases. One of the most recently defined inherited cancer syndromes is that predisposing to gastric cancer and, in particular, the pathologically diffuse type of gastric cancer.[1] An increased incidence of familial gastric cancers has been recognized as a component of several inherited cancer syndromes[2,3] like Lynch type II, Li–Fraumeni, familial adenomatous polyposis, and Peutz–Jeghers syndromes, which exhibit elevated rates of gastric cancer compared with the general population. However, several families have been identified that are specifically predisposed to diffuse gastric cancers (DGCs), together with lobular breast cancer, and that share inherited germline mutations in the *CDH1* gene encoding for the E-cadherin protein. Clinical criteria defining hereditary diffuse gastric cancer (HDGC) families include two or more pathologically documented cases of DGC in first- or second-degree relatives, with at least one diagnosed before the age of 50 years, or three or more DGC cases in first- or second-degree relatives diagnosed at any age.[4]

The incidence of HDGC is relatively low compared with the most common inherited cancer syndromes, accounting for 1 to 3% of gastric adenocarcinomas. Gastric cancer presenting in younger patients with familial clustering has been reported in Mexico,[5] but there are no reports of families with HDGC. Management of patients with HDGC is controversial, ranging from endoscopic surveillance[6] to total gastrectomy, with very few cases of the latter approach reported in the literature.[7,8] We reported four cases of prophylactic total gastrectomy performed in patients from three different families with clinical criteria for HDGC in a tertiary referral center in Mexico City.

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## Case Reports

### Family A

The proband in family 1 (subject III-4; Fig. 1, family a) was a 27-year-old man with strong family history of gastric cancer. The pedigree is shown in Fig. 1, family a. The family was referred to our institution for endoscopic surveillance. Upper endoscopy with chromoendoscopic technique discovered a small lesion in the gastric body in the proband. Biopsy showed diffuse type of gastric cancer. The patient underwent total gastrectomy in February 2003. Pathology report showed multiple foci of signet ring cell adenocarcinoma limited to the mucosal layer in the entire stomach. In March 2003, all of the proband's relatives underwent upper endoscopy with chromoendoscopic technique and magnification with no evidence of disease. One of the proband's brothers, who was 24 years old (subject III-6; Fig. 1, family a), complained of abdominal bloating and discomfort 4 months after a normal upper endoscopy. He was admitted to the hospital 1 month later with massive ascites. Upper endoscopy with chromoendoscopic and magnification techniques was performed with no evidence of abnormality in the stomach. The patient underwent laparoscopy with evidence of diffuse carcinomatosis. Biopsy of peritoneal lesions showed signet ring cell adenocarcinoma. Upper endoscopy was repeated and 27 random biopsies of gastric mucosa were performed; one of them was positive for gastric adenocarcinoma. The patient underwent palliative chemotherapy but died 2 months later because of chemotherapy-related complications.

A DNA sample was obtained from the proband and sent to the Otago University in New Zealand looking for *CDH 1* mutation. No germline mutation inactivating *CDH1* could be detected in this patient. However, a homozygous change in the promoter region (−160C>A) of the gene was reported.

After extensive genetic counseling, two of the proband's brothers underwent elective prophylactic total gastrectomy (subjects III-5 and III-9; Fig. 1, family a). The first surgery was performed in September 2003 on a 25-year-old man (subject III-5; Fig. 1, family a). Extensive pathology sampling was performed with evidence of two microscopic foci of high-grade dysplasia. The patient was asymptomatic during the last clinical consultation, 2-years after surgery. The second prophylactic gastrectomy was performed on a 19-year-old man in June 2004 (subject III-9; Fig. 1, family a). Pathology report showed nodular gastritis in the antrum with no evidence of dysplasia. The patient was in good health during his last follow-up visit, 18 months after prophylactic surgery. Other siblings of the proband (subjects III-1 and III-2; Fig. 1, family a) chose continued endoscopic surveillance.

### Family B

The proband in family 2 (subject III-4; Fig. 1, family b) was a 19-year-old man who was diagnosed with DGC at our institution in 1985. He had stage IV disease at presentation and he underwent palliative chemotherapy. He died of DGC

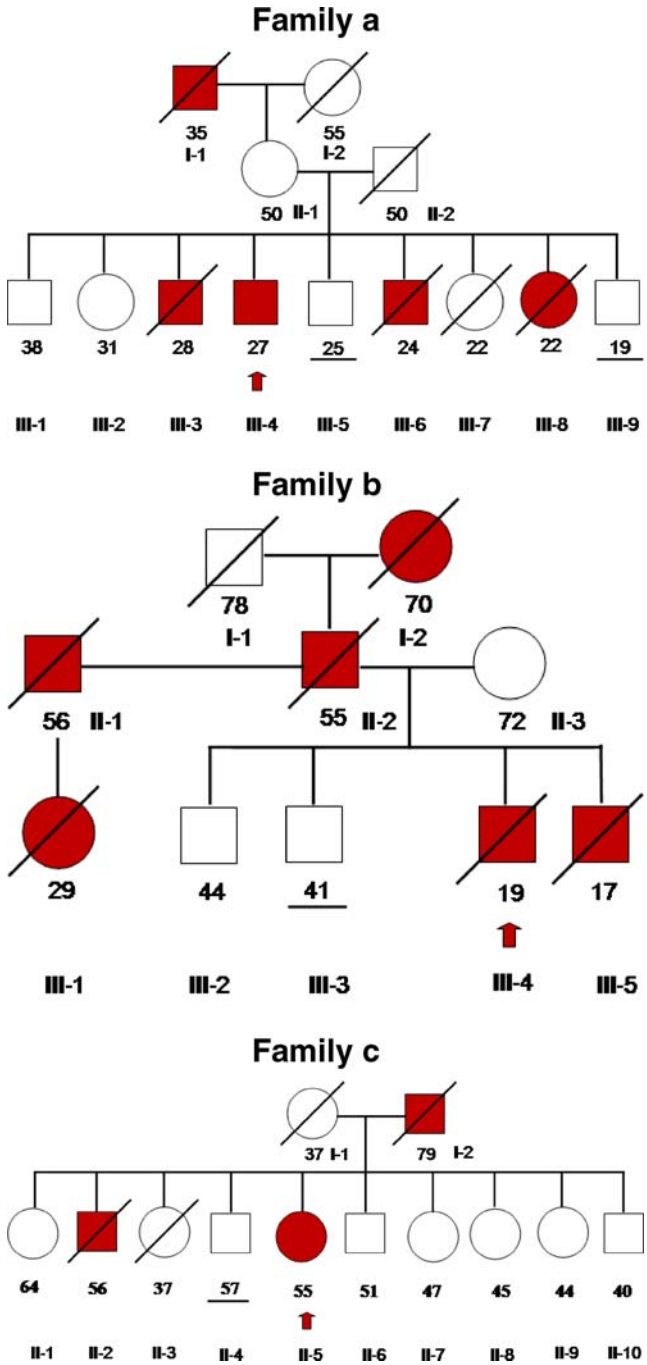


**Figure 1** Pedigrees of families **a**, **b**, and **c**. The squares represent male family members and the circles female family members. Open symbols indicate unaffected persons and solid symbols affected persons. A slash over the symbol denotes death, and a line under the symbol prophylactic gastrectomy. Arrow indicates the index case. The age at diagnosis is indicated under each symbol.

6 months after diagnosis. At the time of admission the patient had a family history of DGC. Pedigree is depicted in Fig. 1, family b. The two remaining brothers of the proband have been followed up at our institution since 1986, with endoscopies with gastric biopsies performed every 6–12 months. Since the year 2001 chromoendoscopic exams have been carried out in these patients. In August 2004, subject III-3 (Fig. 1, family b) underwent routine follow-up examination and a small superficial erosion in the greater curvature of the stomach was found. Biopsy showed two isolated signet ring cells not definitive for carcinoma. DNA analysis did not show inactivating mutation of the *CDH1* gene or any other genetic abnormality. After extensive discussion and genetic counseling, the patient was admitted for surgery. He underwent total gastrectomy with Roux-en-Y reconstruction on September 2004. Pathologic examination showed foci of low-grade dysplasia without evidence of carcinoma. During last follow-up in November 2005, the patient was free of malignant disease. The patient's brother (subject III-1) continued with endoscopic surveillance.

Family C

An orthopedic surgeon (subject II-4; Fig. 1, family c) was referred to our institution because of considerable family history of DGC, which is depicted in Fig. 1, family c. The patient began a chromoendoscopic surveillance program in the year 2000. Pathologic diagnosis from biopsies obtained every 6 months showed intestinal metaplasia with low-grade dysplasia. In December 2001 moderate dysplasia was found, but a new endoscopy in March 2002 demonstrated low-grade dysplasia again. The patient continued under surveillance until October 2005, when gastric biopsies showed intermediate-grade dysplasia. DNA was obtained from the proband (subject II-5; Fig. 1, family c) and no genetic abnormality was found. After extensive discussion, the patient elected prophylactic surgery, and in November 2005 he underwent total gastrectomy. Pathologic analysis showed three foci of high-grade dysplasia in the gastric antrum. No invasive neoplasia was identified.

## Discussion

Gastric cancer ranks second in terms of global cancer burden worldwide.[9] In Mexico, it is the second most frequent gastrointestinal cancer after colon carcinoma according to the most recent reports. Approximately 10% of cases of gastric cancer, both of the diffuse and intestinal types, show familial clustering.[10] The first clear evidence for a gastric cancer susceptibility genetic locus was the identification, in 1998, of a germline inactivating (truncating) mutation in the gene encoding for E-cadherin, called *CDH1*, in a large Maori family from New Zealand with kindred early-onset DGC.[1] From the original description, several families of diverse ethnic backgrounds have been reported with germline inactivating mutations of E-cadherin.[11–13] To our knowledge there are no previous reports of Hispanic families with HDGC. Pathologically, all the gastric cancers with *CDH1* mutations have shown invasive, poorly differentiated, DGC and display signet ring cells. The estimated cumulative risk for gastric cancer by the age of 80 years in HDGC families is 67% for men and 83% for women.[14] The age of onset shows marked variation between and within families, as what occurred in the families we reported. In addition to gastric cancer, several other cancers seem to occur at somewhat elevated incidence in HDGC families. Most notably, lobular breast cancer has been observed to occur in approximately 20 to 40% of women from families who carry *CDH1* mutations.[14] In our families, only cervical cancer was present in one of the members of family 3 (subject II-3), but this cancer is endemic in our country and has not been associated with HDGC.

The International Gastric Cancer Linkage Consortium has developed the clinical criteria defining HDGC families.[4] The suggested clinical criteria are two or more documented cases of DGC in first- or second-degree relatives, with at least one diagnosed before the age of 50 years (families a and b), or three or more cases of documented DGC in first- or second-degree relatives, independent of the age of onset (family c). The same consortium has established that carriers of the germline mutation in *CDH1* have a high lifetime risk of developing gastric cancer, but penetrance is less than 100%. The cumulative risk for developing gastric cancer increased steadily for each generation in men and women, and for individuals younger than 40 years of age, the relative risk of gastric cancer was several thousand times that of the general population. This phenomenon is well represented in the reported families: In all of them, DGC presented in more individuals and at a younger age in each generation.

Based on the clinical criteria for defining HDGC, approximately 25 to 50% of families meeting one of these criterions have identifiable germline mutations in the *CDH1* gene. The other families may have unidentified mutations in regulatory elements or mutations in unidentified genes that also contribute to HDGC. In family A, no germline mutation inactivating *CDH1* could be detected in the proband; however, there was a homozygous change in the promoter region of this gene (−160C>A). The latter variation may have some influence on DGC risk as it has been shown to reduce *CDH1* transcriptional activity in vitro. Actually, this single nucleotide polymorphism (SNP) has been associated with DGC in Italian,[15] but not in Korean populations.[16] At present, our group is conducting a case control study analyzing this SNP in a Mexican

population. Because this SNP cannot be used as genetic testing in the remaining family members, we must rely on clinical criteria for definition and management of these families. Two other reported families fulfill the criteria for HDGC; however, no genetic abnormality could be detected and the surgical decision was based on endoscopic findings.

Because not all patients with clinical criteria of HDGC have the mutation and between individuals with *CDH1* gene inactivating mutation the penetrance is at most 83% in female patients at the age of 80, clinical management in these patients is very challenging. Diagnosing gastric cancer in its early stages provides the best chance for curative resection but is a difficult task. Symptoms attributable to gastric cancer do not appear until the disease is more advanced and are generally nonspecific. When the diagnosis of gastric carcinoma is established, it is most often locally advanced, and in our country, up to 60% of patients present with stage IV disease.[17] Endoscopy is generally considered to be the best method for gastric cancer screening, but diagnosing diffuse gastric carcinoma is most difficult because these lesions tend not to form a grossly visible exophytic mass but rather spread submucosally as single cells or clustered islands of cells. Emerging new technologies for the diagnosis of early DGC lesions include the use of colored or florescence stains to aid in endoscopic detection.[6] However, as demonstrated in family a, even this approach with the aid of magnification could be misleading. On the other hand, two pathology reports from prophylactic gastrectomies have found foci of carcinoma in surgical specimens.[7,8]

At present, at the very least, regular endoscopic examination with random biopsies 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 25 years of age. Because mucosal abnormalities tend to occur late in DGC and delay the endoscopic diagnosis, prophylactic gastrectomy should be seriously considered as a means to prevent gastric carcinoma, although it clearly comes with morbidity. The decision to perform prophylactic gastrectomy should be balanced with age-based risk, based on age-specific penetrance data and many other personal factors. Therefore, it is essential that patients carrying the gene, but also patients that fulfill clinical criteria for HDGC, have the opportunity for extensive counseling, discussion, and reflection with knowledgeable clinicians, geneticists, and counselors before making the decision to proceed.

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