



Our **vision** is a world without stomach cancer.
Our **mission** is to support research and unite the caring power of people worldwide affected by stomach cancer.

Stomach (gastric) cancer is the fourth most common cause of cancer worldwide, and the second leading cause of cancer deaths worldwide. The American Cancer Society has estimated that 21,000 new cases of gastric cancer will be diagnosed in the United States in 2010, and that more than 10,000 Americans would die of gastric cancer during the year.¹ Because gastric cancer is difficult to diagnose, it is often diagnosed at a late stage with a poor prognosis. The treatment for gastric cancer is surgery and chemotherapy.² The overall 5-year survival rate is 24.3%.¹

An estimated 1-3% of cases of gastric cancer are caused by Hereditary Diffuse Gastric Cancer.² Hereditary diffuse gastric cancer (HDGC) is an inherited cancer syndrome that leads to an increased risk for both diffuse gastric cancer and lobular breast cancer. Patients who inherit the genetic mutation for HDGC are at high risk for developing gastric cancer at a young age.³

History of HDGC

In 1964, gastric cancer was noted in a Maori tribal family in New Zealand, following an autosomal dominant pattern of inheritance.⁴ CDH1 gene mutations were first described in patients from three Maori families in 1998. At this time, the International Gastric Cancer Linkage Consortium (IGCLC) was formed, and the name "Hereditary Diffuse Gastric Cancer" was introduced. Families with multiple cases of diffuse gastric cancer, lobular breast cancer, or both may be affected by the hereditary diffuse gastric cancer syndrome.

Genetics

The CDH1 gene, located on chromosome 16, normally encodes for a protein called E-cadherin. The normal function of E-cadherin is to allow cells and tissues to adhere to one another.⁴

When there is a mutation in the CDH1 gene, the function of the E-cadherin protein is disrupted, and cancer often results.^{3,4} The exact mechanism by which this mutation ultimately causes gastric cancer is not entirely known.⁴

Inheritance of the CDH1 gene mutation follows an autosomal dominant pattern, meaning that offspring of mutation carriers have a 50% chance of inheriting the mutant gene.^{3,4} It is estimated that three out of every four CDH1 gene mutation carriers will go on to develop gastric cancer,³ with an average age at diagnosis of 38.^{5,6}

It is important to note that not all HDGC families have a mutation in the CDH1 gene. Other genes that may lead to HDGC are not known at this time.

Diffuse Gastric Cancer

HDGC leads to a cancer called diffuse-type, signet ring cell gastric adenocarcinoma.^{4,5} These signet ring cells appear as isolated cells or in small clusters in the lining of the stomach. Unfortunately, the diffuse type of gastric cancer associated with HDGC is difficult to diagnose because the cancer is not visible on upper endoscopy (looking into the stomach with a small camera). For this reason, most cases of diffuse gastric cancer are diagnosed at late stages (III or IV), when the cancer is incurable.⁵

Management of HDGC Family Members

Hereditary Diffuse Gastric Cancer is diagnosed in families with either two or more cases of diffuse gastric cancer in first- or second-degree relatives, with at least one case diagnosed before the age of 50, or three or more cases of diffuse gastric cancer in first- or second-degree relatives, regardless of the age at diagnosis. Among families that fit this criteria, it is estimated that 25-40% will have a CDH1 gene mutation.^{4,5,6}

Families with multiple cases of diffuse gastric cancer, as well as patients diagnosed with diffuse gastric cancer before age 40, are referred for genetic counseling and testing for CDH1 gene mutations. The genetic testing is performed in two stages, diagnostic testing and predictive testing. Diagnostic testing is done using a blood sample from a patient affected with gastric cancer, to identify if a mutation in the CDH1 gene exists to cause the cancer. If a mutation is identified, healthy family members who are at risk for inheriting the same mutation will undergo predictive testing for the same mutation.⁵

People from HDGC families are at an increased risk of developing diffuse-type gastric cancer. It is estimated that the lifetime risk of developing gastric cancer is 80%. Additionally, female carriers are at an increased risk (60% lifetime risk) for lobular breast cancer.⁷

Gastric Cancer Screening

Patients from HDGC families should be followed by physicians, genetic counselors, gastroenterologists, surgeons, pathologists, oncologists, dieticians, and other health professionals.² Upper endoscopy with random gastric biopsies (small samples of tissue) is currently the best method to screen for gastric cancer.² Unfortunately, diffuse gastric cancer often is not apparent on endoscopy, and biopsies are often negative.³

The current screening recommendations are upper endoscopy with biopsies on an annual basis.^{2,9}

Because hereditary diffuse gastric cancer is nearly impossible to detect at an early stage, however, the recommended procedure to prevent gastric cancer is a total gastrectomy, or complete removal of the stomach.^{3,7,8} Although this procedure is complicated and commonly leads to weight loss, diarrhea, altered eating habits, and vitamin deficiency, it is possibly the only method to prevent stomach cancer.^{2,4,5,9}

Breast Cancer Screening

Women from HDGC families should perform self-breast exams and have clinical breast exams regularly.^{7,9} Screening with yearly mammograms and breast MRI are also recommended, starting a age 35.⁷ There is a possible role for a medication called Tamoxifen to reduce the risk of lobular breast cancer in CDH1 mutation carriers, but this has not yet been determined. If there are many cases of breast cancer in the family, prophylactic mastectomy may also be considered.^{6,10}

Future of HDGC

Research on the genetics, diagnosis, and treatment of HDGC is ongoing. Centers of Excellence have been established worldwide and experts from the International Gastric Cancer Linkage Consortium continue to work together to develop new guidelines and recommendations for patients and families affected by HDGC.

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