



Hereditary diffuse gastric cancer: Is prophylactic gastrectomy indicated for healthy carriers of CDH1 gene mutations?

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Hereditary diffuse gastric cancer (HDGC) is a distinct form of gastric cancer that does not involve *Helicobacter pylori* in its carcinogenesis. Instead, it is an autosomal dominant inherited syndrome, typically caused by an inactivating germline mutation in the CDH1 gene. This mutation leads to a deficiency in the E-cadherin protein, promoting the development and invasion of signet ring cell carcinoma and enabling its spread into adjacent tissues (1).

HDGC follows an autosomal dominant inheritance pattern with incomplete penetrance, and the cumulative risk increases with age. The condition was first described in 1998 among members of a Maori family in New Zealand. Most individuals with HDGC develop gastric cancer before the age of 40. By the age of 80, the cumulative risk of gastric cancer is approximately 70% for men and 56% for women. Additionally, women with the CDH1 mutation have a 42% lifetime risk of developing lobular breast cancer (2).

Most reported cases of HDGC come from Europe and the United States, where hereditary gastric cancer accounts for 1–3% of all gastric cancer cases. Clinically, CDH1 germline mutations are identified in about 25% of families who meet the diagnostic criteria for HDGC (3). Interestingly, despite Japan's significantly higher incidence of gastric cancer compared to Western countries, HDGC has been reported only rarely in Japan (4,5).

HDGC should be suspected if any of the following three criteria are met:

1. A family history of two or more cases of gastric cancer at any age, with at least one confirmed case of diffuse gastric cancer;
2. A diagnosis of diffuse gastric cancer in an individual under the age of 40;
3. A family history that includes both diffuse gastric cancer and lobular breast cancer, with at least one diagnosis occurring before the age of 50 (6).

For individuals carrying a germline CDH1 mutation, prophylactic total gastrectomy is strongly recommended. This procedure is considered a unique and potentially life-saving option for asymptomatic carriers. Endoscopic surveillance is generally ineffective in detecting early-stage HDGC, as cancerous foci are often invisible and lie beneath histologically normal gastric mucosa (5).

The optimal timing for prophylactic gastrectomy remains uncertain. The decision largely depends on a balance between oncological risk and the potential impact on quality of life after surgery. For most patients, prophylactic gastrectomy reveals invasive or at least in situ signet ring cell carcinoma at the time of the procedure.

Currently, surgery is recommended for carriers of the CDH1 mutation typically between the ages of 20 and 30. In most cases, when performed prophy-

lactically, the disease is found to be at an early stage—commonly classified as T1N0. Data from studies on signet ring cell gastric cancer suggest that early-stage detection of this histological subtype is associated with a more favorable prognosis (7).

The goal of prophylactic surgery is to remove as much at-risk tissue as possible, thereby minimizing the likelihood of cancer developing in those areas. The recommended procedure is a total gastrectomy with a **Roux-en-Y** reconstruction.

During prophylactic total gastrectomy, the resection line is made across the distal esophagus to ensure complete removal of the gastric cardia mucosa. Both the proximal (esophageal) and distal (duodenal) margins should be examined using frozen section analysis to confirm the absence of any residual gastric tissue.

In addition, it is recommended to inspect for the presence of a Meckel diverticulum, as gastric mucosa can occasionally be found within this structure. Since the **CDH1** mutation is a germline mutation—present in nearly all cells—it is reasonable to assume that any ectopic gastric mucosa within a Meckel diverticulum would also carry the mutation. As a result, if identified, the diverticulum should be removed to eliminate this potential cancer risk (8,9).

The extent of lymphadenectomy remains a subject of debate. Some recommend **D1 lymphadenectomy**, as most patients undergoing prophylactic surgery present with T1N0-stage disease. However, others advocate for **D2 lymphadenectomy**, as the risk of lymph node metastases in cases of T1a intramucosal cancer is approximately 2–5%, and can rise to 6% in undifferentiated or diffuse histologic subtypes (5,6,7). For T1b cancers, the incidence of lymph node metastasis increases significantly, ranging from 17% to 28% of cases (6,7).

For individuals at risk for hereditary diffuse gastric cancer (HDGC) who decline or wish to delay prophylactic total gastrectomy, close endoscopic surveillance is recommended. It is also suggested to revisit

the possibility of surgery with these patients periodically, as they may reconsider their decision under different life circumstances (10,11).

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