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Hereditary Diffuse Gastric Cancer syndrome: *CDH1* Mutations

Cancer Risks and General Management Recommendations

CDH1 mutations cause a condition known as Hereditary Diffuse Gastric Cancer (HDGC) which is predominantly associated with increased lifetime risks for diffuse gastric cancer and lobular breast cancer. Diffuse gastric cancer is a type of adenocarcinoma that infiltrates and thickens the stomach wall without forming a distinct tumor mass.

Cancer Type	*CDH1* Mutation Carrier Cancer Risks	General Population Lifetime Cancer Risks	Surveillance/Management Recommendations[1-4]
Gastric Cancer	Men: 67-70% Women: 56-83% (average age of diagnosis is 37)[2,4,5]	0.8%	*Surgery** • Ages 18-40 years: Total gastrectomy due to the high mortality rate of diffuse gastric cancer and the low rate of detection by endoscopic screening. • Prophylactic gastrectomy is not typically recommended prior to 18 years of age but may be considered for those with family members diagnosed with gastric cancer prior to age 25. • Baseline endoscopy is recommended prior to gastrectomy with multiple random biopsies to assess for the presence of macroscopic tumor foci or other factors that may lead to a more complex surgery. • Intraoperative frozen sections is recommended to verify that the proximal margin contains esophageal squamous mucosa and distal margin contains duodenal mucosa. A D2 lymph node dissection is not necessary for prophylactic total gastrectomy. • Careful pathologic examination and sampling should occur.[4] *Surveillance* • Those who elect not to undergo prophylactic gastrectomy should undergo upper endoscopy with multiple random biopsies every 6-12 months per published protocols.[2-4] • Microscopic tumor foci are frequently detected on pathology of prophylactic gastrectomy in those who have recently undergone endoscopic screening, highlighting the significant limitations of screening in these high-risk individuals.[6] • Individuals with *CDH1* mutations should be tested for *H. pylori* and treated if infection is present.
Female Breast Cancer	39-52%[4,5,7] (average age of diagnosis is 53)	12.4%	*Surveillance* • Age 30 years: Annual mammogram with consideration of tomosynthesis; consider breast MRI with contrast. ○ Age to initiate breast surveillance may be modified based on family history, typically 5-10 years earlier than the youngest breast cancer diagnosis in the family, but no later than age 30.

			Surgery • Insufficient evidence to support risk-reducing mastectomy based on *CDH1* mutation status alone; management should be based on personal risk factors and family history.
Colorectal Cancer (CRC)	Possibly increased, though data is limited	4.2%	*Surveillance* • NCCN does not currently recommend modification of CRC surveillance based on the presence of a *CDH1* mutation alone. Management should be based on personal risk factors and family history.

*Of note, there is controversy over how to manage gastric cancer risks in individuals with mutations in *CDH1* in the absence of a family history of gastric cancer. However, one small study found that >50% of such individuals has gastric cancer identified at the time of risk-reducing surgery.[8]

Other risks: Cleft lip and/or cleft palate have been associated with *CDH1* mutations.[9]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *CDH1* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.findageneticcounselor.com to find genetic services near them.

References:

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