Hereditary diffuse gastric cancer

Hereditary diffuse gastric cancer (HDGC) is an inherited disorder that greatly increases the chance of developing a form of stomach (gastric) cancer. In this form, known as diffuse gastric cancer, there is no solid tumor. Instead, cancerous (malignant) cells multiply underneath the stomach lining, making the lining thick and rigid. The invasive nature of this type of cancer makes it highly likely that these cancer cells will spread (metastasize) to other tissues, such as the liver or nearby bones.

Symptoms of diffuse gastric cancer occur late in the disease and can include stomach pain, nausea, vomiting, difficulty swallowing (dysphagia), decreased appetite, and weight loss. If the cancer metastasizes to other tissues, it may lead to an enlarged liver, yellowing of the eyes and skin (jaundice), an abnormal buildup of fluid in the abdominal cavity (ascites), firm lumps under the skin, or broken bones.

In HDGC, gastric cancer usually occurs in a person’s late thirties or early forties, although it can develop anytime during adulthood. If diffuse gastric cancer is detected early, the survival rate is high; however, because this type of cancer is hidden underneath the stomach lining, it is usually not diagnosed until the cancer has become widely invasive. At that stage of the disease, the survival rate is approximately 20 percent.

Some people with HDGC have an increased risk of developing other types of cancer, such as a form of breast cancer in women that begins in the milk-producing glands (lobular breast cancer); prostate cancer; and cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. Most people with HDGC have family members who have had one of the types of cancer associated with HDGC. In some families, all the affected members have diffuse gastric cancer. In other families, some affected members have diffuse gastric cancer and others have another associated form of cancer, such as lobular breast cancer. Frequently, HDGC-related cancers develop in individuals before the age of 50.

Frequency

Gastric cancer is the fourth most common form of cancer worldwide, affecting 900,000 people per year. HDGC probably accounts for less than 1 percent of these cases.

 Causes

It is likely that 20 to 40 percent of individuals with HDGC have a mutation in the CDH1 gene. The CDH1 gene provides instructions for making a protein called epithelial cadherin or E-cadherin. This protein is found within the membrane that surrounds epithelial cells, which are the cells that line the surfaces and cavities of the body. E-cadherin helps neighboring cells stick to one another (cell adhesion) to form organized
tissues. E-cadherin has many other functions including acting as a tumor suppressor protein, which means it prevents cells from growing and dividing too rapidly or in an uncontrolled way.

People with HDGC caused by CDH1 gene mutations are born with one mutated copy of the gene in each cell. These mutations cause the production of an abnormally short, nonfunctional version of E-cadherin or alter the protein’s structure. For diffuse gastric cancer to develop, a second mutation involving the other copy of the CDH1 gene must occur in the cells of the stomach lining during a person’s lifetime. Women who are born with one mutated copy of the CDH1 gene have a 56 percent chance of acquiring a second mutation in the other copy of the gene and developing gastric cancer in their lifetimes; men have a 70 percent chance of acquiring a second mutation and developing gastric cancer.

When both copies of the CDH1 gene are mutated in a particular cell, that cell cannot produce any functional E-cadherin. The loss of this protein prevents it from acting as a tumor suppressor, contributing to the uncontrollable growth and division of cells. A lack of E-cadherin also impairs cell adhesion, increasing the likelihood that cancer cells will not come together to form a tumor but will invade the stomach wall and metastasize as small clusters of cancer cells into nearby tissues.

These CDH1 gene mutations also lead to a 40 to 50 percent chance of lobular breast cancer in women, a slightly increased risk of prostate cancer in men, and a slightly increased risk of colorectal cancer. It is unclear why CDH1 gene mutations primarily occur in the stomach lining and these other tissues.

About 60 to 70 percent of individuals with HDGC do not have an identified mutation in the CDH1 gene. In some individuals, mutations in other cancer-inducing genes cause HDGC, but in some cases, the mechanism is unknown.

**Inheritance Pattern**

HDGC is inherited in an autosomal dominant pattern, which means one copy of the altered CDH1 gene in each cell is sufficient to increase the risk of developing cancer. In most cases, an affected person has one parent with the condition.

**Other Names for This Condition**

- E-cadherin-associated hereditary gastric cancer
- familial diffuse gastric cancer
- FDGC
- HDGC
- hereditary diffuse gastric adenocarcinoma
Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting

- Genetic Testing Registry: Hereditary diffuse gastric cancer
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1708349/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22hereditary+diffuse+gastric+cancer%22+OR+%22familial+gastric+cancer%22

Other Diagnosis and Management Resources

- American Cancer Society: How is Stomach Cancer Diagnosed?
  https://www.cancer.org/cancer/stomach-cancer/detection-diagnosis-staging/how-diagnosed.html

- GeneReview: Hereditary Diffuse Gastric Cancer
  https://www.ncbi.nlm.nih.gov/books/NBK1139

- MedlinePlus Encyclopedia: Gastric Cancer
  https://medlineplus.gov/ency/article/000223.htm

- National Cancer Institute: Gastric Cancer Treatment Option Overview
  https://www.cancer.gov/types/stomach/patient/stomach-treatment-pdq

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Gastric Cancer
  https://medlineplus.gov/ency/article/000223.htm

- Health Topic: Stomach Cancer
  https://medlineplus.gov/stomachcancer.html

Genetic and Rare Diseases Information Center

- Hereditary diffuse gastric cancer
  https://rarediseases.info.nih.gov/diseases/10900/hereditary-diffuse-gastric-cancer

Additional NIH Resources

- National Cancer Institute: General Information About Stomach Cancer
  https://www.cancer.gov/types/stomach/patient/stomach-prevention-pdq
Educational Resources

- Cancer.Net
  https://www.cancer.net/cancer-types/hereditary-diffuse-gastric-cancer
- Johns Hopkins Medicine: Gastric Cancer
  https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/esophagus_stomach/gastric_cancer.pdf
- Merck Manual for Patients and Caregivers: Stomach Cancer
  https://www.merckmanuals.com/home/digestive-disorders/tumors-of-the-digestive-system/stomach-cancer
- Mount Sinai Hospital: Zane Cohen Centre for Digestive Diseases (Canada)
  http://www.zanecohencentre.com/gi-cancers/diseases/hdgc
- Orphanet: Hereditary diffuse gastric cancer
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=26106
- Stanford Health Care
  https://stanfordhealthcare.org/medical-conditions/cancer/hdgc.html

Patient Support and Advocacy Resources

- American Cancer Society
  https://www.cancer.org/
- CancerCare
  https://www.cancercare.org/diagnosis/gastric_cancer
- Hereditary Diffuse Gastric Cancer
  https://HereditaryDiffuseGastricCancer.org
- No Stomach for Cancer
  https://www.nostomachforcancer.org/

Clinical Information from GeneReviews

- Hereditary Diffuse Gastric Cancer
  https://www.ncbi.nlm.nih.gov/books/NBK1139

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Stomach+Neoplasms%5BMAJR%5D%29+AND+%28hereditary+diffuse+gastric+cancer%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- GASTRIC CANCER, HEREDITARY DIFFUSE
  http://omim.org/entry/137215
Sources for This Summary

- Carneiro P, Fernandes MS, Figueiredo J, Caldeira J, Carvalho J, Pinheiro H, Leite M, Melo S, Oliveira P, Simões-Correia J, Oliveira MJ, Carneiro F, Figueiredo C, Paredes J, Oliveira C, Seruca R. E-cadherin dysfunction in gastric cancer--cellular consequences, clinical applications and open questions. FEBS Lett. 2012 Aug 31;586(18):2981-9. doi: 10.1016/j.febslet.2012.07.045. Epub 2012 Jul 25. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22841718

- Figueiredo J, Söderberg O, Simões-Correia J, Grannas K, Suriano G, Seruca R. The importance of E-cadherin binding partners to evaluate the pathogenicity of E-cadherin missense mutations associated to HDGC. Eur J Hum Genet. 2013 Mar;21(3):301-9. doi: 10.1038/ejhg.2012.159. Epub 2012 Aug 1. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22850631 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3573198/

- Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, Chung DC, Norton J, Ragunath K, Van Krieken JH, Dwerryhouse S, Caldas C; International Gastric Cancer Linkage Consortium. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. J Med Genet. 2010 Jul;47(7):436-44. doi: 10.1136/jmg.2009.074237. Erratum in: J Med Genet. 2011 Mar;48(3):216. Van Krieken, Nicola [corrected to Van Grieken, Nicola C]. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20591882 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2991043/

- Hansford S, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffer DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lum A, Talhouk A, Baker-Lange K, Richardson S, Lewis I, Linder NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guilford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. JAMA Oncol. 2015 Apr;1(1):23-32. doi: 10.1001/jamaoncol.2014.168. Erratum in: JAMA Oncol. 2015 Apr;1(1):110. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26182300

- Kluijt I, Siemerink EJ, Ausems MG, van Os TA, de Jong D, Simões-Correia J, van Krieken JH, Ligtenberg MJ, Figueiredo J, van Riel E, Sijmons RH, Plukker JT, van Hillegersberg R, Dekker E, Oliveira C, Cats A, Hoogerbrugge N; Dutch Working Group on Hereditary Gastric Cancer. CDH1-related hereditary diffuse gastric cancer syndrome: clinical variations and implications for counseling. Int J Cancer. 2012 Jul 15;131(2):367-76. doi: 10.1002/ijc.26398. Epub 2011 Oct 23. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22020549

- Kluijt I, Sijmons RH, Hoogerbrugge N, Plukker JT, de Jong D, van Krieken JH, van Hillegersberg R, Ligtenberg M, Bleiker E, Cats A; Dutch Working Group on Hereditary Gastric Cancer. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. Fam Cancer. 2012 Sep;11(3):363-9. doi: 10.1007/s10689-012-9521-y. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22388873

- Majewski IJ, Kluijt I, Cats A, Scerri TS, de Jong D, Kluin RJ, Hansford S, Hogen vorst FB, Bosma AJ, Hofland I, Winter M, Huntsman D, Jonkers J, Bahlo M, Bernards R. An α-catenin (CTNNA1) mutation in hereditary diffuse gastric cancer. J Pathol. 2013 Mar;229(4):621-9. doi: 10.1002/path.4152. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23208944
Oliveira C, Seruca R, Hoogerbrugge N, Ligtenberg M, Carneiro F. Clinical utility gene card for: Hereditary diffuse gastric cancer (HDGC). Eur J Hum Genet. 2013 Aug;21(8). doi: 10.1038/ejhg.2012.247. Epub 2013 Feb 27. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23443028
Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3722670/

Simões-Correia J, Figueiredo J, Lopes R, Stricher F, Oliveira C, Serrano L, Seruca R. E-cadherin destabilization accounts for the pathogenicity of missense mutations in hereditary diffuse gastric cancer. PLoS One. 2012;7(3):e33783. doi: 10.1371/journal.pone.0033783. Epub 2012 Mar 21. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22470475
Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3309996/

van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, Caldas C, Schreiber KE, Hardwick RH, Ausems M, Bardram L, Benusiglio PR, Bisseling TM, Blair V, Bleiker E, Boussiotas A, Cats A, Coit D, DeGregorio L, Figueiredo J, Ford JM, Heijkoop E, Hermens R, Humar B, Kaurah P, Keller G, Lai J, Ligtenberg MJ, O'Donovan M, Oliveira C, Pinheiro H, Ragunath K, Rasenberg E, Richardson S, Roviello F, Schackert H, Seruca R, Taylor A, Ter Huurne A, Tischkowitz M, Joe ST, van Dijk B, van Grieken NC, van Hillegersberg R, van Sandick JW, Vehof R, van Krieken JH, Fitzgerald RC. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet. 2015 Jun;52(6):361-74. doi: 10.1136/jmedgenet-2015-103094. Epub 2015 May 15. Review. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25979631
Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4453626/

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