Hereditary Diffuse Gastric Cancer (HDGC)

What you should know about HDGC

Hereditary Diffuse Gastric Cancer (HDGC) is a hereditary cancer syndrome that increases the risk of developing a particular form of stomach cancer (diffuse gastric cancer) and breast cancer. Diffuse gastric cancer is a specific type of invasive stomach cancer that thickens the wall of the stomach wall without forming a distinct tumor. The majority of patients develop diffuse gastric cancer by age 40. Women with HDGC also have a risk for lobular breast cancer, which develops from the milk producing cells in the breast. Approximately 50% of families with HDGC are found to carry a mutation in the \textit{CDH1} gene. However, a mutation is not found in many patients with a clinical diagnosis of HDGC.

Cancer Risks and Features Associated with HDGC

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population Risk</th>
<th>HDGC Risk</th>
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<tbody>
<tr>
<td>Gastric (stomach) cancer</td>
<td>0.9%</td>
<td>67-70% (Men)</td>
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<td></td>
<td></td>
<td>56-83% (Women)</td>
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<tr>
<td>Female breast cancer</td>
<td>12.5%</td>
<td>39-52%</td>
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There may be an increased risk for other cancers including colon. Cleft lip with or without palate has also been associated with \textit{CDH1} mutations.

Genetics and Inheritance of HDGC

Genes are our body's instructions. They provide our body with information about how to grow and develop. When there is a mutation in a gene, it can cause the gene to no longer function correctly. Each person has two copies of every gene. One copy is inherited from their mother and the other copy is inherited from their father.

HDGC is due to a mutation in one copy of the \textit{CDH1} gene. Cancer risks associated with \textit{CDH1} mutations are inherited in an autosomal dominant manner. This means that children, siblings, and parents of individuals with a \textit{CDH1} mutation have a 50% (1 in 2) chance of having the mutation as well. Both males and females can inherit a \textit{CDH1} mutation and can pass it on to their children.

Managing Cancer Risks

When possible, individuals with HDGC should seek management with physicians or centers that are experienced with this condition.

- **Breast Cancer**: Annual mammogram with consideration of tomosynthesis and consider breast MRI starting at age 30 (or 5-10 years earlier than the youngest breast cancer diagnosis in the family, but no later than age 30). Insufficient evidence to support risk-reducing mastectomy based on \textit{CDH1} mutation status alone; management should be based on personal risk factors and family history.

- **Gastric Cancer**: Preventative surgery, involving removal of the stomach (gastrectomy), is typically recommended for \textit{CDH1} mutation carriers in adulthood, but may be considered earlier based on the family history. For individuals who elect not to undergo prophylactic gastrectomy, gastric screening may be considered via upper endoscopy with random biopsies every 6-12 months.
When to Consider Evaluation for HDGC

- Relative with a CDH1 mutation
- The presence of 2 or more family members with diffuse gastric cancer
- Multiple family members with lobular breast cancer
- Diffuse gastric cancer diagnosed before the age of 50
- Diffuse gastric cancer and lobular breast cancer in the same individual

Genetic Counseling

In many families, the cancer history may be due to a combination of genetic and environmental factors. In addition, other genetic conditions (i.e. other gene mutations) may appear to be clinically similar to CDH1 mutations. For this reason, a detailed review of the family history by a genetics professional is important before pursuing genetic testing. A genetic counselor can help determine which, if any, genetic tests may be helpful for a family and review the benefits, risks, and limitations of genetic testing. Genetic testing is usually performed through a blood or saliva sample.

Genetic test results can be complicated and are most useful when interpreted by a genetic professional in the context of an individual's complete personal and family history. To locate a genetic counselor near you, please visit www.nsgc.org and click on the 'Find a Genetic Counselor' link.

Genetic Discrimination

The Genetic Information Nondiscrimination Act (GINA) was signed into federal law in 2008. GINA prohibits health insurers and most employers from discriminating against individuals based on genetic information, including the results of genetic tests and family history information. According to GINA, health insurance companies cannot consider genetic information to be a preexisting condition, nor can they use it to make decisions regarding coverage or rates. GINA also makes it illegal for most employers to use genetic information in making decisions about hiring, firing, promotion, or terms of employment. It is important to note that GINA does not offer protections for life insurance, disability insurance, or long-term care insurance. More information about GINA can be found by contacting a local genetic counselor or by visiting www.ginahelp.org.

Resources

- No Stomach for Cancer – www.nostomachforcancer.org
- Hereditary Diffuse Gastric Cancer Advocacy – www.hereditarydiffusegastriccancer.org

References

- NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer, v.2.2020, nccn.org.