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Estimates of gastric, breast cancer risk in carriers of CDH1 gene mutations

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More precise estimates of age-associated risks of gastric and breast cancer were derived for carriers of the CDH1 gene mutation, a cancer predisposing gene that is abnormal in families meeting criteria for clinically defined hereditary diffuse gastric cancer (HDGC), according to a study published online by *JAMA Oncology*.

Gastric cancer (GC) is the third most common cause of cancer-related death in the world. HDGC is characterized by its early-onset and multigenerational nature, as well as lobular breast cancer. Current cumulative lifetime GC risk in CDH1 mutation carriers is derived from a small number of families with predicted risks ranging from 40 percent to 67 percent in men and 63 percent to 83 percent in women. Female carriers also have a breast cancer risk between 39 percent and 52 percent. The only recommended ways to reduce the risk of GC is screening gastroscopy (endoscopic evaluation of the gut) with multiple random biopsies or surgical removal of the entire stomach to prevent cancer, according to the study background.

David G. Huntsman, M.D., of the British Columbia Cancer Agency, Canada, and coauthors tested for CDH1 germline mutations in 183 new families with HDGC. Penetrance (the proportion of people with a gene mutation who will show clinical disease) was derived from 75 mutation-positive families from this and other study groups comprising 3,858 individuals. Germline DNA from 144 HDGC families without the CDH1 mutations also were screened for 55 cancer-associated genes to determine if other genes are associated with HDGC.

The authors identified 31 distinct CDH1 mutations (14 of them novel) in 34 of 183 families (19 percent). They estimate that by the age of 80, the cumulative incidence of gastric cancer is 70 percent for men and 56 percent for women, with a risk of breast cancer for women of 42 percent. Researchers also identified candidate mutations in 16 of 144 probands (the person who is the starting point in a family being studied), including mutations within genes of high and moderate penetrance.

"These data should assist in the genetic counseling and management of at-risk individuals from CDH1-positive HDGC families," the study concludes.

In a related editorial, James M. Ford, M.D., of the Stanford University School of Medicine, California, writes: "The article by Hansford et al assembles the largest group of genetically defined HDGC families to date (75 families, comprising 3,858 individuals) to determine age-specific penetrance of gastric and breast cancer. ... These updated risk assessments should be considered the new standard for genetic counseling and will be included in the next International Gastric Cancer Linkage Consortium guidelines."

"In the current study by Hansford et al, the investigators take a candidate gene approach and sequence the DNA from 144 individuals with families meeting HDGC criteria but without CDH1 mutations or copy-number changes, finding that nearly 12 percent exhibit germline mutations in 1 of a panel of 55 cancer susceptibility genes enriched for those suspected of having a role in gastric cancer development. This finding is fascinating for several reasons," Ford continues.

"The current article by Hansford et al provide a major advance. Further clinical and genetic research is necessary to identify biomarkers and better methods of screening individuals at high risk," the editorial concludes.

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