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Redefining Risks in CDH1 Hereditary Diffuse Gastric Cancer

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STOMACH

This summary reviews Ryan CE, Fasaye G, Gallanis AF, et al. Germline CDH1 variants and lifetime cancer risk. JAMA. 2024;332(9):722–729.

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STRUCTURED ABSTRACT

Question: What is the lifetime cumulative risk of gastric cancer in those with a *CDH1* pathogenic variant?

Design: Multicenter observational cohort study.

Setting: Academic medical centers: National Cancer Institute and 5 university-based systems.

Patients: Families with a germline pathogenic/likely pathogenic (P/LP) *CDH1* variant.

Interventions: Exposure to a germline pathogenic *CDH1* variant.

Outcomes: Self-reported personal and family histories of advanced gastric cancer (≥pT1b, N1, or any M stage) and breast cancer.

Data Analysis: Cumulative lifetime cancer risk among *CDH1* carriers was estimated using specific hazard ratios (HRs) compared to non-carriers, estimated

using segregation analyses and maximum restricted likelihood methods.

Funding: Intramural Research Program of the National Institutes of Health, National Cancer Institute.

Results: Two hundred and thirteen kindreds (extended families) with *CDH1* P/LP variants, consisting of 7,232 individuals; 85% were White and 49% female. The average age at diagnosis of gastric cancer was 49 (interquartile range [IQR] 39-59), and breast cancer at age 51 (IQR 44-58). The cumulative risk of advanced gastric cancer was 10.3% by age 80 in male carriers, and 6.5% by age 80 in female carriers with a HR 3.5 (95% confidence interval [CI] 0.4-26.2). Among individuals with ≥3 first-degree relatives with gastric cancer, the estimated risk by age 80 was 38% (95% CI 25-64%). The cumulative risk of any gastric cancer (including stage 1A) at the time of prophylactic total gastrectomy was 19.1% (95% CI 11.5-35.9%) among males and 12.6% (95% CI 7.6-24.8%) among females. Whether signet ring cells were found on endoscopic biopsies did not make a significant difference in cumulative risk of any gastric cancer.

COMMENTARY

Why Is This Important?

Although autosomal dominant hereditary diffuse gastric cancer due to *CDH1* is relatively uncommon, the lifetime cumulative risks of diffuse gastric adenocarcinoma (aka linitis plastica) have been historically been estimated up to 70% for male and 83% for female patients, although these studies have been of small sample size or from high-risk families outside of the United States.[1-3] Therefore, guidelines have recommended a prophylactic total gastrectomy for all *CDH1* patients as early as 20 years old.[4] In addition to complications after surgery, this has devastating lifetime impacts on a person's nutritional and fertility status for someone who has nearly their whole life ahead of them. This study redefines that risk to a more realistic expectations and questions the role of prophylactic gastrectomy as a blanket recommendation.

Key Study Findings

The cumulative lifetime risk of advanced gastric cancer (>pT1a) was approximately 10% in male and 7% in female *CDH1* carriers. The cumulative lifetime risk of any gastric cancer including stage IA gastric cancer of 19% in males and 13% in females, and whether or not signet rings were found on endoscopic biopsy seemed to have minimal impact.

Having a strong family history (3 first-degree relatives with gastric cancer) portended a lifetime risk of 38%.

Caution

First, studies have shown that essentially all *CDH1* patients harbor an occult pT1aN0 (stage IA) gastric cancer that itself is regarded as clinically insignificant, but clearly this shows that only a subset of those progress to pT1b and beyond.[5] While this study helps redefine that prophylactic gastrectomy is unlikely the default answer for most *CDH1* patients, particularly without a concerning family history of diffuse gastric cancer, we still do not have an evidence-based approach to surveillance and risk stratification for those who are at risk of future advanced gastric cancer. Second, this study does still have ascertainment bias given its focus on academic medical centers and patients who had germline genetic testing for a personal/family history of cancer, although this is a common issue. Third, the ascertainment of cancer outcomes was based on patient self-report without confirmation of pathologic diagnoses.

My Practice

CDH1 patients represent one of the difficult clinical decision-making conundrums in hereditary gastrointestinal cancers. I discuss this data with patients regarding risks of advanced gastric cancer and often defer prophylactic gastrectomy at age 20 in the absence of a strong family history. However, I do find it useful to still have them meet with a surgical oncologist to discuss what a surgery would entail. I perform surveillance endoscopy every 6-12 months based on the Cambridge protocol depending on their family history of gastric cancer.[6] It is important to take your time with the endoscopy, particularly to look for mucosal abnormalities such as ulcerated lesions, although note that signet ring carcinoma on a random or targeted biopsy of "pale areas" has not been clearly shown to correlate with advanced gastric cancer. Surveillance endoscopies should preferentially be performed at tertiary referral centers by an endoscopist with specific expertise in hereditary digestive cancer, if available.

For Future Research

Current studies are examining both endoscopic and other clinical risk factors for pT1b or advanced gastric cancer in *CDH1* patients to help identify who should undergo gastrectomy and when. This may include specific endoscopic or patient characteristics, incorporation of artificial intelligence into our endoscopic exams, as well as biomarkers.

Conflict of Interest

Dr Yen has no reported conflicts of interest.

Abbreviations

CI, confidence interval; HR, hazard ratios; IQR, interquartile range; P/LP, pathogenic/likely pathogenic.

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