Hereditary Gastric Cancer
An Update at 15 Years

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Like most solid tumors, gastric cancer is currently thought to be a group of molecularly and pathologically distinct subtypes caused by a variety of known and unknown environmental and genetic factors. Understanding these factors better will lead to advances in personalized therapy, prevention, and screening and hopefully to decreased mortality. Gastric cancer is a global public health concern, currently ranking as the third leading cause of cancer mortality worldwide, with a 5-year survival of only 20%. Recent and rapid advances in molecular genetics has provided an understanding of the cause for many inherited cancer syndromes, offering possibilities for individual genetic testing, family counseling, and preventive approaches. Similar to other hereditary cancer syndromes, the majority of individuals meeting defined clinical criteria for hereditary diffuse cancer syndrome (HDGC) based on personal or family history do not all have a germline mutation in the 1 known causative gene, E-cadherin (CDH1)—in fact the minority do—and individuals known to carry pathogenic germline mutations in CDH1 do not all exhibit similar clinical outcomes in terms of age of cancer diagnosis or type of cancers. This suggests that additional uncharacterized alterations in other genes may affect gastric cancer susceptibility and age-specific penetrance. The current article by Hansford et al in this issue of JAMA Oncology provides a major and much needed update in describing both the cancer penetrance and genetic spectrum of risk for HDGC. Discovered over 15 years ago, CDH1-associated HDGC, while rare, is part of the spectrum of cancer syndromes tested for in any major cancer genetics clinic, and criteria for genetic testing, clinical screening, and surgical prophylaxis...
for diffuse gastric cancer and lobular breast cancer in these families have been established. 4 Genetic counselors and medical professionals may be surprised, however, that our current recommendations regarding cancer risk for carriers are based on only a handful of families. The article by Hansford et al3 assembles the largest group of genetically defined HDGC families to date (75 families, comprising 3858 individuals) to determine age-specific penetrance of gastric and breast cancer. The results are generally consistent with those previous estimates provided to patients as part of genetic counseling, but even small differences are critical when decisions include such life-altering procedures as risk-reducing prophylactic gastrectomy. The cumulative risk of gastric cancer for CDH1 mutation carriers by age 80 years is reported as 70% for men and 56% for women. However, it is important to examine eTable 6 in the Supplement that shows a similar and early increase in gastric cancer risk in both men and women from ages 30 to 60 years. 3 Furthermore, the cumulative risk of breast cancer (mostly lobular) for women with a CDH1 mutation is estimated to be 42% by age 80 years. Both show substantial increased relative risk starting before the third decade of life. Also of importance, no evidence was found for risk of other cancer types in individuals with a CDH1 mutation. 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. Current guidelines suggest breast cancer screening using annual magnetic resonance imaging starting at age 30 years and consideration of prophylactic total gastrectomy 5 years younger than the youngest case in the family, with endoscopic screening recommendations remaining poorly defined.

Of note, in the study by Hansford et al, 3 only 19% of families meeting clinical criteria for HDGC were found to have a pathogenic germline CDH1 mutation, with another 2% exhibiting a variant of uncertain significance. This is significantly less than previously described, but regardless, emphasizes the point well known to cancer genetics practitioners that we cannot account genetically for the majority of HDGC families without a personal or family history of diffuse gastric cancer, as well as lobular breast cancer. The current article by Hansford et al 3 provides a major advance. Further clinical and genetic research is necessary to identify biomarkers and better methods for screening individuals at high risk.

Second, it replicates a very similar pattern observed throughout hereditary cancer genetics studies, that when individuals from high-risk families but without a genetic diagnosis are tested using a panel of high- and moderate-penetrance cancer genes, approximately 5% to 10% will harbor potentially pathogenic mutations in other genes. 7 But third, it demonstrates the challenge in proving causation of these germline findings, as tumor genomic assays and family segregation studies are most often limited because of a lack of clinical material. This last point is critical to using such information to provide clinical counseling regarding cancer risk to other family members and represents the biggest need for future research. At this point, CTNNA1 is probably the only additional gene to CDH1 for which germline testing can be recommended on a clinical basis.

Diagnosing gastric cancer in its early stages provides the best chance for curative resection, but it is a difficult task. Symptoms due to gastric cancer do not appear until the disease is more advanced and are generally nonspecific. Endoscopy is generally considered to be the best method to screen for gastric cancer, but diagnosing diffuse gastric carcinoma is difficult because these lesions tend not to form a grossly visible exophytic mass but rather spread submucosally as single cells or clustered islands of cells. 8 Therefore, prophylactic gastrectomy is recommended for most carriers of CDH1 mutations from syndromic families. 9 How to apply these principles to individuals meeting criteria for HDGC but without identified germline CDH1 mutations or one of these newly identified HDGC candidates remains unclear.

A major issue facing the cancer genetics community is presented by the inclusion of CDH1 on many multi-gene cancer panels, primarily because of its role as a high-penetrance breast cancer risk allele. Already, a number of individuals have been identified as CDH1 mutation carriers but without a personal or family history of diffuse gastric cancer or lobular breast cancer. Some of these mutations are identical to those reported in syndromic families in the study by Hansford et al. 3 How should these individuals be counseled regarding their gastric cancer risk, and should they be considered for prophylactic gastrectomies, given the poor diagnostic yield of screening endoscopy? Most genetics professionals would defer to a practical approach based on actual family history, but this is certainly a major question.

Other outstanding and critical research questions include identifying further germline cancer risk alleles for families exhibiting either diffuse or intestinal gastric cancer, as well as lobular breast cancer. The current article by Hansford et al 3 provides a major advance. Further clinical and genetic research is necessary to identify biomarkers and better methods for screening individuals at high risk.
In this issue of *JAMA Oncology*, Gogineni and colleagues report on their empirical inquiry into patient demands,¹ a nemesis that proves to be more mythical than real. The study hypothesis—that patient demands for treatments and scans drove unnecessary costs—was spectacularly unconfirmed when using data collected from physicians themselves. Only 8% of the patient-physician encounters at 3 cancer centers in Philadelphia involved a patient “demand,” and the majority of those “demands” were viewed by the physician as “clinically appropriate.” Suddenly, the demanding cancer patient looks less like a budget buster and more like an urban myth.

In the wake of these findings, the question now deserving of our attention is why does the myth of the demanding patient have so much traction? Surprisingly (as the authors note), no prior empirical study exists to tally patient demands in cancer care, which makes the existence of the demanding patient myth even more curious. My new hypothesis is that these findings say more about our own clinical sensibilities than what they reveal about our patients. We clinicians often, in my own experience, view patients who make a request that is surprising, unjustified, or forceful (eg, a “demand”) as (1) hard to deal with; (2) memorable despite their infrequent appearance; and (3) a convenient target for the bigger, complex, seemingly unsolvable problems we face.

When patients make requests forcefully, it is easy for an unskilled clinician to be pushed off balance. A forceful request often carries an undercurrent of hostility that throws oncologists who are used to being treated with deference. We do not like this, and consequently, hostility from the patient tends to provoke hostility from the clinician. For clinicians who have not been trained to detect and respond to emotion as a core communication skill, it is easy to fall into the trap of responding defensively or angrily. From the outside, this skill can look like magic because it is subtle—it starts with self-monitoring.² The key skill is to notice when you are irritated, and rather than blurt out your defense, pause and step back for a moment. You will then recognize that your patient who is demanding something is actually upset and hurting in a way that is overwhelming their coping skills or, much less often, has a personality such that they deal with everyone in their lives by making demands. A skilled clinician, after the pause, would start with an empathic remark (“Hmm, sounds like this is really important to you”) and modulate accordingly.³ For a patient who is really upset, the emotionally intelligent oncologist might offer more empathy (“I get the feeling you are worried...”) and uncover the real issue (“Yes doctor, I’m just scared”); and when the emotional tone fades, try the information again (“Could I step back—I’ll try to do a better job explaining my recommendations”).

Although demanding patients are not common, they often figure prominently in our memories because our cognitive biases tend to spotlight outliers.⁴ One reason for this is that a demanding, dissatisfied, unhappy patient can tap into our own unhappiness about not being perfect, our own disappointment about not saving the day, and our own dismay about not being appreciated. If we do not have our own skills to emotionally self-regulate and recharge, we tend to give these cognitive biases more influence than they merit. And we have started our day with stress, multitasking, and inadequate sleep—all very common. It is even easier to let our cognitive biases run rampant. A common cognitive bias, misattribution bias, is particularly relevant for this discussion. The demanding patient leaves us with vivid memories, and it is an easy move to pin them (unjustly) with the blame for runaway costs.

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