E-cadherin gene (CDH₁) mutations for the detection of familial occult gastric cancer

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ARTICLE

BACKGROUND
E-cadherin is a calcium-dependent, transmembrane molecule associated with the epithelial cell actin cytoskeleton. When complexed with catenins, it plays a central role in cell-cell adhesion.

Inactivating mutations of the CDH₁ gene that encodes E-cadherin were initially reported in a Maori kindred with hereditary diffuse gastric cancer. In those affected, gastric cancer was usually detected before age 40 years. It has been estimated that this hereditary diffuse form of gastric cancer accounts for less than 3% of all gastric adenocarcinomas, even though about 10% occur in a familial setting, including those associated with hereditary nonpolyposis colorectal cancer and familial colonic polyposis. In those with the potential to develop hereditary gastric cancer, surgical treatment has been offered as a preventive treatment.

The present study involving investigators from several countries (including the British Columbia Cancer Agency, Vancouver and Victoria General Hospital, Victoria, British Columbia) reported genetic screening and pathological changes in young persons with truncating mutations of CDH₁ from two unrelated families with hereditary diffuse gastric cancer.

RESEARCH STUDIES
In the study by Huntsman et al, mutation-specific, predictive genetic testing was performed with one of two methods in two families: polymerase chain reaction amplification, followed by restriction enzyme digestion and DNA sequencing, or heteroduplex analysis. In carriers of the CDH₁ mutation, gastric mucosa obtained from total gastrectomy was examined by extensive histopathological evaluation, in all five patients undergoing gastrectomy, foci of malignant signet ring cells were detected. The authors noted that four of five gastroscopies with random biopsies before surgery did not detect cancer.

DISCUSSION
Using modern molecular genetic methods, prophylactic gastrectomy done in asymptomatic carriers of germline mutations of the CDH₁ gene resulted in the detection of infiltrative, malignant, signet ring cell gastric cancer. Thus, this study showed that genetic testing has the ability to identify high-risk patients that might be targeted for intervention – in this case, total gastrectomy. In the same family, it is noteworthy that one other member also underwent total gastrectomy, but subsequent studies failed to show the CDH₁ mutation or histological evidence of gastric cancer in
the gastrectomy specimen. Signet ring cell cancer of the stomach is insidious and often difficult to diagnose, even if there is a high index of suspicion. Nevertheless, it seemed surprising that screening gastroscopy and biopsies failed to demonstrate carcinoma in any of the reported patients, possibly reflecting the difficulties with sampling of a relatively large, macroscopically normal-appearing mucosal surface with minute endoscopic biopsy specimens – a situation well recognized to occur in many other gastric disorders. Indeed, in this study, using detailed pathological studies, it was estimated that only 2% of the stomach was involved with the malignant process following detection of the gene carrier state.

Although this study demonstrates the feasibility for use of this molecular technology in familial gastric cancer, the natural history of this malignancy is poorly understood. The disease may be ‘chronic’ and long-standing, sometimes present for several years, before becoming clinically evident. The value of prophylactic gastrectomy, in this setting, remains to be defined. Clearly, as the authors indicate, the natural history of these early cancers found in the gastrectomy specimens will never be known, but logically, it seems that some would have become clinically evident. In a young patient faced with this potential diagnosis of gastric cancer, the decision to undergo a total gastrectomy would be extremely difficult, particularly if there are no symptoms. The short term morbidity and mortality of this procedure is significant, and the long term complications of total gastrectomy in the young patient cannot be minimized.

Nevertheless, this paper emphasizes the importance of molecular genetic methods in screening asymptomatic family members, particularly when endoscopic surveillance methods may not be necessarily optimal. The strategy for a positive genetic test if a feasible treatment modality is available, such as an ablative surgical procedure, may be ideal. Alternatively, individuals at high risk, but without a genetic mutation, may be spared unnecessary treatment if the specific mutation is not present. Much needs to be done, but clearly detection of molecular genetic markers should soon offer an important new dimension for future surveillance programs in the detection of occult gastrointestinal cancers.