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Familial Colorectal Cancer

A Genetics Treasure Trove for Medical Discovery

Boris Pasche, MD, PhD

CANCERS OF THE COLON AND RECTUM ARE AMONG the leading causes of cancer deaths worldwide, accounting for 1 million new cases in 2002 and representing 9.4% of the world total.¹ In 2006, more than 148 000 new cases were diagnosed in the United States, accounting for 10.4% of all cancers.² Despite the increased use of screening strategies to identify early stage, more curable colorectal cancers and the availability of novel therapeutic agents, more than one-third of patients with colorectal cancer will eventually die of uncontrolled metastatic spread within a few years of diagnosis. In 2006, 55 000 individuals died of colorectal cancer in the United States, which established colorectal cancer as the second leading cause of cancer deaths for men and the third for women.²

One of the hallmarks of colorectal cancer is its high degree of inheritability. Studies of twins indicate that approximately 35% of colorectal cancers are inherited.³ Furthermore, more than 11% of patients with colorectal cancer have at least 2 close relatives affected with the same disease.⁴ These studies suggest that a significant fraction of colorectal cancers are caused by cancer susceptibility genes. However, current knowledge of cancer genetics is primarily based on the identification of high-penetrance tumor susceptibility genes such as *APC*, *MLH1*, *MSH2*, *MSH6*, and *MYH*.⁵ Germline mutations in these genes only account for up to 6% of all colorectal cancers.⁵ Recent results from genome-wide association studies suggest that several different genomic regions may account for a significant proportion of the remainder of the familial risk.⁶⁻⁸

Whether a family history of colorectal cancer affects the outcome of patients diagnosed with the disease remains a topic of controversy. A study of 15 369 Japanese patients with a diagnosis of colorectal cancer showed that a family history of the disease was associated with a significantly better outcome.⁹ In contrast, in another study of 2236 patients with colorectal cancer from Utah, family history of the disease had no effect on survival.¹⁰

In this issue of *JAMA*, Chan and colleagues¹¹ examined prospectively the association between family history of

colorectal cancer and survival among patients with stage III disease who were enrolled in a large clinical trial of adjuvant therapy.¹² Between April 1999 and April 2001, a total of 1264 patients were randomly assigned to received either a standard combination of fluorouracil plus leucovorin or an experimental combination of irinotecan, fluorouracil, and leucovorin.¹² Eligible patients had completely resected stage III adenocarcinoma of the colon, no radiographic or surgical evidence of distant metastases, and no prior chemotherapy or radiotherapy. At an average of 5.6 years of follow-up, the addition of irinotecan had no effect on either disease-free survival or overall survival.¹² Family history of colorectal cancer was surveyed in 1087 patients, 195 of whom (17.9%) reported a family history in a first-degree relative.¹¹ Baseline characteristics of patients with or without a family history of colorectal cancer were essentially identical except for a higher percentage of clinical bowel obstruction in patients without a family history of colorectal cancer.¹¹

Chan et al¹¹ report that cancer recurrence or death from any cause was significantly lower among patients with a family history of colorectal cancer than among patients without such a history. Interestingly, the risk reduction associated with family history of colorectal cancer became stronger with an increasing number of affected first-degree relatives. The major strengths of these findings are the detailed information regarding tumor stage, treatment, and length of follow-up. Limitations include assessment of family history of colorectal cancer, which was self-reported and did not include information on kindred size. Because the study only included patients with colon cancer, it is also unknown whether family history of colorectal cancer similarly affects the outcome of patients with a diagnosis of rectal cancer.

Analyses of molecular predictors of survival after adjuvant chemotherapy for colon cancer have shown that loss of chromosome 18 correlates with a poor prognosis.^{13,14} Patients with tumors exhibiting microsatellite instability (MSI) have an overall better prognosis than patients with

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MSI-negative tumors. However, there is some evidence that MSI tumors are resistant to fluorouracil-based chemotherapy.¹⁵ Studies of other molecular markers such as expression of thymidylate synthase and *TP53* mutations have not yielded consistent results.^{16,17} In the study by Chan et al,¹¹ the authors examined the role of MSI as well as the expression of the *MLH1* and *MSH2* mismatch repair (MMR) proteins in 68% and 61% of the tumors, respectively. The prevalence of MSI in tumors was 24% and 15%, respectively, among patients with and without a family history of colorectal cancer. The prevalence of tumors deficient for MMR proteins was similarly higher among patients with (21%) than in those without (11%) a family history of colorectal cancer. However, the effect of family history on outcome was essentially unchanged after adjustment for MSI status and MMR protein deficiency. The next obvious step would be to determine whether loss of chromosome 18 is less common in the tumors from patients with a family history of colorectal cancer. However, both MSI and loss of chromosome 18 are somatically acquired genetic features and are not necessarily associated with an inherited predisposition for colorectal cancer.

If these intriguing findings are validated in other studies, family history may well become a new prognostic factor in colorectal cancer. Should this be the case, genome-wide association studies and tumor gene expression profiling studies will be warranted to identify germline and tumor-specific genetic features associated with a family history of colorectal cancer and favorable outcome following adjuvant chemotherapy.

Over the past 2 decades, some of the first major molecular genetics inroads were achieved through careful study of patients with a strong family history of colorectal cancer. This approach led to the discovery of the *APC* gene,^{18,19} followed by the discovery of the MMR mutation genes²⁰⁻²² and more recently the discovery of the *MYH* gene.²³ The study by Chan et al suggests that family history of colorectal cancer will lead to the identification of novel genetic features predictive of response to chemotherapy. Familial colorectal cancer may therefore confirm its role as a genetics treasure trove for medical discovery.

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