A First-Degree Relative with Colorectal Cancer: What Are We Missing?

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Because colorectal cancer (CRC) contributes significantly to the global burden of cancer (1), and familial clustering of CRC is also common (2), a relatively large proportion of the population will have a first-degree relative (parent, sibling, or offspring) with CRC. Although population-based data on the prevalence of having a family history of common cancers are still scant, it is estimated that ~5% of the U.S. population have at least one first-degree relative with CRC (3, 4). Some will have just one relative with CRC diagnosed at an older age, whereas others may have two or more relatives diagnosed before age 50 years. Those with one first-degree relative experience a 2-fold higher risk of CRC, those with two or more relatives, a 4-fold increased risk, independent of age at diagnosis (5).

What underlies this increased risk? The genetic mutations causing familial adenomatous polyposis coli and Lynch syndrome (also called hereditary nonpolyposis colorectal cancer), the two best-characterized inherited syndromes, contributing to perhaps 5% of all CRC, are known. In familial adenomatous polyposis, germ-line mutations are in the APC gene, which is part of the Wnt/β-catenin signaling pathway; hereditary nonpolyposis colorectal cancer is characterized by microsatellite instability caused by germ-line mutations in mismatch repair genes (e.g., MLH1 and MSH2). Other inherited syndromes have been described, such as MYH-associated polyposis (6) and familial colorectal cancer type X (7).

We can speculate that nonfamilial CRC may be the result of, as yet undefined, inherited susceptibility in conjunction with relevant environmental exposures. This susceptibility may be due to a combination of low-penetrance, high-frequency variations in the same genes that are involved in the inherited syndromes; in genes in other pathways; or in genes coding for enzymes involved in other kinds of DNA repair or in the metabolism of carcinogens, nutrients, etc. The most important environmental factors currently recognized to increase nonfamilial CRC risk include being overweight, processed and red meat consumption, alcohol intake, and smoking, whereas physical activity, use of nonsteroidal anti-inflammatory drugs and postmenopausal hormones, and a relatively high intake of foods rich in calcium, vitamin D, folate, and dietary fiber may decrease risk (8). Increased CRC risk among those with a first-degree relative with CRC may be explained by a recessive gene and/or shared environment during a specific time period. Some observational studies show joint effects between a family history in a first-degree relative and environmental factors in CRC risk. For instance, Le Marchand et al. (9), in a large multiethnic population-based case-control study of CRC in Hawaii, observed several interactions between lifestyle and first-degree (parents or siblings) family history of CRC. By using a summary measure of lifestyle, family history was not found to be associated with CRC risk among men who were only moderately exposed to environmental risk factors. In contrast, the odds ratio for men with a family history and at the higher risk tertile for all of the lifestyle variables was 11.7 (95% confidence interval, 5.8-23.9). After adjustment for other covariates, beef and alcohol intakes, especially, showed strong associations with a first-degree family history in increasing the risk of CRC among men. In contrast, among women, no family history-lifestyle interactions were observed (9). In the Nurses’ Health Study, a prospective cohort study among female nurses in which a family history of CRC in parents or siblings was assessed by questionnaire at several time intervals, Fuchs et al. (10) showed that, although folate intake had only a minimally inverse association among women without a first-degree relative with colorectal cancer, greater folate intake was associated with substantially reduced risk among those with a first-degree relative. Further, the influence of family history of CRC on colon cancer risk was markedly diminished among multivitamin users. Based on these findings, the authors suggested that individuals with a family history who use multivitamin supplements for more than 5 years may decrease their risk of colon cancer by almost 50%. This effect was not observed for those without a first-degree relative with CRC. In this same study, moderate to heavy alcohol consumption seemed to increase the risk associated with a first-degree family history in these women (10). The Iowa Women Health Study, however, showed that the association of most dietary components with colon cancer incidence was similar for individuals with and without a family history of CRC in first-degree relative, although intake of total calcium, vitamin E, dietary fiber, fruits, and vegetables was inversely associated with colon cancer only among those without a family history (11).

Several other studies have evaluated the joint effects of family history in a first-degree relative and environmental factors (e.g., refs. 12-16) and results do not seem to be consistent. Inconsistencies may be explained by obvious differences between studies, such as differences in design, geographic area, ethnic and racial characteristics, etc. Differences in the definition of “a positive family history in first-degree relative” and in methods of collecting the data may also exist.

Family history of CRC is usually assessed using self-administered questionnaires. The accuracy of the self-reported data may not be optimal; most crucial is the risk of underreporting. Glanz et al. (17) observed that more than one fourth of those known to have a sibling or parent with CRC reported having no first-degree relatives with CRC. Knowledge about CRC and stage-at-diagnosis seemed to be the strongest predictors of awareness of affected first-degree relatives. When the relative’s cancer was diagnosed at an early age, a sibling or child was statistically significantly less likely to be aware of it. In a case-control study comparing...
self-reported and database-linked family history of cancer data (18), no consistent difference was observed between cases and controls in the accuracy of self-reports. In this study, higher awareness of affected family members was observed among younger as compared with older subjects. The authors concluded that subjects in the case-control study setting are able to accurately report family histories of several common kinds of cancer and that they can do so without observable recall bias (18). In a relatively large case-control study, sensitivity of self-reported positive family history was estimated to be 0.87 among cases and 0.82 among controls, and specificity was estimated to be 0.97 in both groups (19). Although it may always be good to verify both negative and positive family history through review of medical records or linkage to cancer registries, records may also not be accurate, depending on the interviewer and method used to assess family history.

In most studies evaluating joint effects of family history and environmental factors, family history in a first-degree relative is commonly crudely summarized as a binary indicator (yes/no). The number and age distribution of affected and nonaffected relatives, as well as family structures, are not taken into account in either the design or the analysis of these studies. On the condition that information on family size, structure, and age of family members is collected, the approach recently suggested by Yasui et al. (20), using an empirical Bayes estimate of familial relative risk, may more clearly detect effect modification of an environmental risk factor by familial relative risk and vice versa.

We may certainly be missing something if we do not take family history into account as a potential effect modifier when evaluating environmental exposures and vice versa: when we are studying familial risk, potential joint effects with environmental exposures need to be accounted for. The latter may be important not only for nonfamilial CRC but also for the established inherited syndromes, such as hereditary nonpolyposis colorectal cancer. The fact that the clinical expression of hereditary nonpolyposis colorectal cancer tumors varies between regions of the world (21) and changes over time (22) strongly suggests that environmental factors are important in these syndromes (23). For instance, frequently occurring tumors within the hereditary nonpolyposis colorectal cancer syndrome in the developed countries changed similarly to sporadic tumors: stomach tumors seemed to be common in the early 1900s whereas colorectal tumors are now most prevalent. Sex differences in penetrance among carriers of the same mismatch repair mutation also suggest that environmental factors may play a role in hereditary nonpolyposis colorectal cancer—associated carcinogenesis (24). Similarly to a potential association between smoking and microsatellite instability in sporadic CRC (25), tobacco use seems to modulate the clinical manifestations of hereditary nonpolyposis colorectal cancer (26). To date, evidence for gene-environment interactions in the hereditary nonpolyposis colorectal cancer syndrome is limited, although the findings on smoking merit exploration of other lifestyle factors.

As pointed out by Young and Jass (27) in one of the recent issues of this Journal, besides these well-characterized familial syndromes, other pathways exist, including hypermethylation-associated CRC syndromes, in which the nature of the underlying genetic cause of familial cancers remains to be identified and the potential effect modification by environmental factors, such as the availability of methyl-group donors, may need to be considered.

In conclusion, more than identifying relatively rare families with extreme cancer risk, carefully assessing the variable “a first-degree relative with CRC” in the general population may identify a greater number of persons who are at moderately increased cancer risk. Whole genome screening may especially be interesting among this group to further identify combinations of low-penetrance genetic variants that, in combination with environmental factors, may influence the increased CRC risk. Of course, this variable is also highly pertinent in screening programs. High-risk individuals may be more accepting of advice on lifestyle changes, increasing the effectiveness of intervention programs. Finally, given the fact that the incidence of CRC is relatively high and of growing importance in medium-resource countries, putting additional emphasis on those with a first-degree relative with CRC may also prove to be important from a public health perspective, although it is always important to remember that the large majority of individuals who present with CRC have no affected first-degree relatives at all.

References

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