Editorial

Excess Risk of Colon Cancer Associated with a Polymorphism of the APC Gene?

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A new generation of diagnostics leading to presymptomatic detection of genetic predisposition has grown out of the human genome project. Genetic and positional cloning approaches have identified a number of genes in which inherited mutations predispose to various disorders and syndromes, including specific cancers. Strongly predisposing alleles, "genes," have been identified for colon cancer, breast cancer, and many others. Such alleles are relatively rare in the population. Strongly predisposing alleles for breast cancer are the most frequent, with mutations in the BRCA1 accounting for ~3% of diagnosed breast cancer (1).

Identification of these genes and mutant alleles has resulted in opportunities and challenges for practitioners. For example, alleles of the APC gene are responsible for the inherited syndrome familial polyposis, characterized by multiple adenomatous polyps of the colon at an early age. Diagnosis of the condition depended upon the appearance of multiple colonic polyps and led to prophylactic colectomy, usually in the twenties, to prevent colon cancer in the forties. Frequent colonoscopy of all at-risk family members, starting in the early teens and continuing into the twenties, was the preferred screening approach. Diagnosis of the condition was usually possible well before the risk period for cancer. Nevertheless, many individuals who had not inherited the family’s mutant allele also had to undergo years of colonoscopy before a negative diagnosis could be confirmed. Gene-based diagnosis now allows determination of which at-risk individuals in a familial adenomatous polyposis family have inherited the mutant allele, freeing those who have not inherited the family allele from the burden of frequent colonoscopy. More recently, attenuated APC alleles have been identified (2). In these families, at-risk carriers of the mutant allele are at high risk of colon cancer somewhat later in life but may show only one or a few colon polyps and are thus not so easily diagnosed by colonoscopy. This makes genetic diagnosis a much more important issue to resolve what is now a long-term screening burden for those who are not carriers.

In addition to strongly predisposing alleles, it is likely that weakly predisposing alleles of a number of genes may soon be found. Many of these may be much more frequent in the population than the strongly predisposing alleles and, indeed, may account for a significant fraction of the epidemiologists’ estimate of ~20% of cancer being due to familial factors. This next generation of genetic analysis promises even more challenges. Because the penetrance of this class of alleles is expected to be low, the increase in cancer incidence attributable will likewise be modest and will require carefully controlled, large-scale studies to confirm its existence and determine its magnitude.

Several recent articles (3–6) focus attention on the issue of risk of colon carcinoma associated with inheritance of what may be such a low-penetrance allele of the APC gene. The allele, I1307K, is thus far found only among Ashkenazi Jews. The common allele of this polymorphism carries a T at nucleotide 3920, whereas the infrequent I1307K allele carries an A at this position, resulting in conversion of an A3TA4 sequence to an A8 sequence and an isoleucine-to-lysine difference at amino acid 1307. The I1307K allele initially caught the attention of investigators because it was ascertained in an individual with multiple adenomas and a family history of colon cancer. An association study indicated an increased frequency of this allele among Ashkenazi Jews with colon cancer; although 6% of unaffected Baltimore Ashkenazim carried the I1307K allele, ~10% of Ashkenazi colon cancer subjects were carriers (3). The majority of this apparent excess was provided by a subset of subjects with a family history of colorectal cancer. Although the study was not controlled for known environmental risk factors, these observations may reflect an increased risk of colon cancer among carriers.

Additional support for the hypothesis that the I1307K allele may confer increased risk came from analysis of 23 colon tumors from carriers of the I1307K allele, showing that six (26%) had an A insertion into the A8 sequence (3). In the small region tested, codons 1296–1322, a total of 11 somatic mutations was detected, each of these occurring in the I1307K allele. Although this region is a hot spot for sporadic mutation in colon tumors, the A insertion at amino acid 1307 had not been reported previously. This was intriguing because it suggested that perhaps the I1307K allele had created a new hot spot for somatic mutation. If so, the overall frequency of somatic mutation at the I1307K allele might be higher than normal, conferring a predisposition for colorectal tumors on carriers.

Examination of colon tumors from a Toronto Ashkenazim population confirms the relatively frequent insertion of an A into the A8 sequence of the I1307K allele in 49 of 127 tumors (39%) among I1307K carriers (6). Furthermore, in screening codons 1303–1317 for mutation, a total of 53 had occurred in the I1307K allele, whereas only 5 were found in the other, 1307I, allele. Curiously, the canonical hot spot for this region seen in other large surveys, a 5-bp deletion from an AAAAG repeat starting at nucleotide 3921, showed a low frequency in this sample set. Approximately nine such mutations would have been expected (7), but only three were seen, and these were in the normal allele. Studies of somatic mutations in tumors, therefore, indicate that the I1307K allele shows an increased proportion of a specific mutation in exactly the region encoding the polymorphic variant. However, it must also be noted that there was an apparent decrease in the frequency of the common AAAAG deletion, suggesting caution in quantitative interpretations of potential increases in mutation frequency associated with the I1307K allele.

From a clinical screening perspective, the magnitude of the potential increase in relative risk of colon cancer associated with the I1307K allele is the central issue. Where a 5% increase in risk might not be considered significant, a five-fold increase would be highly significant and possibly warrant major screening programs. Because of the relatively small increased risk expected based on the initial study, large and carefully controlled study populations are needed for an accurate assessment. For example, the original study of 211 Ashkenazim with colorectal cancer (3) showed 22 carriers of the I1307K allele (10.1%). Thirteen would have been expected based on the population frequency of 6.1% for the I1307K allele. This is a statistically significant, but not highly significant, difference (P < 0.033). An important consequence is that this difference defines only broad

Received 7/1/98; accepted 8/10/98.

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confidence limits for the relative risk (RO = 1.7; 95% confidence interval, 1.01–2.87); the increase in risk could be almost three-fold—or it could be only 1%.

Furthermore, additional uncertainties in the magnitude of the relative risk are present due to the study design. Matched controls are especially important because the 11307K allele is tightly restricted to a specific ethnic group, the Ashkenazim; the allele was not found among 243 non-Jewish subjects or in a more recent study of an unselected Norwegian population (4). Because this population is made up of numerous subgroups with differing geographic backgrounds, it would not be surprising if there were large variations in the allele frequency among these subgroups of Ashkenazim. This is important here, because the control population consists of Baltimore Ashkenazim and, although most of the colon cancer cases were from Baltimore, those responsible for the apparent association were colon cancer families collected from several diverse geographic regions. In addition, known environmental variables such as diet and exercise parameters must also be assessed for both the test and control population, because these variables can significantly confound signals of the magnitude expected for predisposing alleles of reduced penetrance.

Two recent follow-up reports have appeared that are relevant and demonstrate the difficulties in providing a more accurate estimate. The first of these looked at the family histories of a number of Ashkenazim ascertainment as members of breast or breast-ovarian kindreds (8). The 11307K allele was detected in 12 of 264 (4.5%) members of these families, reflecting 11 of the 158 families. No evidence of colorectal cancer history was found in the families of these carriers, although there was evidence of colorectal cancer history for several noncarriers. However, these 11 families only reflected the cancer history of ~50 first-degree relatives (only one-half expected to carry the 11307K allele) whose ages ranged from their 30s to 80s. Even with a severalfold increase in relative risk, we would have expected only a few cases of colorectal cancer among these individuals. Seeing none, therefore, is not definitive, although it supports the suggestion that the 11307K allele does not strongly predispose to colorectal cancer and indicates that it does not usually create detectable cancer families.

A second report (5) is based on a similar approach, taking advantage of the cancer histories obtained from women participating in family studies of ovarian cancer. Here, cancer histories and 11307K carrier status were obtained for 190 Ashkenazi women with ovarian cancer. It should be noted that the 11307K allele was present in 7.9% of these women. None of these women had colon cancer, but among 1087 first-degree relatives, there were 23 cases of colon cancer. Three of the first-degree relatives of the 100 11307K carriers (3%) were affected with colon cancer, whereas 20 of 987 relatives of noncarriers (2.1%) were affected (relative risk, 1.48; 95% confidence interval, 0.45–4.88). Because of the broad confidence interval, however, these results again provide only marginal help in refining the relative risk associated with the 11307K allele.

What do these observations mean in terms of the utility of genetic screening for the 11307K allele in the Ashkenazi population? The answer may be understood in terms of how individual behavior might differ depending upon whether one carries an allele that may confer only a small or modest increment in colon cancer relative risk. Current standards of practice advocated for everyone propose sigmoidoscopy every few years starting at age 50. There is little significant evidence of a younger age of onset among carriers of the 11307K allele. Although the Baltimore study found a higher frequency of the 11307K allele among younger affecteds, this population was contaminated by the familial cases that may be age biased because of more intense screening in a cancer-family setting, for example. At this point, much larger scale clinical studies to explore the possibility and magnitude of an increase in relative risk among carriers of the 11307K allele and its natural history are very appropriate. Large-scale screening efforts would seem premature.

This is a time, however, of intense media interest in medical research, and reports often focus on the practical consequences of new discoveries. There is a pressing need for restraint on the part of journalists and other partisans of new, but not yet established, discoveries that may have bearing on the incidence, morbidity, and mortality of cancer. For example, the recent report on the angiogenesis drugs endostatin and angiostatin in the New York Times (NYTimes, May 3, 1998) carried dramatic predictions by noted scientists (later withdrawn) of a new cure for cancer within a short period of time. Similar reports in the media followed the publication of the initial Laken study, with one of the authors advocating in a New York Times article (NYTimes, August 26, 1997), “We are certainly recommending that anyone with a family history of colon cancer be tested. . . . None of these patients need to get seriously ill if they have the knowledge,” he said. “This is a totally preventable illness." This report stated that the discovery has the potential to save thousands of lives, because in the United States alone an estimated 360,000 people, or 6% of the six million Ashkenazi Jewish Americans, carry the mutation.

It is especially important to realize that we are now engaging the complexities of the second phase of the human genetic revolution, the identification and characterization of the genetic components of multifactorial disease. The other factors may also be genetic or they may be environmental—and will vary from case to case. In either event, it becomes increasingly important to carefully select and match large control populations to distinguish the possible signal due to a candidate allele from the "noise" due to a background of sporadic cancers. It is also clear that this is a time to proceed cautiously in our advocacy of new interventions based on early reports, as in the caveat from Francis Collins, “This is a new kind of medicine, and I worry about plunging into it too quickly. The public will not be amused if we overestimate the risk of this” (NYTimes, August 26, 1997).

Acknowledgments

I would like to thank Marty Slattery for her thoughtful comments and contribution to the statistical analysis of this article.

References

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