Early studies from tertiary referral centers in the United States and Europe showed that patients with long-standing and extensive inflammatory bowel disease (IBD) have an increased risk of colon cancer. It was subsequently appreciated that the degree of risk depended on the population being studied and on both genetic and environmental factors (eg diet, drugs and prior surgical treatment). Indeed, over the past decade or so, the effects of chronically administered medications, including 5-aminosalicylates (5-ASA), have been explored.

Recently, Bernstein et al (1) from Winnipeg examined the possible role of 5-ASA in chemoprophylaxis, using an IBD database linked to a drug database. A total of 25 patients with a diagnosis of colon cancer (14 with Crohn's disease and 11 with ulcerative colitis) diagnosed between 1997 and 2000 were matched with 348 IBD patients without colon cancer. Their survey examined the likelihood of exposure to 5-ASA, mean total days of 5-ASA use and daily prescribed dose. This result contrasted with an earlier case-control study from the United Kingdom that suggested a protective role for 5-ASA in ulcerative colitis (2). More specifically, any use of 5-ASA, use of 1.2 g or more of 5-ASA daily, or use of 2 g or more of sulphasalazine daily was associated with a lower cancer risk. Most patients with IBD, at least in Canada, are prescribed continuous 5-ASA with a view to reducing inflammation, improving symptoms and, ultimately, maintaining remission. Clearly, if there were an associated chemopreventive benefit related to colon carcinogenesis, this would be a significant bonus and might improve adherence, which, in a United States study, was found to be only 40% for a 5-ASA regimen (3). These recent studies have mostly been useful, however, in drawing further attention to previous studies of the effects of 5-ASA on colon cancer pathogenesis.

Indeed, this notion is not new. It has been recognized that some nonsteroidal anti-inflammatory drugs, such as acetylsalicylic acid, might inhibit colon carcinogenesis. Interestingly, over a decade ago, studies in animals showed that some medications for long-term maintenance of IBD might actually promote carcinogenesis. For example, in the dimethylhydrazine-induced rat colon cancer model, metronidazole, sulphasalazine and low-dose 5-ASA were shown to be co-carcinogenic, in that they increased the number or size of cancers (4). In contrast, the same study demonstrated that a higher dosage of mesalazine inhibited tumor growth, while olsalazine had no effect, suggesting that 5-ASA compounds might differ in their potential to cause malignancy. More recently, inhibitory effects of balsalazide on azoxymethane-induced rat colon cancer and on genetically based B6-Min/+ mouse colon cancer again emphasized the importance of both environmental and genetic factors (5).

Finally, potential mechanisms for the antineoplastic effects of 5-ASA have been explored; especially, induction of apoptosis, antioxidant effect and inhibition of cell proliferation (5-7). The Manitoba study was not able to draw a positive correlation between 5-ASA use and cancer prevention. This may reflect well-known inherent limitations of administrative databases that use coded diagnoses rather than data based on direct physician contact and follow-up. In addition, this study linked a drug database that recorded prescribed instead of actually consumed medication. Adherence with medical advice, as noted by the authors, may be an important confounding variable. Finally, as noted in the animal studies above, not all 5-ASA products, or their dosages, are necessarily identical in their antineoplastic effects. Moreover, recent studies on cancer complicating IBD indicated that most patients were treated with other medications, in addition to 5-ASA (8). Concomitant use of pharmaceuticals and biological agents with carcinogenic potential (eg metronidazole, immunosuppressants and infliximab) might make it more difficult to confirm a chemopreventive
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effect, and drug interactions are likely to be present. Not surprisingly, another Canadian study found that almost all Crohn's disease patients with intestinal cancer had used 5-ASA for years (8).

So, more studies are needed. But is there something from this epidemiological debate that can be relayed to patients now? Adherence with a treatment regimen is presumably important to all physicians that manage IBD. We can tell patients that a British study has suggested that taking their 5-ASA might help to prevent colon cancer, but a balanced discussion should also include the fact that a Canadian study was not able to confirm this chemopreventive benefit.

REFERENCES

The authors respond:
We appreciate Dr Freeman’s commentary on our paper. The role of 5-aminosalicylic acid (5-ASA) as a chemopreventative agent against colorectal cancer in ulcerative colitis (UC) has become a hot topic of late and, in fact, was the subject of a satellite symposium at the Canadian Digestive Diseases Week in 2002 (1). Denmark has been the only country to report that UC is not associated with an increased risk of colorectal cancer (2). Danish investigators have hypothesized that this is due to the practice of maintaining 5-ASA therapy even for patients in longstanding remission. It remains unclear if the low cancer risk is a result of some other genetic or environmental factor specific to Denmark, the tendency for Danish physicians to perform colectomy soon after the diagnosis of pancolitis, or the high rates of proctitis among cases of UC. Nonetheless, their low cancer rates have been remarkable.

The case-control study by Eaden et al (3) has been provocative. A reduced risk was evident with any use of 5-ASA, use of at least 1.2 g/day of 5-ASA, use of at least 2 g/day of sulfasalazine, use of systemic corticosteroids at some time, one to two visits with a doctor per year (compared with none), more than two doctor visits per year, or having one or two colonoscopies over the course of the disease (versus none). It is, therefore, possible that patients who are compliant take better care of themselves and may do other things to limit their cancer risk. Moreover, this study was flawed in that it selected colorectal cancer cases and noncancer cases from distinct populations.

Our study did not demonstrate any benefit of 5-ASA therapy in reducing the likelihood of diagnosing colorectal cancer. Our study examined only two to four years of potential 5-ASA use before the diagnosis of colorectal cancer, because the Manitoba Drug Program Information Network (a population-based prescription drug database) dates back only to 1995. Hence, it remains possible that very long-term 5-ASA use imparts some chemoprophylactic effect. This remains to be proved and is something we will explore again in several years when we have data reflecting lengthier follow-up of 5-ASA use.

I agree with Dr Freeman that it is reasonable to discuss with patients the possibility that 5-ASA use reduces the risk of colorectal cancer. However, we should also tell patients that there is not yet sufficient information to draw definitive conclusions. I agree with Dr Freeman that we need more data.

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REFERENCES