Comment

My worries are no longer behind me

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First they make you drink something that tastes like slime - or British beer. Then you spend the majority of your day in the smallest room in your house. Then they stick a tube into you in a place normally discussed only in scatological humor. And after it's over, you spend the rest of the day producing as much natural gas as Kazakhstan. I've had more fun at faculty meetings.

I had my first colonoscopy last month, at age 59. I should have had it nine years ago. In the US, as in Europe, about 4% of the population will eventually be diagnosed with colon cancer. In the United States alone, the disease accounts for 14% of all deaths from cancer, making it the second most common cause of cancer death. The average age of onset is 64. Like many other diseases, the majority of cases of colon cancer are sporadic, but a familial form, hereditary non-polyposis colorectal cancer (HNPCC), is responsible for approximately 2-7% of the 160,000 cases of colorectal cancer that are diagnosed annually in the US.

Colon cancer is a solid cancerous growth that begins on the inner surface of the colon or rectum. Virtually all colon cancer develops from mushroom-like growths (called adenomatous polyps) that form on the inside wall of the colon. These polyps vary in size, but the larger a polyp is, the greater the likelihood that it will become cancerous. For the most part, it takes years for a polyp to become cancerous, and in fact most polyps never turn malignant. About one in four people develop adenomatous polyps by the age of 50, even though most of them will never develop colon cancer.

Individuals diagnosed with inflammatory bowel disease (not irritable bowel disease) are at increased risk for colon cancer. In addition, other nongenetic factors include age (isn't it always?), above-average consumption of red meat, a high-fat or low-fiber diet, obesity, a sedentary lifestyle, and cigarette smoking. The Japanese, whose diet is relatively high in fiber and low in fat, have significantly lower incidence of colorectal cancer than do Westerners (although their incidence of stomach cancer is higher), but when Japanese men and women live in the West for extended periods of time, their colon cancer rates rise, indicating that diet plays a significant role.

HPNCC (also called Warthin-Lynch syndrome) is inherited in an autosomal dominant fashion and people with this disorder also have an increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, skin, and prostate. Women with this disorder also have a greatly increased risk of endometrial and ovarian cancer. Despite the term nonpolyposis, people with HNPCC occasionally do have colon polyps, which occur at an earlier age than in the general population and are more prone to become cancerous.

Thanks to the tools of genomics, the molecular genetics of colorectal carcinoma are among the best understood of the common human cancers. Typically, inactivation of the *APC* (adenomatous polyposis coli) gene initiates colorectal neoplasia leading to polyp formation. In patients with familial adenomatous polyposis, germline inactivation of *APC* appears to be followed by its somatic inactivation in colorectal epithelium, typically leading to large numbers of polyps. As these progress to malignancy, additional alterations accumulate in proto-oncogenes, including *ras*, and in tumor suppressor genes on chromosome 18q (*DCC*, *Smad2*, or *Smad4*) and 17p (*p53*). The alterations, each of which appears to provide a selective growth advantage, are found in various combinations in colon cancers. About 15% of colorectal cancers are characterized by microsatellite instability (MSI), also termed DNA replication errors or ubiquitous somatic mutations. Inactivation of one of a group of genes whose products participate in postreplicative repair of nucleotide mismatches leads to insertions and deletions of nucleotides in intrinsically unstable repeated sequences (microsatellites) throughout the genome because of defective repair of the slippage mistakes made by DNA polymerases. MSI-positive tumors thus accumulate numerous

frameshift mutations but also have a mutator phenotype that increases both base substitution mutations and frameshift mutations in expressed genes. In patients with HNPCC, germline mutation of *hMSH2* (human MutS homolog 2), *hMLH1* (human MutL homolog 1), *hPMS1* or *hPMS2* (human postmeiotic segregation 1 and 2), or the *GTBP* (guanine/thymidine mismatch-binding protein)/*hMSH6* gene, all of which code for DNA repair proteins, predispose to tumorigenesis. In addition to germline and somatic alterations in these genes in HNPCC, somatic inactivation of mismatch repair genes has been identified as a cause of MSI in sporadic tumors.

The tragedy of colorectal cancer is that it is one of the most preventable of fatal diseases. Symptoms of colon cancer include rectal bleeding, unexplained weight loss, constipation or diarrhea, abdominal pain, and a marked decrease in the diameter of your stools. However, colon cancer often fails to produce any symptoms until the cancer has grown very large or metastasized, so the early identification and subsequent removal of polyps through regular screening is the best method of colon cancer prevention. Surgical removal of polyps before they progress to malignancy or metastasize leads to a very favorable outcome. All adults over 50 years of age should be screened for colon cancer since regular screening has been shown to reduce colon cancer deaths. People who are at increased risk of developing colon cancer (for example, those with a familial history of the disease) should begin screening at a younger age and be screened more frequently. The presence of polyps that are known to progress frequently to malignancy also means that the affected individual should be screened more often than someone with no such growths.

I indicated what the procedure is like at the start of this column. It involves first taking large amounts of laxative to clean out the colon the day before the examination. During the colonoscopy itself, the physician uses a colonoscope (a long, flexible instrument about half an inch in diameter) to view the lining of the colon. The colonoscope is inserted through the rectum and advanced to the large intestine. During the colonoscopy, polyps can be identified and removed for biopsy. In many cases, colonoscopy allows accurate diagnosis and treatment without the need for a major operation. Although the procedure sounds incredibly unpleasant, it's done under intravenous sedation (typically with midazolam and fentanyl or Demerol), and the patient usually has no memory of the procedure at all - I certainly didn't. So the worst part is actually taking the laxative, although periods of flatulence for a day or so are a common aftereffect because of the introduction of air into the colon during the examination (don't ask me how I know this). Colonoscopy has a low (0.2%) risk of serious complications; the most serious is a tear or hole in the lining of the colon called a gastrointestinal perforation, which is life-threatening and requires immediate major surgery for repair. However, the rate of perforation is less than 1 in 2,000 colonoscopies. Still, you want someone to do this procedure who does a lot of them.

The relative merits of colonoscopy versus sigmoidoscopy (which only examines the final two feet of the 4-5 foot long colon) in colon cancer screening has been a source of ongoing debate. Recent articles in *The New England Journal of Medicine* have suggested that colonoscopy is superior to flexible sigmoidoscopy as a colon cancer screening method, but to get regular screening of some sort is more important than what screening tests are used, according to experts.

As I said, I should have had my first screening nine years ago. I finally got one because I have a new primary care physician, who specializes in preventive medicine, and who makes my old army drill sergeant seem like a shrinking violet. Why did I wait so long? It wasn't because I was reluctant to undergo an unpleasant experience (OK, maybe it was a little), or because I was afraid of what might be found. Quite the contrary: with no history of colorectal cancer on either side of my family and an absence of most other risk factors (I've never smoked, I exercise regularly), I figured there was no rush. Now that I know more about the prevalence of this disease and the very high percentage of sporadic cases, I realize that I was stupid to delay being screened. My colonoscopy detected several small polyps, which were removed during the procedure and biopsied. I was relieved to learn that they were not malignant, nor were they the kind that turn malignant, which means that I don't have to undergo another colonoscopy for ten years. I guarantee you that I will have that one on schedule.

So if you're 50 or older, don't wait as long as I did to have your first colonoscopy. Do it now. I have to be honest with you: you won't enjoy the experience. As I said, I've had more fun. But it's a load off my mind. Or wherever.