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Screening for Colon Cancer and Evaluation of Chemoprevention with Coxibs

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Abstract
Although colorectal cancer is one of the most preventable forms of visceral cancer, it remains the second leading cause of cancer death in the United States. Most colorectal cancers are believed to arise from adenomatous polyps, premalignant mucosal masses that account for up to two thirds of colorectal polyps. Early identification and removal of adenomas prevent the development of colorectal cancer. Colonoscopy has emerged as the dominant method for evaluating symptomatic patients with colorectal cancer and for surveillance of patients with previous colon polyps or cancer. In the United States, fecal occult blood testing and flexible sigmoidoscopy are the most commonly used screening methods in average-risk persons, although there is an emerging trend toward the use of colonoscopy. For both screening and surveillance, the type of screening test used and the intervals at which it is performed are based on risk stratification, which also serves as the basis for selecting potential candidates for chemoprevention. Because colonoscopy, like most screening procedures, has several disadvantages, including risk of perforation and bleeding and an inherent “miss rate,” alternative methods of prevention are being explored. A variety of agents with potential chemopreventive benefits have been identified, including cyclooxygenase (COX)-2-specific inhibitors (coxibs) even though these agents have not been approved for this use in the United States. COX-2 is overexpressed in colonic adenomas and cancers, and its inhibition has been shown to produce regression of polyps in familial adenomatous polyposis. Nonselective COX inhibition with nonsteroidal anti-inflammatory drugs (NSAIDs) has been consistently associated with reductions in the risk of mortality and the incidence of colorectal adenomas and cancers in case-control studies. Thus, selective COX-2 inhibition is a potential method of risk reduction in high-risk screening and surveillance groups, and large-scale trials of coxibs for the prevention of recurrence of adenomas after polypectomy are currently underway.


Key Words
Colorectal cancer, COX-2 inhibitors, chemoprevention, familial adenomatous polyposis

Introduction
Colorectal cancer is a major cause of morbidity and mortality, and is the second leading cause of cancer death in the United States.1 It is estimated that up to 6% of Americans over 50 years of age will develop colorectal cancer.
during their lifetime if screening and prevention measures are not employed.\textsuperscript{2,3} Routine screening for colorectal cancer is practiced by less than 20\% of Americans, despite the fact that screening recommendations are widely available and current screening methods are much more effective than for other forms of cancer, such as breast or prostate cancer.\textsuperscript{4–6}

Colorectal cancer is one of the most preventable forms of visceral cancer. In fact, detection and removal of adenomas during the early, curable stages of development prevent progression to cancer.\textsuperscript{3,7} The incidence of colorectal cancer increases with age and is approximately equally distributed between men and women.\textsuperscript{8} More than 90\% of cases occur in people older than age 50 years, and the mean age at diagnosis is 70 years. The incidence of and mortality associated with colorectal cancer have decreased in recent years. Factors that may contribute to this decrease include expanded use of colonoscopy and sigmoidoscopy as screening and diagnostic methods, early detection and removal of precancerous polyps, more accurate diagnosis, and more effective treatment options.\textsuperscript{8} However, it is expected that as the population ages, the actual number of cases of colorectal cancer will increase.

The purpose of this article is to review current recommendations for colorectal cancer screening and to evaluate the role of chemoprevention, with an emphasis on cyclooxygenase (COX)-2-specific inhibitors (coxibs).

**Screening Recommendations**

Screening is the search for polyps and early cancers in individuals who do not show signs or symptoms of colorectal cancer.\textsuperscript{8,9} Surveillance, on the other hand, refers to detection methods used in patients with a previous diagnosis of colorectal polyps or colorectal cancer, or in those with chronic inflammatory bowel disease.

Numerous colorectal cancer screening tools are available for average-risk patients aged 50 years or older.\textsuperscript{8–10} These range from relatively ineffective and inexpensive tests, such as fecal occult blood testing, to tests that are more expensive but also more effective, such as colonoscopy.

Colonoscopy is increasingly recognized as the most effective colon cancer screening strategy. This has contributed to a general trend in recent years toward the acceptance of colonoscopy as an initial screening test, even in average-risk persons.\textsuperscript{9} The results of several studies suggest that there is approximately a 75\% to 90\% reduction in colorectal cancer mortality with the use of colonoscopy and clearing polypectomy, which is substantially higher than the 60\% to 70\% reduction seen with sigmoidoscopy.\textsuperscript{7,11,12}

**Risk Stratification**

Individuals are stratified according to risk factors for colorectal cancer. Identification of a risk-factor category determines the choice of screening procedure and the intervals at which the test is repeated.

**Average-Risk Patients.** Average-risk patients account for approximately 75\% of all colorectal cancer cases in the United States, and include persons aged 50 years or older with no other identifiable risk factors.\textsuperscript{8}

The Agency for Healthcare Research and Quality (AHRQ), the American Cancer Society (ACS), and the American College of Gastroenterology (ACG) differ slightly in their screening recommendations for average-risk patients. The AHRQ recommends a menu of options for average-risk persons, including annual fecal occult blood testing and/or flexible sigmoidoscopy every five years.\textsuperscript{8} Alternative methods include total colon examination with double-contrast barium enema every 5 years or colonoscopy every 10 years.\textsuperscript{10} If a total colon examination is the initial screening method of choice, subsequent annual fecal occult blood tests are not necessary. Colonoscopy, rather than double-contrast barium enema, should be used as the follow-up to a positive fecal occult blood test\textsuperscript{13–15} or sigmoidoscopy.\textsuperscript{16–19} The ACG recommends flexible sigmoidoscopy every five years in conjunction with annual fecal occult blood testing as an alternative to colonoscopy only when resources are limited.\textsuperscript{9} Screening colonoscopy at 10-year intervals has several advantages over other currently available screening methods. First, it could improve patient compliance compared with strategies that must be performed at one- to five-year intervals. Second, colonoscopy allows single-session diagnosis and treatment, reducing patient inconvenience and cost, and reducing the chance of losing patients to follow-up procedures. Most importantly, colonoscopy is expected to have greater effectiveness than other strategies and
equal or better cost-effectiveness. The ACG does not recommend double-contrast barium enema as an initial screening method in average-risk patients because of inadequate polyp sensitivity. Rather, it is considered an acceptable alternative to sigmoidoscopy, in combination with annual fecal occult blood test, in average-risk persons. Another consideration is to alternate sigmoidoscopy with double-contrast barium enema at five-year intervals. Patients with limited life expectancy are not appropriate candidates for colorectal cancer screening, particularly if they have already had negative colonic imaging tests. As of July 1, 2001, Medicare will cover colonoscopy every 10 years as a colorectal cancer screening option in average-risk persons. Many private payers will likely continue not to cover screening colonoscopy. In these instances, it is important to remember that each of the currently available forms of screening has substantial effectiveness. It is more important for patients to have some screening performed than for them to be concerned about which type of screening is best.

**Moderate-Risk Patients.** Moderate-risk patients account for an estimated 15% to 20% of all colorectal cancer cases.8 Patients in this risk category have been diagnosed with colorectal adenomatous polyps, a personal history of resected colorectal cancer, or a positive family history of colorectal adenomas or cancer. A positive family history approximately doubles an individual’s risk for the development of colorectal cancer.9 In general, the risk of developing colorectal cancer depends on the closeness of the familial relationship, the age at onset, and the number of affected family members.9,20 Screening recommendations for individuals with a positive family history are outlined in Table 1. According to the ACS guidelines, patients should undergo total colon examination following colonoscopic removal of all adenomatous polyps.10 The intervals at which the exam is repeated are dependent on the size, multiplicity, and appearance of the adenoma(s). Double-contrast barium enema or flexible sigmoidoscopy followed by double-contrast barium enema are acceptable alternatives in patients who do not wish to undergo colonoscopy, or in situations in which colonoscopy is not available or feasible.

**High-Risk Patients.** High-risk patients account for only 5% to 10% of colorectal cancer cases and include those who have been diagnosed with familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer syndrome (HNPCC), or long-standing inflammatory bowel disease in the colon.8

Familial adenomatous polyposis accounts for approximately 1% of all colorectal cancer cases.21 Affected individuals usually begin developing adenomatous polyps in their teens to 20s, and have an almost 100% chance of developing colorectal cancer by their 40s. Familial adenomatous polyposis is typically characterized by the distribution of hundreds to thousands of polyps throughout the colon. The only currently available treatment is total colectomy. If the rectum remains intact, endoscopy must be performed every 6 months, and polyps, if detected, must be removed or destroyed. Children of individuals with familial adenomatous polyposis should begin sigmoidoscopic screening at 10 to 12 years of age, with repeat testing.

### Table 1

<table>
<thead>
<tr>
<th>American College of Gastroenterology Recommendations for Screening of Individuals with a Positive Family History of Colorectal Cancer* (reproduced from Ref. 9, with permission)</th>
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<tbody>
<tr>
<td><strong>History:</strong></td>
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<tr>
<td>· Single first-degree relative with colorectal cancer diagnosed at age ≥60 y</td>
</tr>
<tr>
<td><strong>Recommendation:</strong></td>
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<tr>
<td>· Begin screening at age 40 y</td>
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<tr>
<td>· Preferred screening: colonoscopy every 10 y</td>
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<tr>
<td><strong>History:</strong></td>
</tr>
<tr>
<td>· Single first-degree relative with colorectal cancer diagnosed at age &lt;60 y or multiple first-degree relatives with colorectal cancer</td>
</tr>
<tr>
<td><strong>Recommendation:</strong></td>
</tr>
<tr>
<td>· Begin screening at age 40 y or 10 y younger than age of diagnosis of the youngest affected relative, whichever is first</td>
</tr>
<tr>
<td>· Preferred screening: colonoscopy every 3–5 y</td>
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*Patients do not meet or approach the modified Amsterdam Criteria for hereditary nonpolyposis colorectal cancer syndrome.
annually thereafter. Once polyps are identified, the timing of colectomy should be considered and discussed with the patient. Other close relatives should undergo colonoscopy at initial screening, and sigmoidoscopy every one to two years thereafter until age 40, when screening can continue in a manner similar to that in individuals at average risk, assuming no polyps have been identified by this time.

The ACG recommends that relatives of individuals with hereditary nonpolyposis colorectal cancer syndrome who meet the modified Amsterdam Criteria should undergo colonoscopy beginning at 20 to 25 years of age, with repeat tests every two years until age 40, then annually thereafter. The modified Amsterdam Criteria are: three relatives with HNPCC-related cancer (two must be first-degree relatives of the third), cancer spanning two generations, and one case diagnosed in a relative younger than 50 years of age. HNPCC-related cancers include colorectal, endometrial, small bowel, renal pelvis, and ureteral.

The presence of extensive ulcerative colitis or Crohn’s disease affecting the colorectum increases the individual’s risk for developing colorectal cancer beginning 8 years after the onset of colorectal symptoms. Cancers in these patients generally arise from areas of dysplasia in flat mucosa rather than from polyps. Individuals with long-standing inflammatory bowel disease are candidates for surveillance with colonoscopy. Effective surveillance requires a systematic biopsy protocol, typically 4-quadrant biopsies every 10 cm. Colonoscopic surveillance should be repeated every one to three years from 8 to 20 years after the onset of colorectal symptoms, and annually thereafter.

**Chemoprevention**

Colonoscopy is currently the most powerful visceral cancer prevention technique in clinical medicine, however, it has several shortcomings. It is not well accepted by a significant fraction of the population. Further, as with all other screening methods, colonoscopy has an inherent “miss rate” for polyploid lesions. Moreover, occasional patients have very small, flat or depressed lesions that often contain high-grade dysplasia or invasive cancer and that are not readily detected with current colonoscopic techniques. Also, there are some sporadic cancers (e.g., HNPCC) that pass through a separate genetic pathway (i.e., the microsatellite instability pathway), whereby adenomas develop and transform into cancer within one to three years. Screening colonoscopy performed every 10 years would, in many cases, not prevent these cancers. Additional disadvantages to the use of colonoscopy include a low risk of perforation. However, in more than 5000 initial average-risk colonoscopies reported, no perforations have occurred. Because of the invasive nature of colonoscopy, as well as its risks and high up-front costs, alternative approaches to colorectal cancer prevention are under investigation. One of these is chemoprevention, or administration of cancer-prevention agents. Although a large number of agents have been studied (e.g., folate, calcium, selenium, and hormone-replacement therapy), aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have had the greatest therapeutic benefits. This review will focus on the potential use of NSAIDs, particularly COX-2-specific inhibitors, for colorectal cancer prevention.

**NSAID Use and Risk of Colorectal Cancer**

Aspirin and other nonselective NSAIDs have been examined for their role in colorectal cancer prevention. Although the exact mechanism of action of these agents is unknown, it has been hypothesized that they act through both COX-dependent and COX-independent mechanisms (Figure 1). COX-2 expression is low or undetectable in normal gastrointestinal mucosa, but is found in approximately half of adenomas and 90% of colorectal cancers. In vitro and in vivo evidence suggests that inhibition of COX-2 can inhibit tumor angiogenesis and promote apoptosis, or programmed cell death, in colorectal cancer. Long-term aspirin use is associated with a 40% to 50% reduction in both the incidence of and mortality associated with colorectal cancer. However, the optimal dose and duration of therapy have not been determined. Comparable risk reduction also has been demonstrated in studies with nonselective NSAIDs, such as ibuprofen and sulindac. Several of these studies have shown that the decreased risk for development of colorectal cancer is linear, and time- and/or dose-dependent. For example, in the study by Peleg and colleagues, there was a significant ($P < 0.01$) decrease in risk of col-
orectal adenoma and, to a greater extent, adenocarcinoma following two years of continuous NSAID use compared with nonuse. The risk reduction was more pronounced in patients who received higher cumulative doses of NSAIDs. In contrast, Smalley and associates demonstrated that low doses of NSAIDs were as effective as high doses for prevention of colon cancer, and no NSAID was more effective than another. Factors associated with increased risk reduction include use of NSAID for at least 12 to 48 months and current NSAID use (i.e., use within the past 12 months). Protection was reduced following 12 months of no NSAID use.

**Role of the Coxibs**

Nonselective NSAIDs have been shown to reduce the number and size of colonic adenomas in animal models, as well as the incidence of and mortality associated with colorectal cancer in humans. It is uncertain whether COX-1 plays a role in cancer development. However, inhibition of this enzyme is responsible for the adverse gastrointestinal effects associated with the use of nonselective NSAIDs. Therefore, researchers have investigated the efficacy of coxibs in the chemoprevention of colorectal cancer, even though these agents have not been approved for use in this condition. As noted earlier, the mechanism of the coxibs in cancer prevention is not fully understood, but likely involves an increase in apoptosis as well as the regulation of angiogenesis (Figure 1).

**Animal Models of Familial Adenomatous Polyposis**

The adenomatous polyposis coli (APC) gene is a tumor-suppressor gene that is reportedly inactive or missing in all patients with familial adenomatous polyposis and in most patients with colorectal cancer. In a murine APC mutation model in which multiple intestinal neoplasia (Min) mice develop intestinal polyps in a manner similar to familial adenomatous polyposis in humans, rofecoxib produced a 55% reduction in the number of intestinal polyps compared with controls ($P < 0.05$). In a similar murine model, rofecoxib produced a dose-dependent reduction in both number and size of intestinal polyps. When administered to mice at a dose that achieves steady-state plasma concentrations comparable to a 25-mg daily dose in humans, rofecoxib produced a 55% reduction
in the number of intestinal polyps compared with controls (Figure 2). Likewise, there was an 80% reduction in the number of polyps larger than 1 mm in diameter with this same dose. A similar study showed a significant (40%–49%) reduction in the incidence and multiplicity of aberrant crypt foci, possible precursors of adenomas and cancer, in the colons of rats treated with celecoxib. The results of these animal studies suggest that coxibs might be useful in the chemoprevention of colon cancer in humans.

**Familial Adenomatous Polyposis**

Because COX-2 is overexpressed in colonic adenomas (Figure 3), and individuals affected with familial adenomatous polyposis have an almost 100% chance of developing colorectal cancer, researchers evaluated the chemopreventive effect of NSAIDs and coxibs in this patient population.

The NSAID sulindac has been shown to reduce the number and size of colorectal polyps in patients with familial adenomatous polyposis, while reportedly causing an increase in the rate of apoptosis in colonic epithelium. Steinbach and colleagues evaluated the efficacy of celecoxib in patients with familial adenomatous polyposis in a randomized, double-blind, placebo-controlled study. Thirty-two patients received 100 mg of celecoxib twice daily (BID), 30 patients received 400 mg of celecoxib BID, and 15 patients received placebo BID. After 6 months of treatment, the 400-mg BID dose of celecoxib was associated with a significant reduction in both mean number of colorectal polyps (28%) and polyp burden (30.7%), as measured by the sum of the polyp diameters ($P = 0.003$ and $P = 0.001$).
vs. placebo, respectively, see Figure 4). Compared with placebo, the celecoxib 100-mg BID dose did not produce statistically significant reductions in polyp number (4.5% vs. 11.9%; \( P = 0.33 \)) or polyp burden (4.9% vs. 14.6%; \( P = 0.09 \)).

The effects of sulindac on polyp size and number in patients with familial adenomatous polyposis are reversible following discontinuation.\(^{64,65} \) Therefore, administration of an NSAID or coxib should not be discontinued in these patients if the end goal is chemoprevention of adenomas or cancer.

Colectomy remains the standard treatment for familial adenomatous polyposis. Coxibs are appropriate adjunctive therapy to endoscopic surveillance in the patient with familial adenomatous polyposis whose rectum remains intact following abdominal colectomy or in whom polyps have developed but colectomy is being postponed. Very young age or a strong family history of desmoids is a common reason for postponing colectomy. Celecoxib is indicated for use in reducing the number of adenomatous colorectal polyps in patients with familial adenomatous polyposis, as an adjunct to usual care.

**Conclusions**

Colorectal cancer is a major cause of morbidity and mortality in the United States. The centerpiece of efforts to prevent colorectal cancer is effective screening with removal of colonic polyps. However, currently available screening methods are imperfect. Chemoprevention with coxibs or nonselective NSAIDs has an established adjunctive role in a patient with familial adenomatous polyposis whose rectum remains intact following abdominal colectomy or in whom colectomy is being postponed. COX-2 overexpression also is a potential target for chemoprevention in sporadic adenomas, and clinical trials in this population are currently under way. Consideration also should be given to the combination of multiple chemopreventive agents that are active at different stages of the adenoma-carcinoma pathway, an approach that may lead to additive or synergistic activity with minimal adverse events. As researchers continue to discover the mechanisms involved with colorectal carcinogenesis, new drugs that interact with the molecular targets may be developed, leading to improved chemopreventive strategies.

Figure 4. Effects of the cyclooxygenase-2 (COX-2)-specific inhibitor, celecoxib, on colorectal polyps in patients with familial adenomatous polyposis.\(^7^2 \) BID = twice daily.
References


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