CRC development is a multi-step process that spans 10 to 15 years, thereby providing an opportunity for early detection and even prevention. The poor survival rate of advanced CRC has prompted the emphasis on prevention of this disease. CRC screening and removal of adenomas is an effective intervention, and is the cornerstone of prevention. However, screening efforts have had limited impact due to less than optimal compliance with guidelines. Chemoprevention involves the long-term use of a variety of oral agents that can delay, prevent or even reverse the development of adenomas in the large bowel, thus interfering with the multi-step progression from adenoma to carcinoma. This effect is of particular importance to individuals with a hereditary predisposition to colorectal neoplasia and to those who are especially susceptible to the environmental causes of CRC. NSAIDs have drawn the most attention as chemoprevention agents. Sulindac and celecoxib are effective in promoting poly regression in high risk individuals with Familial Adenomatous Polyposis (FAP). In the more common sporadic setting the APROVe (refecoxib), APC and PreSAP (Celecoxib) trials have shown a significant reduction in adenoma recurrence but important concerns exist regarding cardiovascular toxicity associated with selective COX-2 inhibitors. These landmark studies are very important, as they provide a proof of concept that we can prevent high risk adenomas that can lead to CRC development. The ideal chemopreventive agent remains to be discovered with great emphasis on need not to harm. Possibly, combinations of agents will maximize effectiveness while limiting drug toxicity. Finally, personalized approaches will include the ability to predict risk and toxicity.

Colorectal cancer (CRC) is the second leading cause of cancer-related death in men (after lung cancer) and third in women (behind lung and breast cancers) in the United States. In recent years, the incidence and mortality of CRC have decreased slightly. It is not clear whether this decrease is due to lifestyle modifications, improvement in therapy, and/or a consequence of wider implementation of screening. Prevention of CRC is especially important because it is such a widely prevalent disease associated with considerable morbidity and mortality. Furthermore, CRC has a natural history of evolution from normal mucosa to adenoma to overt cancer that spans on average 10–20 years, thereby providing a window of opportunity for effective intervention and prevention. Chemoprevention interferes with the process of carcinogenesis by targeting key molecular pathways and is a recent approach to prevention of colorectal neoplasia. CRC screening is the cornerstone of prevention; however, it has limited efficacy due to low compliance with screening guidelines. Prevention of CRC by colonoscopic polypectomy is an effective intervention but is not yet available widely even in developed countries. Early detection of CRC is not an adequate enough objective and as the emphasis of screening shifts toward precancerous adenomas, these lesions become important targets for primary prevention methods. Chemoprevention involves the long-term use of a variety of oral agents that can delay, prevent, or even reverse the development of adenomas in the large bowel and interferes with the multistep progression from adenoma to carcinoma. Chemoprevention is of particular importance to individuals with a hereditary predisposition to colorectal neoplasia and to those who are especially susceptible to the environmental triggers of CRC. The scientific basis of chemoprevention has evolved over the past 2 decades and represents a potential approach to reducing the incidence of and mortality from cancer.

The ideal chemopreventive agent should fulfill the following criteria: (1) the drug must be effective; (2) it should have a convenient dosing schedule, ideally not more than once a day; (3) it should have minimal side effects or an acceptable safety profile in high-risk popu-
lations; (4) it should be easily administered; and (5) it should be inexpensive.

Whenever we administer any agent to a patient, and in particular when we are treating healthy individuals, we must assess carefully the risk/benefit ratio (Figure 1). We wish to emphasize that the profile of safety and efficacy for any given drug varies significantly and depends on the severity of the disease and the tolerance of the individuals receiving the specific drug.

Recent preclinical and clinical trials have provided data on the potential benefit of a number of micronutrients, minerals, and drugs in the chemoprevention setting. Some agents have been found to reduce the risk of adenoma/cancer growth or recurrence. At the same time, other studies have failed to show this protective effect, and some of these agents may be associated with some toxicity.7

Aspirin, Nonsteroidal Anti-Inflammatory Drugs, and Cyclooxygenase-2 Inhibitors

Cyclooxygenase (COX) is probably the most common therapeutic drug target in human history. Inhibitors of this enzyme have been used extensively and widely. Research in this area has been dominated by investigations of the 2 COX enzymes, COX-1 and COX-2, and the therapeutic market has been revolutionized by the development of drugs targeted selectively against COX-2. The hypothesis that nonsteroidal anti-inflammatory drugs (NSAIDs) might inhibit the occurrence or growth of CRC arose in the mid-1970s. Bennett and Del Tacca8 and Jaffe9 reported that the concentration of prostaglandin E2 was higher in CRC than in the surrounding normal mucosa.

Supportive evidence for the role of aspirin and NSAIDs in the prevention of CRC has been derived from more than 200 well-conducted, randomized, placebo-controlled animal studies, in which the administration of various NSAIDs consistently resulted in fewer tumors per animal and fewer animals with tumors, thereby clearly showing a preventive effect on carcinogen-induced colorectal tumorigenesis in rodents.10,11 These findings were also supported by studies in genetically manipulated CRC rodent models12 that reported a reduction in number and size of colorectal neoplasms in animals treated with NSAIDs. Intervention studies in patients with familial adenomatous polyposis have established that NSAIDs exert their effects on human colonic adenoma formation.13 Epidemiologic observations and population-based studies also showed that long-term use of aspirin and other NSAIDs reduced the risk of CRC (see reviews9 –16). The protective effect of NSAIDs has been underscored in 57 of 59 epidemiologic studies, which showed prevention of adenoma recurrence, inhibition of CRC incidence, and even a lower mortality rate in both women and men (Figure 2). This protective effect depends on the dose and type of the drug but more importantly is directly related to the duration of exposure.15,17–20

Aspirin and CRC Chemoprevention

Aspirin was first synthesized more than a century ago, and its benefits are still being discovered. They are indeed remarkable, ranging from relief of pain to potential prevention of cancer. Aspirin has been investigated extensively in the chemoprevention of colorectal adenomas and cancer, based in part on its inhibition of COX-1 and COX-2 enzymes, both of which are important mediators of prostaglandin production. To understand the dilemma of whether or not to use aspirin as a CRC chemopreventive agent, we need to assess the effectiveness of aspirin on prevention or regression of colorectal adenomas and cancer and then estimate whether the expected health benefits of the use of aspirin exceed its expected negative health consequences.

The first population-based case-control study was reported by Kune et al.19 They showed a relative risk (RR)
of 0.53% for CRC among regular aspirin users compared with nonaspirin consumers. The Nurses’ Health Study was initiated in 1976 and included more than 120,000 nurses aged 30–55 years. From 1984 to 1992, 331 new cases of CRC, during 551,651 person-years of follow-up, were identified. Women who consistently took 2 or more aspirin tablets per week had no appreciable reduction in the risk of CRC as compared with nonusers (RR, 0.84; 95% confidence interval [CI], 0.55–1.28). There was a statistically significant reduction after 20 years of consistent use of aspirin (RR, 0.56; 95% CI, 0.36–0.90). The maximal reduction in risk was observed among women who took 4–6 tablets per week; higher doses had a similar apparent benefit.20

In the observational Health Professionals Study of 50,000 individuals, regular aspirin use of more than twice a week was associated with a 32% (95% CI, 0.52–0.92) reduction in mortality from CRC.21 Chan et al22 evaluated CRC risk in a follow-up study (Health Professionals Follow-Up Study) over 18 years with 975 documented CRC cases. It was confirmed that prolonged aspirin use substantially reduces the risk of developing CRC. The effect was dose related, increasing from a RR of 0.94 (95% CI, 0.75–1.18) for men who used 0.5–1.5 standard aspirin (325 mg) per week compared with those who denied any aspirin use to a RR of 0.30 (95% CI, 0.11–0.81) for those using >14 aspirin per week as compared with nonusers. Significant reduction in risk of CRC required at least 6–10 years of aspirin use. The dosage of aspirin required for CRC chemoprevention in the Health Professionals Follow-Up Study was much higher than the lowest aspirin dose (81 mg) and treatment period (3 years) required for reducing adenoma recurrence. At the same time, this dosage (325 mg) causes significant rates of gastrointestinal and other toxicities.22

Recently, Jacobs et al23 examined the associations between long-term daily use of aspirin (325 mg/day) and overall incidence of cancer among 69,810 men and 76,303 women participating in the Cancer Prevention Study II Nutrition Cohort. Aspirin use was reported at enrollment and updated every 2 years. Daily use of aspirin for more than 5 years was associated with lower incidence of CRC (RR, 0.68; 95% CI, 0.52–0.90). On the other hand, 2 large trials of aspirin in primary prevention showed no effect on the occurrence of CRC. The Women’s Health Study randomized healthy women to low-dose aspirin versus placebo. An average of 10 years of follow-up failed to show a primary preventive effect of aspirin (RR, 0.97; 95% CI, 0.77–1.24).24

The Physicians’ Health Study was designed primarily to evaluate the effects of aspirin (325 mg every other day) on the risk of coronary artery disease and cancer in 22,071 male physicians in the United States.25 After 5 years of aspirin therapy, there was no change in the incidence of CRC or adenomatous polyps (nonsignificant odds ratio of 1.15 [95% CI, 0.80–1.65] for CRC and 0.86 [95% CI, 0.68–1.10] for adenomas) between the treatment and the placebo groups.26 Randomized trials of short-term duration (up to 4–5 years) have provided compelling evidence of an inverse relationship between aspirin and colorectal neoplasia. Nonetheless, prospective data on long-term risk of CRC according to dose or duration of therapy remain limited. Similarly, the British Doctors Aspirin Trial26 and the UK-TIA Aspirin Trial27 failed to show a protective effect of aspirin. However, Flossmann and Rothwell17 studied the long-term effect of aspirin in these 2 trials with reliable posttrial follow-up for more than 20 years. They also performed a systematic review of all relevant observational studies and concluded that the use of >300 mg/day of aspirin for at least 5 years in the randomized controlled trial was effective in primary prevention of CRC, with a latency period of about 10 years. These studies were, however, unable to circumvent confounders, such as intermittent and variable dosing, use of other NSAIDs, and risk-modifying drugs.

Four randomized controlled trials in patients with previous adenoma or CRC have shown significant efficacy in preventing polyp recurrence at daily dosages of 81–325 mg/day of aspirin. Aspirin (325 mg/day) or placebo was prescribed to more than 600 patients with a recent history of CRC. A statistically significant reduction in the incidence of colorectal adenomas was found in the treatment arm during a planned interim analysis (17% vs 27%).28 Baron et al29 observed that a statistically significant reduction in the recurrence of adenomas was associated with use of 81- and 325-mg dosages of aspirin (17% and 4%, respectively). It was statistically significant only for the lower dosage. Notably, protection against advanced adenomas (>1 cm, high-grade dysplasia, and villous histology) was more pronounced than the effect on risk of recurrence of any adenoma (eg, reduction rates of 41% and 17%, respectively). Benamouzig et al30 randomized 272 patients with a history of adenoma to receive lysine acetylsalicylate (a form of aspirin) 300 mg, 150 mg, or placebo once a day. Both dosages were effective in reducing polyp recurrence at 1 year in 27% (95% CI, 0.52–1.04). A lesser effect was seen at 4 years, and the lower (160 mg/d) dose was more effective.31 In the UK-CAP trial, 945 patients, within 6 months of polypectomy, were randomized to receive aspirin (300 mg daily) and folic acid (0.5 mg daily). Of those randomized, more than 90% underwent a surveillance colonoscopy 3 years later. Patients receiving aspirin had a 21% reduction in the recurrence of adenoma. The likelihood of recurrence of advanced adenoma was substantially higher (37%).32

The available data would suggest that for chemoprevention, aspirin would need to be ingested in doses greater than used for cardiovascular prevention and for a duration of more than 10 years.17,20 Therefore, the potential benefit of aspirin needs to be carefully weighed against its potential adverse effects. Additional information is required to clarify the optimal dose, starting age,
and duration of aspirin use. Aspirin, however, also decreases fatal cardiovascular events in people with known vascular disease by one sixth and vascular death by 25%.

Perhaps it may also prevent dementia, so it should be carefully evaluated in those likely to receive the greatest benefit. Unfortunately, those at the highest risk for gastrointestinal complications and hemorrhagic stroke may be those most likely to benefit from the chemopreventive effects.

If no risk was associated with ingestion of aspirin, then even with uncertainty about the reduction in the incidence and mortality of colorectal adenomas or CRC, the use of aspirin is preferred to its avoidance. The estimated rates of serious complications in patients taking aspirin are 1.4 per 10,000 person-years in patients younger than 65 years of age and 28–40 per 10,000 person-years in older patients with cerebrovascular disease.

Patients with an annual risk for coronary heart disease of ≥1.5% should consider taking aspirin to prevent cardiovascular mortality. These patients may also benefit from a decrease in the incidence of colorectal adenomas and CRC mortality. It is also confirmed that patients with a low risk of coronary heart disease (less than 0.7% per year) should not take aspirin to prevent cardiovascular events. Aspirin consumption in patients with a moderate annual risk of coronary heart disease (0.7%–1.4%) is optional and depends on patient preferences and attitudes toward risk.

Aspirin should not be prescribed in subjects at low risk for both ischemic heart disease and CRC. Subjects with no family history of CRC who have had normal findings on colonoscopy can be regarded as at low risk for CRC.

The use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with gastrointestinal and renal toxicity caused by the inhibition of COX-1. In 1997, 107,000 hospitalizations and 16,500 deaths in the United States alone were attributed to NSAIDs and aspirin consumption.

When aspirin is given with a proton pump inhibitor, however, especially after Helicobacter pylori eradication, the risk of bleeding complications following aspirin or NSAID use is decreased dramatically (by 50%–90%).

Although chemoprevention of CRC is already possible, drugs that have more acceptable side effect profiles than the currently available aspirin and NSAIDs are required.

**COXs and CRC Chemoprevention**

COX-2 is an inducible enzyme that is overexpressed in sites of inflammation and neoplasia. Genetic evidence supports the role of COX-2 in the development of intestinal neoplasia.

Furthermore, COX-2 is overexpressed in 40%–50% of adenomas and in 85% of CRC.

The benefits of the chemopreventive effects of NSAIDs without the deleterious side effects could potentially be achieved with selective COX-2 inhibition. In patients with familial adenomatous polyposis, the adenoma burden has been shown to be reduced by 28% in patients treated with 400 mg of celecoxib twice daily for 6 months as compared with a reduction of 4.5% in the placebo group ($P = .003$). In patients with sporadic adenomas, 3 prospective, randomized, placebo-controlled, international, multicenter trials of secondary prevention of CRC were launched in 1999 and 2000. Each study recruited between 1500 and 2500 patients from more than 100 sites. The primary end point was the number of patients with adenomatous polyps.

The Adenomatous Polyprop Prevention on Vioxx (APPROVe) trial recruited 2586 patients with a history of colorectal adenomas. They received 25 mg of rofecoxib (Vioxx; Merck, Whitehouse Station, NJ) daily ($n = 1257$) or placebo ($n = 1299$) for 3 years.

A 25% reduction in adenoma recurrence was found in the treatment group. The Adenoma Prevention with Celecoxib (APC) trial included 2026 patients, with randomization to either placebo or celecoxib (200 or 400 mg twice daily). The patients had an adenomatous polyp removed before enrollment or a prior history of adenoma and were followed up for a mean of 33 months while taking the study drug. Follow-up at 3 years found a significant reduction in polyph recurrence ($P < .0001$). The Prevention of Sporadic Adenomatous Polyps (PreSAP) trial was conducted in parallel to the APC trial for the same indication.

A total of 1561 patients with an adenomatous polyp removed up to 3 months before enrollment were randomized (3:2) to receive either 400 mg celecoxib or placebo daily. The adenoma recurrence rate was 33% in the celecoxib group versus 49.3% in the placebo group ($P < .0001$). Of note, in all these studies a greater effect was observed in advanced adenomas.

Although all 3 trials clearly showed that selective COX-2 inhibitors reduced polyph recurrence, in the APPROVe and the APC studies this efficacy was associated with an increased risk of cardiovascular events (mainly myocardial infarction, stroke, and heart failure). In September 2004, Merck announced the early termination of its study. Rofecoxib was subsequently withdrawn from the market due to increased cardiovascular toxicity in patients receiving the drug for more than 18 months.

A total of 46 patients in the rofecoxib group had a confirmed thrombotic event compared with 26 patients in the placebo group (RR, 1.92).

In December 2004, the National Cancer Institute suspended the APC trial. The study was stopped because analysis by an independent cardiovascular adjudication committee, a subcommittee of its Data Safety and Monitoring Board, showed a significant dose-response excess of major cardiovascular events of 2.5 (95% CI, 1.0–6.4) and 3.5 (95% CI, 1.4–8.5) for the celecoxib 200 and 400 mg twice daily groups compared with the placebo group.

At the same time, in the PreSAP trial, the RR of the celecoxib 400 mg once daily group compared with the placebo group was nonsignificant at 1.3 (95% CI, 0.6–2.6).

Short-term use of celecoxib appears to be safe, while long-term use necessary for achieving the goals of chemoprevention confers significant hazards. Determining specific subpopulations of individuals who may benefit
from these drugs, as compared with populations who are at increased risk for side effects, remains an important but yet unrealized objective. These studies confirm an association between the COX-2 enzyme and development of colonic adenomas. They provide a proof of concept for an important step toward developing effective CRC chemoprevention. These trials also confirm that selective COX-2 inhibitors must be used cautiously, especially for patients with a history of cardiovascular disease despite relative safety in terms of gastrointestinal toxicity.44,45

An analysis of data from the APC trial shows that approximately 27 fewer patients per 1000 per year developed advanced colorectal adenomas when using celecoxib twice daily, at a cost of approximately 5 additional patients per 1000 per year who experienced a serious cardiovascular adverse event.15 Comparable figures for the PreSAP trial, with a celecoxib dosage of 400 mg once daily, were 15 fewer patients per 1000 per year who developed advanced adenomas at a cost of 2 additional patients per 1000 per year who developed a serious cardiovascular adverse event.15 The currently available safety and efficacy data extend over only 3 years of continuous treatment with celecoxib. The data show that, with the exception of a few individuals, most patients tolerated 3 years of continuous celecoxib use without drug-related toxicity. However, because of the severity of the drug-related cardiovascular events observed in the APC trial, celecoxib cannot be recommended for routine prevention of sporadic colorectal adenomas or CRC. This is particularly true for patients who have access to colonoscopy with polypectomy, which is a relatively safe and highly effective method of CRC prevention. Data from an additional 2 years of follow-up from both the APC and PreSAP trials are anticipated in 2008.

In both the APC and PreSAP trials, celecoxib was particularly effective in preventing high-risk advanced adenomas, which were relatively common, in the placebo group (17.2% and 10.4%, respectively) despite optimal colonoscopic surveillance. In addition, the APC trial found that patients who developed adenomas despite taking celecoxib had fewer and smaller polyps than those that occurred in patients receiving placebo. This point is important because small tubular adenomas are unlikely to progress to cancer. It is reassuring that celecoxib did not simply reduce tumor number but eliminated more serious lesions and reduced the overall burden of disease in susceptible individuals.41,44,45

An additional contribution of the design of the APC and PreSAP studies was the inclusion of a surveillance colonoscopy after only 1 year of study drug use. These data indicate that agent efficacy in colorectal adenoma prevention trials can be assessed after only 1 year of treatment, instead of using the standard 3-year study interval. Comparison of results from the APC and PreSAP studies suggests that once-daily dosing at 400 mg is safer than a twice-daily dose of 200 mg yet retains significant antitumor efficacy. Unfortunately, because neither of these trials was designed or powered to assess cardiovas-

High Risk:
FAP, HNPCC
Lifetime risk ~ 80-100%
- Screening colonoscopy every year beginning in the first or second decade and chemoprevention
- Prophylactic surgery as needed

Moderate Risk:
Current/prior adenoma, cancer survivor, inflammatory bowel disease
Lifetime risk ~ 10-20%
- Surveillance colonoscopy and chemoprevention in selected high risk individuals

Figure 3. High-risk and medium-risk colorectal cancer.
cular toxicity, this conclusion cannot be reached without further study in a randomized trial. Another intriguing issue involves the duration of therapy. CRC takes years to progress from early adenoma through advanced adenoma to adenocarcinoma. It is possible that chemopreventive agents do not need to be administered during this entire time but can be given intermittently to prevent the initiation of the disease. It is quite possible that shorter treatment duration will reduce treatment toxicity, and these data indicate that celecoxib should retain its anti-tumor efficacy while reducing cardiovascular toxicity through a shorter-duration dosing schedule. Celecoxib with 30%-70% efficacy (Figure 1 point A) in the prevention of adenoma recurrence and 1% to 2% toxicity (Figure 1 point B) is attractive in certain high risk populations. A proof of concept has been achieved, but celecoxib is still not the ultimate drug of choice. Better patient selection and more effective and safer drugs are required.

The unexpected identification of cardiovascular toxicity related to selective COX-2 inhibitors has understandably made development of new agents more difficult in this field. However, to ignore the potential benefit of chemoprevention is to continue to accept a higher than necessary death rate from CRC in patient populations that are not fully compliant with screening for colorectal neoplasia. We are just beginning to understand early tumor formation in a way that permits development of mechanism-based chemoprevention therapies.48 Moving the field of CRC prevention forward will require a better understanding of the molecular alterations associated with early tumor formation that could be targets for pharmacologic intervention, as well as identification of individual factors involved in cancer risk and treatment toxicity so that interventions can be optimized.

Where possible, medical treatment should be personalized, that is, prescription of a specific therapy based on the metabolic characteristics of an individual and the molecular profile of the target lesion. For example, the mechanisms by which NSAIDs and aspirin interdict CRC carcinogenesis are not understood fully. If the agents principally work via COX-2 inhibition, then their use should reduce preferentially the risk of tumors that overexpress COX-2. Indeed, the effect of aspirin differs significantly according to the degree of COX-2 expression. Chan et al49 recently reported that regular use of aspirin reduced the risk of CRC in COX-2-expressing cancers but not in cancers with weak or absent COX-2 expression. The protective effect on COX-2-overexpressing cancers was significantly stronger with both increasing aspirin dose and increasing duration of use. No such association was observed for cancers with weak or absent COX-2 expression.

Polymorphisms in NSAID targets or metabolizing enzymes may affect NSAID efficacy and/or toxicity.50 The literature on these interactions to date is still very limited (eg, COX1 P17L or COX2-765G>C). Reliable detection of gene-NSAID interactions will require greater sample sizes, consistent definitions of NSAID use, and evaluation of clinical trial subjects in chemoprevention studies.51

**Nitric Oxide NSAIDs**

Nitric oxide NSAIDs are a novel group of hybrid NO-releasing NSAIDs. NO is recognized as a critical mediator of gastrointestinal mucosal defense, exerting many of the same actions as prostaglandins in the gastrointestinal tract.52 In experimental animal models, compounds formulated by linking a NO-releasing compound to a NSAID have been found to reduce the severity of gastric injury.52-54 In vivo studies have shown that NO NSAIDs suppress the formation of azoxymethane-induced colonic aberrant crypt foci53 and CRC.55,56 NO aspirin has been shown to effectively reduce intestinal carcinogenesis in the Min mouse model.57 This group of promising drugs is being evaluated in current clinical trials.

**Mesalamine Compounds**

Mesalamine is best studied in the setting of prevention of CRC in patients with inflammatory bowel disease. There are several studies showing an impressive protective effect,58-61 although recent studies have failed to confirm these findings, including large, well-established cohorts of patients with inflammatory bowel disease in Europe and the United States.62,63

In the setting of individuals with a history of sporadic adenomas, a large multicenter, placebo-controlled trial included 598 patients who were randomized to receive either 1 g/day of mesalazine or placebo. In those at low risk (1–2 adenomas) no benefit was observed, while there was a non-significant trend toward reduction in recurrence of adenomas in subjects with >3 adenomas.64 In another small study in patients with small rectosigmoid adenomas, there was no reduction in the size or number of polyps over a 6-month period.65 However, given the low doses of drug used and the short duration of the study, it is premature to claim that mesalamine compounds do not have a chemopreventive effect in sporadic adenomas.

**3-Hydroxy-3-Methylglutaryl–Coenzyme A Reductase Inhibitors**

The statins are the most commonly prescribed class of prescription drugs in the United States. Originally approved to prevent heart disease, statins are now also believed to combat rheumatoid arthritis, Alzheimer’s disease, multiple sclerosis, and, importantly, cancer.66,67 Studies of the mechanisms of statins and observations that cardiovascular benefits are experienced even in subjects with normal levels of cholesterol led to the recognition that the actions of statins extend beyond their cholesterol-lowering properties.66,67 The idea of a widely used class of drugs having dual effects in reducing death from both cardiovascular disease
and cancer certainly has great appeal. Some studies have shown that a low dose ofLovastatin augments sulindacinduced apoptosis in CRC cells and potentiates the chemopreventive effects of sulindac. In an animal model of carcinogen-induced CRC, statins significantly reduced the number of colonic neoplasms. In humans, the relationship between statin use and cancer risk has been evaluated in numerous observational studies and as a secondary outcome in randomized controlled trials evaluating the effects of statins on occurrence of cardiovascular disease. Despite some reports of up to a 50% reduction in the incidence of CRC in long-term statin users, the epidemiologic evidence for a beneficial effect of statins on the incidence of CRC is conflicting.

Two large observational studies of simvastatin and pravastatin in patients with coronary artery disease found a reduction in incidence of CRC. Furthermore, a recent case-control study that analyzed 1953 patients with CRC and 2015 controls found that the use of statins for 5 years was associated with a 47% relative reduction in CRC risk after adjustment for other known risk factors. By contrast, in a nested case-control study in the General Practice Research Database (1987–2003), the use of statins for more than 5 years was not associated with a decreased risk of CRC (odds ratio, 1.0; 95% CI, 0.7–1.5). The General Practice Research Database is a computerized medical record system from the United Kingdom containing complete, prospectively collected prescription data and validated diagnostic information on CRC and other diseases. The study cohort included all patients aged 50 years or older and with more than 5 years of CRC-free initial follow-up in the General Practice Research Database. Cases included all patients with an incident diagnosis of CRC. Up to 10 controls were selected for each case of cancer. The primary exposure of interest was more than 5 years of cumulative statin use. Although there are plausible biological mechanisms to suggest that statins could inhibit cellular proliferation, the epidemiologic data do not show a consistent reduction in cancer risk among statin users, and recent publications have not found an inverse relationship between CRC and statins or even reported an increased risk among statins users.

Clearly, current epidemiologic data are not robust to merit statin use for chemopreventive purposes. Furthermore, the unclear possibility of reducing CRC risk has to be balanced against the known adverse effects of these drugs. Although statins have a generally good safety profile, serious adverse events may occur in up to 5% of patients. Despite the current lack of evidence for a chemopreventive effect, there are several methodological considerations in the studies reported to date that do not permit a definitive conclusion that statins do not reduce the risk of cancer. The randomized controlled trials were powered to detect cardiovascular outcomes, which are much more common, and not CRC and require shorter follow-up to accrue an adequate number of events. Among the 35 randomized controlled trials included in the meta-analysis by Bonovas et al, only 5 studies had an average follow-up of 5 years or longer and only one had 10 years of follow-up. Not surprisingly, with the limited follow-up, the number of cancers in any individual study tended to be fairly small. Two thirds of the studies had fewer than 100 incident cancer cases, and only one study had more than 1000. A class of drugs that is used by more than 10% of the adult population and 25% of the population over the age of 60 years warrants continued reassessment of its risk/benefit ratio.

Bile Salt

Bile acids, specifically secondary bile acids (such as deoxycholic acid), are carcinogenic. Ursodeoxycholic acid is a synthetic bile acid. It acts as a chemopreventive agent by reducing the colonic concentration of deoxycholic acid. Deoxycholic acid is cytotoxic to colonic epithelial cells and induces hyperproliferation by blocking 2 sepa-
rate pathways (by modulating protein kinase C and phospholipase A_2 expression). In addition, it is an antioxidant that stabilizes the mitochondrial membrane, thereby preventing oxidative injury to DNA. Numerous studies have shown the chemopreventive effects of ursodiol in rat models of carcinogenesis, and the results of human studies are now beginning to emerge.\textsuperscript{79} In a study by Alberts \textit{et al},\textsuperscript{80} a protective effect on recurrence of advanced adenoma was observed.

**Difluoromethylornithine**

Difluoromethylornithine (DFMO) is an irreversible inhibitor of ornithine decarboxylase, the first and rate-limiting enzyme in polyamine synthesis. Somatic cells in the majority of colorectal polyps and cancers contain mutations/deletions in the APC tumor suppressor gene. APC influences expression of ornithine decarboxylase through regulation of the \( \epsilon \)-Myc oncogene, hence, loss of APC function leads to alterations in ornithine decarboxylase expression. The polyamine pathway appears to play an essential role in CRC development.\textsuperscript{81} Ornithine decarboxylase and polyamine expression have been found to be elevated in adenomatous polyps and CRCs relative to normal mucosa.\textsuperscript{82,83} In patients with a history of adenomatous polyps, low doses of DFMO suppressed the polyamine levels in rectal mucosa after 1 year of administration with minimal side effects.\textsuperscript{84} Due to ototoxicity, DFMO is under investigation as a chemopreventive agent at lower doses mainly in conjunction with NSAIDs and in particular sulindac (to be discussed in a later section).

**Hormone Replacement Therapy**

During the past 20 years, CRC mortality has decreased only slightly in men but more so in women. In most studies, women who use postmenopausal hormones have an approximately 30\%–40\% decreased risk of CRC. The effect is stronger in women who received continuous hormone therapy for more than 11 years. While the mechanism underlying this protective effect is unclear, estrogen may prevent CRC by decreasing the production of secondary bile acids, decreasing the production of insulin-like growth factor I, or exerting a direct effect on the epithelium and perhaps by a combination of these mechanisms.\textsuperscript{85–87} The Women's Health Initiative hormone replacement therapy study includes estrogen plus progesterone and estrogen-only arms and is part of a large National Institutes of Health–sponsored randomized controlled trial. In the estrogen plus progesterone arm of this study, a 37\% reduction in incidence of CRC was found (odds ratio, 0.56; 95\% CI, 0.38–0.81; \( P = .003 \)). However, there were a greater number of positive lymph nodes in the hormone group (mean ± SD, 3.24 ± 4.1 vs 0.8 ± 1.7; \( P = .002 \)) and the tumors were more advanced (regional or metastatic disease, 76.2\% vs 48.5\%; \( P = .004 \)). Moreover, the subjects in this arm had an increased incidence of cardiovascular events and breast cancer and both arms showed an increased rate of thromboembolic events and stroke.\textsuperscript{88} Due to these findings, hormone replacement therapy is not recommended for use as a chemopreventive agent for CRC.

**Vitamins and Antioxidants**

Vegetables and fruits are the major source of most dietary antioxidants, including vitamins C and E, carotenoids, and selenium. It was hypothesized that vitamins protect the colorectal mucosa by neutralizing free radicals. In addition, selenium was found in low levels in the serum of patients with CRC. However, antioxidant nutrients have yielded mixed results in the prevention of CRC\textsuperscript{90,91} or recurrence of adenoma.\textsuperscript{92} Moreover, large prospective cohort studies found that supplementation with \( \beta \)-carotene or with vitamins A, C, D, or E had no protective effect against CRC carcinogenesis.\textsuperscript{93–95} Other studies show that, past, but not recent, multivitamin use may be associated with a modestly reduced risk of CRC.\textsuperscript{96} At present, there is insufficient evidence to support a recommendation that individuals ingest supplementary sources of antioxidants to reduce their risk of CRC.

Many micronutrients and minerals, including calcium and vitamin D as well as fiber, have been evaluated in animal models and clinical trials. While some trials have been well designed, many are poorly designed or lack follow-up and compliance measurements. Most studies have shown equivocal results, and only a limited number have shown a modest effect. Thus far, there are no guidelines for micronutrient supplementation for the prevention of colorectal neoplasms.

**Folic Acid**

Folic acid and its derivative, folate, are essential nutrients in humans. They play an important role in nucleotide synthesis and methylation reactions. Folate is a micronutrient needed for cell replication and growth that is abundant in vegetables and fruit. Considerable epidemiologic evidence suggests that a low-folate diet is associated with an increased risk of CRC and in particular in concert with alcohol consumption, which can antagonize the metabolism of folate. These studies found that individuals with the highest dietary folate intake had a lower incidence of CRC, whereas individuals with diets that are low in folate appear to have an increased incidence of CRC.\textsuperscript{97} A low serum folate level, in the form of 5-methyl-tetrahydrofolate, may limit the supply of methyl groups required for DNA methylation and other methylation reactions. DNA hypomethylation is an early event in colon carcinogenesis. Folate deficiency also leads to an increased frequency of chromosomal breaks. Thus, the chromosomal changes can be prevented with folic
acid supplementation. Many animal studies support the antineoplastic effect of folate. Nonetheless, in some animal studies, folate deficiency surprisingly protects against, and folate supplementation increases, experimental carcinogenesis.

In the Nurses’ Health Study, women who had regularly taken multivitamins (containing folic acid) for a long period, at least 15 years, showed the greatest reduction in CRC with an RR of 0.25 (95% CI, 0.13–0.51; P = .0003), although the protective effect was not seen in rectal cancer (RR, 1.27; 95% CI, 0.67–2.46). Folic acid was in particular effective in women with a positive family history of CRC. Another prospective cohort study showed that consumption of more than 400 μg/day of folic acid compared with an intake of 200 μg/day or less was associated with a lower risk of CRC (RR, 0.69; 95% CI, 0.52–0.93). In the Canadian National Breast Screening Study, folic acid was found to be inversely associated with CRC, with a 40% lower risk among women in the highest compared with the lowest quintile levels of intake. A large European case-control study also found a significantly reduced risk of CRC when comparing the highest versus the lowest intakes of folate acid.

The long period required for the clinical benefit to become evident suggests that folate acts early in colon carcinogenesis, thereby indicating that long-term folate supplementation may be required. In the UK-CAP trial, folate acid supplementation had no effect on adenoma recurrence. A distinguishing feature of this trial as compared with other trials is that the majority of the participants had baseline advanced adenomas at study entry and not less potentially premalignant adenomas.

Recently, some concerns regarding the protective effects of folic acid have been raised. A double-blind, randomized, placebo-controlled, phase 3 clinical trial randomized 1021 subjects to receive 1 mg/day of folic acid (n = 516) or placebo (n = 505). They were separately randomized to receive aspirin (81 or 325 mg/day) or placebo. Follow-up consisted of colonoscopies at 3 years and 3 or 5 years thereafter. The folic acid component was initially designed to parallel the 3-year investigation for aspirin. However, because longer exposure to folic acid might be required to observe an antineoplastic effect, participants who underwent the first colonoscopy were invited to continue their blinded randomized treatment (folic acid or placebo) for an additional 3–5 years. During the first 3 years, the incidence of at least one colorectal adenoma was 44% and 42% for those receiving folic acid and placebo, respectively (RR, 1.04; 95% CI, 0.90–1.20). A total of 607 participants (59.5%) underwent a second colonoscopy, and the incidence of at least one adenoma was 42% for those receiving folic acid and 37% for those receiving placebo (unadjusted RR, 1.13; 95% CI, 0.93–1.37; P = .23). The incidence of advanced lesions was 11.6% for those receiving folic acid and 6.9% for those receiving placebo (unadjusted RR, 1.67; 95% CI, 1.00–2.80; P = .05).

The conflicting evidence regarding folate suggests that it might have a dual effect on carcinogenesis by protecting against initiation of adenoma formation but enhancing progression of existing colonic lesions.

### Calcium and Vitamin D

Laboratory, clinical, and epidemiologic evidence suggests that calcium may prevent colorectal adenomas. Although the reduction in risk becomes evident less than a year after randomization, the effect does not become stronger with time. Diets rich in red meat and animal fat are associated with an increased risk of colorectal adenomas and CRC. These diets increase the production of secondary bile acids, which may cause hyperproliferation of the colorectal epithelium and promote cancer formation. The postulated mechanisms for the protective effect of calcium are based on its bile acid–binding capacity and direct action on intracellular signaling, as well as cell proliferation, differentiation, and death. Several studies suggest that dietary calcium has a particularly inhibitory effect on tumors with ras mutations.

A total of 930 subjects with a history of colorectal adenomas were assigned randomly to receive 3 g of calcium carbonate or placebo. Colonoscopies were performed after 1 and 4 years. A moderate but significant reduction (RR, 0.85; 95% CI, 0.74–0.98) in adenoma recurrence was noted in the group receiving calcium. A European study in 176 patients followed up for 3 years found a modest but statistically nonsignificant (RR, 0.66; 95% CI, 0.38–1.17) reduction in adenoma recurrence in individuals given 2 g of elemental calcium daily. Analysis of cases from the Nurses’ Health Study and the Health Professionals Follow-Up Study found that consumption of calcium reduced the risk of distal colon cancer but not of proximal cancer.

A potential role for vitamin D in cancer prevention was first suggested in the 1930s by the discovery of the inverse association between sun exposure, which enables cutaneous production of the vitamin, and cancer rates. A daily intake of 1000 IU of vitamin D and a concentration of serum 25-hydroxyvitamin D of 33 ng/mL were each associated with 50% lower risk of CRC.

A combination of vitamin D and calcium may have a sound biological basis. It has been shown that high intake of calcium and vitamin D has been associated with a reduced risk of CRC in epidemiologic studies of polyp recurrence. In the Women’s Health Study involving 36,282 postmenopausal women from 40 Women’s Health Initiative centers, 18,176 women received calcium carbonate (500 mg) and vitamin D₃ (200 IU) twice daily, and 18,106 received a matching placebo for an average of 7 years. The incidence of CRC did not differ significantly between the 2 arms of the study (RR, 1.08; 95% CI, 0.86–1.34). The relatively short duration of follow-up and suboptimal doses of calcium and vitamin D were suggested to account for
the negative effects of this trial, although other factors may also have been responsible.\textsuperscript{118}

Lappe et al\textsuperscript{119} determined the efficacy of calcium alone, and in combination with vitamin D, in reducing incident cancer risk of all types. The subjects were 1179 community-dwelling women selected randomly from the population of healthy postmenopausal women aged older than 55 years. The women were assigned randomly to receive 1400–1500 mg of calcium once daily or calcium plus 1100 IU vitamin D\textsubscript{3} once daily or placebo. The investigators concluded that improving calcium and vitamin D nutritional status substantially reduces all-cancer risk, including CRC, in postmenopausal women (RR, 0.40; 95\% CI, 0.20–0.82). Because of the difficulties in ascertaining accurate dietary histories, the effects of calcium and vitamin D intake are likely to be confounded by other dietary factors and by the intake of anticarcinogenic agents, such as aspirin.

However, dose-limiting hypercalcemic effects have proved a major obstacle to the development of natural vitamin D as a cancer chemopreventive agent. Studies have sought to dissociate the toxicities and chemopreventive activities of vitamin D, and a number of synthetic deltanoids (vitamin D analogues) have shown considerable promise in this regard.\textsuperscript{120} Although vitamin D has been found to be efficacious in preclinical studies, the National Cancer Institute is no longer exploring it in chemoprevention clinical trials. Dose-limiting hypercalcemic effects have proved a major obstacle to the development of the natural vitamin as a chemotherapeutic or chemopreventive agent.\textsuperscript{121}

**Vitamin E**

In a prospective cohort study of 35,215 Iowa women, an inverse association between CRC risk and vitamin E intake was found.\textsuperscript{121} At the same time, the Women’s Health Study found no such association.\textsuperscript{118} In a meta-analysis of 14 randomized trials of supplemental antioxidant vitamins encompassing 170,025 individuals, no evidence of prevention of colorectal adenomas or cancer was found.\textsuperscript{7}

**Selenium**

An inverse association between CRC mortality and selenium consumption in the diet was noted in animal models and epidemiologic studies. The Wheat Bran Fiber Trial, the Polyp Prevention Trial, and the Polyp Prevention Study were interventions in 1763 subjects with a recent adenoma removal. Analysis of pooled data showed that the subjects with blood selenium in the highest quartile, when compared with those in the lowest quartile, had a significantly lower risk of adenoma recurrence (odds ratio, 0.66; 95\% CI, 0.50–0.87).\textsuperscript{122} A chemoprevention trial in 1312 patients, with skin cancer as the primary end point, did not reduce the incidence of skin cancers. However, a significant reduction in the risk of CRC was seen in the treatment arm (RR, 0.42; 95\% CI, 0.18–0.85; \textit{P} = .03).\textsuperscript{123} A large multicenter cohort study, the Prevention of Cancer by Intervention with Selenium Trial (PreCISe), may shed more light on this promising trace element.\textsuperscript{124}

**Combination Therapy**

Although many single compounds and agents have potential benefits, their chemopreventive efficacy in clinical trials has been modest (20\%) and/or they have an unacceptable toxicity profile. For this reason, combining low doses of different agents may be effective in increasing their efficacy while minimizing toxicity. In animal models of carcinogen-induced aberrant crypt foci, a greater reduction in the number of aberrant crypt foci was reported in rats receiving both lovastatin and sulindac, as compared with each of the drugs alone.\textsuperscript{125} Similar results were reported when atorvastatin, celecoxib, and aspirin were studied in the aoxymethane-induced colon cancer animal model. Again, low doses of these agents in combination inhibited colon carcinogenesis more effectively than either of the drugs alone given at a higher dose.\textsuperscript{126} Another study revealed that combined treatment with piroxicam plus DFMO was much more effective than either agent alone and resulted in a significant number of mice totally free of any intestinal adenomas (\textit{P} < .001), in contrast to the 100\% incidence and high multiplicity in the control \textit{Min} mice.\textsuperscript{127} The group from Tel Aviv showed that the combination of curcumin, a diferuloylmethane derived from the plant \textit{Curcuma longa}, and low doses of celecoxib (2–5 \textmu mol/L) synergistically inhibits the growth of malignant cells in vitro and in vivo, as compared with each drug alone.\textsuperscript{128}

Due to these impressive results in the preclinical setting, combination treatment is currently under extensive study in the chemopreventive field. A large randomized study is under way at M. D. Anderson Cancer Center in conjunction with the National Cancer Institute evaluating the effect of celecoxib with or without DFMO in patients with familial adenomatous polyposis (P. Lynch, personal communication, December 2007). DFMO is being studied in combination with sulindac in a phase 3 study in patients with a history of sporadic adenomas (F. Meyskens, personal communication, December 2007).

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**Table 1. Important Paths for Future Developments**

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<th>Path</th>
<th>Description</th>
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<tr>
<td>Better patient selection</td>
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<td>Better risk characterization</td>
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<td>Combinations of agents</td>
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<tr>
<td>Prioritization of agents</td>
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<tr>
<td>Broad range of benefits targeting diseases common in aging populations (eg, anticancer, anti–cardiovascular disease, anti–Alzheimer’s disease)</td>
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Summary and Future Directions

Development of CRC is a multistep process, the progression of which spans 10–15 years, thereby providing an opportunity for early detection and even prevention. Cancer prevention is certain to be a significant focus of translational research and intervention in the future, propelled by the realization that individuals susceptible to specific cancers can be identified, as well as the molecular pathways that can be targeted to retard or completely abrogate the carcinogenic process.

Given the large patient numbers and long periods of follow-up necessary to detect the end points of interest (ie, adenoma or cancer), chemoprevention trials are enormously expensive and a major challenge. In this regard, much more time is required to produce the evidence necessary to approve a drug for marketing. The COX-2 experience has shown that long-term ingestion of an agent that is apparently safe when used for a short time may be unpredictable in its actions and can lead to serious adverse effects. Preclinical study and pharmacogenomic research are required to guide a better selection of drugs for further study and to determine ideal intermediate surrogate markers. In turn, this may prevent withdrawal of drugs from clinical use after the investment of resources for development.

It is entirely possible that effective inhibition or reversal of neoplastic progression involves different mechanisms and requires higher doses of aspirin, and other chemopreventive agents, than prevention of initiation. Thus, in patients who have undergone surgical resection for CRC or had clearing colonoscopies to remove all adenomas, effective CRC chemoprevention may require less intensive and toxic interventions than if neoplastic lesions had not been cleared.

For the present, the only approved chemopreventive agent for chemoprevention of colorectal neoplasia is celecoxib, and only for high-risk patients with familial adenomatous polyposis. Sulindac has also repeatedly shown efficacy in this setting. However, due to a high incidence of a gastrointestinal toxicity profile associated with long-term administration of sulindac, its benefit will have to be weighed against a potential risk. Patients with familial adenomatous polyposis are usually young subjects with minimal cardiovascular risks and a 100% likelihood of CRC development. Hence, they are likely to benefit from the ingestion of COX-2 inhibitors or sulindac (Figure 3).

In the intriguing jigsaw puzzle of cancer prevention, we now have a definite positive answer to the basic question whether effective agents exist, but several other parts of the equation (proper patient selection, ultimate drug, optimal dosage, and duration) are missing. The most challenging task is to find the proper place for these interventions in the entire effort of cancer prevention, in subjects at risk for colorectal neoplasia, and in those at risk for other tumors. The achievement of this important goal may contribute to the conversion of CRC into a largely preventable disease (Table 1).

To be useful, any strategy of chemoprevention should be combined with screening and surveillance colonoscopy. Whether chemoprevention will lengthen periods between consecutive screening/surveillance studies or replace them remains to be determined in the future. The public is receptive to the concept of primary prevention of heart attack and stroke by taking low-dose aspirin. Subjects are likely to be more adherent to prescribed regimens if cardiovascular prophylaxis may be combined with the prevention of CRC. Effective inhibition or even reversal of the neoplastic process is entirely different from prevention. Most likely, inhibition of CRC demands significantly higher dosages of chemopreventive agents than prevention of the very early phase of tumor initiation. Hence, in patients without detectable adenomas (after surgery or colonoscopy), the dosage and duration of the chemopreventive agent might be much lower than in subjects with advanced lesions. Possibly, chemoprevention should be optimally used only after colonoscopic polypectomy in individuals at substantially increased risk. Subjects (85%–90% of the population) with a normal colon or nonadvanced adenomas can be safely monitored with colonoscopy every 5–10 years. Only subjects with advanced adenoma should receive chemopreventive agents. Chemoprevention in this setting is very important because polyp recurrence in this population is around 50%, even with colonoscopic surveillance every 1–3 years (Figure 4).

The ideal chemopreventive agent remains to be discovered, with great emphasis on the need not to harm. Possibly, combinations of agents will maximize effectiveness while limiting drug toxicity. Finally, personalized approaches would include the ability to predict risk as well as benefit for a specific individual based on specific single nucleotide polymorphisms or other genetic profiles.

References


73.解決する方法と結果をそれを私たちについて。Epidemiology 2007;18:194–196.


