Published in final edited form as:

Expert Rev Gastroenterol Hepatol. 2009 August ; 3(4): 369–382. doi:10.1586/egh.09.28.

Current concepts in colorectal cancer prevention

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Abstract

Colorectal cancer chemoprevention, or chemoprophylaxis, is a drug-based approach to prevent colorectal cancer. Preventing colorectal adenomas with currently available agents demonstrates the promise of pharmacologic strategies directed at critical regulatory pathways. However, agent toxicity, lesion breakthrough and competing efficacy from endoscopy procedures challenge population-based implementation. This article reviews the role of colorectal cancer chemoprevention in the context of existing screening and surveillance guidelines and practice. Emphasis is placed on the role of the colorectal adenoma as a cancer precursor and its surrogacy in assessing individual risk and for evaluating chemoprevention efficacy. We discuss the importance of risk stratification for identifying subjects at moderate-to-high risk for colorectal cancer who are most likely to benefit from chemoprevention at an acceptable level of risk.

Keywords

adenoma; chemoprevention; colon cancer; colonoscopy; difluoromethylornithine; NSAID; polyps

Epidemiology of colorectal cancer

The majority of colorectal cancers (CRCs) are adenocarcinomas [1] that can be further divided by their molecular characteristics [2]. These molecular features include chromosomal instability, microsatellite instability and hypermethylation of a set of select genes or a methylator phenotype. Excluding the genetic syndromes of familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), 25% of CRCs are attributable to a family history, while most are sporadic cases (75%) that account for the majority of cancers over the age of 50 years. The risk is greater for men than women and in individuals of African–American ancestry [3]. In addition, a number of well-supported modifiable risk factors have been identified. These include sedentary behavior, obesity, low vitamin D levels, micronutrient deficiencies (e.g., folate, calcium and selenium) and a

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

number of dietary factors, including low dietary fiber and a high intake of red and processed meats [4]. Inflammatory-type bowel diseases, such as Crohn's disease and ulcerative colitis, also increase the risk [5,6].

Colorectal adenoma is a risk factor for CRC

Evidence from patients undergoing colonoscopy suggests that a sizable fraction of the general population risk for CRC resides in individuals who develop colorectal neoplasias or colorectal adenomatous (CRA) polyps. CRC risk increases in direct relation to the severity of clinical and histological findings at endoscopy examination (Figure 1) [7–9]. Risk increases sizably with the detection of more-advanced CRAs at screening (box 1). Conversely, lack of CRAs at screening is associated with very low risk for CRC. A recent study by Imperiale *et al.* confirms low rates of any CRA (16.0%) or advanced CRA (1.3%), and no cancers among subjects who were negative for neoplasia at baseline and followed for an average of 5.3 years [10]. This is in contrast to the risk observed in patients who undergo resection for a CRA (postpolypectomy patients). Martinez *et al.* reported rates of any CRA (46.7%), advanced CRAs (11.2%) and invasive cancers (0.6%) at follow-up colonoscopy in a pooled analysis of 9167 patients who had previously undergone resection for a CRA, and had a mean time to follow-up of 4 years [9].

Taken collectively, these observations support the widely accepted view that the majority of CRCs arise through malignant conversion of a subset of adenomas to carcinomas (Box 2). Between 20 and 35% of the population over the age of 50 years will present with a CRA in their lifetime [11,12], with 20–50% of those individuals experiencing separate, or metachronous occurrence(s) of CRAs at follow-up examinations (typically between 3 and 5 years) [9]. Thus, one of the most relevant risk factors for CRCs in clinical practice is the development of CRAs, particularly if CRA formation is persistent [13].

Current screening & surveillance guidelines & CRA

Incidence and deaths caused by CRC have declined in the USA [14]. CRC mortality rates have been decreasing slowly in women and men for the past 60 and 20 years, respectively. The overall decline in CRC rates with greater use of endoscopy procedures and resultant surgical removal of CRAs is thought to explain part of the continued decline in CRC incidence and mortality in the USA [15]. Results of the National Polyp Study (NPS), a prospective, observational study of patients whose CRAs were removed and then followed-up to their next colonoscopy provided the first evidence for significant CRC risk reduction (75–90%) when CRAs are removed surgically [16]. This significant reduction in risk for CRC forms the basis for current standard of colonoscopy surveillance for the polypectomy patient, which has not been subsequently confirmed in a randomized trial.

Historically, the detection of CRA for the purposes of 'cancer prevention' was not a primary goal of CRC screening; rather, it aimed to detect cancers earlier, when treatment is more effective. The guidelines for CRC screening were updated in 2008 by the US Prevention Services Task Force (USPSTF) [17] and independently by a joint effort of the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology [18]. Each set of recommendations reflects a greater emphasis on endoscopy for identification of CRAs and cancer prevention than in the past [19]. Recognizing the disappointing uptake (~50%) of any CRC screening in the population [20] (especially among the uninsured [~25%] or those without regular health services [~25%] [20]), both groups advocate using some form of CRC screening to offer a variety of testing options to increase screening rates. For the average-risk population, there is general agreement that, when evaluated on risks and benefits, annual of high-sensitivity fecal occult blood testing (FOBT; preferred method high-sensitivity immunochemical testing),

sigmoidoscopy every 5 years with interval FOBT, or colonoscopy every 10 years offer largely equivalent screening benefits for the early detection of CRCs in asymptomatic people. Both groups ascribe greater benefit to the more sensitive endoscopy procedures, particularly optical colonoscopy, which allow the visual detection of advanced CRAs throughout the entirety of the colon, acknowledging the higher risks, costs and burdens on resources associated with this procedure.

In spite of the disappointingly low use of CRC screening at the population level, colonoscopy has emerged as the most commonly prescribed screening modality for CRC in the USA [15,20]. Consequently, CRAs are an increasingly common incidental finding at screening, creating challenges to the delivery of screening when considering the potential 'prevention' benefit of CRA removal with routine surveillance in adenoma formers. The use of colonoscopy for the identification of CRAs and subsequent surveillance in individuals who screen positive for CRA has resulted in extensive use of endoscopy, contributing to increased costs and excess risk from numerous procedures [21]. In clinical practice, the majority of incidental CRA(s) are clinically insignificant lesions. It is estimated that only 2–5% of sporadic CRAs have the potential to progress to malignancy [22].

In 2006, risk-stratification guidelines for endoscopy intervals in the postpolypectomy patient were published to aid in decision-making regarding follow-up intervals. These recommendations were based on the clinical and histologic characteristics of the CRA removed at baseline and included adenoma size, histology, degree of dysplasia and multiplicity (Box 3.) [7]. The benefit of using these low- and high-risk categories in terms of reducing deaths from CRC is unknown. Analyses conducted by Martinez *et al.* found that patients who were classified as high risk experienced an approximately twofold increased risk for advanced neoplasia at follow-up colonoscopy compared with those classified as low risk (mean time to follow-up: 4 years) [9]. Among the 9167 postpolypectomy subjects, 16.3% of the high-risk individuals presented with advanced neoplasia at follow-up compared with 7.4% of the low-risk group. The discriminatory function of these risk categories is modest, resulting in a sizable fraction of unnecessary procedures in the high-risk group and a significant misclassification of individuals in the low-risk group who might go on to develop cancer within 10 years. A similar analysis, conducted by Laiyemo *et al.*, concluded that the current risk stratification used in the guidelines have low predictability for advanced neoplasia and limited clinical usefulness [23]. Inclusion of family history, anatomic location and other lifestyle and environmental risk factors may improve upon the discriminatory function of the risk groups in the future. Currently, however, low confidence in these guidelines limits their use and results in a large number of unnecessary procedures.

Challenges associated with endoscopy-based detection & removal of CRA for prevention

Higher rates of breakthrough or interval cancers in community and pooled chemoprevention study populations under surveillance for CRA raise questions about the actual benefit of colonoscopy-based polypectomy [8,24,25]. Furthering the debate, Baxter *et al.* recently reported a significantly reduced odds of death due to CRC for left-sided cancers among individuals undergoing colonoscopy (odds ratio [OR]: 0.33; CI: 0.28–0.39) but no benefit for right-sided cancers (OR: 0.99; CI: 0.86–1.14) [26]. This finding contributes to the growing evidence that CRAs arising in different anatomic subsites of the colorectum may exhibit unique histological and molecular characteristics and, thus, distinct natural histories. Although currently highly controversial, it has been suggested that CRA arising in the proximal colon are more likely than distal lesions to be flat or depressed, and thus more difficult to detect by colonoscopy [27–31]. In addition to differences in appearance, proximal lesions may harbor a higher inherent risk for neoplasia and, as such, anatomic

location may prove to be an independent predictor of risk factor for neoplasia. These results raise concerns about limitations, at least in practice, regarding the efficacy of colonoscopy for prevention of right-sided or proximal lesions. A number of possible explanations for the development of CRC in individuals under surveillance with colonoscopy have been raised. These include the failure to achieve a high-quality examination of the entire colon [32], lack of complete excision of a high-risk CRA [32,33] and poor visualization of flat or depressed lesions that may be more common in the right side of the colon [28]. Technical advances in endoscopy procedures (e.g., chromendoscopy or dye spraying) offer improvements for detecting such lesions. However, longer procedure times, outstanding questions about the significance of nonpolypoid lesions and increased normal tissue biopsy may limit utility to only those at highest risk, such as hereditary nonpolyposis CRC family members.

Overuse of colonoscopy in surveillance

Gaps in our knowledge about the malignant potential of CRAs challenge the confidence of the patient and physician in the use of the 2006 guidelines to lengthen the colonoscopy interval when based on CRA characteristics alone. A discord between the public-health goal to diminish interval cancers and patient/physician expectations to eliminate them entirely also affects surveillance. Currently, overuse of colonoscopy wastes important resources and tips the balance of colonoscopy benefit toward higher costs and exposures to endoscopy-related risks; valuable resources that might be more judiciously and equitably applied to screening. More widespread adoption and use of computed tomography (CT) colonography offers an endoscopy advance that could prove particularly useful for alleviating the burden of visual endoscopy and the associated high costs in patients with a history of CRA. This procedure is likely to prove particularly valuable for those patients prone to polypoid-type lesions, where CT colonography has shown promise in the detection of larger, higher risk adenomas and early cancers [34]. While highly promising, low sensitivity for smaller and nonpolypoid lesions of unknown cancer relevance and the high rates of extracolonic findings, as well as concerns over radiation exposure, continue to hinder adoption in routine clinical practice and coverage by insurers [35]. As a result, these current limitations support the need for complementary approaches to risk management, including prevention through less expensive, nonendoscopy-based methods.

Box 1. Advanced colorectal neoplasia

Any adenoma that has a diameter greater than 1.0 cm or any adenoma, regardless of size, that exhibits villous histology or high-grade dysplasia is considered an advanced neoplasia. Advanced colorectal neoplasia includes invasive cancer.

Drug-based prevention of colorectal neoplasia

With better understanding of the multifactorial and temporal nature of the genetic and nongenetic events that give rise to CRC, a major paradigm shift in cancer prevention evolved in the late 1970s. Sporn and colleagues were among the earliest to advocate a drug-based strategy to prevent cancer [36]. A purely pharmacologic approach to prevention or chemoprevention is based on the understanding of, first, early-acting molecular and cellular events that give rise to cancer for the development of targeted therapies and, second, the mechanism of action of drugs at the whole-organism level. These concepts are akin to those applied in the development of drugs for the treatment of disease. However, an important caveat in the prevention setting is the need to develop drugs that interrupt or reverse steps in carcinogenesis for prophylactic use in large numbers of healthy people. This aspect of chemoprevention requires the identification of safe agents and/or the identification of persons whose risk for cancer outweighs potential harm from the prevention drug.

Rational targets for the development of chemoprevention agents for colorectal neoplasia

Extensive epidemiologic evidence supports lower CRA and CRC risk in people with certain dietary, lifestyle and environmental factors [4,37]. Factors consistently associated with a lower risk include consumption of diets that are high in fruits and vegetables and low in red meat, as well as high calcium, folate and vitamin D levels [4]. CRA/CRC risk is lower among healthy-weight individuals who are physically active. Additional epidemiologic evidence suggests that regular use of NSAID compounds, such as aspirin [38,39] or hormone-replacement therapy in women [40], are associated with significantly lower CRA/CRC rates.

Experimental and early epidemiologic evidence and presumed low toxicity provided the initial impetus to test diet-derived compounds (e.g., calcium, folate and fiber) as prevention agents for CRC/CRA using pharmacologic dosing in randomized, controlled trials. The results of these diet- and supplement-based prevention trials were recently reviewed in detail [41]. We have summarized the general findings from these studies in Box 4 and discuss in detail later the positive findings from the calcium-supplementation trials. While disappointing, these results are not totally unexpected. Food provides a variety of bioactive compounds that may hold chemo-preventive properties in a biologically relevant matrix that cannot be readily duplicated with a supplement approach. For example, there are over 400 carotenoids consumed in the human diet, each with variable biological effects, bioavailability and uptake in tissue. Thus, it is unlikely that one carotenoid (e.g., β -carotene) will be a magic bullet for chemoprevention, even if it is among the more abundant carotenoids in the human diet.

Box 2. Adenoma-to-carcinoma sequence

The adenoma-to-carcinoma sequence in colorectal carcinogenesis specifically refers to the development of cancers in the colorectum through an intermediate neoplastic step, known as adenoma. The neoplastic step includes tubular, tubular villous and villous adenomas. All adenomas are dysplastic by their nature but present with varying degrees of dysplasia. Serrated adenomas have features of both an adenoma and a hyperplastic polyp and are included as adenomas in most studies. Hyperplastic polyps are not considered neoplasias and, thus, are not thought to be causally related to cancers. The adenoma phase is considered a necessary step in the majority of colorectal cancers and is, therefore, an appropriate target for prevention.

Calcium supplements for the prevention of CRAs

Dietary calcium is protective against bile acid-induced mucosal damage and colorectal tumors in animal models [42]. Calcium has been studied in four randomized, controlled trials with different end points along the spectrum of CRC risk. In the first, Baron *et al.* found that 4-year supplementation with 1200 mg/day elemental calcium reduced the risk of metachronous CRA in subjects with a history of CRA compared with placebo [43]. A 15% reduction in risk of CRA, while modest, occurred in the absence of any agent-related toxicity. In an independent study of metachronous CRA, elemental calcium 2000 mg/day showed similar protective activity [44]. A third combination trial with calcium carbonate 1600 mg plus β -carotene, vitamin C, vitamin E and selenium found a reduction in risk of new CRAs but no activity against pre-existing small CRAs [45]. These results are in contrast to those of the randomized, controlled trial of calcium and vitamin D conducted in the Women's Health Initiative (WHI), where no CRC prevention benefit was observed for calcium [46]. The

relatively high baseline calcium intake of the study population has been suggested to explain the failure to observe an effect of calcium. However, an alternative explanation could be the relatively short duration (7 years) of follow-up for a cancer end point. Assuming that our understanding of the adenoma-to-carcinoma transition is a decade(s)-long process is true, the majority of CRCs in the follow-up interval of WHI would likely arise through prevalent cases of CRA. Hofstad *et al.* found no effect of calcium on the growth of pre-existing CRAs, which might explain the lack of effect of calcium for CRC development in the WHI study [45]. Such inconsistencies across chemoprevention studies for CRA and CRC end points highlight the potential for differences in the activity of agents at different time points in the adenoma-to-carcinoma sequence and suggest caution when comparing results across studies.

Pharmacologic intervention for the prevention of colorectal neoplasia

With the exception of a modest risk-lowering effect of calcium, the overall effect of nutrient and supplement-based prevention strategies have proven disappointing to date. The remainder of this review focuses on the more promising results of drug-based chemoprevention studies designed to target specific biochemical steps in early colorectal carcinogenesis.

Ursodeoxycholic acid to prevent colorectal neoplasia

Bile acids are implicated in the etiology of CRC [47]. Multiple ecological studies [48–51] and case-control studies [52–54], including a meta-analysis [55], support a positive association between fecal bile acid levels and colorectal neoplasia. Bile acids have been shown to induce DNA damage in cell culture [47], but animal studies suggest that bile acids act as incomplete carcinogens, requiring another carcinogen for tumor formation [56].

One of the early, high-interest pharmacologic agents for the chemoprevention of CRC was ursodeoxycholic acid (UDCA). UDCA is a naturally occurring tertiary bile acid found in small quantities in normal human bile. UDCA is a well-tolerated, low-risk agent used clinically for the treatment of primary biliary cirrhosis and primary sclerosing cholangitis [57]. Early work suggested that chronic UDCA use in patients with ulcerative colitis (i.e., years) and primary sclerosing cholangitis reduced the risk of colonic neoplasia [58,59]. UDCA was demonstrated to prevent colorectal carcinogenesis in animal models [60] and to counteract the carcinogenic effects of secondary bile acids, particularly deoxycholic acid (DCA) [47]. In humans, UDCA has been shown to affect fecal levels of bile acids, resulting in proportionally lower concentrations of DCA. A number of antitumor effects have been attributed to UDCA, including inhibitory activity for a number of the same regulatory pathways activated by DCA, such as the MAPK pathway [61,62]. Furthermore, UDCA exhibits suppressive activity on arachidonic acid metabolism, including inhibition of COX-2 and inducible nitric oxide synthase [63,64].

Based on the evidence, a Phase III, double-blind placebo-controlled chemoprevention trial of UDCA was conducted from 1995 to 1999 to evaluate the efficacy of UDCA in persons with a history of CRA [65]. A modest, nonstatistically significant 12% reduction in the recurrence rate of any CRA was observed with UDCA daily for 3 years at 8–10 mg/kg of bodyweight. No significant differences were observed for recurrent adenoma size, villous histology or location between UDCA and placebo groups. The lack of an overall effect of UDCA on CRA was disappointing, especially given the low toxicity of the agent, high compliance and strong preclinical evidence and mechanistic rationale. More disappointing is the widely overlooked secondary analyses that showed a statistically significant (40%) reduction in CRA with high-grade dysplasia with UDCA [41]. This result is consistent with previous studies that found decreased risk of CRC and dysplastic neoplasia with UDCA use in patients with ulcerative colitis [59]. These patients have a higher risk for invasive CRC

[6] that arise more frequently in the proximal colon [66] and independent of the adenoma–carcinoma sequence due to chronic inflammation and, possibly, higher bile acid exposures [67]. Given the low toxicity of the agent and potential benefit in the highest risk subgroup of CRA formers, further study of UDCA in patients prone to high-risk lesions is warranted, perhaps in combination with other low-toxicity agents [6] targeting prostaglandin (PGs) to prevent colorectal neoplasia.

Box 3. Follow-up colonoscopy interval in postpolypectomy patients by risk group

High-risk group (3-year follow-up)

- Three or more adenomas, or
- ≥ 1 cm, or
- Villous histology ($\geq 25\%$), or
- High-grade dysplasia

Low-risk group (5–10-year follow-up)

- 1–2 tubular adenomas
- < 1 cm
- No high-grade dysplasia

Average-risk group (10-year follow-up)

- Hyperplastic polyp = no adenoma at baseline

Data from [7].

Targeting PGs to prevent colorectal neoplasia

One of the most consistent findings across observation-based human studies is the inverse association between NSAID use and CRC incidence and death [69–71]. NSAIDs are a class of drugs used for the treatment of inflammatory conditions that include over-the-counter agents, such as aspirin and the ‘profens’ ibuprofen and naproxen, as well as prescription agents, such as sulindac, indomethacin and piroxicam. The use of NSAIDs in CRC prevention is an area that has been reviewed extensively [69–71]. In this article, we focus on an abbreviated presentation of the basic mechanism of action of these agents in colorectal carcinogenesis and the relevance of these agents for chemoprevention. The efficacy of these agents for familial forms of CRC is discussed elsewhere [72].

Nonsteroidal anti-inflammatory drugs inhibit the COX activity of the enzyme PG G/H synthase [73]. NSAIDs have been shown experimentally to suppress malignant transformation and tumor growth, principally via inducing apoptosis and suppressing angiogenesis by inhibiting COX-2-mediated PG E₂ production in neoplastic tissues [74]. Work in animal models showed that aspirin and other similar nonselective NSAIDs (e.g., sulindac and piroxicam), as well as drugs that are selective COX-2 isoform inhibitors (COXIBs), reduce, but do not eliminate, chemically or genetically induced colorectal neoplasia [70]. In animal models, the benefit is equivalent for COXIBs and nonselective NSAIDs during the early initiating events of tumorigenesis, but efficacy during promotion or progression of lesions to malignancy is greater for COXIBs.

Results from observational studies strongly support a number of the preclinical conclusions about the mechanism and timing of NSAID activity in colorectal carcinogenesis [70]. The most consistent is the evidence that chronic and long duration, low-dose use of NSAIDs,

historically driven by the population use of aspirin, is associated with a reduced risk of CRC incidence and death. Of particular mention, which suggests the potential mechanism of action of aspirin, is the approximate 40% reduction in risk for COX-2-positive, but not COX-2-low-negative, CRCs in individuals with high intakes of aspirin observed in nested analyses of the Nurses' Health Study and the Health Professionals Follow-up Study [75]. While largely consistent across observational studies, the results from the randomized, controlled trials of aspirin with long-term follow-up are less consistent. The Physician's Health Study (aspirin 325 mg every other day with 5-year and post-trial follow-up) [76,77] and the Women's Health Study (aspirin 100 mg every other day with 10-year follow-up) [78] found no efficacy of low-dose aspirin for preventing CRC. By contrast, results from the pooling of two large, randomized, controlled trials [79] conducted in England (British Doctors Aspirin Trial [aspirin 500 mg daily for 5 years] and UK-Transient Ischaemic Attack Aspirin Trial [aspirin 300 or 1200 mg for 1–7 years]) support a significant reduction in the hazard ratio (HR) of CRC (HR: 0.74; 95% CI: 0.56–0.97), especially if aspirin use exceeds 5 years (HR: 0.63; 95% CI: 0.47–0.85). Importantly, the effect of aspirin use was detectable only after a 10-year latency period and was dependent on at least 5 years of trial dosing and subject compliance to the agent (HR: 0.26; 95% CI: 0.12–0.56). These results are highly consistent with those from animal studies that support continuous use of agents to achieve an anticancer benefit.

In the postpolypectomy patient population, Baron *et al.* found modest effects of aspirin at a low dose (81 mg/day) for any metachronous CRA, with greater benefit for advanced neoplasia [80]. No effect was observed for aspirin at a higher dose (325 mg/day). Baron *et al.* argue that, while low-dose aspirin achieves equivalent reductions in tissue PGE₂ production, the higher dosing may overly suppress prostanoids that are important in protecting the bowel from inflammatory damage [80].

While it is widely believed that regular use of NSAIDs reduces the risk of CRC, issues of efficacious dose and agent-related toxicities (e.g., gastrointestinal bleeding) remain unresolved and limit recommendations for use in the chemoprevention for CRC for all but the highest-risk group of FAP patients [72]. Ongoing efforts to understand individual (particularly genetic) differences that influence drug bioavailability, activity and toxicity may help to explain some of the inconsistent findings across studies and improve future use of these agents. For example, a common G–A single nucleotide polymorphism (SNP) at the –316 nucleotide position in the *ODC* gene has been shown to influence the chemoprevention benefit of aspirin for CRA development [81,82]. Barry *et al.* found that regular aspirin use was associated with a lower risk of metachronous CRA only in carriers of the A variant in *ODC* and that subjects with the GG genotype experienced no CRA prevention benefit with aspirin [82]. This enhanced response to aspirin among the carriers of this allele was recently replicated in an independent study [83]. It is presently unclear if the *ODC* polymorphism differentially influences toxicities with aspirin in terms of gastrointestinal bleeds or other toxicities. This example of a gene-by-drug interaction highlights the future use of patient genetic information to identify individuals who might benefit most from specific agents versus those that do not, in order to balance the risk/benefit ratio of relatively low-risk agents, such as aspirin, for use in the prevention of CRC.

Box 4. Findings from randomized, controlled trials testing dietary agents in colorectal neoplasia

- There was no effect of β -carotene 15 mg, vitamin C 150 mg, vitamin E 75 mg, selenium 101 mg and calcium carbonate 1600 mg daily on the growth of pre-existing CRAs, but fewer new CRAs with intervention [45]

- β -carotene or vitamins C and E had no effect on preventing metachronous CRA [138]
- There were modest significant reductions in metachronous CRAs with elemental calcium 1200 mg daily with no agent-related toxicity [43]
- Modest, nonsignificant reduction in metachronous CRA with daily elemental calcium 2 g were observed [44]
- There were no differences in metachronous CRAs with daily wheat-bran fiber 13.5 or 2 g [139]
- Modest significant increases were seen in metachronous CRAs with fiber as ispaghula husk [44,30]
- Daily elemental calcium 1000 mg and vitamin D3 400 IU had no effect on CRC incidence in postmenopausal women [46]
- Folic acid 1000 mg daily had no effect on CRA risk [140]
- Folic acid 500 mg daily had no effect on CRA risk [141]

CRA: Colorectal adenoma; CRC: Colorectal carcinoma.

Summary results of COXIBs

While NSAIDs have shown some promise in CRC prevention, the development of COXIBs for the treatment of inflammatory diseases with reduced gastrointestinal toxicities offered a new, potentially less toxic inhibitor of tumor-promoting PGs in the late 1990s [84]. Three randomized, controlled trials (the Adenomatous Polyp Prevention on Vioxx [AP-PROVe] trial, the Adenoma Prevention with Celecoxib [APC] trial and the Prevention of Sporadic Adenomatous Polyps [PreSAP] trial) were initiated between 1999 and 2000 to test the efficacy of this new class of selective agents to prevent sporadic CRA. These trials and their results were recently reviewed [85,86]. A pooled relative risk for all incident CRA and advanced CRA from these trials has been estimated at 0.72 (95% CI: 0.68–0.77) and 0.56 (95% CI: 0.42–0.75), respectively. While demonstrating the proof of principle for the efficacy of COXIBs in CRA prevention, regular use of COX-2 inhibitor drugs have subsequently been associated with significant, and, in some cases, life-threatening cardiovascular toxicity. Review of adverse events in the APPROVe and APC trials found that COXIBs, at the doses and durations used in the trials for CRA prevention, were positively associated with elevated and unacceptable risks for cardiovascular events, including myocardial infarction, stroke and heart failure. In the APC trial, the risk for an adverse cardiac or thrombotic event increased relative to dose, more than tripling the risk in the 400-mg twice-daily-dose arm. These results ultimately led to the suspension of all ongoing trials of COXIB agents for the prevention of CRA due to unacceptable risks relative to the potential prevention benefit.

The results of these trials, while disappointing, show that COX-2 is a viable target for the prevention of CRA, and support the general assumption that PG production is an important prevention target for CRA. However, the future use of such agents is likely to depend on whether or not the benefits of these agents can be achieved while mitigating the potential risk. This progress will likely require a better understanding of the underlying mechanisms of COXIB toxicity, including dose, duration of exposure and selectivity of the agent, in combination with interactions between the various prostanoids, genetic background and vascular health.

Comparison of NSAIDs with COXIBs

While no randomized, controlled trials have performed direct comparisons of NSAIDs with COXIBs, COXIBs appear to have greater potency than aspirin to prevent the development of metachronous CRA in short trial intervals of 3–5 years, although the magnitude of risk reduction for advanced neoplasias is comparable between the agents. In a recent nested case–control study, increasing numbers of prescriptions (used as a surrogate for dose and length of exposure) were associated with slightly greater reductions for CRC in COXIB users than in individuals prescribed nonselective NSAIDs [87]. However, unlike animal models, where effectiveness of NSAIDs and COXIBs are directly related to dose, the dose relationship of the chemoprevention benefit of either COXIBs or the NSAIDs is not clear and remains an important unanswered question. Similar to the story mentioned for the genetic variation in *ODC* and aspirin response, future efforts to better understand the role of genetic variation in sensitivity to the toxicities of certain agents may allow risk minimization based on genotype. For example, active research into the underlying mechanism of COXIB-related toxicity includes evaluation of polymorphisms in drug-metabolizing enzymes that influence drug levels (e.g., cytochrome P450 2C9 [CYP2C9]) and genes that mediate the downstream effects of COX-2 inhibition in the vasculature (e.g., *PGI2*, a suspect mediator of the cardiovascular risk of COXIBs) [88]. In the APC trial, for instance, carriers of a low-activity polymorphism in the *CYP2C9* gene (*CYP2C9*3*) achieved additional benefit with a higher dose of Celebrex®, whereas carriers of the more active wild-type allele (*CYP2C9*1*) or the common *CYP2C9*2* variant achieved no added benefit with increased dosing. Furthermore, *CYP2C9*1* carriers in both dose groups suffered greater risk of cardiovascular events compared with those on placebo, but the increased risk of such adverse events was present only among the higher dose *CYP2C9*2* and **3* carriers. Thus, genetic background seems important in predicting both a patient's response to celecoxib for the prevention of adenomas, as well as one's susceptibility to adverse cardiovascular effects. Such ongoing efforts may aid in the future identification of individuals most likely to respond to an agent and those at highest risk for adverse effects, allowing for more informed use of chemopreventive agents by balancing the risks and benefits.

Polyamines & prostanoids in colorectal carcinogenesis: role for combination chemoprevention

Loss of or truncating mutations in the *APC* tumor-suppressor gene in germ-line cells are responsible for the dominantly inherited syndrome FAP [89]. Individuals with FAP have a high likelihood of developing CRC through an adenoma-to-carcinoma sequence. The majority of sporadic CRCs are associated with loss of wild-type APC protein in somatic colorectal epithelial cells [90]. Thus, APC-dependent signaling is of great significance in both sporadic and some genetic forms of CRC.

Gene-expression array studies of genetically modified human cells and *Apc*^{Min/+} mice identified a large number of genes dys-regulated by loss of wild-type *APC*, including several involved in polyamine synthesis and transport. These APC-regulated genes include *ODC* [91], the first enzyme in polyamine synthesis and caveolin-1 [92], which acts to regulate polyamine transport [93]. Polyamines are small polycations, which are necessary for normal growth and development in mammals [94–96]. Polyamines have been shown to influence gene transcription [97], RNA stabilization and translational frameshifting [98]. The cellular functions of polyamines include intestinal mucosal maturation [99] and cell migration [100]. Intracellular polyamine concentrations and activity of ODC are elevated in CRC tissues and in premalignant CRAs of cancer patients [101]. Polyamine metabolism is also upregulated in intestinal epithelial tissues in humans with FAP [102]. APC signaling regulates ODC expression in both human cells and *Apc*^{Min/+} mice [91,103].

Inhibition of polyamine synthesis with the ODC inhibitor difluoromethylornithine (DFMO) suppresses intestinal polyamine levels and tumor formation in experimental models of colon carcinogenesis [103–105]. While studies of inhibitors of polyamine synthesis provide evidence for an important role of polyamines in intestinal and colon carcinogenesis, it is important to recognize that tissue polyamine contents are dependent on several mechanisms, in addition to those affecting synthesis. Polyamine contents are also dependent on processes affecting polyamine catabolism and transport into and out of cells [106]. Thus, therapeutic strategies to optimally reduce tissue polyamine contents may need to target features of polyamine metabolism in addition to synthesis.

The DFMO drug is an enzyme-activated, irreversible inhibitor of ODC [107,108]. DFMO reduces putrescine and spermidine contents in normal human colorectal tissues particularly [109,110] and suppresses polyamine contents and carcinogenesis in intestinal tissues of mice, including *Apc*^{Min/+} models [103]. We have conducted DFMO dose-deescalation clinical trials to identify a low oral dose of this drug that inhibits colorectal polyamine contents without causing significant toxicities [110,111].

Sulindac is an arylalkanoic acid class NSAID [112]. Sulindac is metabolized into sulfide and sulfone derivatives. The sulfide derivative nonselectively inhibits both COX-1 and -2, while the sulfone derivative lacks COX-inhibitory activity. However, both these sulindac derivatives show the potential to reduce colon carcinogenesis in rodent models [113,114]. Sulindac can cause regression of colon and intestinal CRAs in patients with FAP [115].

Our strategy for clinical combination CRC chemoprevention by adding NSAIDs to DFMO is based on our findings that certain NSAIDs, including sulindac, aspirin and celecoxib, suppress features of colon carcinogenesis, at least partially, by enhancing polyamine catabolism and export [81,116–119]. This mechanism does not exclude an effect of sulindac on inflammation associated with cancer development. The sulindac effect on polyamine catabolism involves induction of the spermidine and *SAT1*, which is associated with a diamine or acetylpolyamine/arginine antiporter [120]. Dietary arginine and nitric oxide have been implicated in colon carcinogenesis in mouse models [121,122]. Nitric oxide production by nitric oxide synthase 2 has also been shown to influence colonic inflammation in rodents [123]. These data suggest linkages between polyamines and inflammation and colon carcinogenesis.

Beginning in the early 1990s, our group conducted a series of translational clinical trials to establish and validate adequate markers of DFMO in colorectal tissues in normal human volunteers [109,124,125] and mode of DFMO delivery and dose selection in patients with prior CRA [110,111]. These early translational studies established that measures of polyamine content changes, including putrescine, spermidine and spermidine:spermine ratios, were reliable markers of the effect of DFMO in colorectal tissue. These studies also demonstrated that an oral dose of DFMO 500 mg/day reduced rectal mucosal polyamine contents in a statistically significant manner without causing significant toxicities compared with placebo. In separate studies, colleagues from the University of Arizona showed that measurement of PGE₂ was a reliable measure of the effect of the NSAID piroxicam in colorectal tissue in patients treated in a chemoprevention setting [126,127]. From 1997 to 2002, a randomized, placebo-controlled, Phase IIb trial of DFMO (500 mg/day) combined with sulindac (150 mg/day) for 3 years was conducted in patients with prior colon CRA. The primary end points of this study were tissue polyamine and PGE₂ contents.

At completion of the Phase IIb trial of 250 patients, the decision was made to keep this trial blinded and to use the trial cohort as a vanguard for a Phase III trial of combination DFMO and sulindac versus placebo, which would assess metachronous CRA as the primary end

point. The Phase III trial accrued an additional 125 patients for a total of 375 patients in the combined trials. On the advice of the trial Data and Safety Monitoring Board (DSMB), this merged Phase IIB/III trial was stopped for reasons of efficacy in the spring of 2007. The DSMB indicated that their decision was based on two major issues. First, the efficacy question originally asked in this trial would be answered in a statistically significant manner without additional patient accrual. Second, the DSMB decided that due to the small size of the trial (375 patients randomized) no additional information on toxicities of the interventions would be obtained in the context of the existing trial design. Consequently, steps were initiated to close accrual to this trial and evaluate and report the trial results.

The findings from this trial were reported in the inaugural issue of the new cancer prevention journal sponsored by the American Association for Cancer Research [128]. The combination of DFMO and sulindac suppressed total CRA recurrence in this study by 70% (Figure 2). More importantly, the combined therapy reduced recurrence of advanced and/or multiple CRAs by more than 90%. It is the recurrence of advanced CRAs or more than two CRAs that is most closely associated with risk of developing cancer [8,9]. Sporn and Hong provided a commentary with the publication of these clinical trial results [129]. They stated that,

“The spectacular clinical results reported ... represent a landmark advance...[and] ...sets a new, exceptionally high standard for future clinical research on the chemoprevention of cancer.”

The Meyskens *et al.* clinical study represents the first validation of the concept of combination chemoprevention, proposed by Sporn in 1980 [130]. The magnitude of the effect on prevention of those CRAs that most closely associated with cancer risk also suggests, for the first time, that chemoprevention may have some role in the clinical management of patients at risk for CRC. For example, medicines that would significantly reduce metachronous CRAs might decrease the overuse of surveillance colonoscopies in patients with prior CRCs [131].

Toxicity of combination DFMO & sulindac

When proposing a drug for use as a chemopreventive agent, a low-risk safety profile is essential. While the combination DFMO and sulindac therapy for 3 years at the doses administered did not produce any statistically significant clinical toxicities [128], the study was severely underpowered to identify such adverse events. There were troubling nonstatistically significant trends for certain categories of toxicities that might be clinically significant in a larger population setting and if given over longer duration. One example, cardiovascular toxicities, is of special concern. COX-2 selective drugs have been reported to be associated with a high rate of significant cardiovascular toxicity [132,133], and some studies have suggested that such drugs have no role in CRC chemoprevention for patients at an average risk of this disease [134]. A careful analysis of the cardiovascular toxicities in this trial found that their occurrence was associated with patients' cardiovascular risk factors at study entry [135]. This finding is very similar to results reported for patients in the chemoprevention trials using COXIBs to target COX-2 [136], which has resulted in a US FDA-mandated 'black box' warning of cardiovascular risk for all nonselective NSAIDs (including sulindac).

A second category of concern was DFMO-associated oto-toxicity. Beginning in 2005, the DSMB for the DFMO-sulindac clinical trial required that all patients in both arms of the study undergo quantitative audiological testing, in order for drug-related effects on this end point to be understood. There were no statistically significant differences between study arms in ototoxicity, as measured by air conduction audiograms, in the normal speech range

of 500–3000 Hz. However, 9.3% of people in the DFMO–sulindac arm, compared with 2.9% in the placebo arm ($p = 0.02$), experienced a hearing reduction of at least 15 dB from baseline in two or more consecutive frequencies across the entire range tested [17]. The subset of patients experiencing ototoxicity appears to be associated with a SNP affecting the expression of the gene encoding ODC, the target protein for DFMO [ZELL, UNPUBLISHED DATA]. Thus, toxicities associated with combination chemoprevention with DFMO and sulindac may be minimized by careful patient selection. Patients with high cardiovascular risk factors at baseline might be excluded from chemoprevention trials involving NSAIDs, and patients with certain genetic features might be excluded or at least advised about the potential risks in trials involving DFMO. Clearly, all available risk–benefit issues should be considered.

The remarkable effects of this drug combination on recurrence of advanced and/or multiple CRAs suggests that this treatment might be most appropriate in patients with more than an average risk of CRC. These groups would include patients with prior advanced CRA, multiple CRAs, or CRC or those with genetic risk of CRC, such as those with FAP. Table 1 provides an example of how chemoprevention with DFMO–sulindac combination can provide a positive benefit-to-risk ratio when treatment is limited to populations with more than an average risk of CRC and care is taken to minimize known toxicities.

Expert commentary

Colonoscopy is an effective method for the detection and removal of CRAs and, thus, aids the prevention of CRC. However, several lines of evidence indicate that colonoscopy has limitations in clinical practice, especially in the ability to detect and possibly prevent death from right-sided (or proximal) CRC. In addition, surveillance colonoscopy is overused in certain patient groups due to poor risk discrimination, restricting the wider application of screening colonoscopy. Advances in endoscopy techniques, including chromoendoscopy and CT colonography, hold promise to address some of the current issues associated with endoscopy for screening and surveillance. However, their clinical application remains to be envisioned, again owing to a lack of information on individual-level risk and significance of small and nonpolypoid lesions. Chemoprevention has the potential to augment current and future endoscopy approaches in the management of patients at high risk for CRC. Effective chemoprevention agents, such as the combination of DFMO and sulindac, hold the potential to augment or even supplant current endoscopy methods by inhibiting the development of CRAs, minimally lengthening the surveillance window and preventing CRC for some individuals. However, all effective CRA chemopreventive agents tested to date have exhibited some degree of toxicity. This issue continues to challenge the field toward single agents and agent combinations that can be beneficially applied, while considering a risk spectrum that includes both risk of CRC and risk for adverse events from chemoprevention agents. The work to date provides proof of principle for targeting PG synthesis, polyamines and even bile acids for the prevention of CRA and presumably CRC. However, future efficacy of chemoprevention strategies will depend on additional clinical trials designed to derive minimally toxic but effective doses for managing CRC risk in patients at moderate risk (e.g., those with prior localized CRC or with prior advanced and/or multiple adenomas) to high risk (e.g., those with genetic risk such as FAP). Stratification of risk and benefit, using clinical, epidemiologic and pharmacogenetic parameters for novel risk-assessment models, can help to maximize patient benefit while minimizing risk from chemoprevention agents.

Five-year view

There are currently no methods of chemoprevention that are approved by the FDA as effective for use in the usual clinical practice of managing the majority of patients with risk

for CRC. Over the next 5 years, a number of clinical trials will be conducted that will likely identify agents that effectively reduce advanced and/or multiple adenomas. We project these will largely involve agents and agent combinations targeting polyamines, prostanoids, and possibly bile acids, for which effective dosing with minimal toxicity will be prioritized. These trials are envisioned to lead to FDA-approved indications for medicines that can be usefully incorporated into the clinical management of patients, although their acceptance by the US Preventive Services Task Force will require demonstration of individual benefit. Extensive efforts toward a risk-assessment model for colorectal neoplasia with high individual-level prediction are needed but will remain challenged by the fact that we simply do not know which premalignant lesions harbor cancer potential. Perhaps extrapolation from molecular studies of CRC will prove informative on subsets of high-risk preneoplasias. Theoretically, short-term, highly efficacious chemoprevention studies with agents, such as DFMO/sulindac, perhaps combined with improved CT colonography, will open new avenues for randomized clinical trials where all lesions are not removed but rather monitored. We foresee rapid advances in the general understanding of the necessary events to carcinogenesis in the colorectum in the next 5 years. We also forecast that the need to improve the effective use of colonoscopy at the population level will increase owing to greater demands on the healthcare system, possibly driving toward a refocusing on the eradication of CRC and not necessarily every CRA and polyp. This activity is likely to be greatly enhanced by studies, such as the recent work of Chan *et al.* for *CYP2C9* [137], and our own unpublished findings on *ODC* [ZELL, UNPUBLISHED DATA]. Pharmacogenomic, molecular markers and clinical characteristics (e.g., pre-existing cardiovascular disease) will be utilized, allowing for stratification of patients on their risks, including their individual risk of CRC and their risks associated with taking specific medications, such as NSAIDs, DFMO or combinations thereof. Ultimately, we expect that rationally applied screening and surveillance colonoscopies with (for high-risk individuals) and without (low-risk individuals) chemoprevention for CRC will permit better utilization of resources. Such success will promote the continuance of declining rates of CRC mortality in both men and women through increasing eradication of significant precursor events to CRC.

Key issues

- There is a must to capitalize on existing cohorts, covariate, and genetic data, and pool efforts to improve risk assessment to identify groups at greatest risk for advanced neoplasias and colorectal carcinoma.
- Identify minimal doses of single agents and agent combinations with low toxicity that show efficacy for advanced neoplasias. In addition, identify combined lifestyle and agent prevention approaches evaluating their effects on polyamines, prostaglandins and bile acids.
- Mine existing datasets to understand determinants of toxicity and response to interventions with a focus on genetic predictors and the role of pre-existing conditions.
- Design trials to assess efficacy of combination chemoprevention to replace or delay follow-up with endoscopy-based procedures (perhaps integrating computed tomography colonography as the method of surveillance).
- Understand the effect of agents in relation to the underlying biology of the disease that segregates with the proximal and distal colon (e.g., microsatellite instability, *RAS* mutations, *BRAF* mutations, CpG methylator phenotypes and *APC* mutations).

- Evaluate the need for differential risk profiling, intervention strategies and surveillance approaches for rectal versus colon cancer.

Acknowledgments

Eugene Gerner acknowledges his long-time collaboration with Frank Meyskens, Director of the Chao Family Comprehensive Cancer Center at the University of California-Irvine. The authors acknowledge their many close collaborators at the University of Arizona and especially thank Cindy Thompson and Betsy Wertheim for their comments on the manuscript.

Patricia Thompson and Eugene Gerner have been supported by numerous grants from the NIH. Major current support comes from NIH P30CA23074, P01CA41108 and P5095060. Eugene Gerner also has an ownership interest in Cancer Prevention Pharmaceuticals, Tucson, Arizona

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Figure 1. Findings at screening colonoscopy and relative risk for advanced neoplasia at 5-year follow-up

The relative risk of developing an advanced neoplasia based on the clinical or pathologic findings at screening colonoscopy.

TA: Tubular adenoma.

Adapted from the results reported by [8].

Figure 2. Combination DFMO and sulindac chemoprevention and metachronous adenoma at follow-up colonoscopy

All comparisons $p < 0.001$.

DFMO: Difluoromethylornithine.

Adapted from [128].

Table 1

Estimated incidence rates of 3-year colorectal cancer and toxicity events for 1000 patients with colorectal adenoma.

Event	Average risk	Moderate risk		
	<i>No treatment</i>	<i>No treatment</i>	<i>DFMO + sulindac</i>	<i>DFMO + aspirin (325 mg)</i>
Colorectal cancer	3.1	~30*	~3	~3
Cardiovascular	14.6	~15	~15–30	~10–15
Total	17.7	~45	~18.33	~13–18

Modified from [134] for DFMO + NSAID based on observed relative risk for colorectal cancer and cardiovascular disease in the Adenoma Prevention with Celecoxib and the Prevention of Sporadic adenomatous Polyps studies, and risk reduction of 90% observed with the combination of DFMO + sulindac for advanced neoplasias [128]. Risks and benefits are estimated over a 3-year period/1000 individuals with colorectal adenomas.

* In the absence of treatment there is approximately a tenfold increase in risk of advanced neoplasia estimated from the findings of Lieberman [8]. Risk reduction with DFMO + aspirin assumes the same magnitude of benefit as observed with DFMO + sulindac. Increased cardiovascular disease events were estimated for sulindac between 0 and 50% based on risk, with the COX-2 isoform inhibitor as worst-case scenario. The cardiovascular disease risk reduction with low-dose aspirin + DFMO was estimated at 0–30% [134], with the upper-end based on the known benefit of low-dose aspirin on heart health and assuming no cardiovascular disease risk with DFMO.

DFMO: Difluoromethylornithine.