**Special Review**

**Colorectal Adenomas: A Prototype for the Use of Surrogate End Points in the Development of Cancer Prevention Drugs**


1 Division of Cancer Treatment and Diagnostics, National Cancer Institute, Bethesda, Maryland; 2 Biological Sciences Division, University of Chicago, Chicago, Illinois; 3 University of Arizona Cancer Center, Tucson, Arizona; 4 Fred Hutchinson Cancer Research Center, Seattle, Washington; 5 CCS Associates, Mountain View, California; 6 Lilly Research Laboratories, Indianapolis, Indiana; 7 Institute of Alternative Futures, Alexandria, Virginia; and 8 Ontario Cancer Research Network, Toronto, Ontario, Canada

**INTRODUCTION**

Carcinogenesis is a multiyear, multistep, multipath disease of progressive genetic alterations and associated tissue damage. Chemoprevention is the use of drugs or other agents to inhibit, delay, or reverse this process. Despite the enormous population at risk of cancer who would benefit, drug approvals for chemopreventive indications have been slow to emerge. A critical factor is the definition and demonstration of clinical benefit. Historically, reduced cancer incidence or mortality has been required to show chemopreventive benefit. These end points make chemoprevention trials long, large, costly, and, hence, impractical and risky for drug developers. Recent strategies have instead focused on developing chemopreventives as treatments for the disease process of carcinogenesis. Specifically, these strategies focus on prevention or regression of a significant precancerous lesion, intraepithelial neoplasia [IEN (1–7)].

**Why IEN?**  As a near obligate precursor to cancer, IEN is an appropriate target for intervention. Occurring in most epithelial tissue as moderate to severe dysplasia, IEN shares phenotypic and genotypic similarities with invasive disease and is on the causal pathway leading from normal tissue to cancer. In addition, IEN serves as a significant risk marker for cancer. Subjects with IEN, particularly those with severe IEN, are at significantly higher risk than unaffected individuals for developing invasive cancer in the same tissues. This risk in fact exceeds other measurable factors (e.g., age, race, and family history), with the exception of germ-line mutations that occur in genetic syndromes. IEN is also a disease in its own right, in that treatment provides clinical benefit. In standard clinical practice, invasive surgical interventions are used to reduce the burden of IEN. This same goal of reducing IEN burden is thus also appropriate for medical (noninvasive) intervention, not only to reduce invasive cancer risk, but also to reduce surgical morbidity.

**Colorectal Adenomas as an IEN Prototype.** Whereas IEN is a validated precursor in most epithelial tissues, colorectal adenomas are one of the best-characterized IENs and a best-case example for using IEN as surrogate end points in development of drugs for cancer prevention. The adenoma to carcinoma sequence is well characterized. The colorectal cancer (CRC) risk conferred by adenomas is recognized, and screening for and surgical removal of adenomas are already recommended medical practice for prevention of CRC. Further and significantly, strong evidence from epidemiological and clinical studies suggests that drugs that reduce adenoma burden also decrease CRC incidence and mortality. For example, more than 20 studies have demonstrated an association between the frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, and reduced risk of colorectal adenomas, cancers, and cancer-related mortality.

This article states the evidence that establishes colorectal adenoma as a surrogate end point in the clinical development of drugs for CRC prevention. Early end points for intervention and monitoring are identified with a focus on the adenomatous polyp. Assessment of the risk posed by these early lesions and other factors is also addressed. Example trial designs for preventive agents are presented, encompassing recommendations of the March 2002 United States Food and Drug Administration (FDA) Gastrointestinal (GI) Drugs Advisory Committee. Case studies that illustrate the challenges involved in the development of colon cancer prevention drugs are also presented.

**CRC: DISEASE ETIOLOGY, RISKS, AND BURDEN**

Colorectal carcinogenesis is a protracted process that occurs over a period of decades (see Fig. 1). During this time, cancer-associated gene mutations successively accumulate, and a benign (but initiated) enterocyte progresses to an invasive cancer (8). The earliest changes include mutations in key oncogenes and tumor suppressor genes [e.g., APC and K-Ras (9)]. Also associated with the carcinogenic process are epigenetic alterations [e.g., DNA hypermethylation leading to silencing of tumor suppressor genes (10)]. A number of these early molecular events and lesions can be assessed in blood or in cells exfoliated into the stool and may serve as markers of cancer risk and/or of response to therapy. Examples include gene mutations and polymorphisms (e.g., of oncogenes and carcinogen-metabolizing enzymes) as well as alterations in gene expression [e.g., aberrant gene promoter hypermethylation of hMLH1 (11), loss of imprinting of the insulin-like growth factor II gene (12)], as well as secreted cancer-associated proteins and antigens [e.g., carcinoembryonic antigen (13)]. Ongoing developments have focused on applying proteomic, genomic, and gene expression microarray profiling approaches to tissue, blood, or stool tests. For example, a stool-based genomic panel targeting 19 alter-
ations associated with colorectal neoplasia (including mutational hot spots on K-Ras, APC, and p53, as well as long fragment DNA) is currently under evaluation (14, 15).

Among the first histologically detectable changes that may be associated with CRC development are subtle alterations in the regular pattern of the intestinal crypts known as aberrant crypt foci (ACF). ACF appear to arise as the result of premalignant genetic alterations; they often show APC loss (16), as well as K-Ras mutations (17). The number, size, and dysplastic features of ACF correlate with the number of adenomatous polyps [adenomas (18)], which in turn constitute one of the most well-established CRC risk markers (1). The association of adenomas with CRC, first reported in 1928 from St. Mark’s Hospital (19), was later defined by Morson (20–23). Stryker et al. found a relative risk of CRC development of approximately 1% per year for adenomas >1 cm (24). In addition to size, important determinants of CRC risk include adenoma number (25) and clinical features such as histological architectural type. For example, tubular histology is associated with the lowest lifetime risk (5% overall), villous lesions are associated with the highest lifetime risk (up to 50%), and tubulovillous lesions are associated with an intermediate lifetime risk (15–20% (26)).

Screening studies have indicated that CRC is typically diagnosed 10–15 years after adenoma detection (27). This temporal lag presents a compelling rationale and opportunity, if not responsibility, for screening and intervention. Several landmark case-control studies and controlled clinical trials have provided strong, albeit indirect, evidence that adenoma removal decreases CRC incidence (28–34). The incidence of CRC has been declining since 1985, at a rate of 1.6%/year through 1997 (35), likely due to widespread implementation of CRC screening and adenoma removal; hormone replacement therapy use may also have contributed to the decline (36, 37). Additional indirect support for the adenoma–carcinoma sequence includes the overlapping anatomical distribution of adenomas and CRC. CRCs often contain adenoma remnants (38), and most of these remnants (98%) have cancer-associated somatic mutations. Nearly all CRC patients have ACF, and 20–30% have synchronous adenomas (18, 39). Observational studies associating NSAID use with reduced CRC incidence or mortality also show a parallel decrease in adenoma incidence (40–46). The strength of this indirect evidence ethically precludes the conduct of clinical trials to study the natural history of unresected adenomas. Assessment of response of unresected adenomas to nonsurgical intervention is also not feasible.

CRC represents a significant public health burden, especially in developed countries. Adenomas are a very prevalent lesion; nearly half of men and 30% of women develop adenomas by age 50 years (47). More than a million outpatient colon polypectomies are performed annually in the United States (48). For men and women in the United States, CRC ranks as the third most frequently diagnosed cancer, as well as the third leading cause of cancer-related mortality (35). Of the 146,940 new CRC cases projected in the United States for 2004, <60% are likely to survive 5 years. CRC represents >10% of all cancer mortality, with >56,000 American deaths expected in 2004. In addition to environmental and lifestyle factors (dietary fat and calcium, exercise, NSAID use, and so forth), multiple inherited and acquired genetic factors contribute to CRC risk (49). At the highest risk for CRC are patients with familial adenomatous polyposis (FAP), an autosomally dominant hereditary syndrome caused by mutation or truncation of the APC gene. Although FAP is rare, accounting for <1% of CRC cases, the lifetime CRC risk in FAP patients is nearly 100%. The molecular biol-
ogy and etiology of CRC in FAP is thought to parallel sporadic cancers. Indeed, 80% or more of sporadic CRCs contain a mutation in either APC or an associated oncogene, β-catenin (50–53). Other familial CRC syndromes include hereditary nonpolyposis CRC, which accounts for 5% of all CRC cases. Caused by germ-line mutation in one of several DNA mismatch repair genes, hereditary nonpolyposis CRC has an associated lifetime CRC risk of up to 90% (54). Even outside of FAP and hereditary nonpolyposis CRC kindreds, familial clustering of CRC is common; a positive family history is a significant CRC risk factor. Other high-risk populations include patients who have had a prior CRC, as well as patients with inflammatory bowel disease.

These data underscore the need for effective strategies for both CRC prevention and treatment. The following sections address approaches and considerations for developing beneficial preventive strategies. Prototype clinical trial designs, as well as case studies, are presented.

**CRC PREVENTION CLINICAL TRIAL DESIGNS**

An appropriate setting for Phase III clinical testing of pharmacological agents for CRC risk reduction is a 3-year, prospective, randomized trial with the primary end point of adenoma incidence after colonoscopy with polypectomy (Ref. 1; Fig. 2). Secondary end points should include adenoma number, adenoma size, and histological type. Either placebo or another treatment (or control intervention) would give 3:2 to receive either 3 years of intervention or placebo (or control intervention) would give >90% power to demonstrate a 35% decrease in adenoma incidence and a 15–20% increase in polyp-free patients. This general design is presented in Table 1; specific trials will vary with cohort eligibility (e.g., prior adenomatous polyps versus early-stage CRC, frequency of subject monitoring, and so forth). The net clinical benefit on CRC incidence and mortality of such a reduction in adenomas might best be estimated from the National Polyp Study data, which showed a 76–90% reduction in cancer incidence by colonoscopy-based polypectomy after an average of 5.9 years follow-up (29). Such estimates could also be derived from the several large randomized trials, involving nearly 350,000 individuals, of fecal occult blood test screening [which ultimately leads to colonoscopy and polypectomy (59, 60)].

Additional benefits from reducing adenomas medically would also be possible. For example, a 25–50% reduction in colonoscopy complications (which are primarily associated with polypectomy) would constitute a meaningful clinical benefit. The risk of perforation for colonoscopy and sigmoidoscopy is estimated at 1.96 and 0.88 per 1000 procedures, respectively (61). Perforation is, in turn, associated with an approximately 9-fold increased risk of death from either procedure. The possibility of extending the surveillance interval is another intriguing benefit that could reduce morbidity and mortality. The interval between surveillance exams would only be increased after sufficient long-term data are available; for example, if adenoma burden is eliminated by drug intervention. In time, molecularly based risk stratification may also permit a more protracted surveillance schedule in individuals experiencing adenoma reduction in response to medical intervention. Finally, emerging data from ongoing trials of surveillance methodologies may help to inform the definition of an appropriate interval in the context of effective medical intervention.

**Efficacy and Clinical Benefit.** Possible primary efficacy outcomes for this Phase III trial include reduction in adenoma incidence or increase in polyp-free patients. It is anticipated that 25–35% of patients undergoing colonoscopy with polypectomy will have disease at follow-up (28, 29). This figure includes both newly formed adenomas and those missed at the original endoscopy. The level of reduction in the expected adenoma burden that is considered to constitute clinical benefit has been addressed recently by several groups [e.g., AACR’s IEN Task Force (1) and the FDA GI Drugs Advisory Committee]. At a March 2002 meeting, the latter group estimated clinical effectiveness as a 35% reduction in adenoma incidence or a 15–20% increase in patients without adenomas, compared with placebo 3 years after initial polypectomy (57, 58). It was proposed that a Phase III study of approximately 1,500 evaluable patients randomized 3:2 to receive either 3 years of intervention or placebo (or control intervention) would give >90% power to demonstrate a 35% decrease in adenoma incidence and a 15–20% increase in polyp-free patients. This general design is presented in Table 1; specific trials will vary with cohort eligibility (e.g., prior adenomatous polyps versus early-stage CRC, frequency of subject monitoring, and so forth). The net clinical benefit on CRC incidence and mortality of such a reduction in adenomas might best be estimated from the National Polyp Study data, which showed a 76–90% reduction in cancer incidence by colonoscopy-based polypectomy after an average of 5.9 years follow-up (29). Such estimates could also be derived from the several large randomized trials, involving nearly 350,000 individuals, of fecal occult blood test screening [which ultimately leads to colonoscopy and polypectomy (59, 60)].
risk:benefit analyses are necessary to quantitatively estimate whether the risks of intervention outweigh the expected potential benefits in a given population. For example, in the United States, an estimated 100,000 hospitalizations and 16,500 deaths per year result from NSAID use (62). NSAID toxicities tend to occur as a function of increasing age, increasing dose, concomitant use of corticosteroids or anticoagulants, and comorbid conditions (63). Thus, if a low NSAID dose conferred a 35% reduction in adenoma burden, the benefit could outweigh the risk in a young, otherwise healthy cohort who take no other medications. On the other hand, if a high NSAID dose was necessary for efficacy, the risk might outweigh the benefit in an older population with significant comorbidity.

To gather data for such analyses, longer-term safety can be assessed after the demonstration of efficacy by extending the study to include an additional 3 years of intervention with follow-up. Subjects who did not benefit could be excluded from the follow-up cohort. Because re-randomization may not be feasible (e.g., due to ethical constraints or insufficient patient numbers), continued treatment would be optional, but all subjects would be followed. Alternatively, re-randomization at 3 years of the active arm to placebo or continued treatment could be considered, as was done in the National Surgical Adjuvant Breast and Bowel Project trial that examined the optimal duration of tamoxifen therapy (64). Either setting would allow a rigorous and protracted safety evaluation in a controlled setting with the goal of identifying common adverse drug reactions (ADRs) and characterizing serious event rates (65).

In support of this approach, a recent analysis of postmarketing ADR data for 22 drugs found that clinically significant ADRs for most drugs were detected within a year or two of marketing (66). Although often limited by underreporting, posttrial safety surveillance would complement the approach. Whereas the controlled trial would characterize common ADRs, postmarketing pharmacovigilance is more likely to identify idiosyncratic and uncommon (occurring at a rate of 0.5–10%) side effects, as well as patient subgroups at higher risk of ADRs (e.g., based on age, gender, genetic phenotypes of drug-metabolizing enzymes, chronic disease, multiple drug use, and so forth). Many of these subgroup characteristics (including metabolism, pharmacogenetics, demographics, concomitant medications, or physiological or pathophysiological states) can influence drug pharmacokinetics and, in turn, clinical efficacy and safety (66). A drug’s potential for metabolic-based interactions is often a key determinant of ADR development and, in several instances, has led to marketing withdrawal long after approval. For example, terfenadine (Seldane) is metabolized extensively by the cytochrome P-450 isozyme CYP3A4. Coadministration with any of the commonly used drugs that inhibit this isozyme (e.g., ketoconazole, itraconazole, clarithromycin, quinine, and so forth) results in accumulation of terfenadine and enhances the incidence of serious and sometimes fatal QT interval prolongation and ventricular arrhythmia. Based on postmarketing safety reports, terfenadine was withdrawn from the market in 1998, 13 years after approval. This and similar examples of drugs removed from the market (e.g., astemizole and mibefradil) highlight the need for early characterization of the potential for metabolic-based drug-drug and drug-pharmacogenomic interactions, as well as the need of pre- and postmarketing monitoring for resulting ADRs.

Long-Term Clinical Benefit. In addition to the enhanced safety evaluation, continued intervention and follow-up of active arm subjects would permit collection of further data regarding the drug effect in a placebo-controlled or observational setting that is in keeping with the standard of care. Such data will give insight (e.g., how long the treatment should continue) that will dictate costs and influence patient acceptability and utilization, which are in turn significant determinants of net patient benefit. Offering optional 3-year treatment to placebo subjects before the year 6 colonoscopy should also be considered. This approach may enhance accrual (because all subjects will be offered access to active drug) and may bolster the analysis by increasing the population of subjects on drug who undergo rigorous follow-up. This group could also serve as the basis for comparison with subjects who were initially randomized to active drug (for example, to assess durability of the drug effect). Furthermore, offering continued follow-up to placebo subjects who elect not to take drug would provide a comparison group to those subjects taking drug for years 0–3 and followed to year 6 (e.g., to assess potential rebound after ceasing active drug).

The size of the trial would afford opportunities to address important molecular and biological questions regarding preinvasive disease (3). In particular, the relationship between adenoma incidence and other precursor lesions such as ACF could be assessed in nested cohort studies. Detailed molecular analy-
serves of adenomas that develop despite treatment would also be warranted. In particular, a comparison with adenomas found in placebo subjects would help to identify any distinguishing characteristics of these persistent lesions (i.e., whether drug-resistant polyps are more aggressive or confer greater risk for cancer development).

**DRUG INTERVENTION COMPLEMENTS SCREENING**

The complementary roles of screening and drug intervention should be considered in the development of effective strategies to prevent colon cancer. Central to this effort is the definition of appropriate screening techniques and intervals, in both the presence and absence of an effective intervention. Whereas screening by any method is universally endorsed, agreement is lacking on the preferred screening strategy for average-risk individuals beginning at 50 years of age; for example, the American Cancer Society and the American College of Gastroenterology provide differing guidelines, with the latter organization preferentially recommending colonoscopy every 10 years (67, 68). Compelling indirect evidence suggests that colonoscopy is an effective screening tool, but the procedure has an associated risk estimated at 1–3 deaths/10,000 procedures with biopsies (61, 69). Most available screening modalities for adenoma detection have never been directly compared in clinical trials. Considerations for the testing and evaluation of new and current procedures for CRC screening are similar to those applied to drug intervention. Trial designs include a randomized comparison of colonoscopy versus fecal occult blood test or flexible sigmoidoscopy or both. Although a mortality end point is the most direct measure of efficacy and safety of new or current screening modalities, the cost, size, and subject and provider acceptance of the trial would likely be prohibitive. A preferable end point would be an adenoma or advanced adenoma (70). An efficacy trial with an adenoma end point for screening procedures would share many design features with a preventive agent trial (see Table 1), including duration (3 years), size (about 700 per arm), and assessment of benefit (an approximately 35% reduction in adenoma number or colonoscopy complications or a 15–20% increase in adenoma-free patients). As for preventive agents, risk/benefit analyses of screening trial results need to consider issues such as safety, acceptance, and cost of implementing the screening modality. Importantly, such effort will lay the groundwork for the more promising strategy of using efficacious and safe drug interventions in combination with less frequent screening.

**CRC PREVENTION CASE STUDIES**

A number of chemopreventive agents have shown promise in clinical CRC prevention, and several have demonstrated clinical efficacy against colorectal adenomas or neoplasms. Two chemopreventive drugs, celecoxib (Celebrex) and ursodiol (Actigall), are discussed in detail to illustrate challenges to drug development in colon cancer prevention. Clinical data are also presented on two widely used agents, aspirin and calcium. Although neither represent the ideal intervention, these clinical trials demonstrate proof of principle for the trial designs exhibited in Table 1.

**Celecoxib.** Celecoxib has a known molecular target [cyclooxygenase (COX)-2]. Non-COX targets may also contribute to the effect. In 1999, the FDA granted accelerated marketing approval for celecoxib “to reduce the number of adenomatous colorectal polyps in FAP as an adjunct to usual care” (FDA, December 23, 1999). The rationale for testing a specific COX-2 inhibitor in FAP is based on mechanistic data, preclinical efficacy studies, as well as epidemiological and clinical intervention investigations (for recent reviews, see Refs. 71–73). This supporting evidence includes the observation that COX isoenzymes are overexpressed in colorectal adenomas and tumors (74–82). Targeted deletion of the COX-2 gene prevents CRC in animals, and celecoxib as well as other selective COX-2 inhibitors (e.g., JTE-522, NS-398, the tricyclic methyl sulfone derivative MF tricyclic, nimesulide, and rofecoxib) are also effective in preclinical models (83–91). In addition, substantial epidemiological evidence supports a 40–50% protective effect of NSAIDs (primarily aspirin) against colorectal carcinogenesis (see Refs. 40, 41, and 92–95, and more than 30 additional studies are reviewed in Refs. 72, 96, and 97). A number of studies have also shown that the NSAID sulindac regresses adenomas in FAP patients (reviewed in Ref. 98). In a recent study of 21 FAP patients, rofecoxib (25 mg once daily for 9 months) modestly reduced rectal polyp number (9.9% decrease) and size (21.7% decrease (99)).

The Subpart H approval was based on a randomized, double-blind, placebo-controlled study of 83 FAP patients in which 400 mg twice daily celecoxib for 6 months significantly reduced adenoma number by 28% [P = 0.003 compared with the 4.5% reduction with placebo (100)]. In addition, this celecoxib dose significantly reduced adenoma burden (the sum of adenoma diameters) by 30.7% (P = 0.001 compared with the 4.9% reduction with placebo). In patients receiving 100 mg twice daily celecoxib, the reductions in adenoma number and burden were 11.9% and 14.6% (P = 0.33 and P = 0.09 for the comparison with placebo, respectively). A blinded physicians’ assessment indicated a qualitative improvement in the colon and rectum and, to a lesser extent, in the duodenum of treated subjects (101).

Postmarketing studies to show the clinical benefit of celecoxib in FAP are ongoing. These include a two-part Phase II study to evaluate safety and FAP phenotype suppression in genotype-positive children and a Phase II study to determine whether greater efficacy against adenomas and other manifestations of FAP can be achieved by combination of celecoxib with the antiproliferative agent 2-difluoromethylornithine. A separate Phase II study is evaluating the biomarker-based efficacy of celecoxib in hereditary nonpolyposis CRC patients, a cohort for whom no data are yet available regarding the effect (adverse or beneficial) of any potential CRC chemopreventive agent.

The trial data also provided support for Phase III trials in patients with prior sporadic adenomas. As shown in Table 2, these include three Phase III studies with celecoxib alone (400–800 mg/day); a comparable study of rofecoxib (25 mg/day) is also ongoing. In addition, a Phase III trial comparing celecoxib (400 mg/day) and selenium (200 μg/day) is under way. The end point for these trials is adenoma number at 3 years or at 1 and 3 year(s).
Despite the promise of efficacy and the widespread safe use of COX-2 inhibitors, the long-term safety of celecoxib has not yet been established. Like traditional NSAIDs, celecoxib is contraindicated during late pregnancy. Celecoxib also has the same renal, hepatic, and GI side effects that are also associated with aspirin and other NSAIDs (reviewed in Ref. 102). GI events appear to be less frequent and severe with celecoxib than with nonselective agents (103). However, limited postmarketing data suggest a comparable renal side effect profile [2.1% and 0.8% incidence, respectively, of edema and hypertension with celecoxib (104)]. Rare cases of acute renal failure have also been reported (105). These effects highlight the pivotal role of COX-2-dependent prostaglandins in normal renal development and maintenance (106, 107).

In a large clinical trial, myocardial infarction was four times more common with rofecoxib (50 mg qd) than naproxen [500 mg bid; 0.4% versus 0.1% (108)]. However, a recent large retrospective analysis found no increased risk of myocardial infarction among >15,000 and >12,000 short-term users of celecoxib and rofecoxib, respectively, over the age of 66 years (109). A meta-analysis of patients in trials of COX-2 inhibitors found an annualized myocardial infarction rate of 0.8 (P = 0.02) and 0.74 (P = 0.04) for celecoxib and rofecoxib, respectively, versus 0.52 for placebo (110). This analysis is limited by the small absolute number of cardiovascular events (<70) and confounded by statistical methodology as well as heterogeneity among the three pooled study populations (aspirin use, rheumatoid versus osteoarthritis patients versus primary prevention trial participants). Nevertheless, appropriate postapproval surveillance should continue in patients with cardiovascular risk factors.

The potential for drug-drug interactions typically presents safety concerns. Celecoxib inhibits cytochrome P-450 CYP2C9, which metabolizes a number of drugs including warfarin (111, 112). Lithium and fluconazole also potentially interact with celecoxib. As additional postmarketing data accrue, a more complete profile of drugs that should not be used in combination with COX-2 inhibitors will likely emerge.

**Ursodiol.** Actigall is marketed for the treatment of gallstones; it is also used to treat chronic hepatitis, primary biliary cirrhosis, and cholestasis (113). The rationale for chemopreventive testing is supported by mechanistic, preclinical, and clinical trial data (114). Ursodiol is an effective chemopreventive in preclinical colon cancer models (115–117). It is found in small quantities in human and rat bile, where it appears to function in enhancing elimination of the cancer-promoting bile acid deoxycholic acid; ursodiol reduces deoxycholic acid and its cancer-promoting effects on the colonic lumen in patients at risk for CRC. The efficacy of ursodiol against colonic dysplasia in ulcerative colitis has also been studied (118). Other activities of ursodiol that may contribute to chemopreventive efficacy include induction of phase 2 drug-metabolizing enzymes, induction of apoptosis and growth arrest, and inhibition of proliferation (119). GADD153, whose induction in response to ursodiol is controlled by activator protein-1 and CCAAT/enhancer-binding protein, appears to play a key role in the apoptotic effect (120). In addition, extracellular-signal regulated kinase controls sensitivity to ursodiol-induced apoptosis (121).

The chemopreventive development of ursodiol is supported by the longstanding and excellent safety profile of the drug. The drug was approved by the FDA for gallstone treatment in 1987, and it has been used in Japan for more than 100 years. It is effective and safe for treatment of intrahepatic cholestasis in pregnancy (122). In ongoing or completed studies of its effects on gallstones, most reported side effects of Actigall were minor digestive or skin complaints; the most common adverse reaction was diarrhea (1–6%).

In a study of 114 patients with primary biliary cirrhosis, ursodiol significantly decreased adenoma risk [7% versus 28% in controls at 3 years (123)]. The effect correlated with a significant reduction in the proliferation index in colonic epithelial cells. Together with a strong mechanistic rationale and long history of safe use for its approved indications, these data supported the initiation of a randomized, double-blind, Phase III study to evaluate the efficacy of ursodiol (8–10 mg/kg/day for 3 years) in adenoma prevention. The study randomized 1285 patients with previously resected adenomas (at least one of which was ≥3 mm within 6 months of study entry). The primary end point is adenoma incidence at 3 years (analyzed for type, location, number, and size). The trial will also assess the effect...
of the drug on other colonic biomarkers, including cell proliferation and deoxycholic acid. Enrollment was completed in 1999, and study results are expected soon. Few adverse events have been reported (124).

Aspirin and Calcium. As noted above, use of aspirin and other NSAIDs is associated with reduced risk of colorectal adenomas and cancers. Despite this potential benefit, aspirin is associated with significant risk of GI hemorrhage as well as renal and hepatic side effects (reviewed in Ref. 102). In addition, a recent study associated regular aspirin use among women with an increased risk of pancreatic cancer (125). These risks would appear to preclude its application in a chemopreventive setting, especially because selective COX-2 inhibitors (e.g., celecoxib, discussed above) offer improved safety:efficacy profiles. Low-dose aspirin is nevertheless of interest because of the potential for simultaneous cardiovascular risk reduction, although careful risk:benefit analyses may need to define appropriate populations for intervention. Two recent randomized controlled studies exploring its efficacy provide proof of concept and illustrate trial designs for colon cancer chemopreventives. The first study of aspirin (325 mg qd) in patients with previously resected CRC (Dukes’ stage A, B1, B2, or C) was terminated early when the difference between treatment groups reached statistical significance (126). Compared with the placebo group, fewer aspirin patients had adenomas (17% versus 27%; P = 0.004), and the adjusted relative risk for adenomas was 0.65 [95% confidence interval (CI), 0.46–0.91]. Adenoma number was also lower with aspirin treatment (0.3 versus 0.49; P = 0.003), as was the time to adenoma incidence. In a separate study in patients with previous adenomas, 81 mg qd (but not 325 mg qd) aspirin reduced adenoma incidence by 19% (127). Compared with placebo, the relative risks for any adenoma were 0.81 (95% CI, 0.69–0.96) and 0.96 (95% CI, 0.81–1.13) for 81 or 325 mg qd aspirin, respectively; the relative risks for adenomas ≥1 cm were 0.59 (95% CI, 0.38–0.92) and 0.83 (95% CI, 0.55–1.23).

A number of dietary components are also being explored for efficacy in CRC prevention, including folate (127) and calcium (see Table 2). For example, calcium carbonate (3 g qd for 4 years) moderately reduced adenoma risk in a randomized, double-blind, placebo-controlled trial in subjects with a recent prior adenoma [relative risk = 0.85; 95% CI, 0.74–0.98 (55)]. The effect was independent of dietary fat and calcium intake.

The clinical data presented in these examples demonstrate the potential for drug intervention in the prevention of CRC. Many other chemical moieties in a variety of mechanistic classes have also shown promise in early experimentation and evaluation, suggesting additional opportunities in prevention of this disease. The potential public health benefit and large market for prevention of colon cancer should encourage future aggressive ethical drug development.

SUMMARY AND RECOMMENDATIONS

The case for colon cancer prevention is indeed compelling and serves as a model for other disease settings in which precancerous lesions that can serve as targets for intervention and screening have been identified.

Drug Intervention Targeting Colorectal Adenomas: Addressing an Unmet Medical Need. Despite the increasing availability and public awareness of screening and prevention strategies, CRC is still the third most frequently diagnosed cancer and third leading cause of cancer-related mortality in the United States. Fewer than 10% of patients with stage IV disease (at which >20% of patients are diagnosed) survive 5 years; even with treatment engagement, response rates of >40%, median survival for those with stage IV CRC is only 18–24 months. Drug development for CRC has the advantage of many years of productive basic, epidemiological, and clinical research that have defined the adenoma–carcinoma sequence and demonstrated that removal of adenomas is associated with lower risk of cancer and that drug intervention can lower adenoma burden, all critical factors in establishing the adenoma as a surrogate end point biomarker for CRC. Colorectal adenomatous polyps are recognized as precancers and are the target of screening and drug intervention strategies for cancer prevention. The exceptionally strong scientific data supporting colorectal adenomas as a surrogate end point biomarker provide a rationale for revision or improvement of existing policy to accommodate and encourage marketing approvals for prevention of cancer based on treatment or prevention of precancerous lesions.

Expert Scientific Review Needed to Establish Surrogate End Points. In March 2002, the FDA GI Drugs Advisory Committee, an expert group including gastroenterologists, oncologists, basic scientists, and statisticians, considered criteria for obtaining drug marketing approval based on colorectal adenoma end points. This committee and its deliberations provide the model for expert panels that should be convened to insure that rapid progress is made in the development of sound scientifically based strategies for the use of surrogate end points in gaining approval for new cancer drugs. These panels would consider clinical trial design, definition of the surrogate end point biomarkers and their measurement, and specific efficacy and safety criteria for obtaining approvals (both full new drug approvals and accelerated approvals) to allow the earliest possible access to important new drugs.

Intervention Complements Screening. To most effectively prevent colon cancer, clinical research and future public policy need to consider the complementary roles of screening and drug intervention. Despite substantial evidence that screening leading to surgical removal of polyps is effective in preventing CRC, it is unlikely that screening alone will be the optimal preventive strategy. The costs of facilities and trained endoscopists necessary to provide screening and surveillance colonoscopy (either as an initial or definitive test) would be prohibitive for the total population at risk; limited provider and patient acceptance of screening modalities is also a significant barrier to implementation. The associated morbidity of polyectomy and the low mortality incidence also represent hurdles. Because chemopreventive drug intervention shows promise in lowering adenoma burden, it is envisioned that drug intervention and screening would serve complementary roles in providing clinical benefits: reduced risk of CRC; lower cost to patients and healthcare systems; and lower risk from surgical procedures. For example, efficacious drug therapy could permit longer screening and/or surveillance intervals, thereby decreasing requirements for facilities and endoscopists; fewer polyectomies would also...
reduce the patient’s risk of morbidity. For CRC as the prototype and for other cancer settings, strategies integrating screening and early detection with drug intervention would be expected to maximize potential clinical benefit.

For Prevention, Determination of Long-Term Safety Is Critical. Drugs for cancer prevention are administered chronically to diverse populations at varying risk for disease; thus, establishment of their long-term safety and efficacy is critical. The multiple years of drug administration that will be required to collect the safety data required for full approval may cause significant lost opportunity for treating people at risk, may not be practical in a clinical research setting, and may not be economically feasible for drug developers. To ensure safety while making efficacious drugs available at the earliest possible time, a two-phase drug approval process may be appropriate. For example, in the setting of CRC chemoprevention, accelerated approval may follow the demonstration of efficacy against adenomas in a relatively short-term study (3 years for sporadic adenomas or 6 months for FAP patients). Besides follow-up trials in defined study populations (e.g., beyond 3 and up to 5–6 years, as recommended by the GI Drugs Advisory Committee) to substantiate longer term efficacy and safety, full approval may require planned, rigorous postmarketing surveillance.

The Need for Earlier Surrogate End Points for Cancer Prevention. In addition to pursuing full drug approvals based on adenoma prevention, correlative studies using new molecular technologies (e.g., gene expression profiles) need to be more aggressively pursued to evaluate and stratify the end point adenomas based on risk of progression (on active drug therapy versus placebo), as well as on the predictive value of the individual’s risk for other lesions. This evaluation would contribute to the understanding of whether the drug intervention is active against higher-risk adenomas and hence would validate clinical benefit.

Current and future effort should also focus on the identification, validation, and implementation of end points that are reached even sooner than the adenoma. These preadenoma surrogates also offer the efficiency of a reduced sample size required for preliminary efficacy evaluation. This more efficient path to drug development would encourage investment in and testing of novel, promising therapies. Several earlier end points with considerable potential in this regard are already being developed. In particular, significant advances in ACF imaging technology have stimulated exploration of using this early lesion as a potential marker of colorectal cancer risk. Science (Wash DC) 1997:278:1073–7.


64. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst (Bethesda) 2001;93:684–90.


Colorectal Adenomas: A Prototype for the Use of Surrogate End Points in the Development of Cancer Prevention Drugs


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/10/11/3908

Cited articles
This article cites 122 articles, 28 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/10/11/3908.full#ref-list-1

Citing articles
This article has been cited by 5 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/10/11/3908.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.