

## Editorial

# Gastrointestinal Cancer Prevention in the United States: The Road Ahead

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In considering the regulatory process required for approval of new agents to prevent cancer, three important considerations emerge. First, because most individuals who will receive therapy are asymptomatic, the risk/benefit ratio of any such product must be favorable. Second, as therapy is likely to be offered to large segments of the population for prolonged periods, the cost/benefit ratio of treatment will require careful monitoring. Finally, it is critical to identify appropriate validation and outcome parameters that will serve as a platform for gauging efficacy.

Ideally, carefully performed, appropriately powered, placebo-controlled, randomized clinical trials should be required to demonstrate that a candidate agent reduces the subsequent development of cancer with minimal toxicity at low cost. However, such trials by necessity would be very large, long, and costly, thereby reducing the incentive for the pharmaceutical industry and academic research centers to develop such agents (1). One opportunity to circumvent this problem is to identify valid surrogate study end points, which would permit clinical trials of shorter duration. For a surrogate marker to be considered a viable alternative to the optimal outcome measure (*i.e.*, reduction in the development of cancer), it should be able to predict cancer development with fidelity (1). Premalignant lesions (also referred to as IENs<sup>2</sup> by the American Association for Cancer Research Task Force; Ref. 1) may be viewed as near-obligate steps in the path from normal to cancer, essentially validating their consideration as acceptable surrogate markers for use in studies designed to reduce the subsequent development of cancer (1). IEN is a pathological term, which refers to histological findings at a particular point in time. In considering the fact that carcinogenesis is actually an ongoing process (1, 2), premalignancy or preinvasive cancer may be better clinical terms because they imply the progressive nature of the carcinogenesis pathway. It must be stressed that not all IENs behave similarly (1). The risk/benefit ratio for the treatment of one IEN may be very different from another, even if a similar chemoprevention agent is used. Moreover, there may be large differences in the significance of IENs in terms of their clinical relevance. Some may be asymptomatic, whereas others may have clinical effects. Also, the rate at which cancer devel-

ops and the relative risk of cancer supervening in individuals with established precursor lesions may differ significantly from one IEN to another (1). Furthermore, identifying relevant changes in IEN with time may differ significantly from condition to condition. Potential end points include demonstrating a reduced rate of development of IEN lesions in people at risk (*i.e.*, primary prophylaxis), demonstrating a reduced rate of development of new IEN lesions after removal of all apparent index lesions (*i.e.*, secondary prophylaxis), or even demonstrating reduced progression of IENs already identified (*i.e.*, tertiary prophylaxis; Ref. 3). For studies using the latter design, consideration must be given to the ethics of leaving IEN lesions behind.

Within the field of gastroenterology, two prominent cancers readily lend themselves to chemoprevention strategies. The first disease is colorectal cancer. It is well established that adenomatous colonic polyps are precursors to colorectal cancer (1, 4). Moreover, it has been demonstrated that colonoscopy and polypectomy effectively reduce the incidence of colorectal cancer in individuals at risk, and this approach is already considered the standard of care for IEN of the colon (1, 4, 5). Therefore, chemoprevention approaches for colorectal cancer must, by necessity, be designed as secondary prophylaxis trials. Moreover, because the standard of care is effective in reducing the subsequent development of colorectal cancer (1, 5), it may be difficult to demonstrate a truly independent effect for any chemopreventive agent and large studies will be required to demonstrate efficacy for candidate agents used as adjunctive therapy in persons at risk (1). Furthermore, because colonoscopy itself is not an ideal study [ $>20\%$  of adenomas may be missed ( $>5\%$  of lesions  $>1$  cm in size); Ref. 6], a second (clearance) colonoscopy may be required soon after removal of index adenomas to ensure that adenomatous polyps identified during follow-up are truly new IEN lesions. This requirement greatly increases the expense of performing such studies.

Adenocarcinoma of the distal esophagus, the fastest growing cancer in the United States (7, 8) and closely linked to chronic gastroesophageal reflux disease (9), is the second gastrointestinal cancer that merits chemoprevention. Barrett's (intestinal) metaplasia of the esophagus is the precursor lesion (1, 10). One major advantage to studying this model of IEN is that primary prevention strategies are possible. Optimal care of patients with Barrett's esophagus involves surveillance upper endoscopy with biopsy at designated intervals (1, 11). If intestinal metaplasia with high-grade dysplasia is identified and confirmed, therapeutic intervention is required (usually esophagectomy; Refs. 1, 11). However, patients with low-grade dysplasia or no dysplasia do not require surgery. Moreover, the rate at which Barrett's esophagus develops into adenocarcinoma is well established,  $\sim 0.5\%$ /year (12), thereby facilitating accurate power calculations for potential clinical trials. Unfortunately, a major limitation of this chemoprevention model is the lack of predictable interobserver agreement among pathologists in the grading of dysplasia within Barrett's esophagus (1, 13). There-

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<sup>2</sup> The abbreviations used are: IEN, intraepithelial neoplasia; FDA, Food and Drug Administration.

Table 1 Published Phase IIb and Phase III clinical trials of chemopreventive agents in participants at increased risk for colorectal carcinoma

Chemopreventive agent	Putative mechanism of action	Phase IIb or III trial results
ASA	Inhibition of COX-1/COX-2	Reduction of colorectal adenoma recurrence rate by low dose (81 mg/da) ASA (15)
Calcium carbonate	Reduced colorectal crypt cell proliferation indices	Reduction of colorectal adenoma recurrence (16)
a-Difluoromethyl-ornithine	Inhibition of ornithine decarboxylase in colorectal epithelium	Reduced colorectal polyamine cancer in colorectal epithelium (18)
Selenium (Baker's yeast)	Multiple mechanisms, including inhibition of gene methylation	Reduction of colorectal cancer incidence of 2° endpoint of skin cancer prevention trial (19)
Sulindac	Inhibition of COX-1/COX-2	Reduction in number and size of colorectal adenomas in familial adenomatous polyposis patients (20)

<sup>a</sup> ASA, acetylsalicylic acid; COX, cyclooxygenase.

fore, additional effective surrogate markers such as prostaglandin content or indices of cell proliferation (14) need to be factored into these study designs.

A major concern regarding short-term preinvasive studies is whether they can be extrapolated to reflect cancer prevention (1, 3). With continued therapy, the potential risks of treatment increase (although in some cases therapy could conceivably be discontinued once IEN regression has occurred). Moreover, the true benefit of chemoprevention may actually be less than predicted from short-term studies (1, 3). Furthermore, the treatment cost continues for as long as the agent is used and the number of individuals who need to be treated to reduce the subsequent development of cancer in a single individual (*i.e.*, the Number Needed to Treat) cannot be measured reliably using surrogate end point studies. Finally, it would be very useful if reliable genetic and/or environmental markers could be integrated to identify individuals at high risk for the subsequent development of cancer (1, 3).

There are several promising chemopreventive agents that have demonstrated activity in Phase IIb (placebo-controlled, biomarker-focused efficacy studies) and Phase III clinical trials in participants at increased risk for colorectal carcinoma, as shown in Table 1 (clinical trials are listed alphabetically by chemopreventive agent).

Certain agents have already demonstrated efficacy and/or have been approved by the FDA for chemoprevention in patients with familial adenomatous polyposis, a condition with virtually 100% penetrance for the subsequent development of colorectal cancer (17, 20). However, the potential side effects of long-term use of these agents may not be estimated accurately from brief exposure in patients receiving these drugs for other disorders often at lower doses than may be required for effective chemoprevention (17, 21). Although certain agents have shown promise for reducing the incidence of sporadic colorectal cancer in larger population studies (22), the risk and cost/benefit ratios of these treatments have not been clearly defined.

How can the current climate be modulated to permit a more rapid implementation of potential cancer chemoprevention strategies? Public and federal acceptance of IEN as a valid surrogate marker is of paramount importance. From a regulatory viewpoint, acceptance of this concept should not alter the fundamental FDA approval process because new drug applications are each evaluated on their own merits. It is worthwhile, however, to note that a number of diverse constituencies need to work together as partners to move the process forward. These include groups that profit from the business of healthcare (*i.e.*, the pharmaceutical and biotechnology industry as well as medical insurance companies), government organizations involved in regulating access to pharmaceutical agents, or expenditure of

public funds for healthcare delivery or research (*i.e.*, the FDA, the NIH, Medicare, and the Congress of the United States) as well as healthcare practitioners or recipients (*i.e.*, professional medical organizations and the public and public advocacy groups such as The Cancer Prevention Working Group<sup>3</sup>).

The following may be an appropriate agenda to pursue for chemoprevention. Cancers with a large impact on the general health of our population (*i.e.*, colon, lung, breast, prostate and esophagus; Ref. 7) should be targeted initially. Studies should be designed with input from academic medical centers, the FDA, NIH, the pharmaceutical industry, insurance companies, and public advocacy groups to demonstrate the feasibility of IEN and other molecular markers as key surrogate end points by demonstrating a reduction in mutually accepted preinvasive cancer end points. Commitment to follow study cohorts beyond regulatory approval (possibly for decades) to document that the agreed upon surrogate markers are valid predictors of cancer will be essential. This process will also require integration of postmarketing adverse event reporting systems to define true risk/benefit ratios with prolonged use of these agents.

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