Potential Pitfalls in the Use of Surrogate Endpoints in Colorectal Adenoma Chemoprevention

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Colorectal cancer is the second most common cause of cancer death for both men and women in the United States (1). Understanding the relationship between adenomatous polyps and colorectal carcinoma is important in evaluating the effectiveness of chemoprevention. The relationship is complex, with the adenoma-to-carcinoma pathway characterized by a series of genetic alterations involving a number of genes, including APC, K-RAS, DCC, and p53 (2). In colorectal cancers, frequent loss of heterozygosity at multiple chromosomal loci, including 5q, 17p, and 18q, is observed. Such lesions are classified as microsatellite stable. Recent attention has also focused on an alternative pathway involved in the pathogenesis of colorectal cancer that accounts for 15%–20% of colorectal cancers, including hereditary non–polyposis colorectal cancer. This alternative pathway involves microsatellite instability and is also associated with serrated adenomas, hyperplastic aberrant crypt foci, and hyperplastic polyps (3).

For asymptomatic average-risk individuals, the prevalence of adenomatous polyps ranges from 24%–47% (4). The risk of developing a carcinoma from an adenoma is related to its histologic type: tubular histology is associated with a 5% risk, tubulo-villous histology with a 15%–20% risk, and villous histology with up to a 50% risk. Adenoma size is also an important predictor of malignant potential. The risk of developing a carcinoma is approximately 1% for lesions less than 0.5 mm in diameter, 5% for lesions between 6 and 9 mm in diameter, and 20% for lesions greater than 1 cm in diameter (5). The National Polyp Study followed more than 2600 patients, who had all adenomas removed at initial colonoscopy, with surveillance colonoscopy at 1 and 3 years or at 3 years only. Reduction in colorectal cancer incidence was 76%–90% after colonoscopic polypectomy, compared with that in historical reference groups (6). Reduction in the incidence of colorectal cancer in a population that has undergone repeated fecal occult blood test screening is attributable in large measure to colonoscopic intervention (7).

Experimental and observational studies support the use of adenomas as surrogate intermediate markers for colorectal cancer. In a population-based study, nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, were associated with reduced risk of colorectal neoplasia, including adenomas, and with reduced colorectal cancer incidence (8). Approval of celecoxib (by the U.S. Food and Drug Administration [FDA]) for the adjunctive pharmacologic management of familial adenomatous polyposis, in addition to endoscopic surveillance, surgical management, and the conclusions of an expert interdisciplinary committee on intraepithelial neoplasia (9) have all reinforced the relevance of the adenoma as a target for chemoprevention (10).

In addition, research in chemoprevention of colorectal neoplasia has been stimulated by FDA approval of celecoxib, and a number of chemoprevention trials that use a variety of pharmacologic and nutritional compounds are in progress (11).

There are, nonetheless, limitations on the use of adenomas as surrogate biomarkers for colorectal cancer. The most obvious limitation is the relative infrequency of transformation of small adenomas to cancer. However, it is not usually feasible to undertake chemoprevention studies with cancer incidence and/or mortality as reasonable endpoints because of the length of time needed to complete such a study, raising practical issues regarding long-term funding and adherence to prescribed regimens.

Greenberg et al. (12) and Baron et al. (13) have studied the effect of β-carotene supplementation on colorectal adenoma recurrence in a multicenter, double-blind, placebo-controlled trial of antioxidants (β-carotene, vitamin C, and vitamin E) for the prevention of colorectal adenomas. Overall, there was no evidence that β-carotene at a dose of 25 mg daily was associated with a reduction in the incidence of adenoma recurrence (relative risk [RR] = 1.01, 95% confidence interval [CI] = 0.85 to 1.20) (12). In this issue of the Journal, Baron et al. (13) report that, among subjects who neither smoked nor drank alcohol, β-carotene was associated with a decrease in the risk of one or more recurrent adenomas (RR = 0.56, 95% CI = 0.35 to 0.89) but that β-carotene supplementation may have increased the risk of recurrence among those who smoked (RR = 1.36, 95% CI = 0.70 to 2.62) or drank (RR = 1.13, 95% CI = 0.8 to 1.43) (13). For participants who smoked and also drank more than one alcoholic drink per day, β-carotene supplementation was associated with an RR of 2.84 (95% CI = 0.85 to 9.46) (13). These unexpected findings are reminiscent of data from two large, randomized, placebo-controlled studies: the Finnish Alpha-

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Tocopherol, Beta-Carotene Study (14) and the American Beta-Carotene and Retinol Efficacy Trial (15). Investigations in these trials assessed the risk of lung cancers among male smokers and asbestos workers receiving β-carotene supplements. Both showed statistically significant increases in lung cancer among men who received the supplements.

The possible underlying mechanisms responsible for these adverse effects are discussed in detail by Baron et al. (13) and by Greenwald (16). These observations on the action of β-carotene also raise concern about the relevance of epidemiologic studies of diet, composed of many different nutrients, for launching large-scale clinical trials of a single component, in this case, β-carotene. Data from recent randomized, placebo-controlled trials of aspirin have been consistent with previous epidemiologic and experimental data concerning the effect of NSAIDs on colorectal adenomas. Among 517 patients with a history of resected colorectal cancer, aspirin at 325 mg daily was associated with an RR for adenoma development of 0.65 (95% CI 0.46 to 0.91) (17). Among 1084 patients with a history of one or more adenomas, ingestion of aspirin at 81 mg was associated with an RR of 0.81 (95% CI = 0.69 to 0.96) (18). Although the results were encouraging regarding the potential benefits of chemoprevention for colorectal cancer, they raise other questions. For example, what is the likely impact of incomplete protection from adenoma recurrence on the frequency of post-polypectomy endoscopic surveillance?

In the study by Baron et al. (13), the adverse effects of β-carotene in those who consume alcohol and smoke cigarettes may be partly related to the heterogeneous molecular characteristics of colorectal polyps, even within the same individual (19), or they may be related to other factors. Slattery et al. (20) have reported that patients with microsatellite instability (MSI) in colon tumors were more likely to smoke 20 or more cigarettes per day than case subjects with MSI-negative cancers.

In long-term studies of chemoprevention that are based on the surrogate endpoint of adenomatous polyps rather than on the incidence of colorectal cancer, we must be vigilant to the potential for harm when using an indirect marker, however biologically relevant, in an asymptomatic population. This is especially important where an effective method for post-polypectomy management exists in the form of periodic colonoscopic surveillance, albeit expensive and invasive. Stopping trials on the basis of surrogate endpoints such as adenoma incidence rather than on cancer incidence may miss hypothetical harms that may occur later than the surrogate endpoint (Fig. 1) (Kramer B: personal communication). As Fig. 1 illustrates, using surrogate outcomes of benefit but clinical outcomes of harm rather than surrogate outcomes of harm can introduce a systematic bias in our assessment of chemopreventive agents. Moreover, when the FDA grants accelerated approval (Subpart H) for the use of a compound on the basis of surrogate endpoint data, formal postmarketing surveillance to evaluate clinical benefit is required.

Placebo-controlled, randomized trials to suppress adenoma recurrence and thus possibly to diminish colorectal cancer incidence and mortality need to be carefully monitored and to be of sufficient duration to ensure that clinically significant adverse effects can be reliably detected. In addition to identifying molecular targets for chemoprevention with greater precision, advances in genomics and proteomics may well enhance our ability to define more accurately entry criteria into prevention trials and to identify biologic heterogeneity for subsequent correlations with outcome.

REFERENCES


