

# Diet and Colorectal Cancer: Still an Open Question

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The case implicating diet in the etiology of colorectal cancer—a disease that in this country kills each year nearly 60 000 men and women—is growing stronger. A wealth of ecologic, laboratory, and clinical nutrition data supports a diet–colorectal cancer connection (1). Numerous observational epidemiologic studies indicate that risk of developing this malignancy is influenced by intake of fat (2), red (3) [and possibly cooked (4)] meat, fiber (5), resistant (nondigestible) starch (6), fruits and vegetables (7), folate (8), and other (9) dietary factors. In spite of the difficulties in establishing which dietary factors are decisive, an attractive integrative hypothesis is emerging: A dietary pattern characterized by low consumption of fat and red meat and high intake of fruits, vegetables, and grains substantially lowers colorectal cancer risk (1,10).

But the diet–large-bowel cancer case is not ironclad. Some epidemiologic studies (9,11) do not show the associations for dietary fat, red meat, or dietary fiber that have been observed in other studies. Moreover, people eating a lot of fat and red meat and few fruits and vegetables may differ from their low-fat- and low-red meat- and high-fruit- and high-vegetable-consuming counterparts in some characteristics that are the real causes of colorectal cancer. The inability of observational epidemiologic studies to rule out the existence of these confounding characteristics remains a nagging concern (12).

Clinical trials can provide a vital extra dimension of evidence to complement findings from laboratory and epidemiologic studies. The randomized nature of such studies largely circumvents the problem of confounding.

In this issue of the *Journal*, MacLennan et al. (13) report findings from the Australian Polyp Prevention Project, one of the early intervention studies of dietary factors in relation to colorectal neoplasia. We emphasize “neoplasia” here because the end point in this polyp trial is recurrent adenomas, not colorectal cancer per se. The biologic rationale for polyp trials is the increasingly substantiated (14) concept of the adenoma–carcinoma sequence (15): Most large-bowel cancers develop from adenomas. Polyp trials are attractive because the high annual recurrence rate—10% or more (16) (some two orders of magnitude greater than the colorectal cancer incidence rate)—means that such a study can be carried out on a much smaller, quicker, and less expensive scale than an intervention study with cancer as the end point. In spite of some limitations in generalizing their findings to colorectal cancer (17), polyp trials clearly have the potential to yield persuasive and novel evidence. It would be a major advance if we could demonstrate in a randomized trial that a dietary intervention unambiguously reduces the development of neoplastic lesions in the large bowel.

Unfortunately, the findings from the pioneering Australian Polyp Prevention Project are not unambiguous. From the standpoint of the primary hypothesis, this trial is a null study. Within the framework of a  $2 \times 2 \times 2$  factorial design, neither a low-fat eating plan (with a target of 25% calories from fat), a dietary fiber supplement (11 g per day from wheat bran), nor supplementary beta carotene (20 mg per day) significantly lowered the rate of adenoma recurrence in the intervention compared with the control arm. These findings do not, however, constitute strong evidence against the diet–colorectal cancer hypothesis.

The sample size of about 400 participants resulted in wide confidence intervals. The 4-year relative risk of adenoma recurrence, for example, for those in the low-fat compared with the usual diet group was 0.9 with a 95% confidence interval of 0.6–1.5. In other words, the observed 10% reduction in polyp recurrence is compatible with up to a 40% reduction in polyp recurrence, no change at all, or even up to a 50% increase in recurrence. [It is noteworthy, though, that for beta carotene the results are compatible with no effect or a deleterious one but not with any substantial protective effect. Greenberg et al. (18) recently reported results from a larger trial that also were incompatible with a substantial beta-carotene protective effect against adenoma recurrence.]

No 4-year colonoscopy data were available on approximately one quarter of the participants. As MacLennan et al. (13) indicate, this fairly large loss of end-point data potentially compromises the control of confounding factors achieved through the randomized design and diminishes confidence in the study findings.

The dietary change, especially with regard to the low-fat intervention, may have been inadequate. The authors have indicated elsewhere (19) that the percent calories from fat in the intervention group fell at most from 34% to 29%, suggesting that the difference in fat intake between the two groups was not as large as one might like. Further details on the dietary intervention experience will be helpful.

One should consider the possibility that follow-up time was insufficient, although this is a generic alternative interpretation of null results from an intervention study (17). If an intervention operated only in the early stages of adenoma formation, and it

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takes, say, 5 years for a polyp to become detectable at colonoscopy, then observations through 4 years would miss the intervention effects. Longer follow-up would be necessary to observe these effects.

How much credence should we give to the "positive" results in this study, namely, the reduced recurrence of large ( $\geq 10$  mm) adenomas among those in the low-fat arm and in the combined low-fat/fiber supplement group?

Because most recurrent adenomas are small, it is not surprising that only four and 13 participants, respectively, in the low-fat and control arms had large recurrent polyps. Clearly, as MacLennan et al. (13) acknowledge, we can draw only limited inferences from a result based on such a small number of end points.

Furthermore, the analyses of adenoma size and extent of dysplasia are secondary analyses, carried out in the context of a null finding for the primary hypothesis (overall adenoma recurrence). Several possible secondary end points that could be examined in addition to size and dysplasia include adenoma number, histotype, and degree of atypia. By chance alone, one of the interventions might turn out "positive" for one of these several secondary end points.

In summary, the hypothesis that dietary modification alters large-bowel cancer risk is neither refuted nor convincingly supported by the Australian Polyp Prevention Project.

If we consider the addition of a fiber supplement as a dietary intervention (and if we consider the administration of beta carotene and other antioxidant vitamins as falling within the purview of chemoprevention studies), then the Australian Polyp Prevention Project is the third polyp trial to report results of the effect of dietary intervention on adenoma recurrence. DeCosse et al. (20) carried out a fiber-supplement and vitamin intervention study among approximately 60 patients with familial adenomatous polyposis followed for up to 4 years. McKeown-Eyssen et al. (21) conducted an adenoma recurrence trial among approximately 200 participants with 2 years of follow-up; the intervention involved counseling participants to adopt a low-fat, high-fiber eating plan with the addition of a fiber supplement. Both of these studies were null using the primary intention-to-treat analysis.

Studies of this type must be larger. The National Cancer Institute-sponsored Polyp Prevention Trial (22), for example, has 2079 participants at eight clinical centers and has 90% power to detect a 24% reduction in polyp recurrence. The Polyp Prevention Trial and other large trials (23,24) being conducted around the world are expensive and complicated, but the experience with the earlier, smaller studies confirms the necessity of mounting these larger investigations. [Even more ambitious is the current effort within the Women's Health Initiative to investigate the effect of dietary change on the incidence of colorectal cancer (25).]

The timing of colonoscopic end-point assessment is critical in polyp trials. Investigators need to consider at least three issues. First, some time is necessary for the development of adenomas. Second, time (say, a year) has to be allowed for the intervention to be adopted behaviorally and to have an effect biologically. Third, some polyps—at least 15% (26)—are missed at the base-line colonoscopy. If these missed polyps are not cleared at a

subsequent procedure and the intervention cannot cause them to regress completely, then their presence in both the intervention and control arms could substantially reduce study power (27). It is conceivable that missed base-line lesions contributed to the null result in the Australian Polyp Prevention Project.

A single end-point assessment at 2 years may, therefore, be inadequate. A number of trials have adopted the approach used by Greenberg et al. (18): base-line colonoscopy followed by a clearing colonoscopy 1 year later, with the primary end-point assessment taking place 3 years after that. The primary analytic period in such a design is between the end of the 1st year and the end of the 4th year of follow-up. This approach has the virtue of allowing a 1-year lag time for the intervention to work and permits a reasonable effort to eliminate missed base-line polyps. Because of changes in recommended post-polypectomy surveillance (28), with the elimination of the 1-year procedure in many instances, this design may no longer be viable in the future. Without the 1-year clearing colonoscopy, the sample size for a polyp trial will have to be increased to compensate for the missed base-line lesions (27).

Getting people to change qualitatively what and how they eat is daunting—and absolutely necessary if our dietary intervention studies are going to show anything useful. Fortunately, during the last two decades, a substantial body of experience has accumulated in how to communicate to study participants the nutritional information and behavioral skills necessary to make substantial dietary modifications. Data from the Women's Health Trial (29), for example, suggest that such changes can be achieved and maintained over several years. Investigators are now applying this experience in newer studies such as the Polyp Prevention Trial and the Women's Health Initiative.

Earlier dietary intervention studies focused on the separate effects of single nutrients, as reflected in the Australian Polyp Prevention Project's low-fat intervention. Newer trials, like the Polyp Prevention Trial and the Women's Health Initiative, have adopted a more comprehensive intervention approach, with intervention eating plans targeted to changes in consumption of several nutrients or foods (fat, fiber or grains, fruits, and vegetables, for example). Such multifactorial eating plans embrace multiple hypotheses and allow for interactions among known and unknown foods, nutrients, and non-nutrient food constituents, thereby maximizing the chances for demonstrating a dietary effect.

It is not yet proved whether dietary change can prevent colorectal cancer. Results from the next generation of polyp trials (and later from the Women's Health Initiative), taken in concert with findings from large, well-conducted epidemiologic studies, will take us a long way toward settling this question.

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