

**Before the  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

**In re: Food Labeling; Health Claims and )  
Label Statements; Request for ) Docket No. 91N-0098  
Scientific Data and Information ) (Fiber and Colorectal Cancer)  
)**

**SUPPLEMENTAL SUBMISSION OF  
JULIAN M. WHITAKER, M.D.;  
PURE ENCAPSULATIONS, INC.;  
XCEL MEDICAL PHARMACY, LTD;  
THE AMERICAN PREVENTIVE MEDICAL ASSOCIATION; AND  
DURK PEARSON AND SANDY SHAW.**

Julian M. Whitaker, M.D.; Pure Encapsulations, Inc; XCEL Medical Pharmacy, Ltd.; the American Preventive Medical Association; and Durk Pearson and Sandy Shaw (collectively the "Joint Commenters"), by counsel, hereby submit this supplement to their comments filed on November 22, 1999.

**I. ADDITIONAL SCIENTIFIC EVIDENCE SUPPORTS THE  
FIBER/COLORECTAL CANCER HEALTH CLAIM**

Results of recently published scientific literature reviews confirm earlier results of trials conducted by Macrae (1999)<sup>1</sup>; Jansen (1999); Negri (1998); Caygill (1998); Le Marchand (1997); Hill (1995, 1997), and the conclusions of the European Organization for Cancer Prevention (ECP) (1998) which found that dietary fiber has a chemoprotective effect on colorectal tissue, independent of the other components of plants. The American Gastroenterological Association (AGA) recently published its findings and recommendations based upon of an exhaustive literature review of hundreds of studies involving thousands of subjects (Kim, 2000). That review examined experimental,

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animal, observational, epidemiological, correlation, case-controlled, and intervention studies. The AGA concluded that there is strong evidence supporting the protective effects of dietary fiber among correlation and case-control studies conducted in populations with different patterns of diet and colorectal cancer. The AGA noted that three meta-analyses of case-control studies provide strong support for the dose-dependent protective effects of dietary fiber or fiber-rich foods against colorectal carcinogenesis. AGA found that those studies indicate that on average the subjects with the highest intake of dietary fiber have a 50% lower risk of developing colorectal cancer than those with the lowest intake. After weighing the evidence, including seemingly contradictory results, the AGA concludes that increasing total fiber intake to more than 30g/day from the standard 10g/day North American diet can protect against colorectal cancer (Kim, 2000).

Hill (1999) reviewed scientific literature that examined the role of specific diet components and colon carcinogenesis. The review concluded that there is consistent evidence for the claimed association and a plausible mechanism for that association. Giacosa and Hill (1999) published an explanation and restatement of the European Organization for Cancer Prevention (ECP) consensus. The ECP found that based upon a review of 58 studies of diet and colon cancer, 19 of which measured cereal fiber, a diet high in cereal fiber is associated with a reduced risk of colorectal cancer. Reddy (1999) found in his review that several lines of evidence are supportive of dietary fiber's chemopreventive properties. He states "animal model studies clearly suggest that wheat bran consistently inhibits colon carcinogenesis. Case-control studies show reasonably strong evidence that dietary fiber reduces the risk of colon cancer in humans. Dietary

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<sup>1</sup> Abbreviated references in this comment correspond with those presented in full in the bibliographical listing. See Attachment 1.

intervention studies provide evidence that wheat bran supplementation decreases the levels of several putative tumor promoters in the colon.”

Two recent studies having negative results have appeared in the scientific literature. Both studies suffer from flawed controls and both dealt with aging populations with pre-existing colon tumors. There is no plausible biological mechanism by which fiber can be expected to correct the pre-existing genetic damage in people with pre-existing colon tumors. The studies rely upon unscientific self-reporting as the measure for compliance, a methodology generally criticized as yielding unreliable results (Simone, 2000, Muller, 2000).

In the Polyp Prevention Trial (Schatzkin, 2000) adults over the age of 35 who had one or more histologically confirmed colorectal adenomas were studied to determine if a high fiber, low-fat diet would influence the rate of adenoma recurrence. 1,037 people received 50 hours of nutritional counseling over four years and were instructed to consume a daily diet consisting of 18 grams of fiber/day and 20 percent fat. The control group of 1,042 were to make no changes to their diet. The subjects completed a four day food record; the intervention group completed one every six months and all subjects completed one each year. The data from the four day record was incorporated in the study analyses as representative of the entire preceding interval (six months or one year respectively). At the end of 4 years, the rate of adenoma recurrence did not differ between the two groups. The authors concluded that “adopting a diet that is low in fat and high in fiber, fruits, and vegetables does not influence the risk of recurrence of colorectal adenomas.” Remarkably, the low fat, high fiber diet had no effect on weight or cholesterol levels in either the intervention group or control group. A diet that is fat

restricted and has a high fiber content should have lowered weight and cholesterol and yet in this study there was no difference in either weight or cholesterol levels between the intervention group and control.

The most logical explanation is that the subjects were not actually eating the diet that they reported. The alternative conclusion, that low-fat, high-fiber diets do not lower weight or cholesterol, is unacceptable in light of many studies to the contrary.

The second trial studied 1303 people who had colorectal adenomas removed within three months of entrance into the study (Alberts, 2000). Subjects were asked to consume either a high-fiber supplement (13.5 grams/day) or a low-fiber supplement (2 grams/day). The subjects were studied over a 34-month period. At the end of that time, there was no difference in the rate of adenoma recurrence between the two groups. The authors concluded that a dietary supplement of wheat-bran fiber does not protect against recurrent colorectal adenomas. Assurance of compliance was even more questionable in this study than in the Schatzkin study. The investigators stated that “compliance with the protocol was evaluated primarily by counts of returned cereal boxes and fiber bars at each visit and secondarily through a specialized intake calendar.” The authors did not report subject weight or cholesterol levels so objective corroboration of diet compliance is not available.

Dr. Charles B. Simone is a medical oncologist, radiation oncologist, and immunologist who has studied the association between fiber and colorectal cancer for 22 years. Dr. Simone has reviewed the Schatzkin and Alberts studies (Attachment 3). He concludes that neither study is valid because each lacks objective evidence confirming compliance with the protocols. Other scientific critics have also found lack of proof of

compliance to invalidate the studies and, thus, make reliance on them improper. (Ornish, 2000; Davis, 2000; Gerber, 2000). Furthermore, scientists, including the study authors, found that the “findings cannot be interpreted as evidence that a high-fiber cereal supplement or a low-fat high-fiber diet is not effective in protecting against the later stages of development of colorectal cancer” (Byers, 2000) and cannot be applied to primary prevention risk reduction (Muller, 2000).

When the two aforementioned methodologically flawed studies on persons with pre-existing cancer tumors are removed, the entire body of well-designed studies published in the peer-reviewed literature overwhelmingly supports the conclusion that “consumption of fiber may reduce the risk of colorectal cancer.” Accordingly FDA must authorize the claim.

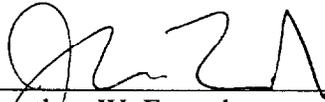
## II. CONCLUSION

The Joint Commenters believe that the scientific evidence overwhelmingly supports the association between fiber and colorectal cancer risk reduction and satisfies the congressionally intended definition of significant scientific agreement. In addition, and consistent with Pearson and the First Amendment, if the agency finds the proposed claim supported by some evidence but not enough to satisfy a defined “significant scientific agreement” standard, the claim must nevertheless be authorized with such disclaimer or disclaimers as the agency reasonably deems necessary to avoid a potentially misleading connotation. Only approval with appropriate disclaimer can ensure compliance with the First Amendment.

Respectfully submitted,

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## ATTACHMENT 1

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**ATTACHMENT 2**

## CEREALS, FIBER, AND CANCER PREVENTION

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All plant foods contain plant cell walls which contain dietary fibre and a range of other anticarcinogenic agents including vitamins, antioxidants, tannins, polyphenolics, and flavonoids. In general, vegetables contain relatively modest amounts of dietary fibre but are rich in a wide array of anticarcinogens, the amounts and classes of which vary between vegetable type. Cereals are relatively rich in dietary fibre and also contain phytate and a range of anticarcinogens. However, these latter are partly removed with the husk during milling. Fruit contains the least dietary fibre but contains an array of anticarcinogens which differ from those in cereals and vegetables.

Current hypotheses suggest that fruit and vegetables provide protection against cancer mainly through the action of their anticarcinogens. In contrast, cereals have been assumed in the past to act mainly through the action of dietary fibre.

In this Consensus Statement "cereals fibre" will imply unrefined or high-extraction cereal, with its husk (and the accompanying anticarcinogens) largely intact. In Europe, cereals may be consumed as breakfast cereals which are often rich in dietary fibre and also rich in B vitamins and anticarcinogens. At other time of day, cereals are usually eaten as breads, pasta, rice, pastries, etc. These are usually made from low-extraction cereals which contain lower levels of dietary fibre and anticarcinogens; wholemeal breads and products are richer in both, however.

Different cereals contain different amounts of dietary fibre and anticarcinogens (rice has least and wheat and rye have most of both). Further, rice is almost always eaten in polished and refined form and so contains even less dietary fibre and anticarcinogen than usual. The cereals which are most often consumed in unrefined and high-extraction form are wheat and rye.

The postulated mechanisms of action indicate that the protective action will be greater in the unrefined cereal than in that in which the husk has been removed by

milling. In most epidemiological studies the cereals are primarily low-extraction products and so are low in dietary fibre and anticarcinogens. A major recommendation was that in future, questionnaires should be framed to distinguish between low-extraction and high-extraction cereals.

On 1997 the European Organization for Cancer Prevention (ECP) held in S. Margherita Ligure (Italy) a Consensus Meeting on the role of cereals, fibre, and cancer prevention. The ECP Panel (reported at the end of this paper) achieved a consensus statement that is reported in the following pages.<sup>1</sup>

## COLORECTAL CANCER

A diet rich in high-fibre cereal is associated with a reduced risk of colorectal cancer. In support of this we cite the review of 58 previous studies of diet and colon cancer, in only 19 of which cereal fibre was measured. Of these, 16 reported an inverse association between cereal fibre and colon cancer risk and the other three showed no relationship 2, 3 (Hill, 1997, 1998). In addition, the review of Food and Agriculture Organization data by Caygill et al.<sup>4</sup> showed that there is an inverse relationship between the risk of colorectal and of breast cancer and cereal and vegetable disappearance, no relationship with fruit and starchy root intake and a positive correlation with total energy intake.

These data are consistent with those from the Italian study;<sup>5</sup> in the context of the Italian diet, high consumption of refined cereal was shown to be a major contributor to high total energy intake and was a risk factor for cancers of the colon and breast. This suggested that the real association was with total energy intake.

This consensus reaffirms and extends the consensus reached by the Colon Group at the World Health Organization (WHO) Consensus Conference in 1996,<sup>6</sup> and with the Committee on Medical Aspects of Food Policy (COMA) recommendations in the United Kingdom.

A variety of mechanisms has been proposed for the protective effect of cereal fibre. Burkitt<sup>7</sup> popularised the idea that a diet high in fibre-rich foods could influence the course of colorectal carcinogenesis: He proposed that it was fermentation of the fibre itself that gave the protection through (1) increased faecal weight; (2) increased frequency of defecation; (3) decreased transit time; and (4) dilution of the colonic contents. The evidence is strongest for (1) and (4) being important, although there is evidence against all four mechanisms. In addition he proposed that fibre metabolism influenced microbial growth in the colon, an area we know very little about.

More recently, mechanisms involving the metabolic consequences of fibre metabolism have been proposed including (5) alteration of energy metabolism. It is now generally accepted that energy restriction will inhibit carcinogenesis and a fibre-rich diet may make a contribution to overall energy management; (6) influence bile acid metabolism, a theory that appears to refuse to go away; (7) production of short-chain fatty acids, which may inhibit carcinogenesis through its effects on colonic pH, and through the supply of butyrate. This latter has been shown *in vitro* to promote apoptosis, and cell differentiation, both of which are central to the carcinogenesis process. *In vivo* verification of these actions is still awaited.

## BREAST CANCER

There is suggestive evidence that cereal fibre provides protection against breast cancer. Although many epidemiological studies have shown that cereal fibre has a protective effect, others have shown no effect and there is insufficient evidence to reach a definitive conclusion. In Stuttgart, the WHO Consensus Group on Breast Cancer concluded that the epidemiological evidence was suggestive of a protective effect (as did we) and recommended that cereal fibre consumption should be increased.

It is generally accepted that high levels of circulating oestrogens and insulin growth factors represent major risks for the development of breast cancer. Diets low in fat and rich in cereal fibre reduce levels of plasma oestrogens, in particular by interfering with their enterohepatic circulation and so increasing the rate of faecal excretion. Such diets also contain phytoestrogens, which have been proposed to be protective. Rose et al.<sup>8</sup> and Woods et al.<sup>9</sup> have shown that diets low in fat and high in wheat bran fibre significantly reduce plasma levels of oestradiol and oestradiol sulphate. Fibre intakes have also been shown to be inversely related to total, subcutaneous and extra-abdominal fat and to lower insulin levels. These findings reflect the influence of fibre in controlling aspects of the insulin-resistance syndrome.

## OTHER SITES

There is good reason to examine seriously the relationship between cereal fibre intake and cancer at other sites. The preliminary analyses reported by La Vecchia and Chatenoud<sup>10</sup> suggested that people who reported consuming whole grain cereals had a lower risk of cancer at a range of other sites in addition to the large bowel and breast. There were many potential confounding factors in these Italian data, and they need to be confirmed. However, there are good theoretical reasons for suspecting a general protective effect. If the mechanisms proposed to explain the protective effects against breast cancer are true, then we would expect them to apply also to other hormone-related cancer sites such as endometrium, ovary, and prostate. Carcinogen binding in the colon lumen might also give rise to a generalised protection, and the presence of anticarcinogens in the cereal husk would provide a mechanism similar to that proposed for vegetables and fruit. If such a generalised protection were to be confirmed it would, of course, strengthen the recommendation to increase intakes of high-fibre cereals.

## GENERAL RECOMMENDATIONS

- Questionnaires need to be directed in future to the study of food groups (e.g. cereals) rather than nutrients or nutrients (e.g. dietary fibre), since the latter are highly heterogeneous and not necessarily well quantitated.
- In view of the data presented in the review by Hill,<sup>2</sup> meta-analyses of the case-control and the cohort studies should be carried out.
- Many of the effects of dietary fibre that provide protection against colorectal and breast cancer are concerned with events in the caecum and proximal colon. We need to understand much more about the ecology of this important but experimentally inaccessible subsite of the large bowel.

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## CARNITINE SYSTEM AND TUMOR

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## 1. INTRODUCING CARNITINE

Carnitine, a name derived from the Latin *carnis* (flesh), was isolated from meat extracts in 1905<sup>1</sup> and early its chemical formula (C<sub>7</sub>H<sub>15</sub>NO<sub>3</sub>) was proposed. Its structure, a trimethylbetaine of  $\gamma$ -amino- $\beta$ -hydroxybutyric acid, was correctly identified and published about twenty years later.<sup>2</sup> Initially, some circumstances led to consider carnitine as a vitamin. By about 1945, all of the important vitamins of the B group had been identified, but the interest in the discovery of still missing B-vitamins, their lack being possibly correlated with anemia, was tremendous. In those years Fraenkel and coworkers observed that the mealworm *Tenebrio molitor* required for normal growth and survival, in addition to at least eight of the known B-vitamins, also folic acid and a new factor contained in brewers yeast or in liver extract, which they tentatively named vitamin-B<sub>T</sub> (T for Tenebrio).<sup>3</sup> The unfavorable properties of this factor (it was hygroscopic and extremely water soluble, thus, hard to crystallize) made its isolation difficult but, finally, the missing vitamin-B<sub>T</sub> was identified as carnitine.<sup>4</sup> The widespread distribution of carnitine was established in microorganisms, lower animals, and in all organs of mammals, and in plants too.<sup>5</sup>

But soon after, the finding that microorganisms as well as higher animals were also able to synthesize carnitine by themselves, came to light.<sup>6-8</sup> Hence, the assumption upon which carnitine was included among vitamins failed.

The physiological role of carnitine in microorganisms has not been elucidated for a long time. To date it is known that the role of carnitine in growth stimulation and metabolism in microorganisms varies depending on species and living conditions. For example in *Escherichia coli*, carnitine and other quaternary compounds, such

## Chemoprevention of Colorectal Cancer

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### Abstract

Epidemiological studies have emphasised the major role of diet in the aetiology of large bowel cancer. Attempts to identify causative or protective factors in epidemiological and experimental studies have led to some discrepancies. The time has come to test the most important hypotheses within the framework of intervention studies. Among studies specifically devoted to colorectal carcinogenesis, eight have been completed and five are ongoing. They evaluate the effect of the intervention on adenoma recurrence and, in three studies, on adenoma growth. Five intervention trials considering cardiovascular diseases and different cancer sites will provide data on the effect of the intervention on colorectal cancer incidence. Vitamins and antioxidants, fibre or calcium supplementation, aspirin therapy and dietary modifications are evaluated. Most of the available data do not support the idea of a protective effect of vitamins and antioxidants against colorectal carcinogenesis. It is too early to draw any conclusions on the effects of fibre, calcium supplementation, aspirin therapy and dietary intervention. The results of ongoing studies will be available within 2 years. If one of the evaluated interventions proves efficient, the benefits of a simple, safe and inexpensive prophylaxis for a very common cancer will be clear.

### Introduction

The most recent estimates of the worldwide incidence of colorectal cancer rank it third among the most frequent cancers, with about 560 700 new cases per year (Parkin et al. 1993). It is a major public health problem in all developed countries in Western Europe, North America and the South Sea Islands. Despite advances in diagnostic techniques and treatment, the 5-year survival rates remain poor and are estimated to be 30% in Europe (Berrino et al. 1995). There is little improvement with time. Strong evidence indicates that a high proportion of colorectal cancers arise in adenomas. These lesions could

be a potential target for secondary prevention as well as for primary prevention. Several arguments lend credence to the notion that the adenoma-carcinoma sequence is a multistep process. Cancer can be prevented by intervention either at the stage of adenoma growth or at that of transformation into carcinoma.

Many case-control studies, and some cohort studies, have provided substantial epidemiological evidence for the overwhelming role of diet in the occurrence of the disease (Potter et al. 1993). There is fairly consistent evidence concerning the effect of vegetables as a protective factor and of caloric intake as a risk factor. There is some evidence relating fat intake or protein intake to colorectal cancer, whereas fibre intake, calcium intake and antioxidant vitamins may be inversely related to colorectal cancer. However, analytical studies have yielded equivocal findings. The data available are not sufficient to serve as a basis for firm specific dietary advice, but they provide attractive hypotheses, which in turn suggest a rational basis for a preventive approach. Faced with this situation, it is important to test these hypotheses within the framework of intervention studies in order to evaluate the possibilities of primary prevention. The objective of this report is to review the design, along with the available results, of randomized colorectal cancer chemoprevention trials. Only studies with cancer or precancerous lesions (i.e. adenomas) as the main end-points are included here. Studies evaluating the effect of drugs are not considered.

### Vitamins and Antioxidant Trials

In recent years, much attention has been paid to the potential advantages of antioxidant vitamins, including  $\beta$ -carotene, retinoids, vitamin C, and vitamin E, and of other micronutrients, such as selenium, as chemopreventive agents for large bowel cancer. The main features of these trials are summarised in Table 1. Among the 15 chemopreventive studies with colorectal carcinogenesis as an end-point, 11 are at least partly concerned with the possible preventive effect of vitamins and/or antioxidants. The population involved is represented as follows: in 6 studies subjects who had previously had adenoma and who were polyp free at the time of recruitment; in 2 studies, individuals with familial adenomatous polyposis previously treated by total colectomy and ileorectal anastomosis (Bussey et al. 1982; De Cosse et al. 1989); and in 3 studies, volunteers included in large trials assessing the effects of micronutrients supplementation on cancer sites and cardiovascular diseases (ATBC Study Group 1994; Physician's Health Study cited in Hennekens et al. 1996; Herberg et al. 1993). The effect of vitamin C alone was tested in 1 study (Bussey et al. 1982), the effect of  $\beta$ -carotene alone in 4 studies (Greenberg et al. 1994; MacLennan et al. 1991; ATBC Study 1994; Hennekens et al. 1996) and the effect of vitamin E alone in 1 study (ATBC Study 1994). Vitamin C and vitamin E were evaluated in 2 studies (De Cosse et al.

1989; McKeown-Eyssen et al. 1988), and various combinations of vitamins and of antioxidants in 4 studies (Roncucci et al. 1993; Hofstad et al. 1995; Bonelli et al. 1994; Hercberg et al. 1993). All these studies were double-blind randomized trials except for the Modena study (Roncucci et al. 1993), in which the reference group had no treatment. All the studies except 2 had a parallel design, meaning that the effect of one or several treatments was compared with the effect of the placebo. A 2x2 factorial design was used in 2 studies (Greenberg et al. 1994; MacLennan et al. 1991). The advantage of this design was that it allowed an estimation of the effect of the two combined treatments and that it gave more power to the study than a parallel scheme with the same number of patients.

The main end-point was adenoma recurrence in 5 studies (McKeown-Eyssen et al. 1988; Roncucci et al. 1993; Greenberg et al. 1994; MacLennan et al. 1995; Bonelli et al. 1994), variation in size of adenomas left in situ in 3 studies (Bussey et al. 1982; De Cosse et al. 1989; Hofstad et al. 1992), and colorectal cancer incidence in 3 studies (ATBC Study 1994; Hennekens et al. 1996; Hercberg et al. 1993). Most trials aimed at evaluating the effect of supplementation on adenoma recurrence or adenoma growth were small. The only large study was the one carried out within the National Polyp Study in the USA (Greenberg et al. 1994). Trials using adenoma recurrence or adenoma growth as the primary outcome have the advantage of being relatively small in size because a large number of events are expected during follow-up. For instance, the rate of patients with new adenomas is expected to be 30% at 3 years. However, whereas a relatively small sample size is sufficient to give the power needed to test the effectiveness of the intervention, some studies are obviously too small to provide any firm conclusion. In contrast, studies with invasive cancers as the main end-point require several tens of thousands of subjects.

The duration of the studies varies according to the main end-point. Trials that use adenoma recurrence or adenoma growth as the main end-point have the advantage of being relatively short in duration, ranging from 2 to 5 years (Table 1). Studies with colorectal cancer as the primary outcome require a longer follow-up period, generally at least 10 years.

The degree of compliance with the supplements is of importance. It was between 70% and 85% in most studies: 73% (Bussey et al. 1982), 79% (De Cosse et al. 1989), 75% (McKeown-Eyssen et al. 1988), 86% (Greenberg et al. 1994), 81% (Hofstad et al. 1995). It was only 45% in 1 study (Roncucci et al. 1993). Compliance with the final endoscopy was 73% in the St. Mark's Study, 79% in the New York Study, 78% in the Toronto Study, 87% in the National Polyp Study, 72% in the Australian Study, 87% in the Oslo Study and only 26% in the Modena Study.

The first chemopreventive study concerning colorectal cancer carcinogenesis was performed at St. Mark's Hospital, London, on patients treated for polyposis coli with the rectum left in place (Bussey et al. 1982). In the treatment group, there was a non-significant trend to a reduction in the number of rectal adenomas and in the adenoma area compared with the control

Table 1. Study designs, end-points and results of chemoprevention trials of vitamins and antioxidants in colorectal cancer carcinogenesis

Study	Subjects with	Intervention	No. of subjects	Duration	End-point results
Bussey et al. 1982, London	Familial polyposis	Vitamin C 2 g/day	49	15-24 months	No significant reduction in the number of rectal adenomas
De Cosse et al. 1989, New York	Familial polyposis	Vitamin C 4 /gd/day + vitamin E 400 mg/day	58	4 years	No effect on the number of rectal adenomas
McKeown-Eyssen et al. 1988, Toronto	Previous adenoma	Vitamin C 400 mg/day + vitamin E 400 mg/day	185	2 years	No effect on adenoma recurrence
Roncucci et al. 1993, Modena	Previous adenoma	Vitamin A 30 000 IU/day + vitamin E 70 mg /day	255	3 years	Significant reduction in adenoma recurrence
Greenberg et al. 1994, USA	Previous adenoma	$\beta$ -Carotene 30 mg/day + vitamin C 1 g/day + vitamin E 400 mg/day	864	4 years	No effect on adenoma recurrence
Hofstad et al. 1995, Oslo	Previous adenoma	$\beta$ -Carotene 15 mg/day + vitamin E 75 mg/day + vitamin C 150 mg/day + selenium 101 mg/day	116	3 years	No effect on adenoma growth or adenoma recurrence
MacLennan et al. 1996, Australia	Previous adenoma	$\beta$ -Carotene 20 mg/day	378	4 years	No effect on adenoma recurrence
Bonelli et al. 1994, Genova	Previous adenoma	$\beta$ -Carotene 15 mg/day + vitamin E 75 mg/day + vitamin C 150 mg/day + selenium 101 mg/day	279	5 years	Adenoma recurrence
ATBC 1994, Finland	Male smokers 50-69 years	$\beta$ -Carotene 20 mg/day + vitamin E 50 mg/day	29133	4-13 years	No effect on colorectal cancer incidence
Hennekens et al. 1996, USA	Medical doctors	$\beta$ -Carotene 50 mg on alternate days	22000	5 years	No effect on cancer incidence
SUVIMAX, France, 1993	Volunteers	$\beta$ -Carotene 6000 mg/day + vitamin C 120 mg/day + vitamin E 15 mg/day + selenium 101 mg/day + zinc 20 mg/day	15000	8 years	Cancer incidence, cardiovascular diseases

group (the reduction was significant at the 9 month follow-up, but disappeared over the next follow-up periods). A study with a similar design was performed in New York (De Cosse et al. 1989). There was no effect of vitamin E and vitamin C on the number of adenomas.

Of the 5 published studies that have tested the effect of antioxidant vitamins on adenoma recurrence, 4 are negative and 1 is still on-going (Bonelli et al. 1994). A Canadian study found no effect of supplemental vitamins C and E on the rate of recurrence of adenomas over a 2-year period (McKeown-Eyssen et al. 1988). In an American study there was no evidence

that  $\beta$ -carotene or vitamin C and vitamin E reduced the risk of new adenomas (Greenberg et al. 1994). Neither diet treatment appeared to be effective in any of the subgroups studied defined according to sex, age, number of previous adenomas and serum level at entry or subtypes of adenoma identified at follow-up examinations (number of colorectal adenomas, size of the largest adenoma and location of the adenomas). In the Oslo study, no effect of a combination of  $\beta$ -carotene, vitamin E, vitamin C, selenium and calcium was found on the adenoma growth of an adenoma <1 cm in size that had not been extirpated (Hofstad et al. 1995). Moreover, there was no effect either from year to year or when the size of the left-in adenoma and/or the location of the adenoma, gender and cancer among first-degree relatives were taken into account. In the Australian study there was the suggestion of an adverse effect: the recurrence rate of large adenomas (>1 cm) increased (borderline significance) in the group receiving  $\beta$ -carotene supplementation. In contrast, a trial in Modena showed a significant reduction in the adenoma recurrence rate in patients receiving vitamins A, C and E compared with non-treated patients (Roncucci et al. 1993). The numbers of patients with a new adenoma at colonoscopy were 4 of 49 treated and 28 of 54 untreated patients. The main limitations of this study were the small number of patients (resulting in a lack of precision in efficacy estimates), the short follow-up period (only a quarter of the subjects had a colonoscopy after 2 years) and the fact that a substantial proportion of randomly assigned patients did not undergo a follow-up colonoscopy at all. Because of these limitations, the results of this study need to be regarded with caution.

Some results are also available from the large trials that have colorectal cancer incidence as an end-point. The Alpha Tocopherol, Beta Carotene, Lung Cancer Prevention Study in Finland was logistically a success (ATBC Study 1994). A total of 29 133 male smokers aged 50–69 years participated in the chemoprevention trial, accumulating 169 751 follow-up years. During the course of the study, 68 incident cases of colorectal cancer appeared in the  $\alpha$ -tocopherol group versus 81 in the group not receiving  $\alpha$ -tocopherol, and 76 in the  $\beta$ -carotene group versus 73 in the group and receiving  $\beta$ -carotene. In the United States, 22 071 male physicians aged 40–84 years were randomized in a double-blind placebo-controlled trial of  $\beta$ -carotene, 50 mg on alternate days. Fewer than 1% had been lost to follow-up and compliance was 78% in the group that received  $\beta$ -carotene. Overall, 167 colorectal cancers were diagnosed in the intervention group and 174 in the placebo group (Hennekens et al. 1996).

The SUVIMAX study in France is still-going (Hercberg et al. 1993). No data on colorectal cancer incidence were reported from the CARET study (Ommen et al. 1996). A total of 18 134 subjects at high risk of lung cancer (heavy smokers and asbestos-exposed workers) were included to assess the effect of  $\beta$ -carotene and vitamin A. This study was stopped prematurely because the active treatment group was found to have a significantly higher risk of lung cancer than the placebo group.

A lot of information is available on the effect of antioxidant vitamins on colorectal cancer carcinogenesis. This information allows the conclusion that antioxidant vitamins and micronutrients have no effect on adenoma recurrence, adenoma growth or colorectal cancer risk.

## Fibre Trials

The results of analytical studies on dietary fibre are rather contradictory. It must be emphasised that dietary fibre is not a homogeneous entity and that different components may have different physiological effects. Food composition tables lack data on the different types of dietary fibre. In this context, studies examining the effect of a single source of fibre on experimental carcinogenesis in rodents are of interest. Pectin, cellulose, lignin, guar gum, alfalfa, carrageen and cutin seem to have little effect (Faivre et al. 1991). However, a protective effect has been observed in most studies for wheat bran and mucilaginous substances (such as ispaghula husk), particularly during the promoting phase. The relevance of these data to human cancer must be evaluated in intervention studies.

Fibre supplementation is proposed in four chemopreventive studies (Table 2). The effect of wheat bran (22.5 g/day) together with vitamins C and E has been evaluated in patients with familial polyposis and with the rectum left in place (De Cosse et al. 1989). Its effect on adenoma recurrence was studied in the Australian study, with a dose of 25 g/day (McLennan et al. 1995), and in the Arizona study, with 13.5 g/day (Vargas and Alberts 1992). A multicenter European study performed within the European Cancer Prevention Organisation (ECP) has been assessing a mucilaginous substance in the form of ispa-

Table 2. Study designs, end-points and results of chemoprevention trials of fibre in colorectal cancer carcinogenesis

Study	Subjects with	Intervention	No. of subjects	Duration	End-point results
De Cosse et al. 1989, New York	Familial polyposis	Wheat bran 22.5 g/day + vitamin C 4 g/day + vitamin E 400 mg/day	58	4 years	Nonsignificant reduction in the number of rectal adenomas
McLennan et al. 1995, Australia	Previous adenoma	Wheat bran 11 g/day	378	4 years	Significant reduction in the number of adenomas >1 cm in the low-fat/high-fibre group
Vargas and Alberts et al. 1992, Arizona	Previous adenoma	Wheat bran 13.5 g/day	1400	5 years	Adenoma recurrence
Faivre et al. 1997, Europe	Previous adenoma	Ispaghula husk 3.8 g/day	656	3 years	Adenoma recurrence

ghula husk, 3.8 g/day (Faivre et al. 1997). This dose was that proposed by the manufacturer to obtain stool bulking. Most of the above-mentioned studies are larger than the chemopreventive trials of vitamins. Their duration varies between 3 and 5 years. The compliance rate for fibre intake was 79% in the New York study (De Cosse et al. 1989) and 74% in the Australian study (MacLennan et al. 1995), and is currently 77% in the ECP study (intermediate results on 564 subjects who ended the study before April 1997). Compliance with the final colonoscopy is of great importance for the interpretation of the results. It was 92% at 2 years and 72% at 4 years in the Australian study (MacLennan et al. 1995). In the ECP study, intermediate results indicate that compliance with the 3 year colonoscopy was 89%.

The first fibre chemopreventive study was performed in patients treated for polyposis coli who had undergone total colectomy and ileorectal anastomosis and who were followed up at the Sloan-Kettering Institute in New York (De Cosse et al. 1989). The ratio between the initial number of adenomas and that at the follow-up examination was the main trial outcome. The intent-to-treat analysis suggested a limited effect of the treatment in the group receiving wheat bran, vitamin C and vitamin E compared with the groups receiving vitamins alone or a placebo. There were significant differences at 33 and 39 months only. When compliance was taken into account there was a stronger benefit in the combined fibre - vitamin group, particularly at the 2-year midpoint of the study.

In the Australian multicentre study there was no evidence that any intervention reduced the recurrence rate of adenomas at 2 or 4 years (MacLennan et al. 1995), but a significant reduction in the incidence of large adenomas ( $\geq 1$  cm) was found in the low-fat diet group. The effect was observed when the low-fat diet was combined with wheat bran. This study suggests that a low-fat diet combined with wheat bran supplementation may reduce the risk of adenoma growth in patients with small adenomas.

The final results from the ECP study and from the Arizona study will be available soon.

In conclusion, the results available provide some evidence for an inhibition of adenoma growth through a high-fibre diet and/or a low-fat diet. The results of ongoing studies are expected to provide further arguments to support these conclusions.

### Calcium Trials

It has been hypothesised that a high intake of calcium may decrease the risk of colorectal cancer. Support for this hypothesis was obtained from a 19-year prospective study in the USA and from the fact that oral intake of calcium may induce a more quiescent equilibrium of epithelial cell proliferation in the colonic mucosa of subjects at high risk of colorectal cancer. However, such results have been reported in only half of the cell proliferation studies,

and only one out of six case-control studies suggests a protective effect of high calcium intake.

Four intervention studies aimed at evaluating the possibility of primary prevention of colorectal cancer with calcium supplements have been carried out or are on-going (Table 3). All these studies are investigating subjects with a previous history of colorectal adenoma. As mentioned before, such trials have the advantage of being both relatively small in size and short in duration. In the ECP study, it was estimated with an assumed 30% recurrence rate at 3 years in the placebo group that 210 subjects per group are needed to detect a 15% difference between the tested group and the placebo group ( $\alpha=0.05$ ; power=0.90, two-tailed test). As for the polyp growth study, it can be estimated that there is an even higher proportion of patients with an increase in size of the unresected adenoma. In the ECP study, eligible patients had to have at least one adenoma over 5 mm in diameter or two adenomas. This gives more power to the study because such subjects have a higher recurrence rate than subjects with only a small adenoma. All these studies use adenoma recurrence as the primary outcome. The Oslo study has the additional feature that the effect of the intervention on the growth rate of an adenoma less than 1 cm in diameter left in situ in the large bowel is to be evaluated. None of the on-going studies has colorectal cancer as the main end-point.

The calcium being tested in the four studies is in the form of calcium carbonate or calcium gluconolactate various doses: 1.2 g/day (Baron et al. 1995), 1.5 g/day (Rooney et al. 1994), 1.6 g/day (with a mixture of antioxidants; Hofstad et al. 1995) and 2 g/day (Faivre et al. 1997). The study duration varies from one to another. It was 2 years in one study, 3 years in two studies and 4 years in one study (Table 3). In the Oslo and the Nottingham studies a control colonoscopy was performed yearly. In the two other studies control colonoscopy has been planned only for the end of the study.

The degree of compliance is an important factor in the success of the study, since the study power depends on both the sample size and the degree of compliance with the intervention. The compliance rate was 88% in the

Table 3. Study designs, end-points and results of chemoprevention trials of calcium in colorectal carcinogenesis

Study	Subjects with	Intervention	No of subjects	Duration	End-point results
Hofstad et al. 1995, Oslo	See Table 1				
Rooney et al. 1994, Nottingham	Previous adenoma	Calcium 1.5 g/day	79	2 years	No effect on adenoma, recurrence
Baron et al. 1995, USA	Previous adenoma	Calcium 1.2 g/day	930	4 years	Adenoma recurrence
Faivre et al. 1997, Europe	Previous adenoma	Calcium 1.0 g/day	656	3 years	Adenoma recurrence

Nottingham study (Rooney et al. 1991), 81% in the Oslo study (Hofstad et al. 1995) and 73% in the ECP study (intermediate results on 564 subjects who ended the study before April 1997). Compliance with the final colonoscopy examination was 88% in the Nottingham study, 87% in the Oslo study and 89% in the ECP study (intermediate results).

The two completed studies were small. In the Nottingham study no effect of calcium was found on adenoma recurrence after 2 years; the recurrence rate was 11% in both the calcium and the placebo groups (Rooney et al. 1994). In the Oslo study no effect on polyp growth was found, but there was a possible protective role of calcium and antioxidants against new adenoma formation. The two on-going studies - the ECP study and the American study - are larger. They will provide complementary information within 1 year.

It is not yet possible to draw firm conclusions on the effects of calcium supplementation in colorectal carcinogenesis, particularly on adenoma growth or adenoma recurrence. On-going studies are expected to provide further information.

### Aspirin Trial

Several lines of evidence support the notion that aspirin and other monosteroid anti-inflammatory drugs may prevent large bowel cancers. Most case-control and cohort studies indicate a 30%-50% reduction in risk of colorectal cancer among regular users of aspirin. The results are consistent both for colon cancer and rectal cancer mortality or incidence and for adenoma occurrence. The results are not uniform, however, and a few studies found no benefit with aspirin use.

Only one chemoprevention study has investigated the effect of aspirin on occurrence of colorectal cancer (Gann et al. 1993). In this study, performed in male physicians in the USA, one aspirin tablet (325 mg) or a placebo was taken every other day. This study was stopped after 5 years because of evidence of protection against myocardial infarction. No protection by aspirin against colorectal tumours was seen. The relative risk was 1.15 for cancer and 0.86 for adenomas for subjects randomized to aspirin group. The relatively short duration of treatment can explain this result. Some data suggest that regular aspirin use for 10 years or longer is required for the inverse association to become apparent. Furthermore, cancers found soon after randomization were probably present when aspirin therapy began and would most likely not have been affected by aspirin use. There is little information regarding the optimal dose of aspirin. Benefits and risks have to be better defined. Because of the known toxicity of aspirin there is not a sufficient basis to recommend aspirin to the public for preventing colorectal cancer.

### Conclusion

Altogether 15 chemopreventive studies (sometimes with several arms) have been performed to evaluate the possibilities of primary prevention of colorectal cancer: 8 in Europe, 6 in North America and 1 in Australia. Study populations are made up of subjects with previous adenomas or with remaining adenomas (i.e. intermediate steps in the natural history of the disease) or of volunteers included in large trials on cardiovascular diseases and/or other cancers in which colorectal cancer risk is one of the end-points. In addition to chemoprevention studies, 3 studies consider dietary interventions. Such studies are more difficult to implement and evaluate than are chemopreventive studies. The first study of this type was performed in Toronto (McKeown-Eyssen et al. 1994). In the intervention group, a low-fat diet (20% of energy from fat) and a high-fibre diet (50 g/day) was advised. After 12 months of counseling, fat consumption was 25% of energy in the intervention group and 33% in the control group, and fibre consumption was 35 g and 15 g, respectively. There was a nonsignificantly reduced risk of adenoma recurrence in women and an opposite risk in men. Thus, the issue of a gender-related effect on adenoma recurrence remains a definite question to be addressed in much larger studies. In the Australian study, as already mentioned, a low-fat diet (<25% of calories from fat) was proposed in one arm of the study (MacLennan et al. 1995). The National Polyp Study proposed a low-fat diet (<20% of total calories from fat), a high-fibre diet (at least 18 g/kcal of wheat bran) and fruit and vegetables (5-8 servings per day) in the intervention arm (Freedman and Schatzkin 1992). Overall, 2094 subjects have been randomized in this study aimed at evaluating adenoma recurrence.

This review does not consider trials with only indirect end-points. In such studies, available results are suggestive of treatment efficacy in reducing colorectal cancer risk, though not decisive. These results are of interest within intervention studies, as they represent a unique opportunity for better understanding of the pathogenesis of colorectal carcinogenesis. Levels of cell proliferation in the intestinal mucosa have been evaluated in several studies (MacLennan et al. 1991; Faivre et al. 1997). Changes in the proliferation pattern have been correlated with the risk of colorectal tumours. It is worth evaluating the effect of the intervention on colonic cell proliferation. A detailed analysis of bile acids and related compounds is also planned in some chemopreventive studies (Hofstad et al. 1995; Faivre et al. 1997). Their involvement in colorectal carcinogenesis has been put forward, and the objective of the intervention is to decrease their toxic effects. In this context, it is important to document changes in their concentrations in faeces, for better definition of their role in the initial phases of colorectal carcinogenesis. Assessments of the underlying nutritional status before and after the intervention are important in the interpretation of the results. Diet needs to be estimated, with particular emphasis on the main hypotheses concerning colorectal cancer carcinogenesis.

It can be concluded that most available data do not support a protective effect of antioxidant vitamins (vitamin C,  $\beta$ -carotene, vitamin E, association

of these vitamins) or micronutrients (selenium, zinc) on adenoma recurrence and growth and/or colorectal cancer risk. Results from small calcium chemopreventive studies are difficult to interpret, and the same applies to the effect of dietary fibre. Although results are conflicting, there are some arguments in favour of a protective effect of dietary fibre and/or a low-fat diet on adenoma growth. The results of on-going preventive studies will provide further data on the effect of calcium and fibre on colorectal carcinogenesis. They will be available within 1 year.

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## LACK OF EFFECT OF A HIGH-FIBER CEREAL SUPPLEMENT ON THE RECURRENCE OF COLORECTAL ADENOMAS

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### ABSTRACT

**Background** The risks of colorectal cancer and adenoma, the precursor lesion, are believed to be influenced by dietary factors. Epidemiologic evidence that cereal fiber protects against colorectal cancer is equivocal. We conducted a randomized trial to determine whether dietary supplementation with wheat-bran fiber reduces the rate of recurrence of colorectal adenomas.

**Methods** We randomly assigned 1429 men and women who were 40 to 80 years of age and who had had one or more histologically confirmed colorectal adenomas removed within three months before recruitment to a supervised program of dietary supplementation with either high amounts (13.5 g per day) or low amounts (2 g per day) of wheat-bran fiber. The primary end point was the presence or absence of new adenomas at the time of follow-up colonoscopy. Subjects and physicians, including colonoscopists, were unaware of the group assignments.

**Results** Of the 1303 subjects who completed the study, 719 had been randomly assigned to the high-fiber group and 584 to the low-fiber group. The median times from randomization to the last follow-up colonoscopy were 34 months in the high-fiber group and 36 months in the low-fiber group. By the time of the last follow-up colonoscopy, at least one adenoma had been identified in 338 subjects in the high-fiber group (47.0 percent) and in 299 subjects in the low-fiber group (51.2 percent). The multivariate adjusted odds ratio for recurrent adenoma in the high-fiber group, as compared with the low-fiber group, was 0.88 (95 percent confidence interval, 0.70 to 1.11;  $P=0.28$ ), and the relative risk of recurrence according to the number of adenomas, in the high-fiber group as compared with the low-fiber group, was 0.99 (95 percent confidence interval, 0.71 to 1.36;  $P=0.93$ ).

**Conclusions** As used in this study, a dietary supplement of wheat-bran fiber does not protect against recurrent colorectal adenomas. (N Engl J Med 2000; 342:1156-62.)

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**T**HE risks of colorectal cancer and adenoma, the precursor lesion, are believed to be influenced by diet.<sup>1</sup> Burkitt's proposal that a high-fiber diet protects against colon cancer was based on the low rates of colorectal cancer in Africa.<sup>2</sup> Insoluble fibers, such as wheat-bran fiber, are thought to protect against colon cancer by absorbing carcinogens in the gastrointestinal tract.<sup>3</sup> Indeed,

wheat-bran fiber has been shown to dilute fecal concentrations of bile acids<sup>4,5</sup> and to bind bile acids, thereby increasing their fecal excretion.<sup>6,7</sup> Although an inverse correlation was observed between mortality rates from colon cancer and per capita cereal consumption,<sup>8</sup> the results of the few analytical epidemiologic studies of associations between the consumption of whole-grain cereal and the risk of colorectal cancer<sup>9-15</sup> or adenoma<sup>16</sup> have been equivocal. Some metabolic end-point studies,<sup>5,17</sup> including our own,<sup>4</sup> have shown that wheat-bran fiber decreases fecal mutagenicity and reduces concentrations of fecal bile acids, although no effect was found on rates of proliferation of rectal mucosal cells.<sup>18</sup> Two studies found that a supplement of wheat-bran fiber had no effect on the risk of recurrent colorectal adenoma.<sup>19,20</sup>

In 1990, we initiated a multicenter trial to determine whether wheat-bran fiber can prevent the recurrence of colorectal adenomas.

### METHODS

#### Study Design and Subjects

Details of the design and methods of the study have been described previously.<sup>21</sup> Briefly, subjects were recruited between September 1990 and July 1995 from multiple centers in the Phoenix, Arizona, metropolitan area. The study protocol was approved by the institutional review boards of the 22 participating health care centers in the Phoenix area and by the human-subjects committee of the University of Arizona. All subjects provided written informed consent.

We identified men and women who were 40 to 80 years of age from whom one or more colorectal adenomas, measuring at least 3 mm in diameter at colonoscopy, had been removed within the three months before recruitment. To be eligible, subjects had to have an adequate nutritional status and normal renal and liver function and to have a Southwest Oncology Group performance status of 0, 1, or 2.<sup>22</sup> We excluded persons who had had invasive cancer within the previous five years; those with a history of colon resection; those who had two or more first-degree relatives with

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colorectal cancer, severe metabolic disorders, or other severe illnesses; and those with an intake of more than 30 g of dietary fiber per day on the basis of their responses to the Arizona Food-Frequency Questionnaire.<sup>23</sup>

Subjects who successfully completed a six-week run-in period by consuming at least 75 percent of the amount of a low-fiber supplement supplied (2 g per day) were randomly assigned to receive a high-fiber supplement (13.5 g per day) or a low-fiber supplement (2 g per day) of wheat-bran cereal. With the exception of the cereal-fiber intervention, no other dietary changes were required. The treatment assignments were not revealed to the subjects, their physicians, or members of the study staff. The fiber supplements were provided by Kellogg (Battle Creek, Mich.) and were available in several forms: unsweetened loop-shaped cereal and sweetened and unsweetened shredded cereal. Analysis of the fiber content per serving showed the following: high-fiber loops, 13 g; low-fiber loops, 2 g; high-fiber unsweetened shredded cereal, 13 g; low-fiber unsweetened shredded cereal, 4 g; high-fiber sweetened shredded cereal, 10 g; and low-fiber sweetened shredded cereal, 3 g. Cereal boxes were color coded into six groups to help maintain the study blinding. Midway through the study, high-fiber wheat-bran-fiber bars (containing 10 g of fiber) and low-fiber bars (4 g of fiber) were developed by Kellogg. Subjects who had completed two years of the study were allowed to elect to consume up to 25 percent of their daily fiber supplement in the form of a fiber bar.

Compliance with the protocol was evaluated primarily by counts of returned cereal boxes and fiber bars at each visit and secondarily through a specialized intake calendar. Each index was used to generate an overall compliance score; subjects who consumed more than 75 percent of the cereal supplement were classified as complying with the protocol. On the basis of these data, members of the clinic research staff initiated individualized measures, as necessary, to increase compliance.

### Colonoscopy

The study protocol specified that follow-up colonoscopy be performed twice after the initial qualifying colonoscopy. The first colonoscopy was to take place one year after randomization (to identify and remove adenomas missed at the qualifying colonoscopy), and the second two years thereafter. However, the national recommendations regarding the frequency of colonoscopic surveillance of patients with a history of colorectal adenomas changed during the study from one and three years after the initial resection to three years after resection.<sup>24-26</sup> Thus, there was a decrease in the rate of colonoscopy at one year among subjects enrolled in the latter part of the trial.

### Data Collection

Results of endoscopy and pathological analysis were collected for each colonoscopy reported during the study. Using standardized guidelines, we abstracted data on the completeness of the examination and on the location, size, and histologic features of any resected adenomas.

Complete blood counts and blood chemical analyses were performed during screening and during the run-in phase of the study and annually thereafter. Diet was assessed according to the same schedule with use of the Arizona Food-Frequency Questionnaire, which has been evaluated with respect to reliability and validity in this population.<sup>27</sup> Information on adverse events was obtained every three months at the time the dietary supplement was dispensed.

### Statistical Analysis

The original trial design and approach to analysis were described in detail by Emerson et al.<sup>28</sup> The target sample size of 1400 subjects was based on a three-year rate of recurrence of adenomas of 40 percent and on an estimate that 10 to 15 percent of adenomas would be missed during the colonoscopy at base line. Given a predicted dropout rate of 25 percent over a period of three years, we estimated that 950 subjects would complete the intervention. Given this sample size, the study had a statistical power of 0.82

to detect a 25 percent reduction in the recurrence of adenomas and a power of 0.94 to detect a 30 percent reduction.

An interim analysis conducted in the latter part of the study suggested a difference between groups in the proportion of subjects who stopped taking the assigned supplement: 12.7 percent stopped in the low-fiber group, and 23.3 percent stopped in the high-fiber group. Therefore, for the remainder of the accrual period, the original 1:1 schedule of randomization was changed to 4:1, with four subjects assigned to the high-fiber group for every one assigned to the low-fiber group.

We counted all adenomas, whether detected during the first colonoscopy (at year 1) or subsequent colonoscopic examinations. Subjects in whom an adenoma was found during the one-year colonoscopy were not withdrawn from the study. Two separate analyses were performed. The first included all subjects who underwent colonoscopy one or more times after randomization, with recurrence defined as the identification of one or more adenomas after randomization. The second set of analyses included only subjects who underwent colonoscopy at one year and one or more times thereafter. Recurrence was defined for these analyses as the identification of any adenoma after the one-year colonoscopy. Differences between the high-fiber group and the low-fiber group in the rates of colonoscopy at one year and during follow-up were analyzed with the use of chi-square tests, and the difference between the groups in the length of time from randomization to the last colonoscopy was assessed with a log-rank test. Differences in characteristics and in the incidence of adverse events among patients with recurrent adenomas in the two groups were tested with chi-square tests.

Multivariate adjustment to test for an effect of wheat-bran fiber was initially performed with the use of logistic regression (presence vs. absence of an adenoma). We used generalized estimating equations with a Poisson link function to model the number of recurrent adenomas at each colonoscopy, adjusting for the timing of colonoscopy and assuming an exchangeable correlation structure among the repeated procedures.<sup>29</sup> Generalized estimating equations were used to estimate the adjusted relative risk of the recurrence of adenomas for the high-fiber group as compared with the low-fiber group, whereas logistic regression was used to estimate the adjusted odds ratio (as an estimate of the adjusted relative risk). Initial models fitted to test the effect of group assignment were adjusted only for the randomization period. Subsequent statistical modeling also adjusted for sex and the number of adenomas at the base-line colonoscopy (both of which are strong predictors of the risk of recurrence) and factors that were found to be significantly different between groups at base line. The significance of the treatment effect was assessed with the Wald statistic.

## RESULTS

### Enrollment and Randomization

We identified 4705 potentially eligible subjects. Of these, 2088 declined to participate, 1006 were found to be ineligible, and 102 dropped out before the run-in phase. The remaining 1509 subjects entered the six-week run-in phase, which consisted of the daily intake of a supplement low in wheat-bran fiber (2 g per day). Of the 3699 eligible subjects, 1429 (38.6 percent) successfully completed the run-in period and underwent randomization, 627 to the low-fiber group and 802 to the high-fiber group.

### Base-Line Characteristics of the Subjects

Table 1 shows the base-line characteristics of all 1429 randomized subjects and of the 1303 subjects (91.2 percent) who completed the study by undergoing at least one colonoscopy after randomization.

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TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS.\*

CHARACTERISTIC	ALL RANDOMIZED SUBJECTS (N=1429)		SUBJECTS WHO COMPLETED THE STUDY (N=1303)	
	LOW-FIBER GROUP (N=627)	HIGH-FIBER GROUP (N=802)	LOW-FIBER GROUP (N=584)	HIGH-FIBER GROUP (N=719)
Age — yr	66.0±8.8	66.8±9.0	66.0±8.8	66.4±8.8
Male sex — no. (%)	409 (65.2)	538 (67.1)	385 (65.9)	486 (67.6)
Dietary intake				
Energy — kcal/day	1875±636	1941±709	1874±629	1939±692
Total fat — g/day	71.0±32.0	75.1±35.1	70.7±31.4	74.7±34.6
Dietary fiber — g/day	18.8±8.3	18.5±8.2	18.9±8.3	18.6±8.1
Calcium — mg/day	852±371	858±385	849±368	856±385
Alcohol — g/day	6.1±10.9	8.1±17.9	6.4±11.1	8.4±18.0
10-year history of regular aspirin use — no. (%)	165 (26.3)	230 (28.7)	154 (26.4)	213 (29.6)
Current smoker — no. (%)	67 (10.7)	136 (17.0)	57 (9.8)	121 (16.8)
History of adenomas before base-line colonoscopy — no./total no. (%)	210/544 (38.6)	272/722 (37.7)	199/504 (39.5)	253/648 (39.0)
History of colorectal cancer in 1 parent or sibling — no. (%)	99 (15.8)	141 (17.6)	91 (15.6)	129 (17.9)
Adenomas				
Size of largest adenoma — mm	9.7±7.1	10.1±7.6	9.5±6.8	10.1±7.7
No. of adenomas	1.8±1.5	1.8±1.2	1.8±1.5	1.8±1.2
Location in proximal colon alone — no./total no. (%)	165/624 (26.4)	220/799 (27.5)	155/581 (26.7)	195/716 (27.2)
Villous histologic findings — no./total no. (%)†	95/625 (15.2)	119/801 (14.9)	91/582 (15.6)	107/718 (14.9)

\*Plus-minus values are means ±SD.

†This category included tubulovillous and villous adenomas.

TABLE 2. SELF-REPORTED COMPLIANCE WITH THE PROTOCOL AMONG THE 1303 SUBJECTS WHO COMPLETED THE STUDY.\*

GROUP	TOTAL NO. OF SUBJECTS	YEAR 1		YEAR 2		YEAR 3	
		COUNT OF BOXES AND BARS	CALENDAR RECORD	COUNT OF BOXES AND BARS	CALENDAR RECORD	COUNT OF BOXES AND BARS	CALENDAR RECORD
		number of subjects/total number (percent)					
Low-fiber	584	548/584 (93.8)	536/534 (91.8)	472/544 (86.8)	459/543 (84.5)	425/508 (83.7)	399/504 (79.2)†
High-fiber	719	626/719 (87.1)	597/719 (83.0)	468/601 (77.9)†	442/598 (73.9)†	409/552 (74.1)†	376/544 (69.1)†

\*Compliance was defined as consumption of more than 75 percent of the assigned dietary supplements. Numbers of subjects do not total 1303 because of dropouts, deaths, or missing data. Compliance was assessed by a count of the boxes of cereal and fiber bars returned at each planned clinic visit and by an assessment of required calendar notations made by subjects concerning the number of cereal boxes or fiber bars consumed each day.

†P<0.05 for the comparison with the low-fiber group.

Of these 1303 subjects, 138 underwent only the one-year colonoscopy. The results for all randomized subjects who underwent colonoscopy after randomization were included in an intention-to-treat analysis.

#### Compliance

We assessed compliance with the dietary-supplement regimen by two methods: a count of cereal boxes returned to the study sites and a calendar record of consumption kept by each subject. With the ex-

ception of the first year of the study, there was a significant difference in compliance between the two groups (Table 2): the proportion of subjects who consumed more than 75 percent of the cereal supplement was lower in the high-fiber group than in the low-fiber group (P<0.05). Counts of returned boxes indicated that compliance declined with each year of the study, so that by the third year, 84 percent of the low-fiber group and 74 percent of the high-fiber group were consuming more than 75 percent of the

supplement. On the basis of responses to the Arizona Food-Frequency Questionnaire, which includes intake of fiber from the wheat-bran-fiber supplement and other sources, the mean total intake of fiber was 27.5 g per day in the high-fiber group and 18.1 g per day in the low-fiber group.

**Recurrence of Adenomas**

As noted in the Methods section, we changed the randomization scheme during the latter part of the study. As a result, 276 of the 1303 subjects underwent randomization according to a 4:1 ratio (high fiber to low fiber) (Table 3). We did not detect significant differences between the high-fiber and low-fiber groups in the number of colonoscopic procedures performed among subjects who underwent randomization ac-

ording to either the initial 1:1 scheme or the 4:1 subsequent scheme; however, subjects who underwent randomization during the later period underwent significantly fewer colonoscopic examinations during year 1 than those who underwent randomization during the initial period. This difference clearly resulted from the change in clinical screening practice.

Table 4 shows the rates of recurrent adenomas among the 1303 subjects who completed the study. The median observation period was 34 months in the high-fiber group and 36 months in the low-fiber group (P=0.006). By the time of the last follow-up colonoscopy, the percentage of subjects with one or more recurrent adenomas was 51.2 percent in the low-fiber group and 47.0 percent in the high-fiber group (P=0.13). After adjustment for the randomization scheme used, the odds ratio for the presence of at least one recurrent adenoma in the high-fiber group, as compared with the low-fiber group, was 0.88 (95 percent confidence interval, 0.70 to 1.11; P=0.28).

When the analysis was restricted to the 889 subjects who underwent both a one-year colonoscopy and another examination two years later, the recurrence rates in the high-fiber and low-fiber groups were not significantly different. With the use of generalized estimating equations, the relative risk in the high-fiber group, as compared with the low-fiber group, was 0.99 (95 percent confidence interval, 0.71 to 1.36; P=0.93) for all 1303 subjects and 1.08 (95 percent confidence interval, 0.71 to 1.64; P=0.73) for the 889 subjects who underwent colonoscopy during year 1. Additional adjustments for sex, the number of colonoscopic examinations, the number of adenomas found at the base-line colonoscopy, and base-line variables that differed significantly between treatment groups did not change the results. Separate analyses revealed no significant differences in the rates of re-

**TABLE 3. NUMBER OF COLONOSCOPIC EXAMINATIONS AFTER RANDOMIZATION, ACCORDING TO TREATMENT GROUP AND RANDOMIZATION SCHEME.\***

VARIABLE	LOW-FIBER GROUP (N=523)	HIGH-FIBER GROUP (N=504)
	1:1 Randomization scheme (n=1027)	
Mean no. of colonoscopies	2.17±0.83	2.15±0.90
1 Colonoscopy — no. (%)	101 (19.3)	113 (22.4)
≥2 Colonoscopies — no. (%)	422 (80.7)	391 (77.6)
	LOW-FIBER GROUP (N=61)	HIGH-FIBER GROUP (N=215)
4:1 Randomization scheme (n=276)		
Mean no. of colonoscopies	1.64±0.61†	1.66±0.58†
1 Colonoscopy — no. (%)	26 (42.6)	86 (40.0)
≥2 Colonoscopies — no. (%)	35 (57.4)	129 (60.0)

\*Plus-minus values are means ±SD.

†P<0.05 for the comparison with the corresponding group in the 1:1 randomization scheme.

**TABLE 4. RISK OF RECURRENT ADENOMAS.\***

FOLLOW-UP PERIOD	NO. ANALYZED	HIGH-FIBER GROUP	LOW-FIBER GROUP	ADJUSTED ODDS RATIO (95% CI)†	HIGH-FIBER GROUP		ADJUSTED RELATIVE RISK (95% CI)‡
					LOW-FIBER GROUP	LOW-FIBER GROUP	
		no. with ≥1 recurrent adenomas/total no. (%)			mean no. of recurrent adenomas		
After randomization	1303	338/719 (47.0)	299/584 (51.2)	0.88 (0.70-1.11)	0.61	0.57	0.99 (0.71-1.36)
After colonoscopy at 1 year	889	168/468 (35.9)	153/421 (36.3)	1.04 (0.79-1.38)	0.60	0.53	1.08 (0.71-1.64)

\*CI denotes confidence interval.

†The odds ratio for the presence of at least one recurrent adenoma in the high-fiber group as compared with the low-fiber group, adjusted for the randomization scheme, is shown.

‡The relative risk of recurrent adenomas in the high-fiber group as compared with the low-fiber group, adjusted for the randomization scheme and timing of colonoscopies with the use of generalized estimating equations (Poisson link function), is shown.

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**TABLE 5. CHARACTERISTICS OF ADENOMAS IDENTIFIED AFTER RANDOMIZATION AMONG SUBJECTS WITH RECURRENT ADENOMAS.**

CHARACTERISTIC	LOW-FIBER GROUP (N=299)	HIGH-FIBER GROUP (N=338)	P VALUE*
	no. of subjects (%)		
Size of largest adenoma			0.71
<1 cm	205 (68.6)	227 (67.2)	
≥1 cm	94 (31.4)	111 (32.8)	
No. of adenomas			0.03
1	145 (48.5)	144 (42.6)	
2	66 (22.1)	61 (18.0)	
≥3	88 (29.4)	133 (39.3)	
Location of adenoma			0.004
Distal colon and rectum	87 (29.1)	77 (22.8)	
Proximal colon	144 (48.2)	140 (41.4)	
Both	60 (20.1)	110 (32.5)	
Not specified	8 (2.7)	11 (3.3)	
Histologic findings			0.51
Tubular adenoma	197 (65.9)	224 (66.3)	
Tubulovillous or villous adenoma	25 (8.4)	28 (8.3)	
Both	10 (3.3)	19 (5.6)	
Not specified	67 (22.4)	67 (19.8)	

\*The chi-square test was used.

currence between women in the low-fiber group and women in the high-fiber group (40.7 percent vs. 40.8 percent,  $P=0.99$ ). Among the men, there were fewer recurrent adenomas in the high-fiber group than in the low-fiber group (50.0 percent vs. 56.6 percent); this difference was of borderline statistical significance ( $P=0.05$ ). There was no evidence of an effect of supplementation with wheat-bran fiber among male subjects who underwent colonoscopy during the first year.

When we assessed the characteristics of the recurrent adenomas (Table 5), there was no significant difference between the two groups regarding the size of the adenomas ( $P=0.71$ ) or their histologic appearance ( $P=0.51$ ). However, there was a significantly higher proportion of subjects with three or more recurrent adenomas in the high-fiber group than in the low-fiber group ( $P=0.03$ ). When subjects were classified according to the sites of the recurrent adenomas (proximal colon or distal colon and rectum or both), the high-fiber and low-fiber groups were significantly different ( $P=0.004$ ); this result was largely due to the higher number of subjects in the high-fiber group who had recurrent adenomas in both the proximal colon and distal colon and rectum.

#### Adverse Events

During the course of the study, nine cases of colorectal cancer were reported, two in the low-fiber group and seven in the high-fiber group ( $P=0.20$ ). As shown in Table 6, among the 1303 subjects who completed the study, there were 23 deaths: 10 in the low-fiber group and 13 in the high-fiber group. There were no significant differences between groups in the

**TABLE 6. INCIDENCE OF DEATH AND OTHER ADVERSE EVENTS AFTER RANDOMIZATION.\***

VARIABLE	LOW-FIBER GROUP (N=584)	HIGH-FIBER GROUP (N=719)
	no. of subjects (%)	
Death	10 (1.7)	13 (1.8)
Disease*		
All cancers	38 (6.5)	51 (7.1)
Cardiovascular disease	11 (1.9)	6 (0.8)
Stroke	5 (0.9)	6 (0.8)
Gastrointestinal effects*		
Nausea	21 (3.6)	44 (6.1)†
Abdominal pain	69 (11.8)	136 (18.9)†
Diarrhea	65 (11.1)	145 (20.2)†
Constipation	78 (13.4)	91 (12.7)
Intestinal gas	135 (23.1)	243 (33.8)†
Abdominal bloating	59 (10.1)	121 (16.8)†

\*Some subjects had more than one adverse event.

† $P<0.01$  for the comparison with the low-fiber group.

occurrence of extracolonic cancer ( $P=0.58$ ), cardiovascular disease ( $P=0.37$ ), or stroke ( $P=0.69$ ). The number of subjects who reported gastrointestinal effects was significantly higher in the high-fiber group than in the low-fiber group for all effects except constipation (Table 6). Most of these adverse effects were mild.

#### DISCUSSION

In this double-blind trial, we found that a dietary supplement of wheat-bran fiber had no statistically significant protective effect against recurrent colorectal adenomas. This finding was unchanged whether the analysis was based on all colonoscopic procedures performed after randomization or only those performed after one year in the study. This method of analysis has been used in other intervention studies of recurrent colorectal adenoma.<sup>30</sup> Moreover, the high-dose supplement of wheat-bran fiber had no effect on the number of recurrent adenomas in subjects who had a recurrence. Our results are consistent with those of the Toronto Polyp Prevention Trial<sup>19</sup> and the Australian Polyp Prevention Project.<sup>20</sup> Although our secondary analyses suggested an effect of the high-fiber supplement among men, this result probably represents a chance finding; in the Toronto Polyp Prevention Trial the effect of a low-fat, high-fiber diet was greater among women than men.<sup>19</sup> Furthermore, contrary to the findings of the Australian trial, we did not see any evidence that the high-fiber supplement we used reduced the rate of recurrence of large adenomas. We observed no protective effect of the high-fiber supplement on the number, location, or histologic fea-

tures of the recurrent adenomas. The combination of these observations argues against the idea that dietary supplementation with wheat-bran fiber can protect against recurrent colorectal adenomas. As reported in this issue of the *Journal*, Schatzkin et al. found that a low-fat, high-fiber diet also failed to lower the risk of recurrence of colorectal adenomas.<sup>31</sup>

We observed a relatively high rate of recurrent adenomas in the proximal colon in both the low-fiber group and the high-fiber group (48.2 percent and 41.4 percent, as compared with respective rates of 26.4 percent and 27.5 percent at base line). When rates of recurrent adenomas in the proximal colon are added to the rates of recurrence occurring in both the proximal colon and the distal colon or rectum, 68.2 percent of the subjects in the low-fiber group and 74.0 percent of those in the high-fiber group had recurrences in the proximal colon. The high rates of recurrent adenomas in the proximal colon strongly suggest that colonoscopy, rather than sigmoidoscopy, is the preferred method of surveillance, especially in patients with a history of adenoma in the proximal colon.

In large, randomized clinical trials, randomization is expected to result in a relatively equal distribution of subjects with respect to risk factors of interest. In our trial, there was a balanced distribution with respect to base-line age and sex, but imbalances in terms of exposure to tobacco, alcohol consumption, and total intake of fat. Nevertheless, the multivariate logistic-regression analysis, after adjustment for randomization period, sex, smoking status, alcohol consumption, and energy intake, did not show a significant effect of supplementation with wheat-bran fiber on the recurrence of colorectal adenomas. Thus, our results do not appear to be related to an imbalance in the base-line characteristics of the subjects or to the change in the randomization scheme from a 1:1 ratio to a 4:1 ratio in favor of the high-fiber group.

Our experience underscores the difficulty of performing large-scale nutritional intervention trials, in terms of both recruitment and compliance with the protocol. Of 3699 eligible subjects, 1303 (35.2 percent) successfully completed the trial. In addition, by the third year of the study, only 74 percent of the subjects in the high-fiber group, as compared with 84 percent of those in the low-fiber group, consumed more than 75 percent of their supplemental cereal on a daily basis (a level we defined as indicative of compliance). Despite these difficulties, the mean intake of total fiber was 27.5 g per day in the high-fiber group and 18.1 g per day in the low-fiber group. It can be argued that this level of intake over a period of three years is inadequate to prevent recurrent adenomas; however, our compliance data indicate that higher daily consumption of wheat-bran fiber for longer periods is not practical in adults older than 65 years of age.

The lack of effect of three years of supplementa-

tion with wheat-bran fiber may reflect inadequate follow-up: three years may be too short. It could be argued that the total amount of dietary and cereal fiber consumed by the subjects in the high-fiber group was insufficient to protect against recurrent adenomas. It is also possible that a high-fiber diet may be beneficial only in persons with lower base-line intakes of total fiber than those in our study. Alternatively, the use of wheat-bran-fiber supplements may only protect against the progression of large adenomas to carcinomas. However, both the Nurses' Health Study<sup>15</sup> and the Health Professionals' Follow-up Study<sup>16</sup> failed to find that cereal fiber prevents colon cancer. Since cereal fiber has potentially healthful effects in the prevention of coronary heart disease,<sup>32,33</sup> public health recommendations<sup>34,35</sup> that emphasize increased consumption of complex carbohydrates, whole-grain foods, and cereal products may nevertheless be appropriate.

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## APPENDIX

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*Editorials*DIET, COLORECTAL ADENOMAS,  
AND COLORECTAL CANCER

BECAUSE colorectal cancers usually arise from adenomatous polyps, it is believed that preventing the growth of adenomas in the colon and rectum or removing any that appear will prevent colorectal cancer.<sup>1</sup> Many have therefore awaited the results of the two important trials published in this issue of the *Journal* — a study of wheat-bran fiber by Alberts et al.<sup>2</sup> and the Polyp Prevention Trial.<sup>3</sup> Both trials are well conceived, well designed, well implemented, and clearly presented. What is disappointing, however, is that the findings of both trials are negative. Three to four years of either taking a daily wheat-bran supplement or following a diet that was low in fat and high in fruits and vegetables had no effect on the incidence of new colorectal adenomas.<sup>2,3</sup> These findings, considered alongside previous negative results of trials that assessed the ability of other nutritional factors to prevent adenomas, lead to a clear conclusion. The relevance of these findings for the prevention of colorectal cancer is less certain, however.

Surveillance by colonoscopy after the diagnosis of an adenoma is a major clinical challenge.<sup>1</sup> If an intervention could be found that reduced the growth of new adenomas, then colonoscopic surveillance could be less frequent for people with a history of adenoma. This approach would reduce the costs and inconvenience of the procedure, while still lowering the risk of adenoma. Several groups have examined the effect of various nutritional interventions on the risk of new colorectal adenomas using the same clinical model employed by Alberts et al. and the Polyp Prevention Trial.<sup>4</sup> In this model, patients who have had an adenoma removed are randomly assigned to a nutritional intervention or to a control group, and the efficacy of the intervention is assessed at the time of the clinically indicated follow-up colonoscopy, one year later, three to four years later, or at both times. Supplementation with vitamin C, vitamin E, beta carotene, or cereal fiber or the adoption of a diet low in fat and high in fruits and vegetables has shown no effect on the incidence of new adenomas.<sup>2,4</sup> Calcium supplements were somewhat effective, but they reduced the incidence of adenomas by only 17 percent.<sup>5</sup> Although there may be other reasons to follow low-fat, high-fiber diets or to take these supplements, it is clear that these interventions do not appreciably reduce the rate of formation of new adenomas within a period of three to four years — the standard length of follow-up in such studies.

Clinical trials are a convenient way to study the

development of new polyps, but they are not a good way to study the role of diet or nutrients in the later stages of the evolution of adenomas to colorectal cancer. In the context of the long course of this evolution, the three- or four-year period assessed by clinical trials is very brief.<sup>6</sup> All the studies conducted to date have been limited to this particular length of time. It is therefore appropriate to question the relevance of these trials for the prevention of colorectal cancer. Although adenomas are a risk factor for colorectal cancer, most adenomas do not evolve into colorectal cancer, of course, and the clinical importance of small adenomas (those that are less than 1 cm in diameter), especially small tubular adenomas that contain neither villous histologic features nor areas of dysplasia, is not clear. The majority of the adenomas found during follow-up in adenoma-prevention trials have been small, tubular adenomas without villous or dysplastic features. In the study by Alberts et al., only 12.9 percent of the recurrent adenomas had villous features, and in the Polyp Prevention Trial, only 16.4 percent of the recurrent adenomas had villous features or dysplasia or were large. In a small Australian trial, the use of a cereal-fiber supplement was associated with a marginally significant reduction in the incidence of larger adenomas,<sup>7</sup> but neither of the two current trials found any evidence of protection against large or advanced adenomas. Although the numbers of cancers were small in the study by Alberts et al. and the Polyp Prevention Trial, it is disappointing that in both trials the incidence of cancer was slightly higher in the intervention group than in the control group (7 cases vs. 2 and 10 cases vs. 4, respectively).

The authors of both trials rightfully concluded that their findings cannot be interpreted as evidence that a high-fiber cereal supplement or a low-fat, high-fiber diet is not effective in protecting against the later stages of development of colorectal cancer. Short-term trials of this type are still reasonable for the assessment of treatments to prevent the growth of new adenomas, but new designs are also needed to study the effects of nutritional and chemopreventive agents on the later stages of the development of colorectal cancer.

Trials in which adenomas are not removed present clinical and ethical problems, although the results of one such study were recently reported, in which polyps were left in place for three years to assess the effects of a combination of nutrients on their growth.<sup>8</sup> No effects on growth were detected, though there were marginally fewer new polyps among the subjects who were receiving a mixture of beta carotene, vitamin C, vitamin E, selenium, and calcium supplements.<sup>8</sup> Perhaps agents like aspirin, selective inhibitors of cyclooxygenase 2, selenium, and folate — alone or in combination — will be found to be useful in the clinical management of adenomas.

A different, though related, question is whether a low-fat, high-fiber diet will reduce the risk of colorectal cancer. Findings from observational studies show that diets high in fruits and vegetables are associated with lower risks of cancer at many sites, including the colon and rectum.<sup>9,10</sup> The idea that the intake of insoluble fiber alone explains population-based differences in the risk of colorectal cancer may well have been overly simplistic and incorrect. In fact, the amount of cereal fiber in the diet has not consistently been associated with the risk of colorectal cancer in observational studies.<sup>9,10</sup> Moreover, cereal fiber taken in the form and amounts used in the study by Alberts et al. not only has no effect on the incidence of colorectal adenomas, but also causes gastrointestinal side effects. In observational studies, the evidence that a low-fat diet reduces the risk of colorectal cancer is also mixed, but a higher intake of fruits and vegetables (especially vegetables) has been found to be beneficial more consistently.<sup>9,10</sup>

Observational studies around the world continue to find that the risk of colorectal cancer is lower among populations with high intakes of fruits and vegetables and that the risk changes on adoption of a different diet, but we still do not understand why.<sup>9,10</sup> It is unclear whether any single aspect of the diet — a particular vitamin, phytochemical, or dietary practice such as the method of cooking meats — accounts for this relation. Randomized, controlled trials are commonly regarded as providing more definitive support for causal inferences than are observational studies, because they can control for confounding by the many factors related to the dietary behavior of interest. Randomized, controlled trials can usually answer only narrowly defined questions, however, and they cannot easily assess the effects of the long-term dietary patterns that have been shown to be associated with a lower risk of colorectal cancer in observational studies. This is clearly true of polyp-prevention trials, since such studies are particularly limited by their short follow-up periods.

Randomized, controlled trials have now shown us that the use of some of the diets and nutritional supplements thought to lower the risk of colorectal cancer has no short-term benefits with respect to preventing adenomas. There may be many reasons to eat a diet that is low in fat and high in fiber, fruits, and vegetables or to supplement the diet with a food high in cereal fiber, but preventing colorectal adenomas, at least for the first three to four years, is not one of them. With regard to questions about diet and colorectal cancer, though, definitive answers still seem to be beyond the reach of both observational epidemiologic studies and randomized, controlled trials.

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## MISSED DIAGNOSES OF ACUTE CORONARY SYNDROMES IN THE EMERGENCY ROOM — CONTINUING CHALLENGES

**P**ATIENTS with suspected acute coronary syndromes, or acute cardiac ischemia, account for nearly 1.7 million hospital admissions per year in the United States. Between 2 and 8 percent of patients with myocardial infarction are mistakenly released from the emergency department.<sup>1-3</sup> In addition to the implications for patient care of the failure to diagnose acute coronary syndromes, the threat of malpractice suits is also of concern. An estimated 20 percent of the money awarded in malpractice suits against emergency department physicians is related to the misdiagnosis and mistreatment of acute coronary syndromes. Thus, it is not surprising that physicians in the emergency department tend to be cautious when making decisions about patients with chest symptoms, admitting far more patients with possible acute coronary syndromes than are ultimately found to have them. Acute myocardial infarction or unstable angina is confirmed in no more than 30 percent of patients who are admitted with suspected acute coronary syndromes. These potentially unnecessary hospitalizations result in health care costs of more than \$5 billion annually in the United States. There is considerable interest in increasing the efficiency of health care delivery in order to reduce the number of

## AGA Technical Review: Impact of Dietary Fiber on Colon Cancer Occurrence

*This literature review and the recommendations therein were prepared for the American Gastroenterological Association (AGA) Clinical Practice and Practice Economics Committee. The paper was approved by the committee on September 25, 1999, and by the AGA Governing Board on November 15, 1999.*

Colorectal cancer (CRC) is one of the most common cancers in the developed world. In the United States, CRC is the fourth most common cancer (after lung, prostate, and breast cancers) and the second most common cause of cancer death (after lung cancer).<sup>1</sup> In 1998 alone, 131,600 new cases of CRC are expected to be diagnosed, and an estimated 56,500 deaths will have been caused by the disease.<sup>1</sup> The development of CRC is thought to be the result of an intimate and still poorly understood interplay between environmental and genetic factors. Dietary and lifestyle factors are among the most important environmental factors implicated.<sup>2,3</sup> It has been estimated that 35% (10%–70%) of all cancers are attributable to diet and that 50%–75% of CRC in the United States may be preventable through dietary modifications.<sup>4</sup> U.S. CRC mortality rates among the white population decreased by 29% from 1950 through 1990, with a more pronounced decrease in women than in men.<sup>5</sup> This decrease is probably attributable to improved early detection as well as lifestyle and dietary changes.<sup>5</sup>

A cause-and-effect relationship between dietary or other lifestyle factors and CRC is difficult to establish. Because of inherent limitations associated with study design, epidemiological, animal, and interventional studies examining this relationship have often produced conflicting results. Therefore, the precise nature of the relationship of CRC with each nutrient or lifestyle factor and the actual magnitude of the relationship are not clear. Among dietary factors implicated in colorectal carcinogenesis, consumption of red meat, animal and saturated fat, refined carbohydrates, and alcohol, as well as total caloric (energy) intake, is believed to be positively related.<sup>2,3</sup> On the other hand, the intake of dietary fiber, vegetables, fruits, antioxidant vitamins, calcium, and folate is negatively associated with the development of CRC.<sup>2,3</sup> In addition, obesity, increased body mass index, and a sedentary lifestyle are associated with increased risk.<sup>2,3</sup>

There tends to be agreement among epidemiological studies regarding the risk of CRC and its relationship with overall diet and lifestyle.<sup>6</sup> However, when many of the findings are examined closely and correlations between CRC and individual dietary and lifestyle factors are

sought, the relationship tends to be less convincing.<sup>6</sup> Therefore, these observations suggest that overall diet and lifestyle, rather than individual factors, play the more important role, thus underscoring the importance of as yet undetermined interactions among dietary components and lifestyle factors in the development of CRC. Investigators have begun to recognize the need to elucidate a unifying mechanism by which these factors modulate colorectal carcinogenesis<sup>7,8</sup> and to examine combinations of dietary and lifestyle modifications in the prevention of CRC (e.g., the Polyp Prevention Trial).<sup>9</sup>

Dietary fiber is one of several factors whose role in colorectal carcinogenesis has been extensively studied. However, the precise nature and magnitude of the relationship between fiber intake and CRC risk have not been clearly established. Dietary guidelines from the American Cancer Society and the National Cancer Institute, which encourage healthy eating habits and lifestyle modifications, recommend that individuals eat more than 5 servings of fresh vegetables and fruits and 20–30 g of fiber per day. However, the validity of these recommendations has not been scrutinized rigorously.

The objective of this technical review is a critical analysis of currently available data from epidemiological and clinical studies in humans of dietary fiber's effect on colorectal carcinogenesis. All human studies concerning CRC and its precursor, adenoma, and fiber, grains, cereals, vegetables, or fruits published in the English language from 1970 through 1999 were considered. These studies were found in the MEDLINE and CANCERLIT databases, in several extensive reviews,<sup>2,3,10–14</sup> and in references in the identified studies. This review emphasizes results from all the published prospective (cohort) epidemiological studies and randomized intervention studies in humans. Seminal studies of a descriptive

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*Abbreviations used in this paper:* CAPP, Concerted Action Polypsis Prevention trial; CI, confidence interval; CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; IGF, insulin-like growth factor; OR, odds ratio; RR, relative risk; SCFA, short-chain fatty acid.

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and case-control epidemiological nature as well as previously published meta-analyses or pooled (combined) analyses of case-control studies are reviewed. Possible mechanisms by which dietary fiber may suppress colorectal carcinogenesis are also discussed.

### Dietary Fiber: Definition, Sources, and Consumption

Because the term *dietary fiber* encompasses a wide range of complex materials, it is difficult to define. There is no internationally accepted definition or method for determining the dietary fiber content of foods.<sup>15</sup> Dietary fiber was initially defined by Burkitt and Trowell<sup>16</sup> as the complex carbohydrate in the diet from plant sources that escapes small bowel digestion and thus reaches the colon. The U.S. Expert Panel on Dietary Fiber defined dietary fiber as the endogenous components of plant materials in the diet that are resistant to digestion by enzymes produced by humans.<sup>17</sup> Analytically, dietary fiber is composed predominantly of nonstarch polysaccharides and nonpolysaccharides (mainly lignins).<sup>18</sup> Nonstarch polysaccharides include cellulose and noncellulosic polysaccharides (e.g., hemicelluloses, pectins, gums, and mucilages).<sup>18</sup> This definition excludes other substances in the plant materials such as phytates, cutins, saponins, lectins, proteins, waxes, silicon, and other organic constituents.<sup>18</sup> Dietary fiber can be further analytically classified as soluble (some hemicelluloses, pectins, gums, and mucilages) and insoluble (most hemicelluloses, celluloses, and lignins), depending on its solubility in water and buffer solution.<sup>18</sup> When the effect of dietary fiber on the colon is being considered, the classification of fiber as fermentable (i.e., metabolized by colonic bacteria) and nonfermentable is also useful. It became apparent in the early 1980s that some starch escapes small bowel digestion and reaches the colon. Stephen et al.<sup>19</sup> estimated that 5%–10% of dietary starch reaches the colon and called this "resistant starch." Dietary fiber and related compounds are summarized in Table 1.

The development of new analytical methods<sup>20–22</sup> to estimate the dietary fiber content of foods allowed epidemiological studies to better define the relationship between the intake of dietary fiber and the risk of CRC. However, these assays still underestimated the actual dietary fiber content in foods. They<sup>20–22</sup> are based on the assumption that all starch is digested in the small bowel and that other complex carbohydrates are completely undegraded; dietary fiber is therefore considered to include all plant polysaccharides except starch and nonpolysaccharides. These assays estimated the amount of nonstarch polysaccharides in the North American diet to

**Table 1.** Dietary Fiber and Related Compounds

Classification
Nonstarch polysaccharides:
Celluloses
Noncelluloses: hemicelluloses, pectins, gums, mucilages
Nonpolysaccharides: lignins
Classification based on solubility
Soluble (highly fermented): pectins, gums, mucilages, some hemicelluloses
Insoluble (poorly fermented): celluloses, lignins, most hemicelluloses
Minor components
Phytates, cutins, saponins, lectins, protein, waxes, silicon
Related components
Resistant starch and protein
Lignans

be in the range of 12–15 g/day.<sup>23</sup> Almost all of the epidemiological studies used these assays to estimate the dietary fiber intake. Currently available assays that account for resistant starch (in the range of 3–5 g/day in the North American diet<sup>24</sup>) estimate the amount of polysaccharides that reach the colon to be in the region of 15–25 g/day. Even with the inclusion of resistant starch in the assessment of dietary fiber intake, currently available assays account for less than one third of total dietary fiber that reaches the colon to sustain the known rate of colonic bacterial synthesis.<sup>11,12</sup> Therefore, although the assays that are currently available to estimate nonstarch polysaccharides and resistant starch are very precise, they do not accurately measure dietary intake and seriously underestimate the amount of dietary fiber that reaches the colon and is available to participate in the mechanisms of CRC prevention.<sup>11,12</sup> Because of these difficulties, epidemiologists began to study the relationship between intake of "fiber-rich" foods (e.g., cereals, fruits, and vegetables) and the risk of CRC; most of these studies suggested a strong inverse relationship.<sup>11,12</sup>

Dietary fiber is found mainly in vegetables, fruits, grains, seeds, nuts, and legumes. In the Second National Health and Nutrition Examination Survey (NHANES II, 1976–1980), mean dietary fiber intake in the U.S. adult population (>19 years old) is 11.1 g/day or 13.3 g/day, depending on the methodology used.<sup>23</sup> On any given day, 50% of the U.S. population reports a dietary fiber intake of <10 g/day, and only ~10% consume >20 g/day.<sup>23</sup> On a per 1000-kcal basis, women consume more dietary fiber (6.5 g/1000 kcal) than men (5.5 g/1000 kcal) at every age.<sup>23</sup> Both men and women show the same pattern of increasing dietary fiber intake with age when fiber is examined in relation to total caloric intake.<sup>23</sup> A marked racial effect is evident; blacks having lower dietary fiber intake than whites in both sexes and all age groups.<sup>23</sup> It is uncertain at present whether mean dietary fiber intake in the U.S. adult population has significantly increased

since the completion of the second NHANES. This issue is being analyzed from the recently completed NHANES III (1988–1994), which included 40,000 noninstitutionalized people aged  $\geq 2$  months and oversampled blacks, Mexican Americans, children, and elderly people.<sup>25</sup> Table 2 lists the fiber content of frequently consumed fruits and vegetables.

### Epidemiological Evidence

The "fiber hypothesis" was first introduced when Burkitt<sup>26,27</sup> recognized the rarity of CRC in most African populations and was impressed by the high fiber and low refined carbohydrate content of the diet in Africa and other underdeveloped areas of the world. Since then, this purported inverse relationship between dietary fiber intake and the risk of CRC has been investigated by 3 types of human epidemiological studies: correlation (or ecological), case-control, and prospective studies.

In nutritional epidemiological studies, dietary intake of certain nutritional factors is assessed by several methods. In the 24-hour recall method, the basis of most national surveys, subjects are asked to report their food intake during the previous day. This method has the advantage of requiring no training or literacy and minimal effort by the participant. The most serious limitation is that dietary intake is highly variable from day to day. In the diet recording (food diary) method, detailed meal-by-meal records are kept of the types and quantities of food and drink consumed during a specified period, typically 3–7 days. This method places a considerable burden on the subject, thus limiting it to literate people who are also highly motivated. The effort involved in keeping diet records may increase consciousness of food intake and encourage alteration of diet. However, the advantages of the diet recording method are that it does not depend on memory and allows direct measurement of portion sizes. Dietary records reduce the problem of day-to-day variation by taking the average of a number of days; in addition, weekday/weekend variability, which in some societies is high, can be accounted for. Short-term recall and dietary recording methods are generally expensive, may be unrepresentative of usual intake, and are inappropriate for assessment of diet history. For these reasons, many investigators now use food frequency questionnaires, which include a food list and a frequency response section for subjects to report how often each food is eaten. Diets tend to be reasonably well correlated from year to year, and subjects are usually asked to describe how frequently they ate each food in the preceding year. Food frequency questionnaires are easy for literate subjects to complete, often as self-administered forms. Processing is readily computerized and inexpensive; even

prospective studies involving repeated assessment of diet among tens of thousands of subjects are feasible.

### Correlation Studies

Correlation studies examine the relationship between the per capita consumption of a dietary factor and the prevalence, incidence, or mortality of CRC in the population. Correlation studies can examine this relationship among populations residing in different countries or among different groups within a country either at a given time or over a certain period (i.e., time-trend). They provide provocative initial evidence that a particular dietary factor has a role in the development of CRC and hence are considered worthy only of hypothesis formation. Of 28 published international, within-country correlation and time-trend studies of CRC and fiber, vegetables, grains, fruits, and cereals, 23 (82%) showed either a strong or a moderate protective effect of dietary fiber or "fiber-rich foods" or equivocal results that were nevertheless consistent with the fiber hypothesis.<sup>2,3,10-14</sup> Four studies found no evidence for a protective effect of fiber, and 1 study showed a significant excess risk of CRC associated with high intake of fiber-rich foods.<sup>2,3,10-14</sup> The limitations of interpretation of data generated from these correlation studies are many. The older international studies are based on intake of crude fiber, which greatly underestimates total dietary fiber levels. Furthermore, correlation studies often fail to correct for unmeasured confounding factors that may be responsible for the observed association. They also do not control for other dietary variables or for any of the other known risk factors associated with CRC. Despite these shortcomings, it is remarkable that most of these correlation studies have indicated a strong inverse relationship between dietary fiber intake and the risk of CRC.

### Case-Control Studies

Case-control studies compare prior consumption of a dietary factor in subjects with CRC and matched control subjects without CRC. Many of the weaknesses of correlation studies can be avoided in case-control studies. Known or suspected potential confounding factors can be controlled or eliminated in the study design or controlled in the data analysis. The most serious limitation in retrospective studies is the accuracy with which intake of dietary factors or supplementation can be established. Individuals may misreport their habitual past diets; if cases and controls differ in the accuracy of their dietary recall, the ensuing comparison will be biased. In addition, some individual aspects of diet, especially nutrient content, may not vary greatly within a population, so case-control studies may not show wide ranges of cancer

Table 2. Provisional Dietary Fiber Table

Food	Fiber (g/100 g) <sup>a</sup>	Fiber (g/serving)
<b>Fruits</b>		
Apple (without skin)	2.1	2.9/1 medium-sized apple
Apple (with skin)	2.5	3.5/1 medium-sized apple
Apricot (fresh)	1.7	1.8/3 apricots
Apricot (dried)	8.1	10.5/1 cup
Banana	2.1	2.5/1 banana
Blueberries	2.7	3.9/1 cup
Cantaloupe	1.0	2.7/half edible portion
Cherries, sweet	1.2	1.2/15 cherries
Dates	7.6	13.5/1 cup (chopped)
Grapefruit	1.3	1.6/half edible portion
Grapes	1.3	2.6/10 grapes
Oranges	2.0	2.6/1 orange
Peach (with skin)	2.1	2.1/1 peach
Peach (without skin)	1.4	1.4/1 peach
Pear (with skin)	2.8	4.6/1 pear
Pear (without skin)	2.3	3.8/1 pear
Pineapple	1.4	2.2/1 cup (diced)
Plums, damsons	1.7	1.7/3 plums
Prunes	11.9	11.9/11 dried prunes
Raisins	8.7	2.2/package
Raspberries	5.1	6.3/1 cup
Strawberries	2.0	3.0/1 cup
Watermelon	0.3	1.3/4 × 8-inch wedge
<b>Juices</b>		
Apple	0.3	0.74/1 cup
Grapefruit	0.4	1.0/1 cup
Grape	0.5	1.3/1 cup
Orange	0.4	1.0/1 cup
Papaya	0.6	1.5/1 cup
<b>Vegetables</b>		
<b>Cooked</b>		
Asparagus, cut	1.5	1.5/7 spears
Beans, string, green	2.6	3.4/1 cup
Broccoli	2.8	5.0/1 stalk
Brussels sprouts	3.0	4.6/7–8 sprouts
Cabbage, red	2.0	2.9/1 cup (cooked)
Cabbage, white	2.0	2.9/1 cup (cooked)
Carrots	3.0	4.6/1 cup
Cauliflower	1.7	2.1/1 cup
Corn, canned	2.8	4.5/1 cup
Kale leaves	2.6	2.9/1 cup (cooked)
Parsnip	3.5	5.4/1 cup (cooked)
Peas	4.5	7.2/1 cup (cooked)
Potato (without skin)	1.0	1.4/1 boiled
Potato (with skin)	1.7	2.3/1 boiled
Spinach	2.3	4.1/1 cup (raw)
Squash, summer	1.6	3.4/1 cup (cooked, diced)
Sweet potatoes	2.4	2.7/1 baked (5 × 2 inches)
Turnip	2.2	3.4/1 cup (cooked, diced)
Zucchini	2.0	4.2/1 cup (cooked, diced)
<b>Raw</b>		
Bean sprout, soy	2.6	2.6/1 cup
Celery, diced	1.5	3.7/1 large stalk
Cucumber	0.8	0.2/6–8 slices with skin
Lettuce, sliced	1.5	2.0/1 wedge iceberg
Mushrooms, sliced	2.5	0.8/half cup (sliced)
Onions, sliced	1.3	1.3/1 cup
Peppers, green, sliced	1.3	1.0/1 pod
Tomato	1.5	1.8/1 tomato
Spinach	4.0	8.0/1 cup (chopped)

Table 2 (continued). Provisional Dietary Fiber Table

Food	Fiber (g/100 g) <sup>a</sup>	Fiber (g/serving)
<b>Legumes</b>		
Baked beans, tomato sauce	7.3	18.6/1 cup
Dried peas, cooked	4.7	4.7/half cup (cooked)
Kidney beans, cooked	7.9	7.4/half cup (cooked)
Lima beans, cooked/canned	5.4	2.6/half cup (cooked)
Lentils, cooked	3.7	1.9/half cup (cooked)
Navy beans, cooked	6.3	3.1/half cup (cooked)
<b>Breads, pastas, and flours</b>		
Bagels	1.1	1.1/half bagel
Bran muffins	6.3	6.3/muffin
Cracked wheat	4.1	4.1/slice
Crisp bread, rye	14.9	
Crisp bread, wheat	12.9	
French bread	2.0	0.67/slice
Italian bread	1.0	0.33/slice
Mixed grains	3.7	
Oatmeal	2.2	5.3/1 cup
Pita bread (5 inches)	0.9	
Pumpernickel bread	3.2	1.0/slice
Raisin bread	2.2	0.55/slice
White bread	2.2	0.55/slice
Whole-wheat bread	5.7	1.66/slice
<b>Pasta and rice—cooked</b>		
Macaroni	0.8	1.0/1 cup (cooked)
Rice, brown	1.2	2.4/1 cup (cooked)
Rice, polished	0.3	0.6/1 cup (cooked)
Spaghetti (regular)	0.8	1.0/1 cup (cooked)
Spaghetti (whole wheat)	2.8	3.0/1 cup (cooked)
<b>Flours and grains</b>		
Bran, corn	62.2	18.7/oz
Bran, oat	27.8	8.3/oz
Bran, wheat	41.2	12.4/oz
Rolled oats	5.7	13.7/1 cup (cooked)
Rye flour (72%)	4.5	5.2/1 cup
Rye flour (100%)	12.8	15.4/1 cup
Wheat flour		
Whole meal (100%)	8.9	10.6/1 cup
Brown (85%)	7.3	8.8/1 cup
White (72%)	2.9	2.9/1 cup
<b>Nuts</b>		
Almonds	7.2	3.6/half cup (sliced)
Peanuts	8.1	11.7/1 cup
Filberts	6.0	2.8/half cup

<sup>a</sup>Dietary fiber values are averages compiled from literature sources. Adapted and reprinted with permission.<sup>23</sup>

risk within that population. Another common problem is that controls are often people with another disease, because hospital patients are convenient subjects to study; their disease might also be diet related. In such situations, the study results could be seriously biased and often may not show any clear difference between cases and controls. For such reasons, the results of case-control studies of diet and cancer are sometimes inconsistent. Another problem associated with case-control studies is selection bias because of the absence of patients who do not survive long enough to be enrolled in the study.

Case-control studies may produce evidence that is significant in isolation. Such evidence is strengthened by corroboration in additional studies conducted in a number of centers and particularly by consistent results from populations with different patterns of diet and of cancer.

Three analyses, conducted in combined analysis or meta-analysis formats, have critically evaluated the bulk of case-control studies that address the role of dietary fiber in CRC.<sup>28-30</sup> Trock et al.<sup>28</sup> analyzed 23 case-control studies that examined the relationship between CRC and consumption of fiber and vegetables. Fifteen (65%) of these studies demonstrated either a strong or moderate protective effect of dietary fiber and vegetables.<sup>28</sup> Six studies (26%) showed equivocally protective effects of fiber that were not statistically significant, that became nonsignificant after adjustment, or that could not be distinguished from other factors in their relation to risk.<sup>28</sup> Only 2 studies (9%) lacked support for a protective effect of fiber.<sup>28</sup> Trock et al.<sup>28</sup> performed a meta-analysis on 16 case-control studies that provided enough data in the published articles. With fiber-rich diets (i.e., combination of fiber and vegetables), a 43% reduction in CRC risk was observed (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.50-0.64) when the highest and lowest quartiles of intake were compared.<sup>28</sup> The extent of risk reduction based on vegetable consumption was 52% (OR, 0.48; 95% CI, 0.41-0.57), whereas one based on an estimate of fiber intake was 42% (OR, 0.58; 95%, 0.51-0.66).<sup>28</sup> The data did not permit discrimination between effects ascribable to the fiber and the nonfiber components of vegetables.<sup>28</sup>

Howe et al.<sup>29</sup> performed a combined (or pooled) analysis of data from 13 case-control studies previously conducted in populations from North America, Europe, Asia, Australia, and South America with differing CRC rates and dietary practices. The individual data records for 5287 case subjects and 10,470 control subjects were pooled for a common analysis. This approach thus differs from the usual meta-analysis, in which estimates of risk are pooled from published summary results. Pooled analyses provide several benefits over meta-analyses of published results or narrative reviews of the literature. When the actual individual subject level data from several studies are combined, detailed analyses are possible. Because the pooled data sets constitute a large body of data, rare exposures can be studied. Furthermore, the consistency of the association across studies can be examined, confounding and interaction of several putative risk factors can be assessed, and previously unrecognized or poorly established associations may be revealed. Using the individual data records has the advantage of eliminating artifactual differences attributable to differ-

ent procedures for coding and analyzing data that may have been used in the respective original analyses.

In this pooled analysis, the risk of CRC was shown to decrease incrementally as dietary fiber intake increased, with ORs of 1.0, 0.79, 0.69, 0.63, and 0.53 for each quintile of consumption from the lowest to highest ( $P$  trend < 0.0001).<sup>29</sup> Consumption of more than 31 g of fiber per day was associated with a 47% reduction in the risk of CRC compared with diets incorporating less than 10 g of fiber per day (95% CI, 0.47-0.61).<sup>29</sup> The strong inverse association observed with fiber intake was not affected by adjustment for total energy intake, age, sex, height, weight, body mass index, and other potential confounding factors, including vitamin C and  $\beta$ -carotene.<sup>29</sup> When the consistency of the fiber effect across the studies was examined by calculating the relative risk of developing CRC in subjects consuming 27 g fiber per day compared with those consuming less than 11 g fiber per day in individual studies, 12 of the 13 studies showed inverse associations with dietary fiber.<sup>29</sup> In 8 of these 12 studies, the decrease in risk was statistically significant.<sup>29</sup> When all of the studies were combined and adjusted for total energy intake, age, and sex, individuals who consumed 27 g fiber per day had a 50% reduction in the risk of developing CRC compared with those who consumed less than 11 g fiber per day (relative risk [RR], 0.51; 95% CI, 0.44-0.59).<sup>29</sup> Estimates of RR per 27 g fiber per day—estimated separately for cases of left-sided (RR, 0.52; 95% CI, 0.42-0.65) and right-sided (RR, 0.45; 95% CI, 0.33-0.61) colon cancer and for rectal cancer (RR, 0.43; 95% CI, 0.34-0.56), for women (RR, 0.60; 95% CI, 0.48-0.75) and men (RR, 0.44; 95% CI 0.37-0.53), and for 2 age groups (<50 years [RR, 0.66; 95% CI, 0.43-0.99] and  $\geq$ 50 years [RR, 0.49; 95% CI, 0.42-0.57])—were consistent for all subgroups.<sup>29</sup>

In the original pooled analysis by Howe et al.,<sup>29</sup> it was assumed that a pooled estimate could be made of the heterogeneous results for dietary fiber and CRC risk. This heterogeneity was not examined, nor was the influence of study quality considered. Therefore, Friedenreich et al.<sup>30</sup> examined the study design features and data collection methods from the 13 case-control studies that had been included in the original pooled analysis<sup>29</sup> to determine whether they influenced the results obtained from a pooled analysis.<sup>30</sup> Friedenreich et al.<sup>30</sup> assessed methods used in each study, estimated a quality score, and used a different model (a random-effects model rather than a fixed-effects model) to re-estimate the pooled OR for the association between dietary fiber and CRC for these data.<sup>30</sup> Key features of the methods used in each study and the quality score were examined in a random-effects model to determine whether the heterogeneity found

between study-specific risk estimates could be explained by these variables.<sup>30</sup> The OR for dietary fiber and CRC was 0.46 (95% CI, 0.34–0.64) for the 13 case-control studies as estimated using a random-effects model,<sup>64</sup> which was slightly lower than the OR estimated with the fixed-effects model in the original pooled analysis (0.51).<sup>30</sup> Two factors, whether the diet questionnaire had been validated before use in the case-control study and whether qualitative data on dietary habits and cooking methods had been incorporated into the nutrient estimation, explained some of the heterogeneity in study results.<sup>30</sup> Risk estimates for dietary fiber and CRC were closer to the null (i.e., 1.0) for studies with these 2 characteristics.<sup>30</sup> These investigators performed another pooled analysis of the 13 case-control studies included in the original pooled analysis and 4 additional case-control studies either excluded from or published after the original analysis.<sup>30</sup> Subjects consuming >27 g fiber per day had a 50% reduction in the risk of developing CRC compared with those taking <11 g fiber per day (OR, 0.49; 95% CI, 0.37–0.65).<sup>30</sup>

Colonic adenomas are well-established precursors of adenocarcinoma.<sup>31</sup> Several case-control studies have also found an inverse relationship between dietary fiber or fiber-rich foods and the risk of colonic adenomas, thereby supporting the association observed with CRC.<sup>31–37</sup> The magnitude of the reduction in the risk ranged from 10% to 60% in these studies.<sup>31–37</sup> Some of these studies also showed a dose-dependent inverse association between colorectal adenoma risk and dietary intake of fiber.<sup>36,37</sup> In some studies, the protective effect associated with dietary fiber was evident only in women<sup>35,36</sup> and for large (>1 cm) adenomas.<sup>34</sup> However, these studies are limited by small sample size.

In summary, most of the published case-control studies show either a strong or a moderate protective effect of dietary fiber or fiber-rich foods or equivocal results that are nevertheless consistent with the fiber hypothesis. Three analyses of case-control studies, conducted in combined analysis or meta-analysis formats, also provide strong support for the protective effect of dietary fiber or fiber-rich foods on colorectal carcinogenesis.<sup>28–30</sup> The strongest argument for the fiber hypothesis that can be made from case-control studies is the remarkable consistency of the protective effect of dietary fiber among studies conducted in populations with different patterns of diet and CRC. The combined analysis and meta-analyses of case-control studies suggest, on average, a 50% reduction in the risk of developing CRC in individuals with the highest dietary fiber intake compared with those with the lowest fiber intake.<sup>28–30</sup> Most of the positive case-control studies and one combined

analysis of case-control studies show a significant inverse dose-dependent relationship between dietary fiber intake and the risk of CRC and colorectal adenomas.<sup>29,36,37</sup> However, several shortcomings associated with case-control studies limit interpretation of the results of these studies. Some of the most serious problems are that a large proportion of the published case-controls used dietary tools, including questionnaires, that had not been validated before use and that these studies did not incorporate qualitative data on dietary habits and cooking methods into the nutrient estimation. Furthermore, because of the limitations associated with analytical methods of determining fiber content in diet, as previously described, the accuracy of estimates of dietary fiber in these studies is in question. Another problem is that potential confounders were not adequately controlled or corrected in some of these studies. Finally, it is difficult to delineate the effect associated with dietary fiber from other potential anticarcinogens present in fiber-rich foods such as vegetables, fruits, cereals, and grains in case-control studies.

### Prospective Studies

Prospective (or cohort) studies assess the diets of a large group of healthy individuals and include follow-up over time, during which a number of cohort members will develop CRC. The relationship of CRC to specific characteristics of individual diets is then analyzed. Prospective studies avoid most of the methodological problems of other epidemiological studies and can control and correct confounding factors more adequately than correlation and case-control studies. They also provide the opportunity to obtain repeated assessments of diet at regular intervals, thus improving the validity of individual dietary assessment. Because of the prospective design, in which diet is assessed before the occurrence of CRC, there is little likelihood of selection or recording bias in cohort studies.

Earlier prospective studies investigated the relationship between dietary fiber intake and CRC mortality. A large cohort study from Japan was designed to investigate the relationship between diet and other lifestyle variables and major causes of deaths in 265,118 subjects, aged  $\geq 40$  years, followed up for 13 years. During the 13-year follow-up period, 39,127 people died.<sup>38</sup> Standardized mortality rates for each cause of death were calculated according to the lifestyle variables that were studied when the subjects were still healthy at the time of the initial interview.<sup>38</sup> This study observed that CRC mortality rate decreased as rice and wheat consumption increased with an RR of 0.6 in those with the highest intake (>720 cm<sup>3</sup> of rice and wheat per day) compared with those with

the lowest intake ( $<180 \text{ cm}^3/\text{day}$ ).<sup>38</sup> A Dutch study involving 871 middle-aged men followed up for 10 years showed a 3-fold reduction in cancer mortality in men in the highest quintile of dietary fiber intake compared with men in the lowest quintile.<sup>39</sup> The 44 men who died of cancer during 10 years of follow-up ate less dietary fiber ( $30.9 \pm 9.7$  vs.  $27.0 \pm 6.9$  g/day;  $P = 0.001$ ) and polysaccharides ( $206.3 \pm 66.1$  vs.  $183.2 \pm 51.5$  g/day;  $P = 0.006$ ) than survivors.<sup>39</sup> However, the number of men who died of colon cancer in this study during 10 years of follow-up was too small to allow statistical analysis.<sup>39</sup> Another study involving 25,493 white California Seventh-Day Adventists followed up for 21 years showed no protective effect of cereal or green salad intake on CRC mortality.<sup>40</sup> However, in the Seventh-Day Adventist population, distribution of dietary fiber may be narrow; therefore, protective effects of fiber may not be observed. Another prospective study examined the risk of developing colonic adenomas in 163 Hawaii Japanese autopsy subjects.<sup>41</sup> They constituted a subset of 8006 men originally examined between 1965 and 1968 and those who died between 1969 and 1984.<sup>41</sup> No significant differences were observed between subjects with and without adenomas in intake of dietary carbohydrates.<sup>41</sup>

Data from Cancer Prevention Study II, an ongoing prospective mortality study, support the protective role of dietary fiber in colorectal carcinogenesis<sup>42</sup>; 1,185,125 men and women (average age, 57 years) in the United States completed a 4-page questionnaire in 1982 on their diet, smoking history, alcohol intake, physical activity, height, weight, medication use, medical illnesses, family history of cancer, and other characteristics. The participants' vital status was determined at 2-year intervals through personal inquiries by the volunteers. Mortality follow-up was assessed through 1988. By this time, 79,820 participants (6.7%) had died (1150 of CRC); 94.2% of participants' causes of death were determined unequivocally. Dietary questions asked about the average consumption of 32 food items and 10 beverages. Multivariate analyses showed that risk of fatal colon cancer decreased with more frequent consumption of vegetables and high-fiber grains ( $P$  trend = 0.031 in men and 0.0012 in women) after adjustment of confounding factors.<sup>42</sup> The RR for the highest vs. lowest quintile of vegetable and high-fiber grains was 0.76 in men (95% CI, 0.57–1.02) and 0.62 in women (95% CI, 0.45–0.86).<sup>42</sup> The strengths of this study are its size and prospective design. Its limitations include its dependence on a single, brief, self-administered questionnaire, lack of information on colon subsite, and relatively short follow-up (6 years). Because of the reliance on mortality, factors that influence survival could not be clearly

differentiated from those that affect incidence. In addition, the study participants were, on average, more educated and affluent than the U.S. population as a whole. Greater access to medical care and screening might have contributed to their lower mortality rates from colon cancer. Therefore, generalization of the findings of this study to groups of lower socioeconomic status is questionable.

Recently, several well-designed and -conducted prospective studies have examined the relationship between dietary fiber intake and the risk of CRC and adenomas, but the findings of these studies are not consistent (Table 3).<sup>43–48</sup> In the Nurses' Health Study,<sup>43</sup> 121,700 female registered nurses between 34 and 59 years of age in the United States completed a mailed questionnaire on known and suspected risk factors for cancer and cardiovascular disease in 1976. Every 2 years thereafter, follow-up questionnaires were sent to identify new cases of cancer and cardiovascular disease. In 1980, the questionnaire was expanded to include an assessment of diet, the Willett semiquantitative food frequency questionnaire<sup>49</sup>; 88,751 women were available for analysis in 1986, representing 6 years of follow-up. Among these women, 150 cases of CRC were identified and confirmed. Energy-adjusted intakes of crude and total dietary fiber were both inversely associated with the risk of colon cancer, but these trends were not statistically significant.<sup>43</sup> When intake of fiber from fruit, vegetables, and cereals were analyzed individually, only fiber from fruit was associated with any appreciable reduction in risk, and the overall trend was not statistically significant.<sup>43</sup> Some limitations of this well-designed prospective study are relatively short follow-up (6 years) and uncontrolled confounding factors (e.g., family history of CRC, physical activity) that might affect the development of CRC.

The observations from this study extended for 16 years of follow-up (1980–1996) have recently been published.<sup>44</sup> During the 16 years of follow-up, 787 new cases of CRC were identified and confirmed among the 88,757 eligible women. After adjustment for age, total energy intake, and most of the established risk factors for CRC in a multivariate model, total dietary fiber intake was not significantly associated with the incidence of CRC; the relative risk for the quintile group with the highest (median 24.9 g/day) compared with the lowest (median 9.8 g/day) total dietary fiber intake was 0.95 (95% CI, 0.73–1.25), and no dose-dependent inverse association was observed ( $P$  trend = 0.59).<sup>44</sup> No protective effect of total fiber intake was observed when events during the first 6 years of follow-up were excluded to examine the possibility that total dietary fiber influences the risk of CRC only after several years or when the analysis was

Table 3. Dietary Fiber Intake and Risk of CRC and Adenoma: Summary of Prospective Studies

Study	Location (yr)	Case diagnosis	Case/control no.	Duration of follow-up (yr)	Highest intake (g/day)	Lowest intake (g/day)	Relative risk highest vs. lowest intake	95% CI	P for inverse association	Comments
Nurses Health Study <sup>43</sup>	USA (1990)	Colon cancer	Female 150/88601	6	≥21.3 (total fiber)	<11.6	0.90	0.54-1.49	0.70	No effect from crude, fruit, vegetable, and cereal fibers
Nurses Health Study <sup>44</sup>	USA (1999)	CRC	Female 787/87970	16	24.9 median (total fiber)	9.8 median	0.95	0.73-1.25	0.59	No effect from cereal and fruit fibers; increased risk with vegetable fiber (P = 0.004)
		Left colon and rectal adenoma	Female 1012/26518	14	24.9 median (total fiber)	9.8 median	0.91	0.71-1.16	0.36	No effect from cereal, fruit, and vegetable fibers
Health Professionals Follow-up Study <sup>45</sup>	USA (1994)	Colon cancer	Male 205/47744	6	32.8 median (total fiber)	14.2 median	1.08	0.68-1.70	0.12	No effect from crude, fruit, vegetable, and cereal fibers
Health Professionals Follow-up Study <sup>46</sup>	USA (1992)	Left colon and rectal adenoma	Male 170/7114	2	≥28.3 (total fiber)	<16.6	0.36	0.22-0.60	<0.0001	Total fiber
							0.27	0.16-0.45	<0.0001	Crude fiber
							0.53	0.28-1.02	0.02	Fruit fiber
							0.53	0.30-1.01	0.003	Vegetable fiber
Health Professionals Follow-up Study <sup>47</sup>	USA (1997)	Left colon and rectal adenoma	Male 690/15758	8	32.3 median (total fiber)	11.6 median	0.44	0.26-0.76	<0.001	Grains fiber
							0.81	0.59-1.11	0.03	No effect from vegetable, cereal, wheat, cruciferous vegetable, and legume fiber
							0.69	0.46-1.03	0.007	No effect from insoluble fibers
					9.4 (soluble fiber)					
Iowa Women's Health Study <sup>48</sup>	USA (1994)	Colon cancer	Female 212/35004	4	>24.7 (total fiber)	<14.5	0.80	0.49-1.31	NS	

NS, not significant.

limited to women who maintained a consistent level of dietary fiber intake during the study period.<sup>44</sup> Cereal and fruit fiber was not associated with any appreciable reduction in CRC risk, whereas greater consumption of vegetable fiber was associated with a significant increase in the risk of CRC (RR, 1.35 in the highest [median 10.0 g/day] compared with the lowest [median 2.7 g/day] quintile; 95% CI, 1.05-1.72; P trend for a dose-dependent relationship = 0.004).<sup>44</sup> However, this adverse effect was no longer observed when the analysis excluded women who altered their fiber intake during the follow-up period (RR, 1.22; 95% CI, 0.50-2.98; P trend for a relationship = 0.39).<sup>44</sup> The relationship between fiber intake and the risk of adenomas in the left side of the colon and the

rectum was also investigated among 27,530 women who reported undergoing colonoscopy or sigmoidoscopy between 1980 and 1994.<sup>44</sup> There was no reduction in the risk of colorectal adenomas with increasing dietary intake of total, cereal, fruit, or vegetable fiber.<sup>44</sup>

The same group of investigators also examined the relationship between dietary fiber and the risk of colon cancer in men.<sup>45</sup> The Health Professional Follow-up Study is a prospective study of heart disease and cancer among 51,529 U.S. male health professionals between the ages of 40 and 75 years who completed the original questionnaire in 1986. Again, dietary intake was assessed using the Willett semiquantitative food frequency questionnaire.<sup>49</sup> Among 47,949 men who were free of

diagnosed cancer in 1986, 205 new cases of colon cancer were diagnosed and confirmed between 1986 and 1992. Analyses were performed in a similar fashion as in the Nurses' Health Study.<sup>43,44</sup> Age, family history of CRC, obesity, physical activity, cigarette use, alcohol consumption, and other confounding factors were adjusted for analysis. No clear association between total dietary fiber intake and risk of colon cancer was observed; the RR for the highest (median 32.8 g/day) compared with the lowest (median 14.2 g/day) quintile group with respect to total dietary fiber intake was 1.08 (95% CI, 0.68–1.70), and no dose-dependent inverse association was observed ( $P$  trend = 0.12).<sup>45</sup> No significant protective effect was observed for total crude, fruit, vegetable, or cereal fiber.<sup>45</sup>

The same group of investigators also examined the relationship between dietary intake of fiber and the risk of colorectal adenoma in the same male cohort of the Health Professional Follow-up Study.<sup>46</sup> The analysis was done on 7284 individuals who had undergone either colonoscopy or flexible sigmoidoscopy. There were 170 cases of endoscopically diagnosed adenomas of the left colon or rectum between 1986 and 1988.<sup>46</sup> Again, most potential confounding factors were adjusted for analysis. Dietary fiber was inversely associated with risk of adenoma ( $P$  for trend < 0.0001); RR for men in the highest (>28.3 g/day) vs. the lowest (<16.6 g/day) quintile was 0.36 (95% CI, 0.22–0.60).<sup>416</sup> All sources of fiber (crude, vegetable, fruit, and grain) were associated with decreased risk ( $P$  < 0.02).<sup>46</sup> The inverse relationship with fiber persisted after adjustment for other nutrients commonly found in fruits and vegetables ( $\beta$ -carotene, potassium, magnesium, and vitamins C and E).<sup>46</sup>

This study<sup>46</sup> was further analyzed with a longer follow-up (1986–1994), a larger cohort (16,448 men), and newly available data on dietary composition for specific fiber components and fiber water solubility.<sup>47</sup> Among 16,448 men who underwent endoscopy between 1986 and 1994, 690 cases of adenoma of the distal colon ( $n = 531$ ) and rectum ( $n = 159$ ) were identified. In the basic model, the risk of distal colon adenoma decreased with increasing intake of total dietary fiber ( $P$  trend = 0.01) and fruit fiber ( $P$  trend = 0.001) but not with fiber from cereals, wheat, vegetables, or cruciferous vegetables (basic model).<sup>47</sup> The RRs comparing the highest (median 32.3 g/day for total fiber and 8.4 g/day for fruit fiber) with the lowest (median 11.6 g/day for total fiber and 1.3 g/day for fruit fiber) quintile were 0.65 (95% CI, 0.46–0.91) for total fiber and 0.67 (95% CI, 0.50–0.90) for fruit fiber.<sup>47</sup> In the full multivariate model that controlled for all potential confounding factors, the risk of distal colon adenomas decreased with increasing intake

of fruit fiber ( $P$  trend = 0.03) and the association with total fiber intake became nonsignificant ( $P$  trend = 0.10).<sup>117</sup> A strongly decreasing risk of distal colon adenomas was observed for soluble fiber ( $P$  trend = 0.0003) but not for insoluble fiber ( $P$  trend = 0.34) in basic models.<sup>47</sup> In the full multivariate model, the strong inverse association between intake of soluble fiber and distal colon adenomas persisted ( $P$  trend = 0.007).<sup>47</sup> No consistent relationship between fiber and rectal adenomas was observed in this study.<sup>47</sup>

In the earlier report of this study, increased total dietary fiber was strongly associated with a decreased risk of total colorectal adenomas ( $P$  < 0.0001), and fiber from vegetables, fruits, and grains was beneficial.<sup>46</sup> However, in the updated report, total dietary fiber was only modestly inversely associated with risk of total colorectal adenomas, and only fiber from fruits (not from vegetables or cereal) appeared to be protective.<sup>47</sup> The major difference between the earlier<sup>46</sup> and updated<sup>47</sup> reports of this prospective study is that the earlier analysis assessed fewer potential confounders, which might have led to an overestimation of the relationship between total fiber or source of fiber and adenoma risk. Another problem in the earlier report is the small number of cases arising during 2 years of follow-up, compared with 8 years in the later report.

The Iowa Women's Health Study<sup>48</sup> included 98,030 postmenopausal women aged 55–69 years who were asked to complete a self-administered questionnaire dealing with various health issues and diet. Nearly half of the women (41,837) returned the questionnaire. This cohort was then followed up for 4 years. Dietary intake of various factors was assessed using the Willett semiquantitative food frequency questionnaire.<sup>49</sup> The occurrence of CRC was documented, and the diagnosis was verified. After specific exclusion criteria were applied, 212 cases and 35,004 noncases remained for analysis. Mean dietary intake was divided into quartiles of incremental increase, and the relative risk for development of CRC was calculated for each quartile compared with the quartile with the lowest intake. A weak and statistically nonsignificant inverse association was observed between dietary fiber intake and the risk of colon cancer, particularly of the distal colon.<sup>48</sup> Furthermore, increased total intake of both vegetables and fruits did not reduce the relative risk of CRC; similar results were obtained when each vegetable or fruit item was independently analyzed except for garlic.<sup>48</sup>

In summary, published large prospective studies have produced equivocal findings. Although the data from earlier prospective studies that examined the relationship

between dietary fiber intake and CRC mortality were inconsistent,<sup>38,40,41</sup> the most recent large prospective study (Cancer Prevention Study II),<sup>42</sup> involving more than 1 million subjects, showed a significant inverse relationship with a 30% reduction of CRC mortality in subjects consuming the highest amount of dietary fiber compared with those consuming the lowest amount. This study also showed that the risk of fatal colon cancer decreased with more frequent consumption of vegetable and high-fiber grains ( $P$  trend = 0.031 in men and 0.0012 in women).<sup>42</sup> More recently published prospective studies of the relationship between dietary fiber intake and the risk of CRC or adenomas have demonstrated a protective effect of dietary fiber against distal colon and rectal adenomas in men<sup>46,47</sup> but not in women (Table 3).<sup>44</sup> When all potential confounding factors were corrected for, however, an inverse dose-responsive association was observed only for fruit and soluble fiber.<sup>47</sup> In these 2 studies,<sup>46,47</sup> there was a 35%–63% reduction in the risk of developing distal colon and rectal adenomas in men with the highest dietary fiber intake compared with those with the lowest fiber intake. These studies also showed a significant inverse dose-responsive relationship ( $P$  trend < 0.001).<sup>46,47</sup> However, it appears that dietary fiber has no significant effect on CRC incidence in men<sup>45</sup> or women (Table 3).<sup>43,44,48</sup> It is possible that, at least in men, dietary fiber influences the early stages of colorectal carcinogenesis and not the late stages. This hypothesis is further supported by the observation that dietary fiber has a protective effect against small (<1 cm) and not large (>1 cm) adenomas.<sup>47</sup>

The strengths of recent prospective studies<sup>43–48</sup> are numerous: the studies were conducted prospectively and involved a large number of subjects for adequate statistical power; most controlled for potential confounders<sup>44,45,47,48</sup>; the largest study followed up study subjects for 14 and 16 years for colorectal adenomas and CRC, respectively<sup>44</sup>; and the studies used the Willett semiquantitative food frequency questionnaire<sup>49</sup> to accurately estimate dietary fiber intake. One of the major weaknesses of these studies is that the investigators attempted to correlate dietary consumption of dietary fiber at baseline with subsequent incidence of CRC or adenomas.<sup>43,45–48</sup> In other words, the dietary intake at baseline was assumed to reflect past and subsequent consumption. Whether the subjects in these studies changed their diets during the follow-up period and how this might have affected the study outcome cannot be deduced. The exception is the largest published study, with a 16-year follow-up, which showed no protective effect of dietary fiber intake even when the analysis included only those who maintained a consistent level of dietary fiber intake

during the first 6 years of follow-up.<sup>44</sup> Except for this one study with a follow-up of 16 years,<sup>44</sup> these studies are limited by the relatively short follow-up (2–8 years).<sup>43,45–48</sup> This issue is important because of the uncertainty regarding the biologically relevant period of exposure before the development of colorectal adenomas or CRC. Another potential shortcoming that limits the interpretation of results is imprecise estimation of dietary fiber intake. Although the Willett semiquantitative food frequency questionnaire has been shown to be reproducible and valid in these cohorts,<sup>50–52</sup> the estimates of dietary fiber intake were dependent on a self-administered questionnaire. As previously mentioned, analytical tools used to determine the fiber content of foods also are relatively imprecise and underestimate amounts of dietary fiber. Therefore, fiber values assigned to each reported food consumed have errors. These prospective studies also lack data on food preparation methods, cooking, and chewing, which can alter the physiological properties of fiber.<sup>53</sup> The 2 cohorts studied in the Nurses' Health Study and Health Professionals Follow-up Study<sup>43–47</sup> are highly educated and affluent professionals with relatively homogeneous lifestyles and dietary habits and thus may not be representative of the general population. Therefore, the applicability of observations made in these cohorts to the general population is in question. One solution to this difficult issue is corroborative evidence from international and cross-cultural prospective studies. The other potential problem is that in the Nurses' Health Study and Health Professionals Follow-up Study cohorts,<sup>43–47</sup> the range of dietary fiber consumed might have been narrow, and thus protective effects of fiber might have not been observed. Therefore, potential protective effects of extremely high intake of dietary fiber (>35–50 g/day) cannot be ruled out. Some studies examined the incidence of colonic adenomas only in the distal colon, and results cannot be extrapolated to the proximal colon.<sup>44,46,47</sup>

### Human Intervention Studies

In theory, randomized intervention studies in humans should provide definitive support for the purported cause-and-effect relationship between a dietary factor and CRC. However, intervention studies are often difficult to carry out because of the slowly progressive nature of neoplastic transformation and the large number of subjects necessary to achieve an adequate statistical power. However, several strategies have been developed to circumvent these problems. One is to study the modulatory effects of nutritional factors on colorectal carcinogenesis in individuals at high risk of developing

CRC. The second strategy is to use so-called intermediate biomarkers of CRC rather than occurrence or recurrence of CRC as the endpoint.<sup>54,55</sup> These biomarkers include adenoma, proliferation markers, mitotic index, DNA aneuploidy aberrant crypts, mucins, and more recently alterations of several molecular biological markers.<sup>54,55</sup> However, all intermediate biomarkers have limitations, and most have not been validated conclusively in clinical studies.<sup>54,55</sup> Furthermore, except for colorectal adenomas,<sup>56,57</sup> changes in any of these intermediate biomarkers have not yet been proven to lead to a reduction in CRC occurrence and mortality.<sup>54,55</sup> Even with adenomas, it is known that few adenomatous polyps progress to cancer; the rate is estimated at approximately 2.5 polyps per 1000 per year.<sup>31</sup> It has also been well established that only adenomatous polyps with certain characteristics (>1 cm, tubulovillous or villous histology, and multiple occur-

rence) are associated with increased risk of developing adenocarcinoma compared with adenomas without these characteristics.<sup>31</sup>

Several randomized or single-arm intervention studies using a high-fiber diet as a component of chemopreventive strategies against the development of CRC have been conducted or are underway (Table 4). The first such study was conducted on 58 subjects with familial adenomatous polyposis (FAP) who had undergone total colectomy and ileorectal anastomosis at least 1 year before entry into the trial.<sup>58</sup> These subjects were randomized to receive either a low-fiber supplement (2.2 g/day) plus placebo (control group), a low-fiber supplement (2.2 g/day) plus ascorbic acid (4 g/day) and  $\alpha$ -tocopherol (400 mg/day), or a high-fiber supplement (22.5 g/day) plus ascorbic acid (4 g/day) and  $\alpha$ -tocopherol (400 mg/day).<sup>58</sup> The fiber supplement was from a grain source. Over the course of 4

**Table 4.** Summary of Intervention Studies Using High Fiber as a Chemopreventive Strategy for CRC

Study	Location (yr)	Case diagnosis	Sample size	Type of study	Intervention	Total fiber intake (g/day)	Duration	Primary endpoint	Outcome	Comments	
De Cosse et al. <sup>58</sup>	USA (1989)	Familial adenomatous polyposis, total colectomy, and ileorectal anastomosis	58	RCT	Low-fiber supplement (2.2 g/day) + Vitamin C (4 g/day) + Vitamin E (400 mg/day)	11.3	4 yr	Adenoma regression/occurrence	High-fiber protective only if >11 g/day	Grain/cereal fiber supplement; small number; poor compliance; substantial degree of intrapatient and intervisit variability in fiber intake	
					vs.						
					High-fiber supplement (22.5 g/day) + Vitamin C (4 g/day) + Vitamin E (400 mg/day)	22.4					Vitamins C, E; trend toward protection
Alberts et al. <sup>59</sup>	USA (1990)	Previous CRC	17	Single arm, uncontrolled	Fiber supplement (wheat bran, 13.5 g/day)	30.9	8 wk	Proliferation Labeling index [ <sup>3</sup> H]Thymidine	Overall 22% decrease compared with baseline	Uncontrolled; small number; limitations with labeling index	
Alberts et al. <sup>60,61</sup>	USA (1997)	Previous colorectal adenomas	100	RCT	2 × 2 factorial Fiber (wheat bran) High (13.5 g/day) Low (2.0 g/day) Calcium High (1500 mg/day) Low (250 mg/day)	14.4–17.5 (low-fiber group) 25.7–28.7 (high-fiber group)	9 mo	Proliferation Labeling index [ <sup>3</sup> H]Thymidine Total fecal bile acids Fecal deoxycholic bile acids	No effect 52% decrease with high fiber (P = 0.01) 36% decrease with high fiber (P = 0.003)	Limitations with labeling index and fecal bile acids as biomarkers; short duration; small number	
Toronto Polyp Prevention Group <sup>62</sup>	Canada (1994)	Previous colorectal adenomas	201	RCT	Dietary counseling to achieve 20% fat calories and 50 g fiber/day	35	2 yr	Adenoma recurrence	Intention-to-treat, no effect Subanalysis in those with substantial dietary counseling, nonsignificant 50% reduction in women and 90% increase in men with high fiber	Poor compliance; high dropout rate; low follow-up colonoscopy rate	
					vs. Placebo	16					
Australian Polyp Prevention Project <sup>64</sup>	Australia (1995)	Previous colorectal adenomas	424	RCT	2 × 2 × 2 factorial <25% fat calories 25 g wheat bran/day $\beta$ -Carotene (20 mg/day)	NA	4 yr	Adenoma recurrence	Low fat, high fiber decreased recurrence of >10-mm adenomas	Small no. of subjects in each of the 8 arms of 2 × 2 × 2 design; small no. of subjects with >10 mm adenomas; some differences at baseline among groups	

years, each participant underwent proctosigmoidoscopy every 3 months, for a total of 18 examinations. Overall consumption of fiber from supplements and dietary sources averaged 12.2 g/day in the placebo group, 11.3 g/day in the vitamin group, and 22.4 g/day in the high-fiber group.<sup>58</sup> When results were analyzed on an intention-to-treat basis, only a weak protective effect of fiber against polyp occurrence was observed.<sup>58</sup> However, when only those with good compliance were analyzed, those who had consumed 11 g of supplemental fiber in addition to their usual dietary fiber intake had a significant reduction in polyp occurrence in the rectal stump, and polyp number decreased incrementally as the amount of ingested, prescribed fiber increased.<sup>58</sup> The effects of vitamins C and E were not significant, although there was a trend toward protection.<sup>58</sup> A significant fault of this study is poor compliance with intervention modalities over the 4 years of the study. Compliance decreased by more than 50% over 4 years in some of the groups.<sup>58</sup> Other legitimate criticisms are uncertainty about whether the 3 groups were similar with respect to dietary intake of components other than fiber, vitamins C and E, and fat and whether any of the groups changed their dietary patterns during the study period.

One study from the Arizona Cancer Center was a single-arm study that investigated the effect of supplemental wheat bran fiber on a proliferation marker ( $[^3\text{H}]$ thymidine labeling index) in patients who had undergone resection for colon or rectal cancer.<sup>59</sup> In this study, 13.5 g of supplemental wheat bran per day significantly reduced colorectal epithelial proliferation during the 8 weeks of follow-up.<sup>59</sup> However, this was not a randomized placebo-controlled study and involved only 17 subjects for the analysis. Furthermore, the  $[^3\text{H}]$ thymidine labeling index is not uniformly accepted as an accurate means of determining the proliferation index of the colonic epithelium.<sup>54,55</sup> Finally, changes in this index have not been proven to decrease the incidence of CRC.<sup>54,55</sup>

The same investigators have recently completed a double-blind, randomized phase II study using a 2 × 2 factorial design to determine the effects of wheat bran (2.0 or 13.5 g/day) and calcium carbonate (250 or 1500 mg/day) supplementation on  $[^3\text{H}]$ thymidine labeling index in rectal mucosal biopsies and fecal bile acid concentrations at 3 months and 9 months.<sup>60,61</sup> Total fiber intake ranged from 14.4 to 17.5 g/day and 25.7 to 28.7 g/day in the low- and high-fiber groups, respectively.<sup>60,61</sup> The results of this study, which included 100 patients who had undergone complete colonoscopy with colonic polyp removal within 24 months of study entry, showed that neither wheat bran fiber nor calcium treatment significantly decreased the labeling index.<sup>60</sup> With respect

to fecal bile acid concentrations and excretion rates, high-dose fiber supplementation for 9 months caused a reduction in fecal concentrations of total bile acids (52% reduction;  $P = 0.001$ ) and deoxycholic acid (48% reduction;  $P = 0.003$ ) compared with baseline concentrations.<sup>61</sup> High-dose calcium supplementation also had a significant but smaller effect on the mean total bile acid (35% reduction;  $P = 0.044$ ) and deoxycholic fecal bile acid (36% reduction;  $P = 0.52$ ) concentrations at 9 months compared with baseline.<sup>61</sup> Presently, the same investigators have included more than 1400 patients in a randomized phase III trial of high-dose (13.5 g/day) vs. low-dose (2 g/day) wheat bran fiber in patients with resected colorectal polyps.<sup>62</sup> Polyp recurrence after 3 years of daily fiber intake serves as the primary endpoint for this dietary intervention trial.<sup>62</sup>

In the trial reported by the Toronto Polyp Prevention Group from Canada, 201 subjects with adenomatous colorectal polyps were randomized after polypectomy to receive intense counseling on a diet low in fat (<50 g/day or 20% of energy) and high in fiber (50 g/day), mainly from wheat bran, or to follow a normal western diet, high in fat and low in fiber.<sup>63</sup> After 12 months of counseling, fat consumption was approximately 25% of energy in the low-fat/high-fiber group and 33% in the western diet group; fiber consumption was 35 g and 16 g respectively.<sup>63</sup> After an average of 2 years of follow-up with colonoscopy, an intention-to-treat analysis showed no significant difference between dietary groups with regard to the recurrence of adenomatous polyps.<sup>63</sup> However, when only those subjects who had received substantial dietary counseling were reanalyzed, it was found that women who ate the low-fat and high-fiber diet showed a nonsignificant 50% reduction in polyp recurrence (RR, 0.5; 95% CI, 0.2–1.9) associated with a reduced concentration of fecal bile acids.<sup>63</sup> Among men, the polyp recurrence rate was increased by approximately 90% in the low-fat/high-fiber diet group compared with the controls (RR, 1.9; 95% CI, 0.8–4.4).<sup>63</sup> This also fell short of statistical significance but was associated with an increased concentration of fecal bile acids in these subjects.<sup>63</sup> The main problems with this study were (1) a high dropout rate (only 82% of 201 subjects received colonoscopic follow-up), (2) noncompliance with the low-fat/high-fiber diet, (3) small sample size, and (4) short duration of follow-up. However, this study points out that physiological differences in fecal bile acids may exist between men and women and that these may account for differences in the rates of the polyp recurrence on the low-fat/high-fiber diet.

In a recently reported study from Australia, 424 subjects with adenomas and a "clean" colon were random-

ized to diets containing <25% of energy as fat, 25 g wheat bran supplement, and/or 20 mg  $\beta$ -carotene per day in a  $2 \times 2 \times 2$ -factorial prospective, randomized, controlled trial.<sup>64</sup> Endpoints were adenomas and CRCs identified by colonoscopies performed at 2 and 4 years.<sup>64</sup> This trial showed that neither low-fat intervention nor wheat bran supplementation alone had a significant effect on adenoma recurrence.<sup>64</sup> However, low-fat intervention combined with wheat bran supplementation significantly reduced the occurrence of large adenomas (>10 mm) at 2 and 4 years of follow-up ( $P < 0.035$ ).<sup>64</sup> In this trial,  $\beta$ -carotene, either alone or in combination with the low-fat or high-fiber intervention, had no effect on adenoma recurrence.<sup>64</sup> Problems with this trial were (1) small number of subjects in each of the 8 arms of the  $2 \times 2 \times 2$ -factorial design; (2) small number of subjects with large adenoma (>1 cm), which was used as the secondary endpoint of the trial, thereby increasing uncertainty of the results; and (3) differences among groups at baseline with respect to prevalence of multiple ( $\geq 2$ ) and large (>1 cm) adenomas.

Several randomized intervention studies using a high-fiber component for the nutritional chemoprevention of CRC are currently ongoing in the United States and Europe (Table 5). The Polyp Prevention Trial is a multi-institutional intervention study recently completed in United States.<sup>9</sup> The primary goal of the trial is to test the ability of a low-fat (20% fat calories), high-fiber (18 g/1000 kcal daily) diet enriched with vegetables and fruits (5–8 servings daily) to decrease the recurrence rate of adenomatous polyps in patients previously treated for colon adenomas.<sup>9</sup> To date, 2079 patients have been randomized to the intervention or control arm.<sup>9</sup> This trial provides 90% power to detect a reduction of 24% in the annual adenoma recurrence rate.<sup>9</sup> The final colonoscopic examinations at 4 years of follow-up were completed in early 1998.<sup>9</sup> The European Cancer Prevention Organization study is an ongoing study to compare 3 groups, one given ispaghula husk (a mucilaginous substance), 3.8 g/day for 3 years; one given calcium, 2 g/day; and one given placebo.<sup>65</sup> All subjects in this study have at least 2 adenomas or 1 adenoma that is >5 mm in

**Table 5.** Summary of Ongoing Randomized, Double-Blind, Placebo-Controlled Intervention Studies Using High-Fiber Diets

Study	Location	Case diagnosis	Sample size (n)	Intervention	Duration (yr)	Primary endpoint	Current status
Phase III Arizona Cancer Center Polyp Prevention Study <sup>62</sup>	USA	Previous colorectal adenomas	1400	High-fiber supplement (13.5 wheat bran/day)	3	Adenoma recurrence	Completed
Polyp Prevention Trial <sup>9</sup>	USA	Previous colorectal adenomas	2079	20% fat calories/day 18 g fiber/1000 kcal/day 5–9 servings of vegetables and fruits/day vs. typical North American diet	4	Adenoma recurrence	Completed
European Cancer Prevention Organization Study <sup>65</sup>	Europe	Previous colorectal adenomas (2 adenomas or 1 adenoma >5 mm)	656	3.8 g ispaghula husk/day vs. 2 g/day calcium vs. placebo	3	Adenoma recurrence (proliferation labeling index and fecal bile acids as secondary endpoints)	Ongoing
Concerted Action Polyposis Prevention 1 <sup>66</sup>	Europe (14 countries)	FAP gene carriers	468	$2 \times 2$ factorial 600 mg aspirin 30 g corn starch (13.2 resistant starch)	2	Incidence or progression of colonic adenomas	150 recruited
Concerted Action Polyposis Prevention 2	Europe (14 countries)	HNPCC gene carriers	1200	$2 \times 2$ factorial 600 mg aspirin 30 g corn starch (13.2 resistant starch)	2	Incidence of colorectal adenomas (extracolonic malignancy, proliferation, apoptosis, genotype as secondary endpoints)	Ongoing

diameter (i.e., subjects with a high adenoma recurrence rate).<sup>65</sup> The primary endpoint is recurrence of adenoma, and secondary endpoints are mucosal cell proliferation rate and fecal bile acids.<sup>65</sup> To date, 656 subjects have been randomized to 3 arms of the study.<sup>65</sup> Two randomized trials (Concerted Action Polyposis Prevention [CAPP] 1 and 2, respectively) designed to test effects of 600 mg aspirin and/or 30 g corn starch (equivalent to 13.2 g of resistant starch) in a factorial design in FAP and hereditary nonpolyposis CRC (HNPCC) gene carriers are ongoing in Europe (14 countries). The primary endpoint of CAPP 1 is incidence or progression of colonic adenomas. To date, CAPP 1 has recruited 150 gene carriers (target  $n = 468$ ) from FAP registries in 14 European countries.<sup>66</sup> The primary endpoint of CAPP 2 is the incidence of colorectal adenoma. The secondary endpoints include the incidence of extracolonic malignancies, crypt cell proliferation, apoptosis, and genotype. CAPP 2 has just begun recruitment (target  $n = 1200$ ).

In summary, 6 intervention studies in humans have been completed and published (Table 4).<sup>58-61,63,64</sup> Most of these studies included a small number of subjects (range 17-424) and a follow-up period of 8 weeks to 4 years.<sup>58-61,63,64</sup> One study<sup>59</sup> was uncontrolled, and 5 were randomized and placebo controlled.<sup>58,60,61,63,64</sup> Except for 1 study<sup>58</sup> that recruited patients with FAP, the participants of most studies were individuals with sporadic colon adenomas.<sup>59-61,63,64</sup> Three studies<sup>58,63,64</sup> used adenoma recurrence or regression as the endpoint of the trial, and the other 3 used less well-established intermediate biomarkers of CRC (labeling index<sup>59,60</sup> and fecal bile acids<sup>61</sup>). All studies<sup>58,60,61,63,64</sup> except one<sup>59</sup> used dietary fiber supplements in conjunction with other dietary factors (vitamins, calcium, low fat). Four studies showed a moderate protective effect of dietary fiber supplements: decreased labeling index in 1 study,<sup>59</sup> decreased fecal bile acids in 1 study,<sup>61</sup> and decreased adenoma recurrence in 2 studies.<sup>58,64</sup> The other 2 showed no effect on labeling index<sup>60</sup> or adenoma recurrence.<sup>63</sup> The strongest evidence to date to support the fiber hypothesis is the Australian Polyp Prevention Project, which showed that a diet high in fiber and low in fat prevents recurrence of large adenomas ( $>10$  mm).<sup>64</sup>

The major weaknesses of these intervention studies are short follow-up, small numbers of subjects, poor compliance with dietary interventions, high dropout rates, and use of less well-established intermediate biomarkers with uncertain functional ramifications in some studies. Another problem is that these studies attempted to intervene in incompletely understood biological pathways in special populations of adults at high risk of developing CRC (e.g., those with FAP or previous colonic adenomas)

who therefore may be at a late, although preclinical, stage of colorectal carcinogenesis or have precancerous lesions. Other limitations are associated with intervention trials in humans. Blind or double-blind trials are usually impossible with foods or dietary macronutrients, which are recognizable. In nonblind studies of foods, subjects in the control group may adopt the dietary behavior of the treatment group if they think the treatment diet is beneficial. Such trends may obscure a real benefit of treatment. In addition, the time between a change in the level of a dietary factor and any expected change in the incidence of cancer is usually uncertain. Trials should therefore be of a long duration. Finally, people who agree to participate in trials tend to be relatively health conscious and highly motivated; people who are at high potential risk on the basis of dietary intake, and thus susceptible to intervention, are likely to be underrepresented. Hence, the validity of generalizing the results is limited. Therefore, results of intervention studies should be interpreted with caution. They are not an epidemiological "gold standard." Controlled trials in which intervention shows beneficial effects are good evidence that the agents used are protective. However, studies in which intervention shows no effect, or even a detrimental effect, do not show that the agents used are irrelevant or harmful in the context of whole diets or among normal, healthy populations. The results of intervention studies should not be treated as a refutation of evidence from other types of epidemiological study, especially when such other evidence is backed by data from animal studies and identification of plausible biological pathways.

### Resistant Starch and Short-Chain Fatty Acids

Resistant starch is defined as that portion of ingested starch that escapes digestion in the small intestine.<sup>19,22</sup> More recently, it has been suggested that resistant starch be defined as "the sum of starch and starch-degradation products that, on average, reach the human large intestine."<sup>67</sup> Similar to nonstarch polysaccharides, resistant starch has been shown to increase stool bulk, decrease fecal pH, alter the colonic microflora, decrease secondary bile acid concentrations and cytotoxicity of fecal water, decrease colonic mucosal proliferation, increase colonic fermentation, and contribute to short-chain fatty acid (SCFA) synthesis, especially butyrate.<sup>68-70</sup> A recently published international correlation study supports the protective role of resistant starch in the development of CRC.<sup>71</sup> In this study, intakes of starch, nonstarch polysaccharides, protein, and fat were compared with CRC incidence in 12 populations world-

wide. After fat and protein intakes were controlled for, there was a strong inverse association between starch consumption and CRC (correlation coefficient,  $r = -0.70$ ); no significant association with nonstarch polysaccharides was observed ( $r = -0.29$ ).<sup>71</sup> When nonstarch polysaccharides were combined with resistant starch to give an estimate of fermentable carbohydrate, the inverse association became significant with  $r = -0.52$ .<sup>71</sup> Resistant starch was observed to either be protective,<sup>72</sup> have no effect,<sup>73</sup> or enhance tumorigenesis<sup>74</sup> in chemical rodent models of CRC. In another study using a knockout murine model of the adenomatous polyposis coli gene (*Apc<sup>1638N</sup>*),<sup>75</sup> resistant starch was shown to significantly increase small bowel tumors.<sup>76</sup> Two randomized, double-blind, placebo-controlled intervention studies designed to test the effect of resistant starch on CRC in both FAP and HNPCC gene carriers are ongoing in Europe (CAPP 1 and 2; Table 5).

Fermentation of dietary fiber and resistant starch by colonic bacteria generates SCFAs. The principal SCFAs are acetate, propionate, and butyrate, which account for 90%–95% of SCFAs in the colon. SCFAs are an important energy source for the colonocytes. Butyrate is the preferred SCFA to meet colonic energy requirements. SCFAs, especially butyrate, have been shown to have anticarcinogenic properties, as discussed in the next section.<sup>77,78</sup> Butyrate has been shown to either suppress<sup>79–81</sup> or have no effect on<sup>82</sup> the development of CRC in animal models. There is a paucity of data from human epidemiological and intervention studies concerning the effects of SCFA on colorectal carcinogenesis.

### Biological Plausibility: Potential Mechanisms of Action

Several potential mechanisms by which dietary fiber can protect against the development of CRC have been proposed and investigated (Table 6).<sup>18,83,84</sup> Burkitt's initial hypothesis was that dietary fiber increases stool bulk, thus diluting potential carcinogens and decreasing transit time, which would permit less contact time between potential carcinogens in the lumen and the gut mucosa.<sup>26</sup> Additional mechanisms also have been proposed (Table 6).<sup>18,83,84</sup>

It has been demonstrated that carcinogens can bind to dietary fiber, but the extent of binding depends on the carcinogen and dietary fiber.<sup>85–87</sup> Dietary fiber has also been shown to bind with bile acids, thus reducing fecal bile acid concentration.<sup>88,89</sup> If the dietary fibers to which the bile acids or bile salts are bound are undegraded in the colon, deconjugation of bile salts and conversion of primary to secondary bile acids by bacterial enzymes may

**Table 6.** Possible Mechanisms of Action of Dietary Fiber

Increased stool bulk
Dilution of potential carcinogens
Decrease in transit time (less contact time for carcinogens)
Binding with potential carcinogens
Binding with bile acids
Decrease in fecal bile acid concentrations
Prevention of conversion of primary to secondary bile acids
Lowers fecal pH
Reduced solubility of free bile acids
Inhibition of 7 $\alpha$ -dehydroxylase, which converts primary to secondary bile acids
Inhibition of bacterial degradation of normal fecal constituents to potential carcinogens
Alters colonic microflora
Inhibition of microbial enzymes involved in carcinogen activation
Changes in bacterial species
Stimulation of bacterial growth, which increases fecal bulk
Fermentation by fecal flora to SCFAs
Inhibition of growth of tumor cell lines
Induction of differentiation
Induction of apoptosis
Modulation of gene expression
Prevention of insulin resistance and hyperinsulinemia

be prevented. The bound bile acids or bile salts may pass out of the alimentary tract in the feces. The possible putative interaction of secondary bile acids and colonic mucosal cells will thus be decreased.

Dietary fiber decreases fecal pH, resulting in reduced solubility of free bile acids; theoretically, this should decrease the potential tumor promoter activity of secondary bile acids.<sup>90</sup> Furthermore, the activity of the colonic bacterial enzyme 7 $\alpha$ -dehydroxylase, which converts primary bile acids to secondary bile acids, is inhibited at a pH of <6–6.5.<sup>91,92</sup> Acidification of colonic contents also increases the availability of calcium for binding to free bile and fatty acids, thereby inhibiting their effects on the colonic mucosa.<sup>93</sup> A number of epidemiological studies have shown that human populations with lower fecal pH have lower rates of colon cancer.<sup>90,94</sup> However, direct experimental acidification of the colon contents in animal models have not always led to a reduction in tumorigenesis.<sup>95</sup> Theoretically, fecal acidification can also inhibit bacterial degradation of normal fecal constituents to potential carcinogens.<sup>18</sup>

Another potential mechanism of dietary fiber relates to alterations in colonic microflora, which can exert marked effects on the colonic environment. These may be characterized by changes in bacterial species, functional changes, or production of microbial enzymes considered to be important in carcinogen activation (e.g.,  $\alpha$ -glucuronidase,  $\alpha$ -glucosidase, azoreductase, and nitroreductase).<sup>96</sup> Although dietary fibers clearly modulate colonic bacterial enzyme activity,<sup>13</sup> the relationship between colonic bacterial enzyme activity and development of human CRC has not been elucidated clearly. Dietary fibers that are

extensively degraded in the colon have been shown to increase fecal bulk by a stimulation of bacterial growth.<sup>97</sup> Bacteria, rather than undegraded dietary fiber, are the major water-holding component of feces.<sup>97</sup> Increased fecal bulk and reduced transit time resulting from increased bacterial growth would reduce the possibility of effective interactions of carcinogens with the colonic mucosa. Dietary fiber also can decrease numbers of anaerobes, resulting in a decrease in secondary bile acids.<sup>15</sup>

SCFAs, especially butyrate, produced by fermentation of dietary fiber and resistant starch by colonic bacteria appear to be an important factor in colorectal carcinogenesis.<sup>77,78</sup> Although butyrate serves as the primary energy source for normal colonic epithelium and stimulates growth of colonic mucosa, in colonic tumor cell lines it inhibits growth<sup>98,99</sup> and induces differentiation<sup>100</sup> and apoptosis.<sup>101</sup> At the molecular level, butyrate has been shown to inhibit histone deacetylase, resulting in hyperacetylation of histones and increased accessibility of DNA to factors controlling gene expression.<sup>102,103</sup> Butyrate also has been shown to alter the binding of regulatory transacting proteins to specific DNA sequences that control the expression of the gene.<sup>104</sup>

A unifying hypothesis that may explain how diet and lifestyle factors modulate colorectal carcinogenesis has recently been put forward by McKeown-Eyssen<sup>7</sup> and Giovannucci.<sup>8</sup> This hypothesis suggests that the putative dietary and lifestyle factors associated with CRC risk cause insulin resistance and hyperinsulinemia and that hyperinsulinemia may in turn stimulate the growth of colorectal tumors.<sup>7,8</sup> Although it remains unproven whether insulin stimulates the growth of colon tumors in humans, several lines of evidence support its role. Insulin is an important growth factor for colonic mucosal cells and is a mitogen of colonic carcinoma cells *in vitro*.<sup>105,106</sup> Colonic cancer tissue has both insulin and insulin-like growth factor (IGF) 1 receptors<sup>107,108</sup>; insulin has been shown to exert its mitogenic effect partly through IGF-1 receptors.<sup>109</sup> Insulin receptors can be bound by IGF-1,<sup>110</sup> and a binding protein from IGF-1 inhibits the growth of colon cancer cells *in vitro*.<sup>111</sup> Another indirect line of evidence comes from the observation that subjects with acromegaly, characterized by chronic growth hormone and IGF-1 hypersecretion, have an increased risk of developing CRC.<sup>112</sup> It has been proposed that stimulation of IGF-1 receptors by IGF-1 or IGF-2 promotes colorectal carcinogenesis in subjects with acromegaly.<sup>112</sup> Although epidemiological studies that have examined the relationship between diabetes mellitus and CRC risk have not consistently supported this hypothesis,<sup>113</sup> 2 recently published large prospective studies indicate a modest increase in CRC risk in subjects with diabetes

compared with nondiabetic control subjects.<sup>114,115</sup> In a population-based cohort study from Sweden ( $n = 153,852$ ), subjects with diabetes mellitus were found to have on average a 40% greater risk of developing colon cancer and a 60% greater risk of dying of colon cancer than the general population.<sup>114</sup> The first Cancer Prevention Study of the American Cancer Society with more than 1 million participants showed that diabetic men had a statistically significant 30% increase in risk of developing CRC compared with nondiabetic men during 13 years of follow-up.<sup>115</sup> Two recently published animal studies have demonstrated that exogenously injected insulin promotes the development of colorectal tumors<sup>116</sup> and the growth of aberrant crypt foci,<sup>117</sup> a putative precursor of colon cancer, thereby providing support for the causal hypothesis linking insulin resistance and CRC. Because dietary fiber, especially soluble fiber, affects glycemia and insulinemia,<sup>118</sup> the insulin hypothesis could be a mechanism by which dietary fiber can modulate colorectal carcinogenesis. As such, this hypothesis merits further consideration.

Epidemiological and experimental evidence indicating a causal association between dietary fiber and CRC is strengthened when a biological pathway or mechanism by which colorectal carcinogenesis may be modified is identified and when this mechanism is biologically plausible. However, it can be argued that epidemiological data, strong and consistent, are an inadequate basis for any definite judgment of causality unless supported by mechanistic evidence.<sup>119</sup> Although investigations to elucidate potential anticarcinogenic mechanisms of dietary fiber have focused on physical properties of dietary fiber, more recent work has expanded into physiological functions and molecular mechanisms of dietary fiber. A better mechanistic understanding of how dietary fiber can modulate colorectal carcinogenesis can lead to a more rational strategy using dietary fiber supplementation to prevent CRC in humans.

## Conclusion

### Summary of Causal Inference

Although valuable information can be obtained from nutritional epidemiological studies examining the effect of diet on cancer, several shortcomings limit interpretation of the results of these studies (Table 7).<sup>120</sup>

The strongest evidence that supports the fiber hypothesis is the remarkable consistency of the protective effect of dietary fiber among correlation and case-control studies conducted in populations with different patterns of diet and CRC. Three combined analyses or meta-analyses of case-control studies also provide strong support for the

**Table 7. Summary of Causal Inference**

Criteria	Supportive	Equivocal	Lack	Comments
Consistency	X			Supportive evidence from most correlation and case-control studies conducted in populations with different patterns of diet and CRC and meta-analyses and combined analyses of case-control studies; data from prospective studies equivocal (only supportive for distal colon and rectal adenomas in men)
Strength of association	X			Average 50% reduction in CRC and adenoma risk
Dose response	X			Significant dose-dependent inverse association in most correlation and case-control studies as well as their meta-analyses and combined analyses; positive prospective studies also demonstrate a dose-responsive association
Experimentation: from human intervention studies		X		Generally supportive of findings published intervention studies; studies limited by small numbers of participants, short durations of follow-up, use of intermediate markers, and poor compliance; 5 large, well-designed studies ongoing at present
Specificity		X		Difficult to delineate effects associated with dietary fiber from other potential anticarcinogens present in fiber-rich foods
Epidemiological coherence	X			Fiber hypothesis consistent with epidemiological observations that suggest significantly lower CRC prevalence, incidence, and mortality in countries or populations with high intake of fiber-rich foods
Analogy	X			Protective effects of fiber against breast, endometrial, ovarian, and prostate cancers
Biological plausibility	X			Several potential physiological and molecular biological mechanisms for fiber

dose-dependent protective effect of dietary fiber or fiber-rich foods against colorectal carcinogenesis.<sup>28-30</sup> These studies suggest on average a 50% reduction in the risk of developing CRC in subjects with the highest dietary fiber intake compared with those with the lowest intake.<sup>28-30</sup> However, large prospective studies conducted in specific populations in the United States do not support the protective effect of dietary fiber on the development of CRC.<sup>43-45,48</sup> On the other hand, these prospective studies suggest a modest dose-dependent protective effect of dietary fiber on distal colonic and rectal adenomas in men only.<sup>46,47</sup> Although these prospective studies provided the least biased approach, the findings need to be corroborated by evidence from similar international and cross-cultural prospective studies.

It is difficult to delineate the effect associated with dietary fiber from other potential anticarcinogens present in the fiber-rich foods such as vegetables, fruits, cereals, and grains in epidemiological studies. However, most of the recently published prospective studies have adjusted for potential confounding factors, including intake of vegetables, fruits, cereals, and grains as well as antioxidant vitamins and folate.<sup>44-48</sup> Some human intervention studies have attempted to test the effect of dietary fiber supplementation on colorectal carcinogenesis while keeping the intake of vegetables, fruits, cereals, and grains constant during the study period.<sup>58-64</sup> It is possible that undetermined interactions among anticarcinogens pres-

ent in fiber-rich foods and fiber are responsible for the observed protective effect of dietary fiber on the development of CRC.

Of the published randomized, double-blind, placebo-controlled studies in humans that have used adenoma recurrence or regression as the endpoint of the trial,<sup>58,63,64</sup> probably the best intermediate biomarker of CRC available to date,<sup>31</sup> 2 have shown significant protective effects of wheat fiber supplementation<sup>58,64</sup>; the other showed no effect.<sup>63</sup> In the largest intervention trial published to date (the Australian Polyp Prevention Project,  $n = 424$ ),<sup>64</sup> a diet high in fiber and low in fat was shown to prevent recurrence of large adenomas ( $>10$  mm), probably a more relevant biomarker than smaller adenomas ( $<10$  mm). Five ongoing large, randomized, double-blind, placebo-controlled studies in the United States and Europe will certainly provide more insight into the effects of dietary fiber on colorectal carcinogenesis (Table 5).

The fiber hypothesis is consistent with epidemiological observations that suggest significantly lower CRC prevalence, incidence, and mortality in countries or populations with high intake of fiber-rich foods, including vegetables, fruits, cereals, and grains.<sup>2,3,11,12,121</sup> The protective effect of dietary fiber on the development of CRC is also analogous to similar observations in breast cancer,<sup>12,122</sup> endometrial cancer,<sup>123,124</sup> ovarian cancer,<sup>125</sup> and prostate cancer,<sup>126</sup> albeit to a lesser degree. More importantly, several biologically plausible mechanisms

exist for dietary fiber that corroborate epidemiological and other evidence (Table 6). However, *in vivo* verification of some of these mechanisms is still needed.

### Magnitude of CRC Risk Reduction

The extent to which CRC mortality rates in the United States might be reduced by practicable dietary means has been estimated at 50%–75%.<sup>4</sup> More recently, the World Cancer Research Fund panel has judged that diets high in vegetables, and therefore high in fiber, and low in meat; avoidance of alcohol; and regular physical activity may reduce the incidence of CRC by 66%–75%.<sup>119</sup> With respect to the extent of CRC risk reduction associated with dietary fiber or fiber-rich foods, 3 combined analyses or meta-analyses of case-control studies suggest a 50% reduction in the risk of developing CRC in subjects with the highest dietary fiber intake compared with those with the lowest intake.<sup>28–30</sup> A large, ongoing prospective mortality study (Cancer Prevention Study II of the American Cancer Society) with more than 1 million participants suggests a 30% reduction in CRC mortality among individuals consuming the highest amount of vegetables and high-fiber grains compared with those consuming the lowest amount.<sup>42</sup> Two large prospective studies suggest a 35%–63% reduction in the risk of developing distal colon and rectal adenomas in men consuming the highest amount of dietary fiber compared with those consuming the lowest amount.<sup>46,47</sup> Although it is difficult to estimate accurately the magnitude of CRC risk reduction attributable solely to dietary fiber or fiber-rich foods, there appears to be a significant degree of reduction.

### Dose of Dietary Fiber Associated With Decreased CRC Risk

The threshold level above which dietary intake of fiber is associated with a significant degree of CRC risk reduction is not well established in epidemiological and intervention studies. Case-control and prospective studies have arbitrarily defined increasing quartiles or quintiles of dietary fiber intake, which are different from study to study and from population to population. In some populations, the difference between extreme quartiles or quintiles is quite small. In some studies, the amount of dietary intake of fiber associated with each quartile or quintile is not stated. Two combined analyses of case-control studies showed a 50% reduction in CRC risk in individuals consuming 27 g/day compared with those consuming less than 11 g/day of fiber.<sup>29,30</sup>

The extreme quartiles or quintiles of dietary fiber intake in the Nurses Health Study<sup>44</sup> and Iowa Women Health Study,<sup>48</sup> which did not show any significant

reduction in CRC risk, were >24.9 and <9.8 g/day and >24.7 and <14.5 g/day, respectively (Table 3). The Health Professionals Follow-up Study, which demonstrated a significantly reduced risk of distal colon adenomas<sup>46,47</sup> but not CRC,<sup>45</sup> generally compared those with dietary intake of fiber of 28.3–32.8 g/day with those with dietary intake of fiber of 11.6–16.6 g/day. Most of the positive case-control and prospective studies also showed significant dose-dependent inverse associations between dietary intake of fiber and CRC or adenoma risk.<sup>29,30,46,47</sup>

Amounts of fiber supplement or total fiber intake chosen for intervention studies vary. Of the 2 published intervention studies that used adenoma recurrence as the endpoint of trial in subjects with sporadic colon adenomas, the Australian Polyp Prevention Project used 25 g wheat bran supplement daily in addition to usual dietary intake of fiber (the total intake of fiber was not stated in the report).<sup>64</sup> In contrast, the Toronto Polyp Prevention Study used 50 g of total fiber intake daily in the high-fiber group compared with the low fiber group, but total fiber intake was 35 g/day in the high-fiber group and 16 g/day in the low-fiber group.<sup>63</sup> The Phase III Arizona Cancer Center Polyp Prevention Study will determine the rate of adenoma recurrence in subjects receiving 13.5 g wheat bran supplement daily in addition to their usual daily intake of dietary fiber compared with those receiving 2.5 g wheat bran supplement daily.<sup>62</sup> The Polyp Prevention Trial will determine the rate of adenoma recurrence in subjects consuming 18 g fiber/1000 kcal daily compared with those consuming usual amounts of dietary fiber.<sup>9</sup>

It appears that most case-control, prospective, and intervention studies have assessed the effect of total fiber intake 3–3.5 times the mean dietary fiber intake in the U.S. adult population (11.1 g/day).<sup>23</sup> The Toronto Polyp Prevention Study, which attempted to determine the effect of 50 g total fiber intake daily, showed only a nonsignificant 50% reduction in adenoma recurrence in women.<sup>63</sup> However, individuals assigned to the high-fiber intake in this trial consumed, on average, only 35 g/day of dietary fiber instead of 50 g/day.

### Duration of Intervention Associated With Decreased CRC Risk

There is often a latency period between exposure to a factor that modifies cancer risk and induction of the tumor itself. A further delay occurs before development of the tumor reaches the stage at which it can be diagnosed; this delay varies with different factors and different sites. Migrant studies suggest a delay between exposure of migrants to urban-industrial diets and emergence of CRC of 10–20 years.<sup>119</sup> It follows that appropri-

ate diets may have their full impact in preventing cancer only decades after they are widely adopted. These delays must be considered in setting realistic targets for CRC prevention with dietary fiber. Therefore, because CRC is strongly age related<sup>21</sup> and its incidence rates increase markedly with age beginning around the sixth decade of life,<sup>119</sup> fiber intervention should begin at least 10–20 years before the peak age for CRC incidence. Prospective and intervention studies, except one,<sup>44</sup> have not had a long enough follow-up to observe any beneficial effects associated with fiber intervention.

### Types of Fiber or Specific Related Components Associated With Decreased CRC Risk

With respect to the exact types and sources of fiber associated with the decreased risk of CRC, animal studies suggest that insoluble and less fermentable fibers and wheat bran are most effective.<sup>13</sup> Information on this issue is lacking in epidemiological and intervention studies in humans. Although an early analysis from the Health Professionals Follow-up Study suggested that all sources of fiber (crude, vegetables, fruits, and grains) were associated with decreased risk of adenoma in men,<sup>46</sup> a more recent analysis of this cohort suggests that only total dietary fiber, fruit fiber, and soluble fiber are significantly associated with decreased risk of colonic adenomas.<sup>47</sup> Most intervention studies have used either wheat bran fiber supplement<sup>58–64</sup> or all sources of fiber.<sup>9</sup> Two published intervention studies have used adenoma recurrence as the endpoint of the trial and wheat bran supplement; results of the Australian Polyp Prevention Project<sup>64</sup> were positive, and results of the Toronto Polyp Prevention Study<sup>63</sup> were negative.

Although the role of resistant starch in colorectal carcinogenesis has recently received much attention, convincing epidemiological evidence is lacking except for one international correlation study that showed a strong inverse association between starch and resistant starch consumption and CRC risk.<sup>71</sup> Similarly, 4 published animal studies to date<sup>72–74,76</sup> have produced conflicting results, with 2 studies<sup>74,76</sup> showing enhanced tumorigenesis associated with resistant starch. In contrast to resistant starch, most of the published animal studies using butyrate demonstrated protective effects of this SCFA on colorectal carcinogenesis.<sup>79,81</sup> Because several biologically plausible mechanisms exist for butyrate, this SCFA warrants further consideration in intervention trials.

### Target Group(s) for Fiber Intervention

Studies that address target groups for intervention are lacking in the literature. Intervention studies have focused on individuals at high risk of developing CRC or adenomas, including those with previous adenomas, CRC, and FAP and gene carriers of FAP or HNPCC. Whether increasing dietary intake of fiber will reduce the CRC risk in the general population must be deduced from epidemiological and intervention studies using high-risk individuals and intermediate biomarkers because of the cost and duration of the studies. At present, it appears that individuals at high risk of developing CRC and adenomas will benefit the most from fiber intervention. As previously discussed, the NHANES II study identified a marked racial effect, with blacks of both sexes and in all age groups having lower dietary fiber intake than whites.<sup>23</sup> Unlike the white population in the United States, blacks have not had substantial improvement in CRC incidence and mortality.<sup>7</sup>

### Recommendations

Given a lack of complete scientific evidence, it is difficult to advise patients with absolute confidence. Nevertheless, the guidelines in this review represent reasonable conclusions based on currently available data. Therefore, it is reasonable to recommend total fiber intake of at least 30–35 g/day. Dietary fiber should be from all sources, including 5–7 servings of vegetables and fruits daily and generous portions of whole-grain cereals as recommended by the World Health Organization and the National Cancer Institute. Because of uncertainty about the types and sources of fiber that are most effective in the prevention of CRC and as yet undetermined potential interactions between fiber and other anticarcinogens present in fiber-rich foods, it is prudent to recommend a high intake of dietary fiber from all sources, including vegetables, fruits, cereals, grains, and legumes. It is clear that as yet undetermined interactions among dietary components and other lifestyle factors play a more important role in colorectal carcinogenesis than individual dietary and lifestyle factors. The dietary guidelines from the American Cancer Society and the National Cancer Institute encourage healthy eating habits and lifestyle modifications. All of the factors in these guidelines have been considered to play an important role in colorectal carcinogenesis as well.<sup>2,3</sup> The guidelines can be used in conjunction with the dietary fiber recommendations. The guidelines are (1) eat each of the 5 food groups daily (meat, dairy products, grains, fruits and vegetables); (2) reduce total fat intake to less than 25%–30% of total calories and saturated fat to less than 10% of total

calories; (3) eat 5 or more servings of fresh vegetables and fruits daily (raw better than cooked; include deep yellow vegetables and dark green cruciferous vegetables); (4) eat red meat infrequently (substitute chicken or fish without skin); (5) eat more fiber-rich foods such as whole-grain cereals, fruits, and vegetables (daily total of 20–30 g fiber); (6) avoid obesity; (7) eat salt-cured, smoked, and nitrite-cure foods in moderation; (8) keep alcohol consumption moderate; (9) participate in daily physical activity; and (10) do not smoke. Increasing total fiber intake to >30 g/day from the standard 10-g North American diet can not only protect against CRC but also potentially decrease cholesterol levels,<sup>127</sup> improve insulin resistance,<sup>128</sup> reduce blood pressure,<sup>129,130</sup> and prevent heart disease.<sup>131</sup>

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Correspondence



High-Fiber Diet and Colorectal Adenomas

To the Editor: I am concerned that the report by Schatzkin and colleagues (April 20 issue)<sup>1</sup> may lead many people to conclude erroneously that diet does not affect susceptibility to colon cancer, even though the hypothesis was not adequately tested. According to Table 3 of the report, dietary fat decreased from 35.6 percent at randomization to 23.8 percent at four years in the intervention group and from 36.0 to 33.9 percent in the control group. Consumption of red meat decreased from 93.2 to 74.5 g per day in the intervention group and from 97.9 to 94.9 g per day in the control group. However, plasma total cholesterol decreased only from 5.30 to 5.27 mg per deciliter in the intervention group and from 5.29 to 5.27 mg per deciliter in the control group (log-transformed values); these decreases represent 2 percent and 1 percent in the absolute cholesterol concentrations, respectively. Reductions of this magnitude in the intake of dietary fat and red meat in the intervention group (if they really occurred) should have caused a greater reduction in the plasma total cholesterol level — in any event, greater than that in the control group, which did not occur. Also, weight was essentially unchanged in both groups.

The logical conclusion is that the patients in the intervention group were actually consuming a diet very similar to that of the control group. This would not be surprising, since it is difficult to motivate people to make and maintain dietary changes in large-scale studies, and it is equally difficult to obtain accurate dietary information in clinical trials. But it is as erroneous to claim that dietary fat and cholesterol intake have no effect on colon cancer as it is to say that they have no effect on plasma total cholesterol.

It is a great disservice for the authors to conclude, "In

summary, our study provided no evidence that a diet low in fat and high in fiber, fruits, and vegetables reduces the risk of recurrent colorectal adenomas." When headlines to this effect appeared widely in the media, they left many people with the belief that diet makes no difference, whereas, in fact, we do not yet know whether this is true.

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1. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 2000; 342:1149-55.

To the Editor: The findings reported by Schatzkin et al. may reflect the failure of dietary counseling to produce a change in diet more than the lack of effect of dietary change on the recurrence of adenomas. The objective or measured, data in Table 3 show very little change in comparison with the changes in reported dietary information. In particular, the reported caloric intake decreased by 102 and 71 kcal per day in the intervention and control groups, respectively. These reductions should have resulted in substantial weight loss, unless there were concomitant decreases in the expenditure of calories. Reductions in activity are plausible in patients in the age group represented by the study sample. However, such changes in activity should have been similar in the two groups, yet there was still a difference between the groups of 31 kcal per day in the change in the reported caloric intake. This difference in caloric intake would be expected to result in a difference in weight between the groups of about 12 lb (5.5 kg) over a period of four years.<sup>1</sup> The absolute difference, 2.5 lb (1.1 kg), is less than a quarter of that predicted by the dietary history. Thus, the patients in the intervention group may have overreported their compliance with the counseling they were given.

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1. Rolls BJ, Bell EA. Dietary approaches to the treatment of obesity. *Med Clin North Am* 2000;84:401-18.

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*To the Editor:* Most of the explanations for the disappointing results of the studies reported by Schatzkin et al.<sup>1</sup> and Alberts et al.<sup>2</sup> are noted in the accompanying editorial by Byers.<sup>3</sup> One question has not been addressed: Was compliance with the regimen sufficiently ascertained? In both studies, the assessment of compliance relied mainly on the study participants, who either returned cereal boxes and recorded supplement consumption on a calendar,<sup>2</sup> or reported daily intake of food and supplements.<sup>1</sup>

The incidence of some adverse gastrointestinal effects can be considered an independent marker of compliance with the use of the high-fiber supplement in the study by Alberts et al.; the incidence was significantly higher in the high-fiber group than in the low-fiber group. Thus, in this study, one can say that insoluble fiber alone does not account for all the effects that have been attributed to a diet high in fruit and vegetables in observational studies and has no short-term benefit in reducing the risk of colorectal adenoma.

In the study by Schatzkin et al., there were two independent markers of compliance: weight loss and serum total carotenoids. (The carotenoid values in Table 3 of their article appear to be 100 times the usual values.) Although significant, the changes were very small after four years, and it is unfortunate that no additional biologic markers were investigated and that such investigations were not performed more often. Thus, it is difficult to say that compliance was satisfactory.

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1. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 2000; 342:1149-55.

2. Alberts DS, Martínez ML, Roe DJ, et al. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. *N Engl J Med* 2000; 342:1156-62.

3. Byers T. Diet, colorectal adenomas, and colorectal cancer. *N Engl J Med* 2000; 342:1206-7.

*To the Editor:* Is it possible that a high-fiber diet may be harmful? The main end point in both the study by Schatzkin et al. and the study by Alberts et al. was the recurrence of polyps, but an even more important consideration is the effect of a high-fiber diet on the occurrence of bowel cancer. In each study, there appeared to be more bowel cancers in the high-fiber group than in the low-fiber or control group: 10 cases as compared with 4 in the study by Schatzkin et al. and 7 cases as compared with 2 in the study by Alberts et al.

In the two studies, the risk ratios for bowel cancer in the high-fiber groups, as compared with the low-fiber and control groups, appear to be similar, and the characteristics of the patients in the two groups were similar. Therefore, we assessed the risk of bowel cancer in the high-fiber groups and in the low-fiber and control groups after combining the data from the two studies. We used the available information in the two studies to estimate the approximate number of person-years for the combined high-fiber groups and the combined low-fiber and control groups. We assumed that the combined high-fiber groups should have had the same frequency of bowel cancer as the combined low-fiber and control groups. However, the estimat-

ed number of expected cancers in the combined high-fiber groups was only 6.4, as compared with the observed number of 17, yielding a risk ratio of 2.6. This unexpected excess number of bowel cancers after dietary modification appears to be significant at the 95 percent level. The surprising finding that the risk of bowel cancer is increased by a factor of two or three after dietary supplementation with fiber, if confirmed by a more detailed analysis of the combined sets of data, suggests that high-fiber diets may actually be harmful and should be avoided in patients with bowel polyps.

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*To the Editor:* Is it possible that in the study by Schatzkin et al. the choice of subjects for enrollment, all of whom had adenomas that were potential precursors of colorectal cancer, had a leveling effect on the variable potentially influenced by dietary change? Does the study ultimately demonstrate only that the dietary changes made, over a period of just four years, do not prevent the recurrence of adenomas or reduce the incidence of colorectal cancer in persons who already have a genetic (or other) predisposition to adenomas?

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*To the Editor:* Although the subjects in the intervention group in the study by Schatzkin et al. were given nutritional information and counseling in order to reach a goal of 20 percent of total calories from fat, the Methods section of the report does not state whether the subjects were encouraged to eat fish known to contain n-3 lipids. Table 3 of the article shows that the ratio of red meat to chicken and fish decreased in the intervention group. However, if the subjects ate more chicken, but not fish, then they still did not increase their dietary intake of n-3 lipids. Table 1 of the article shows data on current aspirin use and the serum levels of two nutrients, total carotenoids and  $\alpha$ -tocopherol, in the control and intervention groups, but serum n-3 lipids are not noted.

I think an assessment of n-3 lipids must be taken into account in evaluating the effects of dietary interventions on the rate of recurrence of colonic adenomas.

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The authors reply:

*To the Editor:* The Polyp Prevention Trial targeted total dietary fat. Because the ratio of dietary-fat subtypes did not change appreciably, it is not surprising that the difference in cholesterol reduction between the intervention and con-

trol groups was minimal.<sup>1</sup> As we stated in our report, our study could not rule out the possibility that greater reductions in fat and red meat or further increases in fiber and fruits and vegetables might be required to reduce the risk of colorectal neoplasia.

The absolute difference in the change in caloric intake between the intervention and control groups was -25 kcal (95 percent confidence interval, -72 to 22). Therefore, the trial did not establish a significant between-group difference in the change in energy consumption. Moreover, the likelihood of underreporting of energy intake in dietary-intervention studies would explain, at least in part, the apparent discrepancy between changes in reported energy intake and observed weight loss in this and other dietary trials.<sup>2</sup>

We are conducting the type of observational analyses suggested by Dr. Davis. All such analyses, however, are subject to confounding: people who adhere to an intervention are often found to be systematically different from those who do not in ways that are related to the clinical outcome. We presented the results of an intention-to-treat analysis, which is an internationally accepted method of analysis.<sup>3</sup>

We did find significant net increases in lutein, alpha carotene, and beta carotene in the intervention group. The relatively small (though statistically significant) increase in carotenoids may reflect the facts that carotenoid-rich fruits and vegetables accounted for only about half the total increase in fruits and vegetables in the intervention group and that carotenoids from fruits and vegetables are substantially less bioavailable than those from supplements.<sup>4</sup> Dr. Gerber correctly points out two errors in the units of measurement for carotenoids in our article: in the third footnote to Table 1, the unit of measurement should be micromoles per liter, and in Table 3 it should be micrograms per deciliter.

If we eliminate the cancers diagnosed within the first year after enrollment, which were likely to have been present when the interventions began (six in the intervention group and two in the control group in our study, and three in the high-fiber group in the study by Alberts et al.), there were a total of nine cancers in the high-fiber groups and four in the control and low-fiber groups — not a statistically significant difference. A thorough investigation of the effects of fiber on the risk of colorectal cancer in intervention studies requires the pooling of data from all the trials that have looked at this issue.

We agree with Dr. Muller: our trial could not determine whether dietary modification affects the risk of colorectal adenoma in persons who have not had a previous adenoma.

In line with Dr. Duprey's suggestion, we will be analyzing the dietary data from our study for n-3 fatty acids. There was only a small, though statistically significant, difference in the consumption of fish between the intervention and control groups (21.5 and 18.6 g, respectively).

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*To the Editor:* We agree with Dr. Gerber that the gastrointestinal side effects caused by the daily intake of 13.5 g of wheat-bran cereal are an independent marker of compliance with the use of the high-fiber supplement in our trial. In our phase 1 and 2 studies of interventions involving wheat-bran fiber, we documented that 13.5 g of this supplement per day could be taken with a reasonable level of compliance by older study participants for periods of a few months.<sup>1,2</sup> However, some older persons may not be able to tolerate high doses of wheat-bran fiber on a daily basis for several years.

Lowenfels and Maisonneuve argue that the high-fiber cereal promoted the development of colorectal cancer. However, our findings do not support this argument. Seven of the nine colorectal cancers that were detected occurred in members of the high-fiber group, but three of these seven cancers were diagnosed 8, 10, and 11 months after randomization; these cancers were probably missed at the qualifying colonoscopy (i.e., before the start of the intervention). Thus, only 4 of the 719 patients in the high-fiber group and 2 of the 584 in the low-fiber group had colorectal cancers that were detected at least 1 year after randomization (range, 19 to 39 months). The difference is not statistically significant.

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### Echinococcosis — An Emerging Disease in Farmers

*To the Editor:* Two echinococcus species — *Echinococcus multilocularis* and *E. granulosus* — are known to exist in central Europe and to cause alveolar and cystic echinococcosis, respectively, in humans. We report a high prevalence of antibodies against these organisms in farmers.

We tested 152 swine farmers (82 men and 70 women; mean age, 42 years [range, 22 to 70]) and 50 subjects who had not been exposed to farm animals (22 men and 28 women; mean age, 41 years [range, 19 to 60]) for serum antibodies against a variety of viral, bacterial, and parasitic zoonotic agents. Anamnestic data and information on risk factors were obtained with use of a detailed questionnaire. All the subjects lived in the Austrian province of Styria. The serologic results were analyzed in relation to the responses to the questionnaires. The results of a similar study involving 137 veterinarians from Styria have been published.<sup>1</sup>

## Prevention of Colon Carcinogenesis by Components of Dietary Fiber

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**Abstract.** *Cancer of the colon is one of the leading causes of cancer death in Western countries and is increasing rapidly in Japan. Epidemiological and laboratory animal model studies have suggested an inverse relationship between colon cancer risk and intake of fiber-rich foods. The protective effect of dietary fiber which comprises a heterogeneous group of nonstarch polysaccharides such as cellulose, hemicellulose, and pectin and non-carbohydrate substances such as phytic acid depends on the nature and source of fiber in the diet. Laboratory animal models have consistently shown that dietary administration of wheat bran reduced colon tumorigenesis. Human diet intervention studies have demonstrated that supplemental wheat bran in the diet decreased the formation of putative metabolites such as secondary bile acids and diacylglycerol in the colon that have been shown to act as tumor promoters in the colon. Among the components of dietary fiber, especially wheat bran, phytic acid (inositol hexaphosphate) has been studied extensively for its chemopreventive properties against colon carcinogenesis in the laboratory animal models. In studies carried out to date, dietary phytic acid reduced the incidence of colonic aberrant crypt foci, putative preneoplastic lesions in rats. Oral administration of phytic acid was shown to inhibit colon carcinogenesis in rodents during the initiation and postinitiation stages. These studies provide evidence for potential chemopreventive properties of phytic acid against colon cancer. With regard to mode of action, phytic acid acts as an antioxidant, to reduce the rate of cell proliferation and to augment the immune response by enhancing the activity of natural killer (NK) cells.*

Cancer of the colon and rectum is the fourth most common cause of cancer deaths worldwide [1]. Cancer of the colon which is one of the leading causes of cancer deaths in both men and women in the Western countries including North America [2] is generally increasing rapidly in Japan including the urban areas of the developing world. Epidemiological

studies have demonstrated that increased consumption of fruits and vegetables and high intake of dietary fiber reduce the risk of colon cancer [3]. Interest in the concept of cancer prevention is growing rapidly because the utilization of nutritional factors and naturally-occurring and synthetic agents that can protect against the development and progression of carcinogenic process is not only an attractive but plausible approach to either inhibit or reverse carcinogenesis.

### Dietary Fiber and Colon Cancer

The hypothesis that a diet high in fiber may protect against colon cancer was first proposed by Burkitt [4] who observed that African Blacks consuming high fibrous and low-fat foods had lower death rates due to colon cancer compared to their white counterparts eating a low-fiber and high fat diets. Subsequent studies demonstrated that, in populations consuming diets high in total fat, the intake of diets high in total fiber, fibrous foods, and certain whole grain foods reduce risk for colon cancer [5,6]. Intracountry comparisons of dietary fiber and colon cancer mortality rates strongly supported the hypothesis that dietary fiber, especially fiber from cereal sources and pulses, protects against colon cancer [7]. Case-control studies on the relationship between the dietary fiber and colon cancer provided convincing results. Out of 19 case-control studies to assess the role of fiber and fiber-containing foods, 3 studies reported no protective effect, 2 found an increased risk, and 13 studies reported a protective effect of fiber-containing foods and vegetables [8]. Howe *et al* [9] examined the results of combined analysis of 13 case control studies of diet and colon cancer with respect to the intakes of dietary fiber. In this analysis, the individual data records for 5287 colon cancer cases and 10470 control subjects have been pooled for a common analysis which provided substantive evidence that intake of fiber-rich foods is inversely related to colon cancer risk with odds ratios of 1.0, 0.8, 0.7, 0.6, 0.5 for each quintile of consumption from lowest to highest. Similar findings have been reported for a meta-analysis of 16 case-control studies, with odds ratio of 0.6 for the highest versus lowest intake of fiber [3].

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**Key Words:** Colon cancer, dietary fiber, phytic acid.

Laboratory animal model studies also indicated that the protective effects of dietary fiber depends on the type of fiber; wheat bran, but neither corn bran nor oat bran, appears to inhibit colon tumor development [10-14]. The effect of dietary wheat bran at 15% level or corn bran plus 5% dietary fat on colon carcinogenesis induced by azoxymethane (AOM) or 3,2'-dimethyl-4-aminobiphenyl (DMBA) was studied in male F344 rats. The composition of diets was adjusted so that all the animals in different experimental groups consumed approximately the same amount of protein, fat, minerals, and vitamins. The animals fed wheat bran had a lower incidence (number of animals with tumors) and multiplicity (number of tumors/animal) of colon tumors than did those fed the control diet whereas corn bran or oat bran had no effect. Thus animal model studies clearly suggest that wheat bran consistently inhibits colon carcinogenesis associated with administration of colon-specific carcinogens.

In human clinical trials, supplements of wheat bran produced a reduction in the incidence of rectal polyps among the individuals genetically predisposed to these lesions [15]. Metabolic epidemiologic studies demonstrated that the individuals consuming high fat and low fiber diets excrete increased levels of fecal mutagens and bile acids compared with those consuming low fat and high fiber or high fat and high fiber diets [16,17]. Additional studies have also provided evidence that wheat-bran supplementation favorably altered a number of biomarkers that are related to the risk of colorectal cancer including fecal mutagenicity [16], fecal secondary bile acids and bacterial 7 $\alpha$ -dehydroxylase [17,18] and rectal cell proliferation [19]. Dietary oat bran had no effect on fecal secondary bile acids or 7 $\alpha$ -dehydroxylase activity, whereas dietary corn bran increased the levels of secondary bile acids and 7 $\alpha$ -dehydroxylase activity. More recent studies have compared the effects of altering both fiber and fat content on fecal secondary bile acids. In this study, healthy subjects who had consumed a typical high fat, low-fiber Western diet and were switched to a low-fat, very-low-fiber diet and then to a low-fat, high-fiber diet showed a dramatic reduction in secondary bile acids during the low-fat and high fiber period, compared with the highfat and low-fiber period. In this connection, several lines of evidence show that dietary fiber affects the metabolic activity of gut microflora; this effect also depends on the type of fiber consumed [17]. There is convincing evidence that these secondary bile acids such as deoxycholic acid and lithocholic acid act as colon tumor promoters. The evidence thus far generated suggests that high dietary fiber including wheat bran reduce the risk of colon cancer.

#### Inositol Hexaphosphate

Inositol hexaphosphate (InsP<sub>6</sub>, phytic acid) is a naturally occurring compound found in substantial amounts in cereals and legumes [20]. As discussed above, intake of several classes of foods with high fiber content, and intake of cereals,

grains and legumes is inversely associated with colon cancer risk. This finding is significant because cereals, grains and legumes are a rich source of phytic acid. It is possible that one of the mechanisms by which dietary fiber inhibits colon carcinogenesis is through the effects of phytic acid on cell proliferation and differentiation.

Phytic acid and inositol have been tested as chemopreventive agents in *in vitro* systems and laboratory animal models for colon cancer. Sakamoto *et al* [21] investigated the effect of phytic acid on proliferation and differentiation of human cancer cell line, HT-29 *in vitro*. These results showed that phytic acid inhibits cell proliferation and concomitantly increases differentiation suggesting that it suppresses not only the malignant phenotype but also allows the maturation of human colon cancer cells to structurally and behaviorally resemble normal cells. In *in vitro* studies, phytic acid reduced cell proliferation of all human and rodent cell lines tested, including MC-7 human breast carcinoma cells [20]. Enhanced differentiation of cancer cells to the point of reversion back to normal phenotype was also observed in several lines, including the HT-29 human colon carcinoma cell line [2]. These studies provide evidence for many potential beneficial actions of phytic acid.

The exact mechanisms by which phytic acid exert its chemopreventive effects have not been clearly demonstrated. Because of the highly charged nature of phytic acid, it was thought that it could not be transported inside the cell [20]; however, Sakamoto *et al* [2] demonstrated that intragastrically administered [<sup>3</sup>H]phytic acid was absorbed from the stomach and upper small intestine, distributed into various organs and appeared in the plasma and urine as inositol and inositol P<sub>1</sub>, indicating metabolism of the parent compound phytic acid. Phytic acid has been shown to act as an antioxidant, to control cell division and reduce the rate of cell proliferation, and to enhance the activity of natural killer cells, which play an important role in the host defense against neoplasia [20].

Chemopreventive activity of phytic acid has been evaluated in preclinical animal models. Aberrant crypt foci (ACF) are recognized as early preneoplastic lesions in the colon from which adenomas and adenocarcinomas may develop in the colon of both rodents and humans. There is evidence that several inhibitors of ACF formation reduce the incidence of colon tumors in laboratory animal models suggesting that ACF can be used to evaluate novel agents for their potential chemopreventive activities against colon cancer [23]. In this connection, Pretlow *et al* [24] demonstrated that the development of larger ACF with 4 or more aberrant crypt/focus was significantly inhibited in F344 rats administered AOM and given 2% phytic acid in drinking water. Phytic acid at 1 and 2% levels in the diet significantly decreased the number of ACF in the colon [25]. Results also showed that 2% phytic acid administered in combination with 2% green tea extract had a synergistic effect exhibiting a total of about 30% reduction in ACF ( $p < 0.02$ ) whereas green tea

extract alone had marginal effect ( $p < 0.14$ ). Colon tumor-inhibitory activity of phytic acid has also been evaluated in animal models. Ullah and Shamsuddin [26] showed that administration of 0.1 and 1.0% phytic acid in drinking water significantly inhibited AOM-induced colon tumor incidence, multiplicity and size. Administration of 1% phytic acid in drinking water reduced colon tumor multiplicity by 52% ( $p < 0.01$ ), tumor frequency by 56% ( $p < 0.001$ ) and tumor size by 62% ( $p < 0.001$ ); 0.1% phytic acid exhibited only reduction in tumor size by 71% ( $p < 0.001$ ). In another study, the effect of phytic acid administered during the postinitiation stage of colon carcinogenesis was investigated by Shamsuddin and Ullah [27]. Phytic acid when administered in drinking water 2 weeks or 5 months after AOM treatment significantly inhibited colon tumor multiplicity, tumor incidence and tumor size in F344 rats suggesting that the beneficial action of phytic acid is not restricted to the prevention of tumor development but perhaps to treatment of existing tumors as well [27]. In support of these results, Pretlow *et al* [24] have also demonstrated that administration of 2% phytic acid in drinking water during postinitiation stage suppressed AOM-induced colon tumor incidence ( $p < 0.004$ ), in F344 rats.

### Conclusions

Animal model studies clearly suggest that wheat bran consistently inhibits colon carcinogenesis. Case-control studies show reasonably strong evidence that dietary fiber reduces the risk of colon cancer in humans. Dietary intervention studies provide evidence that wheat bran supplementation decreases the levels of several putative tumor promoters in the colon. Administration of phytic acid, high levels of which are present in wheat bran and other grains inhibits colon carcinogenesis in animal models.

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## LACK OF EFFECT OF A LOW-FAT, HIGH-FIBER DIET ON THE RECURRENCE OF COLORECTAL ADENOMAS

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### ABSTRACT

**Background** We tested the hypothesis that dietary intervention can inhibit the development of recurrent colorectal adenomas, which are precursors of most large-bowel cancers.

**Methods** We randomly assigned 2079 men and women who were 35 years of age or older and who had had one or more histologically confirmed colorectal adenomas removed within six months before randomization to one of two groups: an intervention group given intensive counseling and assigned to follow a diet that was low in fat (20 percent of total calories) and high in fiber (18 g of dietary fiber per 1000 kcal) and fruits and vegetables (3.5 servings per 1000 kcal), and a control group given a standard brochure on healthy eating and assigned to follow their usual diet. Subjects entered the study after undergoing complete colonoscopy and removal of adenomatous polyps; they remained in the study for approximately four years, undergoing colonoscopy one and four years after randomization.

**Results** A total of 1905 of the randomized subjects (91.6 percent) completed the study. Of the 958 subjects in the intervention group and the 947 in the control group who completed the study, 39.7 percent and 39.5 percent, respectively, had at least one recurrent adenoma; the unadjusted risk ratio was 1.00 (95 percent confidence interval, 0.90 to 1.12). Among subjects with recurrent adenomas, the mean ( $\pm$ SE) number of such lesions was  $1.85 \pm 0.08$  in the intervention group and  $1.84 \pm 0.07$  in the control group. The rate of recurrence of large adenomas (with a maximal diameter of at least 1 cm) and advanced adenomas (defined as lesions that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia, including carcinoma) did not differ significantly between the two groups.

**Conclusions** Adopting a diet that is low in fat and high in fiber, fruits, and vegetables does not influence the risk of recurrence of colorectal adenomas. (N Engl J Med 2000;342:1149-55.)

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**A** WEALTH of laboratory, nutritional, and epidemiologic evidence implicates dietary factors in the pathogenesis of colorectal cancer.<sup>1</sup> International variation in the incidence of and mortality due to large-bowel cancer,<sup>2</sup> rapid increases in the incidence of colorectal cancer in several countries,<sup>3</sup> and data on migration<sup>4</sup> are consistent with a role of diet in the causation of colorectal cancer. Moreover, altering the proportions of dietary fat<sup>5</sup> and fiber<sup>6</sup> influences the development of colon tumors in animals. In humans, diet affects the production of intracolonic metabolic byproducts that may influence carcinogenesis.<sup>7-9</sup> Observational epidemiologic studies suggest that the ingestion of red meat and dietary fat increases the risk of colorectal cancer, whereas the ingestion of vegetables, dietary fiber, and certain micronutrients lowers the risk.<sup>10-14</sup> These results, however, are inconsistent,<sup>15</sup> and the evidence that diet contributes to causing colorectal cancer is hardly conclusive.

We studied whether adults can reduce their risk of colorectal cancer by modifying their diet. Because adenomatous polyps are considered precursors of most large-bowel cancers, we chose recurrence of adenomas as the primary end point.<sup>16</sup>

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Some earlier trials tested the effects of dietary supplements, rather than an explicit dietary change, on the recurrence of adenomas.<sup>17-22</sup> Two pioneering studies did not find that low-fat diets (coupled with fiber supplementation) reduced the recurrence of adenomas,<sup>23,24</sup> but these small trials had limited statistical power. We report the results of the Polyp Prevention Trial, a large multicenter, randomized, controlled trial of the effect of a comprehensive dietary intervention — counseling of patients and assignment to a diet low in fat and high in fiber, fruits, and vegetables — on the recurrence of large-bowel adenomas.

## METHODS

### Study Design and Subjects

Details of the study design, eligibility criteria, randomization procedures, dietary intervention, and end-point assessment have been previously reported.<sup>25,26</sup> In brief, we recruited subjects who were at least 35 years old and who had had one or more histologically confirmed colorectal adenomas removed during a qualifying colonoscopy (in which the cecum was visualized, all polyps were removed, and the bowel was adequately prepared) within six months before randomization. Eligible subjects had no history of colorectal cancer, surgical resection of adenomas, bowel resection, the polyposis syndrome, or inflammatory bowel disease; weighed no more than 150 percent of the recommended level; were taking no lipid-lowering drugs; and had no medical condition or dietary restrictions or practices that would substantially limit compliance with the protocol. The institutional review boards of the National Cancer Institute and each participating center approved the study. All subjects provided written informed consent.

Staff members at eight clinical centers (listed in the Appendix) identified potential subjects through referrals by endoscopists or reviews of the records of the endoscopy service. Of 38,277 potential subjects, we enrolled 2079 (5.4 percent) in the trial. A total of 1037 were randomly assigned to adopt a diet that was low in fat and high in fiber, fruits, and vegetables (the intervention group), and 1042 were randomly assigned to follow their usual diet (the control group). The base-line characteristics of these subjects have been reported previously.<sup>25,26</sup>

### Collection of Data

At one of two clinic visits before randomization, we measured each subject's weight and height. At the base-line visit and at subsequent annual visits at years 1, 2, 3, and 4, each subject answered a questionnaire assessing a variety of demographic, clinical, and behavioral characteristics and provided a venous blood specimen after an overnight fast.

### Dietary Goals and Follow-up

For subjects in the intervention group, the dietary goals were to provide 20 percent of total calories from fat, 18 g of dietary fiber per 1000 kcal, and 3.5 servings of fruits and vegetables per 1000 kcal (range, 5 to 8 daily servings, depending on total energy intake). The intervention program included nutritional information and behavior-modification techniques. We offered each subject more than 50 hours of counseling sessions during the four-year intervention period, including 20 hours in the first year. Each subject in the intervention group was assigned to one nutritionist for counseling and another for dietary assessment. We provided subjects in the control group with general dietary guidelines from the National Dairy Council but gave them no additional nutritional or behavioral information.

We followed the subjects for approximately four years after randomization. Each year all subjects completed a four-day food record followed by a food-frequency questionnaire, the Block Health Hab-

its and History Questionnaire,<sup>27,28</sup> which was modified slightly to reflect the intake of low-fat and high-fiber foods. In addition, subjects in the intervention group completed a four-day food record six months after randomization. Each year we administered unscheduled 24-hour dietary-recall questionnaires to a newly selected random sample of 10 percent of subjects.

### Colonoscopy

Subjects returned to their usual endoscopist for colonoscopy one and four years after randomization. The one-year colonoscopy had to be performed at least 180 days after randomization but less than 2 years afterward. This colonoscopy served to detect and remove any lesions missed by the base-line colonoscopy. We obtained data on any unscheduled endoscopic procedure carried out in addition to the follow-up procedures at one and four years. We asked all investigators and subjects not to discuss a subject's randomization status with the endoscopists.

### Assessment of Adenomas

Two central pathologists, who were unaware of the subjects' group assignment, determined the histologic features and degree of atypia (low-grade vs. high-grade) of all lesions. The endoscopists' reports provided information on the size, number, and location of all polyps.

We defined an adenoma as recurrent if it was found during any endoscopic procedure after the one-year colonoscopy or, for subjects who missed the one-year colonoscopy, during any endoscopic procedure performed at least two years after randomization. Adenomas found during the one-year colonoscopy were not considered recurrent. An end-points committee of gastroenterologists who were unaware of the subjects' group assignment evaluated complicated cases, including those involving lost tissue specimens or failure to reach the cecum. The few colorectal cancers diagnosed after the one-year colonoscopy were counted as recurrent lesions.

### Statistical Analysis

We used the intention-to-treat principle to compare the intervention and control groups, defining groups according to the initial random assignment rather than according to actual or reported compliance with the protocol.<sup>29</sup> The primary end point was the recurrence of adenomas during the interval from the one-year to the four-year colonoscopy. Secondary end points were the number, size, location, and histologic features of the adenomas that were found. We calculated risk ratios and 95 percent confidence intervals in order to compare end-point events in the two groups.<sup>30</sup> We used logistic regression to adjust the effect of intervention for base-line prognostic factors. We used logistic-regression models to determine whether there was an interaction between dietary intervention and various covariates, and where appropriate, we performed covariate stratum-specific analyses.

## RESULTS

### Characteristics of the Subjects

The base-line demographic, clinical, nutritional, and behavioral characteristics were similar in the 958 subjects in the intervention group and the 947 subjects in the control group who completed the study (Table 1). Of these 1905 subjects, 1768 (92.8 percent) underwent a colonoscopy during year 1; the procedure was performed in 93.8 percent of the subjects in the intervention group and 91.8 percent of the subjects in the control group (Table 2). The median observation period (3.05 years) and the mean number of colonoscopic examinations after randomization (2.31) were the same in both groups (Table 2).

Subjects in the intervention group reduced their

LACK OF EFFECT OF A LOW-FAT, HIGH-FIBER DIET ON THE RECURRENCE OF COLORECTAL ADENOMAS

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS WHO COMPLETED THE STUDY.\*

CHARACTERISTIC	INTERVENTION GROUP (N=958)	CONTROL GROUP (N=947)
Age (yr)	61.0±0.3	61.1±0.3
Male sex (%)	65.8	63.2
Minority race or ethnic group (%)	11.7	9.2
More than high school education (%)	65.3	65.2
Married (%)	78.2	80.8
Current smoker (%)	13.4	13.2
Alcohol intake (g/day)	7.4±0.4	8.0±0.5
Body-mass index	27.6±0.1	27.5±0.1
Vigorous or moderate activity or both (hr/wk)	12.6±0.5	11.6±0.4
Current aspirin use (%)	23.3	22.0
Use of calcium supplements (%)	15.4	14.1
Use of vitamin E supplements (%)	18.8	15.1
Plasma total cholesterol (mg/dl)†	202.6±1.8	200.2±1.7
Serum total carotenoids (µg/dl)‡	92.9±2.0	92.4±2.0
Serum α-tocopherol (µg/dl)§	1442±39	1335±27
Family history of colorectal cancer (%)	24.3	26.0
Adenoma ≥1 cm in maximal diameter (%)	27.2	31.5
≥2 Adenomas (%)	35.0	33.8
≥1 Villous or tubulovillous adenomas (%)¶	19.2	21.0
Advanced adenoma (%)	36.0	39.1
History of adenomas within previous 5 yr (%)	19.6	16.9

\*Plus-minus values are means ±SE. Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

†To convert values for cholesterol to millimoles per liter, multiply by 0.02586. A total of 414 subjects in the intervention group and 412 subjects in the control group were assessed after an overnight fast.

‡To convert values for carotenoids to millimoles per liter, multiply by 0.0185. A total of 415 subjects in the intervention group and 411 subjects in the control group were assessed after an overnight fast.

§A total of 418 subjects in the intervention group and 415 subjects in the control group were assessed after an overnight fast.

¶Information is based on the histologic analysis conducted by the central pathologists.

||Advanced adenoma was defined as one that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia (including carcinoma).

fat intake from a mean (±SE) of 35.6±0.2 percent of calories at the beginning of the trial to 23.8±0.2 percent at four years, according to data obtained from the food-frequency questionnaire (Table 3). The values from four-day food records from a random sample of 20 percent of subjects were 32.2 percent at base line and 20.6 percent at four years. Fat intake in the control group declined from 36.0±0.2 percent of calories at base line to 33.9±0.2 percent at four years. The values from four-day food records in this group were 32.5 percent and 31.1 percent, respectively. The absolute difference between the intervention and control groups in the change in dietary fat as a proportion of total calories over the four-year period was 9.7 percent (95 percent confidence interval, 9.0 to 10.3 percent).

TABLE 2. FOLLOW-UP COLONOSCOPY AMONG THE SUBJECTS WHO UNDERWENT RANDOMIZATION.

VARIABLE	INTERVENTION GROUP	CONTROL GROUP
No. randomized	1037	1042
No adenoma at base line — no. (%)	3 (0.3)	1 (0.1)
Lost to follow-up — no. (%)	76 (7.3)	94 (9.0)
Withdrew*	34 (44.7)	48 (51.1)
Died before follow-up colonoscopy	42 (55.3)	46 (48.9)
Follow-up colonoscopy — no. (%)†	958 (92.4)	947 (90.9)
Colonoscopy at year 1‡	899 (93.8)	869 (91.8)
Colonoscopy at year 4	638 (71.0)	550 (63.3)
Colonoscopy at year 4 and unscheduled colonoscopy	150 (16.7)	169 (19.4)
Unscheduled colonoscopy only	111 (12.3)	150 (17.3)
No colonoscopy at year 1	59 (6.2)	78 (8.2)
Colonoscopy only at year 4	19 (32.2)	30 (38.5)
Colonoscopy at year 4 and unscheduled colonoscopy	26 (44.1)	23 (29.5)
Unscheduled colonoscopy only	14 (23.7)	25 (32.1)
Median follow-up — yr	3.05	3.05
No. of procedures — mean ±SE	2.31±0.02	2.31±0.03

\*The reasons for withdrawal were as follows: no colonoscopy at year 4 in 29 subjects in the intervention group and 43 subjects in the control group; refusal to participate in the case of 5 and 4 subjects, respectively; and illness in 1 subject in the control group.

†Among subjects in the intervention group who underwent follow-up colonoscopy, in 38 the cecum was not visualized; in 22 the bowel was poorly prepared, which might have caused small polyps to be overlooked; and in 53 one or more tissue specimens were lost during the procedure and therefore were not analyzed, no slides were available for pathological review, or data on histologic findings were unknown. The respective numbers in the control group were 40, 25, and 44. Five subjects (three in the intervention group and two in the control group) underwent sigmoidoscopy as the follow-up procedure.

‡P=0.10 for the difference between groups.

Subjects in the intervention group raised their fiber intake by nearly 75 percent; subjects in the control group had a slight increase (Table 3). By the end of the study, the difference between the two groups in the change in fiber consumption was 6.9 g of dietary fiber per 1000 kcal (95 percent confidence interval, 6.4 to 7.3). As compared with subjects in the control group, those in the intervention group who consumed 2000 kcal per day increased their fiber intake by nearly 14 g on average. Data from the four-day food records were similar to those from the food-frequency questionnaires.

The number of servings of fruits and vegetables per 1000 kcal increased by about two thirds in the intervention group; subjects in the control group raised their fruit and vegetable intake only slightly (Table 3). The difference between the two groups in the change in fruit and vegetable intake was 1.13 servings per 1000 kcal (95 percent confidence interval, 1.04 to 1.21). As compared with subjects in the control group, subjects in the intervention group who consumed 2000 kcal per day increased their fruit and vegetable intake by approximately 2.25 servings. Data from the

TABLE 3. REPORTED DAILY DIETARY AND SUPPLEMENT INTAKES, BIOMARKERS, AND WEIGHT.\*

VARIABLE	INTERVENTION GROUP		CONTROL GROUP		ABSOLUTE DIFFERENCE IN CHANGE BETWEEN GROUPS (95% CI)†
	AT RANDOMIZATION (N=953)	AT YEAR 4 (N=903)	AT RANDOMIZATION (N=947)	AT YEAR 4 (N=833)	
Fat (% of calories)	35.6±0.2	23.8±0.2	36.0±0.2	33.9±0.2	-9.7 (-10.3 to -9.0)
Fiber (g/1000 kcal)	10.0±0.1	17.4±0.2	9.5±0.1	10.0±0.1	6.9 (6.4 to 7.3)
Fruits and vegetables (servings/1000 kcal)	2.05±0.03	3.41±0.04	2.00±0.03	2.23±0.03	1.13 (1.04 to 1.21)
Calories (kcal/day)	1972±19	1870±16	1981±20	1910±18	-25 (-72 to 22)
Red and processed meat (g/day)	93.2±1.7	74.5±1.4	97.9±1.8	94.9±1.7	-15.8 (-20.2 to -11.5)
Ratio of red meat to chicken and fish	2.6±0.1	1.8±0.1	2.6±0.1	2.9±0.1	-1.0 (-1.3 to 0.7)
Whole grains (g/day)	83.4±2.0	115.3±2.3	76.8±1.9	72.6±1.9	35.9 (30.3 to 41.6)
Legumes (g/day)	14.2±0.6	48.5±1.6	13.7±0.6	16.2±0.7	31.9 (28.9 to 35.0)
Cruciferous vegetables (g/day)	28.9±0.9	44.4±1.5	26.5±1.0	27.7±1.0	14.2 (10.8 to 17.5)
Calcium from food and supplements (mg/day)	1032±20	1193±23	1002±20	1096±23	77.2 (16.1 to 138.3)
Folate from food and supplements (μg/day)	435.0±8.8	593.9±12.7	423.9±9.0	487.5±12.5	95.4 (62.0 to 128.9)
Multivitamin use (%)	36.6	42.2	36.4	41.7	-0.3 (-4.8 to 4.2)
No. of subjects	958	921	947	912	
Plasma total cholesterol (mg/dl)‡	5.30±0.01	5.27±0.01	5.29±0.01	5.27±0.01	-0.01 (-0.03 to 0.01)
No. of subjects	414	372	412	364	
Serum total carotenoids (mg/dl)§	4.46±0.02	4.50±0.02	4.45±0.02	4.42±0.02	0.06 (0.01 to 0.11)
No. of subjects	415	369	411	361	
Weight (lb)¶	179.9±1.1	178.5±1.1	178.3±1.1	179.3±1.1	-2.5 (-3.6 to -1.4)
No. of subjects	958	919	947	907	

\*Plus-minus values are means ±SE. CI denotes confidence interval. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for carotenoids to millimoles per liter, multiply by 0.0185. Cholesterol and carotenoids were measured after an overnight fast.

†Differences were calculated only for subjects who had values at randomization and at year 4.

‡Log-transformed values are shown. The log-transformed values of -0.02 mg per deciliter in the intervention group and -0.01 mg per deciliter in the control group for the difference within groups from randomization to year 4 reflect respective decreases in absolute cholesterol concentrations of approximately 2 percent and 1 percent; the absolute difference in the change between groups is about -1 percent (95 percent confidence interval, -3 percent to 1 percent).

§Log-transformed values are shown. The log-transformed values of 0.04 mg per deciliter in the intervention group and -0.01 mg per deciliter in the control group for the difference within groups from randomization to year 4 reflect an increase of approximately 5 percent in absolute carotenoid concentrations in the intervention group and a decrease of 1 percent in the control group; the absolute difference in the change between groups is about 6 percent (95 percent confidence interval, 1 percent to 11 percent).

¶To convert values for weight to kilograms, divide by 2.2.

four-day food records showed a difference in the change between groups of 1.8 servings per 1000 kcal.

Changes in the intake of fat, fiber, and fruits and vegetables generally occurred within the first year and were subsequently maintained. Data from the food-frequency questionnaire showed that during the first year subjects in the intervention group obtained 24.6 percent of calories from fat, consumed 17.7 g of dietary fiber per 1000 kcal, and ate 3.3 servings of fruits and vegetables per 1000 kcal. These changes were similar for men and women. As compared with subjects in the control group, subjects in the intervention group also significantly altered their intake of other nutrients and foods, including red and processed meat, whole grains, legumes, calcium, and folate (Table 3). Data from the 24-hour dietary recall were similar to those from the four-day food records.

Over the four-year period of observation, the subjects in the intervention group had a significant increase in serum carotenoid concentrations and decrease in weight (Table 3), as compared with changes measured in subjects in the control group. The small reductions in plasma total cholesterol concentrations did not differ significantly between the two groups. The differences in the changes in total cholesterol, total carotenoids, and weight (calculated as the change in the control group over time minus the change in the intervention group over time) were somewhat greater after one year than after four years.

#### Recurrence of Adenomas

Adenomatous polyps recurred in 754 of the 1905 subjects who completed the study (39.6 percent). At least one recurrent adenoma was found in 39.7 per-

TABLE 4. RISK OF RECURRENCE OF ADENOMAS AMONG THE SUBJECTS WHO COMPLETED THE STUDY.

VARIABLE	INTERVENTION GROUP	CONTROL GROUP	RISK RATIO (95% CI)*	P VALUE
	(N=958)	(N=947)		
	no. of subjects (%)			
No. of adenomas				
≥1†	380 (39.7)	374 (39.5)	1.00 (0.90-1.12)	0.98
1	219 (22.9)	217 (22.9)	1.00 (0.85-1.18)	1.00
2	88 (9.2)	82 (8.7)	1.06 (0.80-1.41)	0.75
≥3	73 (7.6)	75 (7.9)	0.96 (0.71-1.31)	0.87
Location of adenomas‡				
Proximal	203 (21.2)	173 (18.3)	1.16 (0.97-1.39)	0.12
Distal	100 (10.4)	124 (13.1)	0.80 (0.62-1.02)	0.08
Proximal and distal	69 (7.2)	72 (7.6)	0.95 (0.69-1.30)	0.81
Unknown	8 (0.8)	5 (0.5)	1.58 (0.52-4.82)	0.59
Largest adenoma ≥1 cm	47 (4.9)	53 (5.6)	0.88 (0.60-1.28)	0.57
Advanced adenomas§	60 (6.3)	66 (7.0)	0.90 (0.64-1.26)	0.60

\*CI denotes confidence interval.

†The absolute difference between groups was 0.2 percent (95 percent confidence interval, -4.2 percent to 4.6 percent). The mean ( $\pm$ SE) number of recurrent adenomas among those with a recurrence was  $1.85 \pm 0.08$  in the intervention group and  $1.84 \pm 0.07$  in the control group. The distributions of adenomas according to size were not significantly different in the two groups ( $P=0.77$ ).

‡Proximal is defined as the portion of the large bowel from the cecum up to, but not including, the splenic flexure. Distal is defined as the portion of the large bowel from the splenic flexure up to and including the rectum. The distributions of adenomas according to location were not significantly different in the two groups ( $P=0.17$ ).

§An advanced adenoma was one that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia (including carcinoma).

cent of subjects in the intervention group and 39.5 percent of subjects in the control group; the unadjusted risk ratio was 1.00 (95 percent confidence interval, 0.90 to 1.12;  $P=0.98$ ) (Table 4). Of these recurrent adenomas, the mean number was  $1.85 \pm 0.08$  in the intervention group and  $1.84 \pm 0.07$  in the control group ( $P=0.93$ ). Among the 638 subjects in the intervention group and 550 subjects in the control group who underwent colonoscopy only at year 1 and year 4 after randomization, 36.7 percent and 35.8 percent, respectively, had one or more recurrent adenomas; the unadjusted risk ratio was 1.02 (95 percent confidence interval, 0.88 to 1.19;  $P=0.81$ ).

The intervention and control groups did not differ significantly with respect to the number with recurrent large adenomas (with a maximal diameter of at least 1 cm) or advanced adenomas (defined as those that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia, including carcinoma); this was true when the analysis included all those who completed the study (Table 4) as well as when it included those who underwent only the scheduled colonoscopies at year 1 and year 4 after randomization (data not shown). In both groups, approximately 27 percent of subjects had at least one recurrent adenoma proximal to the splenic flexure (Table 4). Sixty-three percent of recurrent adenomas were proximal to the splenic flexure, whereas 58 percent of base-line adenomas were distal to that site (data not shown).

Colorectal cancer was diagnosed in 14 subjects after randomization (10 in the intervention group and 4 in the control group); the unadjusted risk ratio was 2.5 (95 percent confidence interval, 0.8 to 7.9;  $P=0.19$ ). Of these 14 subjects, 6 (4 in the intervention group and 2 in the control group) were given a diagnosis after the one-year colonoscopy; the unadjusted risk ratio was 2.0 (95 percent confidence interval, 0.4 to 10.8;  $P=0.69$ ).

To adjust for an imbalance in influential base-line variables between the groups, we used logistic-regression models that included as covariates the random group assignment and the base-line characteristics listed in Table 1. Adjustment for these factors had no effect on the risk of recurrence.

For all but one of the covariates listed in Table 1, we found on logistic-regression analysis that there was no statistically significant ( $P<0.01$ ) interaction with group assignment. We observed a significant interaction ( $P=0.005$  before adjustment for multiple comparisons) between the randomization group and sex. We therefore examined the recurrence of adenomas among men and women separately. Among men, the recurrence rate was lower in the intervention group than in the control group (41.9 percent vs. 46.7 percent); the unadjusted risk ratio was 0.89 (95 percent confidence interval, 0.79 to 1.02;  $P=0.11$ ). Among women, the rate of recurrence was higher in the intervention group than in the control group (35.4 percent vs. 27.2 percent); the unadjusted risk ratio was

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1.30 (95 percent confidence interval, 1.04 to 1.63;  $P=0.03$ ). With respect to both large and advanced recurrent lesions, the differences between groups were not significant for either men or women; the interaction between the randomization group and sex was not significant for either end point. There were also no significant ( $P<0.05$ ) differences between the groups in the number of either deaths or hospitalizations (for all causes and for specific diagnoses).

### DISCUSSION

We found that the rate of recurrent adenomas was not changed by dietary intervention. Our results are compatible with, at most, an absolute reduction related to the intervention of about 4 percent in the incidence of recurrent adenomas (Table 4). We also found no effect of the dietary intervention on the incidence of large or advanced recurrent lesions.

Two previous trials also found that dietary changes had no effect on the overall risk of recurrence of colorectal adenomas. The Toronto Polyp Prevention Trial reported no significant difference in recurrence after two years between subjects in the intervention group and those in the control group (a total of 201 subjects) who reported ingesting 25 and 33 percent of calories from fat and 35 and 16 g of fiber per day, respectively.<sup>23</sup> In the Australian Polyp Prevention Project, which included 424 subjects, none of the interventions (a reduction in dietary fat, use of a wheat-bran-fiber supplement, and supplementation with beta carotene) resulted in a statistically significant reduction in the risk of recurrence after 48 months of observation.<sup>24</sup> The Australian trial did report a marginally significant reduction in the recurrence of large adenomas ( $\geq 1$  cm in diameter) among subjects eating a low-fat diet, but in that study large recurrent adenomas developed in only 17 subjects, as compared with 100 in our study.

The straightforward interpretation of our finding is that a diet that is low in fat, and high in fiber, fruits, and vegetables does not reduce the risk of recurrent adenomas or, by inference, colorectal cancer. Alternative explanations, however, merit consideration.

Most recurrent adenomas were small; only about 5 percent of subjects had a recurrent lesion 1 cm or more in diameter (Table 4). Adopting a diet that was low in fat and high in fiber, fruits, and vegetables might affect only the growth of small adenomas into large adenomas or the transformation of large adenomas into invasive carcinomas.<sup>31</sup>

The dietary-assessment data indicated that the intervention and control groups differed substantially in the consumption of fat, fiber, and fruits and vegetables. The findings regarding carotenoid concentrations and weight were consistent with such differences. (The changes in blood lipid concentrations were minimal but compatible with the results of other studies of dietary intervention as well as with predictions

based on the equation of Keys et al.<sup>32</sup>) These data, however, do not preclude the possibility that in the light of the dietary expectations fostered by the trial, subjects in the intervention group systematically underreported their intake of fat or overreported their consumption of fiber or fruits and vegetables. Another possibility is that the dietary intervention was inadequate; a reduction in fat intake to no more than 15 percent of calories or a greater intake of fiber or fruits and vegetables might be required to reduce the risk of recurrent adenomas. Moreover, we may not have chosen the optimal set of dietary targets. The 20 percent reduction in the consumption of red and processed meat among subjects in the intervention group may have been too small to affect the risk of recurrence of adenomas. The same may be true for reductions in the consumption of meat cooked at high temperatures (which contains high concentrations of heterocyclic amines)<sup>33</sup> or sugar.<sup>11</sup>

The mean age of the subjects at base line was 61 years. If nutritional factors influence critical events in colorectal neoplasia at the molecular, cellular, or tissue level only earlier in life, then a change in diet later in adult life may be ineffective. A relatively short period of dietary intervention (four years) might also fail to reduce the risk of recurrent adenomas. A longer period of intervention as well as follow-up might allow the development of enough adenomas to reveal the protective effect of the intervention, if there were one. In a recent clinical trial of calcium supplementation to prevent colorectal adenoma,<sup>22</sup> however, the average age of the subjects, the duration of the intervention, and the length of follow-up were similar to those in our study, but that study did find a lower recurrence rate among subjects in the intervention group.

Bias is an unlikely explanation for our results. Subjects in the intervention and control groups who completed the study did not differ appreciably with respect to base-line characteristics, and the main results did not change after adjustment for multiple covariates in logistic-regression analysis. Although we could not disguise the group assignments from the subjects or guarantee that the endoscopists were unaware of these assignments, we have no reason to suspect that endoscopists tended to search more diligently for — and therefore find more — adenomas among subjects in the intervention group than in the control group. A series of imputations based on the age and sex of subjects who did not undergo follow-up colonoscopy made no appreciable difference in estimates of recurrence.<sup>34</sup>

The higher rate of recurrent adenomas among women in the intervention group than among those in the control group and the interaction between sex and group was not affected by a multivariate adjustment for age and the number of adenomas at base line (both of which were predictive of the risk of recurrence) and other covariates listed in Table 1. Never-

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theless, we conclude that this interaction resulted from chance observations arising from repeated testing. In the Toronto trial, the rate of recurrence was lower among women in the intervention group but higher among men in that group, as compared with the risk in the control subjects, though these differences were not statistically significant.<sup>23</sup>

In summary, our study provided no evidence that a diet low in fat and high in fiber, fruits, and vegetables reduces the risk of recurrent colorectal adenomas. Nevertheless, we cannot definitively conclude that a change in diet is ineffective in reducing the risk of colorectal cancer. Nor should we overlook the abundant data indicating that a diet low in saturated fats and rich in fruits, vegetables, and whole grains has a favorable influence on the risk of chronic disease and mortality.<sup>35-37</sup>

## APPENDIX

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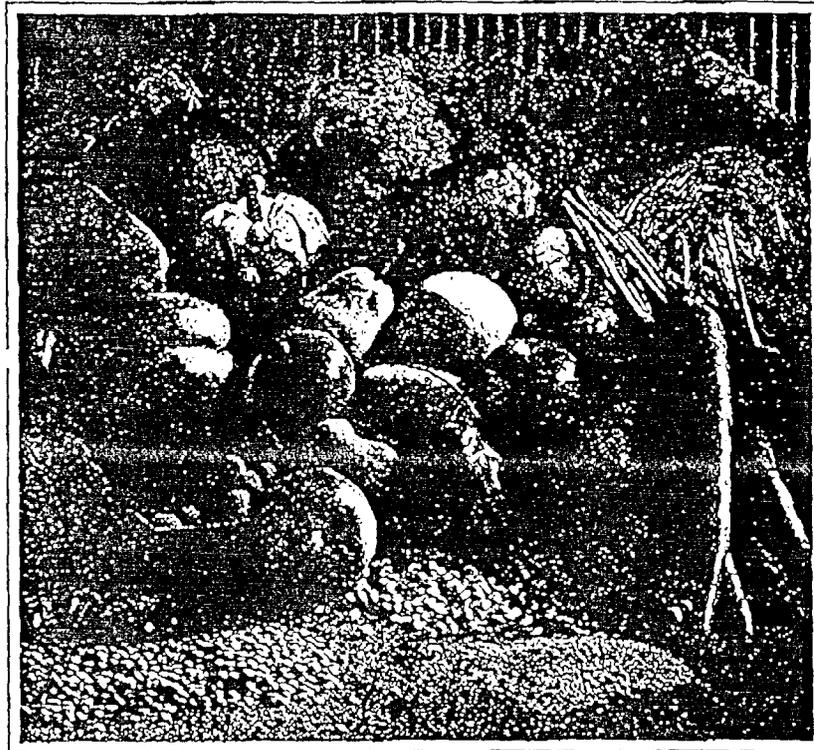
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## CLINICAL APPLICATIONS

# FIBER CONSUMPTION REDUCES THE RISK OF COLORECTAL CANCER

by Charles B. Simone, M.D., Nicole L. Simone, and Charles B. Simone, II



**G**astrointestinal cancers are the second leading cause of death among all cancer patients. The death rate for cancer of the colon and rectum has remained virtually the same since 1930, which means there has been essentially no progress in the treatment of these cancers. The new colorectal cancer cases for 2000 were approximately 130,200. The estimated number of deaths from colorectal cancer is 56,600. A person has a one-in-18 chance of developing colorectal cancer<sup>1</sup> over his or her lifetime.

Major differences in death rates from colorectal cancer occur in different parts of the world, and epidemiological studies show that dietary factors account for the different incidence rates.<sup>2</sup> The more industrialized a country, the higher the rate of colorectal cancer

because the people generally eat less fiber and more animal fat. The highest colorectal cancer rates are found in Western Europe and English-speaking countries. The lowest rates are found in Africa and Asia, but that is changing rapidly for Asians who have adopted a Westernized diet.

In countries with a high incidence of colorectal cancer, most of the cancers are located in the left colon and rectum, whereas in countries with a low incidence, most of the cancers are in the right colon. Carcinogens become progressively more concentrated at the end of the gastrointestinal tract (left colon and rectum). Dr. Denis Burkitt shares the following analogy for this distribution of cancer: "While a man proceeds down a path carrying a leaky pot of water containing a tablet

of dye that is gradually dissolving, the water becomes more deeply colored because the volume will be progressively reduced and the dye more concentrated, and more dye will be progressively dissolved."

#### ROLE OF FIBER

Fiber is a complex carbohydrate consisting of a polysaccharide and a lignin substance that provides the structure of a plant cell. It is undigested residue that reaches the end of the small intestine. The three groups of dietary fiber types are vegetable fibers, which are highly fermentable and have a low undigested content; bran, which is less fermentable; and purified fibers, such as cellulose, which are much less fermentable and have a high undigested content.

Dietary fiber acts as a "glue" for certain chemicals. For instance, unconjugated bile acids, which the body produces, can be absorbed to fiber in the colon and passed out in the stool without intestinal bacteria forming carcinogens from those bile acids. In addition, some fiber binds to cholesterol, lipids, nitrogen, and certain minerals, and eliminates them in the stool. This action lowers the blood concentration of cholesterol and certain other lipids.

Drs. Higginson and Oettle were the first to report in 1960 that dietary fiber consumption was associated with a low risk of developing colon cancer.<sup>3</sup> They noted that the Bantu tribal people in South Africa had a low incidence of colorectal cancer. They also excreted large piles of feces that were related to the large amount of dietary fiber they ate. Dr. Denis Burkitt continued the research and concluded that the high-fiber diet resulted in a rapid transit time for solid material to pass through the gastrointestinal tract and also increased the amount of stool. These two variables are associated with a decreased incidence of colorectal cancer.<sup>4</sup>

Diet in rural Africa and in other similar locations provides about 25 grams of crude fiber daily, whereas Western diets provide only 8 to 15 grams of fiber daily. With a more rapid transit time, bile acids and other carcinogens produced by anaerobic bacteria move out of the gastrointestinal tract more quickly. Furthermore, since the volume of feces is increased, carcinogens that are produced pass through the gut more diluted. Hence, if more dietary fiber is eaten, carcinogens pass out of the gut more quickly and there are fewer carcinogens per square inch.

#### EVALUATING THE DATA

In 1982, the National Academy of Sciences found that, according to strict epidemiological criteria, there was "no conclusive evidence to indicate that dietary fiber exerts a protective effect against colorectal cancer in humans." Nevertheless, the U.S. National Academy of Sciences did issue dietary guidelines because the data were "highly suggestive that reduced fat consumption and increased consumption of cereals, fruit, and vegetables represent the current state of knowledge and form the basis of a diet that

is unlikely to do harm and may have the potential for reducing cancer rates in North America."

Because the evidence from epidemiological and laboratory studies was sufficiently consistent that high-fiber, low-fat diets could lower cancer risk, other U.S. agencies, organizations, and other governments issued interim dietary guidelines in the mid 1980s. These included the United States National Cancer Institute, National Institutes of Health, United States Department of Agriculture, Department of Health and Human Services, American Cancer Society, Australia, Canada, the Joint European Organization for Cooperation in Cancer Prevention, Norway, Sweden, and Japan. They all independently agreed that to reduce cancer risk, people should increase their consumption of green, yellow, and cruciferous vegetables, citrus fruits, and whole-grain cereal products and reduce their intake of fats to about 30 percent.

In 1984, the United States National Cancer Institute recommended an intake of 25-35 grams of fiber daily to decrease the risk of cancer. However, the American public consumes only about 8-15 grams of fiber per day.

During the last 25 years, thousands of *in vitro* and animal studies have been published demonstrating that fiber can decrease the risk of colorectal cancer. These papers have not been included in this review. Since 1980, hundreds of published papers demonstrate that high fiber intake can reduce the incidence of colorectal cancer in humans. Some have been included in this review.<sup>5-10</sup>

#### REPORTS ON FIBER FROM THE NCI

Reports from the United States National Cancer Institute are consistent that dietary fiber can decrease the risk of colorectal cancer:

- "This evaluation clearly suggests a relationship between colon cancer and a diet low in fiber." From 40 epidemiological studies in 55 reports (Greenwald P, et al: Dietary fiber in the reduction of colon cancer risk. *J Am Diet Assoc* 87(9):1178-1188, 1987).

- "The analysis of these studies gives support for a protective effect [against colorectal cancer] associated with fiber-rich diets." From 23 case-control studies, 7 international correlation studies, 8 within-country correlation studies, 2 cohort studies, and 3 time-trend studies (Trock, Lanza, Greenwald: Dietary fiber, vegetables, and colon cancer: critical review and meta-analysis of epidemiological studies. *JNCI* 82:650-661, 1990).

- "Based on current knowledge, recommended nutrition guidelines for reducing the risk of colon cancer include decreased fat consumption, adequate amounts of fruits, vegetables, and calcium, and avoidance of overweight" (Shike, Winawer, Greenwald, et al: Primary prevention of colorectal cancer. *Bull WHO* 68:377-385, 1990).

- "Both prospective and retrospective studies suggest that vegetable and fruit intake may reduce the risk of cancers...including cancer of the colon and rectum" (Ziegler RG: Vegetables, fruits, and carotenoids and the risk of cancer. Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD 20892. *Am J Clin Nutr* 53[1 Suppl]:251S-259S, January 1991).

## CONSENSUS STATEMENTS

Various organizations and governments around the world have issued consensus statements that high fiber consumption can reduce the risk of colorectal cancer.

- 1999 World Health Organization: "The consumption of foods rich in polysaccharides (e.g., dietary fiber or non-starch polysaccharides) is associated with a decreased risk of colorectal adenoma and colorectal cancer" (*Eur J Canc Prev* 3:57-62, 1999).

Recommendation: Vegetables and whole-grain cereals should be consumed in high amounts and should be a major component of the diet.

- 1999 Colon Cancer Prevention Program Project: "13.5 grams of wheat bran per day decreases the recurrence rate of adenomatous colon polyps" (*Am J Med* 106[1A]:435-455, 1999).

- 1999 The Seven Countries Study Conclusion (Croatia, Finland, Greece, Italy, Japan, Netherlands, Serbia, U.S.): "High fiber intake was strongly associated with low colorectal mortality. An increase of 10 grams in the daily intake of fiber was associated with a 33% lower risk of 25-year colorectal cancer mortality" (*Int J Cancer* 84:174-179, 1999).

Recommendation: Increase the daily intake of fiber by 10 grams.

- 1998 European Cancer Prevention Consensus Panel: "A diet rich in high-fiber cereal is associated with a reduced risk of colorectal cancer" (*Eur J Canc Prev* 7[suppl 2]:S1-S3, 1998).

- 1997 American Dietetic Association Position: "Results of all studies provide substantive evidence that intake of fiber-rich foods is inversely related to risks of both colon and rectal cancers. It is estimated that the risk of colorectal cancer in the U.S. population could be reduced by about 31 percent if fiber intake from food sources were increased by an average of about 13 grams per day" (*J Am Diet Assoc* 97[10]:1151-1159, 1997).

Recommendation: Promote food intake patterns consistent with the Food Guide Pyramid. This recommends a wide variety of plant foods to achieve adequate fiber intakes in healthy children and adults. Include at least 2 to 3 servings of whole grains as part of the daily 6 to 11 servings of grains, 2 to 4 servings of fruits, and 3 to 5 servings of vegetables daily, and legumes at least once or twice a week.

- 1995 Australia: "Reduction in the incidence in large adenomas was observed when a low-fat diet was combined with high-fiber wheat bran supplementation of 25 grams per day" (*JNCI* 87:1760-1766, 1995).

Recommendation: 25 grams of fiber daily.

- 1994 United Nations Food and Agriculture Organization: "High fiber intake consisting of vegetables and cereals was protective against colorectal cancer" (*Eur J Canc Prev* 7[suppl 2]:S11-S17, 1998).

### RISK/BENEFIT OF DAILY CONSUMPTION OF FIBER

According to the National Academy of Science, over 40% of North Americans are likely to develop cancer and at least half of them will die from it. The cancer incidence worldwide is increasing. The majority of health budgets will be spent on treating cancer in most developing countries.

Cancer is largely preventable. Fewer than 5% of cancer cases are linked to genetics.

Overwhelming evidence supports the statement that "the consumption of fiber may reduce the risk of colorectal cancer." In fact, based on the volume, credibility, and reliability of the scientific facts, we are convinced that fiber can, not may, but can reduce the risk of colorectal cancer.

### AMOUNT OF FIBER

Depending on the study, North Americans typically consume only about 8-15 grams of fiber each day. Most of the consensus reports recommend 25 to 35 grams of fiber each day to protect against colorectal cancer. Unless North Americans have the time or inclination to become a grazing animal, it would be difficult to attain the protective level of fiber each day without taking a supplement.

### CONCLUSION

- Dietary fiber is safe.
- Hundreds of studies, involving tens of thousands of subjects, demonstrate that 25 to 35 grams of dietary fiber daily can reduce the risk of colorectal cancer.

- Decreased risk is most convincingly linked to fiber from vegetables, followed by fibers from non-soluble polysaccharides, starches, and fiber foods with carotenoids.

- Supplemental wheat bran in the amount of 13.5 grams per day can decrease the recurrence rate of adenomatous colon polyps.

- Since North Americans typically consume an average of only 8 to 15 grams of fiber per day, a dietary fiber supplement may be warranted.

- Currently, 40% of North Americans will develop cancer and the incidence is rising. If preventive measures are not instituted, the cost to the United States and its people will be enormous in terms of dollars, lost productivity, and lives lost.

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Nicole L. Simone, B.S.E., graduated from the Bioengineering department of the University of Pennsylvania. She is currently a medical student at UMDNJ, and is the co-manager of the Laser Capture Microdissection (LCM) Lab. She is also co-director of the Proteomics Branch of the Cancer Genome Anatomy Project at the National Cancer Institute, National Institutes of Health. She has written several articles for journals such as *Science* and *The Lancet*. In addition, she is co-inventor of a technique for protein analysis from microdissected tissue.



Charles B. Simone, II, attends the University of Pennsylvania. He has written articles for journals such as *The Lancet*. He is the recipient of numerous awards, including the USA Today National High School Academic All-Star Team, and Toyota Community Scholars Regional Scholarship. Nicole and Chuck help educate cancer patients and their families about healthy lifestyle modification. They both helped to spearhead the KID START program, designed to teach children, through seminars and health fairs, about healthy lifestyles.

**ATTACHMENT 3**



- b. The second trial studied 1303 people in a 34 month period.<sup>2</sup> Some subjects were asked to consume either a high-fiber supplement (13.5 grams/day) or a low-fiber supplement (2 grams/day). Measurement of compliance was even more "challenging." Compliance with the protocol was evaluated primarily by counts of returned cereal boxes and fiber bars at each visit and secondarily through a specialized intake calendar. Weights and cholesterol levels were not indicated in the paper. Any conclusions based upon this study would be invalid because of a lack of assurance of compliance with trial protocols in the treatment or the control groups. Most of the subjects in this trial were male and had an average age of 66.
6. In reviewing the results of the trials, NCI scientists offered the following as an attempt to explain why the studies' designs did not show an effect of diet on polyp recurrences:<sup>3</sup>
1. Development of colorectal cancer takes decades; an intervention of three to four years may not be long enough.
  2. Nutritional factors may influence critical molecular, cellular, or tissue-level events in colorectal cancer formation well before polyps are formed.
  3. The recurrent polyps tended to be small. Dietary changes might affect only the growth of small polyps into large polyps or large polyps into invasive cancers.
7. Although the points raised by NCI are important, the conclusions of both studies are invalid because there is little or no evidence of compliance and therefore no confirmation of the amount of fiber consumed by either the treatment groups or control groups. The flaws in the study render them outliers, not useful in assessing the weight of scientific evidence concerning the fiber/colorectal cancer association. There is little doubt, based on the overall body of publicly available scientific evidence, that a high-fiber diet reduces the risk of colorectal cancer.<sup>4</sup> Well-designed and reliable studies that stand for this latter proposition are described in the European Cancer Prevention (ECP) Consensus Statement, The Review of Food, Nutrition, and the Prevention of Cancer: A Global Perspective, and the World Health Organization (Exhibit B).

September 20, 2000  
Date Executed

Charles B. Simone MD  
Charles B. Simone, M.M.S., M.D.

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<sup>2</sup> Alberts DS, Martinez ME, Roe DJ, et al, and the Phoenix Colon Cancer Prevention Physicians' Network. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. *N Eng J Med.* 2000; 342:1156-62.

<sup>3</sup> NCI "Trials Show No Effect of Low-Fat, High-Fiber, and High-Fruit and Vegetable Diets on the Growth of New Colorectal Polyps in People with a History of Precancerous Polyps." NCI Press Release, April 19, 2000, [www.nih.gov/news/pr/apr2000/nci-19.htm](http://www.nih.gov/news/pr/apr2000/nci-19.htm).

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## CHARLES B. SIMONE, M.MS., M.D CURRICULUM VITAE

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Date and Place of Birth: June 21, 1949 in Trenton, NJ

Marital Status: Married, two children.

Military Service: 1977-1982 Commander, U.S. Navy, Public Health Service

### Education:

1967-1971 - B.A. (Biological Sciences) - Rutgers University, New Brunswick, NJ

1971-1975 - M.MS. and M.D. - Rutgers Medical College, Piscataway, NJ

### Positions Held:

1967-1971 Research Assistant to Ralph J DeFalco, Professor of Immunology, Rutgers University, New Brunswick

1970-1972 Consultant for criminal investigations requiring immunological corroborations.

1971-1972 Acting Chairperson of Rutgers University Serological Museum.

1974-1975 Research Appointment with Robert A. Good, Ph.D., M.D., President and Director of Memorial Sloan Kettering Cancer Hospital, New York City.

1975-1976 Internship, Department of Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

1976-1977 First Year Assistant Resident, Department of Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

1977-1979 Clinical Associate, Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD.

1978-1980 Clinical Assistant Professor of Medicine, George Washington University School of Medicine, Washington, D.C.

1979-1980 Clinical Associate, Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD.

1980-1982 Investigator, Clinical Pharmacology Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD.

1980- present Founder, Director, Simone Protective Cancer Institute, Lawrenceville, NJ.

1982-1985 Radiation Therapy Department, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

1984-1989 Consultant, New Jersey Education Oncology Program.

1984-1987 Advisor, U.S. Postal Service, Preventive Health.

1984-present Speaker for the American Cancer Society.

1985-1988 Associate Professor, Radiation Therapy and Nuclear Medicine Department, Thomas Jefferson University Hospital, Philadelphia, PA.

1985-1988 Chief, Breast Section, Radiation Therapy and Nuclear Medicine Department, Thomas Jefferson University Hospital, Philadelphia, PA.

1985-1989 Consultant, Immunobiochemistry for BASF

1985-1988 Chairman, Publication Review Committee, Thomas Jefferson University Hospital, Philadelphia, PA.

1986-1991 Consultant for Hoffmann-LaRoche, Nutley, NJ. "Protector Nutrient" Program.

1986-1988 Member, Jefferson Hospital Nutrition Committee.

1986-1988 Speaker for Jefferson Educational Program

1988-1992 Medical Advisor to NJ Governor - Substance Abuse

1989-1991 Consultant to Spain

1989-pres Consultant to Cambodia

1989- pres Consultant to Russia

1990-pres Medical Advisor to National Alliance of Breast Cancer Organizations

1991-pres Consultant to Chechen

1993-pres Advisor to US Senators Tom Harkin and Orin Hatch

1993-1995 Advisor for organization and implementation of Office of Alternative Medicine, National Institutes of Health

1993-pres Consultant to U.S. Senate, Expert Witness

1993-pres Consultant to U.S. House of Representative, Expert Witness

1994 Consultant to Senate Committee: I wrote the language that assured passage of the Dietary Supplement Health and Education Act of 1995 that ensured that all Americans have free access to food supplements.

1995 Consultant to New Jersey Medical Board, Expert Witness

1996-pres Advisor for organization and implementation of Department of Alternative Medicine,

College of Physicians and Surgeons of Columbia University, New York

1997 Judge for Mrs. America Pageant

1997 Participant in National Cancer Institute and Office of Alternative Medicine POEMS Conference

1998 Consultant to U.S. House of Representative, Expert Witness

1998 Consultant to U.S. Senate, Expert Witness

1998 Judge for Mrs. America Pageant

1998-pres Organizing new health care system for Chechen.

1998-pres Editor, Women's Health Alternative Medicine Report

Certification:

Diplomate of the National Board of Medical Examiners 1976

American Board of Internal Medicine, Eligible 1978

Medical Oncology Subspecialty Board, Eligible 1980

Allergy and Immunology Board, Eligible 1980

Radiation Oncology Subspecialty Board, Eligible 1983

Honors:

Honorable Mention Award - SAMA Research Forum April 1973

Visiting Professor in Rheumatology, Cleveland Clinic 1979

Visiting Professor in Clinical Immunology, University of Hawaii 1979

Elected into New York Academy of Sciences 1983

Elected into American College of Immunologists 1983

American Academy of Sciences 1984

Elected, Who's Who in Frontiers of Science and Technology 1984

Elected, Contemporary Authors 1984

Author Citation Award, Nineteenth Annual New Jersey Writers Conference, NJ Institute of Technology, 1986

Visiting Professor in Immunology and Oncology, Cleveland Clinic 1987 and 1989

Invited/Special Lectures:

Lecture to Radiation Therapeutic Oncology Group 1983

Keynote Speaker - 18th Annual Congress, AACIA 1984

Keynote Speaker - Annual Cancer Symposium, University of Louisville 1985

Speaker - New Jersey State Justice Department 1985

Speaker - United States Arsenal, Picattiny, NJ 1985

Keynote Speaker - New Jersey Superintendents' and Principals'

Keynote Speaker - New York Open Center 1986

Keynote Speaker - New Jersey Superintendents' and Principals' Convention 1986

Keynote Speaker - New Jersey State Kiwanis 1985

Speaker for Jefferson Outreach Program

Keynote Speaker - New Jersey Superintendents' and Principals' Convention 1989

Please see Media Events for a More Complete Listing of all Speaking Engagements.

Societies:

New York Academy of Sciences

American College of Immunologists

American Academy of Sciences

Contemporary Authors

Military Service:

1977-1982 Commander, U.S. Public Health Service, Navy

Licensed to Practice Medicine:

New Jersey  
Pennsylvania  
Ohio  
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12. Simone, C.B., and C.Mansfield. 1987. Perioperative Ir-192 implant at time of lumpectomy for breast cancer. *Radiology.* Nov Supplement.
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15. Simone, Charles B. 1993. How to reduce America's runaway health care costs. *Federal Register.* Subcommittee of the Committee on Appropriations United States Senate, Senator Tom Harkin.

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19. Simone, Charles B. 1994. The Scientific Standard Already Exists for Food Supplement Health Claims. Federal Register. I wrote the language that assured passage of the Dietary Supplement Health and Education Act (DSHEA) of 1995 that ensured that all Americans have free access to food supplements.
20. Mansfield, C.M., Komarnicky, L.T., et al. 1994. The role of radiotherapy in the treatment of breast cancer: results of perioperative implantation. Cancer Detect Prev. 18(6): 493-499.
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For other articles, papers, or chapters written by me for the lay audience, please refer to Print Media.

# Consensus meeting on cereals, fibre and colorectal and breast cancers.

## ECP consensus panel on cereals and cancer

This Consensus Meeting was held in Santa Margherita, Italy 2-5 October and was attended by 17 experts in the field of diet and cancer; a further 5 who could not attend the discussions were 'corresponding participants' and gave their views by post and telephone. The agreed consensus statement was as follows:

- A diet rich in high-fibre cereal is associated with a reduced risk of colorectal cancer.
- There is suggestive evidence that cereal fibre protects against breast cancer.
- There is good reason to examine the relationship between cereal fibre intake and risk of cancer at other sites.

### Introduction

All plant foods contain plant cell walls containing dietary fibre (DF) and a range of other agents which are suspected to be protective or anticarcinogenic (eg vitamins, antioxidants, tannins, polyphenolics, flavonoids etc). In general vegetables contain relatively modest amounts of DF but are rich in a wide array of protective agents and anticarcinogens, the amounts and classes of which vary between vegetable type. Whole grain cereals are relatively rich in DF and also contain protective agents such as phytate and a range of anticarcinogens. However these latter are partially removed with the husk during milling. Fruits contain the least DF but contain an array of anticarcinogens which differ from those in cereals and vegetables.

Current hypotheses suggest that fruit and vegetables protect against cancer at a wide range of sites mainly through the action of their anticarcinogens. In contrast cereals have been assumed in the past to act mainly through the action of DF.

In this Consensus Statement 'cereal fibre' will imply cereal retaining a high proportion of its husk (and the accompanying anticarcinogens) intact.

In Europe cereals may be consumed as breakfast cereals which are often rich in DF and also rich in

B vitamins and protective agents. At other times of day cereals are usually eaten as breads, pasta, rice, pastries etc. These are usually made from low extraction cereals which contain lower levels of DF and other protective agents and anticarcinogens; whole-meal breads and products are richer in both.

Different cereals contain different amounts of DF and anticarcinogens (rice has least and wheat and rye have most of both). Further, rice, which is most commonly eaten in Europe in the southern countries, is almost always eaten in polished and refined form and so contains even less DF and anticarcinogen than usual. The cereals which are most often consumed in unrefined and high extraction form are wheat and rye, but rye is rarely consumed in the southern countries.

The postulated mechanisms of action indicate that the protective action will be greater in the unrefined cereal than in that in which the husk has been removed by milling. In most epidemiological studies the cereals are primarily low extraction products and so are low in DF and other protective agents. A major conclusion was that, in future, questionnaires should be framed to distinguish between low extraction and high extraction cereals.

## Colorectal cancer

*A diet rich in high fibre cereal is associated with a reduced risk of colorectal cancer.*

In support of this we cite the review of 58 previous studies of diet and colon cancer; cereal fibre was measured in only 19 studies. Of these, 16 reported an inverse association between cereal fibre and colon cancer risk and the other 3 showed no relation. In addition a review of FAO data showed that there is an inverse relation between the risk of colorectal and of breast cancer and cereal and vegetable disappearance, no relation with fruit and starchy root intake, and a positive correlation with total energy intake. The data are consistent with those from the Italian study where, in the context of the Italian diet, high consumption of pasta was shown to be a major contributor to high total energy intake and was partly or largely related to the risk for cancers of the colon and breast. This suggested that the real association was with total energy intake. This consensus reaffirms and extends that reached by the Colon Group at the WHO Consensus Conference in Stuttgart in 1996 (*European Journal of Cancer Prevention* 6 404-407), and with the COMA recommendations in the UK.

A variety of mechanisms has been proposed for the protective effect of cereal fibre. Burkitt popularised the idea that a diet high in fibre-rich foods could influence the course of colorectal carcinogenesis. He proposed that it was fermentation of the fibre itself that gave the protection through (a) increased faecal weight, (b) increased frequency of defecation, (c) decreased transit time, and (d) dilution of the colonic contents. The evidence is strongest for (a) and (d). In addition he proposed that fibre metabolism influenced microbial growth in the colon – an area about which we know very little. More recently, mechanisms involving the metabolic consequences of fibre metabolism have been proposed including (c) alteration of energy metabolism. It is now generally accepted that energy restriction will inhibit carcinogenesis and a fibre-rich diet may make a contribution to overall energy management; (f) influence on bile acid metabolism, a theory that refuses to go away; (g) production of short-chain fatty acids (SCFA) which may inhibit carcinogenesis through its effect on colonic pH and through the supply of butyrate. This latter has been shown *in vitro* to promote apoptosis and cell differentiation, both of which are central to the carcinogenesis process. *In vivo* verification of these actions is still awaited.

Apart from fermentable cell wall polysaccharide and starch, cereal foods also contain phenolic substances and phytate which may be important intraluminal antioxidants. Faecal material containing trace quantities of free iron has been shown to be a source of free radicals which can probably enhance the production of carcinogens, or damage crypt cell DNA directly. Phytate can chelate iron and hence suppress intraluminal free radical production. Moreover phenolic substances such as flavonols and tannins are effective antioxidants and may quench free radical mediated chain reactions in the gut lumen. Phytates and other low molecular weight species associated with plant cell walls may also act as anticarcinogens by upregulating epithelial cell differentiation, suppressing mitosis or stimulating apoptosis and thereby deleting potentially cancerous cells from the mucosa.

An exciting area which is receiving more and more attention recently is the interaction between environment and genes in the colon. Mutations in several genes controlling cell division, apoptosis and DNA repair have been implicated in tumour development. Already some of this work has implications for the effect of dietary fibre on colon cancer development. Perhaps the most interesting to date is the observation that the short chain fatty acids (SCFA) acetate, propionate and particularly butyrate can induce apoptosis in colonic cells in culture; this gives a plausible hypothesis for the protective action of fermentable fibre in colorectal carcinogenesis. In addition there is evidence that gut factors, including bile acids and SCFA can (i) interact with mutated APC gene, (ii) modulate expression of the p53 tumour suppressor gene, and (iii) modulate expression of transcription factors important in control of cell division. We now need to characterise the interaction of fibre components in the lumen with the above gut factors to ascertain whether fibre is indirectly affecting gene expression in the colon. For example, colonic fibre may be influencing the control of cell division through effects on formation and solubility of secondary bile acids in the colonic lumen.

## Breast cancer

*There is suggestive evidence that cereal fibre protects against breast cancer.*

Although there are many epidemiological studies showing a protective effect of cereal fibre, some others show no such effect and there is insufficient evidence to reach a strong conclusion. The WHO Consensus Group on Breast Cancer, in Stuttgart,

concluded that the epidemiological evidence was suggestive of a protective effect (as did we) and went on to suggest that cereal fibre consumption should therefore be increased.

It is generally accepted that high levels of circulating oestrogens and insulin growth factor (IGF-1, part of the insulin-resistance syndrome together with abdominal obesity, high plasma insulin levels and other hormonal changes) represent major risks for the development of breast cancer. This is because they induce (oestrogens) or are (IGF-1) growth factors for mammary tumour cells. It has been proposed that a high intake of fibre affects the risk of breast cancer through an effect on these factors. Diets low in fat and rich in cereal fibre reduce levels of plasma oestradiol, oestrone and oestrone sulphate. This may be through interfering with their enterohepatic circulation and so increasing their rate of faecal excretion. Dietary fibre contains phytoestrogens (isoflavonoids), which could modulate the activity of endogenous oestrogens. Fibre intakes have also been shown to be inversely related to total, subcutaneous and extra-abdominal fat and to lower insulin levels. These findings reflect the influence of fibre in controlling aspects of the insulin-resistance syndrome. Other mechanisms have been proposed which include the trapping of carcinogens, the regulation of cell proliferation, through a direct effect of isoflavonoids such as genestein and apigenin on the cell cycle, or through an activation of the PKC.

### Other sites

*There is good reason to examine seriously the relationship between cereal fibre intake and cancer at other sites.*

An analysis of the Italian data suggested that people who reported consuming whole grain cereals were at a lower risk of cancer at a range of other sites in addition to the large bowel and breast. There were many potential confounding factors that could explain these Italian data, and they need to be confirmed. However there are good theoretical reasons for suspecting such a general protective effect. If the mechanisms proposed to explain the protective effects against breast cancer are true then we would expect them to apply also to other hormone-related cancer sites such as the endometrium, ovary and prostate. Carcinogen binding in the colon lumen might also give rise to a generalised protection, and the presence of isoflavonoids, tannins and other phenolic compounds in the cereal husk would provide a

mechanism similar to that proposed for vegetables and fruits. If such a generalised protection was confirmed it would of course strengthen the recommendation to increase intake of high fibre cereals.

### General Recommendations

- Questionnaires need to be directed in future also to the study of food groups (eg cereals) rather than nutrients or anutrients (eg dietary fibre), since the latter are highly heterogeneous and not necessarily well quantitated.
- In view of the data presented in the review by Hill (1997), a pooled analysis of the foods and food group rich in cereals and cereal fibre to determine the importance of cereal fibre in the case-control and the cohort studies of diet and colorectal cancer should be carried out.
- Many of the effects of dietary fibre in protecting against colorectal and breast cancers are concerned with events in the caecum and proximal colon. We need to understand much more about the ecology of this important but experimentally inaccessible subsite of the large bowel.

### Signatories to the consensus statement

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