Wheat bran as a means of cancer chemoprevention

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Wheat bran has been widely promoted as a means of cancer chemoprevention, and especially of colon cancer chemoprevention. Nonetheless, there has only been limited evaluation of its actual chemopreventive utility. The Wheat Bran Fiber Trial, a 3-year phase III clinical trial designed to assess the effect of a wheat bran fiber (WBF) intervention on the recurrence of adenomatous polyps, tests the use of fiber as protective against colon cancer. Subjects of 40–80 years of age who had had one or more colorectal adenoma(s) 3 mm or larger identified and removed were recruited from sites in the Phoenix metropolitan area. A total of 1429 participants who successfully completed a 6-week placebo run-in were randomized to a high (13.5 g/day) or low (2 g/day) placebo WBF intervention. Data and specimens collected at baseline and each year throughout the intervention included dietary food frequency; physical activity frequency and intensity; smoking, alcohol, illness and medication history; other risk factor information; blood specimens; rectal biopsies; and polyp tissues. Toxicity monitoring and adherence assessment have been conducted at each study visit. A final colonoscopy conducted 3 years after randomization will be used to assess the effect of the intervention. Among the randomized participants, the majority are male (66%) and white (96%), with a mean age at baseline of 66 years. Monitoring of study subjects at 1 year revealed that the intervention has resulted in a change of 9.5–10 g/day of dietary fiber. The intervention has resulted in little to no change in the intake of other foods that provide fiber. It has had little to no impact upon the intake of micronutrients. At 1 year of intervention, wheat bran fiber appears to have had no impact upon obesity or upon blood lipids. The study will be completed in early 1999.

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lorectal cancer is a major cause of morbidity and mortal- in the USA and is expected to account for approximately 000 cases and 55 000 deaths in 1997.[1] Present incidence u suggest that approximately 6% of Americans will elop colorectal cancer sometime over their lifetime.[2] The jority of colorectal cancers arise from the premalignant on, the adenomatous polyp.[3] Although removal of these ons has been shown to substantially reduce the risk of orectal cancer,[4,5] the logistics of adenoma removal present rmidable obstacle; clearly, some form of chemo- ention is desirable.

Given the public health burden of colorectal cancer, a stantial amount of research has been devoted to the study diet in its etiology. Among the various hypotheses, the st widely recognized is that a diet rich in fiber-containing ds is protective while one high in fat, particularly animal and red meat, is deleterious.[6,7] It has been hypothesized fiber and fat operate through their alteration of bile acids volatile fatty acids: fiber as inhibiting the formation of se, while fat as enhancing it. More recently, investigation etabolic variation among people has suggested that the act of diet upon risk could involve substantial individual ability.[8,9]

Insoluble fibers such as wheat bran are thought to exert protective effect against colon cancer by adsorbing nogens in the gastrointestinal tract. These adsorbed nogenic agents can then be carried out of the body, mini- ng their potential for carcinogenesis.[10] Wheat bran fiber (WBF) has received special attention due to its potential as a daily fiber supplement in colon cancer prevention. Results of some studies of WBF supplementation in humans have shown that it can decrease fecal mutagenicity and reduce concentrations of fecal bile acids.[11–13]

A previously conducted phase II trial assessed the effects of a 9-month WBF and calcium carbonate supplementation on colonic cell proliferation rates and on fecal bile acid concentration and excretion rates.[14] That study indicated that one of the ways by which high WBF and calcium intakes may reduce colorectal carcinogenesis is through a reduction in fecal bile acid concentrations. No reduction in cellular proliferation rates was observed, although the pertinence of cellular proliferation to colonic neoplasia is debatable. Given the extent of interest in the use of WBF as a protective agent, it is striking that there have been no large, long-term, randomized, placebo-controlled trials of the ability of WBF to protect against the formation of even the precursors of colon cancer.

The WBF Trial is designed to assess the effect of supplementation with a WBF intervention on the recurrence of adenomatous polyps among individuals with a recent history of these lesions. This article summarizes the design of the study,

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the characteristics of the study participants at study entry, and the initial impact of the intervention upon dietary practices and key physiologic characteristics of study subjects.

Methods

Study design and patient enrolment

The WBF study is a double-blind, high versus low fiber phase III trial designed to measure the effects of WBF supplementation (13.5 g/day versus 2.0 g/day) for 3 years on adenoma recurrence. Men and women aged 40–80 years who had undergone the removal of one or more colorectal adenoma(s) 3 mm or larger at colonoscopy within 3 months prior to study entry were recruited from three clinical sites in the Phoenix metropolitan area. Eligibility and exclusion criteria are outlined in Table 1.

As part of the screening protocol, the Arizona Food Frequency Questionnaire (AFFQ) was used to assess dietary intake. Based on this assessment, initial dietary eligibility was evaluated. The AFFQ screening criteria for eligibility included energy intake greater than 67% of recommended intake, calcium intake greater than 500 mg/day, and fiber intake of less than 30 g/day. Participants not meeting these criteria were interviewed by the project nutritionist using a different dietary assessment instrument to confirm their status; those not meeting the calcium intake criteria were given the option of increasing calcium intake in order to become eligible.[15]

The Institutional Review Boards of the participating Phoenix-area hospitals and the University of Arizona reviewed and approved the study protocol. Internal and external advisory committees were established to monitor the progress and safety (including all deaths and adverse gastrointestinal events) of the study. Results from the study, including recruitment, adherence, toxicity, adverse events and preliminary end-points, were presented at regular intervals to the External Data Safety and Monitoring Committee.

Recruitment and randomization

Recruitment for the study began in September 1990 and concluded in January 1995. Participants entered the randomization phase of the study between February 1991 and July 1995. During the screening phase, 4705 individuals were identified as potentially eligible for the trial. Of this number, 2088 (44%) declined to participate, 1006 (21%) were found to be ineligible, and 102 (2%) dropped out prior to initiation of study run-in. Thus, 1509 participants entered the 6-week run-in period. This phase, consisting of a low WBF intervention (2 g/day), allowed time for the completion of required

Table 1. Inclusion and exclusion criteria in the Wheat Bran Fiber Trial

Inclusion criteria

- Male and female individuals, ages 40–80, who had removal of one or more colonic adenoma(s) 3 mm or larger at colonoscopy within the 3 months prior to study entry. All other colon polyps above the rectum must have been removed
- Must have adequate nutritional status as determined by the following:
  - (a) had adequate energy intake as determined by the Arizona Food Frequency Questionnaire. Individuals with inadequate intakes were interviewed by a nutritionist to confirm this status
  - (b) serum albumin ≥ 2.5 g/dL
- Had normal renal and liver function defined as serum creatinine ≤ 1.5 mg/dL, serum bilirubin ≤ 2.0 mg/dL, SGOT or SGPT ≤ normal and alkaline phosphatase < 2-fold normal
- Met Southwest Oncology Group performance status criteria of 0–1 (0 = fully active, able to carry on all pre-disease activities without restriction (Karnofsky Scale 90–100); 1 = restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (Karnofsky Scale 70–80))
- Were residents of the greater Phoenix, Arizona metropolitan area including the suburbs of Mesa, Tempe, Scottsdale, Peoria, Sun City, Sun City West, Glendale etc. with no plans to move in the next 36 months
- Were able to provide own transportation and be willing and able to keep required study visits to complete study procedures and questionnaires
- Signed informed consent approved by the University of Arizona Human Subjects Committee
- Successfully completed the run-in period

Exclusion criteria

- Individuals who had invasive cancer (i.e. non-skin cancer) within the past 5 years or who were anticipating further radiation or chemotherapy
- Individuals who had a colon resection of ≥ 20 cm or any resection of the right colon, ileum, jejunum, or ileocecal valve
- Individuals who had familial polyposis or non-polyposis familial colon cancer (i.e. > 3 first degree family members with colon cancer)
- Individuals with severe metabolic disorders or other life-threatening acute or chronic disease including:
  - (a) any severe cardiac disease which is unstable despite use of medication (e.g. daily diuretics, digitalis-type compounds, antiarrhythmic agents etc.)
  - (b) uncontrolled, severe hypertension
  - (c) poorly controlled diabetes mellitus
  - (d) unstable coronary artery disease
  - (e) a history of ulcerative colitis, regional enteritis or Crohn's disease
  - (f) hyperlipidemia requiring treatment with oral bile acid sequestering agents (e.g. cholestyramine)
- Dietary exclusions
  - (a) > 30 g of dietary fiber intake per day
  - (b) total calcium intake of < 500 mg/day; patients can agree to increase calcium intake to become eligible
  - (c) special diet which precludes compliance with study requirements
  - (d) unintentional weight change (i.e. gain or loss) of > 10% body weight in the 6 months prior to study

SGOT, serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

baseline procedures and provided an opportunity for evaluation of adherence to the intervention and study procedures.

Participants were blinded to the fact that the low fiber cereal was used during the run-in period. Participants had to have consumed at least 75% of the supplement to be eligible for randomization. A total of 1429 (95%) individuals successfully completed the run-in phase and were randomized. The intervention phase of the study will be completed in the latter part of 1998.

Participant visits and questionnaire administration

All baseline data collection and procedures were conducted during the screening phase of the study (Table 2). These included a blood collection, recording of medication use, and the administration of a variety of questionnaires which primarily focused on risk factor data (including dietary intake and physical activity). Colonoscopy and/or sigmoidoscopy information and polyp histology on the qualifying procedure were also obtained as part of the review for eligibility. After randomization, clinic appointments were scheduled every 3 months. Toxicity and adherence assessment as well as ascertainment of major medical events were conducted at all study visits following randomization. Blood samples and risk factor data, including the AFFQ and physical activity assessment, were collected annually throughout the course of the study. The lifestyle questionnaire, which assessed health behavior, was administered at the screening visit and at subject's last visit.

Dispensing of supplement and adherence assessment

The fiber supplement was dispensed at each visit. The supplement, provided by the Kellogg's Company, was available in three forms: loops, unsweetened, and sweetened shredded cereal. Cereals were color coded to six color groups to help maintain the study blinding. A combination of the cereal forms was dispensed according to the participant's choice. In 1994, a fiber bar was developed and made available to participants who had completed the second year of the study. Participants were allowed to consume up to 25% of their fiber supplement in the form of fiber bars. The fiber bars were introduced to add variety.

Table 3 describes the fiber composition of the supplement forms. The initial intent of the study was to contrast an extremely low-fiber supplement of 2 g/day to a high-fiber supplement of 13.5 g/day. However, evaluation of the different supplements indicated that it was difficult to maintain blinding without the presence of fiber in most supplement forms in amounts larger than 2 g. The low-fiber bars proved difficult for subjects to consume without some risk of damage to teeth, and unpalatable, unless they contained 4 g of fiber. However, subjects found some forms, especially the high-fiber bars, unacceptable if they contained more than 10 g of fiber. Thus, the difference between high- and low-fiber doses was diminished in the interest of maintaining subject participation.

Participant adherence, monitored at each visit, emphasized two main indices: a fiber intake calendar and an adherence assessment record. In the former, participants recorded the amount of their daily supplement consumption; in the latter, the number of cereal boxes distributed minus the number returned was used to index the number consumed. Details on methodology and results of participant adherence have been published elsewhere.[16] Determination of total fiber consumption for each individual is based on the number of boxes of cereal and fiber bars dispensed, the number of unused boxes returned, adherence data, and the assessment of other dietary fiber consumption calculated from the AFFQ.

Ascertainment of baseline and recurrent polyps

Endoscopic and pathology reports were collected for each colonoscopy and flexible sigmoidoscopy reported by a participant during the course of the study. Guidelines were developed to aid in the consistent interpretation of these reports. Two reviewers who completed colonoscopy forms for data entry read each report. The colonoscopy report form included information on the completeness of the exam (to the cecum), the adequacy of the bowel preparation for visualization of the colon, and the location, size, histology, and method of removal for all polyps observed.

The histological slides and paraffin tissue blocks from all polyps removed during the qualifying colonoscopy and subsequent procedures while on the study were requested from

Table 2. Data and specimen collection schedule in the Wheat Bran Fiber Trial

Parameter	Baseline	Year of trial 1	2	3*
Questionnaire				
Medication use	+		+	+
Physical activity	+		+	+
AFFQ†	+		+	+
Tobacco use	+		+	+
Colon cancer prevention	+		+	+
Lifestyle questionnaire	+			+
Health history		+	+	+
Toxicity monitoring‡		+	+	+
Adherence assessment‡		+	+	+
Specimen Collection				
Blood collection	+	+	+	+
Rectal biopsies§	+	+		+
Colonoscopy/polyp tissue	+**	+††		+‡‡

*3–5 years depending on end-point colonoscopy; †Arizona Food Frequency Questionnaire; ‡updated at each visit throughout the study; §conducted on 345 participants at baseline, 198 in year 1 and 132 in year 3; **performed within 3 months prior to study entry; ††if in accordance with physician's recommendation; ‡‡performed + 6 months after 3 year completion of intervention.

Table 3. Dietary fiber content of supplement samples in the Wheat Bran Fiber study

Sample	Fiber (g) per serving
Low fiber	
Loops*	2.1
Unsweetened shreds†	4.0
Sweetened shreds†	3.0
Bars*	4.3
High fiber	
Loops*‡	12.8
Unsweetened shreds*‡	13.4
Sweetened shreds*‡	9.9
Bars*‡	9.8

*Analyses conducted at the University of Wisconsin; †product manufacturer information; ‡based on multiple samples.

the community pathologist. Retrieved specimens were processed through the project laboratory and the slides were forwarded to the study pathologist who reviewed the slides and documented the histology and level of dysplasia in the polyp. This diagnosis was compared with that of the community pathologist. When disagreements occurred, the slide was re-reviewed in a blinded manner by the study pathologist. Information on all diagnoses was retained in the database.

Statistical considerations and data analysis

The target sample size for the WBF Trial was 1400 randomized participants with an equal number of patients assigned to each study treatment group. Randomization to each treatment group was stratified by clinic. The design of the trial was based on the standard of care recommended at the time[17] which called for a colonoscopy sometime during the first year after the qualifying colonoscopy, allowing for the removal of polyps missed at baseline. The target sample size was based on an adenoma recurrence rate of 40% over the 3-year period and a baseline-polyp miss rate of 10–15%.[18] Additionally, based on a predicted dropout rate of 25% over 3 years it was estimated that 1050 participants would complete the intervention. Thus, based on a final sample size of 1050 participants and a one-tailed significance test at the 5% α-level, there will be a power of 0.82 to detect a 25% drop in polyp recurrence, and a power of 0.94 to detect a 30% drop.[19]

The WBF study design is similar to that of another large adenoma recurrence study initiated at the same time.[20] Thus, the effect of the intervention will be assessed based on the period between the 1-year and end-point colonoscopy. Allowing for early and late 1-year and end-point colonoscopies, this period of time will be between 1.5 and 5 years. For most subjects, it will be very close to 3 years. Initially, the randomization ratio, experimental:control subjects, was 1:1. However, interim analyses indicated that the dropout rate of the high-fiber treatment arm was higher than that of the low-fiber arm. Consequently, the randomization was redesigned to a ratio of high- to low-fiber participants of 4–1 for the remainder of the accrual period in order to compensate for this difference in dropout rates.

The end-point for the primary analysis of the WBF study is adenomatous polyp recurrence and will use the intention to treat approach. The primary explanatory factor in this analysis will be treatment group, low versus high fiber. Secondary analyses will evaluate age, markers of cell proliferation at baseline, history of previous polyps at baseline, dietary practices, and number and size of adenomas at the qualifying colonoscopy as predictors of polyp recurrence. Additionally, in a subset of participants, the effects of WBF intervention on fecal and blood bile acids at final colonoscopy will be assessed. All analyses will be carried out on the entire sample first and then by gender.

Participant accrual

The greatest rate of participants going off supplement in the WBF Trial occurred during the first year of the study, when approximately 2–3% of randomized participants went off the supplement at each visit. After 1 year, the percentage of participants withdrawing between visits dropped to between 1 and 2%, with some suggestion that the withdrawal rate dropped with the passage of time on the supplement. Based on these data, it is estimated that approximately 75% of the randomized participants will remain on the study through to completion with an end-point colonoscopy.

Baseline characteristics

Table 4 summarizes the baseline characteristics of the randomized individuals. The participants were for the most part men, mostly white, and married. The mean (± SD) ages of the participants in each group, respectively, were 65.7 ± 8.9 and 65.8 ± 9.0 years. One of the study clinics (Mesa) provided nearly 60% of both control and experimental study participants. The distributions of control and experimental subjects were similar. In energy intake, as well as in the intake of the macronutrients and most dietary constituents, the control and experimental subject distributions were equivalent. The intakes of fiber and of calcium among controls were essentially identical to those among experimental subjects. A greater proportion of control than of experimental subjects had a history of having smoked cigarettes. However, the years of smoking were virtually the same for experimental and control subjects who smoked.

A higher proportion of males (66%) than females (34%) were randomized into the WBF Trial as was the case in other clinical trials.[20,21] This difference was present even in the eligible pool of individuals. Of the initially identified colonoscoped patients, 3802 individuals were contacted for enrolment; of these 65% were males and 35% were females. A similar proportion of males and females were found to be eligible (1011 (65.5%) and 532 (34.5%)), were randomized

Table 4. Baseline characteristics of randomized participants in the Wheat Bran Fiber Trial by treatment group

Variable	Group 1 (n = 627)	Group 2 (n = 802)
Demographics		
Mean age, years (SD)	65.7 (8.9)	65.8 (9.0)
Male, n (%)	409 (65.2)	538 (67.1)
White, n (%)	600 (95.7)	771 (96.1)
Married, n (%)	513 (81.8)	663 (82.7)
Mean education, years (SD)	13.5 (2.4)	13.5 (2.6)
Clinic		
Sun City, n (%)	157 (25)	205 (26)
Phoenix, n (%)	113 (18)	139 (17)
Mesa, n (%)	357 (57)	458 (57)
Mean (SD) dietary intake		
Energy, kcal/day	1875 (636)	1941 (709)
Protein, g/day	72 (25)	74 (28)
Carbohydrate, g/day	233 (85)	235 (93)
Total fat, g/day	71 (32)	75 (35)
Dietary fiber, g/day	19 (8)	19 (8)
Dietary calcium, mg/day	853 (371)	858 (385)
Alcohol, g/day	6.1 (10.9)	8.1 (17.9)
Non-dietary factors		
Ever smoker, n (%)	346 (55.2)	399 (49.8)
Current smoker, n (%)	67 (10.7)	136 (17.0)
BMI,* mean (SD)	26.5 (4.3)	26.6 (4.5)
Aspirin use, n (%)	165 (26.3)	230 (28.7)
Previous polyp,† n (%)	210 (47.3)	272 (37.7)
History of cancer,†‡ n (%)	36 (6.0)	55 (7.4)

*Body mass index (kg/m^2) ; †numbers do not add up to total due to missing data; ‡personal history of cancer, excluding non-melanoma skin cancer. SD, standard deviation.

(947 (66.3%) and 482 (33.7%)), and have completed the protocol (461 (67%) and 227 (33%)). The cause for this difference in enrolment is most likely due to fewer women than men undergoing endoscopy for cancer screening or symptoms.[22] Clearly, this poses a challenge when conducting analyses by gender.

Results of wheat bran fiber intervention

As mentioned, the goal of this study was to evaluate a 13.5 g/day high-fiber dietary supplement against a 2 g/day low-fiber supplement as a means of decreasing the 3-year probability of adenomatous polyp recurrence. In this population of individuals at elevated risk of adenomatous polyps, however, long-term compliance in taking a high-fiber dietary supplement has proven difficult to implement and maintain. Large numbers of subjects withdrew from the study and others failed to take the full supplement consistently.

Table 5 summarizes the result at 1 year of intervention on the fiber intake of control and experimental subjects. These data were drawn from the AFFQ food frequency questionnaire, from the intake calendar, and from the adherence assessment instrument administered in the clinic. It can be seen that the total fiber intake of control subjects decreased by approximately 1.5 g per day, while that of experimental control subjects increased by approximately 8.6 g per day. As Table 5 shows, this increase was strictly the result of increased bread/cereal fiber intake: this is the category in which the wheat bran supplement was contained. Fiber in the other food sources did not increase and any changes among control subjects were mirrored among experimental subjects.

Table 6 describes changes in energy, fat, and saturated fat intake for control and experimental subjects. The data describing these changes were extracted from the AFFQ food frequency questionnaire. Although the intake of total energy, and of fat and saturated fat tended to decrease, the changes are essentially the same among experimental and control subjects: none of the differences for change among control as opposed to experimental subjects is statistically significant.

Table 7 describes the changes among control and experimental subjects in weight and in body mass index (BMI: weight in kilograms divided by the square of height in metres). It can be seen that the differences in weight and BMI change are trivial.

Table 8 summarizes the changes in blood lipids among control and experimental subjects after 1 year of study follow-up. It can be seen that control and experimental subjects are nearly identical in baseline levels of total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride. It can also be seen that the extent of change among control subjects is nearly identical to that among experimental subjects. There is little to suggest that the addition of this wheat bran fiber supplement to the diet of control and experimental subjects had any impact upon their lipid status.

Table 5. Baseline levels and changes in fiber intake (g/day), Wheat Bran Fiber Trial, by study group and by fiber source

Fiber source	Study group	Baseline	Change
Total diet fiber	Control	18.82	–1.53
	Experimental	18.50	8.65*
Beans, nuts, seeds	Control	1.72	–0.19
	Experimental	1.60	–0.05
Cakes, pastries, cookies	Control	0.44	–0.03
	Experimental	0.45	0.10
Salty snacks	Control	0.75	–0.05
	Experimental	0.69	–0.01
Bread, cereal	Control	4.30	–0.80
	Experimental	4.31	8.71*
Fruits	Control	5.74	–0.36
	Experimental	5.62	–0.20
Juices	Control	0.22	–0.04
	Experimental	0.18	0.01
Vegetables	Control	3.75	0.06
	Experimental	3.71	0.18
Mixed dishes	Control	0.71	–0.02
	Experimental	0.77	–0.04

*Difference in change statistically significant.

Table 6. Baseline and changes in nutrient intake: Wheat Bran Fiber Trial, 570 control and 651 experimental subjects with baseline and 1 year data

Nutrient	Study group	Baseline	Year 1	Change
Energy (kcal)	Control	1862	1814	–48
	Experimental	1926	1874	–52
Total fat (g)	Control	70.2	64.8	–5.4
	Experimental	73.7	67.9	–5.8
Saturated fat (g)	Control	23.1	21.8	–1.3
	Experimental	24.5	22.9	–1.6

Discussion

Double-blind, placebo-controlled clinical trials involving a nutrient intervention have primarily used nutrients in pill form.[21,23,24] These interventions usually do not change the intake of other dietary elements. However, an individual's diet does not consist of single nutrients. Food items are comprised of several nutrients that may affect disease risk. Therefore, it is not always appropriate to equate nutrient intake

Table 7. Baseline and changes in weight and body mass index: Wheat Bran Fiber Trial, 570 control and 651 experimental subjects with baseline and 1 year data

Lipid	Study group	Baseline	Year 1	Change
Weight (kg)	Control	79.1	80.2	1.1
	Experimental	79.5	80.4	0.9
BMI (kg/m^2)	Control	26.5	27.1	0.6
	Experimental	26.5	27.0	0.5

BMI, body mass index.

Table 8. Baseline and changes in blood lipids: Wheat Bran Fiber Trial, 570 control and 651 experimental subjects with baseline and 1 year data

Lipid	Study group	Baseline	Year 1	Change
Total cholesterol (mg/dL)	Control	218.8	215.4	–3.4
	Experimental	218.3	213.4	–4.9
High density lipoprotein (mg/dL)	Control	52.0	52.7	0.7
	Experimental	52.4	52.1	–0.3
Low density lipoprotein (mg/dL)	Control	131.1	126.5	–4.6
	Experimental	132.8	124.6	–8.2
Triglyceride (mg/dl)	Control	167.3	162.3	–5.0
	Experimental	163.6	165.2	1.6

with food intake. Clearly, the design and interpretation of intervention trials using food items present challenges not seen in those based upon the intake of a nutrient in the form of a pill. Some investigators[20,25,26] have designed studies using a dietary intake pattern as the intervention. The complexities and disadvantages associated with the conduct of such studies has been outlined by Lanza *et al.*[27]

In the WBF Trial, the intervention consists of a cereal supplement which allowed a high and low fiber intervention in a double-blind design. We do not yet know whether long-term intake of other nutrients or foods was differentially altered by the intervention. The 1-year data indicate that an intervention even as significant as this one appears to have no impact upon the intake of other fiber sources. It appears to have no impact upon the intake of macronutrients. Further, it appears to have no impact upon the lipid status and upon the BMI of experimental and control subjects. We will have the opportunity to assess this throughout the entire intervention phase due to our yearly administration of the AFFQ. If no dietary modifications occur during the intervention period, the observed effect on polyp recurrence will be largely attributable to the effect of the WBF intervention. An advantage of this intervention is its feasibility: it involves the adoption of a food item commonly available and already consumed by many in the general public (i.e. cereal).

One of the first and greatest challenges to health promotion by means of sustained dietary modification is identifying the changes that need to be made. The next challenge will be motivating people to make these changes. If the WBF intervention proves to be beneficial in terms of decreasing the probability that people form a lesion that is believed to increase the risk of colon cancer, there will be great interest in specific public health recommendations involving fiber intake. It is already widely believed that fiber derived from whole grains may decrease the risk of a range of chronic diseases.[28,29,2] However, the successful adoption of these recommendations by the general public will probably present a challenge. In this study, participants had to be strongly encouraged, in some cases cajoled, to continue taking a WBF supplement. Whether the general public would adopt the use of this supplement, even in the event of a result documenting a protective effect, is not entirely clear.

Among the drawbacks of the present trial is the difficulty of monitoring adherence. Although not as difficult to monitor as interventions changing entire dietary patterns, assessing actual consumption of cereal fiber is not as easy as monitoring pill taking. There are no generally accepted, easily obtained biologic markers of fiber ingestion. Stool samples can be monitored, but the use of these requires the collection of several days of stool: this presents an enormous burden for participants, decreasing participation rates and, among those who participate, compliance.

Adherence problems associated with WBF storage and the monotony of the intervention presented a challenge to the implementation of the trial. Clinical trials such as the WBF study require careful motivation of patients to adhere to the study regimen.

Adherence to the intervention was monitored throughout the trial. Every effort was made to accommodate participants' needs in order to prevent them from going off supplement. These included negotiations for dose reduction, provision of fiber bars for traveling, and mailing of supplement. Furthermore, as part of the protocol to minimize attrition, participants were offered the option of reducing their supplement dose if they were at risk of discontinuing supplementation.

Several organizations recently revised their recommendations for colorectal cancer screening based on new scientific evidence.[30–32] The widespread adoption of these recommendations by healthcare providers in Phoenix resulted in the exclusion of the year 1 colonoscopy among many participants enrolled in the latter part of the WBF Trial. Obviously, this will present a challenge in the analysis of the data as these will need to take into account the difference in ascertainment of recurrence.

A potential limitation of adenoma recurrence trials is the relatively short intervention period. Given the estimated duration interval in the adenoma to carcinoma sequence, it is possible that an effect confined to this stage of carcinogenesis may not be achieved with only a 3-year intervention. The average study participant is over 60 years of age. This participant will have been consuming the diet that preceded and may have contributed to his/her polyp formation for nearly 60 years; it can be argued that a 3-year intervention is not nearly enough to have an impact upon such an extended duration of neoplastic initiation. Clearly, although there is reason to suspect that a 3-year intervention should be adequate to alter the risk of polyp recurrence, the intervention period was selected partly as a compromise with the realities of dealing with funding periods in the USA. If results of the ongoing trials prove to be inconclusive, longer follow-up of these study groups or new trials implementing a longer follow-up period may be proposed. Nonetheless, this WBF study possesses excellent power and the ability to provide important and needed insight into the extent and mechanisms of the impact of WBF on the risk of the premalignant lesion that has been almost conclusively linked to colon cancer.

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