Short Communication

Design and Baseline Characteristics of Study Participants in the Wheat Bran Fiber Trial[1]

María Elena Martínez,[2] Mary E. Reid, José Guillén-Rodríguez, James R. Marshall, Richard Sampliner, Mikel Aickin, Cheryl Ritenbaugh, Barbara van Leeuwen, Nancy Mason-Liddil, Anna Giuliano, Perla A. Vargas, and David S. Alberts

Arizona Cancer Center [M. E. M., M. E. R., J. G-R., J. R. M., R. S., B. v. L., N. M-L., A. G., D. S. A.], Arizona Prevention Center [M. E. M., J. R. M., A. G.], and Department of Medicine [R. S., D. S. A.], University of Arizona Health Sciences Center, Tucson, Arizona 85724; Veterans Affairs Medical Center, Tucson, Arizona 85723 [R. S.]; Center for Health Research, Portland, Oregon 97227 [M. A.]; and Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland 21014 [P. A. V.]

Abstract

The Wheat Bran Fiber (WBF) trial is a Phase III clinical trial designed to assess the effect of a WBF intervention for 3 years on the recurrence of adenomatous polyps. Men and women, 40–80 years of age, who had removal of one or more colorectal adenoma(s) 3 mm or larger within 3 months prior to study entry were recruited from three sites in the Phoenix metropolitan area. After meeting eligibility criteria, 1509 individuals entered a 6-week run-in period, consisting of a low WBF (2 g/day) intervention. Participants (n = 1429) successfully completed this phase and were randomized to a high (13.5 g/day) or low (2 g/day) WBF intervention. Various data and specimens were collected at baseline and throughout the intervention phase, which included dietary intake, physical activity, other risk factor information, blood specimens, rectal biopsies, and polyp tissues. The study design called for a colonoscopy at approximately 1 year after the qualifying colonoscopy; thus, the period between the first year and the final colonoscopy will be used to assess the effect of the intervention, which is expected to be completed in the latter part of 1998.

Introduction

It is estimated that without preventive actions, about 6% of Americans will develop colorectal cancer sometime over their lifetime (1). The majority of colorectal cancers arise from the premalignant lesion, the adenomatous polyp (2), and removal of these lesions has been shown to substantially reduce the subsequent risk for colorectal cancer (3). An abundant amount of research has been devoted to the study of diet in the etiology of this malignancy. Among the various hypotheses, the most widely recognized is that a diet rich in fiber-containing foods is protective, whereas one high in fat, particularly animal fat and red meat, is deleterious (4). Insoluble fibers, such as wheat bran, are thought to exert their protective effect against colon cancer by adsorbing carcinogens in the gastrointestinal tract (5). Results of some studies (6, 7), including our own Phase II, placebo-controlled trial of WBF supplementation (8), have shown a decrease in fecal mutagenicity and reduced concentrations of fecal bile acids.

The WBF trial is a large, prospective, randomized clinical trial 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 and the characteristics of the study participants at the time of entry.

Materials and Methods

Study Design and Patient Enrollment. 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 of ages 40–80 years, who had 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 AFFQ[3] was used to assess dietary intake and evaluate dietary eligibility (9).

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 of the study (including review of all deaths and gastrointestinal adverse events and to monitor the safety of the intervention).

Recruitment and Randomization. Recruitment for the study began in September 1990 and concluded in January 1995. During the screening phase, 4705 individuals were identified as potentially eligible for the trial (Fig. 1). Of this number, 2088 (44%) declined to participate, 1006 (21%) were found to be ineligible, and 102 (2%) dropped out of the study 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 completion of required 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. Because the low fiber cereal used during the run-in period was different from cereals offered

Received 1/19/98; revised 5/18/98; accepted 6/30/98.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] This publication was supported in part by the USPHS Grant CA-41108 from the NIH.
[2] To whom requests for reprints should be addressed, at Arizona Cancer Center, University of Arizona Health Sciences Center, 1515 North Campbell Avenue, Tucson, AZ 85724. Phone: (520) 626-8130; Fax: (520) 626-5348.

[3] The abbreviation used is: AFFQ, Arizona Food Frequency Questionnaire.

Downloaded from cebp.aacrjournals.org on December 1, 2021. © 1998 American Association for Cancer Research.

Table 1 Inclusion and exclusion criteria in the WBF 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 AFFQ. 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, aspartate aminotransferase or alanine aminotransferase less than or equal to normal and alkaline phosphatase <2 times 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, and others 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 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 nonpolyposis 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 that is unstable despite use of medication (*e.g.*, daily diuretics, digitalis-type compounds, antiarrhythmic agents, and others).
  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 that 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 entry.

during the intervention, all participants faced a supplement change at randomization to maintain the blind. At the end of this period, participants who consumed at least 75% of the supplement became eligible for randomization into the trial, and those who consumed less than 75% were ineligible. A total of 1429 (95%) individuals successfully completed the run-in phase and were randomized to one of the treatment groups. It is anticipated that 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. 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, where toxicity, adherence assessment, and major medical events were ascertained. Blood collection for analyses and archival storage and risk factor data, including the administration of the AFFQ and assessment of physical activity, were collected annually throughout the course of the study. The life-style questionnaire, which assessed of aspects of health behavior, was administered at the screening visit and at the end of the study.

Dispensing of Supplement and Adherence Assessment. The fiber supplement, which was provided by the Kellogg's Company, was dispensed at each visit and was available in three forms: loops and unsweetened and sweetened shredded cereal. Cereal boxes were color coded to six groups to help maintain the blind. In 1994, high and low fiber bars were introduced to add variety to the fiber supplement available.

Participant adherence was monitored at each visit focusing on two main indices: a daily record where participants report the amount of supplement consumption and a record of cereal boxes returned at each visit. Formulas were developed to generate overall adherence scores; a score of 75% or greater was considered "good," whereas a score lower than 75% was classified as "non-adherence." Details on methodology have been published elsewhere (10), and results of participant adherence will be published after the completion of the study. Determination of total fiber consumption for each individual will be 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 assessed from the AFFQ.

Ascertainment of Baseline and Recurrent Polyps. Endoscopic and pathology reports were collected for each colonoscopy and flexible sigmoidoscopy reported by participants during the course of the study. Using guidelines developed to aid in the consistent interpretation of these reports, two reviewers completed colonoscopy forms for data entry. The reports 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 detected.

Histological slides and paraffin tissue blocks from all polyps removed during qualifying and follow-up colonoscopies were requested from the community pathologist. Retrieved specimens were processed through the project laboratory, and slides were forwarded to the study pathologist, who reviewed them and documented the histology and level of dysplasia in the polyp. This diagnosis was compared with that of the community pathologist, and when disagreements occurred, the slide was re-reviewed in a blinded manner by the study pathologist.

Downloaded from cebp.aacrjournals.org on December 1, 2021. © 1998 American Association for Cancer Research.

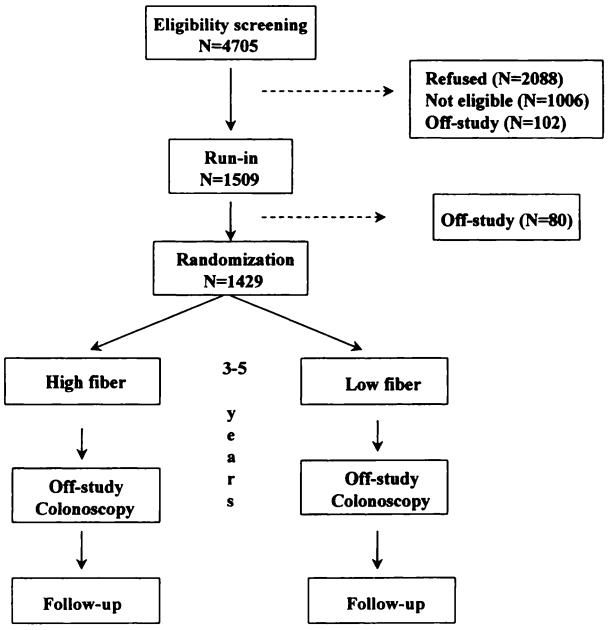

Fig. 1. Study schema of the Wheat Bran Fiber trial.

Statistical Considerations and Data Analysis. The target sample size for the WBF trial was 1400 randomized participants with an equal number assigned to each treatment group and stratified by clinic. The design of the trial was based on the standard of care recommended at the time (11), which called for a colonoscopy sometime during the first year after the qualifying colonoscopy, allowing for the removal of missed polyps at baseline. The target sample size was based on an adenoma recurrence rate of 40% over the 3-year period and a miss rate of baseline polyps of 10–15% (12), which is in accordance with published results from the trial by Greenberg *et al.* (13). 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 sample size of 1050 participants and a two-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 (14).

The WBF study had a similar design as another large adenoma recurrence study initiated at the same time (15), which also called for a colonoscopy at approximately 1 year after the qualifying colonoscopy. 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 3–5 years. Results of interim analyses indicated that there was a differential in dropout rates between the two treatment arms. Consequently, in January of 1994, the randomization was redesigned to a ratio of high to low fiber participants of 4:1 for the remainder of the accrual period to compensate for the difference in dropout rates.

Baseline Characteristics. Table 2 summarizes the baseline characteristics of the randomized individuals. The participants were for the most part males rather than females, mostly white, and married. The mean (±SD) ages of the participants in each treatment group were 65.7 ± 8.9 and 65.8 ± 9.0 years, respectively. A fairly equal distribution between the two groups was achieved for other potentially confounding factors; however, for cigarette smoking, distribution between experimental and control groups was not equal. Intake of total dietary fiber was nearly identical in both groups.

Table 2 Baseline characteristics of randomized participants in the WBF trial by treatment group

	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 (25.0)	205 (25.6)
Phoenix, n (%)	113 (18.0)	139 (17.3)
Mesa, n (%)	357 (57.0)	458 (57.1)
Mean (SD) dietary intake		
Energy, kcal/day	1874.8 (636.3)	1940.8 (709.4)
Protein, g/day	72.3 (24.7)	74.3 (27.5)
Carbohydrate, g/day	233.0 (85.1)	234.6 (92.6)
Total fat, g/day	71.0 (32.0)	75.1 (35.1)
Dietary fiber, g/day	18.8 (8.3)	18.5 (8.2)
Dietary calcium, mg/day	852.2 (371.4)	857.6 (384.7)
Alcohol, g/day	6.1 (10.9)	8.1 (17.9)
Nondietary factors		
Former smoker, n (%)	346 (55.2)	399 (49.8)
Current smoker, n (%)	67 (10.7)	136 (17.0)
BMI,[a] mean (SD)	26.5 (4.3)	26.6 (4.5)
Aspirin use, n (%)	165 (26.3)	230 (28.7)
Previous polyp,[b] n (%)	210 (47.3)	272 (37.7)
History of cancer,[b,c] n (%)	36 (6.0)	55 (7.4)
Family history of colorectal cancer,[d] n (%)	99 (15.8)	141 (17.6)

[a] Body mass index (kg/m^2).
[b] Numbers do not add up to total due to missing data.
[c] Personal history of cancer, excluding nonmelanoma skin cancer.
[d] Includes two or fewer first-degree relatives.

Follow-Up after Supplementation. To increase the total follow-up time beyond the 3-year intervention, follow-up of participants who either completed the study or who went off supplement prior to obtaining an end point colonoscopy was conducted. Consenting participants were initially contacted 6 months after having gone off supplement, and yearly telephone contacts were made thereafter. At these contacts, information regarding gastrointestinal symptoms, changes in medication use, follow-up colonoscopies, physical activity, and fiber intake was updated. In addition, permission to obtain copies of medical reports documenting additional off-supplement colonoscopies was requested from participants at all follow-up contacts.

Results and Discussion

Double-blind, placebo-controlled clinical trials involving a nutrient intervention in pill form are relatively nonintrusive in that they usually do not result in changes in dietary intake. However, because food items are comprised of nutrients as well as other components that may affect outcome, some trials of adenoma recurrence (15, 16) have used a dietary intake pattern modification as the intervention. Although there are several strengths to this type of approach, there are specific challenges associated with the conduct of such studies as outlined by Lanza *et al.* (17).

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 intake of

Downloaded from cebp.aacrjournals.org on December 1, 2021. © 1998 American Association for Cancer Research.

other nutrients or foods was differentially altered between the two groups. However, we will have the opportunity to assess this throughout the intervention phase due to the 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 because it involves the adoption of a food item commonly available to the general public (*i.e.*, cereal). If the WBF intervention proves to be beneficial, specific public health recommendations can be made; however, the successful adoption of these recommendations by the general public may present a challenge.

Several organizations recently revised their recommendations for colorectal cancer screening based on new scientific evidence (1, 18, 19). According to the revised guidelines, individuals who are diagnosed as having adenomatous polyps should have removal of all polyps and a total colonoscopy repeated in 3 years. The adoption of these recommendations by health care providers resulted in the exclusion of the year 1 colonoscopy among participants enrolled in the latter part of the WBF trial. This will present a challenge in the analyses of the data, as these will need to take into account the difference in ascertainment of recurrence. An additional data analysis concern pertains to the change in randomization scheme. Although we committed to an intent-to-treat analysis, given the potential for bias as a result of this change, we will assess time trends in the qualifying colonoscopy information and the risk factor variables outlined in Table 2. If significant trends are noted, we will need to consider stratified analyses by calendar time or alternatively, logistic or Poisson regression analyses with the time variable in the model.

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. Our extended follow-up protocol is designed to help provide additional information in this area. 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 necessary. Results of completed and ongoing intervention studies should provide chemopreventive strategies that could enhance our public health efforts to reduce the impact of colon cancer in our society.

Acknowledgments

We thank Dr. Victor Fulgoni for scientific advice and the Kellogg's Company for supplying the WBF supplements.

References

1. Byers, T., Levin, B., Rothenberger, D., Dodd, G. D., and Smith, R. A. American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: update 1997. CA Cancer J. Clin., *47:* 154–160, 1997.

2. Morson, B. C. Evolution of cancer of the colon and rectum. Cancer (Phila.), *34* (Suppl.)*:* 845–849, 1974.

3. Winawer, S. J., Zauber, A. G., Ho, M. N., O'Brien, M. J., Gottlieb, L. S., Sternberg, S. S., Waye, J. D., Schapiro, M., Bond, J. H., and Panish, J. F. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup [see comment citation in Medline]. N. Engl. J. Med., *329:* 1977–1981, 1993.

4. Potter, J. D. Nutrition and colorectal cancer. Cancer Causes Control, *7:* 127–146, 1996.

5. Klurfeld, D. M. Dietary fiber-mediated mechanisms in carcinogenesis. Cancer Res., *52* (Suppl.)*:* 2055s–2059s, 1992.

6. Reddy, B. S., Simi, B., and Engle, A. Biochemical epidemiology of colon cancer: effect of types of dietary fiber on colonic diacylglycerols in women. Gastroenterology, *106:* 883–889, 1994.

7. Lampe, J. W., Salvin, J. L., Melcher, E. A., and Potter, J. D. Effects of cereal and vegetable fiber feeding on potential risk factors for colon cancer. Cancer Epidemiol. Biomark. Prev., *1:* 207–211, 1992.

8. Alberts, D. S., Ritenbaugh, C., Story, J. A., Aickin, M., Rees-McGee, S., Buller, M. K., Atwood, J., Phelps, J., Ramanujam, P. S., Bellapravalu, S., Patel, J., Bettinger, L., and Clark, L. Randomized, double-blinded, placebo-controlled study of effect of wheat bran fiber and calcium on fecal bile acids in patients with resected adenomatous colon polyps. J. Natl. Cancer Inst., *88:* 81–92, 1996.

9. Ritenbaugh, C., Aickin, M., Taren, D., Teufel, N., Graver, E., Woolf, K., and Alberts, D. S. Use of a food frequency questionnaire to screen for dietary eligibility in a randomized cancer prevention phase III trial. Cancer Epidemiol. Biomark. Prev., *6:* 347–354, 1997.

10. Vargas de Robles, P. A. Predicting adherence to a dietary regimen in a cancer prevention trial. Department of Psychology. Tucson: University of Arizona, 1996.

11. Ransohoff, D. F., Lang, C. A., and Kuo, H. S. Colonoscopic surveillance after polypectomy: considerations of cost effectiveness. Ann. Int. Med., *114:* 177–182, 1991.

12. Emerson, S., McGee, D. L., Fennerty, B., Hixson, L., Harinder, G., and Alberts, D. Design and analysis of studies to reduce the incidence of colon polyps. Statistics Med., *12:* 339–351, 1993.

13. Greenberg, E. R., Baron, J. A., Tosteson, T. D., Freeman, D. H., Beck, G. J., Bond, J. H., Colacchio, T. A., Coller, J. A., Frankl, H. D., and Haile, R. W. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. N. Engl. J. Med., *331:* 141–147, 1994.

14. Lachin, J. M. Introduction to sample size determinations and power analysis for clinical trials. Controlled Clinical Trials, *2:* 93–113, 1981.

15. Schatzkin, A., Lanza, E., Freedman, L. S., Tangrea, J., Cooper, M. R., Marshall, J., Murphy, P. A., Selby, J. V., Shike, M., Schade, R. R., Burt, R. W., Kikendall, J. W., Cahill, J., and the PPT Study Group. The Polyp Prevention Trial I: rationale, design, recruitment, and baseline participant characteristics. Cancer Epidemiol. Biomark. Prev., *5:* 375–383, 1996.

16. McKeown-Eyssen, G. E., Bright-See, E., Bruce, W. B., Jazmaui, V., and the Toronto Polyp Prevention Group. A randomized trial of low fat high fiber diet in the recurrence of colorectal polyps. J. Clin. Epidemiol., *47:* 525–536, 1994.

17. Lanza, E., Schatzkin, A., Ballard-Barbash, R., Clifford, D. C., Paskett, E., Hayes, D., Bote, E., Caan, B., Shike, M., Weissfeld, J., Slattery, M., Mateski, D., and the PPT Study Group. The Polyp Prevention Trial II: dietary intervention program and participant baseline dietary characteristics. Cancer Epidemiol. Biomark. Prev., *5:* 385–392, 1996.

18. United States Preventive Services Task Force. Guide to Clinical Preventive Services: Report from the U. S. Preventive Services Task Force, Ed. 2. Washington, DC: Government Printing Office, 1996.

19. Winawer, S. J., Fletcher, R. H., Miller, L., Godlee, F., Stolar, M. H., Mulrow, C. D., Woolf, S. H., Glick, S. N., Ganiats, T. G., Bond, J. H., Rosen, L., Zapka, J. G., Olsen, S. J., Giardiello, F. M., Sisk, J. E., Van Anturerp, R., Brown-Davis, C., Marcuriark, D. A., and Mayer, R. J. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology, *112:* 594–642, 1997.

Downloaded from cebp.aacrjournals.org on December 1, 2021. © 1998 American Association for Cancer Research.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Design and baseline characteristics of study participants in the Wheat Bran Fiber trial.

M E Martínez, M E Reid, J Guillén-Rodríguez, et al.

Cancer Epidemiol Biomarkers Prev 1998;7:813-816.

Updated version Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/7/9/813

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
http://cebp.aacrjournals.org/content/7/9/813.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cebp.aacrjournals.org on December 1, 2021. © 1998 American Association for Cancer Research.