The Polyp Prevention Trial I: Rationale, Design, Recruitment, and Baseline Participant Characteristics

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Abstract

The Polyp Prevention Trial (PPT) is a multicenter randomized controlled trial examining the effect of a low-fat (20% of total energy intake), high-fiber (18 g/1000 kcal), high-vegetable and -fruit (5–8 daily servings) dietary pattern on the recurrence of adenomatous polyps of the large bowel, precursors of most colorectal malignancies. Eligibility criteria include one or more adenomas removed within 6 months of randomization; complete nonsurgical polyp removal and complete colonic examination to the cecum at the qualifying colonoscopy; age 35 years or more; no history of colorectal cancer, inflammatory bowel disease, or large bowel resection; and satisfactory completion of a food frequency questionnaire and 4-day food record. Of approximately 38,277 potential participants with one or more polyps recently resected, investigators at eight clinical centers randomized 2,079 (5.4%; 1,037 in the intervention and 1,042 in the control arm) between June 1991 and January 1994, making the PPT the largest adenoma recurrence trial ever conducted. Of PPT participants, 35% are women and 10% are minorities. At study entry, participants averaged 61.4 years of age; 14% of them smoked, and 22% used aspirin. At the baseline colonoscopy, 35% of participants had two or more adenomas, and 29% had at least one large (≥1 cm) adenoma. Demographic, behavioral, dietary, and clinical characteristics are comparable across the two study arms. Participants have repeat colonoscopies after 1 (T_1) and 4 (T_4) years of follow-up. The primary end point is adenoma recurrence; secondary end points include number, size, location, and histology of adenomas. All resected lesions are reviewed centrally by gastrointestinal pathologists. The trial provides 90% power to detect a reduction of 24% in the annual adenoma recurrence rate. The primary analytic period, on which sample size calculations were based, is 3 years (T_1 to T_4), which permits a 1-year lag time for the intervention to work and allows a more definitive clearing of lesions at T_1, given that at least 10–15% of polyps may be missed at baseline. The final (T_4) colonoscopies are expected to be completed in early 1998.

Introduction

In 1995, adenocarcinoma of the large bowel killed an estimated 55,300 men and women in the United States, making it the second leading cause of cancer death in this country. Fewer than 60% of the estimated 138,200 people diagnosed with large bowel cancer in the United States in 1995 will survive 5 years (1).

Recent reports suggest that screening with sigmoidoscopy (2) or fecal occult blood testing (3) may reduce mortality from large bowel cancer. Even with the widespread implementation of such screening modalities, however, the residual morbidity and mortality from this disease would remain considerable.

Given the limitations of both treatment and screening in reducing mortality from large bowel cancer, primary prevention remains a high priority. Dietary change has been one of the most promising primary prevention strategies. An abundance of laboratory, human metabolic, and observational epidemiological evidence implicates diet in large bowel carcinogenesis (4). It would be valuable, in this context, to verify experimentally that dietary change can reduce the incidence of large bowel cancer.

The PPT[3] is a multicenter, randomized, controlled trial examining the effect of a low-fat, high-fiber, high-vegetable and -fruit eating plan on the recurrence of adenomatous polyps in the large bowel. This paper describes the rationale for the PPT, reviews its design, and provides data on recruitment and baseline participant characteristics. A full description of the nutrition intervention program, as well as baseline participant dietary characteristics, is presented in a companion report (5).

Rationale

Diet and Large Bowel Cancer

Several lines of ecological evidence strongly suggest that environmental factors play a major role in the etiology of large

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[3] The abbreviations used are: PPT, Polyp Prevention Trial; FFQ, food frequency questionnaire; 4DFR, 4-day food record; DNCC, Data and Nutrition Coordinating Center; NCI, National Cancer Institute.

bowel cancer. Colon cancer mortality varies widely among nations, with a more than 10-fold difference between those countries with the highest and those with the lowest death rates (6). Colon cancer rates have risen substantially in some countries with a historically low incidence of and mortality from this disease. In Japan, colon cancer mortality doubled over the two decades from 1971–1990, from 5.7 to 12.9 per 100,000 people in men and 5.3 to 9.4 per 100,000 in women (6). In Shanghai, China, colon cancer incidence over the period 1972–1974 to 1987–1989 jumped from 6.1 to 11.2 per 100,000 in men and 5.7 to 10.2 per 100,000 in women (7). Numerous studies demonstrate that large bowel cancer mortality rates among migrants approach those of the country of destination, even among those from countries in which rates were initially higher (8). It is particularly noteworthy that this convergence of rates after migration can occur within the lifetime of the migrant (9). The marked change in large bowel cancer rates over a relatively short period, coupled with the wide variation in disease frequency across countries, suggests that alterations in the environment influence the carcinogenic process in the large intestine.

Diet clearly accords with these ecological relations. What people eat varies dramatically among countries. Rather marked dietary changes [increased dietary fat and meat consumption, for example (10)] have occurred in Japan and China over as little as a decade and a half, and diet certainly changes with migration and acculturation. Moreover, on at least two general physiological grounds, diet emerges as a strong etiological candidate. First, food and its metabolites come into direct contact with the epithelium of the large bowel. Second, diet is known to affect a number of physiological parameters that are plausibly involved in large bowel carcinogenesis (11, 12).

Specific Hypotheses: Dietary Fat, Fiber, and Fruits and Vegetables

Several specific nutrients and foods have been implicated in large bowel carcinogenesis. At the time the PPT was designed, three dietary hypotheses showed particular promise:

Dietary Fat. Several studies have demonstrated that dietary fat promotes large bowel tumor development in laboratory animals exposed to chemical carcinogens (13). Countries with higher per capita fat consumption tend to have higher colon cancer mortality rates, with the correlation coefficient being approximately 0.8 (14). A number of observational epidemiological studies have demonstrated a positive association between dietary fat and large bowel cancer, although the evidence is inconsistent (15). Prospective cohort studies of colon cancer in female nurses (16) and large bowel adenomas in male health professionals (17), for example, have recently demonstrated positive associations with dietary fat (primarily of animal origin). Dietary fat could affect large bowel carcinogenesis by its influence on bile acid (18, 19) and free fatty acid (20, 21) production within the intestinal lumen.

Dietary Fiber. The dietary fiber-large bowel cancer hypothesis, first suggested by Burkitt (22) more than two decades ago, is also supported by the observation that countries with high fiber consumption have lower large bowel cancer rates, although the correlation is less strong than that for dietary fat (14). A meta-analysis of 16 case-control studies showed approximately a 35% lower risk of large bowel cancer in persons in the highest, compared to those in the lowest, category of dietary fiber intake (23). Some cohort studies of large bowel cancer (24) and adenomatous polyps (17) have also shown a modest inverse relation to dietary fiber, although the results are not consistent (25). Dietary fiber could protect against the development of malignant tumors in the large bowel by increasing stool bulk (thereby diluting exposure of the epithelium to potentially carcinogenic substances; Ref. 26), binding potential carcinogens (27), or increasing gut bacterial fermentation and the consequent luminal production of short-chain fatty acids (28), which may have antineoplastic effects (29).

Fruits and Vegetables. Numerous case-control studies and some recent cohort studies have shown that vegetable consumption reduces the risk of large bowel neoplasia (4). A few studies implicate specific vegetables, such as cruciferi (30) or garlic (24), but the majority of studies show a generalized vegetable association. Fruits also have been linked to a reduced risk of large bowel cancer, although the number of studies assessing fruit consumption and showing such an inverse association is less than that for vegetables (4). Vegetables and fruits may exert a protective effect due to their high-fiber composition (31) or to a variety of chemical constituents, including carotenoids (32), antioxidant vitamins (33), folic acid (34), and flavonoids (35) that have been shown to inhibit cancer in animal experiments or relate inversely to malignancy in human observational studies.

The PPT Intervention: A Multicomponent Eating Plan

Rather than focus the intervention on one single specific dietary hypothesis, PPT investigators have chosen to intervene with a unique, comprehensive eating plan defined by explicit consumption targets for dietary fat, dietary fiber, and vegetables and fruits. There are several reasons for adopting this multicomponent eating plan rather than a single-nutrient intervention:

a) Each of the three hypotheses above–dietary fat, dietary fiber, vegetables and fruits–is credible. The PPT intervention embraces all three hypotheses to maximize the likelihood of demonstrating an effect of dietary change on neoplasia.

b) There is considerable intercorrelation in the consumption of certain nutrients and foods. Vegetables, for example, contribute over 40% of dietary fiber intake in the United States (31). Therefore, persons who consume a large quantity of vegetables will tend to consume more fiber than those who consume few vegetables. Such persons will also consume more vitamin C, vitamin E, folate, and one or more of several carotenoids because fruits and vegetables contribute substantial amounts of these micronutrients. Those who consume large amounts of red meat tend to consume large amounts of dietary fat and rely less on carbohydrates as a source of energy. Thus, changing the intake of any one macronutrient or food group in a free-living human context often means altering multiple dietary factors. The PPT aims to study the efficacy of a practical, multicomponent eating plan without necessarily determining the independent effects of separate dietary components.

c) Foods contain a plethora of nutrients and nonnutrient chemicals with possible cancer-enhancing or cancer-inhibiting effects. A multicomponent eating plan is more likely to capture the effect of more of these unknown dietary factors than a single-component intervention, thereby further increasing the probability that the intervention will influence neoplasia. The PPT low-fat, high-fiber, high-vegetable and -fruit eating plan may also lead to reduced consumption of red meat, total energy, and food mutagens (36), as well as increased intake of folic acid, several different kinds of carotenoids, flavonoids, and so on. Each of these additional dietary elements has been associated with large bowel neoplasia in one or more studies.

d) Finally, a multicomponent (as opposed to single-component) dietary intervention is much more likely to reflect the biological interactions among nutrients, chemicals, and foods.

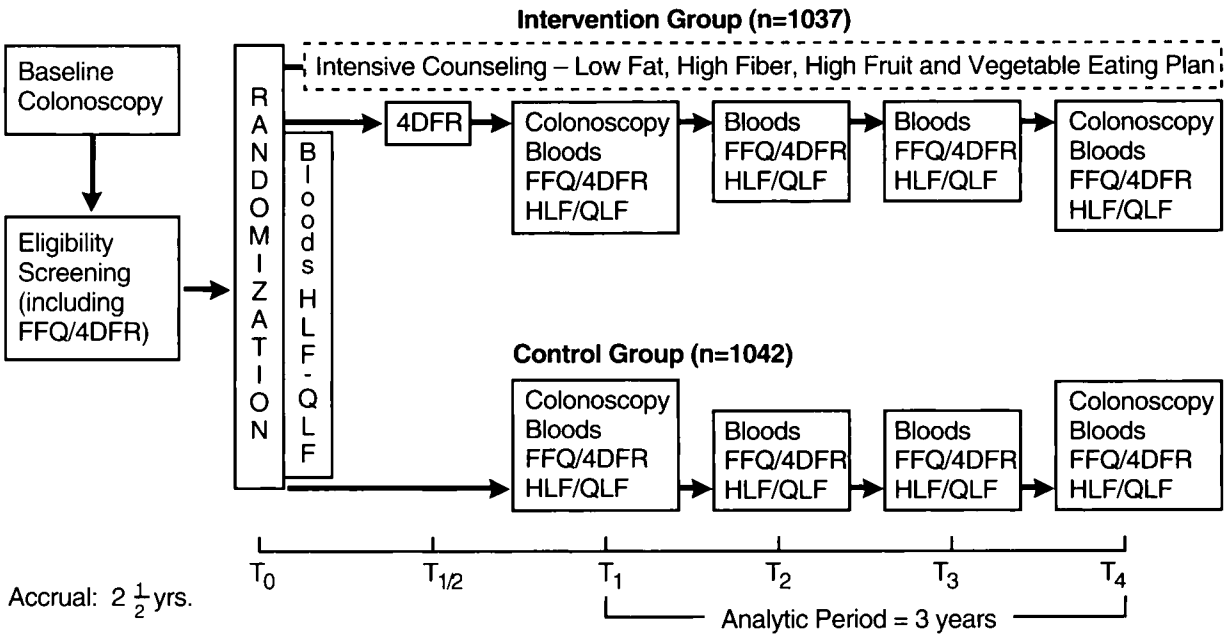

Fig. 1. Schematic diagram of design for the PPT. *HLF*, health and lifestyle form; *QLF*, quality-of-life form.

A given food or nutrient, for example, might affect carcinogenesis differently in a low- as opposed to a high-fat dietary environment (37).

Adenoma Recurrence as Study Outcome

The underlying intent of the PPT is to learn whether dietary change can reduce the risk of large bowel cancer. There are four reasons, one theoretical-biological and three practical, for using large bowel adenoma recurrence (rather than carcinoma incidence *per se*) as the primary study outcome:

The Adenoma-Carcinoma Sequence. Adenomatous polyps are generally considered necessary precursors of most large bowel cancers although only a small proportion of adenomas become malignant. A large body of pathological, clinical, and epidemiological data (38), recently extended by cell biological (39) and molecular genetic findings (40), supports the concept of an adenoma-carcinoma sequence.

Although inferences from adenoma recurrence to cancer incidence are not absolute (41), an intervention that reduces adenoma recurrence is very likely to reduce the incidence of adenocarcinoma of the large bowel.

High Prevalence. A recent review suggests that the prevalence of adenomatous polyps in the United States ranges from 35 to 60% (42). The relatively high prevalence of large bowel adenomas diagnosed by endoscopic procedures ensures a practically accessible and reasonably large pool of potential participants for a prevention trial.

High Recurrence Rate. The recurrence rate of large bowel adenomas is in the range of 10% or more annually (43). ("Recurrence" is defined here as the development of a new adenomatous polyp anywhere in the large bowel subsequent to identification and removal of one or more "index" adenomas.) The incidence rate for large bowel cancer, on the other hand, is some 1 or 2 orders of magnitude lower than the adenoma recurrence rate (1). An intervention study of recurrent adenomas therefore requires a sample size much smaller than that needed in a trial with incident large bowel cancer as the end point.

Integration of Standard Clinical Practice into Study Design. For a number of years, the standard postpolypectomy surveillance involved repeat colonoscopies at 1 and 4 years after initial adenoma diagnosis and removal. This affords PPT investigators the opportunity to examine the study participants for recurrent adenomas as part of standard clinical practice.

Objective

The PPT aims to determine whether a low-fat, high-fiber, high-vegetable and high-fruit eating plan, as compared with usual diet, reduces the recurrence rate of large bowel adenomatous polyps.

Design

The overall design for the PPT is described below and depicted schematically in Fig. 1.

Eligibility Criteria

The PPT randomized men and women 35 years of age or older with one or more histologically confirmed large bowel ade-

nomatous polyps removed within the previous six months. Persons with any of the following characteristics were ineligible for the study: age less than 35 years; failure by Clinical Center trial pathologist to confirm presence of one or more adenomatous polyps; invasive carcinoma in any polyp removed; failure to examine the cecum during baseline colonoscopy; incomplete removal of polyps at baseline colonoscopy; inadequate bowel preparation preventing identification and removal of polyps; surgical removal of polyps; history of familial polyposis or other polyposis syndromes; history of large bowel adenomatous polyp before the age of 35; history of large bowel cancer, including intramucosal carcinoma (history of high-grade dysplasia did not preclude eligibility); history of histologically confirmed inflammatory bowel disease (ulcerative colitis or Crohn's disease); history of large bowel resection; weight greater than 150% of recommended level (according to 1983 Metropolitan Life Insurance Tables); ingestion of lipid-lowering drugs in pharmacological doses within past month; life-limiting conditions; dietary pattern similar to intervention eating plan; any dietary practice, behavior, or attitude that would substantially limit adherence to the intervention eating plan; current participation in any other clinical study that might interfere with participation in the PPT; inability or unwillingness to sign the informed consent form; unreliable or uncooperative provision of dietary information during the prerandomization period; and expectation of moving outside the Clinical Center area during the course of the study.

Eligibility Determination

Clinical Center staff identified potential trial participants by receiving referrals from endoscopists or reviewing medical logs from endoscopy services. Procedures for determining eligibility varied somewhat across the eight Clinical Centers because of differences in the structure of clinical services or the characteristics of participating endoscopists. Usually, potential participants with documented adenoma removal were mailed an introductory letter and study brochure before telephone contact for scheduling an initial Clinical Center visit. The recruitment telephone contact included a brief summary of the study, a review of some of the eligibility criteria, and ascertainment of the potential participant's willingness to schedule an appointment. Exclusion of ineligibles thus could occur before the first visit.

At the first clinic visit, PPT staff reviewed the objectives of the trial with the potential participant and emphasized the demands of the study protocol, the requirements of the intervention eating plan, the implications of randomization, the necessity of completing the required colonoscopies, and the need for the potential participant to remain in the area for follow-up. Height and weight were measured, and informed consent forms were given at this visit. (If they so wished, potential participants were permitted to take the informed consent forms home and return them signed at the second visit.)

To be eligible for the trial, potential participants had to complete a FFQ and 4DFR satisfactorily. This component of screening constituted the equivalent of a "run-in" procedure (44): those unable to complete the dietary assessment instruments satisfactorily were deemed unlikely to adhere to the study protocol and were excluded from participation. Instructions for completing the FFQ and the 4DFR were provided at the first visit, and copies of each instrument were given to the potential participant to take home. Potential participants were instructed to bring the completed instruments to the second visit, as well as all prescribed and over-the-counter medications.

After the review of the FFQ and 4DFR by a nutritionist at the second visit, Clinical Center staff made the final eligibility determination. After the staff concluded that a potential participant was available to begin intervention counseling within 7 weeks of randomization, the central DNCC randomized this participant to either the intervention or control group.

Randomization

In a standardized, computer-assisted telephone call with Clinical Center personnel, staff from the DNCC confirmed the eligibility criteria for each potentially randomizable participant. DNCC staff used a specially designed computer program to assign participants randomly to either the intervention or control group; the program stratified randomization according to Clinical Center.

After randomization, Clinical Center staff made arrangements for obtaining a fasting blood specimen, either during the second visit or at a later date. They administered at this visit a baseline Health and Lifestyle Form that assesses a variety of demographic, clinical, and behavioral characteristics. They also administered at that time a quality-of-life assessment questionnaire to approximately 400 participants randomized after August 1, 1993. (Participants completed these last two forms before learning of group assignment.)

Intervention

Implementing the eating plan requires PPT investigators to specify quantitative targets for each of the three explicit components. These specific targets are 20% of calories from fat, 18 grams of dietary fiber/1000 kcal, and 5–8 servings of fruits and vegetables.

The nutrition intervention program integrates both nutrition education and behavioral modification techniques. Over 50 h of in-person individual and group counseling sessions are provided over the 4-year intervention period. Each participant in the intervention group is assigned a nutritionist for counseling, with a different nutritionist responsible for that participant's dietary assessment. Extensive materials in the form of individual modules are prepared for the participants and nutritionists. The rationale for the selection of the dietary targets and further detail on the design of the dietary intervention program are presented in a companion report (5).

Control group participants are provided with general dietary guidelines from the National Dairy Council (1989). No additional nutritional or behavioral information is provided to the control participants.

Follow-up

PPT investigators follow participants for approximately 4 years after randomization. Each year all trial participants complete a FFQ, a 4DFR, and a Follow-up Health and Lifestyle Form and provide a fasting blood specimen. In addition, intervention (but not control) participants complete a 4DFR at 6 months after randomization.

All participants return to their usual endoscopist to have a repeat colonoscopy one (T_1) and four (T_4) years after randomization. PPT investigators provide each endoscopist with a trial colonoscopy protocol that stresses making all reasonable efforts to reach and examine the cecum, remove all observed polypoid lesions for histological examination, and note the size and location of each lesion. Clinical Center staff collect similar information for colonoscopy examinations performed outside the T_1 and T_4 follow-up intervals. PPT investigators do not

Table 1 Forms and biological specimen collection schedule

	Prerandomization	Baseline	6 Mo.	12 Mo.	24 Mo.	36 Mo.	48 Mo.
Health and lifestyle questionnaire		X		X	X	X	X
Quality-of-life questionnaire[a]		X		X	X	X	X
FFQ	X			X	X	X	X
4 DFR	X		X[b]	X	X	X	X
24-hour dietary recall[c]				(X)	(X)	(X)	(X)
Blood specimens		X		X	X	X	X
Colonoscopy	X			X			X
Rectal biopsies[d]		X		X			X

[a] Administered to approximately 400 participants randomized on or after August 1, 1993.
[b] Intervention group only.
[c] Administered to a random sample of 10% of the participants per year.
[d] Biopsies are obtained for epithelial cell proliferation studies from participants at three Clinical Centers (Kaiser-Oakland, Utah, and Walter Reed).

inform endoscopists of the randomization status of PPT participants. At the time of randomization, Clinical Center personnel ask participants not to divulge group assignment (intervention *versus* control) to endoscopists.

End-Point Review: Pathology

The primary end point of the PPT is adenomatous polyp recurrence. Secondary end points include number, size, location, and histology of recurrent adenomas.

The PPT involves three levels of pathological review. *a*) Local pathologists evaluate all polypoid lesions removed from PPT participants. Clinical Center study coordinators enter these findings into standardized trial endoscopy forms. *b*) Each Clinical Center also designates a Trial Pathologist responsible for reviewing baseline polyp material from each potential participant for eligibility. (The Clinical Center Trial Pathologist does not evaluate T_1 and T_4 lesions.) *c*) The two Central Pathologists review all polyp material for histology and degree of atypia (low- *versus* high-grade). Although the Clinical Center Trial Pathologist determines eligibility (whether or not a potential participant has an adenoma at baseline) according to histological criteria developed by the Central Pathologists, the Central Pathologists make final pathological determinations regarding histology and atypia for baseline, as well as T_1 and T_4 lesions. The Central Pathologists are blinded to a participant's group assignment. In discrepant cases (in which a local pathologist from the Clinical Center diagnoses adenoma but the Central Pathologists find no evidence of adenomatous tissue), the DNCC requests original slides from the Clinical Center for review by the Central Pathologists. The endoscopists' reports provide information on size, multiplicity, and anatomic location of polyps.

Biological Specimen Collection

Clinical Center personnel collect three 10-ml fasting blood samples from each participant at baseline (T_0) and each subsequent annual visit (T_1, T_2, T_3, and T_4). These blood specimens are processed for extracting serum, plasma, and white cells. Serum and plasma are analyzed, respectively, for carotenoids and lipids. Serum is also collected and stored for hormone analysis. White cells will provide DNA for molecular genetic analysis. Blood components are stored as 1-ml aliquots (serum and plasma) or cell pellets (white cells) in plastic cryotubes at a central repository in freezers at −80°C.

At three Clinical Centers, endoscopists obtain rectal biopsy specimens (up to eight per participant) for epithelial cell proliferation assays [bromodeoxyuridine (45) and proliferating cell nuclear antigen (46)]. They obtain these biopsies at baseline and after 1 (T_1) and 4 (T_4) years of follow-up. Each of the participants providing these biopsy specimens signs a separate informed consent form that includes an explicit statement that refusal to participate in the rectal biopsy-epithelial cell proliferation study in no way compromises participation in the main trial. The schedule for collection of forms and biological specimens in the PPT is shown in Table 1.

Sample Size and Other Statistical Considerations

The projected sample size for the PPT was 2000, with 1000 participants in each of the two study groups (intervention and control). Randomization to the two study groups was stratified by Clinical Center. The sample size of 2000 permits the detection, with 90% power, of a 24% reduction in the annual adenoma recurrence rate, corresponding to cumulative recurrence proportions between years 1 and 4 of 21% and 27% in the intervention and control groups, respectively. The control group recurrence rate of 27% was calculated on the basis of a 10% annual recurrence rate, in line with that reported by the National Polyp Study (47). The assumptions underlying the sample size calculations are as follows:

a) a one-tailed significance test using the binomial distribution at the 5% α-level;

b) equal-sized treatment groups;

c) an effect of the nutrition intervention on polyp recurrence that operates 1 year from the start of the intervention; and

d) a 10% loss to follow-up over the course of the study.

The sample size projections were based on a 3-year period of follow-up between the T_1 and T_4 colonoscopies. At least 10–15% of polyps are expected to be missed at baseline (48); at T_1 it is expected that the bowel is effectively "cleared." The 3-year T_1-T_4 interval therefore more accurately reflects newly recurrent polyps without contamination from prevalent polyps missed at baseline.

Interim analyses are presented at 6-month intervals to the Data and Safety Monitoring Committee and focus on recruitment rates, adherence to the dietary intervention, intermediate end points such as body weight and blood levels of lipids and carotenoids, follow-up retention, and adverse events, as well as the adenoma recurrence rates. It was decided not to institute formal statistical stopping criteria on the basis of comparisons of the adenoma recurrence rates on the grounds that such recurrences are not life-threatening events. In addition, there is a relatively short projected window of time (approximately 2½ years) between receiv-

ing the 4-year colonoscopic evaluation of the first-entered patient and the close-out of the study.

Final analysis will also include comparisons of groups with respect to the number, size, location, and histology of polyps. The primary comparisons will be based on the intention-to-treat principle, which defines the treatment groups on the basis of initial random assignment rather than actual (or reported) delivery of treatment. Ineligible participants who were inadvertently entered into the trial (see below) will be included in these analyses, except for those four participants found not to have had an adenomatous polyp at baseline.

Study Organization

The Study Chairpersons from NCI coordinate and oversee the study, approve allocation of funds, and distribute reports to other committees. They monitor and evaluate the performance of the DNCC and Clinical Centers for the duration of the trial.

Each of the eight Clinical Centers in this multicenter collaborative trial randomizes and follows study participants. Five of the eight Clinical Centers are located at academic medical centers; one is based at a Veterans Affairs hospital, one at a military hospital, and one at a large prepaid group practice. institution. The Clinical Centers draw participants from multiple hospitals, clinics, and practices. Each Center consists of clinicians, epidemiologists, nutritionists, study coordinators, nurse-recruiters, and other support personnel. The Clinical Center is directed by a Principal Investigator who represents that Center on the Investigators Group. The participating Clinical Centers are: Bowman Gray School of Medicine (Winston-Salem, NC), State University of New York at Buffalo (Buffalo, NY), Edward Hines, Jr., Hospital (Veterans Affairs Medical Center; Hines, IL), Kaiser Foundation Research Institute (Oakland, CA), Memorial Sloan-Kettering Cancer Center (New York, NY), University of Pittsburgh (Pittsburgh, PA), University of Utah (Salt Lake City, UT), and Walter Reed Army Medical Center (Washington, DC).

The DNCC (Westat, Inc.) has responsibilities in three areas: *a*) data management, including developing and maintaining the study forms, randomization system, and trial data base; *b*) nutrition program coordination, including developing and distributing all nutrition materials, providing centralized Clinical Center staff training in implementing the intervention and dietary assessment, analyzing dietary assessment data, and monitoring intervention progress; and *c*) study coordination, including developing and maintaining the Manual of Operations, randomizing all participants, monitoring Clinical Center operations, preparing and disseminating newsletters, and conducting periodic site visits.

The Steering Committee consists of the Study Chairpersons and other NCI staff from the Cancer Prevention Studies Branch, Diet and Cancer Branch, Applied Research Branch, and Biometry Branch. The committee is chaired by the Study Chairpersons. This group provides overall scientific direction for the study and serves as the major decision-making body for the operational aspects of the study.

The Investigators Group consists of the Steering Committee and the Principal Investigators (and, in some instances, Co-Principal Investigators) from the Clinical Centers and the DNCC. This group meets annually to review the progress of the trial and identify problems needing resolution, especially those pertaining to the operations and responsibilities of the Clinical Centers and DNCC.

The Publications Committee consists of the Study Chairpersons, the Principal Investigator from the DNCC, and one investigator from each of the Clinical Centers. Members of this group are responsible for reviewing all manuscripts and abstracts.

Table 2 Number and percentage of potential participants found ineligible for various reasons

	No.	%
Total participants identified	38,277	
Total participants ineligible	36,198	(100)
Age under 35	541	1.5
No adenomatous polyp	6530	18.0
Carcinoma in polyp	1029	2.8
Failure to reach cecum	1470	4.1
Incomplete polyp removal[a]	3567	9.9
Inadequate bowel preparation	690	1.9
Surgical polyp removal	151	0.4
Familial or other polyposis syndrome	161	0.4
Adenomatous polyp before age 35	73	0.2
History of large bowel cancer	2544	7.0
Inflammatory bowel disease	874	2.4
Large bowel resection	1211	3.3
Weight >150% ideal	266	0.7
Lipid-lowering medication	1204	3.3
Life-limiting condition	3004	8.2
Diet similar to intervention	193	0.5
Adherence-limiting lifestyle	2904	8.0
Other clinical studies	30	0.0
Refused informed consent	5677	15.7
Unreliable dietary information	218	0.6
May not stay in area	479	1.3
Other	3382	9.3
Total participants randomized	2079	
Intervention group	1037	
Control group	1042	

[a] Includes polyps not available for histological review.

Because of the complexity of the nutrition intervention in the PPT, a separate Nutrition Intervention Committee was created for the developmental phase of the nutrition intervention. This committee consisted of the Study Chairpersons, other NCI staff, and senior nutritionists from the Clinical Centers and the DNCC. The primary responsibilities included reviewing nutrition materials, training curricula for the Clinical Center nutritionists, the performance of the DNCC in coordinating and monitoring the nutrition program, the performance of the Clinical Center nutritionists, and the adherence to the nutrition program by trial participants.

The Data and Safety Monitoring Committee comprises a panel of experts outside NCI, including members of the Division of Cancer Prevention and Control Board of Scientific Counsellors. The five committee members provide expertise in gastroenterology, nutrition, statistics, epidemiology, and the conduct of clinical trials. The Committee meets semiannually during the trial. The responsibilities of this group include reviewing quantitative recruitment and adherence progress for the trial, and recommending modifications of the trial protocol or administrative structure in the event these goals are not met. The Committee also reviews tabulated adverse event and end-point data provided by the DNCC. The Committee provides recommendations on the progress of the study to the Study Chairpersons.

Table 3 Baseline demographic, behavioral, and nutritional characteristics of PPT participants

	Intervention group, n = 1037[a]	Control group, n = 1042
Age, mean	61.4 (0.31)	61.5 (0.31)
% women	34 (1.5)	36 (1.5)
% minority[b]	12 (1.0)	9 (0.9)
% with > high school education	65 (1.5)	65 (1.5)
% married	78 (1.3)	79 (1.3)
% currently smoking	14 (1.1)	13 (1.0)
Alcohol, mean drinks/week	3.5 (0.17)	3.8 (0.18)
Body mass index, mean	27.6 (0.13)	27.5 (0.12)
Vigorous and/or moderate activity, mean h/week[c]	11.4 (0.53)	10.3 (0.41)
% current aspirin user	23 (1.3)	22 (1.3)
% calcium supplement user[d]	15 (1.1)	14 (1.1)
% Vitamin E supplement user[d]	42 (1.5)	39 (1.5)
Total plasma cholesterol, mean mg/dl	203.1 (2.59), n = 221	200.8 (2.26), n = 223
Total serum carotenoids, mean μg/dl	92.4 (2.7), n = 219	92.2 (2.7), n = 220
α-Tocopherol, mean μg/dl	1415.3 (55.2), n = 219	1348.7 (41.2), n = 220
% fat calories[d]	35.8 (0.22)	36.0 (0.23)
Fiber, gm/1000 kcal[d]	9.9 (0.12)	9.5 (0.12)
# Vegetable/fruit servings[d]	3.8 (0.05)	3.8 (0.05)

[a] Numbers in parentheses, SE.
[b] Minority comprises black, Hispanic, Indian/Native American, Asian/Pacific, and other.
[c] Moderate activity includes general gardening, lawnmowing, walking (3–4 mph), and singles tennis; vigorous activity includes heavy yardwork, sawing wood, jogging, and canoeing.
[d] From FFQ.

Table 4 Baseline clinical characteristics of PPT participants

	Intervention group[a]	Control group
Reasons for colonoscopy[b]		
Polyp found on sigmoidoscopy or X-ray, %	28 (1.3)[b]	30 (1.3)
Routine postpolypectomy surveillance, %	23 (1.2)	21 (1.1)
Bleeding or anemia, %	15 (1.0)	18 (1.1)
Family history of cancer or polyps, %	9 (0.8)	10 (0.8)
Positive fecal occult blood test, %	9 (0.8)	9 (0.8)
Change in bowel habits, %	6 (0.7)	4 (0.6)
Other, %	10 (0.8)	8 (0.8)
Polyp characteristics (n = 2079 participants)		
% with adenoma ≥1 cm[c]	27 (1.4)	32 (1.4)
% with 2+ adenomas	35 (1.5)	34 (1.5)
% with ≥1 tubular adenoma (no villous/tubulovillous adenomas)	71 (1.4)	69 (1.4)
% with ≥1 villous/tubulovillous adenoma	19 (1.2)	22 (1.3)
% with one adenoma exhibiting high-grade dysplasia	7 (0.8)	8 (0.8)
% with only rectosigmoid adenoma(s)[d]	50 (1.6)	51 (1.6)

[a] Numbers in parentheses, SE.
[b] 1663 participants reported a single reason for colonoscopy; 416 participants reported two or more reasons. The total number of reported reasons is 2538. Percentages in table are based on the total number of reasons reported by intervention (n = 1264 reasons) and control (n = 1274 reasons) participants.
[c] Based on participants for whom size is reported for all adenomas, or for whom at least 1 adenoma is ≥1 cm (n = 1867).
[d] Based on participants for whom location is reported for all adenomas (n = 1679).

Recruitment

Randomization began at three Clinical Centers in June 1991 and at the other five Centers in October of that year. Randomization was completed in early 1994.

The eight Clinical Centers identified approximately 38,277 potential participants who had one or more adenomas recently removed. Of these, 36,198 were found at some point during the screening process to be ineligible. Table 2 lists the frequency of each first-encountered reason for ineligibility.

There were 3,360 potential participants who completed the first visit, and 2,246 completed the second visit; 2,079 participants were ultimately randomized into the PPT, 1,037 into the intervention group, and 1,042 into the control group. Of those persons initially identified as having had an adenoma removed, 5.4% (2,079 of 38,277) were eventually randomized into the trial.

After retrospective review of randomized participants, it was found that 20 ineligible participants were randomized into the trial inadvertently. The reasons for ineligibility were: no adenoma at baseline (4 persons); use of lipid-lowering medications (5 persons); incomplete polyp removal at baseline (4 persons); inadequate bowel preparation (2 persons); cecum not reached (1 person); history of bowel resection (1 person); life-limiting condition (1 person); adherence-compromising lifestyle (1 person); and too much time between polypectomy and randomization (1 person).

All 20 ineligible participants (13 and 7 in the intervention and control arms, respectively) are being maintained on the study protocol.

Participant Characteristics at Baseline

Baseline demographic, behavioral, and nutritional characteristics of participants in the intervention and control groups at baseline are shown in Table 3. Table 4 presents data on participants' baseline clinical characteristics.

Discussion

Recruitment to this study was particularly challenging given the large number of participants who had to be screened (nearly 40,000) to achieve the sample size of 2079. Although the pool of polyp patients in the general population is quite large, the proportion randomized into the PPT was quite small, only about 5%. Other polyp trials involving pill administration (49) have had somewhat higher percentages (around 10%) of identified participants who were ultimately randomized. The lower percentage for the PPT may reflect the substantial participant commitment required by the intensive nutrition intervention program of this trial.

The intervention and control groups appear well balanced with respect to a variety of demographic, behavioral, nutritional, and clinical characteristics. This provides confidence that unmeasured potential confounders of the relation between diet and adenoma recurrence will also have been balanced between the two groups.

Follow-up should be complete by early 1998. With the successful completion of the recruitment phase of the PPT, trial retention and adherence are the major tasks ahead. We are operating in somewhat uncharted waters because, to our knowledge, no previous dietary intervention of this complexity has been conducted for as long as 4 years. Close monitoring of participant adherence to the intervention (with prompt attention to any apparent fall-off in adherence in the trial as a whole and at each Center) is essential for successful completion of the trial.

A number of clinicians, health care providers, and researchers are now recommending that some individuals, especially those found to have only a small solitary tubular adenoma, have follow-up colonoscopy only after 3 years (50). The elimination of the T_1 colonoscopy is potentially troublesome for our end-point assessment. Because *a*) most PPT participants have already had their T_1 colonoscopies, and *b*) our participating endoscopists have been willing to adhere to the T_0-T_1-T_4 colonoscopy protocol at least for study participants, it appears that the PPT will not be especially affected by this transition in postpolypectomy surveillance practice. It is likely that future polyp trials will have to adopt a T_0-T_3 design, which, because missed baseline lesions are not removed at T_1, will inflate sample size requirements considerably.

With a sample size of over 2000 participants, the PPT should have sufficient statistical power to detect whether a low-fat, high-fiber, high-vegetable and -fruit eating plan, compared to a customary U.S. diet, can reduce adenoma recurrence by at least 25% over a 3-year period. This study will make a major contribution toward demonstrating whether dietary change can lower the incidence of large bowel cancer.

Appendix

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