The Polyp Prevention Trial–Continued Follow-up Study: No Effect of a Low-Fat, High-Fiber, High-Fruit, and -Vegetable Diet on Adenoma Recurrence Eight Years after Randomization

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Abstract

The Polyp Prevention Trial (PPT) was a multicenter randomized clinical trial to evaluate the effects of a high-fiber (18 g/1,000 kcal), high-fruit and -vegetable (3.5 servings/1,000 kcal), and low-fat (20% of total energy) diet on the recurrence of adenomatous polyps in the large bowel over a period of 4 years. Although intervention participants reported a significantly reduced intake of dietary fat, and increased fiber, fruit, and vegetable intakes, their risk of recurrent adenomas was not significantly different from that of the controls. Since the PPT intervention lasted only 4 years, it is possible that participants need to be followed for a longer period of time before treatment differences in adenoma recurrence emerge, particularly if diet affects early events in the neoplastic process. The PPT-Continued Follow-up Study (PPT-CFS) was a post-intervention observation of PPT participants for an additional 4 years from the completion of the trial. Of the 1,905 PPT participants, 1,192 consented to participate in the PPT-CFS and confirmed colonoscopy reports were obtained on 801 participants. The mean time between the main trial end point colonoscopy and the first colonoscopy in the PPT-CFS was 3.94 years (intervention group) and 3.87 years (control group). The baseline characteristics of 405 intervention participants and 396 control participants in the PPT-CFS were quite similar. Even though the intervention group participants increased their fat intake and decreased their intakes of fiber, fruits, and vegetables during the PPT-CFS, they did not go back to their prerandomization baseline diet ($P < 0.001$ from paired t tests) and intake for each of the three dietary goals was still significantly different from that in the controls during the PPT-CFS ($P < 0.001$ from t tests). As the CFS participants are a subset of the people in the PPT study, the nonparticipants might not be missing completely at random. Therefore, a multiple imputation method was used to adjust for potential selection bias. The relative risk (95% confidence intervals) of recurrent adenoma in the intervention group compared with the control group was 0.98 (0.88-1.09). There were no significant intervention-control group differences in the relative risk for recurrence of an advanced adenoma (1.06; 0.81-1.39) or multiple adenomas (0.92; 0.77-1.10). We also used a multiple imputation method to examine the cumulative recurrence of adenomas through the end of the PPT-CFS: the intervention-control relative risk (95% confidence intervals) for any adenoma recurrence was 1.04 (0.98-1.09). This study failed to show any effect of a low-fat, high-fiber, high-fruit and -vegetable eating pattern on adenoma recurrence even with 8 years of follow-up. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1745–52)

Introduction

Epidemiologic and animal studies suggest that diet has a major role in colorectal carcinogenesis, that the consumption of dietary fiber, fruits and vegetables, whole-grain cereals, and calcium have a protective effect against colorectal cancer and adenomas; conversely, dietary fat, red meat, and high glycemic index foods might increase risk (1-3). These findings, however, are far from consistent, with many case-control studies finding stronger associations for fat, fiber, and fruits and vegetables than the more recent larger cohort studies (4, 5). Because adenomas are thought to be precursors of most colorectal cancers (6-9), they have been used as an intermediate end point in a number of randomized trials to help clarify the diet–colorectal cancer relationship

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Table 1. Comparison of colonoscopy data in all participants of the PPT and the PPT-CFS by intervention and control group status

	Intervention	Control
Participants with end point colonoscopy (*n*)	958	947
Had T_1 colonoscopy (*n*)	899	869
Length of follow-up, T_1-T_4 (y)	3.06 (0.02)	3.06 (0.02)
No. of procedures, T_1-T_4 (*n*)	1.31 (0.02)	1.31 (0.03)
Participants in the PPT-CFS (*n*)*	603	589
Had CFS colonoscopy (*n*)	405	396
Had T_1 colonoscopy (*n*)	393	374
Length of follow-up, T_1-T_4 (y)	2.97 (0.02)	2.98 (0.03)
No. of procedures, T_1-T_4 (*n*)	1.41 (0.03)	1.51 (0.03)
Length of follow-up, T_4-CFS (y)	3.94 (0.07)	3.87 (0.07)
Length of follow-up, T_0-CFS (y)	8.07 (0.02)	7.99 (0.07)
No. of procedures CFS (*n*)	1.36 (0.04)	1.37 (0.04)

NOTE: Results presented as means and SEs. T_0, baseline (randomization); T_1, clearing colonoscopy (year 1); T_4, PPT trial end point (year 4).
*One thousand one hundred and ninety-four individuals consented to participate in the PPT-CFS; however, on final review of the anonymized data set, two individuals had no colonoscopy data and were therefore omitted from further analysis (*n* = 1,192). All subsequent PPT-CFS analyses herein were done on the individuals (*n* = 801) who underwent CFS colonoscopy.

(10-12). However, adenoma recurrence trials on the effects of a low-fat, high-fiber diet (13, 14), wheat bran supplementation (15), and low-fat, high-fiber, and high-fruit and -vegetable diet (16) have shown no effect on adenoma recurrence rates.

In the Polyp Prevention Trial (PPT), individuals randomized to the dietary intervention group were given intensive counseling and assigned to follow a diet that was low in fat (20% of calories from fat) and high in fiber (18 g of dietary fiber per 1,000 kcal) and fruits and vegetables (3.5 servings/1,000 kcal). The control group members were given a standard brochure on healthy eating and assigned to follow their usual diet. After 4 years, 39.5% of the participants in the control group and 39.5% of the participants in the intervention group had an adenoma recurrence. The unadjusted relative risk (RR) was 1.00 [95% confidence intervals (95% CI), 0.90–1.12; ref. 16]. According to food frequency data, the difference in intakes for the three trial dietary goals in the intervention and control groups at the end of the 4-year trial was −9.7% (±SE) of calories (23.8 ± 0.2 in the intervention group; 33.9 ± 0.2 in the control group), +6.9 g fiber/1,000 kcal (17.4 ± 0.2 in the intervention group; 10.0 ± 0.1 in the control group), and +1.13 servings of fruits and vegetables/1,000 kcal (3.41 ± 0.04 in the intervention group; 2.23 ± 0.03 in the control group; ref. 17). Despite these differences in diet, there was no difference in adenoma recurrence. One possible explanation for the lack of associations in this and other similar trials is their short duration (18, 19). Most of the adenoma recurrence trials have lasted 3 to 4 years (18), whereas colorectal carcinogenesis in humans has been estimated to take 10 to 40 years (20, 21). A dietary intervention could be protective at different stages of adenoma progression to cancer: (*a*) initial appearance, (*b*) growth, or (*c*) transformation into carcinoma. If diet affects early events in the neoplastic process, such as the initial growth of an adenoma, intervention effects might not emerge during the short duration of the original trial. We therefore followed a subcohort of 1,192 (62.6%) of the original trial participants for an additional 4 years. The primary aim of the PPT-Continued Follow-up Study (PPT-CFS) was to compare the recurrence of one or more adenomas, and the number, size and location of adenomas in the intervention and control arms of the PPT 4 years after completion of the original trial.

Materials and Methods

PPT Enrollment. The PPT included 2,079 men and women aged 35 years or older (range, 35-89 years) with at least one histologically confirmed large-bowel adenomatous polyp removed during a colonoscopy procedure (the baseline procedure) within the previous 6 months. To be eligible, participants could have no history of colorectal cancer, surgical resection of adenomas, bowel resection, polyposis syndrome, or inflammatory bowel disease, weigh ≤150% of the recommended level, take no lipid-lowering drugs, and have no medical conditions or dietary restrictions that would substantially limit their ability to complete the study requirements. Recruitment activities occurred at eight U.S. clinical centers, starting in the spring of 1991 and ending in January 1994. More detailed descriptions of the exclusion criteria (22), dietary intervention (17, 23), and trial results (16) are reported elsewhere.

PPT-CFS Enrollment. Individual clinical centers received permission from their institutional review boards to either contact participants directly about the PPT-CFS or to release their names and addresses to the PPT Coordinating Center (Westat) in order to contact the participants. In both cases, the participants were sent letters that explained the purpose of the PPT-CFS, invited them to join the study, and to return an enclosed postcard if interested in participating. The institutional review boards of the National Cancer Institute and Westat, the Data and Coordinating Center, approved the PPT-CFS Study. All participants provided written informed consent. Randomization took place at T_0, with a ''clearing'' colonoscopy 1 year later (T_1). The original PPT end point was 4 years postrandomization, at T_4.

PPT-CFS Data Collection. After completion of the final PPT food frequency questionnaire (FFQ; typically after 4 years on study, i.e., at T_4), participants were asked to provide annual (five) self-administered health and lifestyle questionnaires and a FFQ at 3.5 and 6.5 years later. The CFS health and lifestyle questionnaire provided yearly information on cancers, hospitalization, colonoscopy, and colon and rectum endoscopy procedures. The PPT-CFS FFQ was a Block Health Habits and History Questionnaire (24), modified slightly to reflect the intake of low-fat and high-fiber food. This was the same FFQ used in the PPT. All clinical and pathology reports from large bowel endoscopic procedures performed for the duration of the follow-up as well as all hospitalizations and death certificates were collected. We defined an adenoma as recurrent if it was found in any endoscopy procedure done during the PPT-CFS. The 11 colon cancers diagnosed during the PPT-CFS were counted as recurrent lesions.

Statistical Analyses. We used an intention-to-treat approach, that is, we compared the number of adenomas during the CFS period in the intervention and control

groups according to the initial random assignment regardless of an individual participant's dietary adherence. The primary end point was the recurrence of adenomas. Secondary end points were the number, size, location, and histologic features of adenomas. As the CFS participants are a subset of the people in the PPT study, the nonparticipants might not be missing completely at random. Therefore, a multiple imputation method (25) was used to correct for the potential selection bias. First, a prediction logistic model was created using data from the CFS participants who underwent endoscopies in which the response was adenoma recurrence during the CFS and where predictors were covariates at baseline and during the 4-year trial period, as well as trial responses such as dietary changes during the trial and adenoma recurrence. Predictor variables were chosen based on stepwise regression (0.1 for entering terms in the model and 0.1 for removing terms in the model), potentially including intervention, sex, intervention by age and sex by age interactions, physical activity and dietary variables at T_0 and T_4, and recurrence status and advanced recurrence status at T_4. Predictor variables were fit separately in the intervention and control groups. The prediction model was then applied to predict (or impute) recurrence status for the nonparticipants. The estimated RR (intervention versus control) of an adenoma recurrence was calculated using both the actual data for the CFS participants and the imputed values from the prediction model for the nonparticipants (we did 10 imputations in performing multiple imputation). Standard errors of RR estimators were themselves estimated by the bootstrap (26). Bootstrap estimates were obtained using 1,000 resampled data sets (all randomized patients), whereby prediction models were re-estimated for each resampled data set. The multiple imputation method was

Table 2. Participant demographic, lifestyle, and dietary characteristics in the main PPT compared with those in PPT-CFS Study

	PPT participants not part of PPT-CFS (N = 1,104)*	PPT-CFS participants (N = 801)	P
Intervention participant (% yes)	50	51	0.84
Age (y)	62	60	<0.001
Gender (% males)	64	66	0.35
Race (% Caucasian)	89	90	0.48
Education (% high school or lower)	28	20	<0.001
Married (% yes)	76	84	<0.001
Smoking (% current)	15	11	0.008
NSAIDS (% yes, T_0)	34	33	0.43
Body mass index (kg/m^2)	28	28	0.90
Total physical activity (moderate + vigorous, h/wk)	12	13	0.03
Family history colon or rectal cancer T_0-T_4 (%)	23	32	<0.001
Advanced adenoma at T_0 (%)	36	39	0.17
Multiple adenomas at T_0 (%)	38	33	0.02
Adenomas with high-grade dysplasia at T_0 (%)	0.08	0.06	0.12
Villous adenomas at T_0 (%)	0.02	0.02	0.96
Villous, mixed adenomas at T_0 (%)	0.19	0.18	0.79
Adenoma at T_1 (%)	32	32	0.97
Advanced adenoma at T_1 (%)	5	6	0.22
Adenoma recurrence at T_4 (%,)	38	41	0.16
Advanced adenoma recurrence at T_4 (%)	6	8	0.11
Colon cancer at T_1 or T_4 (%)	1	1	0.82
Weight change since age 18 (% no change)	45	44	0.71
Premenopausal at T_0 (%)	17	17	0.79
Premenopausal at T_4 (%)	14	14	0.97
Estrogen (% yes)	11	13	0.24
Calcium supplement use (% yes)	33	35	0.45
Multiple vitamin supplement (% yes)	36	37	0.54
Vitamin D supplement (% yes)	30	32	0.38
Vitamin E supplement (% yes)	41	42	0.73
Vitamin A supplement (% yes)	33	34	0.58
Alcohol (g/d)	7.1	8.6	0.02
Bran cereals (g/d),	10.30	10.52	0.78
Fish (g/d), T_0	21.67	22.54	0.30
Red + processed meat (g/d),	92.58	93.37	0.73
Dry beans (g/d)	12.16	10.61	0.04
Energy (kcal/d)	1,918	1,929	0.68
Fat (% of energy)	35.71	35.34	0.27
Dietary fiber (g/1,000 kcal)	9.45	9.57	0.49
Fruit and vegetables (servings/1,000 kcal/d)	2.19	2.25	0.23
Change in energy (kcal/d)	−69.65	−64.66	0.83
Change in fat (% of energy)	−6.76	−7.63	0.03
Change of dietary fiber (g/1,000 kcal)	3.97	4.45	0.08
Change fruit and vegetables	1.16	1.20	0.55

NOTE: Results presented as means with P values for differences in means between those participants with a CFS colonoscopy and those without, evaluated by using a t test for continuous values and χ^2 for categorical variables. T_0, baseline (randomization); T_1, clearing colonoscopy (year 1); T_4, PPT trial end point (year 4).

*Refers to the 1,104 PPT participants that either did not participate in the PPT-CFS or did not have a colonoscopy during the PPT-CFS.

Table 3. Participants in the PPT-CFS Study: characteristics that are significantly different between the intervention and control groups

	Control (N = 396)	Intervention (N = 405)	P
Advanced adenoma recurrence at T_4 (%)	10	6	0.04
Physical activity at T_0 (moderate + vigorous MET h/wk)	55.8	65.1	0.03
Change (T_0-T_4) in energy (kcal/d)	−102.0	−28.1	0.03
Change (T_0-T_4) in fat (% of energy)	−2.5	−12.7	<0.001
Change (T_0-T_4) in fiber (g/1,000 kcal)	0.5	8.3	<0.001
Change (T_0-T_4) in fruit and vegetable (servings/1,000 kcal/d)	0.3	2.1	<0.001

NOTE: Only characteristics that are significantly different at $P \leq 0.05$ are shown. Results presented as means with P values for differences in means evaluated by using a t test. T_0, baseline (randomization); T_1, clearing colonoscopy (year 1); T_4, PPT trial end point (year 4).

applied to several end points, e.g., recurrence in CFS only (that is, after T_4), any recurrence at T_4 or CFS, any advanced recurrence at T_4 or CFS, multiple recurrence at T_4 or CFS, and any recurrence at T_1, T_4, or CFS. In addition to the multiple imputation–based estimates of RR, we fit logistic regression models with the outcome being CFS adenoma recurrence, and covariates being baseline and years 1 to 4 dietary variables and adenoma status. We found similar results with these analyses to those presented with the multiple imputations (data not shown).

For intervention-control group comparisons of longitudinal changes in the dietary goal intake (fat, fiber, and fruits and vegetables), we fit a linear mixed model (27). These models included fixed effect terms for intervention group, indicators of whether a measurement was taken during the CFS or before, and the time between when a measurement was taken and the beginning of the CFS for measurements taken during the CFS. A random intercept term was included in the linear mixed model to account for correlation between measurements taken on the same subject. t tests and χ^2 tests were used to compare continuous and categorical variables between intervention and control groups. All P values correspond to two-sided tests.

Table 4. Differences in baseline, change and rate of change for fat, fiber, and fruits and vegetable intake in the intervention and control groups in the PPT and PPT-CFS estimated by a linear mixed model

Time	Difference between intervention and control groups (mean ± SE)	P
Fruits and vegetables (servings 1,000 kcal/d)		
T_0	0.014 ± 0.06	0.81
On study-T_0*	1.63 ± 0.04	<0.001
CFS-T_4†	−0.13 ± 0.03	<0.001
Fiber (g/1,000 kcal/d)		
T_0	0.37 ± 0.23	0.11
On study-T_0*	7.24 ± 0.17	<0.001
CFS-T_4†	−0.70 ± 0.03	<0.001
Fat (% energy)		
T_0	−0.39 ± 0.34	0.26
On study-T_0*	−9.91 ± 0.25	<0.001
CFS-T_4†	1.05 ± 0.05	<0.001

NOTE: Analyses for 780 PPT-CFS participants with FFQ data. The final linear mixed model used indicators for T_1 to T_4, intervention group, time since T_4 and the interaction with intervention: $E(y) = \beta_0 + \beta_1 T_{1\text{-}4 \text{ or CFS}} + \beta_2 \max(0,t\text{-}t_4) + G^* (\beta_3 + \beta_4 T_{1\text{-}0 \text{ or CFS}} + \beta_5 \max(0,t\text{-}t_4)$, $\beta_0 \sim N(\mu, \sigma^2)$ where $T_{1\text{-}4 \text{ or CFS}}$ is an indicator which is equal to one when a measurement is in the trial or the CFS and equal to zero otherwise; t is the year of the measurement from the date of randomization, t_4 is the year of the fourth year of measurement (where $t_4 = 4$) and G is the intervention or control group. The ''on-study'' time point represents a random time point during the PPT. T_0, baseline (randomization); T_1, clearing colonoscopy (year 1); T_4, PPT trial end point (year 4).
*Difference in change between on-study time point and T_0.
† Difference in change per unit time (year) during PPT-CFS.

Results

Of the 1,905 participants (958 intervention, 947 control) who completed the PPT, 1,192 (603 intervention, 589 control) consented to be in the PPT-CFS and 801 participants (405 intervention, 396 control) had a confirmed colonoscopy procedure during the PPT-CFS (Table 1). During the main PPT, the mean time between the year 1 colonoscopy and the trial end point colonoscopy (T_4) was 3.06 years in both the intervention and control groups, and the mean number of colonoscopy procedures after the T_1 was 1.31 in both groups. PPT-CFS participants had slightly more colonoscopy procedures during the main trial with <3 years between their T_1 and T_4 colonoscopies. The time interval between the main trial end point colonoscopy (T_4) and the first colonoscopy during the PPT-CFS was 3.94 years for the intervention group and 3.87 years for the control group, and the time from randomization (trial baseline) to the first PPT-CFS was 8.07 years for the intervention group and 7.99 years for the control group. During the PPT-CFS intervention, participants had an average of 1.36 procedures, whereas the control participants had 1.37 colonoscopies. The top four reasons for undergoing colonoscopy procedures in the PPT-CFS were routine surveillance (31%), personal history of adenomas (19%), family history of colon cancer (14%), and bleeding (11%).

Table 2 compares 44 demographic, lifestyle, dietary, and clinical characteristics previously associated with adenoma recurrence in the PPT and other adenoma studies in the 801 participants that had a colonoscopy during the PPT-CFS compared with the 1,104 PPT participants that either did not participate in the PPT-CFS (n = 713) or did not have a colonoscopy during the PPT-CFS (n = 391). The 801 participants in the PPT-CFS who underwent a colorectal endoscopy procedure during follow-up compared with 1,104 that did not participate or did not have a procedure, were more likely to have smoked less and be younger, more educated, married, and physically active. They were more likely to have had a family history of colorectal cancer, fewer multiple adenomas at baseline, and a T_1 colonoscopy

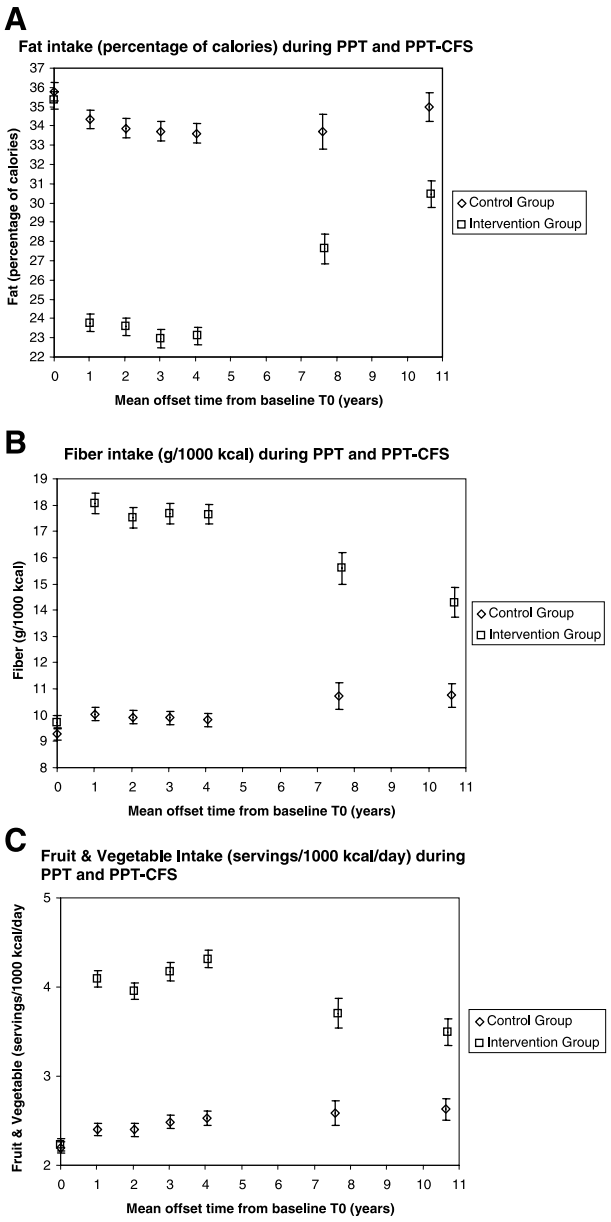

Figure 1. Fat (**A**), fiber (**B**), and fruit and vegetable (**C**) intakes (*points,* mean; *bars,* 95% CIs) during the PPT and the PPT-CFS in the intervention and control groups.

procedure during the main trial. These PPT-CFS participants also drank more alcohol, consumed fewer dry beans at baseline, and showed a greater decrease in fat during the trial. In general, the 801 PPT-CFS participants reporting a follow-up endoscopy procedure tended to have a ''healthier'' lifestyle as well as a family history potentially leading to more follow-up colonoscopies.

We compared the intervention (n = 405) and control (n = 396) group participants in the PPT-CFS for the same 44 variables shown in Table 2. The CFS-PPT participants in the intervention group differed from the control in only six variables, and four of these were for postrandomization change in diet (Table 3). The intervention group participants in the PPT-CFS were less likely to have an advanced adenoma at the end of the main trial (T_4; P = 0.04), and were more likely to have increased physical activity at baseline (T_0; P = 0.04). As expected, the intervention group participants made greater changes in the three dietary goals of the trial: fat, fiber, and fruits and vegetables during the 4 years of the main trial than the control group, and also consumed less fat and more fruits and vegetables at the end of the PPT.

During the main PPT, we collected FFQ dietary measurements at baseline as well as at each year of the PPT. In the PPT-CFS subcohort, there were two post-trial FFQs taken at 7.5 and 10.5 years after randomization. Figure 1 shows a plot of the dietary data for all three PPT dietary goals: percentage of energy from fat (A), grams of dietary fiber/1,000 kcal (B), and servings of fruits and vegetables/1,000 kcal/d (C). The means and 95% CI of these dietary measurements are plotted according to intervention and control groups. Although the intervention group significantly changed each of their dietary goals during the main trial, during the PPT-CFS, the trend for each dietary goal was significantly reversed, with fat increasing, and fiber and fruits and vegetables decreasing in the intervention group compared with the control group.

To model the trend of the dietary change, a random effect model was designed (see Table 4 for formulation) and the intercept term was assumed to be random to account for the correlation of the dietary values within an individual. The intervention and control groups were not different for each of the dietary goals at baseline (T_0), but there were significant differences in the change for each of the goals during the 4 years of the active intervention (Table 4). There were significant differences in the average change for each of the goals during the PPT-CFS. Even though the intervention group participants increased their fat intake and decreased their intake of fiber and fruits and vegetables during the PPT-CFS, when active dietary counseling ceased, they did not go back to their prerandomization baseline diet ($P < 0.001$ from paired t tests) and each of the three dietary goals was still significantly different from the controls during the PPT-CFS ($P < 0.001$ from t tests).

In Table 5, we compare adenoma recurrence in the intervention and control groups, after adjusting for participants missing in the PPT-CFS using multiple imputation. The RR of any recurrent adenoma in the intervention group compared with the control group was 0.98 (0.88-1.09). There were also no significant differences in the RR for either the recurrence of multiple adenomas (0.92; 0.77-1.10) or advanced adenomas in the intervention group compared with the control group (1.06; 0.81-1.39). We also examined ''high-risk'' participants with either an advanced adenoma or three or more adenomas (recent colonoscopy guidelines suggest that this higher risk group should receive more frequent screening; ref. 28). The RR of high-risk adenomas in the intervention compared with the control group was 0.85 (0.67-1.06). We found no significant differences in intervention and control participants in adenoma recurrence by their location in the large bowel. Logistic regression models, used to compare the RR for adenoma recurrence, advanced adenomas, and multiple adenomas in the 405

Table 5. RR and 95% CI estimates of adenoma recurrence by intervention status in the PPT-CFS after adjustment for missing responses by imputation

Adenoma	Control, *n* (%)*	Intervention, *n* (%)*	RR (95% CI) †	*P* ‡
≥1	147 (37.1)	144 (35.6)	0.98 (0.88-1.09)	0.74
1	78 (19.7)	82 (20.2)	1.01 (0.86-1.20)	0.88
2	35 (8.8)	37 (9.1)	1.01 (0.78-1.31)	0.95
≥3	34 (8.6)	25 (6.2)	0.77 (0.57-1.05)	0.10
Multiple (>1)	69 (17.4)	62 (15.3)	0.92 (0.77-1.10)	0.34
Advanced	32 (8.1)	34 (8.4)	1.06 (0.81-1.39)	0.67
High risk	58 (14.6)	48 (11.9)	0.85 (0.67-1.06)	0.16
Proximal	91 (23.0)	80 (19.8)	0.86 (0.73-1.01)	0.06
Distal	57 (14.4)	51 (12.6)	0.94 (0.75-1.18)	0.59

NOTE: The estimated RRs were calculated using both actual data from the PPT-CFS participants and the imputed values from the prediction model for nonparticipants.

* Number and percentage with lesion. Percentages were calculated from the PPT-CFS total for the control (n = 396) and intervention (n = 405) groups. In the case of high-risk, proximal, and distal adenomas, these categories are not mutually exclusive (percentage columns will therefore not sum to 100).

† CIs were computed using the percentile method.

‡ P values were computed from z test.

intervention participants to the 396 controls showed similarly null results (data not shown).

We also used multiple imputation to examine cumulative recurrence of adenomas from baseline through the end of the CFS. As shown in Table 6, intervention-control group RR was 1.04 (0.98-1.09) for any adenoma recurrence, 0.97 (0.89-1.05) for multiple adenoma recurrence, 0.97 (0.84-1.15) for advanced adenoma recurrence, and 0.91 (0.82-1.02) for high-risk adenomas. Using logistic regression models adjusted for significant covariates, we found similar results (data not shown).

Discussion

We found that making a dietary change to a low-fat, high-fiber, high-fruit and -vegetable eating plan during the 4 years of the PPT main trial had no effect on adenoma recurrence (16). After an additional 4 years of follow-up in a subcohort of the PPT, the PPT-CFS, there was no difference in risk of adenoma recurrence by intervention group assignment. Those originally assigned to the intervention group compared with those in the control group had a RR of adenoma recurrence of 0.98 (0.88-1.09). There were also no differences in the risk of multiple or advanced adenoma recurrence. Furthermore, we found no difference in any multiple or advanced adenoma recurrence when we combined end points from both the PPT main trial and PPT-CFS follow-up.

If dietary fat, fiber, and fruits and vegetables truly modulate colorectal carcinogenesis, several possible explanations may be considered to explain why recurrence was not altered in those randomized to an intervention scheme compared with those on the placebo/usual diet. These explanations include (*i*) an inadequate trial length, (*ii*) inappropriate timing in the life course for such a trial, (*iii*) inappropriate end point, or (*iv*) inappropriate intervention (16, 29).

Inadequate Trial Length. Rapid changes in colon cancer risk among migrants from low- to high-incidence regions (or vice versa) indicate an important role for environmental exposures during adult life (5, 30). However, dietary changes might require several decades to affect changes in adenoma recurrence (31). Fearon and Vogelstein (6) developed a genetic model of an adenoma-carcinoma sequence, postulating that the histopathologic transition from adenoma to carcinoma in patients with colorectal carcinoma was associated with an accumulation of genetic events that conferred a significant growth advantage to a clonal population of cells. For a typical epithelial cell to accumulate the multiple genetic alterations required to progress to metastatic disease might

Table 6. RR and 95% CI estimates of adenoma recurrence for PPT-CFS participants by intervention status in either the PPT-CFS or the PPT after adjustment for missing responses by imputation

Adenoma	Control, *n* (%)*	Intervention, *n* (%)*	RR (95% CI) †	*P* ‡
No recurrence	170 (42.9)	177 (43.7)	—	—
Any recurrence	226 (57.1)	228 (56.3)	1.04 (0.98-1.09)	0.21
Multiple	141 (35.6)	135 (33.3)	0.97 (0.89-1.05)	0.46
Advanced	63 (15.9)	49 (12.1)	0.97 (0.84-1.15)	0.79
High risk	94 (23.7)	78 (19.3)	0.91 (0.82-1.02)	0.12
Proximal	161 (40.7)	168 (41.5)	0.99 (0.92-1.05)	0.66
Distal	166 (41.9)	162 (40.0)	0.97 (0.92-1.03)	0.32

NOTE: The estimated RRs were calculated using both actual data from the PPT-CFS participants and the imputed values from the prediction model for nonparticipants.

* Number and percentage with lesion. Percentages were calculated from the PPT-CFS total for the control (n = 396) and intervention (n = 405) groups. In the case of high-risk, proximal, and distal adenomas, these categories are not mutually exclusive (percentage columns will therefore not sum to 100).

† CIs were computed using the percentile method.

‡ P values were computed from a z test.

require 30 to 40 years (21). The actual growth rate of an adenoma to a carcinoma has been difficult to measure because clinical practice requires the removal of all detected adenomas. In familial adenomatous polyposis, a genetic disease caused by a germ line mutation in the *APC* gene, thousands of adenomas form in the colorectum. The median age of cancer diagnosis in patients with untreated familial adenomatous polyposis is 42 years, 25 years earlier than the median age of patients with sporadic colorectal cancer (21). Thus, the 8 years (approximately) of follow-up of the PPT and PPT-CFS might still be inadequate to affect adenoma growth.

Inappropriate Timing in the Life Course for Such a Trial. Successful cancer prevention may require dietary modifications much earlier in the life cycle, such as at birth, early development, and puberty (2, 3, 32). The mean age of the PPT participants was 61 years at baseline; if nutritional factors influence critical events only earlier in life, then a change in diet later in adult life may be ineffective. For example, in the Netherlands Cohort Study, a weak inverse relation was found between energy restriction early in life and subsequent colon carcinoma risk for men and women (33). In addition to mostly null dietary adenoma interventions typically lasting 3 or 4 years (13-15), even the recently completed Women's Health Initiative study with 9 years of intervention found no effect of a low-fat eating plan on colon cancer (34).

Inappropriate End point. Although a large body of evidence suggests that adenomatous polyps are the putative precursor for most colorectal cancers (9, 21, 22, 35, 36); even the adenoma is not a perfectly reliable surrogate (12, 37). One shortcoming of the PPT and other adenoma recurrence trials is that the majority of recurrent adenomas are small (<1 cm), tubular adenomas with low-grade dysplasia that are thought to have less potential of proceeding to cancer compared with advanced adenomas. Only 8% and 7% of the participants in the PPT-CFS and in the PPT, respectively, were classified as having advanced adenomas. If the PPT intervention affects only the growth of small adenomas into large advanced adenomas or advanced adenomas to cancer, then we would fail to detect this effect in our current study design. Furthermore, given that only a small proportion of adenomas progress to invasive cancer, even a true protective effect among this small subset of ''bad'' lesions might not have been detectable (12).

Inappropriate Intervention. Another possibility is that the dietary intervention was inadequate; a reduction in fat intake to ≤15% of calories or a greater intake of fiber or fruits and vegetables might be required to reduce the risk of recurrent adenomas. Moreover, we may not have chosen the optimal set of dietary targets. The 20% reduction in the consumption of red and processed meat among subjects in the PPT intervention group may have been too small to affect the risk of recurrence of adenomas. Since the PPT intervention was a behavior modification trial in which participants self-selected foods to obtain their fat, fiber, and fruit and vegetable goal, the range of intake of specific phytochemicals in foods was enormous. Moreover, in spite of the self-reports of dietary change and the (modest) effects on hard end points such as serum carotenoids and total weight, we cannot rule out the possibility that participants did not in fact make the fairly extensive dietary changes recorded in the dietary assessment instruments.

In summary, our study followed a subgroup of PPT participants for a further 5 years (approximately) after the main PPT and found no evidence that a diet low in fat and high in fiber, fruits, and vegetables reduces the risk of recurrent colorectal adenomas. The null results presented here and those reported previously may be a consequence of study design and limitations so that we cannot definitively conclude that a change in diet is ineffective in reducing the risk of colorectal cancer. Clearly, changes of the magnitude we observed do not decrease the risk of adenoma recurrence. Nonetheless, the abundance of data indicating that a diet low in saturated fats and rich in fruits, vegetables, and whole grains has a favorable influence on the risk of chronic disease and mortality (38-40); it seems appropriate that this type of diet be promoted on the basis of its known healthful effects.

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