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Original Contribution

The Effect of Strict Adherence to a High-Fiber, High-Fruit and -Vegetable, and Low-Fat Eating Pattern on Adenoma Recurrence

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Individual differences in dietary intake are thought to account for substantial variation in cancer incidence. However, there has been a consistent lack of effect for low-fat, high-fiber dietary interventions and risk of colorectal cancer. These inconsistencies may reflect the multistage process of cancer as well as the range and timing of dietary change. Another potential reason for the lack of effect is poor dietary adherence among participants in these trials. The authors examined the effect of strict adherence to a low-fat, high-fiber, high-fruit and -vegetable intervention over 4 years among participants ($n = 1{,}905$) in the US Polyp Prevention Trial (1991–1998) on colorectal adenoma recurrence. There was a wide range of individual variation in the level of compliance among intervention participants. The most adherent participants, defined as ''super compliers'' ($n = 210$), consistently reported that they met or exceeded each of the 3 dietary goals at all 4 annual visits. Multivariate logistic regression models were used to estimate the association between dietary adherence and adenoma recurrence. The authors observed a 35% reduced odds of adenoma recurrence among super compliers compared with controls (odds ratio = 0.65, 95% confidence interval: 0.47, 0.92). Findings suggest that high compliance with a low-fat, high-fiber diet is associated with reduced risk of adenoma recurrence.

adenoma; colorectal neoplasms; dietary fiber; patient compliance; polyps

Despite a recent drop in incidence rates, colorectal cancer remains the second most commonly diagnosed cancer in men and women in the United States and the second leading cause of cancer death (1). Colorectal adenomatous polyps are considered precursors to colorectal cancer. Identifying modifiable risk factors for colorectal adenomas could pinpoint potential targets for colorectal cancer prevention. Individual differences in dietary intake are believed to attribute to more variation in cancer incidence than any other factor and could account for as many as 90% of colorectal cancer deaths in the United States (2). Observations from ecologic cross-sectional studies of colorectal cancer illustrate that colorectal cancer incidence rates vary dramatically around the world, and by population consumption of fat and fiber, suggesting that diet plays a vital role in the risk of colorectal cancer (3–5). Findings from most case-control studies have observed a decreased odds of colorectal cancer associated with low-fat, fiber-rich diets (6, 7). However, recent prospective cohort studies and dietary intervention trials of adenoma recurrence have predominantly yielded null results (8–15).

A number of factors could be responsible for the observed inconsistency in results. First, development of colorectal cancer is a multistage process, and the timing of initiation of the diet or the duration of the intervention may not be appropriate for prevention. Second, the inconsistencies may be due to confounding by other nutritional or lifestyle factors, measurement error, recall bias, or unknown confounding factors. Another potential reason for the lack of effect in dietary intervention trials is the low level of adherence among intervention participants. Intention-to-treat analysis, a conservative approach to address confounding arising in randomized trials, evaluates the effectiveness of the drug (or intervention) in practice, in which the effect of treatment is averaged over those who do and do not adhere to treatment (16). Most trials rarely achieve perfect adherence; if nonadherence exists, the power of the trial to detect an effect of the intervention will be diluted (17, 18).

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One question that remains after the completion of the trial is the effect of adherence or efficacy of the treatment. This less conservative approach requires certain assumptions; however, it may provide meaningful observations about efficacy of the treatment (18, 19). For example, early randomized clinical trials of lipid-lowering drugs failed to observe a mortality benefit for patients in the treatment group compared with placebo (20). In a subgroup analysis, good adherers to the treatment had a significantly lower mortality rate than did poor adherers (20). However, the investigators also observed similar mortality benefits among the good adherers in the placebo group and the good adherers in the treatment group (20). Several statistical approaches for evaluating efficacy that go beyond the intention-to-treat analysis have been proposed. However, there are some limitations to evaluating treatment efficacy in subgroups determined by adherence and defined after randomization, as illustrated in the aforementioned study. We evaluated one such approach proposed by Efron and Feldman (21) in this study, which uses an individual's observed compliance to compare treatment groups (21).

The Polyp Prevention Trial was designed to test the effect of a low-fat, high-fiber, and high-fruit and -vegetable dietary intervention on the recurrence of adenomas in the colon (22). After 4 years of the trial, no difference in the rate of adenoma recurrence between the intervention group and the control group was observed (12). The number of dietary goals met by the intervention group varied greatly; thus, it is possible that lack of adherence in fully attaining the intervention goals may account for the lack of observed effect. In this analysis of the Polyp Prevention Trial, we examined whether greater adherence to the low-fat, high-fiber, and high-fruit and -vegetable intervention goals influenced risk of adenoma recurrence.

MATERIALS AND METHODS

Sample population

The data for this study were drawn from the Polyp Prevention Trial. The overall design, rationale, dietary intervention and endpoint procedures, and results of the trial were reported previously (21–24). Briefly, participants had to be at least 35 years of age; had to have at least one histologically confirmed colorectal adenoma identified; must not have had prior surgically resected adenomatous polyps or diagnoses of colorectal cancer, inflammatory bowel disease, or polyposis syndrome; had to be 150% or more of their recommended weight; and could not be currently using lipid-lowering medications. Among the 2,079 participants recruited between 1991 and 1994, 1,905 (control group, $n = 947$; intervention group, $n = 958$) completed the study and were considered in this analysis. A detailed description of the intervention and the dietary changes achieved was published previously (23).

The study was approved by the institutional review boards of the National Cancer Institute and each of the participating centers. All participants provided written informed consent at entry into the study.

Assessment of dietary intake and supplement use

At baseline and at each of the 4 annual follow-up visits, participants completed an interviewer-administered questionnaire including demographic, clinical, medication and supplement use, and dietary information. In addition, each participant provided a fasting blood sample for analysis. Diet was assessed at each annual visit with a modified Block–National Cancer Institute food frequency questionnaire and DietSys version 3.7 software (24). This analysis was based on data from the food frequency questionnaire exclusively, which asked about frequency of intake during the past year and average serving sizes. Compared with the 4-day food record and the 24-hour recall, the food frequency questionnaire slightly overestimated fat and underestimated fiber, fruit, and vegetable intake (23, 25).

Assessment of adenoma

Participants received full colonoscopies at baseline, their 1-year visit, and the end of the trial intervention, about 4 years after randomization. The colonoscopy at the first annual visit allowed for detection and removal of any lesions missed by the baseline procedure. Pathologically confirmed adenomas diagnosed between the 1-year visit and the end-of-trial colonoscopy were considered recurrent adenomas. Biopsy samples of all adenomas removed during colonoscopy were reviewed independently by 2 pathologists.

Measure of adherence to dietary goals

The specific goals of the dietary intervention were to limit fat to 20% of energy intake and to consume at least 18 g of fiber and 3.5 servings of fruits and vegetables per 1,000 kcal. Dietary goals were calculated as a proportion of each participant's total caloric intake as determined by the baseline food frequency questionnaire, and the specific individual goals were communicated to each participant. Individual goals were calculated for each participant at each yearly follow-up visit, and achievement of target goals was defined as meeting or exceeding the specific goals communicated at baseline. Composite indices of success in meeting dietary goals were then determined both across years for the individual goals and across years and goals for the entire trial, for a total of 12 goals (3 goals/year for 4 years). Participants were then designated as 1) "poor compliers" = met 0–3 goals, 2) "inconsistent compliers" = met 4–8 goals, and 3) "super compliers" = met 9–12 goals.

Statistical analyses

Statistical analyses were performed by using Statistical Analysis Systems (SAS) software, version 9.1 (SAS Institute, Inc., Cary, North Carolina). The characteristics of the super compliers and controls were compared with t tests for continuous variables and the χ^2 test for categorical variables. Odds ratios and 95% confidence intervals for the association between dietary adherence and (any, multiple, and advanced) adenoma recurrence were estimated by using logistic regression. Our main analyses compared adenoma recurrence among the super compliers with that in the entire control group. We ran several different models, including an unadjusted model

Table 1. Selected Baseline Participant Characteristics of Intervention Super Compliers[a] and Controls, Polyp Prevention Trial, 1991–1998

Characteristic	Super Compliers[b] (n = 210)			Controls[b] (n = 947)			*P* Value[c]
	No.	%	Mean (SD)	No.	%	Mean (SD)	
Sociodemographics							
Sex: male	133	63.3		598	63.1		0.960
Race: white	190	90.5		860	90.8		0.879
Age, years			60.4 (8.8)			61.1 (9.8)	0.325
Educational level: high school or less	53	25.2		330	34.8		0.007
Marital status: married	168	80.0		765	80.8		0.795
Baseline health indicators							
Body mass index, kg/m^2			27.5 (4.0)			27.5 (3.9)	0.989
Family history of colon cancer	52	24.7		264	27.9		0.369
Alcohol consumption, g/day			6.4 (11.4)			8.0 (14.3)	0.076
Smoking status							
Never or former	196	93.3		822	86.8		
Current	14	6.7		125	13.2		0.001
Moderate or vigorous exercise, hours/week			12.8 (12.8)			11.6 (11.3)	0.191
Baseline dietary patterns							
Prepares own meals	88	41.9		410	43.3		0.713
Buys own food	88	41.9		432	45.6		0.328
Usual no. of meals							
1 or 2/day	62	29.5		345	36.4		
≥3/day	148	70.5		602	63.6		0.058
Typical no. of meals eaten out							
0 to 1/week	75	35.7		316	33.7		
≥2 /week	135	64.3		623	66.3		0.348
Missing	0			8			
Usual no. of snacks							
0 to 1/day	98	46.9		480	51.0		
≥2 /day	111	53.1		461	49.0		0.540
Missing	1			6			
Caloric intake, kcal/day			1,872.0 (491)			1,928.0 (604)	0.154
Fat, % of calories			31.7 (7.2)			35.8 (7.4)	<0.0001
Fiber, g/1,000 kcal			11.7 (4.7)			9.3 (3.6)	<0.0001
Fruit and vegetables, servings/1,000 kcal			2.8 (1.2)			2.2 (1.1)	<0.0001
Red and processed meats, g/1,000 kcal			40.4 (19.8)			49.1 (21.8)	<0.0001
Ratio of red meat to chicken and fish, g/day			1.6 (1.6)			2.6 (3.8)	<0.0001
Legumes, g/1,000 kcal			7.7 (11.7)			6.0 (8.8)	0.044
Cruciferous vegetables, g/1,000 kcal			17.7 (15.0)			12.8 (12.4)	<0.0001
Bran cereals, g/1,000 kcal			8.3 (12.9)			5.2 (8.4)	0.001
Total carotenoids, mcg/day			10,507.0 (5,284.5)			8,213.8 (4,640)	<0.0001
Baseline vitamin and mineral intake							
Calcium from food, mg/day			893.0 (387.8)			839.6 (445.5)	0.080
Calcium supplement use, mg/day			0.4 (0.5)			0.3 (0.5)	0.003
Folate, g/1,000 kcal			187.6 (57.4)			160.7 (56.5)	<0.0001
Vitamin E from supplements, TE/day			0.5 (0.5)			0.4 (0.5)	0.016
NSAIDs, mg/day			119.6 (381.3)			121.1 (356.5)	0.954
Multiple vitamin use	83	39.5		345	36.4		0.401

Table continues

Table 1. Continued

Characteristic	Super Compliers[b] ($n = 210$)			Controls[b] ($n = 947$)			*P* Value[c]
	No.	%	Mean (SD)	No.	%	Mean (SD)	
Trial characteristics							
Days from randomization to T4 visit			1,434.5 (155.9)			1,410.1 (210.4)	0.057
Time from T1 to T4 colonoscopy, days			1,092.5 (136.2)			1,118.2 (233.6)	0.034
No. of trial colonoscopies			2.3 (0.6)			2.3 (0.8)	0.316
Baseline adenoma characteristics							
Size of the largest adenoma							
≥1 cm	66	34.4		298	34.0		
<1 cm	126	65.6		579	66.0		0.839
Missing	18			70			
Had more than 1 adenoma	78	37.1		334	35.3		0.608
Had a villous/mix adenoma	37	17.6		184	19.4		0.546
Had an advanced adenoma	78	37.1		370	39.1		0.604
Had a high-grade adenoma	11	5.2		73	7.7		0.212

Abbreviations: NSAID, nonsteroidal antiinflammatory drug; SD, standard deviation; TE, tocopherol equivalent.

[a] Super compliers are defined as participants in the Polyp Prevention Trial intervention who completed all 4 annual food frequency questionnaires and met a total of 9–12 food frequency questionnaire goals over the trial period.

[b] Column percentages do not always sum to 100% because of rounding, and sample size varies slightly for some variables because of missing data.

[c] *P* values for differences in means were determined by *t* test, and *P* values for differences in proportions were determined by chi-squared tests.

(model 1); a model adjusted for those covariates significantly different between the compliers and the controls (model 2); a model adjusted for 41 variables previously reported to be associated with either colorectal cancer or adenoma recurrence (model 3); and a model that included all 41 covariates in model 3 as well as baseline serum biomarkers of lipids, selenium, and carotenoids in a subset of patients with these measurements (158 super compliers, 268 controls) (model 4). To develop categorical variables, dietary variables were grouped into quartiles based on the distribution in the entire study population ($n = 1,905$) and were incorporated into models as indicator variables defined by the second–fourth quartiles of intake, with the lowest quartile as the referent group.

Estimating percentile-specific compliance

We applied a methodological approach described by Efron and Feldman (21) that relies on use of the compliance variable itself to compare subjects in both the treatment and the control arms of the trial and uses modeling to investigate associations among compliance, drug or intervention dose, and drug or intervention effect (19). This method selects a comparable set of controls based on ranking dietary adherence rates to further explore the association between super compliance and adenoma recurrence. Specifically, the 210 super compliers, defined as having met at least 9 of 12 dietary goals, correspond to 25.6% of the 821 intervention participants who completed the study and for whom no data on dietary goals were missing. The comparative referent group for our percentile-specific analysis was based on assigning the dietary intervention goals to the control group in a similar manner by using data from the control group's annual food frequency questionnaire. After assigning the intervention dietary goals to the control group, a cutpoint to define the controls who met the most goals was set similar to that for the 25.6% of intervention participants designated as super compliers. This cutpoint was set at meeting 2 or more dietary goals, which included 225 (26.8%) of the 840 controls who completed the study and for whom no missing data on yearly dietary goals were missing. We labeled the group of controls who fit into this group ($n = 225$) as "goal-achieving controls."

Next, we examined whether the effect of the intervention changed by compliance status (i.e., whether there was a stronger intervention effect among the super compliers and goal-achieving controls) by testing for an interaction between randomization group (intervention vs. control) and high compliance (super compliers/goal-achieving controls vs. non-super-compliers/non-goal-achieving controls). Then, we evaluated the association for risk of adenoma recurrence between the super compliers and our defined goal-achieving controls group. All statistical analyses were 2-sided, and *P* values were considered to be significant if <0.05.

RESULTS

Comparison of super compliers and controls

Of 821 (85.9%) of the 956 intervention participants who completed the study, 245 (29.8%) were classified as poor compliers, 366 (44.6%) as inconsistent compliers, and 210 (25.6%) as super compliers. No significant associations were observed among poor compliers or inconsistent compliers compared with controls; thus, there does not appear to be a continuum of the magnitude of association. Therefore, our analysis focused on the associations among super compliers.

Table 2. Association Between Super Compliance and Risk of Colorectal Adenoma Recurrence, Polyp Prevention Trial, 1991–1998

Type of Adenoma Recurrence	Super Compliers[a]		Controls		Unadjusted Model[b]		Partially Adjusted Model[c]		Fully Adjusted Model[d]	
	No.	%	No.	%	OR	95% CI	OR	95% CI	OR	95% CI
Total	210		947							
Any recurrence	65	31.0	374	39.5	0.69	0.50, 0.95	0.65	0.46, 0.92	0.68	0.47, 0.98
Multiple recurrence	20	9.5	157	16.6	0.53	0.32, 0.87	0.52	0.31, 0.87	0.51	0.30, 0.89
Advanced recurrence	7	3.3	66	7.0	0.46	0.21, 1.10	0.44	0.19, 1.01	0.44	0.18, 1.05

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Super compliers are defined as participants in the Polyp Prevention Trial intervention who completed all 4 annual food frequency questionnaires and met a total of 9–12 food frequency questionnaire goals over the trial period.

[b] Logistic regression model unadjusted for any covariates.

[c] Logistic regression model adjusted for all covariates significantly different between controls and super compliers (educational level; smoking status; waist-to-hip ratio; fat intake at baseline; intake of fiber, fruit and vegetables, and red and processed meats; ratio of red meat to chicken and fish; intake of legumes and cruciferous vegetables; calcium supplement use; intake of folate, total carotenoids, bran cereals, and vitamin E from supplements; and days from T1 colonoscopy to T4 colonoscopy).

[d] Logistic regression model adjusted for all covariates. Refer to Table 1 for a list of all covariates.

Descriptive baseline characteristics of the intervention participants classified as super compliers and participants randomized to the control group are presented in Table 1. The mean age and body mass index of both the super compliers and the controls were very similar, 60.4 years versus 61.1 years and 27.5 kg/m^2 versus 27.5 kg/m^2, respectively. Compared with participants in the control arm, super compliers were significantly more educated and were less likely to be current or former smokers at the time of randomization ($P = 0.001$). Super compliers also differed significantly from the control group at baseline with respect to dietary intake. Super compliers had a lower intake of fat (percentage of calories) and of red and processed meats and a higher intake of fiber, fruit and vegetables—including cruciferous vegetables—and total carotenoids. Super compliers reported an average baseline intake of 31.7% for fat (percentage of calories), 11.7 g/1,000 kcal for fiber, and 2.8 servings/1,000 kcal of fruit and vegetables. We did not observe any statistically significant differences in adenoma characteristics between the super compliers and the control group, including the size and number of baseline adenomas and the presence of advanced or high-grade adenomas.

Association between super compliance and adenoma recurrence

The observed effect estimates from 3 different models—unadjusted (model 1), partially adjusted (model 2), and fully adjusted (model 3)—were very similar in magnitude and precision for each of the 3 outcomes. We observed 30% statistically significant decreased odds of adenoma recurrence for super compliers compared with controls in model 1 (odds ratio = 0.69, 95% confidence interval: 0.50, 0.95). After adjusting for the covariates in models 2 and 3, we also observed more than a 30% statistically significant decreased odds ratio for any adenoma recurrence among super compliers (Table 2). In addition, super compliance to the intervention over the 4 years of the trial was associated with approximately 50% statistically significant decreased odds of multiple adenomas for models 1–3 (Table 2). Finally, we observed a stronger, but nonsignificant inverse association for advanced adenoma recurrence in all 3 models (Table 2). In a subset of patients with dietary and biomarker measurements, we observed statistically significant decreased odds of any adenoma recurrence among super compliers (odds ratio = 0.47, 95% confidence interval: 0.24, 0.94) and nonsignificant decreased odds of multiple and advanced recurrence (odds ratio = 0.67, 95% confidence interval: 0.27, 1.67 and odds ratio = 0.49, 95% confidence interval: 0.14, 1.68, respectively).

Percentile-specific compliance effects

In our test for interaction between the intervention and control randomization groups by super compliers and goal-achieving controls, which examined whether the intervention effect differed by compliance status, we observed statistically significant interaction effects for all 3 types of adenoma recurrence outcomes ($P < 0.05$) (Table 3). In a separate analysis, we analyzed the association of recurrence between the super compliers and goal-achieving controls, a comparable compliant control population (Table 4). Although the overall sample size for this subanalysis was much smaller than for our analysis including all controls, we observed similar magnitudes of effect for all 3 adenoma outcomes, and we specifically observed more than 50% statistically significant decreased odds of multiple adenoma recurrence in all 3 models (Table 4).

DISCUSSION

In this study, we examined the effect of a low-fat, high-fiber, and high-fruit and -vegetable diet on adenoma recurrence among participants in the Polyp Prevention Trial who most successfully complied with the dietary requirements of the 4-year trial. We observed more than 30% lower odds of any adenoma recurrence and nearly 50% lower odds of multiple and advanced adenoma recurrence among the super compliers compared with controls. These results suggest that consistent adherence to a low-fat, high-fiber, and high-fruit and -vegetable diet may be effective in preventing recurrence of colorectal adenomas and possibly in

Table 3. Interactions Between Super Compliers/Goal-achieving Controls[a] and the Dietary Randomization Group, Polyp Prevention Trial, 1991–1998

Group	Super Complier/Goal-achieving Control															
	No Recurrence				Any Adenoma Recurrence				Multiple Adenoma Recurrence				Advanced Adenoma Recurrence			
	Yes		No		Yes		No		Yes		No		Yes		No	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Intervention group	145	7.6	433	22.7	65	3.4	315	16.5	20	1.0	141	7.4	7	0.4	51	2.7
Control group	137	7.2	436	22.9	88	4.6	286	15.0	39	2.0	118	6.2	21	1.1	45	2.4
P for interaction[b]	Referent				0.0421				0.0067				0.0117			

[a] Super compliers are defined as participants in the Polyp Prevention Trial intervention who completed all 4 annual food frequency questionnaires and met a total of 9–12 food frequency questionnaire goals over the trial period; goal-achieving controls are controls selected as having a proportion of "dietary compliance" similar to that of the intervention group.

[b] Logistic regression model unadjusted for any covariates.

preventing colorectal cancer. After adjustment for a number of known confounders and risk factors for colorectal adenomas and cancer, the magnitude and precision of our observed associations were virtually unchanged. Furthermore, when we added baseline values of dietary serum biomarkers, including carotenoids, lipids, selenium, and γ-tocopherol, to the model, the magnitude and precision of effect remained very similar.

There is the potential for unobserved and residual confounding effects in the 2 groups, which may induce a different intervention effect; therefore, we used compliance information to compare percentile-specific treatment effects to further investigate the relation between compliance and dietary intervention (21). Our results indicating statistically significant decreased odds of adenoma recurrence among the super compliers compared with goal-achieving controls provided further support for an inverse association between compliance with the intervention diet and adenoma recurrence.

The potential protective effect of a high-fiber and low-fat diet against colorectal cancer has been studied for over 3 decades with inconsistent and inconclusive results. Although evidence from more than a dozen case-control studies of high fiber and high fruit and vegetable intake confers support for the hypothesis, findings from cohort studies failed to confirm this relation. Results from dietary trials of adenoma recurrence investigating a high-fiber, low-fat diet have mostly been null (8, 12, 26–28). Explanations for the inconsistent results include recall bias in case-control studies, the short duration of the trial intervention, or the focus on a single nutrient in most interventions. Finally, achieved adherence rates for the intervention—that is, actual intake—may influence the observed risk among trial participants. When we examined whether strict compliance with any 1 of the 3 individual targeted goals was mainly responsible for the effect observed among the super compliers, the magnitudes of effect for each adenoma outcome were very similar; we observed, however, a slightly stronger effect for the association with compliance with the fat intake goal compared with the other 2 goals. It appears that our observed association was due to compliance with a number of dietary changes and over an adequate duration.

Table 4. Risk of Colorectal Adenoma Recurrence Among Super Compliers Compared With Goal-achieving Controls,[a] Polyp Prevention Trial, 1991–1998

Type of Adenoma Recurrence	Super Compliers		Goal-achieving Controls		Unadjusted Model[b]		Partially Adjusted Model[c]		Fully Adjusted Model[d]	
	No.	%	No.	%	OR	95% CI	OR	95% CI	OR	95% CI
Total	210		225							
Any recurrence	65	30.9	88	39.1	0.70	0.47, 1.04	0.71	0.48, 1.09	0.94	0.59, 1.51
Multiple recurrence	20	9.5	39	17.3	0.38	0.22, 0.67	0.47	0.26, 0.84	0.42	0.20, 0.88
Advanced recurrence	7	3.3	21	9.3	0.35	0.15, 0.85	0.34	0.14, 0.82	0.36	0.13, 1.04

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Super compliers are defined as participants in the Polyp Prevention Trial intervention who completed all 4 annual food frequency questionnaires and met a total of 9–12 food frequency questionnaire goals over the trial period; goal-achieving controls are controls selected as having a proportion of "dietary compliance" similar to that of the intervention group.

[b] Logistic regression model unadjusted for any covariates.

[c] Logistic regression model adjusted for all covariates significantly different between controls and super compliers (educational level; smoking status; waist-to-hip ratio; fat intake at baseline; intake of fiber, fruit and vegetables, and red and processed meats; ratio of red meat to chicken and fish; intake of legumes and cruciferous vegetables; calcium supplement use; intake of folate, total carotenoids, bran cereals, and vitamin E from supplements; and days from T1 colonoscopy to T4 colonoscopy).

[d] Logistic regression model adjusted for all covariates. Refer to Table 1 for a list of all covariates.

Few studies to date have investigated the association between compliance with a healthy dietary pattern and cancer risk, specifically risk of colorectal adenomas or colorectal cancer (9, 29–34). A recent investigation of adherence to recommended dietary guidelines observed that men who complied with the US Department of Agriculture Food Guide recommendations, the DASH Eating Plan, and the Mediterranean dietary pattern had, respectively, a 26%, 25%, and 21% reduced risk of colorectal adenoma incidence (30). Similar inverse associations for adherence and risk of colorectal cancer in men were also observed in a cohort of US retirees (31). In a meta-analysis of 12 prospective cohort studies (32), greater adherence to a traditional Mediterranean diet was observed to be inversely associated with death due to cancer.

These studies are subject to a number of biases and lack a number of the strengths of our study. Unlike some of the aforementioned studies that measured dietary adherence or intake at baseline only, we were able to measure adherence to the intervention diet and other lifestyle factors at multiple time points and over a longer duration, which allowed for better representation of participants' diet. Second, unlike a number of other dietary intervention trials, the Polyp Prevention Trial lasted longer than 1 year, used an intervention that emphasized a number of dietary changes, and included excellent longitudinal follow-up data on dietary intake and compliance. In our study, the magnitude of effects of complying with the 3 goals at each individual time point, however, was not as strong as the effects observed for super compliers. These findings further support the hypothesis that strict adherence to a high-fiber, low-fat diet over a longer duration is important for prevention of adenoma recurrence. Furthermore, all participants underwent a clearing colonoscopy 6 months prior to and 1 year after randomization; thus, we were able to eliminate the bias associated with whether or not the polyp was present before the measure of dietary adherence.

The Polyp Prevention Trial drew a large number of participants from across the country and provided a unique opportunity to assess compliance with multiple dietary changes and risk of adenoma recurrence over a long period of time (4 years); however, it is not without limitations. Trial participants were mostly white, well educated, married, and older than age 50 years, and all participants had a history of a colorectal adenoma before enrolling in the study. In addition, the main dietary variables and most covariates involved self-report, and thus recall bias in self-assessment may have been differentially distributed between super compliers and controls. We recognize that multivariate adjustment does not necessarily rule out a role for unknown or inadequately measured factors associated with both compliance and adenoma recurrence. Randomized controlled trials rely on randomization to help ensure that the proportions of unknown or inadequately measured confounders are equally distributed between the 2 groups.

Further support for a compliance effect on adenoma recurrence comes from our percentile-specific compliance analysis. When we applied the Efron and Feldman method (21) and used compliance as an explanatory variable and transformed the data into equal distributions of strict compliers, we observed significantly decreased odds of recurrence when we separately ranked compliance in the 2 arms of the trial and compared super compliers with goal-achieving controls. However, one of the major assumptions of this method is that complying in the intervention arm is similar to complying in the control arm (19). Therefore, we do not actually know what counterfactual results we would observe. That is, the percentile-specific analysis assumes that if a super complier had been randomized to the control arm instead of the intervention arm, he or she would have acted like a goal-achieving control, and vice versa.

The difficulty of this assumption is that compliance can be affected by treatment, as we observed with our tests for interaction. In addition, because subjects essentially select their own doses (e.g., compliance), it is likely that dose is associated with other lifestyle characteristics. However, after we controlled for a large number of covariates, including dietary and lifestyle covariates that were significantly different between super compliers and controls, the magnitude of our effect estimates was very similar, and we still observed statistically significant decreased odds of multiple and advanced adenoma recurrence among super compliers compared with goal-achieving controls.

In summary, our results show that the effectiveness of dietary intervention trials depends upon participants' adherence to dietary requirements. Findings from our study suggest that strict adherence to a low-fat, high-fiber, and high-fruit and -vegetable diet could prevent colorectal adenoma recurrence and possibly colorectal cancer. Finally, identifying characteristics of participants most likely to comply with the diet or regimen could assist in developing and designing studies and clinical trials of dietary interventions. To focus on testing the biologic effects of an intervention or treatment on the trial, future dietary and treatment trials could target and randomize individuals most likely to comply. Findings from such trials would enhance the validity of our own findings.

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APPENDIX

The members of the Polyp Prevention Trial Study Group, given below, participated in the conduct of the Polyp Prevention Trial. However, the data presented in this manuscript and the conclusions drawn from them are solely the

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