Dietary Flavonoids and Colorectal Adenoma Recurrence in the Polyp Prevention Trial

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Abstract

Two recent case-control studies suggested that some flavonoid subgroups may play a role in preventing colorectal cancer. Previous prospective cohort studies generally reported no association; however, only a small subset of flavonoids was evaluated and partial flavonoid databases were used. We used the newly constructed U.S. Department of Agriculture flavonoid database to examine the association between consumption of total flavonoids, 6 flavonoid subgroups, and 29 individual flavonoids with adenomatous polyp recurrence in the Polyp Prevention Trial. The Polyp Prevention Trial was a randomized dietary intervention trial, which examined the effectiveness of a low-fat, high-fiber, high-fruit, and high-vegetable diet on adenoma recurrence. Intakes of flavonoids were estimated from a food frequency questionnaire. Multivariate logistic regression models (adjusted for age, body mass index, sex, regular non–steroidal anti-inflammatory use, and dietary fiber intake) were used to estimate odds ratios and 95% confidence intervals for both any and advanced adenoma recurrence within quartiles of energy-adjusted flavonoid intake (baseline, during the trial, and change during the trial). Total flavonoid intake was not associated with any or advanced adenoma recurrence. However, high intake of flavonols, which are at greater concentrations in beans, onions, apples, and tea, was associated with decreased risk of advanced adenoma recurrence (4th versus 1st quartile during the trial; odds ratio, 0.24; 95% confidence interval, 0.11, 0.53; P_{trend} = 0.0006). Similar inverse associations were observed to a smaller extent for isoflavonoids, the flavonol kaempferol, and the isoflavonoids genistein and formononetin. Our data suggest that a flavonol-rich diet may decrease the risk of advanced adenoma recurrence. (Cancer Epidemiol Biomarkers Prev 2008;17(6):1344–53)

Introduction

Flavonoids are a group of bioactive polyphenols that constitute a sizable part (189 mg/d per person) of the U.S. diet (1). Flavonoids are distributed widely in the plant kingdom and are especially abundant in fruits, vegetables, seeds, spices, herbs, tea, cocoa, and wine (2). The six major subclasses of flavonoids are anthocyanidins (e.g., cyanidin, delphinidin; primary sources: red berries, red cabbages, cherries, grapes, and onions), flavan-3-ols (e.g., catechin, epicatechin; primary sources: tea, apples, and red wine), flavanones (e.g., hesperitin, naringenin; primary sources: oranges, lemons, and grapefruits), flavones (e.g., apigenin, luteolin; primary sources: celery, parsley, and thyme), flavonols (e.g., kaempferol, myricetin, quercetin; primary sources: apples, beans, broccoli, and onions), and isoflavonoids (e.g., daidzein, genistein; primary sources: beans and soy products).

Dietary change, both feasible and safe, represents a viable strategy for preventing colorectal cancer (CRC). Flavonoids inhibit the growth of human colon cancer cell lines (3-7) and restrict colorectal carcinogenesis in animal studies (8-10). Possible biological mechanisms involved in the anticarcinogenic properties of flavonoids include their antioxidative and anti-inflammatory properties. In addition, flavonoids induce differentiation and apoptosis, and inhibit metabolic carcinogen activation, cell proliferation, tumor cell adhesion and invasion, and angiogenesis (4-6). Prospective cohort studies generally observed no association between flavonoid consumption and CRC (11-16); however, only a small subset of flavonoids was evaluated, the intake ranges were limited (11-16), and the databases only contained a partial list of flavonoids from the major foods (17-21). Two recent case-control studies, both based on larger, updated, and tested flavonoid databases (22-24),

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suggested an inverse association between high flavonoid consumption, in particular flavonols, and CRC risk in humans (25, 26).

The objective of this study was to evaluate the association between consumption of total flavonoids, the 6 major flavonoid subgroups, and 29 individual flavonoids with risk of any or advanced adenoma recurrence in the Polyp Prevention Trial (PPT). We used the recently released 2006 U.S. Department of Agriculture (USDA) flavonoid database (27) and the 2002 USDA isoflavonoid database for foods (23).

Materials and Methods

Study Design and Population. The PPT was a 4-year randomized, multicenter, nutritional intervention trial to evaluate whether changing nutrition patterns toward a high-fiber (goal, ≥4.30 g/MJ or 18 g/1,000 kcal), high-fruit and high-vegetable (goal, ≥0.84 servings/MJ or 5 servings/d), and low-fat (goal, ≤20% of energy) diet is effective in inhibiting colorectal adenoma recurrence. Details of the study and effectiveness have been described previously (28-30). To be eligible for the PPT, participants had to be at least 35 years of age and have had at least one histologic confirmed colorectal adenoma identified by complete colonoscopy in the 6 months before study entry. Furthermore, participants had to be within 150% of their recommended weight, without a history of inflammatory bowel disease, bowel resection, adenomatous polyposis syndrome, or prior history of adenomas or CRC, and not currently using lipid-lowering medications. Between 1991 and 1994, recruited participants (N = 2,079) from eight clinical centers (listed in Appendix 1) were randomly assigned to either the control (n = 1,042) or the intervention (n = 1,037) group. Of the 2,079 participants, 1,905 (control, n = 947; intervention, n = 958) completed the study and were used for this analysis. The other 174 participants were not included because they died before the colonoscopy at year 4 (n = 88), did not have a colonoscopy at year 4 (n = 72), refused to participate (n = 9), had no adenoma at baseline (n = 4), or were seriously ill (n = 1; ref. 29). The institutional review boards of the National Cancer Institute and each participating center approved the study, and all participants provided written, informed consent.

Lifestyle and Dietary Data. At baseline (T_0) and at each of the four annual follow-up visits (T_1, T_2, T_3, T_4), participants were asked to bring all current medications, including dietary supplements. Participants completed an interviewer-administered questionnaire about demographic, clinical, medication and supplement use (including name, dosage, and frequency of use), and dietary information. They also provided a fasting blood sample for analysis of total cholesterol, carotenoids, and other biomarkers. At baseline, participants viewed instructional videos on how to estimate food portion size and how to complete the dietary assessment instruments. Dietary intake was determined using a modified Block-National Cancer Institute Food Frequency Questionnaire (FFQ; ref. 31), 4-day food records, and 24-h dietary recalls. Participants completed a 4-day food record and an FFQ at baseline and at each of the four annual follow-up visits. Trained nutritionists reviewed all FFQs and 4-day food records with participants. On average, participants in the intervention group decreased their fat intake by 30%, increased their fiber intake by 75%, and increased their fruit and vegetable intake, 0.36 to 0.48 servings/MJ (32). Because the PPT intervention was based on behavior modification within the intervention group, there was a range in adherence to the intervention goals with the top 20% of the intervention group far exceeding the actual PPT intervention goals, whereas others made none or little change in their diets (33). Participants in the intervention group decreased their body weight and cholesterol level and increased their serum carotenoid levels over the 4-year intervention period, which was consistent with changes in nutrient intake as assessed by the FFQ (32).

This study was based on data from the FFQ exclusively, which asked about the frequency of intake during the past year of 119 food and beverage items and about the average serving sizes. Compared with the 4-day food record and the 24-h recall, the FFQ slightly overestimated fat and underestimated fiber, fruit, and vegetable intake; and had acceptable correlations of macronutrients and micronutrients (0.46-0.68) when ranking the nutrients (31-34).

Flavonoid Data. The FFQ contained 11 questions on fruit consumption, 21 questions on vegetable consumption (including soups), 12 questions on beverage consumption (including beer, fruit juices, tea, and wine), and 1 question on chocolate consumption. Intakes of most flavonoids were estimated from the 2006 USDA flavonoid database for 394 food items (27); isoflavonoid intakes were estimated from the 2002 USDA-Iowa State University isoflavonoid database for foods (23). Validity and reliability coefficients for the dietary flavonoids in the present study were not calculated. Total flavonoid intake was calculated from the sum of the six flavonoid subgroups: (*a*) anthocyanidins (sum of cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin); (*b*) flavan-3-ols [sum of (−)-epicatechin, (−)-epicatechin 3-gallate, (−)-epigallocatechin, (−)-epigallocatechin 3-gallate, (+)-catechin, (+)-gallocatechin, theaflavin, theaflavin-3,3′-digallate, theaflavin-3′-gallate, theaflavin-3-gallate, and thearubigins]; (*c*) flavanones (sum of hesperitin and naringenin); (*d*) flavones (sum of apigenin and luteolin); (*e*) flavonols (sum of isorhamnetin, kaempferol, myricetin, and quercetin); and (*f*) isoflavonoids (sum of daidzein, genistein, formononetin, and biochanin A).

Adenoma Assessment. Participants had a full colonoscopy at baseline (T_0), at the end of year 1 (T_1), and at the end of year 4 (T_4). The colonoscopy at the end of year 1 was used for detection and removal of any adenomas missed at baseline. If participants missed the year 1 colonoscopy (8.2%), a full colonoscopy was done at the end of year 2. Only pathologically confirmed adenomas diagnosed at the end of year 4 were considered recurrent adenomas. In addition to descriptive data on all adenomas, two independent pathologists determined histologic features and degree of atypia. Recurrence of any adenoma was observed in 724 participants (control, n = 374; intervention, n = 380). Advanced adenoma recurrence, defined as ≥1 cm in size, at least 25% villous component, or exhibiting high-grade dysplasia, was

observed in 126 participants (control, $n = 66$; intervention, $n = 60$).

Statistical Analyses. Statistical analyses were done using Statistical Analysis Systems, version 8.2 (SAS, Inc.) software. Intakes of flavonoids (in mg) and flavonoid-rich foods (in g) at T_0, T_1, T_2, and T_3 were energy adjusted by dividing by total caloric intake at T_0, T_1, T_2, and T_3, respectively (nutrient density method). Following this, we calculated baseline intake (T_0), intake during the trial [average (T_1,T_2,T_3)], intake change [average (T_1,T_2,T_3) − T_0], and overall intake [average (T_0,T_1,T_2,T_3)]. Using other energy-adjusting methods (e.g., residual method and standard multivariate method) did not significantly alter the results. Data from T_4 were not used to avoid potential confounding effects between timing of follow-up colonoscopy and completing the FFQ at T_4. Inclusion of the T_4 data did not substantially change the estimates (results not shown). To test differences between participants with different posttrial adenoma occurrence outcomes (no versus any recurrence, no versus advanced recurrence), the Wilcoxon rank-sum test was used for intakes of flavonoids and flavonoid-rich foods, the t tests for other continuous variables, and the χ^2 tests for categorical variables. The associations among flavonoid subgroups, flavonoid-rich foods, and other cohort characteristics were estimated using Spearman rank correlation coefficient and by using a linear trend test in which cohort characteristics are compared across age-adjusted flavonoid intake quartiles.

To estimate the strength of association between consumption of flavonoids and flavonoid-rich foods and adenoma recurrence (no versus any recurrence and no versus advanced recurrence), logistic regression models were used to compute odds ratios (OR) and 95% confidence intervals (95% CI) using the lowest intake quartile among all participants as the reference category. For evaluating linear trends across intake levels, the median values of each quartile were calculated and combined into a continuous score variable. We evaluated several potential confounders, including age; body mass index; sex; education; regular nonsteroidal anti-inflammatory drug (NSAID); family history of CRC; regular aspirin use; regular multivitamin supplement use; regular vitamin A supplement use; regular vitamin E supplement use; and intakes of folate, fiber, red meat, and saturated fat. The potential confounders were added to the models in a stepwise fashion; if it was associated with both adenoma recurrence and consumption of flavonoids and flavonoid-rich foods, had a χ^2 P value ≤0.20, and changed the OR by more than 10%, it remained in the model. The final models included baseline (T_0) age (in years), body mass index (kg/m^2), sex (% male), regular NSAID use (defined as at least once per month; % yes), and dietary fiber intake (g/1,000 kcal). Effect modification was evaluated by stratified analyses by sex, regular NSAID use, regular aspirin use, regular multivitamin supplement use, regular vitamin A supplement use, and regular vitamin E supplement use. All P values correspond to two-sided tests. Differences were considered to be significant at $P \leq 0.05$ or after adjusting for multiple comparisons using the Bonferroni correction at $P \leq 0.083$.

Results

At baseline, participants of the PPT were on average 61.1 years old, overweight (27.6 kg/m^2), highly educated (75% with more than high school education), Caucasian (90%), and males (64%; Table 1). A high proportion of participants had a history of CRC in first-degree relatives (27%) and used NSAIDs (34%) or aspirin (23%) regularly. Furthermore, many participants regularly took supplements of multivitamins (34%), vitamin A (33%), or vitamin E (41%). Participants with advanced recurrent adenomas were more likely to be male, older, and less likely to use NSAIDs at baseline, and participants with any recurrent adenoma were more likely to be male and older than participants with no adenoma recurrence.

A variety of fruits and vegetables contributed to the consumption of total flavonoids and its subgroups

Table 1. Baseline characteristics of participants in the PPT-based cohort by adenoma recurrence

Characteristic	Overall	No recurrence	Advanced recurrence*		Any recurrence†	
	Mean (SD)	Mean (SD)	Mean (SD)	P	Mean (SD)	P
Sample size	1,905	1,151	125	125/1,151	754	754/11,51
Age, y	61.1 (9.9)	59.9 (10.1)	65.2 (9.2)	<0.0001	62.8 (9.2)	<0.0001
Body mass index (kg/m^2)	27.6 (3.9)	27.4 (4.0)	28.0 (4.1)	0.10	27.8 (3.9)	0.05
Gender (% male)	64	60	70	0.02	72	<0.0001
Race (% Caucasian)	90	90	90	0.99	90	0.97
Education (% ≤high school)	25	24	28	0.35	26	0.49
NSAID use (% yes)	34	35	24	0.01	31	0.11
Aspirin use (% yes)	23	23	19	0.28	22	0.55
Multivitamin use (% yes)	34	35	31	0.34	32	0.18
Vitamin A use (% yes)	33	35	30	0.24	31	0.10
Vitamin E use (% yes)	41	42	38	0.43	40	0.45
Energy intake (MJ/d)	8.05 (2.44)	7.97 (2.36)	7.93 (2.65)	0.86	8.16 (2.55)	0.11
Fruit intake (g/d)	156 (122)	152 (115)	166 (126)	0.19	162 (127)	0.07
Vegetable intake (g/d)	270 (132)	268 (125)	256 (108)	0.25	273 (120)	0.43
Family history of CRC (% yes)	27	27	26	0.96	27	0.77

NOTE: Results are presented as means (SD) for continuous variables and % for categorical variables with P values for differences in means determined by t tests and differences in proportions determined by χ^2 tests. Adenomatous polyp recurrence and advanced adenoma recurrence were diagnosed using full colonoscopy at the end of year 4.

*Comparison between the advanced adenoma recurrence group to the no adenoma recurrence group.

†Comparison between the any adenoma recurrence group to the no adenoma recurrence group.

Table 2. Main dietary sources of total flavonoids and flavonoid subgroups among participants during the PPT (n = 1,859)

Flavonoid	Main dietary sources (≥5% of total intake)*
Total flavonoids	Tea (30.0%), citrus fruit juices (17.2%), other fruits (grapes, plums, pineapples: 8.9%), oranges (7.2%), dry beans (6.0%), grapefruits (5.6%)
Anthocyanins	Other fruits (grapes, plums, pineapples: 44.8%), bananas (18.7%), other fruit juices (apple, cranberry, and grape juices: 13.5%), fresh strawberries (7.0%), apples (5.4%)
Flavan-3-ols	Tea (70.5%), other fruits (grapes, plums, pineapples: 6.2%), apples (6.2%), bananas (5.1%)
Flavanones	Citrus fruit juices (57.1%), oranges (23.4%), grapefruit (18.5%)
Flavones	Other vegetables (onions, cucumbers, celery, radishes, peppers: 39.5%), oranges (19.1%), iceberg/red leaf lettuce (7.4%), watermelons (7.3%), wine (7.0%)
Flavonols	Dry beans (32.2%), other vegetables (onions, cucumbers, celery, radishes, peppers: 17.8%), tea (9.6%), apples (5.4%)
Isoflavonoids	Dry beans (47.1%), peas (43.6%), chili (5.1%)

*Flavonoid contents of foods based on USDA flavonoid database release 2 (27); isoflavonoid contents of foods based on USDA isoflavonoid database release 1.3 (23). Contributions of individual foods to composite foods (e.g., other fruits, other fruit juices, other vegetables) are described in Table 3.

(Table 2). Total flavonoid intake was correlated positively with dietary fiber, fruit, and vegetable intakes (r = 0.42, 0.49, and 0.38, respectively), and with flavonoid subgroups (between r = 0.32 for isoflavonoids and r = 0.80 for flavan-3-ols).

Before the trial (T_0), no significant differences in intakes of total flavonoids, flavonoid subgroups, and flavonoid-rich foods were observed among participants with different adenoma recurrence outcomes (data not shown).

During the trial [average (T_1, T_2, T_3)], participants randomized to the intervention group increased their flavonoid consumption more than the dietary control group [median, 30.0 mg/1,000 kcal; interquartile range (IQR), 11.5-49.4 mg/1,000 kcal versus median, 5.5 mg/1,000 kcal; IQR, −9.3 to 21.8 mg/1,000 kcal; P < 0.0001]. Significant differences in consumption of flavanones (lower; P = 0.005), flavonols (higher; P = 0.002), and isoflavonoids (higher; P = 0.007), but not total flavonoids (P = 0.74), were observed among participants with no adenoma recurrence versus advanced adenoma recurrence (Table 3). We observed a statistically significant increased risk of advanced adenoma recurrence for the highest intake quartile of flavanones compared with the lowest (OR, 2.32; 95% CI, 1.28-4.20), which was not significant after adjusting for multiple comparisons or main dietary sources of flavanones (data not shown).

Table 3. Energy-adjusted medians and IQRs of daily intakes of total flavonoids, flavonoid subgroups, and flavonoid-rich foods among participants during the PPT by adenoma recurrence

Dietary component*	Overall	No recurrence	Advanced recurrence†		Any recurrence‡	
	Median (IQR)	Median (IQR)	Median (IQR)	P	Median (IQR)	P
	1,859	1,123	123	123/1123	736	736/1,123
Flavonoids (in mg/1,000 kcal)						
Total flavonoids	76.2 (50.9-106.1)	76.1 (50.1-105.3)	72.2 (51.1-104.6)	0.74	76.3 (52.2-106.4)	0.53
Anthocyanins	10.1 (5.70-15.6)	10.2 (5.61-16.0)	9.85 (5.68-13.91)	0.52	9.83 (5.82-15.3)	0.30
Flavan-3-ols	17.3 (10.2-38.6)	17.8 (10.4-39.4)	15.7 (9.20-29.9)	0.13	16.7 (9.92-37.6)	0.36
Flavanones	22.7 (10.6-36.9)	21.6 (9.88-35.3)	24.5 (14.4-44.8)	0.005	24.2 (12.5-39.5)	0.002
Flavones	0.73 (0.46-1.10)	0.73 (0.46-1.09)	0.72 (0.43-1.11)	0.56	0.73 (0.45-1.11)	0.59
Flavonols	12.0 (9.12-17.3)	12.3 (8.19-17.6)	10.3 (7.55-14.1)	0.002	11.5 (8.04-17.1)	0.30
Isoflavonoids	0.08 (0.04-0.13)	0.08 (0.04-0.14)	0.07 (0.04-0.10)	0.007	0.07 (0.05-0.13)	0.46
Flavonoid-rich foods (in g/1,000 kcal)						
Bananas	23.5 (10.5-43.1)	23.5 (10.7-42.6)	23.6 (12.0-45.2)	0.57	23.4 (10.2-43.6)	0.91
Grapefruits	4.36 (0-15.9)	3.84 (0-14.6)	6.22 (1.23-18.3)	0.02	5.20 (0.77-18.0)	0.004
Oranges	10.5 (3.55-23.96)	10.2 (3.41-22.8)	11.9 (4.19-28.6)	0.51	11.3 (4.10-25.9)	0.21
Citrus fruit juices	34.1 (8.04-78.1)	32.9 (7.32-76.8)	40.9 (9.98-84.6)	0.10	36.7 (8.78-81.9)	0.04
Other fruits§	12.3 (3.72-28.3)	12.7 (3.74-30.0)	9.70 (3.60-25.2)	0.25	11.1 (3.66-26.9)	0.25
Other fruit juices‖	9.31 (1.30-32.4)	9.92 (1.41-33.0)	10.1 (1.05-30.7)	0.80	8.25 (1.17-29.4)	0.12
Dry beans	8.58 (3.63-19.4)	8.85 (3.67-20.0)	6.17 (3.41-13.43)	0.006	8.02 (3.52-19.0)	0.30
Peas	4.86 (2.44-8.76)	4.88 (2.37-8.74)	4.75 (2.19-7.91)	0.46	4.81 (2.47-8.82)	0.80
Other vegetables¶	25.4 (12.3-45.7)	25.9 (11.8-46.6)	20.8 (9.76-35.6)	0.009	25.0 (13.2-44.4)	0.99
Tea	7.05 (0-49.8)	7.60 (0-52.5)	3.00 (0-38.4)	0.07	6.30 (0-47.6)	0.48

NOTE: Daily intakes of flavonoids and flavonoid-rich foods (contributed ≥5% of total flavonoid or ≥10% of flavonoid subgroup consumption) are for the first 3 y of the PPT and were energy adjusted by dividing through total caloric intake in 1,000 kcal (4.184 MJ). Adenomatous polyp recurrence (any or advanced) was diagnosed through postintervention at year 4.

*Energy-adjusted intakes of flavonoids and flavonoid-rich foods are presented as energy-adjusted medians and interquartile ranges with P values for differences in energy-adjusted means determined by Wilcoxon rank sum test.

†Comparison between the adenoma recurrence group to the no adenoma recurrence group.

‡Comparison between the advanced adenoma recurrence group to the no adenoma recurrence group.

§Other fruits (46% grapes, 31% plums, and 23% pineapples).

‖Other fruit juices (50% apple juice, 25% cranberry juice, and 25% grape juice).

¶Other vegetables (30% white onions, 5% red onion, 27% cucumbers, 16% celery, 12% radishes, and 10% pepper).

We observed a statistically significant decreased risk for the highest intake quartile of flavonols compared with the lowest (OR, 0.24; 95% CI, 0.11-0.53) and, to a smaller extent, for the highest intake quartile of isoflavonoids (OR, 0.46; 95% CI, 0.22-0.95; Table 4). The protective effect of higher isoflavonoid intake attenuated after adjusting for multiple comparisons and when the model was adjusted for intakes of dry beans and flavonols, whereas this was not the case for increased flavonol intake even after adjusting for isoflavonoid intake (data not shown). Of the individual flavonols and isoflavonoids examined, we observed a statistically significant decreased risk for advanced adenoma recurrence for greater intakes of genistein, isorhamnetin, kaempferol, and formononetin (Table 5). Greater intakes of apigenin (4th versus 1st quartile; OR, 0.60; 95% CI, 0.32-1.14; P_{trend} = 0.04) and (−)-epigallocatechin 3-gallate (4th versus 1st quartile; OR, 0.55; 95% CI, 0.32-0.96; P_{trend} = 0.05) were additionally inversely associated with advanced adenoma recurrence.

The protective effects of flavonol and isoflavonoid intake were observed only at higher intake levels. At baseline, intakes of flavonols (4th quartile daily intake >11.53 mg/1,000 kcal) and isoflavonoids (4th quartile daily intake >0.077 mg/1,000 kcal) were lower than during the trial (flavonols, 4th quartile daily intake >17.30 mg/1,000 kcal; isoflavonoids: 4th quartile daily intake >0.133 mg/1,000 kcal), and no significant associations between intake of flavonols (4th versus 1st quartile; OR, 0.69; 95% CI, 0.38-1.24; P_{trend} = 0.14) and isoflavonoids (4th versus 1st quartile; OR, 0.74; 95% CI, 0.41-1.35; P_{trend} = 0.29) and advanced adenoma recurrence were

Table 4. Association between total flavonoid and flavonoid subgroup consumption and colorectal adenoma recurrence among participants during the PPT (*n* = 1,859)

Quartile	Range	No recurrence	Advanced recurrence		Any recurrence	
		Controls	Cases	OR (95% CI)	Cases	OR (95% CI)
			123		736	
Total flavonoids						
1	<50.87*	293	30	1.00†	171	1.00†
2	50.87-76.12	269	36	1.32(0.76-2.27)	196	1.27(0.96-1.68)
3	76.21-106.0	283	27	0.97(0.54-1.76)	182	1.14(0.85-1.53)
4	>106.0	278	30	1.15(0.64-2.07)	187	1.25(0.93-1.67)
P_{trend}				0.94		0.27
Anthocyanins						
1	<5.70	289	31	1.00	175	1.00
2	5.70-10.06	265	32	1.13(0.64-1.98)	200	1.27(0.96-1.69)
3	10.07-15.58	281	30	1.06(0.57-1.95)	184	1.17(0.86-1.59)
4	>15.58	288	30	1.13(0.57-2.25)	177	1.13(0.80-1.60)
P_{trend}				0.80		0.65
Flavan-3-ols						
1	<10.22	273	35	1.00	191	1.00
2	10.23-17.22	273	35	1.05 (0.62-1.80)	192	1.03 (0.78-1.36)
3	17.30-38.57	292	30	0.92 (0.53-1.60)	173	0.89 (0.67-1.18)
4	>38.57	285	23	0.65 (0.37-1.15)	180	0.94 (0.71-1.23)
P_{trend}				0.12		0.44
Flavanones						
1	<10.57	305	20	1.00	159	1.00
2	10.79-21.97	281	34	1.74 (0.96-3.15)	184	1.21 (0.92-1.59)
3	22.00-36.86	280	37	1.39 (0.75-2.57)	185	1.21 (0.92-1.60)
4	>36.87	257	42	2.32 (1.28-4.20)	208	1.48 (1.11-1.96)
P_{trend}				0.02		0.01
Flavones						
1	<0.46	277	36	1.00	187	1.00
2	0.46-0.73	285	29	0.79 (0.45-1.37)	180	0.97 (0.73-1.28)
3	>0.73-1.10	286	27	0.84 (0.46-1.55)	179	1.05 (0.77-1.42)
4	>1.10	275	31	1.08 (0.55-2.10)	190	1.18 (0.84-1.66)
P_{trend}				0.82		0.31
Flavonols						
1	<8.12	277	39	1.00	187	1.00
2	8.12-12.01	263	40	0.97 (0.58-1.62)	202	1.19 (0.91-1.57)
3	12.03-17.30	294	31	0.61 (0.34-1.10)	171	0.89 (0.66-1.20)
4	>17.30	289	13	0.24 (0.11-0.53)	176	0.96 (0.68-1.36)
P_{trend}				0.0006		0.47
Isoflavonoids						
1	<0.045	286	37	1.00	178	1.00
2	0.045-0.079	261	41	1.04(0.63-1.72)	204	1.17(0.90-1.54)
3	>0.079-0.133	286	26	0.59(0.33-1.06)	179	0.96(0.72-1.29)
4	>0.133	290	19	0.46(0.22-0.95)	175	1.02(0.74-1.42)
P_{trend}				0.01		0.81

All models were adjusted for age, sex, body mass index, dietary fiber consumption, and regular NSAID use. Adenomatous polyp recurrence (any or advanced) was diagnosed through postintervention at year 4.

*Average daily total flavonoid and individual flavonoid intakes (in mg) are for the first 3 y of the PPT and were energy-adjusted by dividing through total caloric intake in 1,000 kcal (4.184 MJ).

†Reference category.

Table 5. Association between individual flavanone, flavonol, and isoflavonoid consumption and colorectal adenoma recurrence among participants during the PPT (*n* = 1,859)

Quartile	Ranges	No recurrence	Advanced recurrence		Any recurrence	
		Controls	Cases	OR (95% CI)	Cases	OR (95% CI)
			123		736	
Flavanones						
Hesperetin						
1	<6.13*	300	22	1.00 †	164	1.00 †
2	6.14-13.98	284	26	1.15 (0.63-2.11)	181	1.14 (0.86-1.49)
3	13.99-25.35	262	38	1.89 (1.07-3.33)	203	1.40 (1.07-1.84)
4	>25.35	277	37	1.66 (0.94-2.95)	188	1.16 (0.88-1.53)
P_{trend}				0.03		0.14
Naringenin						
1	<2.93	301	24	1.00	163	1.00
2	2.93-5.72	283	27	1.18 (0.66-2.13)	182	1.18 (0.90-1.55)
3	5.73-10.47	282	38	1.59 (0.90-2.80)	183	1.17 (0.88-1.54)
4	>10.47	257	34	1.52 (0.84-2.77)	208	1.46 (1.09-1.95)
P_{trend}				0.11		0.02
Flavonols						
Isorhamnetin						
1	<0.15	290	36	1.00	174	1.00
2	0.15-0.28	266	37	1.12 (0.68-1.87)	199	1.26 (0.96-1.65)
3	>0.28-0.46	278	35	1.02 (0.60-1.74)	187	1.16 (0.88-1.55)
4	>0.46	289	15	0.44 (0.21-0.90)	176	1.11 (0.81-1.53)
P_{trend}				0.07		0.60
Kaempferol						
1	<2.69	274	35	1.00	190	1.00
2	2.69-4.73	284	41	1.07 (0.65-1.77)	181	0.90 (0.68-1.17)
3	4.75-8.63	274	30	0.83 (0.47-1.46)	191	1.00 (0.75-1.33)
4	>8.64	291	17	0.44 (0.22-0.89)	174	0.91 (0.66-1.25)
P_{trend}				0.03		0.73
Myricetin						
1	<0.35	278	28	1.00	186	1.00
2	0.35-0.54	279	40	1.57 (0.93-2.67)	186	1.06 (0.81-1.38)
3	>0.54-0.89	278	28	1.10 (0.62-1.93)	187	1.05 (0.80-1.38)
4	>0.89	288	27	1.01 (0.57-1.77)	177	1.01 (0.77-1.32)
P_{trend}				0.67		0.98
Quercetin						
1	<4.12	292	34	1.00	172	1.00
2	4.12-5.88	249	45	1.55 (0.93-2.58)	216	1.60 (1.21-2.12)
3	5.89-7.92	291	25	0.68 (0.36-1.27)	174	1.11 (0.82-1.51)
4	>7.92	291	19	0.59 (0.29-1.20)	174	1.23 (0.88-1.73)
P_{trend}				0.04		0.71
Isoflavonoids						
Biochanin A						
1	<0.027	283	36	1.00	181	1.00
2	0.027-0.050	269	34	0.90 (0.53-1.52)	196	1.08 (0.82-1.42)
3	>0.050-0.084	276	34	0.87 (0.50-1.52)	189	1.03 (0.77-1.38)
4	>0.084	295	19	0.50 (0.25-1.04)	170	0.95 (0.69-1.33)
P_{trend}				0.11		0.75
Daidzein						
1	<0.0012	290	37	1.00	174	1.00
2	0.0012-0.0019	265	37	1.09 (0.66-1.81)	200	1.20 (0.91-1.57)
3	0.0020-0.0030	285	38	0.78 (0.45-1.37)	180	1.05 (0.79-1.39)
4	>0.0030	283	21	0.62 (0.32-1.17)	182	1.13 (0.83-1.53)
P_{trend}				0.10		0.64
Formononetin						
1	<0.0004	275	39	1.00	189	1.00
2	0.0004-0.0007	279	38	0.87 (0.53-1.42)	186	0.90 (0.68-1.18)
3	0.0007-0.0011	283	25	0.61 (0.34-1.10)	182	0.92 (0.70-1.23)
4	>0.0011	286	21	0.49 (0.26-0.95)	179	0.94 (0.69-1.29)
P_{trend}				0.02		0.76
Genistein						
1	<0.016	283	40	1.00	181	1.00
2	0.016-0.028	271	41	0.93 (0.57-1.51)	194	1.04 (0.79-1.36)
3	>0.028-0.046	278	24	0.55 (0.31-0.99)	187	1.04 (0.78-1.38)
4	>0.046	291	18	0.38 (0.19-0.76)	174	0.98 (0.71-1.35)
P_{trend}				0.003		0.93

NOTE: All models were adjusted for age, sex, body mass index, dietary fiber consumption, and regular NSAID use. Adenomatous polyp recurrence (any or advanced) was diagnosed through postintervention at year 4.

*Average daily individual flavanone, flavonol, and isoflavonoid intakes (in mg) are for the first 3 y of the PPT and were energy-adjusted by dividing through total caloric intake in 1,000 kcal (4.184 MJ).

†Reference category.

observed. During the trial, the intervention group had higher daily flavonol (median, 16.2 mg/1,000 kcal; IQR, 11.7 to 22.0 mg/1,000 kcal versus median, 9.1 mg/1,000 kcal; IQR, 6.6 to 12.2 mg/1,000 kcal) and isoflavonoid (median, 0.209 mg/1,000 kcal; IQR, 0.133 to 0.311 mg/1,000 kcal versus median, 0.097 mg/1,000 kcal; IQR, 0.061 to 0.153 mg/1,000 kcal) consumption than the control group. After stratification by experimental group, the protective associations between advanced adenoma recurrence and intakes of flavonols (4th versus 1st quartile; OR, 0.10; 95% CI, 0.03-0.29; $P_{trend} < 0.0001$) and isoflavonoids (4th versus 1st quartile; OR, 0.29; 95% CI, 0.11-0.79; $P_{trend} = 0.002$) during the PPT were strong for the intervention group, whereas no meaningful risk estimates could be calculated for the control group because only a small number of control group participants had high flavonol intakes.

With regard to any adenoma recurrence during the trial [average (T_1, T_2, T_3)], participants with any adenoma recurrence had higher intake levels of flavanones than participants with no adenoma recurrence ($P = 0.002$; Table 3), which was reflected in an increased risk of any adenoma recurrence of participants in the highest quartile of flavanone intake (OR, 1.48; 95% CI, 1.11-1.96). The observed associations were not significant after adjusting for multiple comparisons or main dietary sources of flavanones (data not shown).

Discussion

This study is among the first to examine the association between flavonoid intake and colorectal adenoma recurrence. Total flavonoid intake was not associated with colorectal adenoma recurrence; however, we detected a reduced risk of advanced adenoma recurrence with greater flavonol consumption during the trial. Participants in the highest flavonol (in particular, isorhamnetin and kaempferol) intake quartile had a 76% decreased risk of recurrence of advanced colorectal adenomas compared with the lowest intake group. The protective effect was even stronger in the intervention group (90% decreased risk). Our results also suggest that a 4-year intervention with a flavonol-rich diet might be effective in reducing the risk of advanced colorectal adenomas.

Consistent with our results, an Italian hospital–based case-control study and a Scottish population–based case-control study reported significant 36% and 27% reduced risks of CRC, respectively, for those in the highest quartile of flavonol intake (25, 26). Both studies used new, large, rigorously tested flavonoid databases (22-24) and examined multiple flavonoids; however, limitations were potential dietary recall bias and limited external validity, particularly for the hospital-based case-control study. The prospective design of our study reduces these limitations.

No association between flavonol intake and CRC cancer risk was observed in the Dutch Cohort Study on Diet and Cancer (12), the Finnish Alpha-Tocopherol Beta-Carotene Study (13), the Finnish Mobile Clinic Health Examination Survey (14, 15), and the U.S. Nurses' Health Study and Health Professional Follow-up Study (16). However, these five prospective cohort studies used older and smaller flavonoid databases (17-21) and evaluated the effect of flavonols over an intake range similar or narrower than that of our participants at baseline (median, 14.9 mg/d; IQR, 10.1-21.2 mg/d), for which we also did not observe a protective association. In comparison, the median flavonol intake of our intervention group during the PPT was 29.5 mg/d (IQR, 20.7-39.8 mg/d). In support of our findings, other studies have reported a minimum of five servings of vegetables per day must be consumed before a reduction in rectal cancer risk can be observed (35) and a minimum of five servings of fruits per day before a reduction in colorectal adenomas is observed (36). Therefore, our results suggest that the protective association between flavonols and CRC might be achieved only at flavonol intake levels that are higher than what is commonly consumed by Western populations (1, 2).

A protective effect of flavonols against colorectal carcinogenesis has also been reported in experimental CRC animal model studies (37-42). It has been well documented that there are a number of underlying molecular mechanisms by which flavonols inhibit CRC *in vitro*. These mechanisms include inhibition of cancer initiation by its antioxidative (43, 44) and antimutagenic properties (45) and inhibiting the promotion phase of cancer by its anti-inflammatory (44, 46), antiproliferative (47, 48), and anti–cell transformation properties (49, 50). In addition, flavonols could also delay cancer progression by inducing apoptosis (41, 47) and inhibiting matrix metalloproteinases (51) and angiogenesis (52). The cancer-protective properties of individual flavonoids are associated with the number of hydroxyl groups on their B-ring. Consistent with our risk estimates, flavonols with a low number of hydroxyl groups (kaempferol, quercetin) exert cancer protective properties at lower concentrations than myricetin (53-55), which has the most hydroxyl groups on its B-ring.

The results for the associations between intakes of isoflavonoids and adenoma recurrence are encouraging. A protective relationship for isoflavonoid intake (24%) against CRC has been reported previously (25), whereas another study reported no association between phytoestrogens intake, which is the sum of isoflavonoids and the nonflavonoid lignans and coumestrol, and CRC risk (26). No association between flavanone consumption and CRC was reported in either study (25, 26). The associations with isoflavonoid and flavanone intakes in our study were attenuated after adjusting for their major dietary sources, which might be overadjustment, and were not statistically significant after adjusting P values for multiple comparisons. Further studies will help to evaluate whether these associations are true or occurred by chance.

Rossi et al. (25) reported a protective effect of flavone (22%) and anthocyanidin intake (23%) and no effect of flavan-3-ol intake against CRC. Theodoratou et al. (26) did not observe an association between flavone or flavan-3-ol intake and CRC, and did not estimate anthocyanidin intake. The lack of an association between flavone intake and adenoma recurrence in this study has to be interpreted with caution given that the FFQ did not specifically ask for foods high in flavones, which are mostly used as garnishes. A similar limitation has to be considered for anthocyanidins because the PPT FFQ did not specifically ask for foods high in anthocyanidins. It cannot be excluded that the lack of an association

between adenoma recurrence and intakes of anthocyanidins and flavan-3-ols could be partly due to the fact that our intake ranges did not cover dosages that would be protective. Specifically, anthocyanidins are prone to intestinal degradation (56) and have been shown in animal studies to be protective at concentrations much higher than examined in this study (9, 57).

There are several limitations to our study. Random as well as systematic measurement error related to both the dietary assessment techniques and the nutrient database is likely present and could bias risk estimates. Participants in the intervention arm of the study were aware what dietary patterns were expected from them and might have answered the FFQ during follow-up according to the expectations of the nutritionists. However, all three types of associations (protective, null, and detrimental) for different flavonoid subgroups would be unlikely in the case of systematic measurement error.

It has to be taken into account that this is a secondary analysis and that participants were not assigned randomly to a high- or low-flavonoid diet. Significant associations between flavonoid subgroups and adenoma recurrence could have arisen by chance due to multiple comparisons. However, the gradual decreasing ORs across most of the higher flavonol intake quartiles, the strength of the association, and the consistency of the protective association across most individual flavonols are less likely due to chance.

Flavonol intake is invariably linked to a healthful diet (i.e., low saturated fat and red meat intake and high dietary fiber and folate intake) because flavonols are found in fruits and vegetables, most of which are high in phytosterols, fiber, and vitamins and low in total and saturated fatty acids. Despite adjusting for fiber intake, residual and unmeasured confounding cannot be completely excluded, although adjusting for other potential dietary CRC confounders (e.g., folate, red meat, saturated fat, and vitamin supplements) did not substantially alter the risk estimates. Furthermore, high flavonol content is a common link between all frequently consumed vegetables (dry beans, green beans and peas, and green salad) that had been reported previously in the PPT to be protective (58). Adjusting individually for those vegetables did not attenuate the risk estimates.

Our study findings may not be generalizable to the general population because most of the participants were highly educated nonsmokers that engaged in a health-promoting life style (28, 30). The protective intake levels of flavonols are far greater than what is commonly consumed in the United States and other Western countries (1, 2). On the other hand, the PPT provided an excellent opportunity to examine in humans how high intake levels of flavonoids affect adenoma recurrence risk estimates. In addition, the short duration of the PPT (4 years) might require higher dietary intake levels of flavonoids than commonly consumed in the United States to see a statistically significant effect. Furthermore, dosages used in animal and cell culture studies refer to intake levels of flavonoids much higher than that consumed in the Western population.

In conclusion, our results suggest that intake of a flavonol-rich diet may reduce the risk of advanced colorectal adenoma recurrence. Our results should be considered with caution given the relatively small number of cases with advanced adenoma recurrence, the lack of a protective effect in the underlying randomized clinical trial, the relative health consciousness of the participants, and the fact that this is one of the first studies that examined the association between flavonoid intake and adenoma recurrence. Verification of these results in studies examining the association between flavonol intake and adenoma occurrence and CRC in other prospective cohorts with high-quality dietary measures and high flavonol intakes are needed to clarify the potential role of high dietary flavonol intakes in preventing CRC.

Appendix 1: The Polyp Prevention Study Group

The members of the Polyp Prevention Study Group participated in the conduct of the Polyp Prevention Trial. However, the data presented in the manuscript and the conclusions drawn from them are solely the responsibility of the above listed co-authors.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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