American Journal of Epidemiology
Vol. 164, No. 7
DOI: 10.1093/aje/kwj296
Advance Access publication August 21, 2006
Copyright © 2006 by the Johns Hopkins Bloomberg School of Public Health
All rights reserved; printed in U.S.A.

Original Contribution

Flavonoid Intake and Colorectal Cancer Risk in Men and Women

Jennifer Lin[1], Shumin M. Zhang[1,2], Kana Wu[3], Walter C. Willett[2,3,4], Charles S. Fuchs[4,5], and Edward Giovannucci[2,3,4]

[1] Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
[2] Department of Epidemiology, Harvard School of Public Health, Boston, MA.
[3] Department of Nutrition, Harvard School of Public Health, Boston, MA.
[4] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
[5] Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA.

Received for publication October 11, 2005; accepted for publication January 25, 2006.

Dietary flavonoids can inhibit cancer development by protecting tissues against free oxygen radicals and inhibiting cell proliferation, but observational studies of flavonoid intake and colorectal cancer incidence are sparse. The authors prospectively evaluated the association between intake of flavonoids and colorectal cancer incidence in 71,976 women from the Nurses' Health Study and 35,425 men from the Health Professionals Follow-Up Study. Dietary intake was assessed in 1990, 1994, and 1998 by means of a food frequency questionnaire. The authors used Cox proportional hazards models with time-varying variables to estimate relative risks of colorectal cancer. Between 1990 and 2000, the authors documented 878 incident cases of colorectal cancer (498 in women and 380 in men). Total flavonoid intake was not inversely associated with colorectal cancer risk among women and men combined. The combined relative risk for the highest quintile of total flavonoid intake compared with the lowest was 1.19 (95% confidence interval: 0.94, 1.49; p for trend $= 0.15$). Higher intakes of individual flavonols, including quercetin, myricetin, and kaempferol, were also not related to a lower risk of colorectal cancer. These data provide little support for the hypothesis of an association between flavonoid intake and colorectal cancer risk, at least within the ranges of intakes consumed in the populations studied.

colorectal neoplasms; flavones; flavonoids; flavonols

Abbreviations: FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; SD, standard deviation.

Flavonoids are polyphenolic compounds that occur naturally in various foods and beverages of plant origin. These polyphenolic compounds have been demonstrated in vitro to inhibit colon cancer cell proliferation, possibly because of the involvement of the reduced mRNA levels of tumor-promoting enzymes such as cyclooxygenase-2 and nuclear transcription factor κB (1, 2). Many flavonoids are also antioxidants, because they scavenge for free radicals (3). Flavonoids are categorized into several subgroups, such as flavonols and flavones. Major flavonols include quercetin, myricetin and kaempferol, which are present in various fruits, vegetables, and beverages such as tea. Flavones include compounds such as apigenin and luteolin, which are found in parsley and thyme. Because of the differences in their chemical structures, these flavonoid compounds may have different effects on human health (4–7).

Observational data relating flavonoid intake to risk of colorectal cancer are sparse. In one cohort study of women,

Correspondence to Dr. Jennifer Lin, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue East, Boston, MA 02215 (e-mail: jhlin@rics.bwh.harvard.edu).

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022

Arts et al. (8) observed an inverse association between certain flavonoid subgroups and risk of rectal cancer. However, in three other cohort studies, investigators did not observe a lower risk of colorectal cancer with flavonoid intake (9–11). The relation of colorectal cancer to flavonoids from food sources, such as tea and apples, has also been examined in many studies, but findings have been inconclusive (9–28).

In this analysis, we prospectively examined the relation between intakes of flavonoids and flavonoid subgroups and colorectal cancer risk in men and women from two large prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). We additionally examined the associations between major food sources of flavonoids and colorectal cancer risk in the NHS and HPFS cohorts.

MATERIALS AND METHODS

The study population

The NHS was established in 1976 when 121,700 female registered nurses aged 30–55 years from 11 US states were enrolled. The HPFS was established in 1986 when 51,529 US male dentists, podiatrists, pharmacists, optometrists, osteopaths, and veterinarians aged 40–75 years were enrolled. Every 2 years, participants in both cohorts have completed a mailed questionnaire asking for information on various risk factors and the occurrence of diseases, including colorectal cancer.

In the present analysis, we excluded participants who reported a daily energy intake outside the plausible range of 600–3,500 kcal/day (for women) or 800–4,200 kcal/day (for men) on the dietary questionnaire, as well as those who reported having had a diagnosis of cancer (except nonmelanoma skin cancer). These exclusions left a total of 71,976 women and 35,425 men for the analyses.

Dietary assessment

Dietary intake data were collected from the NHS and HPFS participants in 1990, 1994, and 1998 using a 131-item food frequency questionnaire (FFQ) (29, 30). For each food or beverage item on the FFQ, participants reported their average consumption during the past year. Participants chose from nine answers ranging from ''never'' or ''less than one serving per month'' to ''six or more servings per day.'' Individual nutrient intakes were calculated by multiplying the frequency of each food consumed by the nutrient content of the specified portion size. This information was obtained from the US Department of Agriculture (31) and was supplemented by information supplied by food manufacturers.

We created our flavonoid database by first analyzing foods known to be important dietary sources of flavonoids, including apples, apple juice, onions, tea, red wine, avocado, cantaloupe, watermelon, blueberries, green beans, corn, alfalfa sprouts, yellow squash, green pepper, and tofu (30). For foods that were not analyzed, we utilized values from a previous analysis of Dutch foods (32). We also imputed values for 46 foods using values from related foods; half of these foods were listed on the questionnaire and others were written in by participants (30). Intakes of flavonols and flavones, including quercetin, kaempferol, myricetin, apigenin, and luteolin, were calculated as the sums of the products of frequency and flavonoid content (frequency of consumption of each food $\times$ flavonoid content for the specified serving size) (33). The measure ''total flavonoids'' represents the sum of these five compounds.

The reproducibility and validity of the dietary questionnaire were assessed previously by comparing responses from the FFQ with responses from two 1-week dietary records in women (29). Although the reproducibility and validity of values for flavonoid intake could not be directly tested, we examined correlations between the questionnaire and the dietary records for the major food sources of flavonoids. The Pearson correlation coefficients were 0.90 for tea, 0.66 for apples, 0.49 for broccoli, and 0.44 for tomatoes (29).

Case ascertainment

On each biennial questionnaire, we asked participants whether they had been diagnosed with colon or rectal cancer in the prior 2 years. We sought permission to obtain hospital records and pathology reports for persons who reported a diagnosis of colorectal cancer and persons who were deceased. Physicians who were blinded to exposure data reviewed and extracted information on histology, anatomic location, and stage of cancer. Between 1990 and 2000, we documented 878 incident cases of colorectal cancer—498 in women and 380 in men. Specifically, 408 women and 293 men had a primary tumor of the colon and 90 women and 87 men had rectal cancer.

Data analysis

In the present study, we did not analyze intakes of two flavones, luteolin and apigenin, which contributed very minor amounts to total flavonoid intakes in both cohorts (<0.1 mg/day). We first grouped intakes of flavonoids and individual flavonols (i.e., quercetin, myricetin, and kaempferol) in both cohorts into quintiles. Intakes of the major food sources of flavonoids, including tea, onions, broccoli, apples, and tomatoes, were categorized a priori. Intake of onions included onion consumed as a garnish or as a vegetable. Apple sources included apple juice or cider and fresh apple. Tomato sources included tomato juice, tomato sauce, and fresh tomato. We evaluated the long-term intakes of flavonoids, individual flavonols, and major food items from the baseline FFQ (1990) and follow-up FFQs (1994 and 1998) and computed cumulative average intakes.

We calculated person-years of observation for each participant from the date of return of the baseline questionnaire (June 1990 for the NHS and January 1990 for the HPFS) to the date of a report of colorectal cancer, other cancer, or death or the end of follow-up (June 2000 for the NHS and January 2000 for the HPFS). We first analyzed the NHS and HPFS cohorts separately. We used Cox proportional hazards models with time-varying variables to model the relative risks of colorectal cancer, comparing higher quintiles with

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022

TABLE 1. Age-adjusted data on risk factors for colorectal cancer according to quintiles* (Q) of flavonoid intake at baseline among participants in the Nurses' Health Study and the Health Professionals Follow-up Study, 1990

	Nurses' Health Study (women)					Health Professionals Follow-up Study (men)				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
No. of participants	14,611	14,222	14,544	14,244	14,332	7,129	6,949	7,088	7,016	7,007
Age (years)	55.5	56.0	56.4	56.8	56.7	56.7	56.5	57.3	57.8	58.2
Body mass index† (kg/m^2)	25.6	25.7	25.7	25.7	25.8	25.6	25.6	25.5	25.6	25.7
Family history of colorectal cancer‡ (%)	10.2	10.1	10.2	11.0	10.1	10.3	11.0	11.9	10.9	12.1
Prior colorectal polyps (%)	1.3	1.2	1.3	1.2	1.3	3.9	3.9	4.0	4.1	4.1
Prior screening sigmoidoscopy or colonoscopy (%)	9.8	9.8	10.6	10.4	10.7	13.5	13.8	14.8	15.0	13.7
Current smoking (%)	23.4	16.9	14.2	14.0	14.2	11.4	7.5	5.8	5.4	6.4
Alcohol consumption (g/day)	6.0	5.4	5.0	4.7	4.3	11.9	10.8	9.7	9.3	9.0
Regular physical activity (metabolic equivalents/week)	13.2	15.7	16.2	17.0	16.2	32.9	36.2	38.8	39.0	41.2
Current postmenopausal hormone replacement therapy (%)	27.4	28.3	29.1	28.6	27.6					
Current aspirin use (%)	44.0	46.4	46.6	45.5	45.1	32.4	32.1	33.6	33.1	34.2
Current multivitamin supplement use (%)	35.9	38.1	38.8	39.6	38.0	36.8	39.3	38.0	39.5	39.1
Total caloric intake (kcal/day)	1,706	1,752	1,772	1,772	1,729	1,898	1,926	1,927	1,938	1,913
Red meat intake (servings/day)	0.6	0.6	0.5	0.5	0.5	0.7	0.7	0.6	0.6	0.6
Total folate intake (μg/day)	385	418	437	451	463	451	492	505	530	551
Total fiber intake (g/day)	14.9	17.5	18.8	19.5	19.9	17.9	20.9	22.9	24.3	25.6
Total calcium intake (mg/day)	968	994	991	987	969	937	917	909	906	884

* Ranges of flavonoid intakes in the quintiles were 0–9.6, >9.6–13.7, >13.7–19.5, >19.5–31.1, and >31.1 mg/day for the Nurses' Health Study cohort and 0–10.7, >10.7–14.9, >14.9–20.5, >20.5–30.5, and >30.5 mg/day for the Health Professionals Follow-up Study cohort.

† Weight (kg)/height (m)^2.

‡ History of colorectal cancer in a first-degree relative.

the lowest quintile (referent). In the multivariable models, results were adjusted for age (in 5-year categories) and potential risk factors for colorectal cancer, including: body mass index (weight (kg)/height (m)^2; <23, 23–<25, 25–<27, 27–<30, or ≥30 kg/m^2); physical activity (metabolic equivalents/week, in quintiles); history of colorectal cancer in a first-degree relative (yes/no); previous colorectal polyps (yes/no); prior screening sigmoidoscopy or colonoscopy (yes/no); smoking status (never, past, or current); current multivitamin use (yes/no); current aspirin use (yes/no); alcohol consumption (never use or <10, 10–<20, or ≥20 g/day); energy intake (kcal/day, in quintiles); red meat intake (servings/day, in quintiles); total calcium intake (mg/day, in quintiles); total folate intake (mg/day, in quintiles); and total fiber intake (mg/day, in quintiles). We additionally adjusted for postmenopausal hormone therapy (never, past, or current) in the NHS cohort. Covariates were assessed repeatedly and updated throughout the analysis.

We performed tests for trend by using the nutrient intake values to construct continuous variables (for nutrient analysis) or by using the frequency responses in servings per day or per week (for food analysis). All p values were two-sided.

We also combined relative risk estimates from the NHS and HPFS cohorts using a random-effects model developed by DerSimonian and Laird (34).

RESULTS

The baseline mean intakes of flavonoids were similar in the NHS and HPFS cohorts: 21.7 mg/day (standard deviation (SD), 15.1) and 22.4 mg/day (SD, 14.5) in women and men, respectively. Of the individual flavonols, quercetins (15.9 mg/day (SD, 10.2) in women, 16.8 mg/day (SD, 10.3) in men) were the major contributor to intake of flavonoids, followed by kaempferol (4.8 mg/day (SD, 5.2) in women, 4.3 mg/day (SD, 4.8) in men) and myricetin (0.98 mg/day (SD, 1.1) in women, 1.1 mg/day (SD, 1.0) in men). The major food sources of flavonoids in both cohorts were tea (35 percent in women and 25 percent in men), onions (23 percent in women, 25 percent in men), apples (8 percent in women, 10 percent in men), broccoli (8 percent in women, 7 percent in men), and tomatoes (6 percent in women, 7 percent in men). Together, these accounted for approximately 80 percent of food sources of flavonoids in both women and men.

Table 1 presents the baseline distributions of risk factors for colorectal cancer according to quintiles of flavonoid intake in the NHS and HPFS cohorts. Participants who consumed greater amounts of flavonoids were less likely to be current smokers, consumed less alcohol, and were more likely to be physically active. Persons reporting a higher

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022

TABLE 2. Relative risk of colorectal cancer according to quintiles of intake of flavonoids and their subclasses (updated cumulatively) in the Nurses' Health Study and the Health Professionals Follow-up Study, 1990–2000

	Quintile of intake									
	1 (referent)	2		3		4		5		p_{trend}
		RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	
Total flavonoids										
NHS* (women)†	1.00	0.92	0.68, 1.24	0.95	0.70, 1.28	0.95	0.70, 1.29	1.13	0.83, 1.52	0.42
HPFS* (men)†	1.00	1.08	0.75, 1.53	1.07	0.75, 1.54	1.10	0.77, 1.58	1.28	0.89, 1.83	0.21
Pooled	1.00	0.99	0.78, 1.23	1.00	0.79, 1.26	1.01	0.80, 1.28	1.19	0.94, 1.49	0.15
Total no. of cases	171	170		165		172		200		
Subclasses										
Quercetin										
NHS (women)†	1.00	0.72	0.53, 0.98	0.86	0.64, 1.15	0.80	0.59, 1.09	1.01	0.75, 1.35	0.40
HPFS (men)†	1.00	1.22	0.86, 1.74	1.06	0.74, 1.54	1.29	0.90, 1.85	1.16	0.80, 1.68	0.40
Pooled	1.00	0.93	0.55, 1.57‡	0.93	0.74, 1.18	1.01	0.63, 1.60‡	1.06	0.84, 1.34	0.23
Total no. of cases	178	105		165		175		195		
Kaempferol										
NHS (women)†	1.00	1.07	0.81, 1.43	0.88	0.65, 1.19	0.78	0.57, 1.07	1.14	0.85, 1.52	0.55
HPFS (men)†	1.00	0.79	0.55, 1.13	0.99	0.71, 1.39	1.01	0.72, 1.42	1.09	0.78, 1.52	0.29
Pooled	1.00	0.94	0.70, 1.26	0.93	0.74, 1.16	0.88	0.68, 1.14	1.12	0.90, 1.39	0.25
Total no. of cases	183	170		168		158		199		
Myricetin										
NHS (women)†	1.00	0.74	0.55, 0.99	0.69	0.52, 0.93	0.84	0.63, 1.11	0.89	0.67, 1.18	0.96
HPFS (men)†	1.00	1.10	0.77, 1.79	1.22	0.86, 1.73	1.10	0.77, 1.58	1.33	0.93, 1.89	0.43
Pooled	1.00	0.89	0.60, 1.31	0.91	0.53, 1.58‡	0.94	0.72, 1.23	1.07	0.67, 1.59	0.70
Total no. of cases	183	164		165		173		193		

* RR, relative risk; CI, confidence interval; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

† In multivariable models, results were adjusted for age, body mass index, family history of colorectal cancer (first-degree relative), history of colorectal polyps, prior sigmoidoscopy screening, physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, total calcium intake, total folate intake, total fiber intake, aspirin use, and multivitamin use. Among women, multivariate models also included adjustment for postmenopausal hormone replacement therapy. See table 1 for quintile cutpoints for total flavonoids.

‡ Test for heterogeneity by sex was statistically significant.

intake of flavonoids also reported higher intakes of total folate and total fiber.

Total flavonoid intake was not significantly associated with risk of colorectal cancer in the NHS cohort; the age-adjusted relative risks in the higher quintiles of flavonoid intake relative to the lowest quintile were 0.88, 0.83, 0.83, and 0.98 (p for trend = 0.93). The respective values among men were 1.12, 1.03, 1.06, and 1.24 (p for trend = 0.33). Additional adjustment for risk factors for colorectal cancer did not substantially alter the results; the multivariable relative risks comparing the highest category of flavonoid intake with the lowest were 1.13 (95 percent confidence interval: 0.83, 1.52; p for trend = 0.42) in women and 1.28 (95 percent confidence interval: 0.89, 1.83; p for trend = 0.21) in men. Accordingly, we report multivariable results from each cohort and from both cohorts combined for the relation of flavonoid intake to colorectal cancer risk (table 2).

Intakes of individual flavonols were also not appreciably associated with colorectal cancer risk. In the pooled analysis combining the two cohorts, no evidence for inverse associations was observed between intakes of individual flavonoids, including quercetin, kaempferol, and myricetin, and risk of colorectal cancer (table 2).

We further examined the primary food sources of flavonoids in relation to risk of colorectal cancer in both men and women. Intakes of tea, onions, broccoli, and tomatoes were not significantly associated with risk of colorectal cancer in either women or men (table 3). Higher apple consumption was weakly associated with a lower risk of colorectal cancer in men; the relative risk in the highest intake category ($\geq$2 servings/day) relative to the lowest ($\leq$2 servings/week) was 0.82 (95 percent confidence interval: 0.51, 1.30; p for trend = 0.06). However, no overall linear trend was noted in men and women combined (p = 0.11) (table 3).

In analyses carried out using intake at baseline (i.e., 1990) without cumulative updating, results (data not shown) were similar to the findings obtained using cumulative updating. Additional analyses carried out according to tumor site also revealed no significant associations between intakes of

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022

TABLE 3. Multivariate-adjusted relative risk of colorectal cancer according to five intake categories of major food sources of flavonoids (updated cumulatively) in the Nurses' Health Study and the Health Professionals Follow-up Study, 1990–2000

Flavonoid food source	Intake category									p_{trend}
	1 (referent)	2		3		4		5		
		RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	
Tea	*0–0.5 servings/week*	*0.6–1 servings/week*		*2–4 servings/week*		*5–6 servings/week*		*≥1 serving/day*		
NHS* (women)†	1.00	0.72	0.49, 1.05	0.75	0.57, 0.98	0.71	0.46, 1.09	0.90	0.72, 1.13	0.65
HPFS* (men)†	1.00	0.92	0.62, 1.36	0.69	0.49, 0.97	0.98	0.62, 1.55	1.15	0.88, 1.52	0.11
Pooled	1.00	0.81	0.62, 1.06	0.72	0.58, 0.90	0.82	0.60, 1.13	1.01	0.79, 1.28	0.18
Total no. of cases	431	68		114		50		215		
Onions	*0–0.5 servings/week*	*0.6–1 servings/week*		*2–4 servings/week*		*5–6 servings/week*		*≥1 serving/day*		
NHS (women)†	1.00	1.06	0.70, 1.60	1.19	0.88, 1.61	1.16	0.86, 1.56	1.13	0.84, 1.53	0.81
HPFS (men)†	1.00	0.79	0.51, 1.21	1.00	0.73, 1.37	1.00	0.73, 1.39	0.92	0.65, 1.29	0.64
Pooled	1.00	0.92	0.68, 1.24	1.09	0.87, 1.36	1.08	0.87, 1.35	1.03	0.82, 1.29	0.92
Total no. of cases	168	69		202		215		224		
Broccoli‡	*0–0.5 servings/week*	*0.6–1 servings/week*		*2–4 servings/week*		*≥5 servings/week*				
NHS (women)†	1.00	1.08	0.83, 1.40	1.11	0.84, 1.47	0.93	0.53, 1.62			0.98
HPFS (men)†	1.00	0.83	0.64, 1.09	0.95	0.71, 1.27	0.92	0.49, 1.72			0.82
Pooled	1.00	0.95	0.74, 1.22	1.03	0.84, 1.26	0.92	0.61, 1.40			0.90
Total no. of cases	234	301		309		34				
Apples	*0–2 servings/week*	*3–4 servings/week*		*5–6 servings/week*		*1 serving/day*		*≥2 servings/day*		
NHS (women)†	1.00	1.07	0.86, 1.34	1.23	0.91, 1.66	0.78	0.47, 1.28	0.64	0.35, 1.17	0.74
HPFS (men)†	1.00	1.01	0.77, 1.31	1.07	0.76, 1.50	0.46	0.25, 0.87	0.82	0.51, 1.30	0.06
Pooled	1.00	1.04	0.88, 1.24	1.16	0.92, 1.45	0.62	0.38, 1.02	0.75	0.52, 1.08	0.11
Total no. of cases	425	256		121		34		43		
Tomatoes	*0–2 servings/week*	*3–4 servings/week*		*5–6 servings/week*		*1 serving/day*		*≥2 servings/day*		
NHS (women)†	1.00	1.18	0.92, 1.52	1.22	0.92, 1.61	1.06	0.71, 1.59	1.02	0.70, 1.48	0.81
HPFS (men)†	1.00	1.10	0.83, 1.46	1.11	0.80, 1.54	1.10	0.70, 1.73	1.23	0.84, 1.80	0.31
Pooled	1.00	1.15	0.95, 1.38	1.17	0.95, 1.45	1.08	0.80, 1.46	1.12	0.86, 1.46	0.55
Total no. of cases	221	295		200		65		97		

* RR, relative risk; CI, confidence interval; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

† In multivariable models, results were adjusted for age, body mass index, family history of colorectal cancer (first-degree relative), history of colorectal polyps, prior sigmoidoscopy screening, physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, total calcium intake, total folate intake, total fiber intake, aspirin use, and multivitamin use. Among women, multivariate models also included adjustment for postmenopausal hormone replacement therapy.

‡ For broccoli, categories 4 and 5 were combined because of the limited number of cases in each category.

flavonoids or individual flavonols and colon or rectal cancer (data not shown).

DISCUSSION

In this prospective study, we observed no associations between intakes of flavonoids or individual flavonols, including quercetin, kaempferol, and myricetin, and risk of colorectal cancer. Intakes of primary food sources of flavonoids were also not significantly associated with risk of colorectal cancer.

Observational studies on the association between flavonoids and colorectal cancer risk have been limited. Similar to our findings, the findings of most of these studies have not supported the hypothesis of an inverse association with colorectal cancer risk or mortality (9–11). In the Seven Countries Study, which comprised 16 cohorts, flavonoid intake was not related to colorectal cancer mortality during 25 years of follow-up (11). In the Finnish Mobile Clinic Health Examination Survey, a cohort study of 5,309 men and 4,745 women, Knekt et al. (9) also observed a null association between flavonoid intake and incidence of colorectal cancer, although investigators from a previous small study reported

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022

a suggestive inverse association (20). Moreover, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, intakes of total flavonols and flavones were weakly positively associated with risk of colorectal cancer among 27,110 male smokers (10). To our knowledge, only one cohort study of women has observed an inverse association with intake of catechins, the flavonoid subclass, but the inverse association was confined to rectal cancer (8). The overall observations suggest a lack of inverse association between flavonoid intake and colorectal cancer, raising the question of whether the protective effects obtained in in vitro studies can be achieved in humans.

Findings relating foods rich in flavonoids to colorectal cancer risk have been inconclusive. Results from the Finnish Mobile Clinic Health Examination Survey suggested that apple consumption may explain an inverse association observed with total cancer incidence (9, 20), while our study and another cohort study (21) revealed no significant association. Intake of broccoli has been linked to reduced risk of colorectal cancer in some studies (22, 23) but not in our study or the Iowa Women's Health Study (24). In addition, some (25, 26) but not all (21, 27) studies have reported an inverse association between tomato intake and colorectal cancer risk. In our study, tomato consumption did not appear to be protective against colorectal cancer. Studies investigating the association between onion intake and colorectal cancer risk have been limited; in our study and in several others (10, 20, 28), no association with onion intake was observed.

Tea was another major food source of flavonoids in our cohorts. Investigators in at least two observational studies have reported a lower risk of colorectal cancer among participants who drank tea frequently than in those who never drank tea (12, 13). However, our study and several others (14–19) did not reveal an inverse association of tea intake with risk of colorectal cancer. On the basis of findings from seven cohort studies and 12 case-control studies, Tavani and La Vecchia (19) concluded that there is no overall association between tea intake and risk of colon or rectal cancer. Their review provides little support for the hypothesis that tea may be a potent protective agent against colorectal carcinogenesis.

Most flavonoids present in foods are in the form of esters, glycosides, or polymers that cannot be absorbed in their native form (35). They are usually absorbed by passive diffusion after being converted to aglycons in the gastrointestinal tract (36, 37). It has been shown that a large fraction of flavonoids remains unabsorbed; the amount that is bioavailable is only a small proportion of the ingested amount, ranging from 0.2–0.9 percent for tea catechins to 20 percent for quercetin and isoflavones (38, 39). While recent studies have suggested that the bioavailability of certain flavonoids from food (e.g., onions) may be higher than expected (40), it remains unclear whether the beneficial effects of antiproliferation and antioxidation from in vitro studies would also be present in humans, since these effects were often obtained with much greater concentrations than can be achieved in humans through diet (37). Furthermore, the microorganisms in the colon act as enzymes in catalyzing flavonoids into an array of metabolites (41). Interindividual variation in the possession of colonic microbial flora and the variable influences of foods on microbial metabolite production add further complexity.

At least two strengths were present in this study. The first was the prospective collection of the dietary information for analysis of colorectal cancer, which makes it unlikely that flavonoid intake was biased by the existence of disease. Biased detection of disease status is also unlikely to have affected our findings, since screening histories did not differ appreciably by flavonoid intake. In addition, repeated assessments of diet were available in the two cohorts, and the use of cumulatively updated data allowed for better assessment of long-term diet by reducing random within-person measurement error.

However, several limitations were also present in this study. Although we controlled for risk factors for colorectal cancer, we cannot exclude the possibility of residual confounding from these variables. However, as table 1 shows, several healthy behaviors were positively correlated with flavonoid intake. Thus, if residual confounding due to health-conscious behavior existed, we would expect to see a protective association with flavonoid intake. In addition, our FFQ may be subject to incomplete assessment of dietary flavonoids. Because flavonoid content derived from foods varies with numerous factors, such as processing, storage, and species variety (42), different types of foods such as apples and tomatoes, as well as different classes of beverages such as red wine and tea, are likely to have different concentrations of flavonoids. However, our FFQ obtains no such specific information on types or classes of most foods. Furthermore, data on other major subclasses of flavonoids, such as flavan-3-ols (e.g., epicatechin, epicatechin 3-gallate, and epigallocatechin 3-gallate), were not available in the present study. Apples and tea were two major food sources of flavan-3-ols in our cohorts (43), similar to a Dutch cohort study in which consumption of tea and apples accounted for more than 95 percent of flavan-3-ol intake (44). Although the association between flavan-3-ol intake and colorectal cancer was not directly examined in the present study, we tested the associations with intakes of apples and tea, two major food sources of flavan-3-ols, and found that the associations were not significant.

In conclusion, our data provide little support for an association between flavonoid intake and risk of colorectal cancer, at least within the ranges of intakes consumed in our population. We were also unable to confirm inverse associations between the major food sources of flavonoids consumed in our cohorts and colorectal cancer risk.

ACKNOWLEDGMENTS

The Nurses' Health Study and the Health Professionals' Follow-up Study were supported by grants CA87969 and CA55075 from the National Institutes of Health and by the National Colorectal Cancer Research Alliance. Dr. Jennifer Lin is a recipient of a National Cancer Institute Career Development Award (KCA112529).

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022

The authors thank the staffs of the Nurses' Health Study and the Health Professionals' Follow-up Study for providing relevant information.

Conflict of interest: none declared.

REFERENCES

1. Wenzel U, Kuntz S, Brendel MD, et al. Dietary flavone is a potent apoptosis inducer in human colon carcinoma cells. Cancer Res 2000;60:3823–31.
2. Kuo SM, Morehouse HF Jr, Lin CP. Effect of antiproliferative flavonoids on ascorbic acid accumulation in human colon adenocarcinoma cells. Cancer Lett 1997;116:131–7.
3. Duthie SJ, Dobson VL. Dietary flavonoids protect human colonocyte DNA from oxidative attack in vitro. Eur J Nutr 1999;38:28–34.
4. Noroozi M, Angerson WJ, Lean ME. Effects of flavonoids and vitamin C on oxidative DNA damage to human lymphocytes. Am J Clin Nutr 1998;67:1210–18.
5. Knekt P, Jarvinen R, Dich J, et al. Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and *N*-nitroso compounds: a follow-up study. Int J Cancer 1999; 80:852–6.
6. Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Biol Med 1996;20:933–56.
7. Miksicek RJ. Estrogenic flavonoids: structural requirements for biological activity. Proc Soc Exp Biol Med 1995;208: 44–50.
8. Arts IC, Jacobs DR Jr, Gross M, et al. Dietary catechins and cancer incidence among postmenopausal women: the Iowa Women's Health Study (United States). Cancer Causes Control 2002;13:373–82.
9. Knekt P, Kumpulainen J, Jarvinen R, et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr 2002;76: 560–8.
10. Hirvonen T, Virtamo J, Korhonen P, et al. Flavonol and flavone intake and the risk of cancer in male smokers (Finland). Cancer Causes Control 2001;12:789–96.
11. Hertog MG, Kromhout D, Aravanis C, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. Arch Intern Med 1995;155: 381–6.
12. Baron JA, Gerhardsson de Verdier M, Ekbom A. Coffee, tea, tobacco, and cancer of the large bowel. Cancer Epidemiol Biomarkers Prev 1994;3:565–70.
13. Su LJ, Arab L. Tea consumption and the reduced risk of colon cancer—results from a national prospective cohort study. Public Health Nutr 2002;5:419–25.
14. Goldbohm RA, Hertog MG, Brants HA, et al. Consumption of black tea and cancer risk: a prospective cohort study. J Natl Cancer Inst 1996;88:93–100.
15. Cerhan JR, Putnam SD, Bianchi GD, et al. Tea consumption and risk of cancer of the colon and rectum. Nutr Cancer 2001;41:33–40.
16. Il'yasova D, Martin C, Sandler RS. Tea intake and risk of colon cancer in African-Americans and whites: North Carolina Colon Cancer Study. Cancer Causes Control 2003;14: 767–72.
17. Michels KB, Willett WC, Fuchs CS, et al. Coffee, tea, and caffeine consumption and incidence of colon and rectal cancer. J Natl Cancer Inst 2005;97:282–92.
18. Arts IC, Hollman PC, Bueno De Mesquita HB, et al. Dietary catechins and epithelial cancer incidence: The Zutphen Elderly Study. Int J Cancer 2001;92:298–302.
19. Tavani A, La Vecchia C. Coffee, decaffeinated coffee, tea and cancer of the colon and rectum: a review of epidemiological studies, 1990–2003. Cancer Causes Control 2004;15: 743–57.
20. Knekt P, Jarvinen R, Seppanen R, et al. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol 1997;146:223–30.
21. Voorrips LE, Goldbohm RA, van Poppel G, et al. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands Cohort Study on Diet and Cancer. Am J Epidemiol 2000;152:1081–92.
22. Hara M, Hanaoka T, Kobayashi M, et al. Cruciferous vegetables, mushrooms, and gastrointestinal cancer risks in a multicenter, hospital-based case-control study in Japan. Nutr Cancer 2003;46:138–47.
23. Lin HJ, Probst-Hensch NM, Louie AD, et al. Glutathione transferase null genotype, broccoli, and lower prevalence of colorectal adenomas. Cancer Epidemiol Biomarkers Prev 1998;7:647–52.
24. Steinmetz KA, Kushi LH, Bostick RM, et al. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. Am J Epidemiol 1994;139:1–15.
25. La Vecchia C. Mediterranean epidemiological evidence on tomatoes and the prevention of digestive-tract cancers. Proc Soc Exp Biol Med 1998;218:125–8.
26. McCullough ML, Robertson AS, Chao A, et al. A prospective study of whole grains, fruits, vegetables and colon cancer risk. Cancer Causes Control 2003;14:959–70.
27. Michels KB, Edward G, Joshipura KJ, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. J Natl Cancer Inst 2000;92: 1740–52.
28. Dorant E, van den Brandt PA, Goldbohm RA. A prospective cohort study on the relationship between onion and leek consumption, garlic supplement use and the risk of colorectal carcinoma in the Netherlands. Carcinogenesis 1996;17: 477–84.
29. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18: 858–67.
30. Sampson L, Rimm E, Hollman PC, et al. Flavonol and flavone intakes in US health professionals. J Am Diet Assoc 2002; 102:1414–20.
31. Agricultural Research Service, US Department of Agriculture. National Nutrient Database for Standard Reference. Release 10. Washington, DC: US Department of Agriculture, 1993. (http://www.nal.usda.gov/fnic/foodcomp/search/).
32. Hertog MG, Hollman PC, Katan MB, et al. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. Nutr Cancer 1993;20:21–9.
33. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–99.
34. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
35. Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79: 727–47.
36. Kuhnau J. The flavonoids. A class of semi-essential food components: their role in human nutrition. World Rev Nutr Diet 1976;24:117–91.

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022

37. Yang CS, Landau JM, Huang MT, et al. Inhibition of carcinogenesis by dietary polyphenolic compounds. Annu Rev Nutr 2001;21:381–406.
38. Hollman PC, de Vries JH, van Leeuwen SD, et al. Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. Am J Clin Nutr 1995;62:1276–82.
39. Lee MJ, Wang ZY, Li H, et al. Analysis of plasma and urinary tea polyphenols in human subjects. Cancer Epidemiol Biomarkers Prev 1995;4:393–9.
40. Hollman PC, van Trijp JM, Buysman MN, et al. Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. FEBS Lett 1997;418:152–6.
41. Spencer JP. Metabolism of tea flavonoids in the gastrointestinal tract. J Nutr 2003;133(suppl):3255S–61S.
42. Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. Annu Rev Nutr 2002;22:19–34.
43. Agricultural Research Service, US Department of Agriculture. USDA database for the flavonoid content of selected foods—2003. Washington, DC: US Department of Agriculture, 2003. (http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html).
44. Arts IC, Hollman PC, Feskens EJ, et al. Catechin intake might explain the inverse relation between tea consumption and ischemic heart disease: The Zutphen Elderly Study. Am J Clin Nutr 2001;74:227–32.

Downloaded from https://academic.oup.com/aje/article/164/7/644/63067 by U.S. Department of Justice user on 16 August 2022