American Journal of Epidemiology Advance Access published February 23, 2014

American Journal of Epidemiology

DOI: 10.1093/aje/kwu006

Original Contribution

Dietary Flavonoid and Proanthocyanidin Intakes and Prostate Cancer Risk in a Prospective Cohort of US Men

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Initially submitted July 24, 2013; accepted for publication January 7, 2014.

Higher dietary intakes of flavonoids and proanthocyanidins have been associated with a lower risk of several cancers. Few prospective epidemiologic studies have examined individual flavonoids and proanthocyanidins in relation to prostate cancer. We examined these associations in a prospective US cohort of 43,268 men with a mean age of 70 years who completed detailed self-administered questionnaires in 1999–2000. During a mean follow-up of 7.8 years, 3,974 total prostate cancers, including 567 high-grade cases and 362 advanced cases, were ascertained. Cox proportional hazards regression models were used to calculate multivariable-adjusted relative risks and 95% confidence intervals. Residual energy-adjusted total flavonoids (for fifth quintile vs. first quintile, relative risk = 1.11, 95% confidence interval: 1.01, 1.23; *P* for trend = 0.02) and several subclasses were positively associated with overall prostate cancer risk, mostly limited to the top quintile and the first 2 years of follow-up. The associations for total flavonoids, flavan-3-ols, and proanthocyanidins with high-grade prostate cancer risk varied by follow-up time. During follow-up from 2002 to 2009, we observed suggestive inverse trends with higher total flavonoids (*P* for trend = 0.05) and proanthocyanidins (*P* for trend = 0.04) with high-grade prostate cancer, but not with advanced prostate cancer. Although evidence is limited, a possible role of total flavonoids and proanthocyanidins in prostate cancer tumor progression deserves further study.

flavonoids; proanthocyanidins; prospective cohort study; prostate cancer

Abbreviations: CI, confidence interval; CPS-II, Cancer Prevention Study II; FFQ, food-frequency questionnaire; PSA, prostate-specific antigen.

Prostate cancer is the most common nonskin cancer and the second leading cause of cancer death among men in the United States. It is estimated that 238,590 men will be diagnosed with and 29,720 men will die of prostate cancer in 2013 (1, 2). Advanced age, race, and a family history of prostate cancer are established risk factors, but they are nonmodifiable. Diet, a modifiable risk factor, has been suggested to play a role in the pathogenesis of prostate cancer, given the evidence that foreign-born Asian Americans had higher prostate cancer risk with increasing years of residence in North America and higher concomitant intake of saturated fat (3, 4).

Consuming a more plant-based diet for cancer prevention is recommended by the World Cancer Research Fund/American Institute for Cancer Research and the American Cancer Society (5, 6). Among the numerous potentially beneficial components present in a plant-based diet, flavonoids appear to have important antitumor properties, perhaps because of their antioxidant, antiinflammatory, and antiproliferative properties (7). Flavonoids are a large group of polyphenolic compounds, with 6 classes of monomers mainly found in the human diet (flavonols, flavan-3-ols, anthocyanidins, flavones, flavanones, and isoflavones). Proanthocyanidins, the polymers of flavan-3-ols, are different from other monomeric flavonoids because of their complex structures and high molecular weights. In vitro studies of cell systems have found that proanthocyanidins are inhibitors of apoptosis suppressor proteins, nuclear factor-κB, the PI3K/Akt pathway, and other molecular targets, which may contribute to antiproliferative and proapoptotic effects (8).

Higher intakes of dietary flavonoids have been associated with a lower risk of breast, colorectal, gastrointestinal, lung, oral, and reproductive cancers (9, 10), although the evidence is inconsistent. Epidemiologic studies on flavonoids and prostate cancer are sparse (11–18). Most of the prospective cohort studies on this topic have focused on 1 or 2 subclasses of flavonoids, such as isoflavones, flavonols, and flavones (12, 13, 16, 18). In the last decade, more comprehensive flavonoid databases became available (19, 20). Only 1 case-control study in Italy investigated all 6 subclasses of dietary flavonoids with overall prostate cancer risk and found no significant associations (17). Two studies stratified the analysis by prostate cancer tumor stage (16, 18). In the Multiethnic Cohort Study, isoflavone intake was not associated with prostate cancer, regardless of stage (16). In the Netherlands Cohort Study, there was a statistically significant lower risk of stage IV prostate cancer, but not overall prostate cancer, with greater catechin and flavonol consumption (18). None of the published epidemiologic studies have investigated the association between proanthocyanidins and prostate cancer risk.

Using more complete and recent databases of flavonoid subclasses than were used in other studies, we investigated the associations of 6 dietary flavonoid subclasses and proanthocyanidin intakes with overall prostate cancer risk and by tumor grade and stage in the Cancer Prevention Study II (CPS-II) Nutrition Cohort (21).

METHODS

Study population

Men in the present study were drawn from the 86,404 men enrolled in the CPS-II Nutrition Cohort, a prospective cohort study of cancer incidence and death that was initiated in 1992 and has been described in detail elsewhere (21). Briefly, the CPS-II Nutrition Cohort is a subgroup of approximately 1.2 million US adults in the CPS-II, a prospective cohort study of cancer death established by the American Cancer Society in 1982 (22). In 1992–1993, participants in the CPS-II cohort who resided in 21 states with population-based cancer registries and who were 50–74 years of age were invited to participate in the Nutrition Cohort. At enrollment in 1992–1993, participants completed a 10-page, mailed, self-administered questionnaire that included anthropometric, demographic, dietary, lifestyle, and medical information. Follow-up questionnaires were sent to the cohort participants in 1997 and every other year thereafter to update exposures and to ascertain newly diagnosed cancers. The response rate for each of the follow-up questionnaires was 86% or greater. All aspects of the Nutrition Cohort study were approved by the Emory University institutional review board (Atlanta, Georgia).

Exposure assessment

At the CPS-II Nutrition Cohort's baseline (in 1992–1993), dietary data were collected from the participants using a semiquantitative modified Block food frequency questionnaire (FFQ) that consists of 68 food items (21). In 1999–2000, dietary data were updated using a semiquantitative modified 152-item Willett FFQ, which included additional questions on flavonoid-rich foods (e.g., tea, chocolate, soy). The questionnaire used in the present study is available online (23). Six classes of flavonoid and total proanthocyanidin contents of foods in the 1999 FFQ were derived from 3 US Department of Agriculture databases on flavonoids (24), proanthocyanidins (19), and isoflavones (25), and other published research (26–28), as described in detail elsewhere (29). In this paper, total flavonoids were calculated as the sum of these 7 types of polyphenols, including anthocyanidins, flavones, flavanones, flavan-3-ols, flavonols, isoflavones, and proanthocyanidins. Proanthocyanidins were the sum of monomers, dimers, trimers, 4–6 mers, 7–10 mers, and >10 mers.

Analytical cohort

Of the 58,553 male participants who returned the FFQ in 1999, we excluded 1,534 men who did not return subsequent surveys and 12,210 men who reported any prevalent cancer except nonmelanoma skin cancer on or before the 1999 questionnaire. We also excluded unverified self-reported prostate cancer cases whose last cancer-free survey was in 1999 (n = 39), as well as nonadenocarcinoma cases (n = 3). We further excluded people who reported extreme energy intakes (<800 or >4,200 kcal/day) or who had more than 70 missing line items on the FFQ (n = 7,512) or 50% or more missing flavonoid-rich food items (n = 138). The top 0.1% of individual flavonoid class intakes was excluded to remove possible erroneous values (n = 246). The final analytical cohort consisted of 43,268 men.

Outcome ascertainment

A total of 3,974 prostate cancer cases were identified between 1999 and June 30, 2009. Most of the incident cases (n = 3,887) were self-reported and subsequently verified through medical records (n = 3,154) or by linkage with state cancer registries (n = 733). An additional 41 cases not self-reported were identified during the process of verifying another cancer through linkage with state cancer registries. Finally, 46 cases were ascertained through the National Death Index listing of prostate cancer as the primary cause of death (30). Additional clinical information was obtained for 19 of the 46 deaths through linkage with medical records (n = 1) and the state cancer registries (n = 18).

High-grade prostate cancer was defined as a Gleason score of 8 or higher at diagnosis (n = 567). Cases were classified as advanced if they were stage III or stage IV tumors according to the American Joint Committee on Cancer staging system (31), or if prostate cancer was listed as the primary cause of death when grade or stage information was missing (n = 362).

Statistical analysis

Follow-up time for the present analytical cohort started from the return of the 1999 FFQ and ended at the date of prostate cancer diagnosis or prostate cancer death (9.2%), the date of the last survey returned (8.7%), the date of other death (20.8%), the date of self-report if not verified (0.8%), or June 30, 2009 (60.5%), whichever came first. The mean follow-up time was 7.8 years.

Table 1. Major Food Sources of Dietary Flavonoids and Proanthocyanidins in 43,268 US Men in the Cancer Prevention Study II Nutrition Cohort, 1999–2009

Food Item/Food Group by Flavonoid	Ranking	Mean Intake, mg/day	%
Total flavonoids			
Nonherbal tea	1	76.71	25.7
Fresh apples or pears	2	48.88	16.4
Herbal tea or decaffeinated tea	3	25.97	8.7
Nonchocolate sweets and baked goods[a]	4	20.09	6.7
Red wine	5	17.43	5.8
Punch, lemonade, other noncarbonated fruit drinks, or sugared iced tea	6	11.13	3.7
Blueberries (fresh, frozen, or canned)	7	10.96	3.7
Oranges	8	9.48	3.2
Strawberries (fresh, frozen, or canned)	9	9.47	3.2
Bananas	10	8.36	2.8
Anthocyanidins			
Blueberries (fresh, frozen, or canned)	1	4.47	31.2
Bananas	2	3.66	25.6
Red wine	3	1.99	13.9
Strawberries (fresh, frozen, or canned)	4	1.75	12.3
Muffins (regular) or biscuits	5	1.08	7.6
Fresh apples or pears	6	0.98	6.9
Nonchocolate sweets or baked goods[a]	7	0.16	1.1
Fruit juices	8	0.08	0.5
Nuts[b]	9	0.06	0.4
Prunes	10	0.05	0.3
Flavan-3-ols			
Nonherbal tea	1	16.61	48.9
Bananas	2	3.03	8.9
Fresh apples or pears	3	2.97	8.7
Beer	4	2.51	7.4
Red wine	5	2.04	6.0
Blueberries (fresh, frozen, or canned)	6	1.41	4.2
Applesauce	7	1.21	3.6
Herbal or decaffeinated tea	8	0.89	2.6
Apple juice or cider	9	0.69	2.0
Nonchocolate sweets or baked goods[a]	10	0.43	1.3
Flavanones			
Oranges	1	9.11	33.0
Grapefruit	2	7.2	26.1
Orange juice	3	6.51	23.6
Grapefruit juice	4	1.88	6.8
Orange juice (calcium fortified)	5	1.57	5.7
Red wine	6	0.47	1.7
Punch, lemonade, other noncarbonated fruit drinks, or sugared iced tea	7	0.38	1.4
Tomatoes	8	0.26	0.9
White wine	9	0.11	0.4
Frozen yogurt, sherbet, or nonfat ice cream	10	0.08	0.3

Table continues

Table 1. Continued

Food Item/Food Group by Flavonoid	Ranking	Mean Intake, mg/day	%
Flavones			
Peppers (green or red)	1	0.53	32.9
Red wine	2	0.26	15.9
Oranges	3	0.24	15.0
Celery	4	0.17	10.4
Garlic	5	0.11	6.9
Cantaloupe	6	0.1	6.0
Dark orange (winter) squash	7	0.04	2.7
Peas or lima beans (fresh, frozen, or canned)	8	0.03	2.1
Lettuce (iceberg or head)	9	0.03	1.6
Mixed vegetables or vegetable soup	10	0.02	1.0
Flavonols			
Onions	1	2.24	13.1
Nonherbal tea	2	2.24	13.1
Herbal or decaffeinated tea	3	1.69	9.9
Fresh apples or pears	4	1.44	8.4
Potatoes (baked, boiled, or mashed)	5	0.81	4.7
Red wine	6	0.66	3.9
Beer	7	0.57	3.4
Orange juice	8	0.56	3.3
Lettuce (romaine or leaf)	9	0.44	2.6
Punch, lemonade, other noncarbonated fruit drinks, or sugared iced tea	10	0.4	2.3
Isoflavones			
Tofu or soybeans	1	0.386	61.5
Soy milk	2	0.213	34.0
Peanut butter	3	0.012	2.0
Peanuts	4	0.011	1.7
Beans or lentils (baked or dried)	5	0.003	0.6
String beans	6	0.001	0.2
Proanthocyanidins			
Nonherbal tea	1	57.86	28.4
Fresh apples or pears	2	43.48	21.4
Herbal tea or decaffeinated tea	3	23.38	11.5
Nonchocolate sweets and baked goods[a]	4	19.12	9.4
Red wine	5	12.01	5.9
Punch, lemonade, other noncarbonated fruit drink, or sugared iced tea	6	9.99	4.9
Strawberries (fresh, frozen, or canned)	7	7.39	3.6
Applesauce	8	5.83	2.9
Chocolate candy[c]	9	5.18	2.5
Blueberries (fresh, frozen, or canned)	10	4.82	2.4

[a] Includes cookies (fat free or reduced fat, home baked, other ready make), cakes, pies, brownies, jams, jellies, preserves, syrup, or honey.
[b] Includes peanuts, peanut butter, walnuts, and other nuts.
[c] Includes pure chocolate candy bar or packet (e.g., Hershey's, M & M's), candy bars, (e.g., Snickers, Milky Way, Reese's).

Cox proportional hazards regression models were used to calculate hazard ratios and 95% confidence intervals as estimates of relative risks of incident prostate cancer associated with quintiles of energy-adjusted flavonoids and proanthocyanidin consumption. Energy-adjusted values of flavonoids and proanthocyanidins were calculated using the residual method (32). When high-grade or advanced cases were examined as a separate outcome, cases that were non–high-grade or nonadvanced were censored at the date of diagnosis. All Cox models were stratified on single year of age at enrollment to adjust for age. Other covariates in the multivariable model included race (white, black, other/unknown), family history of prostate cancer (yes, no/unknown), body mass index (weight (kg)/height $(m)^2$) in 1999 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, unknown), smoking status (never/unknown, former, current), aspirin use (no regular use/unknown, 1–14, 15–29, 30–59, ≥60 pills/month), and energy intake (quintiles in kcal/day). In addition, history of PSA screening (never, ≥2 years ago, <2 years ago, unknown) was coded as a time-dependent variable. History of diabetes (yes, no/unknown), which has been associated with reduced risk of prostate cancer in this cohort (33), was also included in the model as a time-dependent variable. Other potential covariates considered included education; energy-adjusted intakes of total calcium (diet plus supplements), saturated fat, total vitamin E (diet plus supplements), dietary lycopene, red meat, and total fish; multivitamin use; and physical activity. Beer and alcohol intakes were also examined as covariates as an alternative to ethanol to limit overcontrol, because wine is a major source of flavonoids. None of these covariates was included in the model, because their inclusion did not change the relative risk of the fifth category of exposures by 5% or more. Trend tests were carried out by substituting values in each category of exposure by the median value in that category and modeling it as a continuous variable.

The proportional hazards assumption was tested by modeling an interaction term between each exposure and log-transformed follow-up time using extended Cox regression models. We also evaluated whether the associations of each exposure with overall prostate cancer were modified by age, body mass index, or smoking status by using the likelihood ratio test (34). All *P* values are 2-sided and considered statistically significant at the <0.05 level. SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina) was used to conduct all statistical analyses.

RESULTS

The mean intake of energy-adjusted total flavonoids in the analytical cohort was 270 mg/day, to which proanthocyanidins contributed 68%. The top 10 food sources of 6 flavonoid classes, proanthocyanidins, and total flavonoids are listed in Table 1. The classes of flavonoids shared several food sources, and many of them were highly correlated with each other, especially proanthocyanidins and total flavonoids, as shown in Table 2. At baseline, men with higher dietary total flavonoid intakes were less likely to be overweight or obese, to smoke, and to have a history of type 2 diabetes, and they were more likely to take aspirin regularly and to have a history of PSA screening. As expected, high flavonoid consumers also drank more tea and wine and reported eating more fruits and vegetables (Table 3).

The associations of dietary flavonoid and proanthocyanidin intakes with total prostate cancer are shown in Table 4. After adjustment for covariates, positive associations with total prostate cancer were observed for total flavonoids, flavan-3-ols, isoflavones, and proanthocyanidins (*P* for trend < 0.05). The positive associations were mostly driven by the cases that occurred during the first 2 years of follow-up; total flavonoids and proanthocyanidins that had no significant association with overall prostate cancer risk after the first 2 years of follow-up were excluded from the analysis (data not shown). In the analyses of dietary flavonoids and high-grade prostate cancer, the hazard ratios varied significantly over follow-up time for total flavonoids (*P* for interaction < 0.01), flavan-3-ols (*P* for interaction = 0.04), and proanthocyanidins (*P* for interaction < 0.01). These interactions were no longer significant after analyses were stratified on follow-up time (1999–2001 vs. 2002–2009). The associations of dietary flavonoid intakes with both high-grade and advanced prostate cancer stratified on follow-up time are shown in Table 5. Within the first 2 years of follow-up, men in the top quintile of dietary total flavonoids, flavan-3-ols, and proanthocyanidins had a higher risk of high-grade prostate cancer compared with men in the bottom quintile (for total flavonoids, relative risk = 2.68, 95% confidence

Table 2. Spearman's Rank Correlation Coefficients for Dietary Flavonoids in 43,268 US Men in the Cancer Prevention Study II Nutrition Cohort, 1999–2009

Dietary Flavonoids	Total Flavonoids	Anthocyanidins	Flavan-3-ols	Flavanones	Flavones	Flavonols	Isoflavones	Proanthocyanidins
Total flavonoids	1.00	0.47	0.84	0.32	0.34	0.80	0.09	0.97
Anthocyanidins		1.00	0.45	0.26	0.42	0.35	0.12	0.40
Flavan-3-ols			1.00	0.14	0.28	0.74	0.07	0.81
Flavanones				1.00	0.38	0.21	0.03	0.16
Flavones					1.00	0.48	0.16	0.25
Flavonols						1.00	0.12	0.74
Isoflavones							1.00	0.08
Proanthocyanidins								1.00

Table 3. Baseline Characteristics by Quintiles of Total Flavonoid Intake in 43,268 US Men in the Cancer Prevention Study II Nutrition Cohort, 1999–2009

Characteristic	%	Quintile of Total Flavonoid Intake									
		First (n = 8,653)		Second (n = 8,654)		Third (n = 8,654)		Fourth (n = 8,654)		Fifth (n = 8,653)	
		Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	
Intake, mg/day		99.0 (0.6–126.5)[a]		151.3 (126.6–176.1)[a]		205.6 (176.2–240.5)[a]		287.5 (240.6–359.4)[a]		504.8 (359.5–2,106.3)[a]	
Age, years		69.6 (5.7)		70.0 (5.7)		70.3 (5.8)		70.6 (5.8)		70.5 (5.8)	
Race[b]											
White	98.4		98.2		97.8		97.8		97.3		
Black	0.5		0.8		1.0		1.0		1.0		
Other/unknown	1.1		1.0		1.2		1.2		1.7		
Family history of prostate cancer	12.1		11.9		12.1		11.9		12.5		
Body mass index[c] in 1999[d]											
<25.0	29.5		31.0		33.7		35.1		37.3		
25.0–29.9	45.1		47.0		44.9		45.6		43.4		
30.0–34.9	14.4		12.7		12.4		11.0		10.8		
≥35.0	3.8		3.0		2.6		2.4		2.4		
Smoking history											
Never smoker/unknown	27.6		33.2		35.3		37.2		37.7		
Current smoker	8.5		4.7		3.1		2.6		2.7		
Former smoker	63.9		62.0		61.6		60.3		59.6		
Aspirin use in 1999, pills/month											
No regular use/unknown	45.3		42.9		42.7		41.3		42.5		
1–14	8.9		9.0		9.1		9.1		8.6		
15–29	6.6		7.2		7.5		7.3		6.9		
30–59	35.2		36.6		37.1		38.6		38.3		
≥60	4.0		4.3		3.7		3.7		3.9		
History of prostate-specific antigen screening[d]											
Never	10.2		7.6		6.8		6.2		7.2		
In the past 2 years	15.8		14.6		13.8		13.1		13.7		
More than 2 years ago	69.6		74.3		76.2		77.2		76.4		
History of diabetes											
No/unknown	83.2		86.1		85.9		85.9		84.4		
Yes	16.8		13.9		14.1		14.1		15.6		

Table continues

Table 3. Continued

Characteristic	%	Quintile of Total Flavonoid Intake									
		First (n = 8,653)		Second (n = 8,654)		Third (n = 8,654)		Fourth (n = 8,654)		Fifth (n = 8,653)	
		Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	
Dietary intakes											
Energy, kcal		1,868 (6.2)		1,930 (6.2)		1,941 (6.2)		1,920 (6.2)		1,850 (6.2)	
Total tea, servings/week		0.14 (0.05)		0.36 (0.05)		0.87 (0.05)		2.31 (0.05)		10.52 (0.05)	
Wine, servings/week		0.83 (0.04)		1.39 (0.04)		1.89 (0.04)		2.69 (0.04)		3.08 (0.04)	
Fruit and fruit juice, servings/day		1.5 (0.01)		2.2 (0.01)		2.7 (0.01)		3.0 (0.01)		3.0 (0.01)	
Vegetables and vegetable juice, servings/day		2.3 (0.02)		2.8 (0.02)		3.1 (0.02)		3.3 (0.02)		3.3 (0.02)	

Abbreviation: SE, standard error.
[a] Value expressed as median (range).
[b] Percentages were adjusted to the age distribution of the entire study population.
[c] Calculated as weight (kg)/height $(m)^2$.
[d] Percentages may not sum to 100 because of missing data.

interval (CI): 1.50, 4.79; for flavan-3-ols, relative risk = 2.04, 95% CI: 1.14, 3.65; for proanthocyanidins, relative risk = 2.72, 95% CI: 1.53, 4.85). However, associations were inverse after excluding the first 2 years of follow-up. For total flavonoids and proanthocyanidins, there was a suggestion of lower risk of high-grade prostate cancer with higher intake levels (P for trend = 0.05 and 0.04, respectively), although the relative risks of the fifth quintile were not statistically significant. No significant associations with advanced prostate cancer were observed for any flavonoid subclasses or total flavonoids. We did not observe significant statistical interactions between flavonoid intake and age (<70 years, ≥70 years), body mass index (<25.0, 25.0–29.9, ≥30.0), or smoking status (never, ever) (data not shown).

DISCUSSION

To our knowledge, the present study was the first prospective study to comprehensively examine dietary flavonoid and proanthocyanidin intakes with prostate cancer risk by tumor grade and stage in US men. Overall, greater flavonoid intake was positively associated with total prostate cancer risk, mostly driven by associations during the first 2 years of follow-up. Total flavonoids, especially proanthocyanidins, showed suggestive protective associations with high-grade prostate cancer among men who were followed from 2 years after returning the 1999 survey. No subclass of flavonoids was significantly associated with advanced disease.

Several potential explanations may account for the positive associations with overall prostate cancer seen in our study. First, higher dietary flavonoid intake was associated with several healthier lifestyle factors, such as less smoking, less overweight or obesity, and lower prevalence of type 2 diabetes. Being overweight and having a history of diabetes have been associated with a lower risk of overall prostate cancer in the CPS-II cohort (33, 35). Although body mass index and history of diabetes were included in the multivariable models, residual confounding may exist and contribute to the positive associations for total flavonoids and some subclasses with overall prostate cancer risk. Secondly, the prevalence of PSA screening was higher in men in the top categories of dietary total flavonoid intake than in men in the lowest category, and a history of PSA screening was positively associated with nonaggressive prostate cancer in this cohort. As reported by other studies, PSA screening has increased the likelihood of diagnosis of early-stage tumors (36, 37). Third, the positive associations of total flavonoids and some individual flavonoids with high-grade prostate cancer risk within the first 2 years of follow-up, mostly driven by the top quintile, also need to be interpreted with caution. These associations might be due to reverse causality, in that men who had symptoms were likely to improve their diets. Isoflavones are the most commonly studied flavonoid class in relation to prostate cancer because of the hypothesized protective effects of phytoestrogens on hormone-related cancers (38), but associations remain inconclusive. A recent meta-analysis of 2 cohort studies and 6 case-control studies on dietary isoflavones and prostate cancer revealed a combined relative risk/odds ratio of 0.88 (95% CI: 0.76, 1.02; P = 0.09) (39). Two of the 6 case-control studies reported a lower risk

Table 4. Relative Risk for Prostate Cancer Across Quintiles of Dietary Flavonoid Intake in 43,268 US Men in the Cancer Prevention Study II Nutrition Cohort, 1999–2009

Intake of Dietary Flavonoids by Quintile	Median, mg/day	Range, mg/day	No. of Cases	Total Prostate Cancer ($n = 3,974$)			
				Age-Adjusted RR	95% CI	Multivariable-Adjusted RR[a]	95% CI
Total flavonoids							
First	99.0	<126.6	756	1.00		1.00	
Second	151.3	126.6–176.1	785	1.02	0.93, 1.13	1.00	0.90, 1.10
Third	205.6	176.2–240.5	797	1.05	0.95, 1.16	1.01	0.91, 1.12
Fourth	287.5	240.6–359.4	770	1.02	0.92, 1.13	0.98	0.89, 1.09
Fifth	504.8	≥359.5	866	1.15	1.04, 1.27	1.11	1.01, 1.23
P for trend[b]				<0.01		0.02	
Anthocyanidins							
First	4.1	<5.9	718	1.00		1.00	
Second	7.5	5.9–8.9	803	1.10	1.00, 1.22	1.08	0.98, 1.20
Third	10.7	9.0–12.4	803	1.10	1.00, 1.22	1.08	0.98, 1.20
Fourth	14.8	12.5–17.9	817	1.11	1.01, 1.23	1.08	0.98, 1.20
Fifth	23.8	≥18.0	833	1.14	1.03, 1.25	1.10	1.00, 1.22
P for trend[b]				0.04		0.13	
Flavan-3-ols							
First	7.6	<10.4	711	1.00			
Second	12.9	10.4–15.3	799	1.11	1.00, 1.23	1.09	0.98, 1.20
Third	18.2	15.4–21.8	812	1.12	1.01, 1.24	1.10	0.99, 1.22
Fourth	27.5	21.9–37.8	787	1.08	0.98, 1.20	1.05	0.95, 1.17
Fifth	63.9	≥37.9	865	1.20	1.09, 1.33	1.18	1.06, 1.30
P for trend[b]				<0.01		0.01	
Flavanones							
First	3.8	<7.5	729	1.00		1.00	
Second	11.4	7.6–14.9	831	1.12	1.01, 1.24	1.10	0.99, 1.21
Third	18.7	15.0–23.2	799	1.08	0.98, 1.19	1.04	0.94, 1.16
Fourth	29.4	23.3–38.1	825	1.11	1.01, 1.23	1.08	0.98, 1.19
Fifth	53.9	≥38.2	790	1.11	1.00, 1.23	1.08	0.98, 1.20
P for trend[b]				0.15		0.31	

Table continues

and the others found no association (39). These 2 studies were conducted in Asian countries where the daily amount of isoflavones consumed (approximately 70 mg/day) was substantially higher than that consumed in Western countries (14, 40). However, the 2 cohort studies included in the meta-analysis did not observe an inverse association between isoflavone intake and prostate cancer risk. One was a Japanese cohort study (41) with an average isoflavone intake of 79 mg/day in the top quartile, and the other was the Multiethnic Cohort Study that included 5 ethnic groups in the United States (mean intake = 11.8 mg/day) with a mean follow-up period of 8 years (16). The mean intake of 0.58 mg/day of isoflavones in the present study was markedly lower and unlikely to have important health effects at this low dose. Although we found a dose-dependent positive association between isoflavone intake and overall prostate cancer risk, when we further divided men in the top quintile of dietary isoflavones evenly into 3 groups (0.14–0.55, 0.56–1.0, and ≥1.1 mg/day), the significantly higher risk was limited to men consuming 0.14–0.55 mg/day, and not men in the highest intake group (median, 2.9 mg/day, range, 1.1–48.8 mg/day). Therefore, caution is needed in interpreting the positive association with total prostate cancer risk seen in this study.

Few studies have examined other individual subclasses of flavonoids in relation to prostate cancer. A case-control study conducted in New York with population-based controls reported a lower risk of prostate cancer for men in the highest quartile of quercetin, a flavonol, though no trend was seen (odds ratio = 0.66, 95% CI: 0.47, 0.92; *P* for trend = 0.12) (15). An Italian hospital-based case-control study examined 6 classes of flavonoids in relation to prostate cancer. No association was reported, but men in the top quintile of dietary flavan-3-ol intake had 30% higher risk compared with men in the bottom quintile (odds ratio = 1.30, 95% CI: 1.01,

Table 4. Continued

Intake of Dietary Flavonoids by Quintile	Median, mg/day	Range, mg/day	No. of Cases	Total Prostate Cancer ($n = 3,974$)			
				Age-Adjusted RR	95% CI	Multivariable-Adjusted RR[a]	95% CI
Flavones							
First	0.4	<0.5	754	1.00		1.00	
Second	0.7	0.5–0.8	752	0.98	0.89, 1.09	0.98	0.88, 1.08
Third	1.1	0.9–1.2	808	1.05	0.95, 1.16	1.04	0.94, 1.15
Fourth	1.7	1.3–2.1	828	1.08	0.98, 1.19	1.06	0.96, 1.17
Fifth	3.2	≥2.2	832	1.07	0.97, 1.18	1.05	0.95, 1.16
P for trend[b]				0.09		0.19	
Flavonols							
First	7.2	<8.9	741	1.00		1.00	
Second	10.3	8.9–11.6	781	1.04	0.94, 1.15	1.02	0.92, 1.13
Third	13.2	11.7–14.9	804	1.07	0.97, 1.18	1.05	0.95, 1.16
Fourth	17.3	15.0–20.4	815	1.08	0.98, 1.20	1.06	0.96, 1.17
Fifth	26.6	≥20.5	833	1.12	1.01, 1.23	1.10	0.99, 1.21
P for trend[b]				0.03		0.05	
Isoflavones							
First	0.026	<0.029	770	1.00		1.00	
Second	0.032	0.029–0.035	798	1.04	0.94, 1.14	1.04	0.94, 1.14
Third	0.042	0.036–0.050	758	0.97	0.88, 1.07	0.96	0.87, 1.06
Fourth	0.067	0.051–0.143	733	0.94	0.85, 1.03	0.93	0.84, 1.03
Fifth	0.72	≥0.144	915	1.14	1.04, 1.26	1.11	1.01, 1.22
P for trend[b]				<0.001		<0.001	
Total proanthocyanidins							
First	54.4	<73.1	766	1.00		1.00	
Second	91.2	73.1–110.1	780	1.01	0.91, 1.12	0.98	0.89, 1.09
Third	131.8	110.2–158.4	795	1.03	0.93, 1.14	1.00	0.90, 1.10
Fourth	194.7	158.5–249.4	772	1.01	0.91, 1.12	0.97	0.88, 1.07
Fifth	364.7	≥249.5	861	1.13	1.02, 1.24	1.09	0.99, 1.21
P for trend[b]				0.01		0.03	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age, race, family history of prostate cancer, body mass index (weight (kg)/height (m)^2) in 1999, smoking status, aspirin use, total energy intake, history of prostate-specific antigen screening, and history of diabetes.

[b] Test for trend by using median values for each category and modeling as a continuous variable.

1.69; *P* for trend = 0.48) (17). Two Finnish cohort studies investigated flavonols and flavones in relation to overall prostate cancer risk; 1 found no association after a mean follow-up of 6.1 years (12), and the other observed an inverse association for myricetin, a flavonol, after 28 years of follow-up (13). The Netherlands Cohort Study recently showed that higher intakes of total catechin, epicatechin, kaempferol, and myricetin were associated with a 22%–29% lower risk of stage IV prostate cancer after a mean follow-up of 17.3 years (18). We did not observe lower risks with higher prostate cancer stage. Compared with that in the Netherlands Cohort Study, a mean follow-up time of 7.8 years in this cohort might not be long enough to observe significant protective associations for dietary flavonoids with advanced prostate cancer.

Higher proanthocyanidin intake was associated with a borderline lower risk of high-grade prostate cancer during 2002–2009, but we found no protective association of flavan-3-ols—monomers of proanthocyanidins—and any prostate cancer risk. These results are consistent with studies showing that the degree of polymerization of proanthocyanidins may be related to different health benefits (42, 43). Two Italian case-control studies found that proanthocyanidin intake was inversely associated with colorectal cancer and stomach cancer risk, with stronger associations found for a higher degree of polymerization of proanthocyanidins (42, 43). An in vitro study found that proanthocyanidins have a higher antioxidant capacity than flavan-3-ols (44). An isolated cell study demonstrated that grape seed extract, which has a higher mean

Table 5. Relative Risks for Prostate Cancer Across Quintiles of Dietary Flavonoid Intake in US Men in the Cancer Prevention Study II Nutrition Cohort During the First 2 Years of Follow-up (1999–2001) and the Subsequent 8 Years of Follow-up (2002–2009)

Intake of Dietary Flavonoids by Quintile	Median, mg/day	Range, mg/day	High-Grade Prostate Cancer[a] (*n* = 567)						Advanced Prostate Cancer[b] (*n* = 362)					
			1999–2001			2002–2009			1999–2001			2002–2009		
			No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI
Total flavonoids														
First	99.0	<126.6	16	1.00		90	1.00		20	1.00		51	1.00	
Second	151.3	126.6–176.1	29	1.77	0.96, 3.26	98	1.07	0.80, 1.43	25	1.21	0.67, 2.18	52	0.99	0.67, 1.45
Third	205.6	176.2–240.5	31	1.88	1.03, 3.46	91	0.99	0.74, 1.33	20	0.95	0.51, 1.78	53	1.01	0.68, 1.48
Fourth	287.5	240.6–359.4	23	1.41	0.74, 2.68	70	0.77	0.56, 1.05	14	0.67	0.34, 1.33	45	0.86	0.57, 1.29
Fifth	504.8	≥359.5	43	2.68	1.50, 4.79	76	0.83	0.61, 1.13	29	1.41	0.79, 2.50	53	1.02	0.69, 1.50
P for trend[d]					<0.01			0.05			0.26			0.89
Anthocyanidins														
First	4.1	<5.9	19	1.00		79	1.00		25	1.00		57	1.00	
Second	7.5	5.9–8.9	31	1.64	0.93, 2.91	98	1.22	0.90, 1.64	26	1.01	0.58, 1.76	53	0.92	0.63, 1.33
Third	10.7	9.0–12.4	32	1.69	0.95, 3.00	88	1.09	0.80, 1.48	22	0.85	0.48, 1.52	43	0.74	0.50, 1.10
Fourth	14.8	12.5–17.9	34	1.80	1.02, 3.18	76	0.93	0.68, 1.28	18	0.70	0.38, 1.29	54	0.93	0.63, 1.35
Fifth	23.8	≥18.0	26	1.38	0.76, 2.52	84	1.04	0.76, 1.42	17	0.68	0.36, 1.27	47	0.81	0.55, 1.20
P for trend[d]					0.63			0.49			0.10			0.33
Flavan-3-ols														
First	7.6	<10.4	17			84	1.00		23	1.00		49	1.00	
Second	12.9	10.4–15.3	29	1.69	0.92, 3.07	102	1.20	0.90, 1.60	16	0.75	0.39, 1.44	51	1.03	0.69, 1.52
Third	18.2	15.4–21.8	34	1.98	1.10, 3.56	87	1.02	0.75, 1.37	19	0.86	0.46, 1.60	47	0.94	0.63, 1.41
Fourth	27.5	21.9–37.8	27	1.55	0.84, 2.86	79	0.92	0.68, 1.26	25	1.07	0.59, 1.95	52	1.03	0.70, 1.53
Fifth	63.9	≥37.9	35	2.04	1.14, 3.65	73	0.86	0.63, 1.18	25	1.15	0.64, 2.05	55	1.09	0.74, 1.61
P for trend[d]					0.09			0.08			0.30			0.69
Flavanones														
First	3.8	<7.5	20	1.00		74	1.00		19	1.00		44	1.00	
Second	11.4	7.6–14.9	22	1.08	0.59, 1.98	105	1.38	1.02, 1.86	21	1.06	0.57, 1.98	61	1.32	0.90, 1.96
Third	18.7	15.0–23.2	31	1.52	0.86, 2.68	89	1.18	0.87, 1.61	25	1.26	0.69, 2.29	49	1.07	0.71, 1.61
Fourth	29.4	23.3–38.1	34	1.69	0.97, 2.95	71	0.94	0.68, 1.31	18	0.91	0.48, 1.75	47	1.03	0.68, 1.55
Fifth	53.9	≥38.2	35	1.78	1.02, 3.10	86	1.18	0.86, 1.62	25	1.30	0.71, 2.37	53	1.23	0.82, 1.84
P for trend[d]					<0.05			0.64			0.52			0.71

Table continues

Table 5. Continued

Intake of Dietary Flavonoids by Quintile	Median, mg/day	Range, mg/day	High-Grade Prostate Cancer[a] (*n* = 567)						Advanced Prostate Cancer[b] (*n* = 362)					
			1999–2001			2002–2009			1999–2001			2002–2009		
			No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI	No. of Cases	RR[c]	95% CI
Flavones														
First	0.4	<0.5	30	1.00		80	1.00		23	1.00		53	1.00	
Second	0.7	0.5–0.8	18	0.60	0.33, 1.07	82	1.00	0.74, 1.36	18	0.79	0.42, 1.46	53	0.98	0.67, 1.43
Third	1.1	0.9–1.2	40	1.34	0.83, 2.16	100	1.22	0.91, 1.63	25	1.11	0.63, 1.95	50	0.92	0.62, 1.35
Fourth	1.7	1.3–2.1	26	0.87	0.51, 1.47	82	0.99	0.73, 1.35	19	0.85	0.46, 1.57	55	1.00	0.68, 1.46
Fifth	3.2	≥2.2	28	0.92	0.55, 1.55	81	0.98	0.72, 1.34	23	1.04	0.58, 1.86	43	0.77	0.52, 1.16
P for trend[d]					0.92			0.67			0.65			0.15
Flavonols														
First	7.2	<8.9	21	1.00		83	1.00		20	1.00		41	1.00	
Second	10.3	8.9–11.6	25	1.17	0.65, 2.09	90	1.06	0.79, 1.43	22	1.10	0.60, 2.01	55	1.31	0.88, 1.97
Third	13.2	11.7–14.9	33	1.51	0.87, 2.62	91	1.08	0.80, 1.46	20	1.00	0.54, 1.87	58	1.39	0.93, 2.07
Fourth	17.3	15.0–20.4	27	1.24	0.70, 2.20	77	0.91	0.66, 1.24	16	0.80	0.41, 1.55	51	1.20	0.79, 1.81
Fifth	26.6	≥20.5	36	1.70	0.99, 2.91	84	1.00	0.74, 1.36	30	1.53	0.87, 2.71	49	1.18	0.78, 1.79
P for trend[d]					0.06			0.66			0.13			0.98
Isoflavones														
First	0.026	<0.029	23	1.00		77	1.00		18	1.00		52	1.00	
Second	0.032	0.029–0.035	33	1.47	0.86, 2.51	101	1.32	0.98, 1.77	23	1.32	0.71, 2.46	43	0.85	0.57, 1.28
Third	0.042	0.036–0.050	26	1.16	0.66, 2.04	76	0.96	0.70, 1.33	23	1.33	0.72, 2.47	53	1.03	0.70, 1.51
Fourth	0.067	0.051–0.143	29	1.28	0.74, 2.22	86	1.08	0.80, 1.48	22	1.29	0.69, 2.40	41	0.80	0.53, 1.21
Fifth	0.72	≥0.144	31	1.35	0.78, 2.32	85	1.05	0.77, 1.43	22	1.25	0.67, 2.34	65	1.19	0.82, 1.72
P for trend[d]					0.43			0.85			0.86			0.09
Total proanthocyanidins														
First	54.4	<73.1	16	1.00		91	1.00		19	1.00		57	1.00	
Second	91.2	73.1–110.1	34	2.08	1.14, 3.77	95	1.03	0.77, 1.37	28	1.40	0.78, 2.52	47	0.79	0.54, 1.17
Third	131.8	110.2–158.4	32	1.92	1.05, 3.52	97	1.05	0.79, 1.41	17	0.83	0.43, 1.61	58	0.98	0.68, 1.41
Fourth	194.7	158.5–249.4	16	0.96	0.48, 1.93	67	0.72	0.52, 0.99	14	0.69	0.34, 1.38	40	0.67	0.45, 1.01
Fifth	364.7	≥249.5	44	2.72	1.53, 4.85	75	0.82	0.60, 1.11	30	1.50	0.84, 2.68	52	0.89	0.61, 1.29
P for trend[d]					<0.01			0.04			0.21			0.52

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Gleason score ≥8.

[b] American Joint Committee on Cancer stage III/IV or fatal cases with no grade or stage information.

[c] Adjusted for age, race, family history of prostate cancer, body mass index (weight (kg)/height $(m)^2$) in 1999, smoking status, aspirin use, total energy intake, history of prostate-specific antigen screening, and history of diabetes.

[d] Test for trend by using median values for each category and modeling as a continuous variable.

degree of polymerization percentage of gallate ester proanthocyanidins compared to pine bark extract, was more effective in inhibiting cell proliferation, arresting the cell cycle in the G2 phase, and inducing apoptosis than pine bark extract. In addition, a recent cohort study reported that grapeseed supplement users had a significantly lower risk of total prostate cancer compared with nonusers (45).

Tea, particularly nonherbal tea, is a major food source of flavan-3-ols and proanthocyanidins (46, 47). Recently, a Japanese cohort study reported that men who consumed 5 or more cups of green tea per day had a 48% lower risk of advanced, but not localized, prostate cancer compared with men who consumed less than 1 cup per day (48). The Netherlands Cohort study reported that consumption of 5 or more cups of black tea per day was associated with lower risk of high-stage prostate cancer (18). The low tea consumption (averaging less than 0.5 cups/day) and low range of intakes in the CPS-II Nutrition Cohort preclude a detailed analysis of tea in relation to prostate cancer risk. Moreover, no single food or beverage reflects a high proportion of proanthocyanidin intake in this cohort. Therefore, we chose to focus our analysis on nutrients instead of on individual foods or beverages.

This study has several strengths, including its prospective study design and large sample size that enabled us to examine subpopulations by prostate cancer grade or stage. Limitations include the narrow range of isoflavone intakes among men in our cohort. In addition, dietary flavonoid assessment was not specifically validated in the CPS-II cohort, and it is possible that measurement error obscured an ability to observe inverse associations. However, the instrument on which our FFQ is based has been validated in similar populations (49, 50), and we previously showed that dietary flavonoid intake was inversely associated with cardiovascular disease death in the CPS-II Nutrition Cohort (51), consistent with expectations and supporting the predictive validity of our dietary data. Although potential covariates were carefully examined, residual confounding due to incomplete classification of covariates, including a missing category for some covariates, or other unmeasured factors may have influenced risk estimates.

In conclusion, our study found positive associations with flavonoid intake and overall prostate cancer, potentially influenced by behaviors related to prostate cancer screening. An inverse association between dietary total flavonoids, especially proanthocyanidin consumption, and high-grade prostate cancer was also observed. Although evidence is limited, these findings warrant further study.

ACKNOWLEDGMENTS

Author affiliations: Epidemiology Research Program, American Cancer Society, Atlanta, Georgia (Ying Wang, Victoria L. Stevens, Roma Shah, Susan M. Gapstur, Marjorie L. McCullough); Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts (Julia J. Peterson); and School of Medicine and Jean Mayer United States Department of Agriculture Human Nutrition Center on Aging, Tufts University, Boston, Massachusetts (Johanna T. Dwyer).

This work was supported in part with resources from the US Department of Agriculture, Agricultural Research Service (agreement 58-1950-7-707). The American Cancer Society funds the creation, maintenance, and updating of the Cancer Prevention Study-II (CPS-II) cohort.

We thank the CPS-II participants and Study Management Group for their invaluable contributions to this research. We also acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, as well as cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program.

Conflict of interest: none declared.

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