Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Dietary Flavonoid Intake and Thyroid Cancer Risk in the NIH–AARP Diet and Health Study

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Abstract

Experimental studies suggested that flavonoids may influence thyroid carcinogenesis, but epidemiologic evidence is sparse. No study has examined different classes of flavonoids in relation to thyroid cancer risk. Using data from the NIH–AARP Diet and Health Study, which enrolled 491,840 U.S. men and women, ages 50 to 71 years at baseline, we prospectively examined the risk of thyroid cancer in relation to dietary intakes of catechins, flavanones, flavonols, anthocyanidins, flavones, isoflavones, and total flavonoids. Dietary intakes were assessed using a food frequency questionnaire. Cancer cases were ascertained by linkage to state cancer registries. Multivariable-adjusted Cox proportional hazard models were used to estimate HRs and 95% confidence intervals (CI). During follow up (mean = 9 years), we identified 586 thyroid cancer cases. Thyroid cancer risk was inversely associated with dietary flavan-3-ols [$HR_{Q5\ vs.\ Q1}$ (95% CI): 0.70 (0.55, 0.91), P_{Trend} = 0.03], but positively associated with flavanones [$HR_{Q5\ vs.\ Q1}$ (95% CI): 1.50 (1.14, 1.96), P_{Trend} = 0.004]. Other classes of flavonoids and total flavonoids were not associated with thyroid cancer risk. Similar associations were found for papillary thyroid cancer. Our findings suggest that dietary intake of different classes of dietary flavonoids may have divergent effects on thyroid cancer risk. More studies are needed to clarify a role of flavonoids in thyroid cancer development. Results from our study suggest a potential nutritional etiology of thyroid cancer. *Cancer Epidemiol Biomarkers Prev; 23(6); 1102–8. ©2014 AACR.*

Introduction

The incidence of thyroid cancer, the most common endocrine cancer, varies widely by geographic area and ethnicity (1). Such variation may reflect differences in genetic background, environmental factors, and access to health care (2). Few risk factors for thyroid cancer have been identified apart from female sex (3), ionizing radiation in childhood (4), benign thyroid conditions (5), obesity (6), smoking and alcohol consumption (7). Although thyroid cancer has long been considered to have a nutritional etiology, few studies have investigated the relationship between dietary components and thyroid cancer risk (5).

Flavonoids are a large group of bioactive chemicals found in fruits, vegetables, tea, wine, and other plant products that may have anticarcinogenic effects (8). Epidemiologic studies have linked high dietary intakes of flavonoids with reduced risks of multiple cancers (8). Little evidence exists regarding a potential relationship between dietary flavonoids and thyroid cancer risk. Some mechanistic studies support a protective role of flavonoids on thyroid cancer (9), whereas others suggest possible carcinogenic effects (10). To our knowledge, no previous observational study has evaluated total flavonoid intake and intakes of different classes of flavonoids (other than isoflavones; ref. 11) in relation to thyroid cancer risk. Therefore, in the NIH–AARP Diet and Health Study, a large U.S. cohort with over 500 incident thyroid cancers diagnosed during follow-up, we prospectively examined dietary intakes of total and specific classes of flavonoids in relation to thyroid cancer risk.

Materials and Methods

Study population

The NIH–AARP Diet and Health Study was established in 1995 to 1996 when health questionnaires were mailed to AARP members 50 to 71 years old and residing in 6 U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or 2 metropolitan areas (Atlanta and Detroit; ref. 12). Of the 566,398 participants who satisfactorily completed the baseline questionnaire, we excluded those who were proxy respondents (n = 15,760), had prevalent cancer other than nonmelanoma skin cancer (n = 53,366) or end-stage renal disease (n = 997), had missing or extreme (>2 times the interquartile ranges) values for calories (n = 4,391), and zero person-years of follow-up (n = 44). The analytic cohort included 491,840

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participants (234,597 men and 198,593 women). The study was approved by the National Cancer Institute Special Studies Institutional Review Board.

Dietary and covariate assessment

Demographics, lifestyle-related factors, family history, and dietary intake were assessed at baseline using a self-administered food-frequency questionnaire (FFQ). Participants reported intakes of each item during the past year in 10 frequency categories and 3 portions sizes. Flavonoids content of each food items were obtained from the 2007 USDA flavonoid database and the 2002 USDA isoflavonoid database. Individual intakes of flavonoids were calculated by multiplying the amount of intake with the nutrient values of the 6 flavonoids subgroups (flavan-3-ols (catechins), flavanones, flavonols, anthocyanidins, flavones, and isoflavones; ref. 13). Total flavonoid intake was calculated by combining the intakes of all subgroups. Dietary intakes were adjusted for total energy intake by dividing intake amount by total calories. We defined top dietary sources of flavonoids as foods or drinks that contributed over 20% to total flavonoids or any of the flavonoid subtypes.

Case ascertainment

Incident thyroid cancers [*International Classification of Disease for Oncology*, Third Edition [ICD-O-3] codes C73; ref. 14] were identified through December 31, 2006 by probabilistic linkage with state cancer registries and the National Death Index (15). Subtypes of thyroid cancer were defined by ICD-O-3 morphological codes (papillary, 8050, 8260, 8340–8344, 8350, and 8450–8460, follicular, 8290, 8330–8335, medullary, 8345, 8510–8513, and anaplastic carcinoma, 8020–8035), and the rest were classified as unknown subtype. A previous validation study showed that 89% of all cancer cases identified through the cancer registries were valid (15).

Statistical analysis

Spearman correlation coefficients were calculated to evaluate correlations between flavonoid subtypes among the entire study population. We used Cox proportional hazards regression models to estimate HRs and 95% confidence intervals (CI). Person-years were calculated from baseline until the date of primary cancer diagnosis, relocation from the registry areas, death, or the end of follow-up (December 31, 2006), whichever came sooner. All models used age as the underlying time metric. None of the models were found to be in violation of the proportional hazards assumption.

Dietary intakes of total flavonoids, flavonoid subtypes, and flavonoid-rich foods were categorized into quintiles. Tea consumption was categorized by frequency of consumption. Model covariates were potential risk factors for thyroid cancer, including sex, race/ethnicity, education, body mass index (BMI), family history of cancer, alcohol intake, and smoking. Additional adjustment for menopausal hormone therapy use (never, current, former, and unknown), and vigorous leisure-time physical activity (never, rarely, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and 5+ times/wk) had little influence on the HRs, so these variables were not retained in the models. To test for trend, we modeled categorical variables as continuous and evaluated this coefficient using the Wald test. We performed subgroup analyses by sex, smoking, and BMI. Statistical significance for interactions between any 2 factors was tested using the likelihood ratio test comparing a model with the cross-product term to one without. Analyses were carried out using Stata 12 (StataCorp).

Results

During a total of 4,475,064 person-years of follow-up, we identified 586 thyroid cancer cases, including 417 papillary, 113 follicular, 24 medullary, and 15 anaplastic cases. We presented selected characteristics of study participants by quintiles of total dietary flavonoids in Table 1. Compared with the lowest quintile of intake, participants in the top 4 quintiles were more likely to have a college education and less likely to be current smokers. Main dietary sources of flavonoids included tea, citrus fruits and juices, legumes, and other fruits and vegetables (Supplementary Table S1). Of the 6 flavonoid subgroups, flavonols and flavan-3-ols, isoflavones and flavan-3-ols, isoflavones and flavonols, and flavones and anthocyanidins were moderately to highly correlated (Spearman correlation coefficient: 0.8, 0.5, 0.6, and 0.6, respectively).

In Table 2, we presented associations between total and subgroups of flavonoids and thyroid cancer risk. We found that thyroid cancer risk was inversely associated with flavan-3-ols [$HR_{Q5\ vs.\ Q1}$ (95% CI): 0.66 (0.51, 0.85), $P_{Trend} = 0.01$], but positively associated with flavanones [$HR_{Q5\ vs.\ Q1}$ (95% CI): 1.46 (1.11, 1.91), $P_{Trend} = 0.01$]. Other flavonoid subtypes and total flavonoids were not associated with thyroid cancer risk.

Because of the wide gap in thyroid cancer incidence between the sexes and the suspected sex-specific difference in etiology (3), we also evaluated these associations in men and women separately (Supplementary Table S2). Although the aforementioned associations between thyroid cancer and flavan-3-ols and flavanones seemed to be stronger in men than in women, overall we did not detect any significant interactions with sex. We did not detect statistically significant differences in the associations between dietary flavonoids and thyroid cancer by smoking status or BMI (data not shown). Results restricted to papillary thyroid cancer, the main subtype that accounted for 76% of all incident cases, were largely similar (Supplementary Table S3).

We further examined the relationship between intakes of top dietary sources of flavonoids and risk of thyroid cancer (Table 3). We found an elevated risk with increased intakes of orange and grapefruit juice consumption [$HR_{Q5\ vs.\ Q1}$ (95% CI): 1.55 (1.18, 2.03), $P_{Trend} = 0.004$]. Tea consumption and intakes of other flavonoid-rich foods were not associated with thyroid cancer risk. The results are similar when we used predetermined cutoff points for

Table 1. Characteristics of study participants by sex-specific quintiles of intake of dietary flavonoids in the NIH–AARP Diet and Health Study (1995–1996)

	Sex-specific quintile of intake				
	Q1	Q2	Q3	Q4	Q5
No. males	58,650	58,649	58,650	58,649	58,649
No. females	39,719	39,719	39,718	39,719	39,718
Age at entry, median (IQR), year	62 (57–66)	63 (58–67)	63 (58–67)	63 (58, 67)	63 (58–67)
Race/ethnicity (%)					
White, non-Hispanic	91	91	91	91	91
Black, non-Hispanic	4	4	4	4	3
Hispanic	2	2	2	2	1
Asian, Pacific Islander, Native American	1	1	1	2	3
Education (%)					
Less than high school	29	24	24	25	25
High school graduate	10	9	9	10	10
Some college	24	23	23	23	23
College graduate	33	40	41	39	39
Body mass index (%)					
<25 kg/m^2	34	36	35	33	35
25–29.9 kg/m^2	41	41	42	42	42
30–34.9 kg/m^2	16	15	15	16	15
≥35 kg/m^2	7	6	6	6	6
Cigarette smoking status (%)					
Never	30	34	37	38	37
Former	48	51	50	49	48
Current	18	11	9	10	11
Family history of cancer (%)					
No	46	46	46	46	47
Yes	49	49	49	48	48
Alcohol intake, median (IQR), g/d	1.4 (0.0–11.7)	2.6 (0.2–15.4)	2.3 (0.2–13.1)	1.8 (0.2–9.8)	1.5 (0.2–7.8)
Tea consumption, >1 cup/d, %	3	9	26	61	91
Total caloric intake, median (IQR), kcal/d	1,794 (1,339–2,380)	1,736 (1,321–2,269)	1,667 (1,276–2,175)	1,709 (1,282–2,253)	1,561 (1,189–2,024)
Intakes of flavonoids-rich foods, median (IQR)					
Orange and tangelos, cups/d/1,000 cal	0.03 (0.01–0.07)	0.07 (0.03–0.20)	0.07 (0.03–0.32)	0.07 (0.03–0.35)	0.07 (0.03–0.20)
Orange and grape fruit juice, cups/d/1,000 cal	0.04 (0.01–0.16)	0.17 (0.04–0.41)	0.27 (0.05–0.56)	0.26 (0.05–0.58)	0.19 (0.04–0.50)
Legume, cups/d/1,000 cal	0.05 (0.02–0.12)	0.06 (0.03–0.14)	0.06 (0.03–0.14)	0.06 (0.03–0.13)	0.05 (0.02–0.10)
Grape, servings/d/1,000 cal	0.02 (0.01–0.05)	0.02 (0.01–0.05)	0.02 (0.01–0.13)	0.02 (0.01–0.13)	0.02 (0.01–0.05)
Banana, servings/d/1,000 cal	0.03 (0.00–0.15)	0.05 (0.00–0.20)	0.05 (0.00–0.32)	0.05 (0.00–0.21)	0.05 (0.00–0.15)

NOTE: Percentages did not add up to 100% because of missing (<5%).

Table 2. Multivariable[a] HRs and 95% CIs for risk of thyroid cancer across quintiles of intake of dietary flavonoids in the NIH–AARP Diet and Health Study (1995–1996)

	Sex-specific quintile of intake					
	1	2	3	4	5	P_{Trend}
Flavan, 3, ols (catechins)						
Median intake (range)[b]	8.58 (0.00–17.16)	22.86 (13.67–42.29)	50.97 (30.36–95.52)	118.53 (64.28–233.71)	330.58 (161.89–7205.21)	
Cases/person-years	144/885,594	108/896,345	112/897,558	123/897,257	99/899,310	
HR (95% CI)	ref	0.75 (0.59, 0.97)	0.77 (0.60, 0.99)	0.83 (0.65, 1.06)	0.66 (0.51, 0.85)	0.01
Flavanones						
Median intake (range)[b]	2.65 (0.00–5.96)	8.95 (4.96–14.93)	18.56 (12.66–26.49)	30.58 (22.60–42.85)	45.95 (28.70–378.26)	
Cases/person-years	89/890,426	118/898,920	112/896,547	129/895,703	138/894,468	
HR (95% CI)	ref	1.30 (0.99, 1.72)	1.23 (0.93, 1.63)	1.40 (1.06, 1.84)	1.46 (1.11, 1.91)	0.01
Flavonols						
Median intake (range)[b]	4.66 (0.08–6.70)	7.15 (5.64–9.37)	9.56 (7.74–12.64)	12.94 (10.13–18.39)	21.15 (14.02–250.53)	
Cases/person-years	133/883,545	116/895,302	109/897,710	114/899,931	114/899,577	
HR (95% CI)	Ref	0.85 (0.66, 1.10)	0.80 (0.62, 1.03)	0.83 (0.64, 1.07)	0.81 (0.63, 1.04)	0.11
Anthocyanidins						
Median intake (range)[b]	2.12 (0.00–4.06)	4.25 (2.83–6.45)	6.36 (4.65–9.10)	9.20 (6.74–13.24)	15.16 (9.98–128.04)	
Cases/person-years	108/886,900	110/894,085	120/896,822	121/899,066	127/899,191	
HR (95% CI)	ref	0.96 (0.73, 1.25)	1.03 (0.79, 1.33)	1.03 (0.79, 1.34)	1.09 (0.84, 1.42)	0.39
Flavones						
Median intake (range)[b]	0.18 (0.00–0.35)	0.37 (0.24–0.58)	0.58 (0.41–0.88)	0.90 (0.63–1.34)	1.57 (1.00–19.10)	
Cases/person-years	97/886,466	122/897,193	108/896,938	133/898,630	126/896,836	
HR (95% CI)	Ref	1.20 (0.82, 1.57)	1.06 (0.80, 1.39)	1.31 (1.00, 1.72)	1.27 (0.96, 1.66)	0.07
Isoflavones						
Median intake (range)[b]	0.10 (0.00–0.17)	0.19 (0.13–0.26)	0.28 (0.21–0.38)	0.40 (0.30–0.57)	0.67 (0.45–5.29)	
Cases/person-years	119/889,405	107/893,821	137/895,186	96/898,826	127/898,826	
HR (95% CI)	Ref	0.87 (0.67, 1.13)	1.09 (0.85, 1.40)	0.75 (0.57, 0.99)	0.98 (0.76, 1.26)	0.57
Total flavonoids						
Median intake (range)[b]	34.29 (0.41–58.35)	65.14 (46.04–95.93)	101.56 (73.79–154.15)	171.15 (114.27–291.69)	387.33 (209.29–7521.44)	
Cases/person-years	113/886,982	125/895,707	120/896,406	125/897,416	103/899,553	
HR (95% CI)	ref	1.08 (0.84, 1.40)	1.02 (0.79, 1.32)	1.05 (0.81, 1.36)	0.85 (0.65, 1.11)	0.24

[a]Adjusted for sex (male and female), total caloric intake (continuous), smoking status (current, former, and never), education level (less than 12 years, high school graduate, some college, college graduate, and missing), alcohol intake (0–<0.05, 0.05–<0.5, 0.5–<1, 1+ drinks per day), race (white, black, other, and missing), body mass index (<25, 25–<30, 30–<35, 35+ kg/m^2), family history of cancer (no, yes, and missing).

[b]mg/1,000 cal, adjusted for total caloric intake using the density method.

Table 3. Multivariable[a] HRs and 95% CIs for risk of thyroid cancer across categories of tea consumption and intakes of oranges and tangelo, orange and grapefruit juice, legumes, grapes, and bananas in the NIH–AARP Diet and Health Study (1995–1996)

	Categories of intake					
	Tea, frequency of consumption					
	0	≤1 cup/wk	>1 cup/wk–1 cup/d	>1–3 cup/d	>3 cup/d	P_{Trend}
Cases	62/436,791	122/879,965	171/1,448,058	139/1,122,152	92/589,096	
HR (95% CI)	Ref	0.95 (0.70, 1.29)	0.79 (0.59, 1.06)	0.80 (0.59, 1.09)	0.97 (0.70, 1.35)	0.81
	Top dietary contributors of flavonoids, quintile					
	1	2	3	4	5	
Oranges and tangelos						
Cases	106/884,298	116/897,352	118/898,369	130/899,732	116/896,313	
Median intake (range)[b]	0.00 (0.00–0.04)	0.03 (0.00–0.12)	0.07 (0.01–0.32)	0.20 (0.03–0.99)	0.48 (0.07–3.52)	
HR (95% CI)	Ref	1.06 (0.81, 1.39)	1.04 (0.80, 1.37)	1.14 (0.88, 1.48)	1.00 (0.77, 1.31)	0.79
Orange and grapefruit juice						
Cases	86/888,222	125/899,581	110/898,523	125/896,001	140/893,737	
Median intake (range)[b]	0.01 (0.00–0.02)	0.04 (0.02–0.09)	0.16 (0.07–0.27)	0.38 (0.26–0.53)	0.76 (0.51–7.26)	
HR (95% CI)	Ref	1.42 (1.08, 1.87)	1.29 (0.97, 1.71)	1.46 (1.11, 1.93)	1.55 (1.18, 2.03)	0.004
Legumes						
Cases[c]	171/1,133,648	85/768,574	135/937,389	99/780,399	96/856,054	
Median intake (range)[b]	0.01 (0.00–0.03)	0.03 (0.02–0.05)	0.06 (0.04–0.08)	0.10 (0.07–0.16)	0.23 (0.13–5.34)	
HR (95% CI)	Ref	0.75 (0.58, 0.97)	1.01 (0.81, 1.27)	0.94 (0.73, 1.21)	0.86 (0.66, 1.12)	0.62
Grape						
Cases[c]	163/1,303,239	125/836,769	114/784,333	102/793,922	82/757,802	
Median intake (range)[b]	0.00 (0.00–0.01)	0.02 (0.01–0.02)	0.05 (0.02–0.05)	0.05 (0.05–0.13)	0.32 (0.13–3.90)	
HR (95% CI)	Ref	1.19 (0.95, 1.51)	1.13 (0.89, 1.44)	1.05 (0.82, 1.35)	0.90 (0.69, 1.18)	0.49
Banana						
Cases[c]	183/1,395,806	110/895,308	137/961,281	73/562,437	83/661,197	
Median intake (range)[b]	0.03 (0.00–0.05)	0.15 (0.07–0.15)	0.35 (0.18–0.35)	0.54 (0.42–0.54)	0.74 (0.68–1.94)	
HR (95% CI)	Ref	0.93 (0.73, 1.18)	1.07 (0.86, 1.34)	0.98 (0.75, 1.29)	0.96 (0.74, 1.25)	0.97

[a]Adjusted for sex (male and female), total caloric intake (continuous), smoking status (current, former, and never), education level (less than 12 years, high school graduate, some college, college graduate, and missing), alcohol intake (0–<0.05, 0.05–<0.5, 0.5–<1, 1+ drinks per day), race (white, black, other, and missing), body mass index (<25, 25–<30, 30–<35, 35+ kg/m^2), and family history of cancer (no, yes, and missing).

[b]Serving/d/1,000 cal.

[c]The quintiles were not equally distributed because of the clusters of participants with the same values of intake.

categories of intakes, except for legumes, for which 2+ servings per week was associated with a significantly reduced risk [$HR_{Q5\ vs.\ Q1}$ (95% CI): 0.38 (0.21, 0.68); Supplementary Table S4]. In subgroup analysis by sex (Supplementary Table S5), we found a significant interaction between grape intake and sex, with higher intakes associated with lower thyroid cancer risk in men [$HR_{Q5\ vs.\ Q1}$ (95% CI): 0.68 (0.46, 0.99), $P_{Trend} = 0.01$], but not in women. Results were similar when we restricted the analysis to papillary thyroid cancer (Supplementary Table S6).

Discussion

In this large cohort, we found that thyroid cancer risk was inversely associated with flavan-3-ols, but positively associated with flavanones. Other classes of flavonoids and total flavonoids were not associated with thyroid cancer risk.

Epidemiologic evidence on flavonoids and thyroid cancer is limited. Several previous studies examined the intakes of flavonoid-rich foods, such as tea, wine, and citrus fruit, in relation to thyroid cancer, and reported inconsistent findings (16–18). In a case–control study conducted in San Francisco (11), the authors reported a 35% risk reduction in thyroid cancer comparing the highest versus lowest quintile of isoflavone intake [OR (95% CI): 0.65 (0.41, 1.00)]. In contrast, we did not observe an association between isoflavones and thyroid cancer risk in either men or women. There are several key differences between our study and the San Francisco study that may account for the different results. The San Francisco study had on average younger

participants, with a mean age of 42, and a higher proportion of nonwhite women, including 35% Asian and 14% other race/ethnicity. Also, the dietary intake of isoflavones in the San Francisco study was much higher than that in our study: the 90th percentile in our study, 1.11 mg/d (unadjusted for total calorie), was only slightly above the 20th percentile in their study (1.05 mg/d). In the San Francisco study, a reduced risk of thyroid cancer was only observed in the highest quintile of isoflavone intake. Therefore, there may be a threshold effect, whereby isoflavones only protect against thyroid cancer at relatively high intakes. Moreover, food sources may also differ substantially between the 2 populations. Soy-based foods were top contributors of phytoestrogen in the San Francisco study, whereas soy consumption was low among the white Americans (19) and probably did not make significant contribution to isoflavone intake in our study.

Our finding suggest that the relationship between flavonoids and thyroid cancer might differ by flavonoid subgroups, which may reflect their diverse influence on carcinogenic pathways as demonstrated in *in vitro* and *in vivo* studies. Flavonoids have been shown to interfere with molecular targets, including mitogen-activated protein kinase, protein kinase C, phosphatidylinositol 3-kinase, NF-κB, and β-catenin, to produce antiproliferation, anti-inflammatory, and proapoptotic activities that may lead to reduced cancer risk (8). In contrast, flavonoids may have carcinogenic effects by affecting key enzymes in thyroid hormone biosynthesis and metabolism (20). Flavonoids may inhibit the activity of thyroid peroxidase (TPO), the enzyme that catalyzes thyroid hormone biosynthesis (10). As animal studies suggested, this may lower the level of thyroid hormone, which would enhance the secretion of thyroid stimulating hormone (TSH) and lead to the development of goiter (21, 22), a well-established risk factor for thyroid cancer (5). The anti-carcinogenesis and/or anti-thyroid effects may vary among different classes of flavonoids, because of differences in chemical structures that render distinct biochemical properties. Early studies have reported large variation among flavonoids in their efficacy in blocking cell proliferation (9) or inhibiting TPO activity (10). Therefore, the overall effect of each flavonoid class would be determined by the summation of both beneficial and adverse effects, which could potentially explain the different effects of different types of flavonoids on thyroid cancer observed in our study. Furthermore, this may also partially explain why generally no association was observed in our study for flavonoid-rich foods, such as tea, which contains more than one class of flavonoids with potentially opposite physiological effects.

Our study had several limitations. Self-reported nutrition intake via FFQs is prone to measurement error, although an early validation study in this population reported moderate-to-high agreement for flavonoids (23). Also, the FFQ did not specifically inquire about some flavonoid-rich foods such as soy, berries other than strawberries, peppers, and spices. Some participants may have included artificially flavored drinks in their report of fruit consumption, specifically orange and grapefruit juice consumption, leading to potentially false positive associations between thyroid cancer and orange and grapefruit juice consumption as well as thyroid cancer and consumption of flavanones, whose main dietary source in the study was orange and grapefruit juice. Although we controlled for potential risk factors for thyroid cancer in multivariable models, we could not exclude the possibility that the observed association was because residual confounding. For instance, dietary sources of flavonoids may contain other nutrients such as vitamin C, selenium, and iodine, which could independently influence thyroid cancer risk (5). Finally, our population of U.S. adults who were predominantly white may have had lower intakes of flavonoids compared with other populations, and thus our findings may have limited generalizability. Nonetheless, the large sample size and relatively long follow-up time allowed for an evaluation of effect modification by gender and other risk factors. Also, the prospective design decreased the likelihood of differential recall bias, an important limitation of case–control studies.

In conclusion, our findings suggest that dietary flavonoids may influence thyroid cancer risk, whereas different subgroups of flavonoids may have divergent effects. More studies are needed to elucidate the biological mechanisms underlying such associations.

Disclosure of Potential Conflicts of Interest

A.R. Hollenbeck is a consultant/advisory board member of Love/Avon Army of Women and Society of Psychologists in Management. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.R. Hollenbeck, C.M. Kitahara
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Park, A.R. Hollenbeck, C.M. Kitahara
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Q. Xiao, Y. Park
Writing, review, and/or revision of the manuscript: Q. Xiao, Y. Park, A.R. Hollenbeck, C.M. Kitahara
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Park, A.R. Hollenbeck
Study supervision: C.M. Kitahara

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