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# Dietary Flavonoid Intake Reduces the Risk of Head and Neck but Not Esophageal or Gastric Cancer in US Men and Women

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## Abstract

**Background:** Flavonoids are bioactive polyphenolic compounds found in fruits, vegetables, and beverages of plant origin. Previous studies have shown that flavonoid intake reduces the risk of certain cancers; however, few studies to date have examined associations of flavonoids with upper gastrointestinal cancers or used prospective cohorts.

**Objective:** Our study examined the association between intake of flavonoids (anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, and isoflavones) and risk of head and neck, esophageal, and gastric cancers.

**Methods:** The NIH-AARP Diet and Health Study is a prospective cohort study that consists of 469,008 participants. Over a mean 12-y follow-up, 2453 head and neck (including 1078 oral cavity, 424 pharyngeal, and 817 laryngeal), 1165 esophageal (890 adenocarcinoma and 275 squamous cell carcinoma), and 1297 gastric (625 cardia and 672 noncardia) cancer cases were identified. We used Cox proportional hazards regression models to estimate HRs and CIs for the associations between flavonoid intake assessed at study baseline and cancer outcomes. For 56 hypotheses examined, *P*-trend values were adjusted using the Benjamini-Hochberg (BH) procedure for false discovery rate control.

**Results:** The highest quintile of total flavonoid intake was associated with a 24% lower risk of head and neck cancer (HR: 0.76; 95% CI: 0.66, 0.86; BH-adjusted 95% CI: 0.63, 0.91; *P*-trend = 0.02) compared with the lowest quintile. Notably, anthocyanidins were associated with a 28% lower risk of head and neck cancer (HR: 0.72; 95% CI: 0.62, 0.82; BH-adjusted 95% CI: 0.59, 0.87; *P*-trend = 0.0005), and flavanones were associated with a 22% lower risk of head and neck cancer (HR: 0.78; 95% CI: 0.68, 0.89; BH-adjusted 95% CI: 0.64, 0.94; *P*-trend: 0.02). No associations between flavonoid intake and risk of esophageal or gastric cancers were found.

**Conclusions:** Our results indicate that flavonoid intake is associated with lower head and neck cancer risk. These associations suggest a protective effect of dietary flavonoids on head and neck cancer risk, and thus potential as a risk reduction strategy. *J Nutr* 2017;147:1729–38.

**Keywords:** epidemiology, esophageal cancer, flavonoids, food-frequency questionnaire, gastric cancer, head and neck cancer

## Introduction

Flavonoids are a group of bioactive polyphenolic compounds, which are commonly consumed through dietary intake of fruits, vegetables, and beverages of plant origin (1). Epidemiologic studies have shown that diets high in fruits and vegetables are associated with a decreased risk of upper gastrointestinal cancers, including cancers of the head and neck (2), esophagus (3, 4), and stomach (5). Flavonoids are hypothesized to account for a portion of this risk reduction through chemopreventive mechanisms of cell cycle regulation, cellular proliferation, apoptosis, and modulation of carcinogen metabolism and inflammatory pathways (6).

Upper gastrointestinal cancers represent an etiologically diverse group of cancers and can be divided by histologic classifications (i.e., squamous cell carcinoma or adenocarcinoma).

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Head and neck cancers include squamous cell carcinomas of the oral cavity, pharynx, and larynx. The primary risk factors for head and neck cancer are tobacco use and alcohol consumption (7–9). Esophageal cancer consists of squamous cell carcinoma, which can occur throughout the esophagus, and adenocarcinoma, which is typically located in the distal third of the esophagus near the gastroesophageal junction (10). The primary risk factors for esophageal squamous cell carcinoma are squamous dysplasia (11) and tobacco use and alcohol consumption (12), whereas esophageal adenocarcinoma risk factors include gastroesophageal reflux disease (13), obesity (14), and tobacco use (15). Gastric cancers include adenocarcinomas of the cardia (i.e., the proximal portion of the stomach near the gastroesophageal junction) and noncardia (i.e., the distal portion of the stomach) (16). The primary risk factors for gastric cardia adenocarcinoma are similar to esophageal adenocarcinoma (13–15), whereas risk factors for noncardia gastric adenocarcinoma include *Helicobacter pylori* and gastric ulcers (16) and tobacco use (12).

Epidemiologic studies have shown inverse associations between flavonoids and cancers of the head and neck (17–19), esophagus (20), and stomach (21–29). However, few studies to date have examined associations using a prospective cohort, and no prospective studies to date have examined head and neck cancer. Clarification of these associations may help elucidate the underlying etiology and provide empirical support for utilizing flavonoid compounds as potential cancer risk reduction strategies.

We used data from the NIH-AARP Diet and Health Study to investigate the relation between dietary intake of flavonoids and incidence of head and neck, esophageal, and gastric cancers.

## Methods

*Study population.* The NIH-AARP Diet and Health Study is a prospective cohort study consisting of AARP (formerly known as the American Association of Retired Persons) members residing in 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) (30). Between 1995 and 1996, baseline information including dietary intake, demographic characteristics, and health behaviors was collected from AARP members aged 50–71 y. This information was collected by mailing questionnaires to 3.5 million members; 566,398 members completed the questionnaire and consented to participate in the study. The National Cancer Institute Institutional Review Board approved the NIH-AARP study protocol. We excluded subjects with cancer at baseline ($n$ = 52,708), death-only reports of cancer ($n$ = 4421), proxy reports ($n$ = 14,245), and total energy intake outside the range of 500–3500 kcal/d for women and 800–4000 kcal/d for men ($n$ = 26,016) (31). Our analytic sample included 275,982 men and 193,026 women (**Supplemental Figure 1**).

*Cohort follow-up and case ascertainment.* Study participants were followed from the date baseline information was collected to the date of the first cancer diagnosis, the date of death, the date the individual moved out of case ascertainment area, or the end of the study period (31 December 2011). Cancer cases were identified by probabilistic linkage with 11 cancer registries (including states and areas of participant recruitment and Arizona, Nevada, and Texas). This method of case ascertainment was previously shown to detect ~90% of all incident cancer cases in the NIH-AARP cohort (32).

The cases were classified using topography and morphology codes from the third edition of the International Classification of Disease for Oncology (33). All cases of head and neck cancer with squamous cell carcinoma histology (morphology codes 8010, 8020, 8021, 8032, 8045, 8050, 8051, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, and 8083) were included in this analysis (topography codes C00.0–C13.9, C14.0, C14.2, C14.8, and C32.0–C32.9). The site of head and neck cancer was classified as follows: oral cavity (C00.0–C06.9), oro- and hypopharynx (C09.0–C09.9, C10.0–C10.9, C12.9, and C13.0–C13.9), and larynx (C32.0–C32.9). Cancers were classified as esophageal with topography codes of C15.0–C15.9. Esophageal cancers were further classified by squamous cell carcinoma (morphology codes 8070, 8071, 8072, and 8074) and adenocarcinoma (8140, 8142, 8144, 8260, 8261, 8263, 8310, 8480, 8481, 8490, and 8570) histology. All cases of gastric cancer with adenocarcinoma histology (morphology codes: 8010, 8012, 8021, 8140, 8142, 8143, 8144, 8145, 8210, 8211, 8255, 8260, 8261, 8263, 8310, 8480, 8481, 8490, 8510, and 8574) were included in this analysis. Gastric adenocarcinomas were classified as cardia (C16.0) and noncardia (C16.1–C16.9).

*Dietary data.* Dietary data for the previous 12 mo were collected at baseline using an early version of the National Cancer Institute Diet History Questionnaire (http://dietandhealth.cancer.gov/docs/diet_questionnaire_baseline.pdf), which is a self-administered FFQ. Study participants reported the frequency of consumption for 124 food items and corresponding portion sizes for 116 food items.

Flavonoid content for each food item was obtained using the 2015 USDA Expanded Flavonoid Database for the Assessment of Dietary Intakes (34). The USDA Nutrient Data Laboratory constructed this flavonoid database based on the analytical values from the 2013 USDA Database for the Flavonoid Content of Selected Foods for 506 foods (35) and the 2008 USDA Database for the Isoflavone Content of Selected Foods for 557 foods (36). To create the expanded flavonoid database, analytical flavonoid values were first assigned to foods with direct matches from either of the above-mentioned 2008 or 2013 USDA databases. Next, values were assigned to foods that lacked a direct match using ≥1 of the following criteria: moisture adjustment, retention factors, food yield factors, substitution with similar foods, market share, generic profiles, and other sources [e.g., Phenol-Explorer, release 2.0 (37)] (34). Overall, the expanded flavonoid database contains data on 29 individual flavonoids and 6 flavonoid classes (anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, and isoflavones) for 2926 foods found in the USDA National Nutrient Database for Standard Reference (38).

The FFQ line-item weights were based on "usual" population consumption, which was estimated using 24-h recall data from the 1994–1996 USDA Continuing Survey of Food Intakes by Individuals (CSFII) (39). Generally, these weights are determined by some metric of usual population consumption, but often these are based on a more restrictive list. For example, an FFQ may typically define the weights of the line item "Other fruit juice or fruit juice mixture (such as apple, grape, pineapple, or others)" as 50% of consumption from apple juice, 40% from grape juice, and 10% from pineapple juice. However, in the NIH-AARP study, any other reported type of fruit juice (e.g., guava juice drink or grapefruit juice) would receive a portion of the line-item weight, corresponding to the frequency of report on the 24-h recalls. Thus, foods and beverages reported on CSFII 24-h recalls were placed into food groups consistent with line items on the NIH-AARP study FFQ, and nutrient estimates were calculated based on a weighted mean of foods in each group. Because the CSFII nutrient database did not include flavonoid values, we added them to the original CSFII database to create NIH-AARP study FFQ flavonoid values using methodology consistent with previous reports (40). For a few foods (e.g., poblano peppers), flavonoid values were not available in the database. We thus matched these to a similar food (i.e., green hot chili peppers), which we thought would have similar flavonoid values. This database was then linked with an individual participant's reported frequency of consumption and the corresponding portion size for each line item. Dietary sources of flavonoid intake are presented in **Supplemental Table 1**.

We derived intakes of 6 flavonoid classes: anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin), flavan-3-ols (catechin, epicatechin, epicatechin 3-gallate, epigallocatechin, epigallocatechin 3-gallate, gallocatechin, theaflavin, theaflavin 3-gallate, theaflavin 3′-gallate, theaflavin 3,3′-digallate, thearubigins), flavanones (eriodictyol, hesperetin, naringenin), flavones (apigenin, luteolin), flavonols (isorhamnetin, kaempferol,

**TABLE 1** Baseline demographics of NIH-AARP Diet and Health Study participants by quintiles of total flavonoid intake[1]

| | Quintile of total flavonoid intake, mg/d | | | | |
|---|---|---|---|---|---|
| Variable | 1 (0–84.1) | 2 (84.2–140.9) | 3 (141.0–225.6) | 4 (225.7–437.9) | 5 (438.0–4211.2) |
| Participants | 93,798 | 93,806 | 93,801 | 93,801 | 93,802 |
| Person-years | 1,133,033 | 1,149,053 | 1,152,861 | 1,154,631 | 1,161,263 |
| Sex | | | | | |
| Male | 54,367 (58.0) | 56,788 (60.5) | 57,587 (61.4) | 55,109 (58.8) | 52,131 (55.6) |
| Female | 39,431 (42.0) | 37,018 (39.5) | 36,214 (38.6) | 38,692 (41.2) | 41,671 (44.4) |
| Age, y | | | | | |
| <55 | 13,246 (14.1) | 12,240 (13.0) | 12,381 (13.2) | 12,933 (13.8) | 12,737 (13.6) |
| 55–59 | 21,228 (22.6) | 20,864 (22.2) | 21,078 (22.5) | 21,715 (23.2) | 21,571 (23.0) |
| 60–64 | 26,015 (27.7) | 26,339 (28.1) | 26,565 (28.3) | 26,641 (28.4) | 26,537 (28.3) |
| 65–69 | 30,028 (32.0) | 30,918 (33.0) | 30,320 (32.3) | 29,397 (31.3) | 29,614 (31.6) |
| >70 | 3281 (3.5) | 3445 (3.7) | 3457 (3.7) | 3115 (3.3) | 3343 (3.6) |
| Race | | | | | |
| Non-Hispanic white | 85,757 (92.7) | 86,143 (92.9) | 86,092 (92.8) | 85,755 (92.6) | 85,718 (92.6) |
| Non-Hispanic black | 3435 (3.7) | 3476 (3.7) | 3677 (4.0) | 3843 (4.1) | 2971 (3.2) |
| Other | 3353 (3.6) | 3077 (3.4) | 3019 (3.2) | 3032 (3.3) | 3840 (4.2) |
| Missing | 1253 | 1110 | 1013 | 1171 | 1273 |
| Education | | | | | |
| Less than high school | 6742 (7.4) | 4900 (5.4) | 4606 (5.0) | 5360 (5.9) | 5379 (5.9) |
| High school degree | 29,954 (32.9) | 25,970 (28.4) | 25,281 (27.7) | 27,457 (30.1) | 28,563 (31.3) |
| College graduate | 39,192 (43.1) | 40,798 (44.7) | 40,577 (44.4) | 39,086 (42.9) | 38,151 (41.9) |
| Postgraduate | 15,074 (16.6) | 19,632 (21.5) | 20,905 (22.9) | 19,195 (21.1) | 19,025 (20.9) |
| Missing | 2836 | 2506 | 2432 | 2703 | 2684 |
| BMI, kg/m$^2$ | | | | | |
| <25 | 32,883 (36.0) | 33,492 (36.5) | 32,993 (36.0) | 31,752 (34.7) | 32,604 (35.6) |
| 25 to <30 | 38,288 (41.9) | 39,402 (43.0) | 39,705 (43.3) | 39,142 (42.7) | 38,173 (41.7) |
| ≥30 | 20,257 (22.2) | 18,837 (20.5) | 19,033 (20.7) | 20,737 (22.6) | 20,730 (22.7) |
| Missing | 2370 | 2075 | 2070 | 2170 | 2295 |
| Quartile of alcohol intake, g/d | 10.6 | 12.3 | 12.1 | 10.3 | 9.4 |
| 0–0.19 | 28,249 (30.1) | 21,918 (23.4) | 20,682 (22.0) | 22,972 (24.5) | 22,054 (23.5) |
| 0.20–1.83 | 23,929 (25.5) | 22,213 (23.7) | 22,147 (23.6) | 24,136 (25.7) | 26,228 (28.0) |
| 1.84–11.5 | 20,600 (22.0) | 23,474 (25.0) | 24,163 (25.8) | 24,291(25.9) | 24,638 (26.3) |
| 11.6–450.94 | 21,020 (22.4) | 26,201 (27.9) | 26,809 (28.6) | 22,402 (23.9) | 20,882 (22.3) |
| Cigarette smoking status | | | | | |
| Never | 28,766 (31.9) | 32,290 (35.7) | 34,054 (37.7) | 35,204 (39.0) | 35,831 (39.8) |
| Former | 45,967 (50.9) | 48,169 (53.2) | 47,649 (52.7) | 45,435 (50.3) | 43,707 (48.5) |
| Current | 15,561 (17.2) | 10,004 (11.1) | 8732 (09.7) | 9722 (10.8) | 10,582 (11.7) |
| Missing | 3504 | 3343 | 3366 | 3440 | 3682 |
| Cancer site | | | | | |
| Head and neck | 636 | 486 | 458 | 438 | 435 |
| Esophageal | 259 | 234 | 226 | 215 | 231 |
| Gastric | 274 | 244 | 256 | 253 | 270 |

[1] Values are presented as *n* or *n* (%) unless otherwise indicated. Ranges for quintiles of total flavonoid intake are given in parentheses.

myricetin, quercetin), and isoflavones (daidzein, genistein, glycitein). We also derived intakes of total flavonoids (summation of all classes).

*Statistical analysis.* Cox proportional hazards models were used to calculate HRs and 95% CIs for the association between flavonoid intake and incidence of each tumor type as distinct outcomes, with years of follow-up as the underlying time metric. Follow-up of the analytic cohort occurred from the time at completion of baseline questionnaire until an event (i.e., incident upper gastrointestinal cancer) or right-censoring (i.e., other cancer diagnosis, death, loss to follow-up, or last date of follow-up), whichever occurred first. In models examining one upper gastrointestinal cancer (e.g., head and neck cancer) as the primary outcome, the other upper gastrointestinal cancers (i.e., esophageal and gastric cancer) were censored events and vice versa. Subjects with missing values were removed from the models. The proportional hazards assumption was tested using an interaction term between total flavonoids (defined as continuous and categorical) and log(time) in models that included confounders, and no interaction was observed ($P \geq 0.05$).

For our primary analysis, absolute flavonoid intakes were categorized as quintiles, based on the distribution of intake among all study participants (31). Tests of linear trend were performed based on the quintile-specific medians of flavonoid intake. Because continuous flavonoid intake (expressed as mg/d) was right skewed, flavonoid intakes were also analyzed as $\log_2$-transformed continuous variables. The HR in relation to a 1-unit change in $\log_2$-transformed flavonoid intake corresponds to a doubling of absolute flavonoid intake (**Supplemental Table 2**).

Effect modification by age, sex, race, education, smoking status, BMI (in kg/m$^2$), energy intake, alcohol intake, self-rated health, and vigorous physical activity was assessed using likelihood ratio tests comparing

**TABLE 2** Adjusted HRs and 95% CIs for associations between flavonoid intake and risk of head and neck cancers for NIH-AARP Diet and Health Study participants[1]

| | Cancer site | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Head and neck | | Oral cavity | | Orohypopharyngeal | | Laryngeal | |
| Quintile of intake, mg/d | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) |
| Total flavonoids | | | | | | | | |
| 1 (0–84.1) | 567 | 1.00 (—) | 239 | 1.00 (—) | 102 | 1.00 (—) | 195 | 1.00 (—) |
| 2 (84.2–140.9) | 443 | 0.83 (0.74, 0.95) | 203 | 0.86 (0.71, 1.04) | 70 | 0.75 (0.55, 1.02) | 144 | 0.83 (0.67, 1.03) |
| 3 (141.0–225.6) | 408 | 0.78 (0.69, 0.89) | 177 | 0.76 (0.62, 0.92) | 83 | 0.92 (0.68, 1.24) | 122 | 0.72 (0.57, 0.91) |
| 4 (225.7–437.9) | 385 | 0.76 (0.66, 0.86) | 180 | 0.80 (0.65, 0.97) | 60 | 0.68 (0.49, 0.94) | 123 | 0.73 (0.58, 0.93) |
| 5 (438.0–4211.2) | 381 | 0.76 (0.66, 0.86) | 176 | 0.79 (0.64, 0.96) | 60 | 0.69 (0.50, 0.96) | 132 | 0.79 (0.63, 1.00) |
| *P*-trend[2] | | 0.001 | | 0.09 | | 0.04 | | 0.2 |
| BH-adjusted *P*-trend[3] | | 0.02 | | 0.3 | | 0.2 | | 0.4 |
| Anthocyanidins | | | | | | | | |
| 1 (0–3.8) | 604 | 1.00 (—) | 233 | 1.00 (—) | 114 | 1.00 (—) | 220 | 1.00 (—) |
| 2 (3.9–7.0) | 427 | 0.83 (0.73, 0.94) | 209 | 0.98 (0.81, 1.19) | 70 | 0.76 (0.56, 1.03) | 133 | 0.74 (0.59, 0.92) |
| 3 (7.1–11.7) | 422 | 0.89 (0.78, 1.01) | 190 | 0.94 (0.77, 1.15) | 61 | 0.74 (0.54, 1.02) | 145 | 0.91 (0.73, 1.13) |
| 4 (11.8–20.6) | 342 | 0.73 (0.63, 0.84) | 159 | 0.77 (0.62, 0.95) | 55 | 0.67 (0.48, 0.94) | 112 | 0.74 (0.58, 0.94) |
| 5 (20.7–376.6) | 389 | 0.72 (0.62, 0.82) | 184 | 0.78 (0.63, 0.96) | 75 | 0.74 (0.54, 1.02) | 106 | 0.62 (0.48, 0.80) |
| *P*-trend | | <0.0001 | | 0.005 | | 0.2 | | 0.0008 |
| BH-adjusted *P*-trend | | 0.0005 | | 0.04 | | 0.4 | | 0.02 |
| Flavan-3-ols | | | | | | | | |
| 1 (0–25.6) | 532 | 1.00 (—) | 221 | 1.00 (—) | 88 | 1.00 (—) | 193 | 1.00 (—) |
| 2 (25.7–60.6) | 453 | 0.91 (0.80, 1.03) | 208 | 0.95 (0.79, 1.16) | 81 | 1.00 (0.73, 1.35) | 142 | 0.83 (0.66, 1.03) |
| 3 (60.7–129.2) | 404 | 0.83 (0.73, 0.95) | 173 | 0.81 (0.67, 1.00) | 76 | 0.97 (0.71, 1.33) | 123 | 0.73 (0.58, 0.92) |
| 4 (129.3–346.6) | 394 | 0.82 (0.72, 0.94) | 195 | 0.94 (0.77, 1.14) | 64 | 0.83 (0.60, 1.15) | 117 | 0.70 (0.55, 0.88) |
| 5 (346.7–3828.7) | 401 | 0.84 (0.74, 0.96) | 178 | 0.86 (0.70, 1.05) | 66 | 0.87 (0.63, 1.20) | 141 | 0.84 (0.67, 1.05) |
| *P*-trend | | 0.05 | | 0.3 | | 0.3 | | 0.5 |
| BH-adjusted *P*-trend | | 0.2 | | 0.6 | | 0.5 | | 0.7 |
| Flavanones | | | | | | | | |
| 1 (0–8.8) | 590 | 1.00 (—) | 244 | 1.00 (—) | 111 | 1.00 (—) | 202 | 1.00 (—) |
| 2 (8.9–23.7) | 445 | 0.84 (0.74, 0.95) | 210 | 0.91 (0.75, 1.09) | 82 | 0.84 (0.63, 1.12) | 129 | 0.75 (0.60, 0.94) |
| 3 (23.8–43.7) | 380 | 0.75 (0.66, 0.86) | 171 | 0.75 (0.62, 0.92) | 64 | 0.71 (0.52, 0.98) | 123 | 0.78 (0.62, 0.98) |
| 4 (43.8–65.9) | 383 | 0.74 (0.65, 0.85) | 150 | 0.65 (0.53, 0.80) | 67 | 0.74 (0.54, 1.01) | 142 | 0.88 (0.70, 1.10) |
| 5 (66.0–978.9) | 386 | 0.78 (0.68, 0.89) | 200 | 0.90 (0.74, 1.10) | 51 | 0.58 (0.41, 0.82) | 120 | 0.76 (0.60, 0.96) |
| *P*-trend | | 0.001 | | 0.2 | | 0.003 | | 0.2 |
| BH-adjusted *P*-trend | | 0.02 | | 0.5 | | 0.03 | | 0.4 |
| Flavones | | | | | | | | |
| 1 (0–0.44) | 512 | 1.00 (—) | 218 | 1.00 (—) | 91 | 1.00 (—) | 170 | 1.00 (—) |
| 2 (0.45–0.67) | 455 | 0.92 (0.81, 1.05) | 205 | 0.93 (0.77, 1.13) | 70 | 0.82 (0.60, 1.13) | 161 | 1.03 (0.83, 1.28) |
| 3 (0.68–0.96) | 428 | 0.91 (0.79, 1.03) | 198 | 0.91 (0.75, 1.11) | 79 | 0.98 (0.72, 1.33) | 128 | 0.87 (0.69, 1.10) |
| 4 (0.97–1.45) | 393 | 0.85 (0.74, 0.97) | 176 | 0.82 (0.66, 1.00) | 64 | 0.81 (0.58, 1.14) | 129 | 0.90 (0.71, 1.15) |
| 5 (1.46–29.02) | 396 | 0.89 (0.77, 1.03) | 178 | 0.86 (0.69, 1.07) | 71 | 0.95 (0.68, 1.33) | 128 | 0.93 (0.73, 1.19) |
| *P*-trend | | 0.1 | | 0.2 | | 0.9 | | 0.5 |
| BH-adjusted *P*-trend | | 0.4 | | 0.4 | | 0.9 | | 0.7 |
| Flavonols | | | | | | | | |
| 1 (0–10.4) | 492 | 1.00 (—) | 228 | 1.00 (—) | 93 | 1.00 (—) | 143 | 1.00 (—) |
| 2 (10.5–14.9) | 454 | 0.89 (0.78, 1.01) | 190 | 0.79 (0.65, 0.96) | 69 | 0.71 (0.52, 0.97) | 172 | 1.18 (0.94, 1.47) |
| 3 (15.0–20.9) | 419 | 0.80 (0.70, 0.92) | 180 | 0.73 (0.60, 0.90) | 80 | 0.79 (0.58, 1.08) | 129 | 0.87 (0.68, 1.11) |
| 4 (21.0–30.4) | 386 | 0.74 (0.64, 0.85) | 184 | 0.76 (0.62, 0.93) | 54 | 0.53 (0.38, 0.76) | 126 | 0.84 (0.65, 1.08) |
| 5 (30.5–188.3) | 433 | 0.84 (0.73, 0.97) | 193 | 0.81 (0.65, 0.99) | 79 | 0.78 (0.56, 1.08) | 146 | 0.97 (0.76, 1.25) |
| *P*-trend | | 0.04 | | 0.3 | | 0.3 | | 0.4 |
| BH-adjusted *P*-trend | | 0.2 | | 0.5 | | 0.5 | | 0.6 |
| Isoflavones | | | | | | | | |
| 1 (0–0.16) | 408 | 1.00 (—) | 184 | 1.00 (—) | 82 | 1.00 (—) | 118 | 1.00 (—) |
| 2 (0.17–0.22) | 431 | 0.94 (0.82, 1.08) | 206 | 1.01 (0.83, 1.23) | 74 | 0.79 (0.57, 1.08) | 128 | 0.94 (0.73, 1.21) |
| 3 (0.23–0.31) | 390 | 0.84 (0.73, 0.97) | 166 | 0.89 (0.66, 1.02) | 65 | 0.67 (0.48, 0.94) | 135 | 0.94 (0.73, 1.22) |

*(Continued)*

**TABLE 2** *Continued*

| | Cancer site | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Head and neck | | Oral cavity | | Orohypopharyngeal | | Laryngeal | |
| Quintile of intake, mg/d | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) |
| 4 (0.32–0.45) | 490 | 0.92 (0.80, 1.06) | 239 | 0.89 (0.86, 1.30) | 76 | 0.67 (0.48, 0.93) | 153 | 0.91 (0.70, 1.17) |
| 5 (0.46–5.36) | 465 | 0.81 (0.69, 0.95) | 180 | 0.88 (0.61, 0.98) | 78 | 0.61 (0.43, 0.88) | 182 | 0.95 (0.73, 1.24) |
| *P*-trend | | 0.02 | | 0.05 | | 0.03 | | 0.9 |
| BH-adjusted *P*-trend | | 0.1 | | 0.2 | | 0.2 | | 0.9 |

[1] Ranges for quintiles of total flavonoid intake are given in parentheses. HRs are adjusted for age at baseline (<55, 55–59, 60–64, 65–69, or ≥70 y), sex, race (non-Hispanic white, non-Hispanic black, or other), education (less than high school, completed high school or post–high school training other than college, some college or college graduate, or postgraduate), smoking status (never smoker, former smoker of ≤20 or >20 cigarettes/d, or current smoker of ≤20 or >20 cigarettes/d), BMI (in kg/m$^2$: <25, 25 to <30, or ≥30), alcohol intake (0–0.19, 0.20–1.83, 1.84–11.5, or 11.6–450.94 g/d), self-reported health (excellent, very good, good, fair, or poor), vigorous physical activity of ≥20 min (never, rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk), and total energy intake (expressed as kcal/d). HRs compare the risk of developing cancer for participants in each quintile of flavonoid intake to participants in the lowest quintile of flavonoid intake, holding all other covariates constant. BH, Benjamini-Hochberg.

[2] For all *P*-trend values, tests for linear trend were calculated by assigning the median of each quintile as scores.

[3] For all BH-adjusted *P*-trend values, the linear trend tests were adjusted for multiple comparisons using the BH procedure for false discovery rate control at the 0.05 level for 56 comparisons (44).

regression models with and without a multiplicative term (41). We found no evidence of effect modification ($P \geq 0.05$).

We conducted a backward stepwise regression to evaluate potential confounders. Variables remained in the adjusted model if they were significant ($P < 0.10$) in the backward stepwise selection (42). All covariates met the inclusion criteria and were included in the final models as follows: age at baseline (<55, 55–59, 60–64, 65–69, or ≥70 y), sex, race (non-Hispanic white, non-Hispanic black, or other), education (less than high school, completed high school or post–high school training other than college, some college or college graduate, or postgraduate), smoking status (never smoker, former smoker of ≤20 or >20 cigarettes/d, or current smoker of ≤20 or >20 cigarettes/d), BMI (<25, 25 to <30, or ≥30), alcohol intake (quartiles of intake: 0–0.19, 0.20–1.83, 1.84–11.5, or 11.6–450.94 g/d), self-rated health (excellent, very good, good, fair, or poor), and vigorous physical activity of ≥20 min (never, rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk). Total energy intake (expressed as kcal/d) was included for adjustment as an a priori confounder (43).

The linear trend tests were adjusted for multiple comparisons using the Benjamini-Hochberg (BH) procedure for false discovery rate control at the 0.05 level for 56 comparisons (44). In addition, for the 6 associations discovered by the BH procedure, we calculated BH-adjusted CIs (45) for a comparison of quintile 5 and quintile 1 [i.e., CI at level $1 - 0.05 \times (6/56)$]. The BH-adjusted CIs controlled the false coverage rate (45), which is the expected fraction of CIs not covering their true parameters among the discovered associations, at the 0.05 level. All *P* values were 2 sided. Statistical analyses were conducted using SAS software (version 9.3; SAS Institute).

*Sensitivity analysis.* We conducted a sensitivity analysis comparing the results from the standard multivariate model, the nutrient density model (**Supplemental Table 3**), and the residual model (**Supplemental Table 4**) (31). The estimated HRs were not substantially different; therefore, we chose to present results adjusted utilizing the standard multivariate approach for ease of interpretation. Finally, we conducted a 5-y lag analysis, excluding cases that developed cancer within the first 5-y of follow-up by delaying the start of follow-up for all participants (**Supplemental Tables 5–7**), as individuals with symptoms attributed to cancer (e.g., dysphagia) may have altered their dietary habits.

## Results

Over a mean follow-up of 12 y, 2453 head and neck (including 1078 oral cavity, 424 pharyngeal, and 817 laryngeal), 1165 esophageal (890 adenocarcinoma, and 275 squamous cell carcinoma), and 1297 gastric (625 cardia and 672 noncardia) cancer cases were identified. Demographic characteristics of our study cohort by quintile of total flavonoid intake are presented in **Table 1**. Compared with the lowest quintile, participants in the highest quintile of total flavonoid intake were more likely to have a postgraduate education and were less likely to be smokers.

The highest quintile of total flavonoid intake was associated with a 24% lower risk of head and neck cancer (HR: 0.76; 95% CI: 0.66, 0.86; BH-adjusted 95% CI: 0.63, 0.91; *P*-trend = 0.02) compared with the lowest quintile (**Table 2**). Dietary intake of anthocyanidins was associated with a 28% lower risk of head and neck cancer (HR: 0.72; 95% CI: 0.62, 0.82; BH-adjusted 95% CI: 0.59, 0.87; *P*-trend = 0.0005), which was also seen by subsite of oral cavity (HR: 0.78; 95% CI: 0.63, 0.96; BH-adjusted 95% CI: 0.58, 1.05; *P*-trend = 0.04) and laryngeal (HR: 0.62; 95% CI: 0.48, 0.80; BH-adjusted 95% CI: 0.44, 0.89; *P*-trend = 0.02). Flavanone intake was associated with a 22% lower risk of head and neck cancer (HR: 0.78; 95% CI: 0.68, 0.89; BH-adjusted 95% CI: 0.64, 0.94; *P*-trend = 0.02), which was also seen for subsite of pharyngeal (HR: 0.58; 95% CI: 0.41, 0.82; BH-adjusted 95% CI: 0.36, 0.95; *P*-trend = 0.03).

No association was observed between flavonoid intake and esophageal adenocarcinoma or esophageal squamous cell carcinoma (total flavonoids: BH-adjusted *P*-trend = 0.8 and 0.8, respectively) (**Table 3**). Similar to esophageal cancer, no association was found between flavonoid intake and gastric cardia adenocarcinoma or noncardia gastric adenocarcinoma (total flavonoids: BH-adjusted *P*-trend = 0.8 and 0.5, respectively) (**Table 4**).

## Discussion

In this large prospective study, we observed that total dietary flavonoid intake was associated with a 24% lower risk of head and neck but not esophageal or gastric cancer. Anthocyanidins and flavanones were also associated with a lower risk of head and neck cancer, but these inverse associations varied by tumor subsite. No association was observed between any flavonoid class and esophageal or gastric cancer.

Our findings for head and neck cancer are consistent with 2 previous case-control studies from Italy, which reported that intake of total flavonoids, flavanones, and flavonols was inversely

**TABLE 3** Adjusted HRs and 95% CIs for associations between flavonoid intake and risk of esophageal cancer for NIH-AARP Diet and Health Study participants[1]

| Quintile of intake, mg/d | Adenocarcinoma | | Squamous cell carcinoma | |
|---|---|---|---|---|
| | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) |
| Total flavonoids | | | | |
| 1 (0–84.1) | 163 | 1.00 (—) | 60 | 1.00 (—) |
| 2 (84.2–140.9) | 155 | 0.95 (0.76, 1.19) | 52 | 0.89 (0.61, 1.29) |
| 3 (141.0–225.6) | 159 | 0.99 (0.79, 1.23) | 39 | 0.68 (0.45, 1.03) |
| 4 (225.7–437.9) | 157 | 1.01 (0.80, 1.26) | 39 | 0.71 (0.47, 1.07) |
| 5 (438.0–4211.2) | 154 | 1.03 (0.82, 1.29) | 47 | 0.86 (0.58, 1.27) |
| *P*-trend[2] | | 0.6 | | 0.7 |
| BH-adjusted *P*-trend[3] | | 0.8 | | 0.8 |
| Anthocyanidins | | | | |
| 1 (0–3.8) | 194 | 1.00 (—) | 67 | 1.00 (—) |
| 2 (3.9–7.0) | 157 | 0.85 (0.69, 1.05) | 52 | 0.91 (0.63, 1.31) |
| 3 (7.1–11.7) | 141 | 0.84 (0.67, 1.05) | 31 | 0.58 (0.38, 0.90) |
| 4 (11.8–20.6) | 143 | 0.90 (0.72, 1.13) | 36 | 0.63 (0.41, 0.96) |
| 5 (20.7–376.6) | 153 | 0.89 (0.70, 1.11) | 51 | 0.68 (0.46, 1.00) |
| *P*-trend | | 0.7 | | 0.1 |
| BH-adjusted *P*-trend | | 0.8 | | 0.3 |
| Flavan-3-ols | | | | |
| 1 (0–25.6) | 159 | 1.00 (—) | 60 | 1.00 (—) |
| 2 (25.7–60.6) | 152 | 0.98 (0.78, 1.22) | 47 | 0.80 (0.54, 1.17) |
| 3 (60.7–129.2) | 164 | 1.05 (0.85, 1.31) | 45 | 0.82 (0.55, 1.21) |
| 4 (129.3–346.6) | 151 | 0.99 (0.79, 1.25) | 34 | 0.65 (0.42, 0.99) |
| 5 (346.7–3828.7) | 162 | 1.10 (0.88, 1.37) | 51 | 0.95 (0.65, 1.39) |
| *P*-trend | | 0.4 | | 0.8 |
| BH-adjusted *P*-trend | | 0.6 | | 0.9 |
| Flavanones | | | | |
| 1 (0–8.8) | 171 | 1.00 (—) | 56 | 1.00 (—) |
| 2 (8.9–23.7) | 149 | 0.89 (0.71, 1.11) | 59 | 1.14 (0.79, 1.65) |
| 3 (23.8–43.7) | 147 | 0.90 (0.72, 1.12) | 51 | 1.02 (0.69, 1.51) |
| 4 (43.8–65.9) | 159 | 0.95 (0.76, 1.18) | 37 | 0.72 (0.47, 1.10) |
| 5 (66.0–978.9) | 162 | 0.99 (0.79, 1.24) | 34 | 0.67 (0.43, 1.05) |
| *P*-trend | | 0.7 | | 0.01 |
| BH-adjusted *P*-trend | | 0.8 | | 0.09 |
| Flavones | | | | |
| 1 (0–0.44) | 167 | 1.00 (—) | 55 | 1.00 (—) |
| 2 (0.45–0.67) | 169 | 0.98 (0.79, 1.22) | 52 | 0.92 (0.63, 1.36) |
| 3 (0.68–0.96) | 164 | 0.99 (0.79, 1.23) | 49 | 0.86 (0.58, 1.29) |
| 4 (0.97–1.45) | 147 | 0.90 (0.72, 1.14) | 33 | 0.56 (0.36, 0.88) |
| 5 (1.46–29.02) | 141 | 0.93 (0.73, 1.19) | 48 | 0.80 (0.53, 1.23) |
| *P*-trend | | 0.5 | | 0.2 |
| BH-adjusted *P*-trend | | 0.7 | | 0.5 |
| Flavonols | | | | |
| 1 (0–10.4) | 144 | 1.00 (—) | 44 | 1.00 (—) |
| 2 (10.5–14.9) | 177 | 1.14 (0.91, 1.42) | 50 | 1.07 (0.71, 1.62) |
| 3 (15.0–20.9) | 157 | 1.01 (0.80, 1.27) | 46 | 0.96 (0.62, 1.47) |
| 4 (21.0–30.4) | 150 | 0.97 (0.76, 1.23) | 40 | 0.84 (0.53, 1.31) |
| 5 (30.5–188.3) | 160 | 1.10 (0.86, 1.40) | 57 | 1.17 (0.76, 1.80) |
| *P*-trend | | 0.8 | | 0.5 |
| BH-adjusted *P*-trend | | 0.9 | | 0.7 |
| Isoflavones | | | | |
| 1 (0–0.16) | 142 | 1.00 (—) | 39 | 1.00 (—) |
| 2 (0.17–0.22) | 141 | 0.86 (0.68, 1.09) | 38 | 0.90 (0.57, 1.41) |
| 3 (0.23–0.31) | 163 | 0.98 (0.78, 1.24) | 51 | 1.22 (0.80, 1.88) |
| 4 (0.32–0.45) | 158 | 0.84 (0.66, 1.07) | 52 | 1.12 (0.72, 1.74) |
| 5 (0.46–5.36) | 184 | 0.94 (0.72, 1.21) | 57 | 1.19 (0.74, 1.90) |
| *P*-trend | | 0.8 | | 0.4 |
| BH-adjusted *P*-trend | | 0.9 | | 0.6 |

[1] Ranges for quintiles of total flavonoid intake are given in parentheses. HRs are adjusted for age at baseline (<55, 55–59, 60–64, 65–69, or ≥70 y), sex, race (non-Hispanic white, non-Hispanic black, or other), education (less than high school, completed high school or post–high school training other than college, some college or college graduate, or postgraduate), smoking status (never smoker, former smoker of ≤20 or >20 cigarettes/d, or current smoker of ≤20 or >20 cigarettes/d), BMI (in kg/m$^2$: <25, 25 to <30, or ≥30), alcohol intake (0–0.19, 0.20–1.83, 1.84–11.5, or 11.6–450.94 g/d), self-reported health (excellent, very good, good, fair, or poor), vigorous physical activity of ≥20 min (never, rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk), and total energy intake (expressed as kcal/d). The HR compares the risk of developing cancer for participants in each quintile of flavonoid intake to participants in the lowest quintile of flavonoid intake, holding all other covariates constant. BH, Benjamini-Hochberg.

[2] For all *P*-trend values, tests for linear trends were calculated by assigning the median of each quintile as scores.

[3] For all BH-adjusted *P*-trend values, the linear trend tests were adjusted for multiple comparisons using the BH procedure for false discovery rate control at the 0.05 level for 56 comparisons (44).

associated with all head and neck cancers (17, 46). Two previous epidemiologic studies showed an inverse association between intake of anthocyanidins and risk of esophageal adenocarcinoma and esophageal squamous cell carcinoma (21, 47). However, in our study, we found no association between flavonoid intake and risk of esophageal adenocarcinoma or esophageal squamous cell carcinoma. In addition, we report no association between flavonoid intake and gastric cancers, contrary to previous studies that showed inverse associations between gastric cancer and intake of total flavonoids (23), anthocyanidins (23), flavan-3-ols (23), flavanones (22), flavones (22, 23), and flavonols (22, 23, 25, 26). Possible reasons for the discrepancies between our study and previous studies could be differences in the underlying population and in adjustment factors. To date, the NIH-AARP study does not have information on *H. pylori* infection or gastroesophageal reflux disease, both of which could be potential confounders for some subsites.

An inverse association between flavonoid intake and cancer risk is biologically plausible. In vitro studies showed that flavonoids have a number of chemopreventive mechanisms, including cell cycle regulation, cellular proliferation, apoptosis, and modulation of carcinogen metabolism and inflammatory pathways (6). In vivo clinical and animal studies provide support for the potential chemopreventive effects of flavonoids. Similar to our reported findings, flavonoids were shown to reduce the incidence of oral cancers in rodent models. Flavan-3-ols (i.e., catechin and epicatechin 3-gallate), flavanones (i.e., naringenin), flavones (i.e., apigenin), and flavonols (i.e., quercetin) all reduced the incidence of oral tumors in hamster models (e.g., 7,12-dimethylbenz[*a*] anthracene–induced carcinogenesis) (48).

To address the issue of multiple comparisons, we calculated BH-adjusted *P* values. At a threshold of BH-adjusted *P*-trend values ≤ 0.05, total flavonoids, anthocyanidins, and flavanones were the only flavonoids considered to be statistically significantly associated with head and neck cancer. Adjusting for multiple comparisons in this way protects against making >5% false-positive associations across the 56 tests of trend. Thus, we drew our main conclusions from these BH-adjusted *P* values, but

**TABLE 4** Adjusted HRs and 95% CIs for associations between flavonoid intake and risk of gastric cancer for NIH-AARP Diet and Health Study participants[1]

| | Cardia | | Noncardia | |
|---|---|---|---|---|
| Quintile of intake, mg/d | Cases, *n* | HR (95% CI) | Cases, *n* | HR (95% CI) |
| Total flavonoids | | | | |
| 1 (0–84.1) | 116 | 1.00 (—) | 118 | 1.00 (—) |
| 2 (84.2–140.9) | 108 | 0.96 (0.73, 1.25) | 102 | 0.89 (0.68, 1.17) |
| 3 (141.0–225.6) | 100 | 0.90 (0.69, 1.18) | 118 | 1.05 (0.81, 1.36) |
| 4 (225.7–437.9) | 118 | 1.10 (0.84, 1.43) | 114 | 1.02 (0.79, 1.33) |
| 5 (438.0–4211.2) | 105 | 1.02 (0.78, 1.34) | 124 | 1.11 (0.86, 1.44) |
| *P*-trend[2] | | 0.6 | | 0.2 |
| BH-adjusted *P*-trend[3] | | 0.8 | | 0.5 |
| Anthocyanidins | | | | |
| 1 (0–3.8) | 123 | 1.00 (—) | 138 | 1.00 (—) |
| 2 (3.9–7.0) | 118 | 1.05 (0.81, 1.35) | 119 | 0.91 (0.71, 1.17) |
| 3 (7.1–11.7) | 99 | 0.97 (0.74, 1.27) | 104 | 0.84 (0.65, 1.10) |
| 4 (11.8–20.6) | 96 | 0.99 (0.75, 1.31) | 100 | 0.84 (0.64, 1.10) |
| 5 (20.7–376.6) | 111 | 1.05 (0.80, 1.39) | 115 | 0.94 (0.72, 1.23) |
| *P*-trend | | 0.8 | | 0.9 |
| BH-adjusted *P*-trend | | 0.9 | | 0.9 |
| Flavan-3-ols | | | | |
| 1 (0–25.6) | 116 | 1.00 (—) | 117 | 1.00 (—) |
| 2 (25.7–60.6) | 107 | 0.96 (0.74, 1.25) | 109 | 0.98 (0.76, 1.28) |
| 3 (60.7–129.2) | 107 | 0.97 (0.75, 1.27) | 114 | 1.06 (0.82, 1.37) |
| 4 (129.3–346.6) | 109 | 1.02 (0.78, 1.33) | 107 | 1.00 (0.77, 1.31) |
| 5 (346.7–3828.7) | 108 | 1.04 (0.80, 1.36) | 129 | 1.19 (0.92, 1.54) |
| *P*-trend | | 0.6 | | 0.1 |
| BH-adjusted *P*-trend | | 0.8 | | 0.4 |
| Flavanones | | | | |
| 1 (0–8.8) | 143 | 1.00 (—) | 116 | 1.00 (—) |
| 2 (8.9–23.7) | 83 | 0.61 (0.46, 0.80) | 116 | 1.04 (0.80, 1.35) |
| 3 (23.8–43.7) | 88 | 0.66 (0.50, 0.86) | 106 | 0.94 (0.72, 1.22) |
| 4 (43.8–65.9) | 116 | 0.85 (0.66, 1.09) | 119 | 1.02 (0.79, 1.32) |
| 5 (66.0–978.9) | 117 | 0.87 (0.68, 1.13) | 119 | 0.99 (0.76, 1.30) |
| *P*-trend | | 0.5 | | 0.9 |
| BH-adjusted *P*-trend | | 0.8 | | 0.9 |
| Flavones | | | | |
| 1 (0–0.44) | 102 | 1.00 (—) | 117 | 1.00 (—) |
| 2 (0.45–0.67) | 127 | 1.25 (0.96, 1.62) | 115 | 1.01 (0.78, 1.31) |
| 3 (0.68–0.96) | 99 | 1.02 (0.77, 1.35) | 113 | 1.03 (0.79, 1.34) |
| 4 (0.97–1.45) | 131 | 1.38 (1.05, 1.81) | 118 | 1.08 (0.83, 1.41) |
| 5 (1.46–29.02) | 88 | 0.99 (0.73, 1.34) | 113 | 1.06 (0.80, 1.40) |
| *P*-trend | | 0.7 | | 0.7 |
| BH-adjusted *P*-trend | | 0.9 | | 0.8 |
| Flavonols | | | | |
| 1 (0–10.4) | 101 | 1.00 (—) | 108 | 1.00 (—) |
| 2 (10.5–14.9) | 110 | 1.05 (0.80, 1.38) | 110 | 1.06 (0.81, 1.38) |
| 3 (15.0–20.9) | 112 | 1.07 (0.81, 1.42) | 121 | 1.18 (0.90, 1.54) |
| 4 (21.0–30.4) | 120 | 1.17 (0.88, 1.55) | 111 | 1.09 (0.82, 1.43) |
| 5 (30.5–188.3) | 104 | 1.08 (0.80, 1.45) | 126 | 1.25 (0.94, 1.65) |
| *P*-trend | | 0.6 | | 0.1 |
| BH-adjusted *P*-trend | | 0.8 | | 0.4 |
| Isoflavones | | | | |
| 1 (0–0.16) | 104 | 1.00 (—) | 126 | 1.00 (—) |
| 2 (0.17–0.22) | 85 | 0.74 (0.55, 0.99) | 100 | 0.75 (0.58, 0.98) |
| 3 (0.23–0.31) | 112 | 0.98 (0.75, 1.29) | 109 | 0.83 (0.63, 1.08) |
| 4 (0.32–0.45) | 118 | 0.93 (0.70, 1.24) | 127 | 0.87 (0.67, 1.14) |
| 5 (0.46–5.36) | 128 | 0.99 (0.73, 1.34) | 114 | 0.73 (0.54, 0.98) |
| *P*-trend | | 0.5 | | 0.2 |
| BH-adjusted *P*-trend | | 0.7 | | 0.4 |

[1] Ranges for quintiles of total flavonoid intake are given in parentheses. HRs are adjusted for age at baseline (<55, 55–59, 60–64, 65–69, or ≥70 y), sex, race (non-Hispanic white, non-Hispanic black, or other), education (less than high school, completed high school or post–high school training other than college, some college or college graduate, or postgraduate), smoking status (never smoker, former smoker of ≤20 or >20 cigarettes/d, or current smoker of ≤20 or >20 cigarettes/d), BMI (in kg/m$^2$: <25, 25 to <30, or ≥30), alcohol intake (0–0.19, 0.20–1.83, 1.84–11.5, or 11.6–450.94 g/d), self-reported health (excellent, very good, good, fair, or poor), vigorous physical activity of ≥20 min (never, rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk), and total energy intake (expressed as kcal/d). HRs compare the risk of developing cancer for participants in each quintile of flavonoid intake to participants in the lowest quintile of flavonoid intake, holding all other covariates constant. BH, Benjamini-Hochberg.

[2] For all *P*-trend values, tests for linear trend were calculated by assigning the median of each quintile as scores.

[3] For all BH-adjusted *P*-trend values, the linear trend tests were adjusted for multiple comparisons using the BH procedure for false discovery rate control at the 0.05 level for 56 comparisons (44).

we also present unadjusted *P* values and 95% CIs in Tables 2–4 for the reader's convenience (31, 49).

Our study has several limitations. The first potential source of error is in estimating individual flavonoid intakes based on linking foods reported in the FFQ to the USDA flavonoid database. Flavonoid content of individual food items, particularly fruits and vegetables, varies by plant varieties, degree of ripeness, storage conditions, distance transported to market, environmental factors affecting plant growth, horticultural practices, industrial processing, and cooking methods (50). Therefore, the study population may consume foods that differ from the foods utilized to create estimates of flavonoid content in the nutrient database (34). In addition, the NIH-AARP study population is from 8 different states. Thus, there may be differences in the amount of flavonoids consumed by study participants as a result of regional differences. We examined the association between total flavonoids and head and neck cancer and did not find substantial differences by state (data not shown). To determine the extent of flavonoid variability, the USDA Food Composition and Nutrient Data Laboratories also sampled >60 fruits, vegetables, and nuts from 4 US regions at 2 times of the year. Although flavonoid content was variable within and between foods, flavonoid values reported in the USDA databases were similar to the mean flavonoid content determined by the USDA Food Composition and Nutrient Data Laboratories (51). This issue of flavonoid content estimation applies to all studies utilizing nutritional databases to estimate values for dietary intake (31).

The difference we observed in the median intake of total flavonoids between participants in the fifth compared with the first quintiles was roughly equivalent to 2 cups tea/d (~473 mL). However, the FFQ used for the NIH-AARP cohort did not include line items on certain flavonoid-rich foods like berries (other than strawberries) and tofu. Although the FFQ did ask about tea consumption, it did not capture the types of tea (e.g., black versus green), which differ in flavonoid concentration. Thus, individual estimates of flavonoid intake may be misclassified. However, consumption of these flavonoid-rich foods in the US population is low (52) and is therefore unlikely to considerably change the mean measured flavonoid intake. FFQs also cannot

include every possible food item and therefore must be selective in which foods are included. The FFQ utilized in our study was designed to reflect the "typical" American diet; thus, there is potential misclassification of flavonoid intake for subjects with ethnic or specialty diets. For example, vegetarians are more likely to consume tofu or tofu-based products, which are not assessed on this FFQ and thus lead to misclassification. In addition, FFQs are known to suffer from measurement error. We attempted to minimize measurement error, which commonly results in attenuated risk estimates (53), by adjusting the models for energy intake (54). However, we cannot exclude the possibility that some error remains.

Bioavailability is also another source of measurement misclassification. Measured dietary intake of flavonoids may differ from the internal dose. Little is known about the bioavailability of flavonoids, how metabolism of flavonoids varies by individuals, and the directed effect of flavonoids on epithelial surfaces as flavonoids traverse the upper gastrointestinal tract (55). In addition, flavonoid absorption profiles are variable, with maximum circulating concentrations reached between 0.5 and 9 h after dietary intake (56). Thus, biomarkers of flavonoid intake may not be highly correlated with usual adult dietary intake. However, flavonoid biomarkers in 24-h urine samples have shown good correlation with fruit and vegetable intake calculated from a prior-month FFQ (validity coefficients = 0.43–0.66) (57).

Dysphagia (or difficulty swallowing) is a common symptom of upper gastrointestinal cancers, which can lead individuals to alter dietary habits. However, we observed similar results when we conducted a 5-y lag analysis, excluding cases that developed cancer within the first 5-y of follow-up by delaying the start of follow-up for all participants. Thus, an altered dietary state owing to underlying disease is unlikely to account for the associations, or lack thereof, that we observed.

Previous studies using the NIH-AARP data have reported on the association between fruit and vegetable intake and upper gastrointestinal cancers (58–60). An inverse association between fruit and vegetable intake and head and neck cancer was reported (58), but the associations with esophageal (59) and gastric (60) cancer were limited. Because flavonoids are concentrated in fruits and vegetables (50), the association between flavonoids and head and neck cancer incidence may reflect diets with greater consumption of such foods or a healthy lifestyle in general. Because of issues of collinearity between fruit and vegetable intake and flavonoids (61), we were unable to assess the effects of flavonoids independent of fruit and vegetable intake. In addition, ingestion of fatty foods can result in a proinflammatory response (62). Some foods that contribute to dietary flavonoid intake, such as donuts and hotdogs, also have high fat content. However, these foods contribute little to total flavonoid consumption. For instance, a medium plain cake-type donut contains ~2.9 mg of flavonoids, whereas a beef hotdog contains ~0.9 mg (34).

Finally, internal and external validity of the NIH-AARP cohort may be lacking because of the low response rate (17.6%). Responders to the baseline questionnaire were predominately white, predominately noncurrent smokers, and more educated, and they consumed less red meat and fat and more fruits and vegetables compared with the general US population (30). In addition, the dietary intake distributions were wider than what has been reported in the general US population. This combination of altered and widened dietary intake distributions may have compensated for the low response rate by allowing for adequate numbers of individuals in the dietary intake extremes (30). These results are still generalizable to those at highest risk of developing esophageal adenocarcinoma and gastric cardia adenocarcinoma, because the majority of the NIH-AARP cohort consists of non-Hispanic white men and the rates of esophageal adenocarcinoma and gastric cardia adenocarcinoma are highest in this racial/ethnic group (63). However, studies show that rates of head and neck cancer (64), esophageal squamous cell carcinoma, and noncardia gastric adenocarcinoma (63) are higher among black men. Thus, the results from our study may not be generalizable to individuals at the highest risk for these cancer types.

Strengths of our study include its large sample size and long follow-up, which yielded large numbers of outcomes for these rare cancer types. In addition, we utilized the USDA expanded flavonoid database, which included a greater scope of foods than used in previous studies and also accounts for cooking methods not previously accounted for in the USDA flavonoid databases. Our use of this updated and expanded flavonoid database improves the accuracy of our intake measurement.

Another strength of our study is its prospective cohort design, which minimizes differential information bias from self-reported dietary intake compared with previous case-control studies. In addition, the data collected from the FFQs administered in the NIH-AARP cohort were validated against 2 nonconsecutive 24-h dietary recalls, administered within a year of the baseline questionnaire to a stratified random sample of participants (54). Deattenuated flavonoid correlation coefficients were 0.57 for men and 0.65 for women (65), which are consistent with other macro- and micronutrients examined in the NIH-AARP study (40, 54).

In conclusion, our findings suggest that dietary intake of flavonoids is associated with a lower risk of head and neck cancers. This evidence suggests that dietary flavonoids could potentially be used as a risk reduction strategy for individuals at high risk of head and neck cancer to reduce the incidence of these highly fatal cancers. However, further laboratory, clinical, and epidemiologic research is warranted before definitive conclusions can be drawn about the chemopreventive potential, or lack thereof, of dietary flavonoids and upper gastrointestinal cancers.


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