# Dietary Flavonoid Intake and Lung Cancer—A Population-based Case-control Study

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**BACKGROUND.** Laboratory studies suggest that flavonoids are antimutagenic and anticarcinogenic. To investigate the associations between commonly consumed flavonoid compounds and lung cancer, the authors conducted a population-based case–control study of 558 lung cancer cases and a group of 837 controls.

**METHODS.** Dietary intakes of flavonoids were estimated by combining the intake frequency (collected by a food frequency questionnaire), portion size, and food composition data. Unconditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence limits (95% CLs) with an adjustment for potential confounders, including age, sex, race-ethnicity, years of schooling, smoking status, pack-years of tobacco smoking, and daily energy intake.

**RESULTS.** Lung cancer was associated inversely with the consumption of epicatechin (in 10 mg per day increment: OR, 0.64; 95% CL, 0.46–0.88), catechin (4 mg per day increment: OR, 0.49; 95% CL, 0.35–0.70), quercetin (9 mg per day increment: OR, 0.65; 95% CL, 0.44–0.95), and kaempferol (2 mg per day increment: OR, 0.68; 95% CL, 0.51–0.90) among tobacco smokers. There was little association between lung cancer and the flavonoid compounds mentioned above among nonsmokers. Regardless of smoking status, there was little association with total flavonoids: thearubigins, hesperetin, naringenin, and myricetin. In addition, consumption of vegetables, tea, and wine, all of which are rich sources of flavonoids, was associated inversely with lung cancer among tobacco smokers.

**CONCLUSIONS.** Certain flavonoid compounds, including epicatechin, catechin, quercetin, and kaempferol, were associated inversely with lung cancer among tobacco smokers, but not among nonsmokers. Further studies of these associations may be warranted. ***Cancer*** **2008;112:2241–8.** © *2008 American Cancer Society.*

**KEYWORDS: lung cancer, flavonoids, epicatechin, catechin, quercetin, kaempferol.**

Epidemiologic studies have identified inverse associations between the consumption of fruits and vegetables and various cancers.[1,2] Plant-derived foods contain a wide variety of antioxidants, such as phytochemicals, and vitamins that scavenge reactive oxygen species (ROS) and may interact to prevent cancers. Considerable attention has been paid to vitamins C and E and carotenoids from fruits and vegetables because of their antioxidant properties. However, to date, large randomized trials have not demonstrated

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the expected protective effects of these micronutrients,[3,4] suggesting that other plant compounds may be responsible for the epidemiologic observations. Laboratory studies indicate that other phytochemicals are major contributors to the antioxidant activity of fruits and vegetables, and a strong, positive correlation has been observed between the antioxidant activity and total content of polyphenols, which are the major components of phytochemicals.[5,6]

Polyphenols comprise flavonoids, phenolic acids, stilbenes, and lignans.[7] Flavonoids are the most widely distributed and account for approximately two-thirds of plant polyphenols in the human diet. Cao et al. observed that some flavonoids have much stronger antioxidant activities against peroxyl radicals than vitamins C and E and glutathione.[8] It has been estimated that the average daily intake of flavonoids in the United States population is between 20 mg and 1 g.[9] Although storage conditions may influence their levels, flavonoids are heat stable and are subject to relatively low loss during cooking and frying.[10] Furthermore, dietary ingredient interactions may have little influence on the bioavailability of flavonoids.[9]

Several flavonoids exhibit anticancer activity in various in vitro and in vivo models.[11] Various mechanisms for these effects have been proposed and supported by laboratory experiments, including antioxidation, induction of detoxification enzymes and inhibition of bioactivation enzymes, estrogenic and antiestrogenic activity, antiproliferation, cell cycle arrest and apoptosis, promotion of differentiation, regulation of host-immune function, and inhibition of angiogenesis.[9,11] However, the aforementioned laboratory experimental studies have largely have involved concentrations that are much higher than those in human diets.[12] Thus, there is a need for epidemiologic studies of natural human intake levels. Herein, we report a population-based case–control study in Los Angeles County in which we evaluated dietary flavonoid compounds in association with lung cancer.

## MATERIALS AND METHODS

### Study Design and Subject Selection

Study design, recruitment, and data collection have been described in detail elsewhere.[13] In brief, we conducted a population-based case–control study in Los Angeles County during the period from 1999 to 2004. The study involved 611 newly diagnosed cases of lung cancer, 601 newly diagnosed cases of upper aerodigestive tract cancers, and a group of 1040 cancer-free controls. Histologically confirmed cases were obtained by using the rapid ascertainment system of the Cancer Surveillance Program for Los Angeles County. Controls with no history of investigated cancers were recruited from the neighborhood of the cases. Cases and controls were matched by age (within 10-year categories) and sex. Participants were residents of Los Angeles County at the time of diagnosis for cases or at study entry for controls. Participants ranged in age from 18 years to 65 years during the enrollment period, and spoke English, or Spanish, or had translators available at home. In-person interviews were conducted by using standardized questionnaires to collect information on sociodemographic characteristics, history of tobacco smoking, environmental tobacco smoking, drug and alcohol use, occupational and environmental exposures, selected clinical factors, dietary history, family history of cancer, and other potential risk or protective factors associated with lung and head and neck cancers.

The current study focuses on lung cancer only. We excluded participants who had no food frequency questionnaire (FFQ) data (44 lung cancer cases and 183 controls) or who had an energy intake $<$500 calories per day or $>$4500 calories per day (9 lung cancer cases and 12 controls). We also excluded 8 controls from the study because they were $>$3 years younger than the youngest case or 3 years older than the oldest case. This left 558 lung cancer cases and 837 controls. The Institutional Review Boards of the University of California at Los Angeles and the University of Southern California approved the research protocol. Informed consent was obtained from all study participants.

### Nutrient Intake Assessment

The semiquantitative FFQ that was used in this study was based on the validated "Brief Block FFQ" (National Cancer Institute), which has been validated for estimating essential nutrients.[14] To enhance our ability to estimate micronutrients and phytochemicals, we included more vegetable and fruit items in the questionnaire. The reference period of the dietary intake was 1 year before diagnosis for cases and 1 year before interview for controls. For seasonal foods, the reference period was limited to the period during which each food was available. Frequencies consumed were sought for 78 food items, including tea, wine, and commonly consumed vegetables (beans, tofu/soy beans, raw tomatoes, cooked tomatoes/tomato sauce, salsa/picante/taco sauce, broccoli, spinach, mustard greens/turnip greens/collards, cole slaw/cabbage, carrots, winter squash, green salad, and sweet potatoes/yams) and fruits (apples/pears, cantaloupe, watermelon, oranges, orange juice/grape

juice, grapefruit, peaches/nectarines/apricots/plums, bananas, strawberries, and other fruit juices).

The daily nutrient intake from a given food was calculated by multiplying its portion size (in grams) by the number of servings per day and its nutrient contents. Then, the daily nutrient intake for each study participant was calculated by summing across all food items. The portion sizes of food items from the original Brief Block FFQ and of the added items were obtained from Dietsys (version 4.02; available from: http://appliedresearch.cancer.gov/DietSys/materials.html; accessed on February 26, 2008) and the U.S. Department of Agriculture (USDA) portion size database, respectively. Food composition data from Dietsys were applied to estimate the intake of macronutrients, vitamins, and minerals. The composition data from the USDA were used to estimate the intake of flavonoids (available from: http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html; accessed on February 26, 2008). A seasonality factor was used to adjust the intake frequencies of seasonal foods. For any food item composed of multiple foods, a given nutrient content was calculated as the weighted mean content of those combined multiple foods. The mean intake for each food, estimated from the Continuing Survey of Food Intakes by Individuals, 1994–1996, was used as its weight.

**TABLE 1**
**Distributions of Selected Demographic and Potential Confounding Factors**

| Variable | No. (%) | |
|---|---|---|
| | Lung cancer cases, n = 558 | Controls, n = 837 |
| Mean ± SD age, y | 52 ± 5 | 50 ± 7 |
| Sex | | |
| Women | 274 (49.1) | 339 (40.5) |
| Men | 284 (50.9) | 498 (59.5) |
| Race-ethnicity | | |
| Non-Hispanic white | 332 (59.5) | 530 (63.3) |
| Black | 86 (15.4) | 83 (9.9) |
| Hispanic | 61 (10.9) | 146 (17.5) |
| Other | 79 (14.2) | 78 (9.3) |
| Mean ± SD schooling, y | 13 ± 3 | 14 ± 4 |
| Smoking status | | |
| Never | 96 (17.2) | 390 (46.6) |
| Ever | 462 (82.8) | 447 (53.4) |
| Median pack-years for ever-smokers [interquartile range] | 35 [26] | 12 [27] |
| Mean ± SD daily energy intake, calories | 1529 ± 667 | 1480 ± 597 |

SD indicates standard deviation.

### Statistical Analysis

We used unconditional logistic regression analysis that included matching factors as indicators, which allowed us to include cases with no matched controls and all available controls that met the inclusion criteria. Odds ratios (ORs) and 95% confidence limits (95% CLs) were calculated with an adjustment for potential confounders, including age, sex, race/ethnicity (non-Hispanic white, black, Hispanic, other), educational level (years of schooling), tobacco smoking (pack-years and status), and daily energy intake (calories). To minimize age confounding, age was controlled in fine categories (ages 29–34 years, 35–36 years, 37–38 years, 39–40 years, 41–42 years, 43–44 years, 45–46 years, 47–48 years, 49–50 years, 51–52 years, 53–54 years, 55–56 years, 57–58 years, and 59–62 years). Dietary intakes of nutrients were adjusted for total energy intake by using the residual method described by Willett et al.[15] These nutrients were analyzed either as continuous variables (with rescaling and exclusion of outliers to avoid the leverage) or as categorical variables. The rescaling units for the continuous analyses were chosen to fall within the span of the data and to correspond to feasible intervention ranges. All data analyses were performed in SAS version 8.2 (SAS Institute, Cary, NC), and all *P* values were 2-sided.

## RESULTS

Distributions of selected demographic and potential confounding factors by disease status are summarized in Table 1. Compared with the control group, the case group had a similar age but lower proportions of men, whites, and Hispanics. Overall, cases consumed more tobacco and calories and they had less educational background than controls.

The median intake of total flavonoids among controls was approximately 60 mg per day, and the intake amount varied considerably (interquartile range, ≈75 mg per day). Flavan-3-ols (median, 15 mg per day; interquartile range, 40 mg per day), flavanones (median, 22 mg per day; interquartile range, 35 mg per day), and flavonols (median, 6 mg per day; interquartile range, 5 mg per day) were main contributors to flavonoid intake in this population; whereas isoflavonoids (median, 60 μg per day; interquartile range, 1306 μg per day), flavones (median, 19 μg per day; interquartile range, 62 μg per day), and anthocyanidins (median, 0.9 μg per day; interquartile range, 387 μg per day) only contributed to a

trace amount of flavonoids. Thearubigins (median, 4 mg per day; interquartile range, 24 mg per day), epicatechin (median, 5 mg per day; interquartile range, 7 mg per day), and catechin (median, 2 mg per day; interquartile range, 2 mg per day) were the commonly consumed flavan-3-ols; hesperetin (median, 14 mg per day; interquartile range, 22 mg per day) and naringenin (median, 6 mg per day; interquartile range, 13 mg per day) were the commonly consumed flavanones; and quercetin (median, 5 mg per day; interquartile range, 4 mg per day), kaempferol (median, 734 μg per day; interquartile range, 1070 μg per day), and myricetin (median, 405 μg per day; interquartile range, 692 μg per day) were the commonly consumed flavonols.

Table 2 shows the distribution of total flavonoid intake stratified on selected characteristics among controls. Only small differences in total flavonoid intake were detected among different groups defined separately by age, education, and daily energy intake. In contrast, women and nonsmokers or light smokers ingested more flavonoids than men and heavy smokers (>20 pack-years), respectively. In addition, blacks consumed less flavonoids than other groups.

The adjusted associations between dietary intakes of total flavonoids and commonly consumed flavonoid compounds and lung cancer are summarized in Table 3. We detected little association between lung cancer and total flavonoids, thearubigins, naringenin, and myricetin. In contrast, lung cancer was associated inversely with the consumption of epicatechin (10 mg per day increment: OR, 0.64; 95% CL, 0.46–0.88; *P* value for trend [$P_{trend}$] = .0066), catechin (4 mg per day increment: OR, 0.49; 95% CL, 0.35–0.70; $P_{trend} < .0001$), quercetin (9 mg per day increment: OR, 0.65; 95% CL, 0.44–0.95; $P_{trend} = .0025$), and kaempferol (2 mg per day increment: OR, 0.68; 95% CL, 0.51–0.90; $P_{trend} = .0079$) among tobacco smokers. Nonetheless, there was little association between lung cancer and epicatechin, catechin, quercetin, and kaempferol among nonsmokers. In addition, there was some evidence of hesperetin associated positively with lung cancer (≥30 mg per day vs <10 mg per day; OR, 1.6; 95% CL, 1.0–2.4) among tobacco smokers in categorical analysis, although little association was observed in continuous analysis.

Vegetables, fruits, tea, and wine are rich sources of epicatechin, catechin, quercetin, and kaempferol. We observed an inverse association of lung cancer with vegetables (3 servings per day increment: OR, 0.59; 95% CL, 0.42–0.83; $P_{trend} = .0026$) and tea (1 cup per day increment: OR, 0.79; 95% CL, 0.63–0.98; $P_{trend} = .033$) consumed in the past year among tobacco smokers (Table 4). Nonetheless, little association was observed among nonsmokers. Similarly, wine intake in the past year was associated inversely with lung cancer among smokers (1 glass per day increment: OR, 0.76; 95% CL, 0.59, 0.97; $P_{trend} = .029$); Among nonsmokers, there were too few data to make a determination. When assessing life-time wine drinking history, the inverse association among smokers was detected only among those who drank moderately (no more than 1 glass per day). Further investigation on the association between wine intake and lung cancer risk is warranted given the seemingly inconsistent results. In addition, total fruit intake was not associated with lung cancer, regardless of smoking status.

**TABLE 2**
**Distribution of Total Flavonoid Intake Stratified on Selected Characteristics Among Controls**

| | No. (%) of controls within categories of total flavonoid intake | | | |
|---|---|---|---|---|
| **Key variable** | **<30 mg/d** | **30–<60 mg/d** | **60–<90 mg/d** | **>90 mg/d** |
| Age, y | | | | |
| 17–44 | 43 (25) | 47 (27) | 27 (16) | 55 (32) |
| 45–54 | 105 (26) | 106 (26) | 75 (18) | 120 (30) |
| >54 | 60 (23) | 55 (21) | 47 (18) | 97 (38) |
| Sex | | | | |
| Men | 134 (27) | 135 (27) | 84 (17) | 145 (29) |
| Women | 74 (22) | 73 (22) | 65 (19) | 127 (37) |
| Race-ethnicity | | | | |
| White | 140 (26) | 132 (25) | 90 (17) | 168 (32) |
| Black | 27 (32) | 19 (23) | 14 (17) | 23 (28) |
| Hispanic | 27 (19) | 37 (25) | 34 (23) | 48 (33) |
| Other | 14 (17) | 20 (26) | 11 (14) | 33 (43) |
| Education, y | | | | |
| 0–12 | 58 (24) | 57 (24) | 44 (19) | 79 (33) |
| 13–16 | 101 (26) | 101 (26) | 77 (20) | 112 (28) |
| >16 | 49 (24) | 50 (24) | 28 (13) | 81 (39) |
| Pack-years of tobacco smoking | | | | |
| Never | 85 (22) | 97 (25) | 84 (21) | 124 (32) |
| 1–20 | 72 (25) | 63 (22) | 46 (16) | 107 (37) |
| >20 | 51 (32) | 48 (30) | 19 (12) | 41 (26) |
| Daily energy intake, calories | | | | |
| <1000 | 51 (30) | 47 (28) | 31 (18) | 41 (24) |
| 1000–2000 | 124 (23) | 125 (24) | 89 (17) | 188 (36) |
| >2000 | 33 (23) | 36 (26) | 29 (21) | 43 (30) |

## DISCUSSION

Consistent with our findings, in 1 hospital-based case–control study, an inverse association was observed between black tea consumption and lung cancer (OR, 0.34; 95% CL, 0.14, 0.84) among smoking men.[16] An anticarcinogenic effect of tea consumption may arise through scavenging of ROS, inhibition of

**TABLE 3**
**Associations of Total Flavonoids and Commonly Consumed Flavonoid Compounds With Lung Cancer Risk**

| | All study participants | | | Smokers | | | Nonsmokers | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. (%) | | | No. (%) | | | No. (%) | | |
| Compound | Cases | Controls | OR [95% CL]* | Cases | Controls | OR [(95% CL]* | Cases | Controls | OR [95% CL]† |
| Total flavonoids | | | | | | | | | |
| 200 mg/d‡ | 558 (100) | 837 (100) | 1.1 [0.84–1.4] | 462 (100) | 447 (100) | 0.93 [0. 69–1.3] | 96 (100) | 390 (100) | 1.3 [0.86–1.9] |
| $P_{trend}$ | | | .53 | | | .63 | | | .23 |
| <30 mg/d | 174 (31) | 209 (25) | 1.0 | 160 (35) | 124 (28) | 1.0 | 14 (15) | 85 (22) | 1.0 |
| 30–<60 mg/d | 130 (23) | 206 (25) | 0.98 [0.68–1.4] | 109 (24) | 112 (25) | 0.94 [0.62–1.4] | 21 (22) | 94 (24) | 1.2 [0.53–2.6] |
| 60–<90 mg/d | 73 (13) | 137 (16) | 0.87 [0.57–1.3] | 61 (13) | 60 (13) | 0.98 [0.59–1.6] | 12 (12) | 77 (20) | 0.70 [0.29–1.7] |
| ≥9 mg/d | 181 (33) | 285 (34) | 1.1 [0.80–1.6] | 132 (28) | 151 (34) | 0.97 [0.65–1.5] | 49 (51) | 134 (34) | 1.4 [0.68–2.8] |
| Thearubigins | | | | | | | | | |
| 40 mg/d‡ | 539 (97) | 819 (98) | 0.85 [0.72–1.0] | 445 (96) | 437 (98) | 0.81 [0.65–1.0] | 94 (98) | 382 (98) | 0.93 [0.68–1.3] |
| $P_{trend}$ | | | .081 | | | .062 | | | .63 |
| <5 mg/d | 325 (58) | 460 (55) | 1.0 | 276 (60) | 241 (54) | 1.0 | 49 (51) | 219 (56) | 1.0 |
| 5–<25 mg/d | 103 (19) | 166 (20) | 0.90 [0.64–1.3] | 81 (17) | 83 (19) | 0.83 [0.54–1.3] | 22 (23) | 83 (21) | 1.2 [0.65–2.3] |
| ≥25 mg/d | 130 (23) | 211 (25) | 0.86 [0.63–1.2] | 105 (23) | 123 (27) | 0.77 [0.53–1.1] | 25 (26) | 88 (23) | 1.1 [0.59–2.0] |
| Epicatechin | | | | | | | | | |
| 10 mg/d‡ | 558 (100) | 837 (100) | 0.69 [0.53–0.91] | 462 (100) | 447 (100) | 0.64 [0.46–0.88] | 96 (100) | 390 (100) | 0.85 [0.53–1.4] |
| $P_{trend}$ | | | .0073 | | | .0066 | | | .52 |
| <3 mg/d | 242 (44) | 270 (32) | 1.0 | 210 (46) | 145 (32) | 1.0 | 32 (33) | 125 (32) | 1.0 |
| 3–<6 mg/d | 129 (23) | 250 (25) | 0.88 [0.63–1.2] | 102 (22) | 106 (24) | 0.82 [0.54–1.2] | 27 (28) | 99 (25) | 1.1 [0.56–2.0] |
| 6–<9 mg/d | 80 (14) | 154 (18) | 0.67 [0.45–0.99] | 62 (13) | 87 (20) | 0.55 [0.34–0.89] | 18 (19) | 67 (18) | 1.1 [0.52–2.3] |
| ≥9 mg/d | 107 (19) | 208 (25) | 0.66 [0.46–0.94] | 88 (19) | 109 (24) | 0.61 [0.40–0.93] | 19 (20) | 99 (25) | 0.81 [0.40–1.6] |
| Catechin | | | | | | | | | |
| 4 mg/d‡ | 548 (98) | 820 (98) | 0.56 [0.41–0.76] | 454 (98) | 437 (98) | 0.49 [0.35–0.70] | 94 (98) | 383 (98) | 0.77 [0.41–1.4] |
| $P_{trend}$ | | | .0002 | | | <.0001 | | | .41 |
| <1 mg/d | 216 (39) | 202 (24) | 1.0 | 189 (41) | 104 (23) | 1.0 | 27 (28) | 98 (25) | 1.0 |
| 1–<2 mg/d | 130 (23) | 185 (22) | 0.77 [0.54–1.1] | 100 (22) | 100 (23) | 0.67 [0.43–1.0] | 30 (31) | 85 (22) | 1.1 [0.54–2.1] |
| 2–<3 mg/d | 72 (13) | 172 (21) | 0.38 [0.25–0.57] | 58 (12) | 86 (19) | 0.33 [0.20–0.55] | 14 (15) | 86 (22) | 0.44 [0.20–0.97] |
| ≥3 mg/d | 140 (25) | 278 (33) | 0.54 [0.38–0.76] | 115 (25) | 157 (35) | 0.44 [0.29–0.66] | 25 (26) | 121 (31) | 0.77 [0.39–1.5] |
| Hesperetin | | | | | | | | | |
| 80 mg/d‡ | 549 (98) | 826 (99) | 1.7 [1.0–2.9] | 456 (99) | 441 (99) | 1.7 [0.88–3.3] | 93 (97) | 385 (99) | 1.5 [0.61–3.8] |
| $P_{trend}$ | | | .044 | | | .11 | | | .37 |
| <10 mg/d | 256 (46) | 341 (41) | 1.0 | 236 (51) | 212 (48) | 1.0 | 20 (21) | 129 (33) | 1.0 |
| 10–<20 mg/d | 92 (16) | 170 (20) | 1.1 [0.77–1.6] | 74 (16) | 86 (19) | 1.1 [0.71–1.7] | 18 (19) | 84 (22) | 1.5 [0.69–3.1] |
| 20–<30 mg/d | 76 (14) | 123 (15) | 1.2 [0.82–1.8] | 59 (13) | 63 (14) | 1.2 [0.73–1.9] | 17 (18) | 60 (15) | 1.6 [0.75–3.6] |
| ≥30 mg/d | 134 (24) | 203 (24) | 1.6 [1.1–2.2] | 93 (20) | 86 (19) | 1.6 [1.0–2.4] | 41 (42) | 117 (30) | 1.7 [0.88–3.3] |
| Naringenin | | | | | | | | | |
| 30 mg/d‡ | 546 (98) | 825 (99) | 1.2 [0.92–1.6] | 453 (98) | 440 (98) | 1.3 [0.87–1.8] | 93 (97) | 385 (99) | 1.1 [0.71–1.7] |
| $P_{trend}$ | | | .17 | | | .22 | | | .65 |
| <5 mg/d | 273 (49) | 370 (44) | 1.0 | 244 (53) | 227 (51) | 1.0 | 29 (30) | 143 (36) | 1.0 |
| 5–<10 mg/d | 111 (20) | 184 (22) | 1.2 [0.82–1.7] | 92 (20) | 91 (20) | 1.3 [0.84–1.9] | 19 (20) | 93 (24) | 1.0 [0.53–2.1] |
| 10–<15 mg/d | 57 (10) | 78 (9) | 1.8 [1.2–2.9] | 43 (9) | 32 (7) | 2.2 [1.2–3.9] | 14 (15) | 46 (12) | 1.4 [0.60–3.1] |
| ≥15 mg/d | 117 (21) | 205 (25) | 1.3 [0.95–1.9] | 83 (18) | 97 (22) | 1.4 [0.90–2.1] | 34 (35) | 108 (28) | 1.1 [0.61–2.1] |
| Quercetin | | | | | | | | | |
| 9 mg/d‡ | 558 (100) | 837 (100) | 0.77 [0.56–1.1] | 462 (100) | 447 (100) | 0.65 [0.44–0.95] | 96 (100) | 390 (100) | 1.1 [0.64–1.9] |
| $P_{trend}$ | | | .11 | | | .025 | | | .72 |
| <2.5 mg/d | 151 (27) | 148 (18) | 1.0 | 137 (30) | 88 (20) | 1.0 | 14 (15) | 60 (16) | 1.0 |
| 2.5–<5 mg/d | 206 (37) | 286 (34) | 0.92 [0.65–1.3] | 175 (38) | 148 (33) | 0.92 [0.61–1.4] | 31 (32) | 138 (35) | 1.1 [0.50–2.4] |
| 5–<7.5 mg/d | 99 (18) | 208 (25) | 0.66 [0.44–0.98] | 71 (15) | 102 (23) | 0.54 [0.33–0.87] | 28 (29) | 106 (27) | 1.1 [0.48–2.5] |
| ≥7.5 mg/d | 102 (18) | 195 (23) | 0.71 [0.47–1.1] | 79 (17) | 109 (24) | 0.63 [0.39–1.0] | 23 (24) | 86 (22) | 0.98 [0.43–2.3] |
| Kaempferol | | | | | | | | | |
| 2 mg/d‡ | 551 (99) | 837 (100) | 0.72 [0.56–0.91] | 457 (99) | 447 (100) | 0.68 [0.51–0.90] | 94 (98) | 390 (100) | 0.76 [0.48–1.2] |
| $P_{trend}$ | | | .0069 | | | .0079 | | | .25 |
| <0.5 mg/d | 246 (44) | 303 (36) | 1.0 | 215 (47) | 162 (36) | 1.0 | 31 (32) | 141 (36) | 1.0 |
| 0.5–<1 mg/d | 141 (25) | 217 (26) | 0.97 [0.70–1.3] | 120 (26) | 111 (25) | 0.98 [0.67–1.4] | 21 (22) | 106 (27) | 0.97 [0.49–1.9] |
| 1–<1.5 mg/d | 70 (13) | 133 (16) | 0.73 [0.49–1.1] | 53 (11) | 75 (17) | 0.59 [0.36–0.96] | 17 (18) | 58 (15) | 1.1 [0.55–2.4] |

(*continued*)

**TABLE 3**
**(*continued*)**

| | All study participants | | | Smokers | | | Nonsmokers | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. (%) | | | No. (%) | | | No. (%) | | |
| Compound | Cases | Controls | OR [95% CL]* | Cases | Controls | OR [(95% CL]* | Cases | Controls | OR [95% CL]† |
| ≥1.5 mg/d | 101 (18) | 184 (22) | 0.77 [0.54–1.1] | 74 (16) | 99 (22) | 0.66 [0.42–1.0] | 27 (28) | 85 (22) | 1.1 [0.55–2.0] |
| Myricetin | | | | | | | | | |
| 1 mg/d‡ | 538 (96) | 811 (97) | 0.86 [0.70–1.1] | 445 (96) | 429 (96) | 0.83 [0.62–1.1] | 93 (97) | 382 (98) | 0.86 [0.55–1.3] |
| $P_{trend}$ | | | .21 | | | .22 | | | .52 |
| <200 μg/d | 148 (26) | 219 (26) | 1.0 | 110 (24) | 94 (21) | 1.0 | 38 (40) | 125 (32) | 1.0 |
| 200–<400 μg/d | 112 (20) | 182 (22) | 0.68 [0.46–1.0] | 95 (21) | 90 (20) | 0.70 [0.44–1.1] | 17 (18) | 92 (24) | 0.64 [0.32–1.3] |
| 400–<600 μg/d | 77 (14) | 131 (16) | 0.71 [0.46–1.1] | 70 (15) | 78 (18) | 0.71 [0.43–1.2] | 7 (7) | 53 (13) | 0.52 [0.20–1.3] |
| ≥600 μg/d | 221 (40) | 305 (36) | 0.77 [0.55–1.1] | 187 (40) | 185 (41) | 0.68 [0.45–1.0] | 34 (35) | 120 (31) | 0.94 [0.51–1.7] |

OR indicates odds ratio; 95% CL, 95% confidence limits.

*Adjusted for age (in 14 fine categories), sex, race-ethnicity (non-Hispanic white, black, Hispanic, other), years of schooling, smoking status (ever vs never), pack-years of tobacco smoking, and daily energy intake.

†Adjusted for age (in 14 fine categories), sex, race-ethnicity (non-Hispanic white, black, Hispanic, other), years of schooling, and daily energy intake.

‡ Treating intakes of flavonoid compounds as continuous variables with rescaling and exclusion of outliers.

angiogenesis, and induction of apoptosis and enzymes involved in carcinogen detoxification.[17,18] Both green tea and black tea extracts can inhibit lung tumorigenesis induced by tobacco-specific nitrosamine and benzo(a)pyrene in animals.[18–20] Catechins appear to have antimutagenic and anticarcinogenic activities against a wide variety of mutagens, including benzo(a)pyrene and aflatoxin B1, and their activities are several times more powerful than those of vitamin C.[17] Nonetheless, previous epidemiologic studies of the association of lung cancer with tea consumption and intake of catechins have been inconsistent, with most of those studies reporting no associations.[21–24]

Experimental studies have demonstrated that quercetin inhibits carcinogenesis in human lung cancer cells in vitro and inhibits N-nitrosodiethylamine-induced lung tumorigenesis in animal models.[25] Quercetin exerts its anticancer effect through multiple pathways, including scavenging of ROS, inhibition of carcinogen bioactivation enzymes, induction of carcinogen-conjugating enzymes, and induction of cell cycle arrest and apoptosis.[26–28] We observed an inverse association between quercetin intake and lung cancer, suggesting its protective effect. The inverse association was consistent with some previous studies. One cohort study observed an inverse association of quercetin and lung cancer (risk ratio [RR], 0.42; 95% CL, 0.25–0.72).[29] Similarly, a population-based case–control study in Hawaii observed an inverse association of lung cancer with the main source of quercetin: onions (OR, 0.5; 95% CL, 0.3–0.9) and apples (OR, 0.6; 95% CL–0.4, 1.0).[21] By using baseline data collected in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, an inverse association (RR, 0.56; 95% CL, 0.45–0.69) between flavonol and flavone intake and lung cancer was observed among male smokers.[30] In that study, >85% of the intake of flavonols and flavones was ascribed to quercetin.

Two epidemiologic studies reported little association between the dietary intake of kaempferol, another rich flavonol compound, and lung cancer.[21,29] In contrast, we observed that kaempferol was associated inversely with lung cancer. Kaempferol, which is structurally similar to quercetin, may be an important chemopreventive agent, because of the findings that 1) it is a potent scavenger of superoxide anion and peroxynitrite, thereby blocking oxidative stress[31]; 2) it can inhibit the activity of several enzymes involved in cell growth and signal transduction pathways including cyclic AMP phosphodiesterase[32]; and 3) it inhibits cell growth and induces apoptosis in A549 lung cancer cells.[33]

Some flavonoid compounds that were investigated in the current study were not associated with lung cancer. The estimated effect differences among various flavonoid compounds may have been caused by chance or by differences in their chemical structure, bioavailability, distribution, and metabolism.[34] In vitro studies have indicated considerable differences in the antioxidative potential of different flavonoid compounds.[34] It was striking that the inverse associations between epicatechin, catechin, querce-

**TABLE 4**
**Intakes of Vegetables, Fruits, Tea, and Wine in Association With Lung Cancer Risk**

| | OR (95% CL) | | |
|---|---|---|---|
| **Intake** | **All study participants*** | **Smokers*** | **Nonsmokers†** |
| Total vegetables (servings per day) | | | |
| 3‡ | 0.68 (0.51–0.90) | 0.59 (0.42–0.83) | 0.94 (0.56–1.6) |
| $P_{trend}$ | .0079 | .0026 | .83 |
| <1 | 1.0 | 1.0 | 1.0 |
| 1 to <2 | 0.98 (0.66–1.5) | 0.84 (0.53–1.3) | 2.0 (0.82–4.8) |
| 2 to <3 | 0.80 (0.53–1.2) | 0.69 (0.43–1.1) | 1.6 (0.62–3.9) |
| ≥3 | 0.56 (0.37–0.87) | 0.49 (0.29–0.82) | 1.0 (0.40–2.7) |
| Total fruits (servings per day) | | | |
| 3‡ | 1.1 (0.85–1.4) | 1.0 (0.76–1.4) | 1.1 (0.74–1.5) |
| $P_{trend}$ | .57 | .79 | .75 |
| <1 | 1.0 | 1.0 | 1.0 |
| 1 to <2 | 0.88 (0.63–1.2) | 0.92 (0.62–1.4) | 0.85 (0.41–1.7) |
| 2 to <3 | 0.97 (0.67–1.4) | 1.0 (0.64–1.6) | 0.94 (0.44–2.0) |
| ≥3 | 1.0 (0.71–1.5) | 0.98 (0.62–1.6) | 1.1 (0.51–2.3) |
| Tea (cups per day) | | | |
| 1‡ | 0.83 (0.69–1.0) | 0.79 (0.63–0.98) | 0.90 (0.63–1.3) |
| $P_{trend}$ | .054 | .033 | .56 |
| 0 | 1.0 | 1.0 | 1.0 |
| >0 to 1 | 0.64 (0.49–0.85) | 0.61 (0.44–0.85) | 0.83 (0.49–1.4) |
| >1 | 0.42 (0.24–0.73) | 0.37 (0.19–0.72) | 0.52 (0.18–1.5) |
| Wine (glasses per day in the past year)‖ | | | |
| 1‡ | 0.78 (0.61–0.98) | 0.76 (0.59–0.97) | 1.07 (0.43–2.69) |
| $P_{trend}$ | .037 | .029 | .89 |
| 0 | 1.0 | 1.0 | 1.0 |
| >0 to 1 | 0.68 (0.50–0.94) | 0.50 (0.34–0.74) | 1.27 (0.69–2.36) |
| >1 | 0.33 (0.15–0.75) | 0.32 (0.14–0.74) | —§ |
| Wine (glasses per day, life-time average)‖ | | | |
| 1‡ | 0.94 (0.68–1.31) | 0.96 (0.67–1.38) | 0.88 (0.37–2.12) |
| $P_{trend}$ | .73 | .82 | .78 |
| 0 | 1.0 | 1.0 | 1.0 |
| >0 to 1 | 0.66 (0.48–0.90) | 0.58 (0.40–0.83) | 0.81 (0.41–1.59) |
| >1 | 1.27 (0.72–2.25) | 1.21 (0.65–2.27) | 1.35 (0.33–5.63) |

OR indicates odds ratio; 95% CL, 95% confidence limits.

* Adjusted for age (in 14 fine categories), sex, race-ethnicity (non-Hispanic white, black, Hispanic, other), years of schooling, smoking status (ever vs never), pack-years of tobacco smoking, and daily energy intake.

† Adjusted for age (in 14 fine categories), sex, race-ethnicity (non-Hispanic white, black, Hispanic, other), years of schooling, and daily energy intake.

‡ Treating intakes of vegetable, fruit, tea, and wine as continuous variables with rescaling and exclusion of outliers.

§ No estimation because of sparse data.

‖ Data on wine intake in the past year were collected by the food frequency questionnaire; life-time average wine intake was recorded in the alcoholic beverage drinking history. Beer and liquor drinking also was controlled in the model.

tin, kaempferol, and lung cancer were present only among smokers. Those results may reflect the finding that these flavonoid compounds are strong antioxidants against ROS generated by tobacco smoking. This interpretation also is supported by the finding that these compounds can inhibit tobacco-specific, carcinogen-induced lung tumorigenesis in animal models.[11]

Among the strengths of the current study are its population-based study design, relatively large sample size, and comprehensive questionnaire data. Nonetheless, there are several limitations. Measurement error must be considerable because of retrospective data collection and intrinsic limitations of the FFQ. The reference period of our FFQ is 1 year before diagnosis for cases and 1 year before interview for controls. Therefore, the collected intake data may not reflect relevant exposures (dietary intakes of more than a few years ago) considering the long latency of lung cancer. Previous studies have demonstrated that individuals tend to over-report their intake of fruits and vegetables.[35] Bias would occur if there was differential misreporting of fruit and vegetable intake by disease status. Unfortunately, we have no data to assess the direction and magnitude of the potential bias. Because of the intrinsic limitations of FFQ, the error in measuring micronutrient intake could be substantial. Furthermore, the intake of onions, which are rich sources of quercetin and kaempferol, was not recorded in our study.

Nonparticipation and unwillingness of some participants to provide food intake information may have led to selection bias. For this bias to occur, the association between flavonoid intake and selection would have to differ for cases and controls, which seems unlikely. Moreover, we observed similar distributions for age, sex, educational level, and tobacco smoking between individuals with and without FFQ information.

Residual confounding might exist when evaluating the effects of various flavonoid compounds, although we controlled for well-documented risk factors. Vegetables, fruits, tea, and wine may contain unknown biologically active compounds, which may be correlated with flavonoid compounds but were not controlled for in the study. In addition, flavonoid compounds are usually correlated with each other, because they share common rich sources. The high correlation between epicatechin, catechin, quercetin, and kaempferol limited our ability to separate their effects. Nonetheless, when we included epicatechin, catechin, quercetin, and kaempferol as covariates along with the risk factors that were controlled in previous models, the inverse association with lung cancer remained only for catechin.

The median age at diagnosis for lung cancer in the United States is 70 years.[36] Because our study was restricted to individuals aged <65 years, study cases were relatively young (median age, 52 years). Therefore, our study results may not be generalizable to older populations.

In conclusion, we observed inverse associations of epicatechin, catechin, quercetin, and kaempferol

intakes with lung cancer among tobacco smokers. Although these observations are consistent with laboratory findings, large randomized trials would be needed to determine whether they indeed represent preventive effects.

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