Published in final edited form as:
Int J Cancer. 2008 August 1; 123(3): 664–671. doi:10.1002/ijc.23564.

Dietary flavonoid intake and risk of cancer in postmenopausal women: The Iowa Women's Health Study

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Abstract

Flavonoids, which are found in certain plant foods, are thought to lower cancer risk through their antioxidant, antiestrogenic and antiproliferative properties. We examined the association of intake of total flavonoids and 7 flavonoid subclasses with risk of lung, colorectal, breast, pancreatic and upper aerodigestive cancer among women in a large prospective cohort study. Study participants were 34,708 postmenopausal women in the Iowa Women's Health Study who completed a food frequency questionnaire and were followed for cancer occurrence from 1986 through 2004. Flavonoid intake was estimated from 3 databases developed by the USDA Nutrient Data Laboratory (NDL). Hazard ratios (HR) for cancer risk were calculated across total flavonoid and flavonoid subclass intake categories. Interactions between smoking history and flavonoid intake were also examined. After multivariable adjustment, lung cancer incidence was inversely associated with intakes of flavanones (HR = 0.68; 95% CI: 0.53−0.86, all results highest *vs*. lowest quintile) and proanthocyanidins (HR = 0.75; 95% CI: 0.57−0.97). Among current and past smokers, those with intakes in the highest quintile for flavanones (HR = 0.66; 95% CI: 0.50−0.86), and proanthocyanidins (HR = 0.66; 95% CI; 0.49−0.89) had significantly lower lung cancer incidence than those in the lowest quintile. Similar associations were not seen in never smokers. Isoflavone intake was inversely associated with overall cancer incidence (HR = 0.93, 95% CI: 0.86−1.00). This study provides further support for a beneficial effect of flavonoid intake on lung cancer risk, especially among current and past smokers.

Keywords

flavonoids; lung cancer; colorectal cancer; breast cancer; postmenopausal women

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In general, data from epidemiologic studies have supported an association between greater fruit and vegetable intake and a lower risk of cancer,[1] but it is unclear which bioactive compounds are responsible, or if the associations are a function of synergistic effects of the whole food.

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[2-4] Flavonoids are part of a large group of polyphenolic compounds found in foods of plant origin, including vegetables, fruits, legumes, tea and wine.[2,3] There are ~5,000 flavonoids, which are generally categorized into the following subclasses: flavonols, flavanones, flavones, flavan-3-ols, isoflavones and anthocyanidins.[4] Proanthocyanidins are another important but often overlooked polyphenol subclass.[5] The lower risk of cancer seen with greater fruit and vegetable intake may be explained through multiple biological effects of flavonoids including antioxidant activity, inflammation inhibition, antimutagenic and antiproliferative properties, and involvement in cell signaling, cell cycle regulation and angiogenesis.[2-4] Although data from *in vitro* studies and animal models suggest that flavonoids have the ability to influence important cellular and molecular mechanisms related to carcinogenesis, data from human populations are limited and inconclusive.[4]

The association between flavonoid intake and risk of several cancers has been studied, but the most consistent findings have been for a reduced risk of lung cancer.[2,4,6-12] Associations between flavonoid intake and risk of other cancers are less consistent. Several studies report a lower risk of colorectal,[13,14] rectal[15] or breast cancer[16,17] with greater flavonoid intake, while others have found no statistically significant associations.[7-9,15,18,19] Significant inverse associations have been reported between flavonoid intake and pancreatic cancer risk,[20] and flavonoid intake and upper aerodigestive cancer risk.[21-24] An earlier analysis in the Iowa Women's Health Study also reported inverse associations between flavonoid intake and pancreatic and upper aerodigestive cancer, although both were nonsignificant.[15] The inconsistency seen in studies examining flavonoid intake and cancer risk may be attributed to differences in the various nutrient databases used across studies, each with incomplete information on flavonoid content in foods. Recently, the US Department of Agriculture (USDA) released 2 new databases, providing more complete information on flavonoid concentrations in foods than was previously available.[25,26]

The purpose of the current analysis was to examine the associations between flavonoid intake (total flavonoids and the following subclasses: flavonols, flavanones, flavones, flavan-3-ols, isoflavones, anthocyanidins and proanthocyanidins) and cancer incidence (total and breast, colorectal, lung, pancreatic and upper aero-digestive) in a large prospective cohort study of postmenopausal women using recently available nutrient composition information. Our hypothesis was that higher intake of total flavonoids and each flavonoid subclass would be associated with a lower risk of cancer. Likewise, we hypothesized that consumption of foods with high flavonoid content would be inversely related to risk of cancer.

Material and methods

Study design and population

The Iowa Women's Health Study (IWHS) is a prospective cohort study designed to examine the relation of lifestyle factors with cancer. In 1986, a mailed questionnaire was sent to 99,826 women between the ages of 55 and 69 years randomly drawn from the 1985 Iowa Department of Transportation list of licensed drivers. 41,836 women responded to the baseline questionnaire (42% response rate). Subjects were followed through 5 follow-up questionnaires (1987, 1989, 1992, 1997, 2004), and vital status was obtained through linkage to Iowa death records and the National Death Index.

Data collection

The baseline questionnaire collected information on education, physical activity, individual medical history and family cancer history, anthropometric variables, reproductive health and smoking history. Participants also completed a 127-item food frequency questionnaire (FFQ) developed and validated by Willett and coworkers,[27,28] with reliability and validity demonstrated in the IWHS.[29] The FFQ asked participants to report average consumption over the past year, including the following flavonoid-containing foods: fruit (15 items), vegetables (29 items), tea, chocolate and red wine. Although some important sources of flavonoids in the diet were not specifically included (e.g., onions and berries other than blueberries and strawberries), women were asked to report foods regularly eaten that were not included on the FFQ, and a few did so. A common unit or portion size was specified for each food, and response options ranged from "never or less than once per month" to "six or more times per day." The questionnaire also assessed the use of multivitamins and single vitamin and mineral supplements. Daily intakes of nutrients were calculated using the Harvard Nutrient Database.

The development of the dietary flavonoid intake variables for analysis in IWHS is described in detail elsewhere.[30] Briefly, the flavonoid content of food items in the FFQ were determined from 3 flavonoid food composition databases developed by the USDA Nutrient Data Laboratory (NDL).[25,26,31] These databases include values for the following flavonoid classes: anthocyanidins, flavones, flavanones, flavonols, flavan-3-ols (monomers), isoflavones and proanthocyanidins (condensed tannins or flavan-3-ol polymers). Total proanthocyanidins include proanthocyanidins and flavan-3-ols. To calculate the flavonoid content of each participant's diet, the reported consumption frequency of each food as assessed by the responses on the FFQ was multiplied by the flavonoid content of each food. FFQ questions that asked about intake of multiple foods (e.g., fresh apples or pears) were assigned a value weighted according to the mean per capita consumption of each food in 1986 (baseline of IWHS).[32] In the absence of such data, the USDA's Continuing Survey of Food Intake by Individuals was used.[33] Foods that contained several ingredients (mixed dishes) were assigned a weighted value based on a USDA standard recipe.

Data on weight and body dimensions were self-reported.[34] Body mass index was used as a measure of relative weight, and was calculated as weight (kg) divided by the square of height (m^2). History of screening mammography was assessed as part of the 1989 follow-up questionnaire. Physical activity level was categorized into 3 levels based on responses to questions assessing moderate and vigorous activity.[35]

Incident cases of cancer were identified between 1986 and 2004 through linkage to the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology and End Results program (SEER). Person-years of follow-up were calculated from baseline until the first of one of the following 5 outcomes: date of cancer diagnosis, date of death (if death occurred in Iowa), midpoint of the interval between the date of last contact and date of death (if death occurred outside of Iowa), date of emigration from Iowa (if known), midpoint of the interval between the last follow-up contact and December 31, 2004 (if date of emigration from Iowa not known). All others contributed follow-up time until December 31, 2004.

Statistical analysis

For the analyses reported herein we excluded women who reported any cancer other than non-melanoma skin cancer at baseline (n = 3,830) or who were pre-menopausal at baseline (n = 569). Also, women were excluded if they left 30 or more food items blank on the food frequency questionnaire, or had a total energy intake less than 600 kcal/day or more than 5000 kcal/day (n = 2,712). Exclusion categories were not mutually exclusive. A sensitivity analysis was performed excluding participants diagnosed with cancer within the first 2 years after dietary assessment. Results were not significantly altered, and thus, these participants were included in the analysis.

Total daily flavonoid intake and intake of each flavonoid subclass (except anthocyanidins) were categorized into quintiles. Because of a skewed distribution and low intake in the majority of women, anthocyanidin intake was modeled as a 3-level variable (zero intake, < median, ≥

median). Selected baseline characteristics were examined according to total flavonoid intake quintiles. Cox proportional hazards regression (Proc PHREG, SAS institute, version 8.2), was used to estimate hazard ratios for all cancer, lung cancer, colorectal cancer, breast cancer, pancreatic cancer and upper aerodigestive cancer according to baseline flavonoid intake using the lowest category as the referent. Upper aerodigestive cancers included esophageal, oropharyngeal and nasopharyngeal/salivary cancers. For all analyses, cancer cases were restricted to the earliest primary cancer. Tests for trend across flavonoid intake categories were performed by assigning each category its median flavonoid intake value and treating the variable as a continuous term in the model.

Hazard ratios were also estimated according to intake of specific foods and food groups that are high in flavonoids including the following: fresh apples and pears, berries (strawberries, blueberries and other reported berries), raisins and grapes, broccoli, bran added to foods, citrus fruits and juices (grapefruits, grapefruit juice, oranges, orange juice), soy, chocolate, tea and red wine. Hazard ratios for cancer were calculated according to intake frequency categories of each food/food group with the lowest category as the referent, and varied depending on the spread of the data (<1 time/week *vs.* ≥1 time/week for berries, raisins/grapes, broccoli, bran, soy, chocolate, tea, red wine; <1 time/week, 1−3 times/week and >3 times/week for apples and pears; <4 times/week, 4−8 times/week and >8 times/week for citrus fruits and juices). In addition, hazard ratios were estimated according to intake of flavonoid-rich food groups. Food groups were formed by adding servings per week of the highest flavonoid containing foods for selected flavonoids and intake was categorized into quintiles. Hazard ratios for lung cancer were estimated using the lowest flavonoid-rich food group category as the referent.

Stratified analyses were also performed to examine if smoking history modified the association between flavonoid intake and cancer risk. Tests for interaction between smoking history (ever smoker *vs.* never smoker) and intake of total flavonoids and each flavonoid subclass (all categorized into quintiles except the 3-level variable used for anothcyanidins) were performed by adding a cross-product term to the multivariable model. A χ^2 test for interaction was used to calculate *p*-values.

Potential confounding factors were included in the model if they had biological relevance, had been previously shown and established as a risk factor for the specific cancer, or if they notably altered the association between total flavonoid intake and cancer risk. In model 1, we adjusted for age at baseline (years) and daily energy intake (kcal/day). The multivariable model (model 2) included age, daily energy intake, education category (< high school, =high school, > high school), race (white/nonwhite), BMI (kg/m^2), multivitamin use (yes/no), activity level (low, medium, high), smoking history (ever/never), and pack years (0, 1−19, 20−39 and 40+). Analyses for breast cancer also included first degree relative with breast cancer (yes/no), menopausal estrogen use (ever/never), parity (0, 1−2, 3−4 and 5+), age at first live birth (<20, 20−24, 25−29 and 30+), and mammogram history (prior to 1989, yes/no/missing) as covariates. Analyses for colorectal cancer included first degree relative with colon cancer (yes/no), NSAID use (yes/no), and menopausal estrogen use (ever/never) as covariates. Adjusting for additional dietary variables (total fat, fiber, folate, carotenoids, dairy, alcohol and red meat) did not appreciably alter risk estimates, and therefore, these variables were not included in the final model (data not shown). In addition, adjusting the analysis of each flavonoid subclass for intake of the other flavonoid subclasses did not appreciably alter risk estimates, and therefore, these variables were also not included in the final model (data not shown).

Results

A total of 34,708 women met the eligibility criteria for this analysis. Demographic and lifestyle characteristics of the study participants by quintile of total flavonoid intake are presented in

Table I. Age, BMI, energy intake, education, physical activity level, multivitamin use, smoking history and pack years of smoking were significantly associated with flavonoid intake ($p < 0.01$). The median intake of total flavonoids was 239.2 mg/day, with a range of 0.6–3,524.4 mg/day.

Although women in the highest quintile of total flavonoid intake had a 12% lower incidence of any cancer compared to women in the lowest quintile in age and energy adjusted models, this association was no longer observed after multivariable adjustment (Table II). Similar results were observed for flavanones, flavonols, flavan-3-ols, proanthocyanidins and total proanthocyanidins. After multivariable adjustment, only isoflavone intake was associated with a modestly reduced incidence of any cancer, with women in the highest quintile of intake having a 7% lower incidence compared to those in the lowest quintile, but this association was of borderline significance (HR = 0.93; 95% CI: 0.86–1.00, *p* for trend across quintiles = 0.03).

After multivariable adjustment, women in the highest quintile of flavanone intake had a 32% lower incidence of lung cancer compared to women in the lowest quintile of intake (HR = 0.68; 95% CI: 0.53–0.86, *p*-trend = <0.01). Lung cancer incidence was 25% lower for women in the highest quintile of proanthocyanidin intake compared to women whose intake placed them in the lowest quintile (HR = 0.75; 95% CI: 0.57–0.97, *p*-trend = 0.12).

In multivariable-adjusted analyses stratified by smoking history, no statistically significant associations between flavonoids and lung cancer were observed among those who had never smoked (Table III). In contrast, among current and past smokers statistically significant inverse associations were observed for lung cancer incidence in women in the highest quintile versus lowest quintile of flavanone intake (HR = 0.66; 95% CI: 0.50–0.86, *p*-trend = <0.01, *p* for interaction = 0.18) and proanthocyanidin intake (HR = 0.66; 95% CI: 0.49–0.89, *p*-trend = 0.04, *p* for interaction = 0.04).

We also examined the relative incidence of breast, pancreatic, upper aerodigestive and colorectal cancer by total flavonoid intake and flavonoid subclass intake. No significant observations were observed. In multivariable-adjusted analyses stratified by smoking history, no statistically significant associations were observed between total flavonoid intake and incidence of breast, colorectal, upper aerodigestive, pancreatic or any cancer among current and past smokers or among never smokers.

When stratified by smoking history, intake of soy, bran, red wine, chocolate, all berries, tea, raisins/grapes and apples were not associated with incidence of all cancers or lung cancer after multivariable adjustment. However, for citrus fruits and juices, current and past smokers who reported eating 8 or more servings per week had a 27% lower incidence of lung cancer compared to current and past smokers who reported eating less than 4 servings of citrus per week (HR = 0.73; 95% CI: 0.60–0.89, *p*-trend = <0.01, *p* for interaction = 0.03) (Table IV). No significant association between citrus fruit and juice intake and lung cancer incidence was observed in never smokers. Current and past smokers who reported eating 8 or more servings of citrus fruits and juices per week had a 8% lower incidence of any cancer compared to current and past smokers who reported eating less than 4 servings per week (HR = 0.92; 95% CI: 0.84–1.01, *p*-trend = 0.08, *p* for interaction = 0.73), and never smokers who reported eating 8 or more servings per week had an 7% lower incidence when compared to never smokers eating less than 4 serving per week (HR = 0.93; 95% CI:0.87–1.00, *p*-trend = 0.06).

Associations between intake of the flavonoid-rich food groups and lung cancer incidence were similar to the results found for the quantitative flavonoids. In multivariable-adjusted analyses stratified by smoking history, past and current smokers within the highest quintile of intake of the flavanone-rich food group had a statistically significant reduction in lung cancer incidence compare to past and current smokers in the lowest quintile of intake (HR = 0.64; 95% CI: 0.49

−0.84, *p*-trend = <0.01, *p* for interaction = 0.08). No statistically significant associations between flavonoid-rich food groups and lung cancer incidence were observed among those who had never smoked. Correlations between the flavonoid-rich food groups and the corresponding quantitative flavonoids were high (*r* = 0.94 for flavanones).

Discussion

In our study of predominately white, postmenopausal women, we observed a statistically significant inverse association between dietary intake of isoflavones and incidence of all cancers. We observed inverse associations between dietary intake of flavanones and proanthocyanidins and incidence of lung cancer in women who were current or former smokers, but not among women who were never smokers. Highest versus lowest intake of citrus fruits and juices, major contributors to the flavanones subclass, resulted in a 28% lower risk of lung cancer in past and current smokers, but was not significantly associated with risk in never smokers. A nonsignificant inverse association was also observed between intake of citrus fruits and juices and incidence of all cancers in past, current and never smokers. Highest versus lowest intake of the food group summarizing foods that are rich in flavanones resulted in a reduced incidence of lung cancer in past and current smokers, but not in never smokers, similar to the results seen with the quantitative flavonoids. Therefore these data directly indicate that a food group high in flavonoids might protect against lung cancer in past and current smokers. Purified supplemental flavonoids might also be helpful, but this could not be examined in the current study. The flavanone-rich food group included grapefruit, oranges, grapefruit juice, orange juice, other fruit juices, lemons and lemon juice concentrate.

Other studies have also reported inverse associations between intake of flavanones, proanthocyanidins and isoflavones and cancer risk. Increased flavanone intake was associated with a decreased risk of oral and pharyngeal cancer, laryngeal cancer and squamous cell esophageal cancer[22-24], while increased proanthocyanidin and isoflavone intake have been associated with a decreased risk of colorectal cancer.[13,14] Several studies have reported statistically significant inverse association between intake of flavonoids and lung cancer risk. Similar to our results, 2 case-control studies found a lower risk of lung cancer with a higher intake of citrus fruits.[6,10] De Stefani *et al*.[6] reported that higher intake of oranges resulted in a lower risk of lung cancer in both men and women. Le Marchand *et al*.[10] reported higher intake of white and pink grapefruit resulted in a lower risk of lung cancer, although their study only included men. Various case-control and prospective cohort studies have reported a decreased risk of lung cancer with higher intake of flavonols, quercetin (a specific flavonol compound), or quercetin-rich foods like onions and apples.[6-10,12] We did not find a significant association between apple intake or flavonol intake and risk of lung cancer. The lack of association between cancer incidence and flavonol intake in our study may be partly due to the fact that intake of onions, a major source of quercetin, was not queried by our food frequency questionnaire.

One of the most serious problems with studies examining the association between flavonoid intake and lung cancer risk to date has been residual confounding by smoking status, and studies examining associations in lifelong never smokers along with past and current smokers are the most effective way to rule out spurious associations.[2] To our knowledge, only 2 other studies have examined the association of flavonoid intake and lung cancer risk in smokers and nonsmokers separately, while another 2 studies have examined associations in smokers only. In a case-control study focusing solely on dietary phytoestrogens (including isoflavones), Schabath *et al*.[11] reported a reduced risk of lung cancer with higher intake of total isoflavones compared to lower intake among both current smokers and those who have never smoked. In this study no significant association was observed in former smokers. In a prospective study of Finnish men and women, Knekt *et al*.[8] reported a reduced risk of lung cancer in men and women reporting the highest intake of total flavonoids compared to those who reported the lowest intake (‘total’ including the flavonol compounds quercetin, kaempferol, myricetin and the flavone compounds luteolin and apigenin), but when stratified by smoking status, a reduced risk was observed among nonsmokers only. Two other prospective studies have examined flavonoid intake and lung cancer risk in cohorts of male smokers.[7,12] One study reported that male smokers in the highest quartile of flavonol and flavone intake had a 44% reduction in lung cancer risk compared to male smokers in the lowest quintile.[7] In the other, male smokers in the highest quintile of an antioxidant index (based on intake of the flavan-3-ol compounds catechins, epicatechins, kaempferol and the flavonol compounds myricetin and quercetin) had a 16% decreased risk of lung cancer compared to male smokers in the lowest quintile.[12]

The observed inverse associations between flavonoid intake and cancer risk may be explained by their influence on a variety of biological functions.[4] In animal models and in vitro systems, flavonoids have been shown to scavenge free-radicals, modulate enzymatic activity, induce apoptosis and inhibit inflammation, cellular proliferation and angiogenesis.[2-4] The function of flavonoids as antioxidants may explain the reduction of lung cancer risk seen in smokers in this study since smoking increases oxidative stress.[20,36] Some evidence suggests flavonoid intake may be related to events early in the carcinogenesis pathway, highlighting the importance of cohort studies that assess dietary intake many years prior to cancer diagnosis.[4]

Limitations of this study must be considered. Exposure measurement error is an important limitation of all flavonoid studies, including ours, that rely on data from a single FFQ because of underreporting of dietary intake or missing information on certain flavonoid containing foods.[2] Unfortunately, for most flavonoid compounds there are no biomarkers that accurately reflect long-term exposure.[2] Furthermore, the flavonoid content and bioavailability of foods can be influenced by food preparation and processing, climate, sunlight, or season, contributing to the lack of consistency between study findings.[3,4] Another important limitation of this study was the lack of assessment of onion intake and limited assessment of intake of berries. Onions contain quercetin and both onions and berries are important contributors to the flavonoid subclass of flavonols, which has been most commonly associated with decreased risk of lung cancer at this point, although this may be due to the fact that it has been more frequently quantified and studied. In addition, the flavonoid content in foods presented in this paper does not include data from an updated USDA flavonoid database released in January 2007.[37] We also had limited power to detect associations between flavonoid intake and pancreatic and upper aerodigestive cancer, along with lung cancer in never smokers, because of the small number of cases in this cohort. Strengths of the current study include its large size, prospective design, the relative comprehensiveness of the flavonoid data in our nutrient database, and the virtually complete follow-up of the cohort for cancer incidence.

In conclusion, this study provides further support for a beneficial effect of flavonoid intake on risk of lung cancer, perhaps most notably in women who formerly or currently smoke. Further studies are needed that take advantage of the more complete databases now available, and consider the possible protective factors (other than flavonoids) that might be present in plant foods.

Acknowledgements

The authors thank Dr. Aaron R. Folsom for providing access to the Iowa Women's Health Study data, and Ms. Ching Ping Hong for statistical consultation and assistance in data preparation prior to analysis.

Grant sponsor: National Cancer Institute; Grant number: R01 CA039742; Grant sponsor: International Life Sciences Institute (ILSI).

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TABLE I

SELECT BASELINE DEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS ALONG WITH CANCER CASES DIAGNOSED BETWEEN 1986 AND 2004 ACCORDING TO QUINTILE OF TOTAL FLAVONOID INTAKE IN 34,708 POSTMENOPAUSAL WOMEN IN THE IOWA WOMEN'S HEALTH STUDY

	Overall	Quintile of total flavonoid intake					p for trend[1]
		1	2	3	4	5	
N	34,708	6941	6942	6942	6942	6941	
Median intake (mg/d)	239.2	91.0	167.5	240.1	342.8	680.0	
Intake range (mg/d)	0.6−3524.4	0.6−133.6	133.6−201.7	201.7−282.0	282.0−425.2	425.3−3524.4	
Age (years)[2]	61.6 ± 4.2	61.2 ± 4.1	61.4 ± 4.2	61.6 ± 4.2	61.8 ± 4.2	61.8 ± 4.2	<0.01
BMI (kg/m^2)	27.0 ± 5.1	27.0 ± 5.2	27.1 ± 5.1	27.1 ± 5.1	27.0 ± 5.0	26.8 ± 5.0	<0.01
Energy intake (kcal/d)[2]	1799 ± 607	1470 ± 484	1679 ± 509	1824 ± 552	1953 ± 581	2069 ± 698	<0.01
Ethnicity (%)							
White	99.2	99.4	99.2	99.3	99.1	99.0	
Other	0.8	0.6	0.8	0.7	0.9	1.0	<0.01
Physical activity (%)							
Low	47.5	59.8	50.5	44.8	42.1	40.4	
Moderate	27.5	23.0	27.7	29.2	29.2	28.5	
High	25.0	17.3	21.8	26.1	28.7	31.1	<0.01
Education (%)							
<High school	18.1	21.1	17.7	17.0	17.2	17.4	
=High school	42.1	45.9	44.3	42.4	39.6	38.1	
>High school	39.8	33.0	38.0	40.6	43.2	44.5	<0.01
Smoking status (%)							
Never	65.6	54.9	64.2	68.7	71.1	69.2	
Ever	34.4	45.1	35.8	31.3	28.9	30.8	<0.01
Pack yrs of smoking (%)							
0	66.2	55.5	64.7	69.2	71.6	69.8	
1−19	13.6	13.6	13.8	13.2	13.2	14.1	
20−39	11.4	16.4	12.1	10.6	9.1	9.0	
40+	8.8	14.5	9.4	7.0	6.1	7.1	<0.01
Multivitamin use (%)							
No	66.7	71.4	68.3	66.6	64.3	62.9	
Yes	33.3	28.6	31.7	33.4	35.7	37.1	<0.01
All cancer (cases)	7534	1582	1559	1487	1442	1464	
Lung cancer (cases)	849	266	169	150	119	145	
Breast cancer (cases)	2529	491	506	497	501	534	
Colorectal cancer (cases)	1292	277	271	257	249	238	
Pancreatic cancer (cases)	230	34	49	54	43	50	
Upper aerodigestive cancer (cases)[3]	138	35	34	16	31	22	

[1] Tests for trend across intake categories were performed by assigning each quintile its median intake value and treating the variable as a linear term.

[2] Mean ± SD.

[3] Includes esophageal, oropharyngeal, and nasopharyngeal/salivary cancer.

TABLE II

RELATIVE RISKS (RR) OF CANCER ACCORDING TO QUINTILE OF FLAVONOID INTAKE IN 34,708 POSTMENOPAUSAL WOMEN IN THE IOWA WOMEN'S HEALTH STUDY

	Quintile of flavonoid intake					*p* for trend[1]
	1	2	3	4	5	
Total flavonoids						
Mean intake (mg/d)	91.0	167.5	240.1	342.8	680.0	
Intake range (mg/d)	0.6–133.6	133.6–201.7	201.7–282.0	282.0–425.2	425.3–3524.4	
Cases	1582	1559	1487	1442	1464	
Person-years	104,591	104,729	105,804	106,309	105,358	
Age + energy[2]	1.0 (reference)	0.97 (0.90–1.04)	0.90 (0.84–0.97)	0.86 (0.80–0.93)	0.88 (0.82–0.95)	<0.01
Multivariate[3]	1.0 (reference)	1.04 (0.96–1.11)	0.99 (0.92–1.07)	0.96 (0.89–1.04)	1.00 (0.92–1.08)	0.65
Isoflavones						
Mean intake (mg/d)	0.07	0.16	0.25	0.33	1.83	
Intake range (mg/d)	0–0.13	0.13–0.23	0.23–0.27	0.27–0.51	0.52–107.8	
Cases	1528	1551	1519	1515	1421	
Person-years	104,362	104,888	105,742	105,904	105,896	
Age + energy[2]	1.0 (reference)	1.00 (0.93–1.07)	0.97 (0.90–1.04)	0.96 (0.89–1.03)	0.90 (0.83–0.97)	<0.01
Multivariate[3]	1.0 (reference)	1.00 (0.93–1.08)	0.99 (0.92–1.07)	1.00 (0.92–1.07)	0.93 (0.86–1.00)	0.03
Anthocyanidins[3]						
Mean intake (mg/d)	0	0.02	5.8			
Intake range (mg/d)	-	0.005–0.1	0.1–1040.0			
Cases	2588	2555	2391			
Person-years	180,349	172,594	173,849			
Age + energy[2]	1.0 (reference)	1.03 (0.98–1.09)	0.96 (0.91–1.02)			0.04
Multivariate[3]	1.0 (reference)	1.02 (0.97–1.08)	0.97 (0.92–1.03)			0.12
Flavones						
Mean intake (mg/d)	0.11	0.26	0.40	0.80	1.75	
Intake range (mg/d)	0–0.19	0.19–0.32	0.32–0.51	0.51–0.96	0.96–42.7	
Cases	1519	1527	1521	1512	1455	
Person-years	105,081	105,401	105,509	105,581	105,220	
Age + energy[2]	1.0 (reference)	1.00 (0.93–1.08)	1.00 (0.93–1.07)	0.99 (0.92–1.06)	0.95 (0.88–1.02)	0.10
Multivariate[3]	1.0 (reference)	1.00 (0.93–1.08)	0.99 (0.92–1.07)	0.98 (0.91–1.06)	0.94 (0.87–1.02)	0.09
Flavanones						
Mean intake (mg/d)	7.4	26.0	41.0	60.7	107.2	
Intake range (mg/d)	0–15.9	15.9–34.0	34.0–49.8	49.8–73.2	73.2–833.2	
Cases	1589	1565	1485	1468	1427	
Person-years	104,328	105,465	106,193	105,500	105,306	
Age + energy[2]	1.0 (reference)	0.96 (0.90–1.03)	0.90 (0.84–0.97)	0.89 (0.83–0.96)	0.86 (0.80–0.93)	<0.01
Multivariate[3]	1.0 (reference)	1.01 (0.94–1.08)	0.96 (0.89–1.03)	0.96 (0.90–1.04)	0.95 (0.88–1.02)	0.10
Flavonols						
Mean intake (mg/d)	3.9	6.6	8.9	12.2	23.2	
Intake range (mg/d)	0.2–5.4	5.4–7.7	7.7–10.3	10.3–14.6	14.6–125.5	
Cases	1561	1503	1492	1517	1461	
Person-years	104,253	106,418	105,902	105,172	105,047	
Age + energy[2]	1.0 (reference)	0.94 (0.88–1.01)	0.93 (0.87–1.00)	0.95 (0.88–1.02)	0.92 (0.85–0.99)	0.10
Multivariate[3]	1.0 (reference)	0.96 (0.89–1.03)	0.97 (0.89–1.03)	1.02 (0.94–1.10)	0.97 (0.90–1.05)	0.86
Flavan-3-ols						
Mean intake (mg/d)	4.1	10.2	21.0	60.7	314.6	
Intake range (mg/d)	<0.001–6.7	6.7–15.0	15.0–29.2	29.2–134.8	134.8–1051.6	
Cases	1603	1535	1455	1461	1480	
Person-years	104,402	104,741	106,086	106,280	105,282	
Age + energy[2]	1.0 (reference)	0.94 (0.88–1.01)	0.88 (0.82–0.95)	0.88 (0.82–0.95)	0.90 (0.84–0.97)	0.06

	Quintile of flavonoid intake					p for trend[1]
	1	2	3	4	5	
Multivariate[3]	1.0 (reference)	0.96 (0.89−1.03)	0.97 (0.90−1.05)	1.02 (0.94−1.10)	0.97 (0.90−1.05)	0.55
Proanthocyanidins						
Mean intake (mg/d)	45.6	87.5	125.3	174.7	365.1	
Intake range (mg/d)	0−69.4	69.4−105.8	105.8−146.2	146.2−211.2	211.2−2721.1	
Cases	1573	1499	1529	1483	1450	
Person-years	103,841	105,577	105,516	105,784	106,074	
Age + energy[2]	1.0 (reference)	0.93 (0.86−0.99)	0.94 (0.87−1.01)	0.90 (0.84−0.97)	0.86 (0.80−0.93)	<0.01
Multivariate[3]	1.0 (reference)	0.96 (0.89−1.03)	1.02 (0.94−1.09)	1.00 (0.92−1.07)	0.98 (0.90−1.06)	0.86
Total Proanthocyanidins						
Mean intake (mg/d)	58.2	116.7	175.9	267.0	591.0	
Intake range (mg/d)	<0.001−89.5	89.5−143.8	143.8−212.2	212.2−342.7	342.7−3225.6	
Cases	1550	1551	1529	1426	1478	
Person-years	104,408	105,183	105,113	106,375	105,712	
Age + energy[2]	1.0 (reference)	0.98 (0.91−1.05)	0.95 (0.89−1.02)	0.87 (0.80−0.93)	0.91 (0.84−0.98)	<0.01
Multivariate[3]	1.0 (reference)	1.03 (0.96−1.10)	1.04 (0.97−1.12)	0.95 (0.89−1.03)	1.01 (0.94−1.03)	0.88

[4]Because of skewed distribution, anthocyanidins were categorized as a 3-level variable (zero intake, < median, ≥ median).

[1]Tests for trend across intake categories were performed by assigning each quintile its median intake value and treating the variable as a linear term.

[2]Adjusted for age (years) and energy (kcal/day).

[3]Adjusted for above variables plus education level (<high school; =high school; >high school), race (white/nonwhite), BMI (kg/m^2), multivitamin use (yes/no), activity level (low, medium, high), smoking history (ever/never), and pack years (0, 1−19, 20−39, 40+).

TABLE III

RELATIVE RISKS (RR) OF LUNG CANCER ACCORDING TO QUINTILE OF FLAVONOID INTAKE IN 34,708 POSTMENOPAUSAL WOMEN IN THE IOWA WOMEN'S HEALTH STUDY STRATIFIED BY SMOKING STATUS

	Quintile of Flavonoid Intake					*p* for trend[1]
	1	2	3	4	5	
Total Flavonoids						
Never smokers						
Cases	15	21	26	25	26	
Person-years	63,643	74,035	79,723	81,774	79,278	
Multivariate[2]	1.0 (reference)	1.14 (0.59−2.22)	1.27 (0.66−2.43)	1.17 (0.60−2.27)	1.19 (0.60−2.34)	0.80
Ever smokers						
Cases	222	137	107	80	101	
Person-years	47,323	37,702	33,093	30,767	32,468	
Multivariate[2]	1.0 (reference)	0.88 (0.71−1.10)	0.91 (0.71−1.15)	0.73 (0.55−0.96)	0.90 (0.70−1.16)	0.39
Flavanones						
Never smokers						
Cases	20	20	25	25	23	
Person-years	65,566	74,557	79,086	79,373	79,871	
Multivariate[2]	1.0 (reference)	0.84 (0.45−1.56)	0.96 (0.53−1.74)	0.91 (0.50−1.66)	0.85 (0.46−1.58)	0.70
Ever smokers						
Cases	236	140	104	85	82	
Person-years	45,382	37,664	33,744	32,807	31,756	
Multivariate[2]	1.0 (reference)	0.84 (0.68−1.04)	0.78 (0.61−0.98)	0.70 (0.54−0.91)	0.66 (0.50−0.86)	<0.01
Proanthocyanidins						
Never smokers						
Cases	15	20	22	28	28	
Person-years	64,475	72,225	77,815	81,774	82,166	
Multivariate[2]	1.0 (reference)	1.15 (0.59−2.25)	1.15 (0.59−2.24)	1.31 (0.68−2.53)	1.32 (0.67−2.61)	0.44
Ever smokers						
Cases	209	133	123	112	70	
Person-years	45,800	40,179	34,093	30,970	30,311	
Multivariate[2]	1.0 (reference)	0.79 (0.63−0.99)	0.95 (0.75−1.19)	1.03 (0.81−1.32)	0.66 (0.49−0.89)	0.04
Isoflavones						
Never smokers						
Cases	18	31	18	27	19	
Person-years	67,032	74,349	77,335	80,760	78,978	
Multivariate[2]	1.0 (reference)	1.48 (0.82−2.65)	0.78 (0.40−1.51)	1.13 (0.61−2.09)	0.80 (0.41−1.58)	0.19
Ever smokers						
Cases	153	135	132	112	115	
Person-years	43,539	37,930	34,842	31,881	33,162	
Multivariate[2]	1.0 (reference)	1.03 (0.82−1.31)	1.09 (0.86−1.38)	1.08 (0.83−1.40)	1.03 (0.80−1.34)	0.91
Flavones						
Never smokers						
Cases	26	21	28	19	19	
Person-years	76,031	76,262	75,300	77,724	73,136	
Multivariate[2]	1.0 (reference)	0.75 (0.42−1.34)	1.01 (0.59−1.74)	0.65 (0.35−1.18)	0.66 (0.36−1.23)	0.16
Ever smokers						
Cases	152	133	133	109	120	
Person-years	35,604	35,735	36,544	35,069	38,402	
Multivariate[2]	1.0 (reference)	0.97 (0.76−1.23)	1.05 (0.82−1.34)	0.89 (0.69−1.15)	1.00 (0.78−1.30)	0.85
Flavonols						
Never smokers						
Cases	19	19	24	27	24	

	Quintile of Flavonoid Intake					p for trend[1]
	1	2	3	4	5	
Person-years	70,241	76,070	76,640	78,483	77,020	
Multivariate[2]	1.0 (reference)	0.87 (0.46−1.65)	1.08 (0.58−1.99)	1.11 (0.60−2.06)	1.05 (0.55−1.99)	0.75
Ever smokers						
Cases	179	142	109	98	119	
Person-years	40,879	36,576	35,974	33,586	34,338	
Multivariate[2]	1.0 (reference)	0.93 (0.74−1.17)	0.82 (0.64−1.05)	0.90 (0.69−1.16)	1.00 (0.78−1.29)	0.79
Flavan-3-ols						
Never smokers						
Cases	16	27	19	29	22	
Person-years	66,790	75,398	77,217	80,353	78,694	
Multivariate[2]	1.0 (reference)	1.41 (0.75−2.64)	0.96 (0.49−1.89)	1.40 (0.75−2.62)	1.04 (0.54−2.02)	0.81
Ever smokers						
Cases	188	137	123	82	117	
Person-years	44,044	35,804	35,529	32,886	33,090	
Multivariate[2]	1.0 (reference)	1.01 (0.80−1.26)	0.96 (0.76−1.22)	0.73 (0.55−0.96)	1.07 (0.85−1.36)	0.76
Anthocyanidins[3]						
Never smokers						
Cases	34	41	38			
Person-years	135,742	121,661	121,051			
Multivariate[2]	1.0 (reference)	1.29 (0.82−2.04)	1.15 (0.71−1.85)			1.00
Ever smokers						
Cases	243	224	180			
Person-years	55,529	61,880	63,944			
Multivariate[2]	1.0 (reference)	0.93 (0.77−1.12)	0.83 (0.67−1.01)			0.10
Total Proanthocyanidins						
Never smokers						
Cases	12	22	28	29	22	
Person-years	64,103	73,418	79,304	82,255	79,373	
Multivariate[2]	1.0 (reference)	1.39 (0.73−2.65)	1.45 (0.78−2.72)	1.42 (0.76−2.68)	1.12 (0.57−2.21)	0.82
Ever smokers						
Cases	194	148	121	78	106	
Person-years	46,625	38,458	33,078	30,387	32,805	
Multivariate[2]	1.0 (reference)	0.94 (0.76−1.18)	1.07 (0.85−1.36)	0.70 (0.53−0.94)	1.00 (0.78−1.29)	0.95

[1] Tests for trend across intake categories were performed by assigning each quintile its median intake value and treating the variable as a linear term.

[2] Adjusted for age (years), energy (kcal/day), education level (<high school, = high school, > high school), race (white/non-white), BMI (kg/m^2), multivitamin use (yes/no), activity level (low, medium, high), and pack years (0, 1−19, 20−39, 40+).

[3] Because of skewed distribution, anthocyanidins were categorized as a 3-level variable (zero intake, < median, ≥ median).

TABLE IV

RELATIVE RISKS (RR) OF CANCER AND LUNG CANCER ACCORDING TO CATEGORY OF CITRUS FRUIT/ JUICE INTAKE 34,708 POSTMENOPAUSAL WOMEN IN THE IOWA WOMEN'S HEALTH STUDY STRATIFIED BY SMOKING HISTORY

	Servings of citrus fruit or juice per week			***p* for trend**[1]
	<4	**4−8**	**>8**	
All cancer				
Never smokers				
Cases	1554	1225	1668	
Person-years	119,628	96,730	135,464	
Multivariate[2]	1.0 (reference)	0.96 (0.89−1.04)	0.93 (0.87−1.00)	0.06
Ever smokers				
Cases	1322	780	892	
Person-years	70,458	43,019	54,512	
Multivariate[2]	1.0 (reference)	0.97 (0.89−1.07)	0.92 (0.84−1.01)	0.08
Lung Cancer				
Never smokers				
Cases	33	36	44	
Person-years	129,012	104,042	145,399	
Multivariate[2]	1.0 (reference)	1.26 (0.78−2.04)	1.12 (0.70−1.76)	0.61
Ever smokers				
Cases	354	136	157	
Person-years	75,843	46,609	58,901	
Multivariate[2]	1.0 (reference)	0.75 (0.61−0.92)	0.73 (0.60−0.89)	<0.01

[1] Tests for trend across intake categories were performed by assigning each quintile its median intake value and treating the variable as a linear term.

[2] Adjusted for age (years) and energy (kcal/day), education level (<high school, = high school, > high school), race (white/nonwhite), BMI (kg/m^2), multivitamin use (yes/no), activity level (low, medium, high), and pack years (0, 1−19, 20−39, 40+).