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A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer

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Flavonoids are antioxidant compounds found in plants, including fruits, vegetables and tea. No prior prospective studies have examined the association between intake of flavonoids in the flavonol and flavone subclasses and ovarian cancer risk. We analyzed the association between intake of 5 common dietary flavonoids and incidence of epithelial ovarian cancer among 66,940 women in the Nurses' Health Study. We calculated each participant's intake of myricetin, kaempferol, quercetin, luteolin and apigenin from dietary data collected at multiple time points, and used Cox proportional hazards regression to model the incidence rate ratio (RR) of ovarian cancer for each quintile of intake. Our analysis included 347 cases diagnosed between 1984 and 2002, and 950,347 person-years of follow-up. There was no clear association between total intake of the 5 flavonoids examined and incidence of ovarian cancer (RR = 0.75 for the highest *versus* lowest quintile, 95% confidence interval [CI] = 0.51–1.09). However, there was a significant 40% decrease in ovarian cancer incidence for the highest *versus* lowest quintile of kaempferol intake (RR = 0.60, 95% CI = 0.42–0.87; *p*-trend = 0.002), and a significant 34% decrease in incidence for the highest *versus* lowest quintile of luteolin intake (RR = 0.66, 95% CI = 0.49–0.91; *p*-trend = 0.01). There was evidence of an inverse association with consumption of tea (nonherbal) and broccoli, the primary contributors to kaempferol intake in our population. These data suggest that dietary intake of certain flavonoids may reduce ovarian cancer risk, although additional prospective studies are needed to further evaluate this association. If confirmed, these results would provide an important target for ovarian cancer prevention.

Key words: flavonoids; flavonols; flavones; diet; ovarian cancer

There are few lifestyle factors known to reduce ovarian cancer risk, and no dietary exposure, with the possible exception of lactose,[1] has been clearly associated with risk. Flavonoids are polyphenol chemicals found naturally in fruits, vegetables, tea and other plant-derived foods and beverages. Experimental evidence suggests that flavonoids have several potential anticarcinogenic characteristics, including antioxidant, antiestrogenic, antiproliferative and antiinflammatory properties.[2–5]

Flavonoids are defined by their chemical structure, which includes 2 aromatic rings (the "A" and "B" rings) linked by a three-carbon bridge that comprises part of a third six-member "C" ring.[6] There are over 5,000 individual flavonoid compounds and at least 10 subclasses of flavonoids, which are characterized further by the structure of the C ring and the connection of the B and C rings.[2,6,7] Flavonoids from 6 of these subclasses—flavones, flavonols, flavanols (catechins), flavanones, isoflavones and anthocyanidins—are common in the human diet.[2,7]

Three studies have previously evaluated the association between dietary flavonoid intake and ovarian cancer risk.[8–10] However, only one of these studies examined the association with nonisoflavone flavonoids. Although this study was suggestive of an inverse association, it was limited by the sample size, the availability of only a single, retrospective dietary assessment, and the analysis of only 2 flavonoids from a single flavonoid subclass. We therefore examined the association between intake of 5 common dietary flavonoids from the flavonol and flavone subclasses and ovarian cancer incidence in the Nurses' Health Study, a large prospective cohort with dietary information available from multiple time points over 18 years of follow-up.

Methods

Study population

In 1976, 121,701 female registered nurses responded to a mailed questionnaire about known and suspected risk factors for cancer and coronary heart disease, leading to the establishment of the Nurses' Health Study. All participants were married, resided in one of 11 U.S. states, and were between ages 30 and 55 at study enrollment. Participants completed follow-up questionnaires every 2 years, providing updated risk factor data and information on new diagnoses of disease. In 1984, 1990 and every 4 years thereafter, the questionnaire included a comprehensive, 126-item semiquantitative food frequency questionnaire (FFQ). We obtained follow-up information (a questionnaire response or reported death) for 98.7% of the total possible person-years through June 2002 for participants who completed the 1984 FFQ, who comprise the study population for our primary analysis. All study participants provided implied consent by completing and returning the baseline questionnaire, and the Institutional Review Board of Brigham and Women's Hospital, Boston, MA approved both the Nurses' Health Study and this analysis.

Ascertainment of flavonoid intake

Each FFQ requested the participant's average intake of a specified serving size of each food or beverage during the year prior to completion of the questionnaire, with 9 choices for the frequency of consumption ranging from never/almost never to 6 or more times per day. Additional details of the semiquantitative FFQ and its validation and reproducibility in this cohort are available elsewhere.[11–13] Although flavonoid intake has not been validated directly, comparisons of reported intake of foods and beverages from a 61-item FFQ and 28 days of diet records yielded corrected correlation coefficients of 0.93 for tea, 0.80 for apples, 0.69 for broccoli and 0.50 for beans/lentils, indicating that the FFQ adequately captures consumption of several of the primary contributors to flavonoid intake in our population.[13]

We used published and unpublished data on the flavonoid content of Dutch foods, supplemented with data for 15 foods and beverages purchased from supermarkets in the Boston area and

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analyzed for flavonoid content in the Netherlands, to create nutrient tables for each food and beverage of interest.[14,15] Using these nutrient tables and the FFQ data, we calculated each participant's intake of 3 flavonols (myricetin, kaempferol and quercetin) and 2 flavones (luteolin and apigenin) in 1984, 1990, 1994 and 1998. At each time point, we summed the intake values for the 5 individual flavonoids to obtain an estimate of total flavonoid intake for each participant. The 1984 FFQ did not include a question on consumption of onions, a major contributor to quercetin and total flavonoid intake. As a result, the 1984 flavonoid values use onion data from a 29-item dietary assessment included on the 1982 questionnaire.

Because of changes in the food items included on each FFQ and updated data on the flavonoid content of certain foods, the methods used to calculate flavonoid intake varied over time, particularly for luteolin and apigenin. In 1984 and 1990 the primary contributors to luteolin intake included several "other" food items selectively written in by participants who consumed these foods at least once per week; as a result there was little variation in luteolin intake in our study population at these time points. In 1994 and 1998 the variability in intake increased because of the addition of green peppers to the FFQ, although the mean intake of luteolin remained low. The calculation for apigenin intake changed in 1998 when we added celery, tomato sauce and pizza as contributors to the calculation, because of the availability of new data on the flavonoid content of these foods. Because information on consumption of these 3 foods was available for the earlier time periods, we recalculated the 1984, 1990 and 1994 apigenin values for this analysis by using the 1998 flavonoid content values with the earlier FFQ data. For the other flavonoids, where changes in the calculations over time were primarily because of the addition of new foods to the FFQ, we used the original flavonoid intake values calculated at the time the FFQ was processed.

Assessment of other covariates

The baseline questionnaire collected information on date of birth, age at menarche, age at first birth and height, which we used to calculate body mass index (BMI) for each follow-up cycle. Each questionnaire included questions on menopausal status, age at menopause, postmenopausal hormone use, hysterectomy, oophorectomy, smoking status and current weight. In our analysis, we updated the values for these covariates with each questionnaire cycle until the end of follow-up. For the other covariates of interest, for which questions were included on multiple but not all questionnaires, we updated the value for each covariate when new information was available from subsequent questionnaires and otherwise carried forward the value from the previous follow-up cycle. Oral contraceptive use was included on every questionnaire until 1982, at which time oral contraceptive use was uncommon due to the age distribution of our cohort. We assessed parity on every questionnaire until 1984, and history of tubal ligation on every questionnaire from 1976 to 1982 and again in 1994. Most questionnaires between 1980 and 2000 included questions on physical activity, with the exception of the 1984 and 1990 questionnaires. Because data on physical activity are not available from 1984, we used the data from 1982 for the follow-up period from 1984 to 1986. We assessed family history of ovarian cancer in a first-degree relative in 1992, 1996 and 2000.

Identification of ovarian cancer cases

We collected information on diagnoses of ovarian cancer on each questionnaire. For all reported ovarian cancer diagnoses, as well as deaths due to ovarian cancer identified through family members, the U.S. National Death Index, or the U.S. Postal Service, Nurses' Health Study researchers contacted the study participant or their family to request permission to obtain pathology reports and other medical records related to the diagnosis. An estimated 98% of all deaths in the Nurses' Health Study cohort are captured through the U.S. National Death Index.[16,17] A gynecologic pathologist (J.L.H.) blinded to the participant's exposure status reviewed the medical records to confirm the diagnosis, stage, histologic type and subtype and degree of invasiveness for each case. Our analysis included all epithelial ovarian cancer cases diagnosed between 1984 and June 2002 and confirmed by pathology report review. A validation study comparing pathology reports to a standardized review of slides (by J.L.H.) for a subset of 215 ovarian cancer cases found an overall concordance of 83% for histologic subtype and 98% for invasiveness. Of the cancers with serous histology based on the original pathology report, 85% were concordant for histologic subtype on the standardized slide review. In our analyses of each subtype, we used the histology and invasiveness coding from the medical record review.

Statistical analysis

We excluded participants who did not complete the 1984 FFQ, had an implausible caloric intake in 1984 ($<$600 or $>$3,500 kilocalories/day), or left more than 70 items blank on the 1984 FFQ (n = 39,944), as well as participants who did not have flavonoid data available in 1984 (n = 851). Additionally, we excluded women diagnosed with any cancer other than nonmelanoma skin cancer prior to 1984 (n = 4,432) and women who reported a prior bilateral oophorectomy (n = 9,460) or menopause due to pelvic irradiation (n = 74). Participants accrued person-time from the return date of the 1984 questionnaire until the earliest of the following events: the date of ovarian cancer diagnosis, the return date of the last questionnaire prior to the diagnosis of any other cancer (excluding nonmelanoma skin cancer), the reported date of bilateral oophorectomy or pelvic irradiation, the date of death or the end of follow-up, June 1, 2002.

To best capture long-term flavonoid intake and to minimize within-person variation, we used cumulative updated flavonoid intake as the primary exposure. With this method, we used the flavonoid intake values from 1984 as the exposure for the follow-up period from 1984 to 1990, the average of the 1984 and 1990 values as the exposure for 1990 to 1994, the average of the 1984, 1990 and 1994 values as the exposure for 1994 to 1998, and so on. In additional analyses, we examined other methods of characterizing exposure, including using current flavonoid intake updated with each FFQ, using 1984 flavonoid intake alone, and using 1990 as the baseline assessment, since the 1990 FFQ was the first to include questions on onions and all other flavonoid sources of interest. In all analyses we adjusted the flavonoid intake values for total energy intake using the nutrient residual method.[18]

We calculated quintiles of total flavonoid intake and quintiles of intake of each individual flavonoid across our population, and created indicator variables for each quintile. We used Cox proportional hazards regression to model the incidence rate ratio (RR) of epithelial ovarian cancer and the 95% confidence interval (CI) for each quintile of intake, relative to the lowest quintile. We also tested for a linear trend across quintiles of intake using the median of each quintile as a continuous variable, and we calculated the p-value for trend using the Wald test. For the analyses of cumulative and current updated flavonoid intake, where the exposure was updated over time, we recalculated the quintile cut points and redefined the quintile variables at each FFQ time point, as this approach maintained an even distribution of person-time across quintiles of flavonoid intake throughout follow-up. For these analyses, women only contributed person-time for the follow-up periods where they contributed flavonoid data. For example, if a participant completed all FFQs except the 1990 FFQ, we used the 1984 flavonoid data for the follow-up period from 1984 to 1990, excluded from the analysis the follow-up period from 1990 to 1994 for that individual, used the average of the 1984 and 1994 flavonoid intake values for the period from 1994 to 1998, and so on.

In our final model, we adjusted for age in months (continuous), duration of oral contraceptive use (none, $<$3, 3–$<$5, 5+ years), parity (0, 1–2, 3–4, 5+), history of tubal ligation (yes, no), smoking status (never, past, current), history of postmenopausal

TABLE I – BASELINE CHARACTERISTICS BY QUINTILE OF TOTAL FLAVONOID INTAKE IN 1984 AMONG 66,940 WOMEN IN THE NURSES' HEALTH STUDY[1]

	Quintile of total flavonoid intake				
	1	2	3	4	5
Number of women	13,391	13,383	13,389	13,388	13,389
Median total flavonoid intake (mg/day)[2,3]	7.3	11.9	17.7	27.2	45.9
Mean					
Age in years	50	50	51	51	51
Parity	3.0	2.9	3.0	3.0	2.9
Duration oral contraceptive use (months)[4]	54	52	51	52	50
Duration of lactation (months)[5]	5.6	6.3	6.5	6.5	6.5
Vigorous physical activity (hours/week)[6]	2.1	2.3	2.4	2.5	2.6
Body mass index (kg/m^2)	24.9	24.9	24.9	25.1	25.1
Percent of study population					
Never user of oral contraceptives	49	49	50	50	51
Current postmenopausal hormone user[7]	14	15	14	14	14
Never smoker	40	44	45	45	45
Current smoker	33	24	22	22	23
History of tubal ligation	18	18	18	17	18
Family history of ovarian cancer[8]	2.4	2.5	2.9	2.7	2.4
Mean dietary intake					
Total energy (kilocalories/day)	1,721	1,743	1,792	1,800	1,682
Lactose (g/day)[3]	12.7	12.1	11.7	11.6	11.5

[1]Standardized by age in six categories ($\leq$40, 40–44, 45–49, 50–54, 55–59, $\geq$60) as of 1984.–[2]Includes data on onion consumption from 1982.–[3]Adjusted for total energy intake.–[4]Duration among women with any history of oral contraceptive use.–[5]Total duration among parous women; collected in 1986.–[6]Collected in 1982.–[7]Among postmenopausal women in 1984.–[8]Collected in 1992.

hormone use (never, past, current), cumulative updated physical activity (<1, 1–<2, 2–<4, 4–<7, 7+ hrs/week), quintile of cumulative updated energy-adjusted lactose intake, and cumulative updated total caloric intake. We evaluated several other covariates as potential confounding variables, including BMI, menopausal status, age at menarche, age at menopause, age at first birth, hysterectomy status, caffeine intake, alcohol intake, consumption of skim or whole milk, and intake of nutrients including folate, vitamin A, vitamin C, α-carotene and lycopene. Adjusting for these covariates did not change our effect estimates, so we excluded them from our final model. We did not evaluate family history of ovarian cancer in a first-degree relative or duration of lactation as potential confounding variables, because information on these covariates was not collected until 1992 and 1986, respectively. However, there was little variation in the mean number of months of lactation or the percent of women reporting a family history of ovarian cancer across quintiles of total flavonoid intake in 1984 (Table I) or 1990 (data not shown), suggesting that there would be minimal confounding by these variables.

In additional analyses, we examined the association between flavonoid intake and the major histologic subtypes of ovarian cancer, as there is evidence that the etiology of each subtype may differ.[19] We also evaluated the association with flavonoid intake defined as a continuous variable, as well as variables for both continuous and categorical consumption of flavonoid-rich foods, cumulatively updated beginning in 1984. We assessed the impact of different exposure latencies, as well as any influence of subclinical disease on diet, by running models using baseline flavonoid intake only, current updated flavonoid intake, and current or cumulative updated flavonoid intake with either a two- or four-year lag between exposure assessment and the beginning of follow-up. For the lagged analyses, we excluded cases diagnosed during the first two to four years after the baseline exposure assessment, and used the FFQ data for the follow-up period beginning two to four years after completion of the FFQ. For example, for the four-year lag with flavonoid intake cumulatively updated, we excluded the follow-up period from 1984 to 1988 and used the 1984 flavonoid data for the follow-up period from 1988 to 1994, the average of the 1984 and 1990 flavonoid values for the follow-up period from 1994 to 1998, and so on. Finally, we evaluated whether the association between flavonoid intake and incidence of ovarian cancer differed by level of several potential effect modifiers, including oral contraceptive use, parity, BMI, lactose intake, and menopausal status.

Results

Our analysis included 66,940 women with 950,347 person-years of follow-up between 1984 and June 2002, and 347 confirmed cases of epithelial ovarian cancer. During follow-up we identified 577 possible cases of newly diagnosed ovarian cancer in our population, and we confirmed 450 of these cases (78%) upon review of the medical records. Of the unconfirmed cases, medical records were unobtainable for 43 cases (7%), 29 women denied their diagnosis (5%), 43 diagnoses (7%) were incorrect based on review of the medical records, and 12 cases (2%) were metastases from a nonovarian primary. Of the 450 confirmed cases, 401 were primary epithelial ovarian tumors (89%). Fifty-four cases were excluded due to a prior cancer or missing dietary data, leaving 347 cases for analysis. Of these, 192 were serous (55%), 26 were mucinous (7%), 55 were endometrioid (16%), 15 were clear cell (4%), 29 were poorly differentiated (8%) and 30 were other subtypes or had mixed or unknown histology (9%).

The characteristics of women in our study population were similar across quintiles of total flavonoid intake in 1984 (Table I). Women with greater total flavonoid intake were slightly older, had higher levels of physical activity, had lower daily consumption of lactose, and were less likely to smoke. As expected, intake of nutrients that were correlated with flavonoid intake, including vitamin A, vitamin C, folate, α-carotene, and lycopene, increased with increasing quintile of total flavonoid intake (data not shown). The results were similar when we examined characteristics of our population across quintiles of myricetin, kaempferol, quercetin and apigenin intake in 1984, and quintiles of luteolin intake in 1994 (data not shown).

Total flavonoid intake was not significantly associated with ovarian cancer risk (Table II). The adjusted RR for the highest *versus* lowest quintile of total flavonoid intake was 0.75 (95% CI = 0.51–1.09; p-trend = 0.02). Although the p-value for the test for trend was statistically significant, this trend was driven in part by an elevated RR for quintile 2 and may have occurred by chance, given the small difference in the median total flavonoid intake for quintiles 1 and 2 of intake. However, an analysis with

TABLE II – INCIDENCE RATE RATIOS AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN CUMULATIVE UPDATED FLAVONOID INTAKE AND INCIDENCE OF TOTAL EPITHELIAL OVARIAN CANCER FROM 1984 THROUGH 2002 AMONG 66,940 WOMEN IN THE NURSES' HEALTH STUDY

	Quintile of intake					*p*-trend[1]
	1	2	3	4	5	
Total flavonoids[2]						
Median intake[3]	8.5	13.4	18.7	26.5	42.6	
Number of cases	62	86	73	77	49	
Person-years	190,328	190,041	190,057	189,854	190,066	
Age-adjusted RR	1.00 (ref.)	1.37	1.12	1.17	0.75	0.02
Multivariable RR[4]	1.00 (ref.)	1.39 (1.00, 1.94)	1.14 (0.81, 1.61)	1.20 (0.85, 1.69)	0.75 (0.51, 1.09)	0.02
Myricetin						
Median intake[3]	0.1	0.4	0.6	1.1	2.4	
Number of cases	73	74	81	67	52	
Person-years	189,934	189,607	191,704	189,232	189,870	
Age-adjusted RR	1.00 (ref.)	1.02	1.07	0.90	0.72	0.01
Multivariable RR[4]	1.00 (ref.)	1.04 (0.75, 1.45)	1.09 (0.79, 1.51)	0.92 (0.66, 1.29)	0.72 (0.50, 1.04)	0.01
Flavonoid-adj. RR[5]	1.00 (ref.)	1.02 (0.73, 1.43)	1.11 (0.78, 1.57)	1.06 (0.72, 1.58)	1.03 (0.64, 1.66)	0.49
Kaempferol						
Median intake[3]	0.8	1.6	2.9	5.0	11.0	
Number of cases	80	75	82	63	47	
Person-years	189,261	190,654	190,096	190,069	190,267	
Age-adjusted RR	1.00 (ref.)	0.94	1.03	0.78	0.60	0.001
Multivariable RR[4]	1.00 (ref.)	0.94 (0.68, 1.29)	1.05 (0.77, 1.43)	0.80 (0.57, 1.12)	0.60 (0.42, 0.87)	0.002
Flavonoid-adj. RR[5]	1.00 (ref.)	0.88 (0.63, 1.21)	0.95 (0.67, 1.33)	0.70 (0.47, 1.05)	0.57 (0.34, 0.96)	0.02
Quercetin						
Median intake[3]	6.3	9.9	13.5	19.2	30.7	
Number of cases	61	84	73	76	53	
Person-years	190,390	190,038	190,084	189,883	189,951	
Age-adjusted RR	1.00 (ref.)	1.36	1.13	1.19	0.80	0.04
Multivariable RR[4]	1.00 (ref.)	1.38 (0.99, 1.93)	1.16 (0.82, 1.63)	1.22 (0.87, 1.72)	0.80 (0.55, 1.16)	0.04
Flavonoid-adj. RR[5]	1.00 (ref.)	1.43 (1.01, 2.02)	1.28 (0.88, 1.87)	1.51 (1.03, 2.22)	1.05 (0.68, 1.62)	0.52
Luteolin						
Median intake[3]	0.01	0.01	0.02	0.03	0.07	
Number of cases	186	25	49	32	55	
Person-years	497,851	49,108	132,902	75,848	194,638	
Age-adjusted RR	1.00 (ref.)	1.11	0.85	0.91	0.67	0.01
Multivariable RR[4]	1.00 (ref.)	1.11 (0.70, 1.78)	0.88 (0.63, 1.23)	0.93 (0.60, 1.43)	0.66 (0.49, 0.91)	0.01
Flavonoid-adj. RR[5]	1.00 (ref.)	1.08 (0.68, 1.73)	0.82 (0.59, 1.15)	0.84 (0.54, 1.30)	0.59 (0.42, 0.81)	0.001
Apigenin						
Median intake[3]	0.2	0.3	0.4	0.7	1.3	
Number of cases	66	47	77	65	92	
Person-years	190,356	189,808	190,466	189,752	189,964	
Age-adjusted RR	1.00 (ref.)	0.74	1.23	0.99	1.33	0.02
Multivariable RR[4]	1.00 (ref.)	0.75 (0.52, 1.10)	1.25 (0.90, 1.75)	1.01 (0.71, 1.43)	1.33 (0.96, 1.83)	0.03
Flavonoid-adj. RR[5]	1.00 (ref.)	0.74 (0.51, 1.09)	1.27 (0.91, 1.79)	1.06 (0.74, 1.51)	1.51 (1.08, 2.13)	0.004

[1]Weighted by median of each quintile and calculated using the Wald test.–[2]Total intake of five flavonoids (myricetin, kaempferol, quercetin, luteolin and apigenin).–[3]Median intake in milligrams/day; based on a single set of quintile cutpoints across all person-time.–[4]Adjusted for age, duration of oral contraceptive use, parity, history of tubal ligation, smoking status, history of postmenopausal hormone use, physical activity, quintile of cumulative updated energy-adjusted lactose intake and cumulative updated total energy intake.–[5]Adjusted for above variables, plus quintile of intake of each other individual flavonoid.

total flavonoid intake modeled continuously was also indicative of a significant trend ($p = 0.03$). There was a significant 40% decrease in ovarian cancer incidence for the highest *versus* lowest quintile of kaempferol (RR = 0.60, 95% CI = 0.42–0.87; *p*-trend = 0.002), a significant 34% decrease in incidence for the highest *versus* lowest category of luteolin (RR = 0.66, 95% CI = 0.49–0.91; *p*-trend = 0.01), and a nonsignificant 28% decrease in incidence for the highest *versus* lowest quintile of myricetin (RR = 0.72, 95% CI = 0.50–1.04; *p*-trend = 0.01). There was little evidence of an association between quercetin intake and disease risk. Although we observed a significant trend for increasing incidence of ovarian cancer with increasing apigenin intake ($p = 0.03$), this trend was not monotonic and the quintile-specific RRs were not statistically significant. Further, there was no evidence of an association between cumulative updated apigenin intake modeled continuously and ovarian cancer incidence ($p = 0.50$).

Intakes of myricetin, kaempferol, and quercetin were highly correlated, with Spearman correlation coefficients of 0.53 for myricetin and quercetin, 0.57 for kaempferol and quercetin, and 0.77 for myricetin and kaempferol in 1984. Correlations between the other individual flavonoids in 1984 ranged from 0.05 for myricetin and luteolin to 0.25 for apigenin and luteolin. These correlations remained similar over time, as did the median and range of intake of each flavonoid. In analyses adjusted for each of the other 4 individual flavonoids, the findings for kaempferol and luteolin were essentially unchanged, and the trends remained statistically significant (Table II). In a secondary analysis of cumulative updated luteolin intake beginning in 1994, when intake was higher due to the addition of green peppers to the FFQ, there remained a suggestion of an inverse association with ovarian cancer incidence. However, the effect estimate for the highest *versus* lowest quintile of intake was no longer statistically significant because of the loss of 10 years of follow-up and the decrease in power (RR = 0.76, 95% CI = 0.47–1.22).

The primary contributors to flavonoid intake in the Nurses' Health Study in 1984 and 1994 included tea (nonherbal), onions, broccoli, apples and tomato sauce (Table III). The contributors to flavonoid intake for the 66,940 women in our analysis were similar to the contributors for all participants in the Nurses' Health Study who completed the relevant FFQ. Although modifications

TABLE III – PRIMARY CONTRIBUTORS TO FLAVONOID INTAKE IN 1984 AND 1994 AMONG PARTICIPANTS IN THE NURSES' HEALTH STUDY

Flavonoid	Year	
	1984	1994
Total flavonoids[1]	Tea, nonherbal (33.8)	Tea, nonherbal (30.5)
	Onions (29.5)[2]	Onions (25.8)
	Apples (7.2)	Broccoli (7.8)
	Broccoli (6.4)	Apples (7.1)
	Tomato sauce (3.5)	Tomato sauce (4.1)
Myricetin	Tea, nonherbal (66.4)	Tea, nonherbal (51.5)
	Beans (26.1)	Beans (34.0)
	Raisins (7.3)	Raisins (9.0)
Kaempferol	Tea, nonherbal (68.3)	Tea, nonherbal (58.8)
	Broccoli (22.7)	Broccoli (26.4)
	Kale (6.0)	Kale (6.5)
Quercetin	Onions (38.8)[2]	Onions (34.6)
	Tea, nonherbal (23.2)	Tea, nonherbal (21.4)
	Apples (9.4)	Apples (9.6)
Luteolin	Carrots (70.3)	Peppers (64.3)
	Other (29.7)[3]	Carrots (21.6)
		Cabbage (10.4)
Apigenin	Celery (76.5)	Celery (72.6)
	Tomato sauce (14.5)	Tomato sauce (18.5)
	Pizza (4.6)	Pizza (3.8)

Values in parentheses indicate the percentage contributed to flavonoid intake.
[1]Total intake of five flavonoids (myricetin, kaempferol, quercetin, luteolin and apigenin).–[2]Data on onion consumption collected in 1982.–[3]Other contributors to luteolin intake in 1984 include peppers, parsley, hot peppers, carrot juice, chili and V8; these foods were not included on the 1984 FFQ but were written in by participants who usually consumed these items at least once per week.

to the FFQ and to the flavonoid calculations changed the contribution of certain foods over time, the primary contributors to flavonoid intake were generally similar at each FFQ time point.

In analyses of flavonoid-rich foods (Table IV), drinking 2 or more cups of nonherbal tea per day *versus* less than or equal to 1 cup/week was associated with a significant 37% decrease in ovarian cancer incidence (RR = 0.63, 95% CI = 0.40–0.99; *p*-trend = 0.03). Women who consumed broccoli 2 or more times per week had a borderline significant 33% decrease in ovarian cancer incidence, compared with individuals who rarely consumed broccoli (RR = 0.67, 95% CI = 0.45–1.01; *p*-trend = 0.06). No other foods examined were significantly associated with ovarian cancer risk. However, few women in our population frequently consumed certain foods (*e.g*. beans, kale), which limited some of these analyses.

There was no clear evidence of heterogeneity in the effect estimates for the major ovarian cancer subtypes. A competing risks analysis did not suggest a significant difference in the parameter estimates for continuous flavonoid intake and incidence of the serous, endometrioid, and mucinous subtypes (*p*-value for heterogeneity >0.07). Intake of kaempferol was associated with decreased incidence of serous tumors (RR, highest *versus* lowest quintile = 0.57, 95% CI = 0.36–0.90; *p*-trend = 0.004), but there was no clear association between intake of total flavonoids or the other individual flavonoids and incidence of the serous subtype. Although there was some evidence of an inverse association between luteolin intake and incidence of the mucinous and endometrioid subtypes, and between both quercetin intake and total flavonoid intake and incidence of mucinous tumors, the small number of nonserous cases limited these analyses.

In analyses of current updated flavonoid intake beginning in 1984 or current and cumulative updated intake beginning in 1990 or and total epithelial ovarian cancer, the results were similar to those for the primary analyses but generally were slightly attenuated. The results for analyses of flavonoid intake from a single FFQ, in either 1984 or 1990, were essentially null, suggesting that long-term average flavonoid intake may be important. In these analyses, only kaempferol intake in 1990 was associated with a borderline significant decrease in ovarian cancer incidence (RR, highest *versus* lowest quintile = 0.67, 95% CI = 0.45–1.00; *p*-trend = 0.06). The results for analyses with a two- or four-year lag between exposure assessment and follow-up were similar to the analyses without a lag, indicating that the associations observed were not simply due to changes in dietary habits or reporting of diet among women with prediagnostic ovarian cancer.

We did not observe strong evidence of effect modification by the covariates examined (data not shown). There was a suggestion that the inverse association between flavonoid intake and ovarian cancer risk was stronger among women with greater BMI ($\geq$25 kg/m^2) and among women with higher intake of lactose (>10 g/day); however, none of the interactions were statistically significant (all *p*-values for interaction >0.05). The other covariates examined did not appear to substantially modify the association between flavonoid intake and ovarian cancer risk.

Discussion

In this first prospective assessment of intake of nonisoflavone flavonoids and ovarian cancer risk, we found no clear association between total intake of 5 dietary flavonoids from the flavonol and flavone subclasses and ovarian cancer incidence. However, our results suggest that consuming a diet rich in specific flavonoids, particularly kaempferol and luteolin, may be associated with a reduced risk of ovarian cancer. These inverse associations remained after controlling for potential confounding variables and intake of other flavonoids. We also observed a suggestion of a positive association between apigenin intake and ovarian cancer incidence. This result may be due to chance, based on the absence of a monotonic trend across quintiles of intake and the lack of a significant association with continuous intake of apigenin, in conjunction with biologic data that do not support a positive association.[20,21] However, this should be evaluated in future studies, to rule out the possibility of a harmful association with apigenin or specific foods that contribute to apigenin intake.

We found evidence that consumption of tea (nonherbal) and broccoli, both of which contain high levels of kaempferol and other flavonoids, may be inversely associated with ovarian cancer risk. For other flavonoid-rich foods, including onions and beans, there was a suggestion that women in the highest category of intake had reduced incidence of ovarian cancer. However, the number of women who frequently consumed these foods was not large

TABLE IV – INCIDENCE RATE RATIOS AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN CUMULATIVE UPDATED CONSUMPTION OF FLAVONOID-RICH FOODS AND INCIDENCE OF TOTAL EPITHELIAL OVARIAN CANCER FROM 1984 TO 2002 AMONG 66,940 WOMEN IN THE NURSES' HEALTH STUDY

Food	Servings	Cases	Person-years	Multivariable RR (95% CI)[1,2]
Tea, nonherbal	≤1/week	163	429,200	1.00 (ref.)
	2–6/week	121	290,270	1.08 (0.84, 1.37)
	1/day	41	132,009	0.86 (0.61, 1.21)
	2+/day	22	98,868	0.63 (0.40, 0.99)
				$p = 0.03$
Onions	Never or <2/month	139	396,140	1.00 (ref.)
	2/month to <1/week	80	213,424	1.08 (0.81, 1.43)
	1/week	71	161,278	1.19 (0.89, 1.60)
	2–3/week	39	115,210	0.95 (0.66, 1.36)
	4+/week	18	64,295	0.78 (0.47, 1.30)
				$p = 0.56$
Apples	Never or <2/month	48	115,535	1.00 (ref.)
	2/month to <1/week	74	197,955	0.98 (0.68, 1.41)
	1/week	67	214,260	0.77 (0.53, 1.13)
	2–3/week	91	253,007	0.90 (0.62, 1.29)
	4+/week	67	169,590	0.97 (0.66, 1.44)
				$p = 0.41$
Broccoli	Never or <2/month	34	70,640	1.00 (ref.)
	2/month to <1/week	110	277,055	0.87 (0.59, 1.29)
	1/week	121	329,926	0.80 (0.54, 1.17)
	2+week	82	272,725	0.67 (0.45, 1.01)
				$p = 0.06$
Tomato sauce	Never or <2/month	39	109,707	1.00 (ref.)
	2/month to <1/week	152	402,956	1.30 (0.91, 1.87)
	1/week	115	309,584	1.49 (1.02, 2.19)
	2+/week	41	128,100	1.44 (0.90, 2.29)
				$p = 0.09$
Beans	Never or <2/month	161	440,852	1.00 (ref.)
	2/month to <1/week	129	361,675	1.01 (0.79, 1.27)
	1/week	51	116,586	1.18 (0.85, 1.64)
	2+/week	6	31,235	0.57 (0.25, 1.29)
				$p = 0.89$
Carrots	Never or <2/month	21	60,694	1.00 (ref.)
	2/month to <1/week	76	188,590	1.15 (0.71, 1.88)
	1/week	117	314,198	1.04 (0.65, 1.66)
	2–3/week	86	244,243	0.91 (0.56, 1.49)
	4+/week	47	142,622	0.84 (0.49, 1.43)
				$p = 0.13$
Celery	Never or <2/month	57	184,514	1.00 (ref.)
	2/month to <1/week	93	253,160	1.25 (0.90, 1.75)
	1/week	70	205,617	1.10 (0.77, 1.56)
	2–3/week	87	214,228	1.30 (0.92, 1.83)
	4+/week	40	92,828	1.35 (0.89, 2.05)
				$p = 0.44$

[1] p-values are for the test for trend for continuous intake in servings/week; calculated using the Wald test.–[2]Adjusted for age, duration of oral contraceptive use, parity, history of tubal ligation, smoking status, history of postmenopausal hormone use, physical activity, lactose intake, and total energy intake

enough to clearly characterize the associations. Interestingly, we did not observe an association between flavonoid intake from a single FFQ and ovarian cancer incidence, suggesting that long-term flavonoid intake over several years may be important for decreasing ovarian cancer risk, or that the reduction in within-person variation achieved by using cumulative average data from multiple FFQs is important to accurately characterize flavonoid intake. The absence of an association with flavonoid intake from a single FFQ could also potentially be explained by misclassification in the flavonoid intake values for specific questionnaire years, because of the omission of important flavonoid sources or inaccuracies in the flavonoid calculations. However, for both tea and broccoli the associations with intake from a single questionnaire were also null, while the associations with cumulative average intake were significant or borderline significant, despite the inclusion of similar or identical questions on consumption of these foods on every FFQ. Although there was no clear evidence of effect modification in these data, there was a suggestion of a stronger association between flavonoid intake and ovarian cancer risk among overweight women and women with greater lactose intake. Additional prospective studies are needed to further evaluate these associations.

Our results for the analyses of flavonol intake and total epithelial ovarian cancer risk are consistent with those observed in the available retrospective case–control study of this association. McCann *et al*. analyzed the association between dietary intake of kaempferol and quercetin and ovarian cancer risk in a population of 124 cases and 696 controls from western New York.[8] In this study, women in the highest quintile of quercetin intake had a nonsignificant 29% decrease in ovarian cancer risk and women in the highest quintile of kaempferol intake had a non significant 27% decrease in risk, relative to women with the lowest intake of each flavonoid. The two available studies of the isoflavone flavonoid subclass and ovarian cancer risk both found inverse associations with total isoflavone intake. Zhang and colleagues evaluated the association between isoflavone intake and ovarian cancer risk among 254 cases and 652 controls from Hangzhou, China.[9] Women who consumed the highest levels of isoflavones had a significant 49% decrease in ovarian cancer risk, when compared with women in the lowest quartile of isoflavone intake. The associations were similar for the analyses with total consumption of soy foods and intake of individual flavonoids in the isoflavone subclass. In a recent study, Chang *et al*. examined the association with isoflavone intake in the California Teachers Study, a large

cohort of women with 280 ovarian cancer cases diagnosed through 2003.[10] Women consuming over 3 mg of isoflavones per day had a significant 44% decrease in ovarian cancer incidence, compared to women consuming less than 1 mg of isoflavones per day. This study also found evidence of inverse associations with intake of individual isoflavones and consumption of tofu/bean curd, although these associations were not statistically significant. Additional studies have evaluated the association between flavonoid-rich foods and beverages and ovarian cancer risk.[10,22–45] Although some studies have found inverse associations with consumption of certain vegetables and fruits, tea and other dietary sources of flavonoids,[22,26–28,31,33,39,42,45] overall the data are equivocal. The same flavonoid can be present in multiple foods and beverages, which suggests that an association between flavonoid intake and ovarian cancer risk could exist despite the absence of a clear association with consumption of certain flavonoid-rich foods.

There are several mechanisms by which flavonoids may inhibit ovarian carcinogenesis. Free radicals, which are formed during normal metabolic processes and after exposure to certain exogenous substances, can react with DNA to cause strand breaks and other damage.[46] Experimental evidence suggests that flavonoids may inhibit oxidation and the resulting DNA damage by decreasing free radical formation, scavenging free radicals, or enhancing the body's antioxidant systems, such as by upregulating activity of glutathione S-transferase and other detoxifying enzymes.[3,4] Inflammation can also result in DNA damage, due to the release of cytokines, oxygen radicals and other toxic substances.[47,48] Certain flavonoids, including quercetin, luteolin and apigenin, appear to reduce inflammation through their inhibitory effect on the enzymes cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase, both of which are important mediators of inflammatory reactions.[2,49–51] There is evidence that flavonoids in the isoflavone, flavone and flavonol subclasses may modulate sex steroid hormone levels through either an estrogenic or antiestrogenic effect.[4,52,53] This may be important in ovarian carcinogenesis due to the estrogen-rich environment surrounding the ovaries and the proliferative effect of estrogen on ovarian epithelial cells.[54] Finally, evidence from *in vitro* studies of human ovarian cancer cell lines suggests that certain flavonoids can inhibit tumor growth and angiogenesis, interrupt the cell cycle, and induce apoptosis, all of which may be relevant mechanisms for an inverse association between flavonoid intake and ovarian cancer.[20,21,55–57] Although the flavonoid concentrations used in these experimental studies generally exceeded the levels obtainable with typical dietary intake, there was some overlap with the plasma levels of flavonoids observed in feeding studies in humans. For example, the quercetin plasma concentrations observed in several studies where participants ingested 20–100 mg of quercetin, levels comparable with the intakes for women in quintiles 4 and 5 of our study population, were within the range of the quercetin concentrations associated with decreased proliferation of ovarian cancer cells in a study by Scambia *et al*.[57–59]

This analysis is the largest and most comprehensive assessment of the association between total dietary flavonoid intake and ovarian cancer risk to date. Strengths include the prospective data with multiple dietary assessments over 18 years of follow-up, and detailed covariate information. Although we carefully controlled for potential confounders, we cannot rule out the possibility of residual confounding by an unknown risk factor for ovarian cancer or unidentified aspects of a healthy lifestyle, including other components of flavonoid-rich foods. However, the fact that we observed inverse associations with both tea and broccoli, the primary contributors to kaempferol intake in our study population but foods that are otherwise dissimilar, suggests that the observed association with kaempferol is not due to other components of these foods. While our sample size was fairly large, the number of cases with specific histologic subtypes was small, which limited our power to detect an association with these subtypes. Although our analyses did not indicate significant heterogeneity in the associations for the major histologic subtypes of ovarian cancer, analyses in larger study populations would help to further characterize these associations.

Additional limitations of our analysis include the lack of data on onion consumption in 1984, and the increased potential for exposure misclassification because of the use of onion data from 1982 to calculate the 1984 flavonoid values. We were unable to account for variation in the flavonoid content of foods caused by differences in the variety, growth, preparation or processing of each food, which most likely introduced some additional nondifferential exposure misclassification; however, this type of error would tend to result in an underestimation of the true association. We were unable to evaluate the association between ovarian cancer risk and other flavonoids or flavonoid subclasses, or with foods not included on the questionnaires. The distribution of luteolin intake in our population was narrow, with most women having very low intake; this precluded the allocation of the person-years of follow-up into equal quintiles of intake. It is possible that the results might differ in a population with greater variability in consumption of foods containing luteolin. However, the fact that we observed a significant inverse association for the highest quintile of luteolin intake, where the median intake was less than 0.1 mg/day, suggests that even low levels of intake of luteolin may decrease ovarian cancer risk.

According to the results of this prospective study, total intake of 5 common dietary flavonoids from the flavonol and flavone subclasses is not clearly associated with ovarian cancer risk. However, intake of specific flavonoids, in particular kaempferol and luteolin, appears to be associated with a decreased risk of ovarian cancer. Although these results are promising, additional studies are needed to confirm our findings. In particular, analyses in other prospective populations would help to minimize the possibility of recall bias, which is a greater concern in retrospective case–control studies of dietary factors, and would allow further characterization of the most relevant timeframe of exposure. If confirmed in other populations, an inverse association between flavonoid intake and ovarian cancer risk would provide an important opportunity for ovarian cancer prevention.

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