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Flavonoid intake and ovarian cancer risk in a population-based case-control study

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Abstract

Several recent studies have evaluated the association between dietary flavonoid intake and ovarian cancer risk, and all reported significant or suggestive inverse associations with certain flavonoids or flavonoid subclasses; however, most of these studies were small to moderate in size. We therefore examined this association in a large, population-based case-control study. We calculated intake of five common dietary flavonoids (myricetin, kaempferol, quercetin, luteolin, and apigenin), as well as total intake of these flavonoids, for 1,141 cases and 1,183 frequency-matched controls. We used unconditional logistic regression to estimate the relative risk (RR) of ovarian cancer for each quintile of flavonoid intake, compared to the lowest quintile. We did not observe an association between total flavonoid intake and ovarian cancer risk. The multivariable-adjusted RR for the highest versus lowest quintile of total flavonoid intake was 1.06 (95% confidence interval [CI]=0.78–1.45). In analyses of each individual flavonoid, only intake of apigenin was associated with a borderline significant decrease in risk (RR, highest versus lowest quintile=0.79, 95% CI=0.59–1.06; *p*-trend=0.26), and this association was significant after adjustment for intake of the other four individual flavonoids (comparable RR=0.72, 95% CI=0.53–0.98; *p*-trend=0.09). These results provide limited support for an association between flavonoid intake and ovarian cancer risk. However, given the findings of previous studies and the biologic plausibility of this association, additional studies are warranted.

Keywords

Flavonoids; flavonols; flavones; diet; ovarian cancer; epidemiology

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Novelty and impact of paper: In this large, population-based case-control study of flavonoid intake and ovarian cancer risk, we observed evidence of an inverse association with intake of apigenin, but no association with total intake of five flavonoids in the flavonol and flavone subclasses. Although our results do not provide clear support for an association between flavonol and flavone intake and risk of ovarian cancer, additional epidemiologic and mechanistic studies are warranted to examine the association with apigenin and other flavonoids.

INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer death among women in the United States, accounting for an estimated 15,520 deaths per year.1 Although few modifiable risk factors for ovarian cancer have been firmly established, several recent studies have reported inverse associations with dietary intake of flavonoids.2–6

Flavonoids are phytochemicals found in fruits, vegetables, tea, wine, and other foods and beverages derived from plant sources. The flavonoid chemical structure consists of two aromatic rings connected by a three-carbon bridge contained within a third six-member ring; individual flavonoid compounds are grouped into classes based on further similarities in their structure.7, 8 Six flavonoid subclasses are common in the human diet,7, 8 and three – the isoflavone, flavonol, and flavone subclasses – have been associated with a decrease in ovarian cancer risk in previous studies.2–6 Flavonoids exhibit several anti-carcinogenic properties *in vitro*, and specific flavonoids may decrease ovarian cancer risk by altering levels of estrogen and other sex steroid hormones, inhibiting oxidation or inflammation, decreasing angiogenesis or cell proliferation, or inducing apoptosis.7, 9–11

Three prior case-control studies2, 3, 6 and two cohort studies4, 5 have evaluated the association between flavonoid intake and ovarian cancer risk to date, and all reported statistically significant or suggestive inverse associations with one or more flavonoids or flavonoid subclasses. In three studies, women with the highest levels of intake of total isoflavones had a 44 to 49% decrease in ovarian cancer risk.3, 4, 6 Three studies examined the association with flavonoids in the flavone and/or flavonol subclasses; these studies observed 20 to 40% reductions in ovarian cancer risk among women in the highest quintile of intake of kaempferol, quercetin, myricetin, luteolin, or total flavonol or flavone intake.2, 5, 6 However, not all of these associations were statistically significant, and in one study there was some evidence of a positive association with intake of apigenin,5 a flavone found in parsley, red wine, celery, tomato sauce, and several other foods.12 Although the results of these prior studies of flavonoid intake and ovarian cancer risk are encouraging, most of the studies were small to moderate in size, with between 124 and 347 cases in four of the five studies. We therefore examined the association between intake of five common flavonoids from the flavonol and flavone subclasses and risk of epithelial ovarian cancer in a large, population-based case-control study of ovarian cancer.

METHODS

Study population

A total of 1,231 epithelial ovarian cancer cases and 1,244 controls from Massachusetts or New Hampshire were enrolled in the study between May 1992 and March 1997 (phase 1; 563 cases and 523 controls) or between July 1998 and July 2003 (phase 2; 668 cases and 721 controls). The institutional review boards of Brigham and Women's Hospital and Dartmouth Medical School approved both phases of the study, and all participants provided written informed consent. Using information from hospital tumor boards and state cancer registries, study investigators identified 2,347 incident cases of ovarian cancer (phase 1: 1,080 cases, phase 2: 1,267 cases). Investigators reviewed pathology reports for each case prior to study enrollment, to confirm the diagnosis and histology and to classify the histologic subtype. Cases were ineligible if they died before enrollment (n=210), were found to have a non-ovarian primary (n=93), did not speak English (n=37), or if they did not have a telephone, lived outside the study area, or could not be contacted due to an address change (n=162). Of the 1,845 (79%) eligible cases, 1,231 epithelial cases and 75 non-epithelial cases were enrolled in the study; reasons for non-enrollment included physician refusal (n=232) or patient refusal (n=307).

Controls were frequency-matched to cases by age and state, and were excluded if they had died, were seriously ill, did not have a telephone, had moved, did not speak English, or had no ovaries. During phase 1 of enrollment, investigators used random digit dialing to contact potential controls, supplemented by Massachusetts town resident lists to identify additional women over age 60. Of the households contacted using random digit dialing, 10% had a potentially eligible control, and 72% (n=421) of these women agreed to participate in the study. Investigators identified 328 additional possible controls using Massachusetts town resident lists. Of these, 21% were unreachable, 18% were ineligible, and 30% declined to participate; the remaining 31% (n=102) were enrolled in the study. During phase 2, investigators identified 1,843 potential controls using Massachusetts town resident lists and New Hampshire drivers' license records; 197 women returned a postcard to "opt-out" of the study and were not contacted, and 576 additional women were ineligible or could not be contacted because they had died, moved, or did not have a working telephone. Of the 1,070 remaining potential controls, 349 declined to participate by phone and 721 were successfully enrolled.

Exposure and covariate assessment

Trained interviewers administered a comprehensive questionnaire to cases and controls during an in-person interview to collect information on potential risk factors for ovarian cancer and other covariates of interest. To avoid capturing changes related to disease status, interviewers asked participants about exposures that occurred at least one year prior to the date of diagnosis for cases or the interview date for controls. Participants also completed a self-administered, 126-item semi-quantitative food frequency questionnaire (FFQ). Participants reported their average consumption of each food and beverage, excluding any changes in diet during the year prior to diagnosis or study enrollment. The FFQ collected the frequency of consumption of a specified serving size of each food, with nine choices ranging from "never, or less than once per month" to "6+ per day". The FFQ also included space for participants to write in the name, serving size, and frequency of consumption of additional foods that they usually consumed at least once per week. Validation studies of this FFQ in a different population of U.S. women are described elsewhere;[13–15] correlation coefficients for food and beverage intake reported on the FFQ versus diet records ranged from 0.50 to 0.93 for the several of the primary contributors to flavonoid intake in our population, suggesting that the FFQ adequately captures intake of common dietary sources of flavonoids.[15]

Using the FFQ data and information on the flavonoid content of each food and beverage of interest, we calculated each participant's intake of three flavonols (myricetin, kaempferol, and quercetin), two flavones (luteolin and apigenin), and total intake of these five flavonoids. Flavonoid intake values were calculated by the Harvard School of Public Health Department of Nutrition. Flavonoid values were assigned to 43 foods and beverages using published data from the U.S. Department of Agriculture (USDA) Database for the Flavonoid Content of Selected Foods, Release 2.1.[12] For foods not included in the USDA database, flavonoid values were assigned through imputation or recipe calculation, using the following methods: 1) dry weight ratios were used to calculate values for cooked/raw and dried/fresh foods; 2) published retention data were used to estimate losses due to heat processing and storage for canned foods; 3) recipes were written using ingredients and nutrient profiles from manufacturers' labels.[8, 16–22] Guidance for imputing and calculating missing values was provided by Dr. Aedin Cassidy, Professor of Diet and Health, School of Medicine, University of East Anglia, Norwich, UK, and Dr. Julia Peterson, Tufts University School of Nutrition Science and Policy. The FFQ used in this study did not include a question on consumption of onions, a major contributor to quercetin intake. As a result, the calculated quercetin intake values most likely underestimate each participant's true intake.

Statistical analysis

We excluded women who did not adequately complete the FFQ (>70 items blank) or who had missing flavonoid data (n=63), and women with an improbable caloric intake of <600 or >3500 calories per day (n=88). Using the distribution of flavonoid intake in the control population, we calculated quintile cut points for intake of each individual flavonoid and total flavonoids. We used unconditional logistic regression to calculate the odds ratio, as an estimate of the relative risk (RR), and the 95% confidence interval (CI) for each quintile of intake, compared to the lowest quintile. We also used the Wald test to examine linear trends with a continuous variable weighted by the median of each quintile and with log-transformed continuous intake. In both study phases, controls were frequency-matched to the cases so that the age and geographic location distributions of the cases and controls were similar. Because the cases and controls were not individually matched, we did not retain the matching in our analysis and instead included the matching factors as covariates in our models.

In addition to the matching factors, we adjusted all analyses for duration of oral contraceptive use (<3 months, 3 months-<3 years, 3-<5 years, 5+ years), parity (0, 1–2, 3–4, 5+), history of tubal ligation, physical activity (<1, 1-<2, 2-<4, 4-<7, 7+ hours/week), total duration of breastfeeding (0, 1–6, 7-<12, 12-<18, 18+ months), quintile of energy-adjusted fiber and carotenoid (alpha carotene, beta carotene, beta cryptoxanthin, lycopene, and lutein) intake, and total energy intake (continuous). In addition to controlling for energy intake in our models, we also adjusted intake of each flavonoid for total energy intake using the nutrient residual method, to examine the effect of flavonoid composition of the diet independent of total energy intake.[23, 24] We evaluated multiple additional covariates as potential confounders, including smoking history, postmenopausal hormone use, body mass index (BMI), menopausal status, age at menarche and menopause, age at first birth, simple hysterectomy, family history of breast or ovarian cancer, and intake of lactose, caffeine, alcohol, folate, calcium, dietary fat, and vitamins A, C, D, and E. However, controlling for these covariates did not change our estimates, so we did not include them in the final model.

In additional analyses we examined associations with intake of the flavonol and flavone subclasses, and with consumption of flavonoid-rich foods and beverages. We also analyzed the association between flavonoid intake and the major histologic subtypes of ovarian cancer. Finally, we assessed whether the association between flavonoid intake and ovarian cancer risk differed by level of several covariates, including BMI, lactose intake, caffeine intake, and menopausal status. We calculated the *p*-value for interaction using the chi-square test for the difference between the log likelihoods for models with and without interaction terms between flavonoid intake and the covariate of interest. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

After excluding women with missing or questionable dietary data, our analysis included 1,141 epithelial ovarian cancer cases and 1,183 controls. Of the cancers, 614 had serous histology (54%), 139 were mucinous (12%), 161 were endometrioid (14%), 61 were clear cell (5%), 83 were mixed with an endometrioid or clear cell component (7%), and 83 had other/undifferentiated histology (7%). Of the 614 serous tumors, 27% were borderline (low malignant potential) and 73% were invasive. As expected, the cases and controls differed with respect to the known risk factors for ovarian cancer (Table 1). In addition to these differences, the cases had slightly higher BMI and higher daily caloric intake. Mean flavonoid intake and intake of other nutrients were similar for the cases and controls, although the controls appeared to have a slightly healthier diet overall, with higher mean intake of total carotene, fiber, and total flavonoids. The geometric mean intake of each

nutrient was lower than the mean intake, due to the positively skewed distributions of intake; however, the relationship between the case and control values was similar for both the mean and the geometric mean intakes of each nutrient (results not shown).

Among the controls, women with higher total flavonoid intake were, on average, older, more physically active, leaner, and less likely to smoke, and they had a longer mean duration of breastfeeding (Table 2). In addition, total flavonoid intake was positively correlated with total carotene and fiber intake among the controls. Controls from phase 1 and phase 2 of enrollment were similar, although on average the phase 2 controls were older (52 versus 49 years), more physically active (3.3 versus 2.1 hours/week), heavier (25.9 versus 25.3 kg/m^2), and had a longer mean duration of breastfeeding (8.3 versus 6.0 months). In addition, the controls in phase 2 were more likely to have used oral contraceptives (66% versus 53%) and were less likely to currently smoke (12% versus 28%; results not shown).

In the entire study population, myricetin, kaempferol, quercetin, and total flavonoid intake were all strongly correlated, with correlation coefficients ranging from 0.71 for kaempferol and quercetin to 0.96 for quercetin and total flavonoids (results not shown). Apigenin and luteolin were less strongly correlated with the other flavonoid measures; the correlation coefficients ranged from 0.16 for luteolin and kaempferol intake to 0.47 for luteolin and total flavonoid intake.

We observed no evidence of an association between total flavonoid intake and ovarian cancer risk (Table 3). In an analysis adjusted for age and study center only, there was a nonsignificant 15% decrease in risk for the highest versus lowest quintile of total flavonoid intake; however, this association disappeared after controlling for multiple covariates (RR=1.06, 95% CI=0.78–1.45). Differences between the age- and multivariable-adjusted results were primarily due to confounding by carotenoid and fiber intake. In multivariable-adjusted analyses of each individual flavonoid, there was no significant association with intake of luteolin or intake of each of the three flavonols. Women in the highest quintile of kaempferol intake had a nonsignificant 21% decrease in risk, compared to women in the lowest quintile of intake, after adjustment for multiple covariates and intake of the other four individual flavonoids; however, there was no evidence of a trend with increasing intake of kaempferol. Only apigenin was associated with a suggestive decrease in ovarian cancer risk; the multivariable-adjusted RR for the highest versus lowest quintile of intake was 0.79 (95% CI=0.59–1.06; *p*-trend=0.26). After adjusting for intake of the other four individual flavonoids, the association with apigenin intake was statistically significant, although the test for trend was not significant (RR=0.72, 95% CI=0.53–0.98; *p*-trend=0.09). In an analysis of log-transformed apigenin intake modeled continuously, the test for trend was statistically significant after adjusting for intake of the other four flavonoids (*p*-trend=0.01).

The primary contributors to between-person variation in total flavonoid intake in our study population were tea, red wine, and apples (Table 4). For apigenin, the major contributors to variation in intake were red wine, celery, and tomato sauce. In multivariable-adjusted analyses of these and other flavonoid-rich foods and beverages, only raisins and cauliflower were associated with a borderline significant decrease in ovarian cancer risk (Table 5). For cauliflower, which contains both kaempferol and quercetin,12 the *p*-value for the test for trend with continuous intake in servings per day was 0.05, and the RR for the highest versus lowest category of cauliflower consumption was 0.68 (95% CI=0.45–1.02). The test for trend for raisin consumption was statistically significant (*p*-trend=0.03), but the RR for each category of intake was nonsignificant. Among the other foods examined, there was evidence of a decrease in ovarian cancer risk among women in the highest category of consumption of nuts, chocolate, kale, tomato sauce, beans, spinach, and carrots (Table 5; some results not shown). The RRs for the highest versus lowest category of consumption of each of these

foods ranged from 0.62 for nuts to 0.80 for beans; however, these estimates and the tests for trend with continuous intake in servings per day were not statistically significant.

The results for the flavonol and flavone subclasses were similar to those for the individual flavonoids contributing to intake of each subclass (results not shown). For flavonol intake, the multivariable-adjusted RR for the highest versus lowest quintile of intake was 1.12 (95% CI=0.82–1.52; *p*-trend=0.72), while the comparable RR for flavone intake was 0.61 (95% CI=0.38–0.97; *p*-trend=0.06).

There was no evidence of heterogeneity in the results for the major histologic subtypes of ovarian cancer (results not shown). Apigenin intake was most strongly associated with endometrioid tumors (RR, highest versus lowest quintile of intake=0.59, 95% CI=0.33–1.04; *p*-trend=0.24), although this association was not statistically significant. There were also nonsignificant inverse associations between apigenin intake and risk of the serous borderline (comparable RR=0.69, 95% CI=0.38–1.23; *p*-trend=0.51) and clear cell subtypes (comparable RR=0.71, 95% CI=0.37–1.39; *p*-trend=0.25). Apigenin intake was unassociated with the mucinous histologic subtype, and the other flavonoid measures were not significantly associated with any histologic subtype of ovarian cancer.

When we examined the association between flavonoid intake and total ovarian cancer risk among women with and without a history of tubal ligation, the association between apigenin intake and risk of ovarian cancer was stronger among women without a prior tubal ligation (*p*-value for interaction=0.009). For women with no history of tubal ligation, those in quintiles four and five of apigenin intake had significant 43% and 29% decreases in risk, respectively, when compared to women in the lowest quintile of intake. There were no apparent differences in the results by level of any other covariate examined, including body mass index and lactose intake.

DISCUSSION

These results provide limited support for an association between intake of flavonol and flavone flavonoids and risk of ovarian cancer. Total flavonoid intake was unassociated with risk in this study, and, of the five individual flavonoids examined, only intake of apigenin was associated with ovarian cancer risk. The association with apigenin intake was statistically significant in the model adjusted for multiple covariates and intake of the other four individual flavonoids, but was not significant in the model unadjusted for intake of the other individual flavonoids. Although none of the individual foods contributing to apigenin intake in this study population were significantly associated with ovarian cancer risk, there was a suggestion of an inverse association with increasing consumption of cauliflower, raisins, tomato sauce, and several other flavonoid-rich foods. We observed a stronger association between apigenin intake and ovarian cancer risk among women without a history of tubal ligation; however, as there is no clear explanation for an interaction with tubal ligation history, it is possible that this result occurred by chance.

Only one previous study has examined the association between apigenin intake and ovarian cancer risk.5 In a prospective analysis of 66,940 women from the Nurses' Health Study (NHS) cohort, including 347 incident cases of ovarian cancer, there was evidence of a positive association with cumulative average intake of apigenin over 18 years of follow-up. Women in the highest quintile of apigenin intake had a significant 51% increase in ovarian cancer risk after adjusting for intake of the other individual flavonoids, although the relative risks did not increase monotonically across quintiles of apigenin intake and the test for trend for continuous intake was not statistically significant. The NHS results and those of the current analysis were similar in magnitude but opposite in direction. Although this disparity

could be related to differences in the design of the two studies, such as the differing timeframe of exposure or the increased potential for recall bias in the retrospective data, it is also possible that the findings in one or both studies were due to chance. The distribution of apigenin intake was narrow in both populations and was based on consumption of a small number of foods, predominantly celery and tomato sauce in the NHS and red wine, celery, and tomato sauce in the current study.

The NHS analysis also examined the association with intake of myricetin, kaempferol, quercetin, and luteolin, as well as total intake of all five flavonoids. In contrast to the null results in the current study, in the NHS there were significant 40% and 34% decreases in risk for women in the highest versus lowest quintile of intake of kaempferol and luteolin, respectively. There were also inverse trends with intake of kaempferol, luteolin, myricetin, quercetin, and total flavonoids; however, among the individual flavonoids only the trends with kaempferol and luteolin remained statistically significant after controlling for intake of the other individual flavonoids. McCann and colleagues examined the association between dietary intake of quercetin and kaempferol and risk of ovarian cancer in a retrospective study of 124 cases and 696 population-based controls from western New York.2 Both quercetin and kaempferol were associated with a nonsignificant decrease in ovarian cancer risk; for the highest versus lowest quintile of intake, the RR was 0.71 (95% CI=0.38–1.32) for quercetin and 0.73 (95% CI=0.39–1.34) for kaempferol. In an Italian study of 1,031 cases and 2,411 hospital-based controls, Rossi et al. observed a significant decrease in ovarian cancer risk with intake of the flavonol subclass (RR, highest versus lowest quintile of intake=0.63, 95% CI=0.47–0.84; *p*-trend=0.009) and a borderline significant decrease in risk with intake of the flavone subclass (comparable RR=0.79, 95% CI=0.60–1.04; *p*-trend=0.11).6 Previous studies,4, 5, 25–50 including an analysis of phase 1 of the current study population,51 have examined the association between consumption of specific flavonoid-rich foods and ovarian cancer risk. Several prospective and retrospective studies have reported inverse associations with tea,5, 25, 37, 49 vegetables,27, 41, 45, 51 and other flavonoid-rich foods;30, 32, 48, 51 however, overall the results have been inconsistent.

There are several potential reasons for the observed differences in the results of this study and those of the previous studies of flavonol and flavone intake and ovarian cancer risk. In the NHS, the inverse associations with intake of kaempferol and luteolin were strongest when cumulative average intake (updated using data from multiple FFQs completed over 18 years of follow-up) was used as the exposure. However, in analyses of flavonoid intake from a single time point in the NHS, only the association with kaempferol intake approached statistical significance.5 Similarly, in the NHS there were inverse associations with non-herbal tea and broccoli, two primary contributors to kaempferol intake, in the cumulatively updated analysis only. It is possible that long-term intake of high levels of flavonoids over a period of years or decades is necessary to reduce ovarian cancer risk, or that diet further in the past is important. Alternatively, flavonoids could act differently toward normal cells and cancerous cells, such that high flavonoid intake inhibits initiation of a tumor but not progression of an existing tumor. The inconsistencies between our study and the two previous case-control studies could be due to differences in the study populations or the methods used to ascertain or calculate flavonoid intake, or simply due to chance. Flavonol intake levels in our study population generally were slightly lower than levels in previous studies, even compared to what would be expected if data on onion consumption were available, while flavone intake levels generally were higher in our population. Differences in flavonoid intake levels across populations may have contributed to the observed differences in the results, particularly if only very high flavonoid intake is associated with a decrease in ovarian cancer risk. Additional studies are needed to determine which flavonoids, if any, act to inhibit ovarian carcinogenesis. In particular, further studies with prospective dietary data would help to characterize the most relevant period of exposure.

Researchers have identified several mechanisms by which apigenin and other flavonoids might decrease ovarian cancer risk. Certain flavonoids, including isoflavones, kaempferol, and apigenin, may decrease endogenous estrogen activity or circulating estrogen levels by competing for estrogen receptors or inhibiting aromatase activity and estrogen biosynthesis.[52, 53] These mechanisms could be important in inhibiting ovarian carcinogenesis, due to the estrogen-rich environment within the ovaries and the proliferative effect of estrogen on ovarian epithelial cells.[54] Flavonoids may also decrease oxidation and DNA damage by scavenging free radicals, reducing free radical formation, or upregulating expression of antioxidant enzymes.[10] In a randomized crossover trial in which participants consumed either a low-flavone diet or a diet rich in apigenin from parsley, the apigenin-rich diet was associated with increased activity of two antioxidant enzymes, superoxide dismutase and erythrocyte glutathione reductase.[55]

Our reliance upon a single dietary assessment that measured relatively recent diet is a limitation of this study, as this precluded the analysis of associations with long-term flavonoid intake. In addition, there are other aspects of the study design that may have affected our results. Although precautions were taken to minimize bias in the study design, it is possible that recall or selection bias occurred. We contacted cases and enrolled them in the study as soon as possible after their diagnosis; however, some cases were too ill to participate or died before they could be enrolled in the study. This may have affected our results if the association with flavonoid intake differs for more aggressive cancers, although analyses by histologic subtype did not suggest that this would be a problem, since our estimates for the serous invasive and serous borderline subtypes were similar.

The FFQ used in this study was not designed to capture flavonoid intake; as a result, not all dietary sources of flavonoids were included on the questionnaire. In particular, the unavailability of information on onion consumption is a weakness of our dietary data, as onions are a major contributor to quercetin intake. The non-differential misclassification resulting from the missing onion data would be expected to attenuate the results and may have limited our ability to observe an association with quercetin and total flavonoid intake. The other foods omitted from the FFQ should contribute only marginally to total flavonoid intake, since the FFQ includes the most commonly consumed sources of flavonoids. The distribution of apigenin in our study population was relatively narrow and was calculated based on a small number of foods; therefore, the association might differ in a population with more variation in intake or a larger number of foods contributing to intake.

This study also has multiple strengths, including the large number of cases, the comprehensive dietary information, and the detailed covariate data, which allowed for careful control for confounding. In addition, the associations with several known protective factors for ovarian cancer, including pregnancy, breastfeeding, and oral contraceptive use, have been similar in this and other retrospective and prospective study populations.[56–60] This suggests that biases related to the study design may not be a major issue, although the dietary data may have been more susceptible to recall bias than the non-dietary covariates. Adjusting for total caloric intake may have helped to decrease this potential bias if cases tended to over- or under-report their total intake but reported the relative composition of their diet accurately.

Overall, the results of this large case-control study provide limited support for an association between flavonoid intake and risk of ovarian cancer. However, given the promising findings from other studies, as well as the evidence of an inverse association with apigenin intake in this analysis, additional studies of flavonoid intake and ovarian cancer risk are warranted. Prospective studies that are able to examine flavonoid intake over time and different latency periods between exposure and diagnosis would be particularly informative, as would studies

of potential mechanisms of action. If confirmed, an inverse association with intake of apigenin or other flavonoids would provide an important and modifiable means of ovarian cancer prevention.

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Table 1

Characteristics of 1,141 ovarian cancer cases and 1,183 frequency-matched controls

Characteristic	Cases	Controls	*P*-value[f]
Mean value (standard deviation)			
Age in years	51 (13)	51 (13)	0.54
Duration oral contraceptive use (months)[a]	52 (53)	61 (56)	0.002
Parity[b]	2.5 (1.3)	2.7 (1.4)	0.002
Duration of lactation (months)[b]	4.9 (10.3)	7.3 (13.1)	<0.001
Physical activity (hours/week)	2.6 (4.8)	2.8 (4.7)	0.29
Body mass index (kg/m^2)	26.2 (6.1)	25.6 (5.5)	0.03
Percent of study population			
Never user of oral contraceptives	52	39	<0.001
Parous	68	81	<0.001
Current smoker	22	19	0.08
History of tubal ligation	14	18	0.006
Family history of ovarian cancer	5.0	3.0	0.01
Mean dietary intake (standard deviation)			
Total energy (kcal/day)	1889 (573)	1842 (573)	0.04
Lactose (grams/day)[c]	13.1 (10.1)	13.3 (9.6)	0.55
Total carotene intake (IU/day)[c]	9194 (6859)	9766 (6820)	0.04
Dietary fiber intake (grams/day)[c,d]	16.8 (5.6)	17.7 (5.3)	0.02
AOAC fiber intake (grams/day)[c,d]	16.4 (5.5)	16.6 (5.0)	0.67
Total flavonoids (mg/day)[c,e]	14.4 (8.9)	15.1 (9.9)	0.08
Myricetin (mg/day)[c]	1.3 (1.0)	1.3 (1.1)	0.79
Kaempferol (mg/day)[c]	2.8 (2.9)	2.9 (3.0)	0.51
Quercetin (mg/day)[c]	8.5 (5.2)	9.1 (6.4)	0.03
Luteolin (mg/day)[c]	1.5 (1.2)	1.5 (1.2)	0.79
Apigenin (mg/day)[c]	0.3 (0.6)	0.3 (0.6)	0.11

[a] Among 544 cases and 717 controls with any history of oral contraceptive use

[b] Among 776 parous cases and 962 parous controls

[c] Adjusted for total energy intake

[d] Dietary fiber intake is available for women enrolled in phase one of study enrollment, while AOAC fiber intake is available for women enrolled in phase two of enrollment

[e] Total intake of five flavonoids (myricetin, kaempferol, quercetin, luteolin, apigenin)

[f] *P*-values calculated using proc ttest (continuous variables) or a chi-square test (binary variables)

Table 2

Characteristics of 1,183 controls by quintile of total flavonoid intake

	Quintile of total flavonoid intake				
	1	**2**	**3**	**4**	**5**
Number of women	231	238	239	235	240
Median total flavonoid intake (mg/day)	6.0	9.4	12.6	17.1	27.5
Range of total flavonoid intake (mg/day)	0.9–7.5	7.5–10.9	10.9–14.5	14.5–20.3	20.3–95
Mean					
Age in years	48.7	49.4	50.5	52.1	53.9
Duration oral contraceptive use[a]	61	62	63	57	64
Parity[b]	2.8	2.8	2.7	2.6	2.8
Duration of lactation (months)[b]	4.3	6.6	8.4	8.4	8.7
Physical activity (hours/week)	2.2	2.6	2.8	2.9	3.4
Body mass index (kg/m^2)	26.9	25.4	25.4	25.5	25.1
Percent of study population					
Never user of oral contraceptives	39	37	38	42	41
Parous	82	78	82	81	83
Current smoker	30	23	15	14	12
History of tubal ligation	23	16	19	19	15
Family history of ovarian cancer	3.9	2.5	2.9	1.7	3.8
Mean dietary intake					
Total energy (kcal/day)	1824	1854	1859	1817	1854
Lactose (grams/day)[c]	13.8	14.4	13.5	11.8	13.2
Total carotene intake (IU/day)[c]	5964	8828	10244	11221	12454
Dietary fiber intake (grams/day)[c,d]	14.2	16.6	18.6	19.2	20.3
AOAC fiber intake (grams/day)[c,d]	12.7	14.7	17.0	18.3	19.2

[a] Duration in months among women with a history of oral contraceptive use

[b] Among parous women

[c] Adjusted for total energy intake

[d] Dietary fiber intake is available for women enrolled in phase one of study enrollment, while AOAC fiber intake is available for women enrolled in phase two of enrollment

Table 3

Relative risks (RRs) and 95% confidence intervals for the association between flavonoid intake and epithelial ovarian cancer among 1,141 cases and 1,183 controls

	Quintile of intake					*P* -trend[a]
	1	2	3	4	5	
Total flavonoid intake[b]						
Median intake[c]	6.0	9.4	12.6	17.1	27.5	
Cases/controls	228/231	249/238	221/239	239/235	204/240	
Age-adjusted RR[d]	1.00 (ref.)	1.06 (0.82, 1.37)	0.93 (0.72, 1.21)	1.03 (0.79, 1.33)	0.85 (0.65, 1.11)	0.17; 0.07
Multivariable RR[e]	1.00 (ref.)	1.23 (0.92, 1.63)	1.12 (0.83, 1.52)	1.22 (0.90, 1.67)	1.06 (0.78, 1.45)	0.85; 0.77
Myricetin intake						
Median intake[c]	0.4	0.6	0.9	1.4	2.8	
Cases/controls	218/231	225/239	238/234	234/240	226/239	
Age-adjusted RR[d]	1.00 (ref.)	1.00 (0.77, 1.29)	1.08 (0.83, 1.39)	1.03 (0.79, 1.33)	0.99 (0.77, 1.29)	0.90; 0.59
Multivariable RR[e]	1.00 (ref.)	1.09 (0.83, 1.44)	1.18 (0.89, 1.56)	1.14 (0.87, 1.51)	1.12 (0.85, 1.49)	0.61; 0.66
Flavonoid-adj. RR[f]	1.00 (ref.)	1.10 (0.83, 1.47)	1.21 (0.89, 1.66)	1.25 (0.86, 1.80)	1.40 (0.88, 2.24)	0.21; 0.44
Kaempferol intake						
Median intake[c]	0.5	1.1	1.8	3.2	6.9	
Cases/controls	249/232	228/235	204/239	247/239	213/238	
Age-adjusted RR[d]	1.00 (ref.)	0.91 (0.70, 1.17)	0.80 (0.62, 1.04)	0.97 (0.75, 1.24)	0.83 (0.64, 1.08)	0.36; 0.31
Multivariable RR[e]	1.00 (ref.)	1.09 (0.82, 1.46)	0.97 (0.72, 1.31)	1.07 (0.80, 1.43)	0.98 (0.73, 1.32)	0.75; 0.79
Flavonoid-adj. RR[f]	1.00 (ref.)	1.04 (0.77, 1.40)	0.85 (0.61, 1.18)	0.93 (0.65, 1.32)	0.79 (0.51, 1.22)	0.29; 0.61
Quercetin intake						
Median intake[c]	3.5	5.6	7.6	10.3	16.5	
Cases/controls	230/233	256/236	226/237	217/238	212/239	
Age-adjusted RR[d]	1.00 (ref.)	1.10 (0.85, 1.42)	0.96 (0.74, 1.25)	0.92 (0.71, 1.19	0.89 (0.68, 1.15)	0.16; 0.04
Multivariable RR[e]	1.00 (ref.)	1.29 (0.97, 1.71)	1.25 (0.93, 1.69)	1.13 (0.83, 1.55)	1.14 (0.84, 1.56)	1.00; 0.79
Flavonoid-adj. RR[f]	1.00 (ref.)	1.30 (0.96, 1.76)	1.23 (0.86, 1.76)	1.10 (0.74, 1.64)	1.09 (0.67, 1.75)	0.80; 0.42

	Quintile of intake					*P* -trend[a]
	1	**2**	**3**	**4**	**5**	
Luteolin intake						
Median intake[c]	0.3	0.7	1.2	1.9	2.9	
Cases/controls	220/231	239/238	217/232	237/243	228/239	
Age-adjusted RR[d]	1.00 (ref.)	1.06 (0.82, 1.37)	0.98 (0.76, 1.27)	1.02 (0.79, 1.32)	0.99 (0.76, 1.29)	0.84; 0.65
Multivariable RR[e]	1.00 (ref.)	1.14 (0.82, 1.58)	0.97 (0.65, 1.46)	0.91 (0.57, 1.47)	1.01 (0.58, 1.74)	0.88; 0.94
Flavonoid-adj. RR[f]	1.00 (ref.)	1.15 (0.82, 1.60)	0.95 (0.63, 1.44)	0.91 (0.56, 1.47)	1.04 (0.59, 1.81)	0.99; 0.93
Apigenin intake						
Median intake[c]	0.03	0.1	0.2	0.3	0.7	
Cases/controls	299/234	208/235	253/238	182/239	199/237	
Age-adjusted RR[d]	1.00 (ref.)	0.69 (0.54, 0.89)	0.83 (0.65, 1.06)	0.59 (0.46, 0.77)	0.65 (0.51, 0.85)	0.01; <0.001
Multivariable RR[e]	1.00 (ref.)	0.78 (0.59, 1.02)	0.98 (0.74, 1.29)	0.69 (0.51, 0.92)	0.79 (0.59, 1.06)	0.26; 0.07
Flavonoid-adj. RR[f]	1.00 (ref.)	0.75 (0.57, 0.99)	0.95 (0.72, 1.25)	0.65 (0.49, 0.88)	0.72 (0.53, 0.98)	0.09; 0.01

[a] *P* -values for test for trend calculated using the Wald test; first *p* -value is for a continuous variable weighted by median of each quintile; second *p* -value is for log-transformed continuous intake

[b] Total intake of five flavonoids (myricetin, kaempferol, quercetin, luteolin, apigenin)

[c] Intake in milligrams/day among controls

[d] Adjusted for age in years and study center

[e] Adjusted for age in years, study center, duration of oral contraceptive use, parity, history of tubal ligation, physical activity, total duration of breastfeeding, dietary intake of carotenoids, fiber intake, and total energy intake

[f] Adjusted for variables above, plus quintile of intake of each other individual flavonoid

Table 4

Primary contributors to between-person variation in intake of each flavonoid

Flavonoid	Food and percent of between-person variation contributed[a]
Total flavonoids[b,c]	Tea (82%)
	Red wine (3%)
	Apples (3%)
	Romaine or leaf lettuce (2%)
	Orange juice (2%)
Myricetin	Tea (63%)
	Blueberries (13%)
	Other fruit juice (12%)[d]
	Red wine (9%)
Kaempferol	Tea (81%)
	Kale (12%)
	Raw spinach (2%)
Quercetin[c]	Tea (69%)
	Romaine or leaf lettuce (10%)
	Apples (8%)
	Chili (2%)
	Red wine (2%)
Luteolin	Orange juice (73%)
	Oranges (20%)
	Grapefruit (3%)
Apigenin	Red wine (76%)
	Celery (11%)
	Tomato sauce (3%)

[a] Percent each food contributed to between-person variation is presented as an estimate of the percent contributed to intake of each flavonoid

[b] Total intake of five flavonoids (myricetin, kaempferol, quercetin, luteolin, apigenin)

[c] Data on onion consumption not available

[d] Other fruit juice excludes apple, orange, and grapefruit juice

Table 5

Relative risks (RRs) and 95% confidence intervals for the association between flavonoid-rich foods and epithelial ovarian cancer among 1,141 cases and 1,183 controls

Food	Servings	Cases	Controls	Multivariable RR[a,b]
Tea, non-herbal	<=1/week	697	723	1.00 (ref.)
	2–6/week	182	197	0.94 (0.74, 1.20)
	1/day	133	140	0.95 (0.72, 1.25)
	2+/day	129	123	1.13 (0.85, 1.50)
				p -trend = 0.53
Red wine	<1/month	746	738	1.00 (ref.)
	1–3/month	186	198	1.01 (0.80, 1.29)
	1/week	77	89	1.03 (0.73, 1.45)
	2–4/week	81	94	0.96 (0.69, 1.35)
	5+/week	51	64	0.83 (0.55, 1.25)
				p -trend = 0.18
Kale	<1/month	1,020	1,049	1.00 (ref.)
	1–3/month	83	87	0.96 (0.67, 1.37)
	1/week	27	28	0.99 (0.54, 1.79)
	2+/week	11	19	0.66 (0.30, 1.48)
				p -trend = 0.46
Broccoli	<1/month	154	129	1.00 (ref.)
	1–3/month	301	313	0.88 (0.65, 1.19)
	1/week	374	390	1.02 (0.75, 1.39)
	2+/week	312	351	1.05 (0.76, 1.46)
				p -trend = 0.93
Celery	<1/month	382	328	1.00 (ref.)
	1–3/month	358	366	0.91 (0.73, 1.14)
	1/week	196	238	0.81 (0.62, 1.06)
	2–4/week	144	189	0.67 (0.50, 0.90)
	5+/week	61	62	0.92 (0.60, 1.39)
				p -trend = 0.11
Blueberries	<1/month	622	579	1.00 (ref.)
	1–3/month	314	372	0.86 (0.70, 1.06)
	1/week	119	158	0.77 (0.58, 1.02)
	2+/week	86	74	1.13 (0.78, 1.64)
				p -trend = 0.41
Raisins	<1/month	481	462	1.00 (ref.)
	1–3/month	370	404	0.93 (0.76, 1.15)
	1/week	148	147	1.06 (0.80, 1.41)
	2–4/week	97	121	0.83 (0.60, 1.15)
	5+/week	45	49	0.86 (0.54, 1.37)
				p -trend = 0.03

Food	Servings	Cases	Controls	Multivariable RR[a,b]
Cauliflower	<1/month	593	571	1.00 (ref.)
	1–3/month	345	387	0.88 (0.72, 1.08)
	1/week	150	154	0.93 (0.70, 1.23)
	2+/week	53	71	0.68 (0.45, 1.02)
				p -trend = 0.05

[a] *P* -values are for the test for trend for continuous intake in servings/day; calculated using the Wald test

[b] Adjusted for age in years, study center, duration of oral contraceptive use, parity, history of tubal ligation, physical activity, total duration of breastfeeding, dietary intake of carotenoids, fiber intake, and total energy intake