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Diet and Risk of Ovarian Cancer in the California Teachers Study Cohort

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Abstract

Dietary phytochemical compounds, including isoflavones and isothiocyanates, may inhibit cancer development but have not yet been examined in prospective epidemiologic studies of ovarian cancer. The authors have investigated the association between consumption of these and other nutrients and ovarian cancer risk in a prospective cohort study. Among 97,275 eligible women in the California Teachers Study cohort who completed the baseline dietary assessment in 1995–1996, 280 women developed invasive or borderline ovarian cancer by December 31, 2003. Multivariable Cox proportional hazards regression, with age as the timescale, was used to estimate relative risks and 95% confidence intervals; all statistical tests were two sided. Intake of isoflavones was associated with lower risk of ovarian cancer. Compared with the risk for women who consumed less than 1 mg of total isoflavones per day, the relative risk of ovarian cancer associated with consumption of more than 3 mg/day was 0.56 (95% confidence interval: 0.33, 0.96). Intake of isothiocyanates or foods high in isothiocyanates was not associated with ovarian cancer risk, nor was intake of macronutrients, antioxidant vitamins, or other micronutrients. Although dietary consumption of isoflavones may be associated with decreased ovarian cancer risk, most dietary factors are unlikely to play a major role in ovarian cancer development.

Keywords

antioxidants; cohort studies; diet; isoflavones; isothiocyanates; nutrition; ovarian neoplasms; women's health

Our limited understanding of ovarian cancer epidemiology inhibits opportunities to develop prevention strategies against this sixth most common and seventh most deadly malignancy in women worldwide (1). Marked geographic variation in incidence rates (1) suggests an important role of behavioral—and potentially modifiable—factors such as diet in ovarian

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cancer development. However, there is no clear etiologic role of dietary intake in ovarian cancer.

Several epidemiologic studies have examined the relation between dietary factors and ovarian cancer (refer to review by Schulz et al. (2)). Intake of milk, lactose (3–5), or eggs (3,6,7) was associated with increased ovarian cancer risk in some prospective cohorts. In two cohorts (8, 9), ovarian cancer risk was inversely associated with folate intake among moderate alcohol drinkers. Null associations were reported for intake of dietary fat or high-fat foods (3,7), meat (3,7), total fruits and vegetables (10–12), and dietary antioxidants (10,13). Pooled analyses of 12 prospective cohorts corroborate the lack of association with consumption of fruits, vegetables (14), and dietary fat (15) and do not support associations with dairy products (16), eggs, or cholesterol (15). Most case-control studies also suggest no association with intake of dairy products, eggs, fruits, grain products, fish, or fats (2). Altogether, existing data offer little indication that dietary modification can reduce ovarian cancer risk.

Recently, interest has been directed toward the possible anticarcinogenic properties of nonnutritive phytochemical compounds, including phytoestrogens and isothiocyanates. Isoflavones, a class of phytoestrogens found in soy-based foods, have antiestrogenic and antiproliferative effects (17) and inhibit the growth and proliferation of ovarian cancer cells in vitro (18). Isothiocyanates, precursors of which are found in cruciferous vegetables, can inhibit metabolic activation and enhance detoxification of carcinogens (19), alter apoptosis, protect against oxidative damage, and exert antiestrogenic effects (20), possibly in synergy with isoflavones (21). We have investigated the role of isoflavones and isothiocyanates, as well as other dietary factors, in the development of ovarian cancer in the prospective California Teachers Study cohort.

Materials and Methods

Study population

The California Teachers Study cohort comprises 133,479 active and retired female public school teachers and administrators who participated in the California State Teachers Retirement System and returned a mailed questionnaire in 1995–1996 that addressed a wide variety of issues related to cancer risk and women's health (22). This research was approved by the Northern California Cancer Center Institutional Review Board. The California Teachers Study is also overseen by the institutional review boards at the University of Southern California, the University of California, Irvine, and the California State Health Department.

For this analysis, we excluded women (in a hierarchical manner) who, at baseline, were not residents of California ($n = 8,867$); had an unknown prior history of cancer ($n = 662$); consented to participate only in analyses of breast cancer ($n = 18$); had previously been diagnosed with ovarian cancer ($n = 640$); reported having had a bilateral oophorectomy ($n = 14,422$); were aged 85 years or older ($n = 1,874$); had never had a first menstrual period ($n = 51$); had missing, invalid, or inconsistent dietary data ($n = 2,942$); reported food consumption that was very low (<600 kcal/day) or very high (>5,000 kcal/day) ($n = 1,565$ and 69, respectively); or had missing, invalid, or inconsistent data with respect to alcohol intake during the previous year ($n = 5,094$). Of the 97,275 women included in this analysis, 252 were diagnosed with invasive ovarian cancer and 28 with borderline ovarian cancer on or before December 31, 2003.

Dietary assessment

Dietary intake during the year prior to baseline (year 1995, for most women) was assessed by use of an early version of the 1995 food frequency questionnaire developed and validated by Dr. Gladys Block (23–25). Women were asked how often, on average, they had consumed 103

food and beverage items or groups during the previous year and whether they usually consumed a small, medium, or large serving size of each item, relative to a standard "medium" serving size. Women who reported taking vitamins or minerals regularly (≥1 time/week) were asked how many days per week, for how many years, and at what dosage they had taken multivitamins, vitamin A, beta-carotene, vitamin C, vitamin E, and selenium. A handful of additional food and beverage items, including coffee and tea separately, were assessed in a follow-up questionnaire in 1997–1998. For this study, analyses of coffee and tea intakes were based on the 72,182 eligible women who completed the follow-up questionnaire, including 154 women with incident ovarian cancer diagnosed after completing the follow-up questionnaire and before December 31, 2003.

The original Block nutrient database was updated by use of data from various sources (26, 27). Two supplementary databases were added, one containing information on isothiocyanates per 100 g of food (Pamela L. Horn-Ross, Northern California Cancer Center, personal communication, 2006) and the other containing information on phytoestrogenic compounds (including the isoflavones genistein, daidzein, biochanin A, and formononetin) per 100 g of food (28). Estimated dietary intake of isoflavones was shown to be reproducible and valid when compared with 24-hour dietary recalls and 24-hour excreted urinary levels in a sample of cohort members (29). Average daily caloric and nutrient intakes were calculated on the basis of the reported frequency of intake and portion size. We also calculated a total antioxidant score, measured by the oxygen radical absorbance capacity assay, for antioxidant capacity against oxygen radicals on the basis of fruit and vegetable consumption (30–32), and we calculated three antioxidant indices (i.e., antioxidant capacity against peroxyl radicals, hydroxyl radicals, and radicals produced by oxidation of a transition metal (30)) to measure the dietary antioxidant capacity of consumed vegetables.

Follow-up

Women contributed person-days to the analysis, starting from the date of completion of the baseline questionnaire and continuing until the date of first diagnosis with borderline or invasive ovarian cancer, date of relocation to a residence outside California, date of death, or December 31, 2003, whichever occurred earliest. Cohort members are followed for cancer diagnosis, death, and change of address.

Information on incident ovarian cancer (*International Classification of Diseases for Oncology*, Third Edition, site C569, excluding morphology codes 9590–9989 (33)) and tumor characteristics was identified through linkage to the population-based California Cancer Registry, which has 99 percent coverage of new cancer diagnoses in the state (34). Linkages with the California state mortality file and the national Social Security Administration death master file, as well as reports from relatives, were used to ascertain date and cause of death. Address changes were obtained through annual mailed newsletters, notifications by participants, and record linkages with multiple sources.

Statistical analysis

Multivariable Cox proportional hazards regression was used to evaluate associations between dietary intake and risk of ovarian cancer, by use of age (in days) to define the timescale (35). Dietary intake was categorized into quintiles on the basis of the distribution in the eligible study population. For certain nutrients and foods with a limited range of intake, fewer categories were created. In analyses of total intakes of vitamins and minerals (i.e., from food and supplements), to minimize biases resulting from recent use of dietary supplements by individuals with prediagnostic symptoms or other indications of poor health (36), we included only nonusers of supplements and women who had used multivitamins or the supplement of interest for at least the past 2 years; that is, short-term users were excluded. In analyses of

dietary micronutrient intake (i.e., from food only), we excluded all users of each dietary supplement (with various numbers of women excluded according to the type of supplement) to avoid underestimating their overall exposure to that micronutrient.

Models were adjusted for race (White or non-White) and total daily caloric intake (continuous kilocalories) only or for race, total daily caloric intake, parity (zero, 1–2, or ≥3 full-term pregnancies), use of oral contraceptives (never, <5 years, or ≥5 years), average strenuous physical exercise (<0.5, 0.5–3.99, or ≥4 hours/week during the lifetime up to age 54 years), average daily consumption of alcohol from wine in the year before baseline (continuous grams), menopausal status/use of hormone therapy (premenopausal; peri-/postmenopausal and never used hormone therapy, used combination estrogenprogestin hormone therapy, used a mixture of combination and estrogen-only ("mixed") hormone therapy, used estrogen-only hormone therapy for ≤5 years, used estrogen-only hormone therapy for >5 years, used estrogen-only hormone therapy for an unknown duration, or unknown hormone therapy use; or unknown menopausal status), and an interaction term between menopausal status/hormone therapy use and the timescale (because menopausal status/hormone therapy use violated the proportionality assumption), and they were stratified by age at baseline (in years). Analyses of total micronutrient intake were additionally adjusted for use of any dietary supplements (yes for ≥2 years or none). These potential confounders were chosen on the basis of statistically significant ($p \leq 0.05$) associations with risk of ovarian cancer and on the basis of prior subject matter knowledge. Missing values were included in the models as indicator variables; missingness was not associated with ovarian cancer risk. Hazard ratios, presented as relative risks, and corresponding 95 percent confidence intervals were estimated to compare categories of dietary intake with the lowest category as the referent group. Using the median of each category, we conducted Wald tests for trend with the exposure coded as an ordinal variable. Tests for nonlinearity of trend were based on likelihood ratio tests to compare models with the exposure coded as an ordinal versus as a categorical variable (37). The proportional hazards assumption was tested for each dietary covariate by use of significance tests of interactions between the covariate and the timescale and by visual examination of scaled Schoenfeld residual plots (38); there were no meaningful violations of the proportionality assumption. All tests of statistical significance were two sided.

Dietary intake of macronutrients was adjusted for total energy intake by use of the multivariable nutrient density method (39), in which nutrient intake is divided by total energy intake, and total energy is simultaneously included as a separate variable in the model. Intake of micronutrients or food items was energy adjusted by including total energy intake independently in the model. All nutrient analyses were repeated with energy adjustment by use of the residual method (39). Analyses were first performed for all eligible women and then repeated after restricting the cohort to women who were perior postmenopausal at baseline (n = 45,630). In addition, secondary analyses were performed with restriction of the cases to invasive ovarian cancer (n = 252) and then to serous ovarian cancer (*International Classification of Diseases for Oncology*, Third Edition, morphology codes 8441, 8442, 8461–8462 (33); n = 120). All analyses were performed using SAS, version 9.1, statistical software (SAS Institute, Cary, North Carolina).

Results

Table 1 presents the distributions of demographic characteristics and ovarian cancer risk factors in eligible women. The median duration of follow-up was 2,959 days (8.1 years), the median age at baseline was 50 years, and the median total daily caloric intake was 1,501 kcal.

Macronutrients

Total daily caloric intake was not associated with risk of ovarian cancer; the multivariable adjusted relative risk comparing the highest with the lowest quintile of total energy intake was 1.36 (95 percent confidence interval (CI): 0.47, 3.93; $p_{trend} = 0.64$). Furthermore, consumption of dietary fiber (quintile 5 vs. quintile 1: relative risk (RR) = 1.24, 95 percent CI: 0.84, 1.84; $p_{trend} = 0.66$) or any macronutrient, including total fat (RR = 0.85, 95 percent CI: 0.58, 1.24; $p_{trend} = 0.26$), saturated fat (RR = 0.72, 95 percent CI: 0.48, 1.08; $p_{trend} = 0.10$), carbohydrate (RR = 1.14, 95 percent CI: 0.79, 1.65; $p_{trend} = 0.34$), and protein (RR = 1.03, 95 percent CI: 0.72, 1.50; $p_{trend} = 0.78$), was unrelated to ovarian cancer risk. Neither the ratio of total fat to dietary fiber consumption (RR = 0.84, 95 percent CI: 0.58, 1.22; $p_{trend} = 0.39$) nor the ratio of carbohydrate to protein consumption (RR = 1.13, 95 percent CI: 0.80, 1.60; $p_{trend} = 0.35$) was associated with risk of ovarian cancer.

Micronutrients and dietary antioxidants

Intake of calcium, retinol, vitamin D, phosphorus, or folate was not associated with risk of ovarian cancer (table 2). Because calcium, retinol, and phosphorus are negative regulators of biologically available levels of active vitamin D (40,41), we simultaneously adjusted for these four nutrients but still observed no association with ovarian cancer risk (data not shown). The null association between total folate consumption and ovarian cancer risk did not vary by level of alcohol intake in a comparison of women who did not drink alcohol with those who drank 20 or more g of alcohol per day ($p_{heterogeneity} = 0.18$).

None of the four indices of dietary antioxidant intake examined was associated with risk of ovarian cancer (table 3). Although higher total consumption of some antioxidant micronutrients, including beta-carotene and vitamin C, was associated with marginally increased ovarian cancer risk, none showed both a statistically significant dose-response relation with ovarian cancer risk and a significantly elevated risk of ovarian cancer in the highest quintile of intake compared with the lowest (table 3). Likewise, dietary intakes of these vitamins from food sources only (among women who did not take supplemental vitamins) were not associated with ovarian cancer risk. Comparing the highest with the lowest quintile of intake, the multivariable adjusted relative risk of ovarian cancer associated with dietary beta-carotene intake was 1.78 (95 percent CI: 0.83, 3.80; $p_{trend} = 0.64$), and that associated with dietary vitamin C intake was 1.50 (95 percent CI: 0.71, 3.19; $p_{trend} = 0.21$). Dietary intake of vitamin E or total or individual carotenoids (including alpha-carotene, lycopene, lutein, and cryptoxanthin) was similarly unrelated to risk of ovarian cancer (latter data not shown).

Dietary phytochemical compounds

Dietary intake of isoflavones was marginally associated with decreased risk of ovarian cancer (table 4). Women who consumed more than 3 mg of total isoflavones per day had 44 percent lower risk of ovarian cancer than did women who consumed less than 1 mg per day. Forty-eight percent of Asian/Pacific Islander women in the cohort versus 11 percent of non-Hispanic White women consumed more than 3 mg of isoflavones per day ($p_{chi\text{-}square} < 0.001$). Genistein and daidzein, the two main isoflavones in soy foods, accounted for most of the risk reduction associated with total isoflavone intake, whereas biochanin A and formononetin, which are found in a limited number of foods and consumed at low levels (generally <0.05 mg/day), were not associated with ovarian cancer risk (data not shown). The inverse associations between ovarian cancer risk and intake of foods high in isoflavones—specifically, tofu/bean curd or soy-containing meat substitutes—were not statistically significant, although these foods were not frequently consumed and were not the only sources of isoflavones in the cohort (42), and the highest levels of intake examined were relatively low.

Total isothiocyanate intake was not associated with risk of ovarian cancer (table 4). Likewise, consumption of foods high in isothiocyanates, including cauliflower/brussels sprouts, broccoli, mustard greens/turnip greens/collards, and cabbage/cole slaw, was unrelated to risk of ovarian cancer. Comparing women who consumed both greater than 2 mg of isoflavones per day and greater than 10 μmol of isothiocyanates per day with women who consumed less than 1 mg of isoflavones per day and less than 5 μmol of isothiocyanates per day, we found the multivariable adjusted relative risk of ovarian cancer to be 0.55 (95 percent CI: 0.29, 1.04).

Foods previously associated with risk of ovarian cancer

Consumption of dairy products, milk, coffee, tea, or eggs was not associated with risk of ovarian cancer. In a comparison of the highest with the lowest quintile of intake, the estimated multivariable adjusted relative risks for the association with ovarian cancer were as follows: for dairy products (including milk, half and half, butter, cheese, yogurt, and ice cream), relative risk = 0.84 (95 percent CI: 0.56, 1.26; $p_{trend} = 0.56$); for milk, relative risk = 0.97 (95 percent CI: 0.67, 1.42; $p_{trend} = 0.94$); for coffee, relative risk = 1.02 (95 percent CI: 0.55, 1.90; $p_{trend} = 0.78$); for tea, relative risk = 1.27 (95 percent CI: 0.79, 2.06; $p_{trend} = 0.08$); and for eggs, relative risk = 0.78 (95 percent CI: 0.53, 1.15; $p_{trend} = 0.23$).

Additional analyses

All analyses of micro- and macronutrient consumption were repeated with adjustment for total energy intake by use of the residual method, and there were no meaningful differences in the results (data not shown). Additional control for indicators of socioeconomic status or geographic region of residence (43) did not affect the estimates (data not shown). There were no substantial differences in the observed associations with nutrient or food intake when the analysis was restricted to peri-/postmenopausal women, nor when the cases were limited to invasive or serous ovarian cancer only (data not shown).

Discussion

In this cohort of California teachers, we found little evidence that specific foods or nutrients, other than perhaps isoflavones, are associated with risk of ovarian cancer. Thus, our results extend the null findings of the pooled analysis of cohort studies, in which no association was observed between dietary factors and ovarian cancer risk (14–16). The inverse association between consumption of isoflavones and risk of ovarian cancer is intriguing, because it can be explained by a cogent biologic mechanism. The preponderance of scientific evidence suggests that estrogens promote the development of ovarian cancer, possibly by stimulating the growth and proliferation of ovarian surface epithelial cells, which express estrogen and androgen receptors (44,45). As a corollary, phytoestrogens may inhibit ovarian cancer development by decreasing endogenous estrogen levels through stimulation of sex-hormone binding globulin production by the liver, thereby decreasing the levels of bioavailable estrogens (46); through competitive binding to estrogen receptors (47); and/or through inhibition of the activity of aromatase, the enzyme responsible for conversion of androgens to estrogens (48). Indeed, previous studies have shown that phytoestrogens inhibit the growth and proliferation of ovarian cancer cell lines (18), although these effects may also be mediated through estrogen-independent pathways (17). Two case-control studies found an inverse association between dietary intake of phytoestrogens (isoflavones or lignans) and ovarian cancer risk (49,50). Because food frequency questionnaire assessment of dietary lignan intake was poorly correlated with measured urinary excretion of lignans in women in our cohort (29), we did not examine the association between dietary lignan consumption and risk of ovarian cancer.

Although isothiocyanates, too, have antiestrogenic properties (20), as well as antioxidant and detoxifying effects (19), we did not observe any association between isothiocyanate

consumption and risk of ovarian cancer. This result is consistent with the lack of association between cruciferous vegetable intake and ovarian cancer risk in previous case-control studies (2). Moreover, we found no association between consumption of other antioxidant nutrients or indices of overall dietary antioxidant intake and risk of ovarian cancer. These results corroborate those from two other prospective cohorts in which there was no association between consumption of vitamin A, C, or E, carotenoids, or fruits and/or vegetables and risk of ovarian cancer (10,13). Although findings of an inverse association between tea drinking and risk of ovarian cancer in a Swedish cohort (51) and a Chinese case-control study (52) were speculatively attributed to the antioxidant effects of polyphenols in tea, no such association with tea drinking—even at a comparable frequency—was observed in our study or those of others (53,54). The discrepancy in results among studies may be due to cultural differences in the types of tea consumed, bias, or chance. In combination with the substantial evidence of no association between fruit and vegetable consumption and risk of ovarian cancer (10–12,14), our findings do not substantiate a protective effect of dietary antioxidants against ovarian cancer development.

Despite the considerable strengths of our study, including its large size, prospective exposure assessment, and virtually complete case ascertainment, there are several limitations to consider. We assessed usual dietary intake only at one point in adulthood, and our study cohort has a broad age range; it could be that diet during some other age or time period or cumulative intake or change in dietary habits over time is more relevant to ovarian cancer risk. In addition, we tested many potential associations, and the observed inverse association with isoflavone intake —although hypothesized a priori—may have been due to chance. Conversely, the absence of any other significant associations with ovarian cancer risk could be due to a lack of sufficient statistical power to detect associations in our cohort.

Our study is also subject to the limitations of all observational studies of dietary intake. For instance, food frequency questionnaires have a limited capacity to capture detailed information about food and nutrient consumption (55). However, misclassification in our cohort was likely to be nondifferential, because exposure information was collected prospectively; also, the food frequency questionnaire and nutrient database used in our study were thoroughly validated (23–25,29). Another potential limitation is that the observed inverse association of ovarian cancer risk with intake of isoflavones, as well as the marginal positive associations with intake of antioxidant micronutrients, could be explained by other factors correlated with both dietary habits and ovarian cancer risk, such as socioeconomic status, although adjustment for a neighborhood-based measure of socioeconomic status did not impact our estimates. Similarly, the lack of other apparent associations could be due to confounding by uncontrolled or imperfectly adjusted factors.

Bearing these caveats in mind, we conclude that our study does not support a major role of diet in ovarian cancer development, at least in this predominantly (87 percent) non-Hispanic White cohort. High consumption of isoflavones may decrease ovarian cancer risk and may be partly responsible for the markedly lower incidence rates of ovarian cancer in Asian populations (including natives and migrants), among whom dietary intake of soy products is typically high, than in Western populations, whose soy intake is generally low (1,56). However, international and racial/ethnic discrepancies in ovarian cancer incidence could also be explained by other environmental and genetic differences. Therefore, nondietary, potentially modifiable environmental differences must be ascertained and understood in order to identify feasible methods to prevent the development of ovarian cancer in the general population.

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Abbreviations

CI
confidence interval

RR
relative risk

TABLE 1

Selected baseline characteristics of the California Teachers Study cohort included in the present analysis (n = 97,275), from 1995–1996 to 2003

Characteristic	No.	%
Age at baseline (years)		
<35	11,183	11.5
35–44	19,630	20.2
45–54	30,350	31.2
55–64	17,593	18.1
65–74	12,536	12.9
75–84	5,983	6.2
Race/ethnicity		
White	84,471	86.8
Hispanic	4,267	4.4
Asian/Pacific Islander	3,546	3.6
Black	2,324	2.4
Native American/other/mixed	1,957	2.0
Unknown	710	0.7
Total energy intake (kcal/day)		
600–1,100	18,503	19.0
1,101–1,300	14,389	14.8
1,301–1,500	15,639	16.1
1,501–1,700	14,314	14.7
1,701–2,000	15,616	16.1
≥2,001	18,814	19.3
Parity (full-term pregnancies)		
None	25,626	26.3
1–2	46,947	48.3
≥3	23,101	23.7
Unknown	1,601	1.6
Oral contraceptive use (years)		
None	28,743	29.5
<5	29,648	30.5
≥5	34,971	36.0
Unknown	3,913	4.0
Strenuous physical activity (hours/week)		
<0.5	27,119	27.9
0.5–3.9	53,276	54.8
≥4.0	16,482	16.9
Unknown	398	0.4
Wine consumption in past year (g of alcohol/day)		
None	38,898	40.0
<11.1 (<1 glass)	41,235	42.4
≥11.1 (≥1 glass)	17,142	17.6
Menopausal status		
Premenopausal	44,956	46.2
Perimenopausal	2,363	2.4
Postmenopausal	43,267	44.5
Unknown	6,689	6.9
Hormone therapy use (peri-/postmenopausal women only)		
None	14,060	30.8
Combination estrogen + progestin hormone therapy	15,417	33.8
Estrogen-only hormone therapy, ≤5 years	4,747	10.4
Estrogen-only hormone therapy, >5 years	5,348	11.7
Estrogen-only hormone therapy, unknown duration	365	0.8
Mixed combination and estrogen-only hormone therapy	5,253	11.5
Unknown	440	1.0

TABLE 2

Relative risks and 95% confidence intervals for associations between consumption of selected micronutrients and risk of ovarian cancer in the California Teachers Study cohort, from 1995–1996 to 2003

Nutrient intake/day	Median	No. of cases	Relative risk*	95% confidence interval	Relative risk†	95% confidence interval
Total calcium (mg)‡						
≤461	361	63	1.00	Referent	1.00	Referent
>461–630	546	53	0.86	0.59, 1.24	0.81	0.56, 1.19
>630–816	717	52	0.89	0.61, 1.31	0.83	0.56, 1.24
>816–1,127	939	48	0.89	0.59, 1.35	0.82	0.54, 1.26
>1,127	1,469	50	0.96	0.62, 1.50	0.90	0.57, 1.43
				p_{trend} = 0.92§		p_{trend} = 0.93
Dietary retinol (μg)¶						
≤233	172	19	1.00	Referent	1.00	Referent
>233–346	297	20	1.17	0.62, 2.21	1.16	0.61, 2.20
>346–466	413	21	1.32	0.69, 1.53	1.34	0.70, 2.59
>466–659	559	18	1.25	0.62, 2.54	1.24	0.61, 2.53
>659	851	14	1.17	0.52, 2.64	1.17	0.52, 2.66
				p_{trend} = 0.75		p_{trend} = 0.75
Total vitamin D (IU)‡						
≤115	77	43	1.00	Referent	1.00	Referent
>115–210	156	50	1.18	0.78, 1.79	1.16	0.76, 1.75
>210–435	313	49	1.19	0.78, 1.82	1.09	0.71, 1.69
>435–550	495	66	1.32	0.89, 1.94	1.08	0.70, 1.68
>550	639	58	1.19	0.79, 1.80	0.97	0.61, 1.56
				p_{trend} = 0.36		p_{trend} = 0.70
Dietary phosphorus (mg)¶						
≤692	586	27	1.00	Referent	1.00	Referent
>692–888	814	19	0.84	0.46, 1.56	0.84	0.45, 1.55
>888–1,090	1,012	14	0.73	0.35, 1.50	0.73	0.35, 1.51
>1,090–1,399	1,255	18	1.14	0.53, 2.42	1.12	0.52, 2.40
>1,399	1,729	14	1.11	0.44, 2.80	1.08	0.43, 2.75
				p_{trend} = 0.63		p_{trend} = 0.68
Total folate (μg)‡						
≤272	215	54	1.00	Referent	1.00	Referent
>272–385	324	47	1.02	0.68, 1.53	0.98	0.65, 1.48
>385–572	473	54	1.25	0.84, 1.85	1.07	0.71, 1.63
>572–711	643	65	1.17	0.81, 1.70	0.92	0.61, 1.40
>711	802	46	1.04	0.67, 1.61	0.81	0.49, 1.32
				p_{trend} = 0.61		p_{trend} = 0.34

*Adjusted for race and total energy intake; stratified by age at baseline.

†Adjusted for race, total energy intake, parity, oral contraceptive use, strenuous exercise, wine consumption, and menopausal status/hormone therapy use; stratified by age at baseline.

‡Additionally adjusted for use of dietary supplements; excluded short-term supplement users (for <2 years).

§All *p* values are two sided.

¶Excluded multivitamin users.

TABLE 3

Relative risks and 95% confidence intervals for associations between indices of dietary antioxidant intake or total consumption of antioxidant micronutrients and risk of ovarian cancer in the California Teachers Study cohort, from 1995–1996 to 2003

Nutrient or food intake/day	Median	No. of cases	Relative risk*	95% confidence interval	Relative risk†	95% confidence interval
Indices of dietary antioxidant intake						
Total antioxidant score (μmol of Trolox‡ equivalent/g)						
≤8.2	6.0	38	1.00	Referent	1.00	Referent
>8.2–12.4	10.3	63	1.49	0.99, 2.23	1.47	0.98, 2.21
>12.4–17.4	14.8	50	1.12	0.73, 1.71	1.10	0.72, 1.70
>17.4–24.8	20.6	61	1.33	0.87, 2.02	1.30	0.86, 1.98
>24.8	31.9	68	1.39	0.91, 2.12	1.40	0.92, 2.14
				$p_{trend} = 0.32$§		$p_{trend} = 0.30$
Peroxyl radical absorbance capacity (μmol of Trolox equivalent/g)						
≤2.1	1.5	45	1.00	Referent	1.00	Referent
>2.1–3.3	2.7	67	1.35	0.92, 1.98	1.34	0.92, 1.96
>3.3–4.7	3.9	52	0.99	0.66, 1.49	0.99	0.66, 1.49
>4.7–7.0	5.6	60	1.11	0.74, 1.65	1.10	0.74, 1.64
>7.0	9.2	56	1.05	0.69, 1.58	1.05	0.69, 1.59
				$p_{trend} = 0.67$		$p_{trend} = 0.69$
Hydroxyl radical absorbance capacity (μmol of Trolox equivalent/g)						
≤0.8	0.6	50	1.00	Referent	1.00	Referent
>0.8–1.2	1.0	66	1.24	0.86, 1.79	1.23	0.85, 1.78
>1.2–1.7	1.4	41	0.72	0.47, 1.09	0.72	0.47, 1.09
>1.7–2.5	2.0	59	1.01	0.69, 1.50	1.01	0.68, 1.49
>2.5	3.2	64	1.10	0.74, 1.63	1.10	0.74, 1.64
				$p_{trend} = 0.77$		$p_{trend} = 0.73$
Antioxidant capacity against transition metals (μmol of Trolox equivalent/g)						
≤0.4	0.3	46	1.00	Referent	1.00	Referent
>0.4–0.5	0.5	67	1.38	0.94, 2.01	1.36	0.93, 1.99
>0.5–0.8	0.6	53	1.03	0.67, 1.54	1.03	0.69, 1.54
>0.8–1.1	0.9	56	1.09	0.73, 1.63	1.08	0.73, 1.62
>1.1	1.4	58	1.12	0.75, 1.69	1.13	0.75, 1.70
				$p_{trend} = 0.93$		$p_{trend} = 0.95$
Antioxidant micronutrients						
Total beta-carotene (μg)¶						
≤1,409	978	32	1.00	Referent	1.00	Referent
>1,409–2,150	1,790	41	1.15	0.72, 1.84	1.09	0.67, 1.75
>2,150–2,961	2,521	48	1.24	0.78, 1.95	1.11	0.68, 1.81
>2,961–4,601	3,554	49	1.20	0.75, 1.90	1.06	0.64, 1.77
>4,601	8,602	70	1.61	1.04, 2.49	1.41	0.85, 2.33
				$p_{trend} = 0.02$#		$p_{trend} = 0.08$#
Total vitamin C (mg)¶						
≤75	51	27	1.00	Referent	1.00	Referent
>75–122	98	43	1.46	0.90, 2.37	1.45	0.88, 2.39
>122–205	153	55	1.79	1.12, 2.86	1.76	1.04, 2.97
>205–665	369	55	1.71	1.07, 2.73	1.67	0.94, 2.96
>665	1,122	75	2.03	1.30, 3.19	1.96	1.11, 3.46
				$p_{trend} = 0.02$#		$p_{trend} = 0.17$

Nutrient or food intake/day	Median	No. of cases	Relative risk*	95% confidence interval	Relative risk†	95% confidence interval
Total vitamin E (α-tocopherol equivalent, mg)¶						
≤7	6	37	1.00	Referent	1.00	Referent
>7–14	10	36	1.20	0.74, 1.93	1.18	0.72, 1.92
>14–28	24	52	1.46	0.96, 2.24	1.33	0.71, 2.47
>28–207	37	46	1.32	0.84, 2.07	1.20	0.61, 2.37
>207	295	78	1.64	1.10, 2.45	1.46	0.76, 2.79
				$p_{trend} = 0.04$#		$p_{trend} = 0.28$

*Adjusted for race and total energy intake; stratified by age at baseline.

†Adjusted for race, total energy intake, parity, oral contraceptive use, strenuous exercise, wine consumption, and menopausal status/hormone therapy use; stratified by age at baseline.

‡Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid).

§All *p* values are two sided.

¶Additionally adjusted for use of dietary supplements; excluded short-term supplement users (for <2 years).

#*p*nonlinearity of trend > 0.05.

TABLE 4

Relative risks and 95% confidence intervals for associations between dietary intake of isoflavones or isothiocyanates (or foods high in these compounds) and risk of ovarian cancer in the California Teachers Study cohort, from 1995–1996 to 2003

Nutrient or food intake/day	Median	No. of cases	Relative risk*	95% confidence interval	Relative risk†	95% confidence interval
Total isoflavones (mg)						
≤0.7	0.5	70	1.00	Referent	1.00	Referent
>0.7–0.9	0.8	64	1.00	0.71, 1.41	1.00	0.71, 1.41
>0.9–1.3	1.1	55	0.93	0.64, 1.35	0.94	0.65, 1.36
>1.3–2.1	1.6	57	1.07	0.73, 1.57	1.08	0.74, 1.59
>2.1	3.3	34	0.71	0.45, 1.10	0.71	0.46, 1.12
				p_{trend} = 0.11‡		p_{trend} = 0.13
<1	0.7	144	1.00	Referent	1.00	Referent
1–3	1.5	120	1.00	0.77, 1.30	1.01	0.78, 1.32
>3	4.5	16	0.56	0.33, 0.96	0.56	0.33, 0.96
				p_{trend} = 0.04§		p_{trend} = 0.04¶
Genistein (mg)						
≤0.3	0.2	74	1.00	Referent	1.00	Referent
>0.3–0.5	0.4	63	0.94	0.67, 1.32	0.94	0.67, 1.32
>0.5–0.7	0.5	54	0.90	0.62, 1.30	0.90	0.63, 1.30
>0.7–1.1	0.8	57	1.04	0.71, 1.51	1.05	0.72, 1.54
>1.1	1.8	32	0.65	0.41, 1.01	0.65	0.42, 1.02
				p_{trend} = 0.06¶		p_{trend} = 0.07¶
Daidzein (mg)						
≤0.3	0.2	70	1.00	Referent	1.00	Referent
>0.3–0.4	0.4	56	0.84	0.59, 1.20	0.85	0.59, 1.21
>0.4–0.6	0.5	55	0.90	0.63, 1.31	0.90	0.62, 1.31
>0.6–0.9	0.7	62	1.13	0.77, 1.64	1.15	0.79, 1.67
>0.9	1.4	37	0.75	0.48, 1.15	0.75	0.49, 1.16
				p_{trend} = 0.31		p_{trend} = 0.33
Foods high in isoflavones						
Tofu/bean curd (g)						
0	0.0	244	1.00	Referent	1.00	Referent
>0–<10	4.3	19	0.87	0.55, 1.39	0.87	0.55, 1.39
≥10	17.1	17	0.76	0.46, 1.24	0.76	0.46, 1.24
				p_{trend} = 0.24		p_{trend} = 0.22
Meat substitutes made from soy						
None	0.00	256	1.00	Referent	1.00	Referent
Any	6.25	24	0.84	0.55, 1.28	0.83	0.55, 1.27
				$p_{chi\text{-}square}$ = 0.41		$p_{chi\text{-}square}$ = 0.40
Total isothiocyanates (μmol)						
≤2.0	0.7	51	1.00	Referent	1.00	Referent
>2.0–4.7	3.4	54	0.94	0.64, 1.37	0.93	0.63, 1.36
>4.7–8.0	6.4	61	1.00	0.69, 1.45	0.99	0.68, 1.44
>8.0–14.2	10.6	57	0.89	0.61, 1.30	0.89	.61, 1.30
>14.2	21.9	57	0.89	0.61, 1.31	0.89	0.61, 1.31
				p_{trend} = 0.53		p_{trend} = 0.56
<5	2.1	114	1.00	Referent	1.00	Referent
5–20	9.3	135	0.93	0.72, 1.19	0.93	0.72, 1.19
>20	27.2	31	0.83	0.55, 1.24	0.84	0.56, 1.26
				p_{trend} = 0.35		p_{trend} = 0.38
Foods high in isothiocyanates						
Cauliflower/brussels sprouts (g)						
0.0	0.0	99	1.00	Referent	1.00	Referent
>0.0–2.1	1.1	42	0.87	0.61, 1.25	0.87	0.61, 1.25

Nutrient or food intake/day	Median	No. of cases	Relative risk*	95% confidence interval	Relative risk†	95% confidence interval
>2.1–4.1	2.5	43	0.78	0.54, 1.12	0.77	0.54, 1.11
>4.1–8.0	5.4	49	0.86	0.60, 1.21	0.86	0.61, 1.22
>8.0	12.8	47	0.79	0.56, 1.13	0.80	0.56, 1.15
				p_{trend} = 0.29		p_{trend} = 0.33
Broccoli (g)						
≤3.3	0.8	51	1.00	Referent	1.00	Referent
>3.3–7.8	5.4	59	1.03	0.71, 1.51	1.03	0.71, 1.50
>7.8–14.4	10.2	54	0.96	0.65, 1.41	0.97	0.66, 1.42
>14.4–23.5	16.3	67	1.24	0.86, 1.80	1.24	0.86, 1.79
>23.5	40.0	49	0.91	0.61, 1.35	0.91	0.61, 1.36
				p_{trend} = 0.62		p_{trend} = 0.64
Mustard greens/turnip greens/ collards						
None	0.0	242	1.00	Referent	1.00	Referent
Any	3.9	38	1.00	0.71, 1.43	1.01	0.71, 1.44
				$p_{chi\text{-}square}$ = 0.98		$p_{chi\text{-}square}$ = 0.95
Cabbage/cole slaw (g)						
0.0	0.0	83	1.00	Referent	1.00	Referent
>0.0–1.1	0.7	36	0.79	0.54, 1.18	0.78	0.53, 1.16
>1.1–1.8	1.4	44	0.90	0.62, 1.31	0.89	0.62, 1.29
>1.8–3.6	3.4	57	1.05	0.75, 1.49	1.05	0.74, 1.48
>3.6	7.4	60	1.13	0.79, 1.60	1.12	0.79, 1.59
				p_{trend} = 0.22		p_{trend} = 0.21

*Adjusted for race and total energy intake; stratified by age at baseline.

†Adjusted for race, total energy intake, parity, oral contraceptive use, strenuous exercise, wine consumption, and menopausal status/hormone therapy use; stratified by age at baseline.

‡All *p* values are two sided.

§$p_{nonlinearity\ of\ trend}$ = 0.02.

¶$p_{nonlinearity\ of\ trend}$ > 0.05.