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Dietary phytocompounds and risk of lymphoid malignancies in the California Teachers Study cohort

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Abstract

Objective—We examined whether dietary intake of isoflavones, lignans, isothiocyanates, antioxidants, or specific foods rich in these compounds is associated with reduced risk of B-cell non-Hodgkin lymphoma (NHL), multiple myeloma (MM), or Hodgkin lymphoma (HL) in a large, prospective cohort of women.

Methods—Between 1995-1996 and December 31, 2007, among 110,215 eligible members of the California Teachers Study cohort, 536 women developed incident B-cell NHL, 104 developed MM, and 34 developed HL. Cox proportional hazards regression, with age as the time-scale, was used to estimate adjusted rate ratios (RRs) with 95% confidence intervals (CIs) for risk of lymphoid malignancies.

Results—Weak inverse associations with risk of diffuse large B-cell lymphoma were observed for isothiocyanates (RR for ≥12.1 vs. <2.7 mcM/day=0.67, 95% CI: 0.43-1.05) and an antioxidant index measuring hydroxyl radical absorbance capacity (RR for ≥2.2 vs. <0.9 μM Trolox equiv/g/day=0.68, 95% CI: 0.42-1.10; p_{trend}=0.08). Risk of other NHL subtypes, overall B-cell NHL, MM, or HL was not generally associated with dietary intake of isoflavones, lignans, isothiocyanates, antioxidants, or major food sources of these compounds.

Conclusions—Isoflavones, lignans, isothiocyanates, and antioxidant compounds are not associated with risk of most B-cell malignancies, but some phytocompounds may decrease risk of selected subtypes.

MeSH keywords

lymphoma; diet; isothiocyanates; antioxidants; cohort studies

Introduction

Lymphoid malignancies are a heterogeneous group of immune cancers arising from B, T, or NK cells. Few modifiable risk factors have been established, but several dietary components have been proposed to influence lymphomagenesis (1). In particular, more than 10 retrospective case-control studies (1) and two of three prospective cohort studies (2-5) found

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significant inverse associations between fruit and/or vegetable intake and risk of non-Hodgkin lymphoma (NHL), and similar associations have been reported in case-control studies of multiple myeloma (MM) (6,7), but not Hodgkin lymphoma (HL) (6). The observed inverse associations may be attributable to a variety of anti-carcinogenic nutrients and non-nutritive compounds found in plant foods. Among these, some of the most promising potentially chemopreventive agents are phytoestrogens, including isoflavones (from soy) and lignans (from seeds, nuts, and whole grains), which have anti-proliferative, antioxidant, and both pro- and anti-estrogenic properties (8); isothiocyanates (from cruciferous vegetables), which have detoxifying, pro-apoptotic, and antioxidant effects (9); and antioxidant micronutrients (mostly from fruits and vegetables), which can enhance the immune response and counteract the DNA-damaging effects of reactive oxygen species (10). Indeed, isoflavones and a few other antioxidant micronutrients were recently shown to be inversely associated with follicular lymphoma risk in the Iowa Women's Health Study cohort (5), although no such association with isoflavones was observed in a US population-based case-control study of NHL (11).

We know of no previous prospective studies that have examined whether overall dietary antioxidant capacity, lignans, and isothiocyanates are related to risk of NHL, MM, or HL, and could thus represent modifiable risk factors for lymphoid malignancies. We therefore investigated these associations among women in the large, prospective California Teachers Study (CTS) cohort.

Methods

Study population

The CTS cohort, which has been described in detail elsewhere (12), comprises 133,479 active and retired female public school teachers and administrators who completed a mailed risk-factor questionnaire at baseline in 1995-1996. For this analysis, we sequentially excluded women who, at baseline, were not California residents (*N*=8,867), had an unknown history of cancer (*N*=663), consented to participate only in analyses of breast cancer (*N*=18), had a history of hematopoietic cancer prior to joining the cohort (*N*=536), were aged 85 years or older (*N*=2,179), had missing, invalid, or inconsistent dietary data (*N*=3,393), reported very low or high total energy intake (<600 or >5,000 kcals/day; *N*=1,845 and 85, respectively), or had missing, invalid, or inconsistent data on recent alcohol intake (precluding calculation of total energy intake; *N*=5,678), leaving 110,215 women for follow-up.

Dietary assessment

Dietary intake during the year prior to baseline (1995, for most participants) was assessed using an early version of the Block 1995 Health History and Habits food frequency questionnaire (13), which included average frequency and portion size of 103 food and beverage items and dietary supplements. Estimated intakes of macro- and micronutrients were shown to be reproducible and valid when compared with 24-hour dietary recalls (14). We updated our nutrient database information on total isothiocyanates (Horn-Ross, unpublished data), lignans (15), and isoflavones per 100 grams of food, as previously described (16). Estimated isoflavone intake, based on the daidzein, genistein, biochanin A, and formononetin content of foods, was reproducible and valid when compared with 24-hour dietary recalls and 24-hour excreted urinary levels in a subset of 195 participants (17). We also calculated a total antioxidant score based on oxygen radical absorbance capacity derived from fruit and vegetable consumption; and three separate antioxidant indices (antioxidant capacity against peroxyl radicals, hydroxyl radicals, and radicals produced by oxidation of a transition metal) measuring dietary antioxidant capacity derived from

vegetables, based on an automated oxygen radical absorbance capacity assay (18-20). The index measuring antioxidant capacity against peroxyl radicals reflects the activity of vitamins C and E, beta-carotene, glutathione, melatonin, flavonoids, and other antioxidants. The index measuring antioxidant activity against hydroxyl radicals reflects the activity of glucose, proteins, uric acid, and other compounds. The third index reflects both antioxidant activity and the transition-metal-initiated prooxidant activity of compounds such as ascorbic acid and flavonoids (19). For intake of specific foods, we calculated the number of "medium" servings per day by multiplying the frequency of consumption of that food by a factor of >1 for a large or extra-large portion and <1 for a small portion. The values for portion sizes were food- and age-specific and based on the grams assigned to each serving size for that food.

Follow-up

Participants were followed from the date they completed the baseline questionnaire until December 31, 2007 (median follow-up=12.1 person-years), relocation out of California, death, or the date of first diagnosis with B-cell NHL (ICD-O-3 morphology codes 9590, 9591, 9670-9699, 9727, 9728, 9761, 9764, 9820, 9823, 9832, 9833, 9835, 9836, 9940, and 9970, excluding T- and NK-cell types; *N*=536, including 145 women with diffuse large B-cell lymphoma [DLBCL, codes 9678-9680, 9684], 115 with follicular lymphoma [FL, codes 9690-9698], and 117 with chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL, codes 9670, 9823]), MM (codes 9731-9734; *N*=104), or classical HL (codes 9650-9655, 9661-9667; *N*=34), whichever occurred earliest. Participants diagnosed with T- or NK-cell NHL, NHL of unknown histologic type, or leukemias other than prolymphocytic leukemias and CLL (all other codes between 9590 and 9989 not specified above) during follow-up were censored on their dates of diagnosis; similarly, in analyses of NHL subtypes, MM, or HL, women who developed any of the other hematologic malignancies were censored at diagnosis.

Incident cancers were identified through annual linkage with the population-based California Cancer Registry, which has over 99% complete data on new cancer diagnoses statewide and maintains high data-quality standards as part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Dates and causes of death were ascertained through linkages with the California state mortality file, the national Social Security Administration death master file, and the National Death Index. Address changes were obtained through multiple database linkages, US Postal Service change-of-address forms, and proactive notifications by participants.

Statistical analysis

We calculated hazard rate ratios, as estimates of incidence rate ratios (RR), for associations with risk of lymphoid malignancies by using Cox proportional hazards regression, with age in days as the time-scale and stratifying by age in years at baseline to adjust for calendar-year effects. Quartiles of each dietary variable were defined within the entire eligible cohort, with the lowest quartile serving as the reference group. Tests for trend were conducted with each exposure coded as an ordinal variable using the median of each quartile. Tests for non-linearity of trend were based on likelihood ratio tests comparing models with each exposure coded as an ordinal versus categorical variable (21).

Potential confounders, including race, birthplace, total energy intake, body mass index, alcohol consumption, vitamin use, sunburn history, family history of hematopoietic cancer, personal history of melanoma or other skin cancer, number of older siblings, age at menarche, oral contraceptive use, menopausal status and hormone therapy use, pesticide/herbicide/insecticide use at various ages, urban/rural residence, school employment, and

neighborhood-level socioeconomic status, were evaluated based on independent associations with risk of each outcome and changes in RR estimates. Those that altered associations with exposures of interest by approximately 10% or more were included in multivariable models. Models for overall B-cell NHL risk were adjusted for total energy intake (<1,500 or ≥1,500 kcals/day, as the model fit better with dichotomized than continuous total energy intake); models for CLL/SLL risk were adjusted for race/birthplace (non-Hispanic white and North-American-born, other races and/or birthplaces, or missing) and alcohol consumption (consistent never-drinker, former drinker, current drinker, or missing/invalid data on past consumption); and models for HL risk were adjusted for body mass index (BMI; <30, ≥30 kg/m^2, or missing/invalid). Otherwise, models were adjusted only for age and calendar year; total energy intake was not associated with risk of any outcomes other than overall B-cell NHL. A sensitivity analysis with additional adjustment of all multivariable models for the same covariates (total energy intake, race/birthplace, alcohol consumption, and BMI) yielded equivalent results (data not shown).

Based on tests for interactions between each covariate and the time-scale, as well as scaled Schoenfeld residual plots, we found no meaningful violations of the proportional hazards assumption. All statistical tests were two-sided. Analyses were performed with SAS v.9.1.3 (Cary, NC).

Results

The distribution of covariates included as confounders in site-specific multivariable models, stratified by intake of vegetables and fruits as the primary sources of dietary phytocompounds, is shown in Table 1. On average, women who consumed more vegetables or fruits were more likely to be older, non-Hispanic white and born in North America, and non-obese, and had higher total energy intake than women who consumed fewer vegetables or fruits.

As shown in Table 2, several of the RR point estimates associated with moderate consumption of phytocompounds were statistically significant, but dose-response trends were not observed. Of the associations seen, perhaps the most notable was that between isothiocyanate consumption and risk of DLBCL, with moderate (2.7-<6.4 mcM/day) and high (≥12.1 mcM/day) levels of consumption, compared with <2.7 mcM/day, being associated with more than a 30% reduction in DLBCL risk, although the test for trend was nonsignificant. In addition, the highest quartile of the antioxidant index measuring hydroxyl radical absorbance capacity was marginally associated with a 32% reduction in DLBCL risk. Other statistically significant associations were observed with other outcomes, but generally lacked consistency. For example, moderate but not high intake of isoflavones was inversely associated with risk of CLL/SLL, with no apparent dose-response trend; and a significant dose-response trend was observed between isothiocyanates and risk of MM, yet no RR point estimate was significantly different from the null (Table 2), and continuous isothiocyanate intake was not associated with MM risk (RR per 10-mcM increase=1.11, 95% CI: 0.94-1.31). Risk of overall B-cell NHL, FL, MM, or HL was not associated with dietary intake of isoflavones, lignans, or isothiocyanates, or with absorbance capacity against total oxygen radicals (i.e., total antioxidant score), peroxyl radicals, hydroxyl radicals, or radicals produced by oxidation of a transition metal. When the highest category of isoflavone intake was defined as >2500 mcg/day, a level previously shown to be inversely associated with FL risk (5), we still observed no associations with risk of any lymphoid malignancies examined (data not shown). In a secondary analysis restricted to women who reported no use of multivitamins or single-vitamin supplements (vitamin A, beta-carotene, vitamin C, vitamin E, or selenium) at baseline (*N*=37,925, 34% of the cohort), the four antioxidant indices remained unassociated with risk of overall B-cell NHL (*N*=143 cases) (data not shown).

Because obesity, smoking, and alcohol intake can modify the effects of antioxidants (22-24) and possibly other dietary compounds, we performed secondary analyses of overall B-cell NHL restricted to women with BMI ≥30 kg/m^2, those who had ever smoked at least 100 cigarettes, or those who drank alcohol at baseline. In these subgroups, we detected an inverse association between modest isothiocyanate consumption and risk of overall B-cell NHL among obese women (RR for 2.7-<6.4 vs. <2.7 mcM/day=0.33, 95% CI: 0.16-0.69) and ever smokers (RR=0.67, 95% CI: 0.45-0.98), but no other associations with any of the compounds examined (other data not shown).

We also examined whether major food sources of isoflavones, lignans, isothiocyanates, or antioxidants in the CTS cohort were associated with risk of lymphoid malignancies (Table 3). We found no convincing associations between consumption of tofu (high in isoflavones), dark/whole grain breads (high in lignans), cruciferous vegetables (high in isothiocyanates), or vegetables, fruits, or vegetables and fruits combined (high in antioxidants) and risk of overall B-cell NHL, DLBCL, FL, CLL/SLL, MM, or HL. Scattered statistically significant associations between specific foods and risk of overall B-cell NHL (vegetables and fruits), FL (tofu), and HL (dark/whole grain breads) did not demonstrate dose-response trends and were not consistent with the results for phytocompounds, as we observed no associations of these outcomes with consumption of antioxidants, isoflavones, or lignans, respectively.

Discussion

In this prospective cohort study of 110,215 women, we found limited evidence that isothiocyanates and hydroxyl radical absorbance capacity are associated with reduced risk of DLBCL. However, we found no compelling evidence that isoflavones, lignans, isothiocyanates, or antioxidant compounds are associated with risk of other major NHL subtypes, overall B-cell NHL, MM, or HL. The major food sources of these compounds, including total fruits and vegetables, were not consistently associated with risk of lymphoid malignancies. The latter findings contradict those of previous case-control and cohort studies that found an inverse association between fruit and/or vegetable intake and risk of NHL or MM (1-3,5-7). However, our results accord with those from the large, prospective European Prospective Investigation into Cancer and Nutrition (EPIC), which showed no association with risk of overall lymphomas, NHL subtypes, or HL, although the investigators found an inverse association between total fruit intake and MM risk (4). In general, recent null findings from prospective cohort studies suggest that the strong inverse associations with fruit and vegetable intake previously detected in retrospective case-control studies may have been overstated, and may have resulted from selection, recall, or survival bias (25).

Our results contrast with those of Thompson *et al*., who found that intake of several antioxidants (e.g., dietary vitamin C and alpha-carotene), fruits, and vegetables was significantly inversely associated with risk of overall NHL and FL in particular in the Iowa Women's Health Study (WHS) cohort. While our finding of an inverse association between moderate isoflavone intake and CLL/SLL risk somewhat accords with their observation of a similar association with overall NHL risk (5), the lack of a dose-response trend in our data and the very low levels of intake at which statistically significant associations were observed lead us to believe that our findings are not biologically meaningful. Zhang *et al*. also detected an inverse association between intake of fruits and vegetables, but not antioxidants, and overall NHL risk in the Nurses' Health Study (NHS) cohort (3). The difference in findings is unlikely to be due to lesser statistical power to detect these associations in our study, as the number of cases in the CTS (*N*=518, including 145 DLBCL and 115 FL) was comparable to that in the WHS (*N*=415, including 184 DLBCL and 90 FL) and the NHS (*N*=199). One potential explanation for the discrepancy is that average consumption of fruits

and vegetables (and, consequently, antioxidants) was higher in both other cohorts than in ours, and we may have lacked sufficient exposure variation to detect an association with the highest levels of fruit, vegetable, and antioxidant consumption. However, Rohrmann *et al*. detected no such association in the EPIC cohort, which had levels of intake comparable to those in the WHS and NHS (4), and we did not observe inverse associations with B-cell NHL or FL risk even when we categorized intake using the same cutpoints as Thompson *et al*. or Zhang *et al*. (data not shown). Other possible explanations for the different results include chance, residual confounding, effect modification by characteristics that varied between the cohorts (e.g., other dietary factors, physical activity), differences in the types of vegetables and fruits commonly consumed in each cohort, and perhaps varying effects of diet by age or time period, as the mean age of the NHS at the baseline dietary assessment in 1980 was 45 years, that of the WHS at baseline in 1986 was 62 years, and that of the CTS cohort at baseline in 1995-1996 was 52 years.

The weak inverse associations of DLBCL risk with isothiocyanates and hydroxyl radical absorbance capacity suggest that phytocompounds may have a minor protective effect against risk of certain B-cell NHL subtypes. Specifically, isothiocyanates may help to prevent DLBCL by inducing phase II cellular detoxification enzymes or by promoting apoptosis of malignant cells (9). Antioxidant activity against hydroxyl radicals is highest in kale, brussels sprouts, alfalfa sprouts, beets, spinach, and broccoli flowers (19)—plant foods that have some overlap with those high in isothiocyanates, but enough dissimilarity perhaps to indicate an independent effect of hydroxyl radicals—the most reactive of all free radicals (26)—in DLBCL development. However, given the lack of dose-response trends and the large number of tests performed in our study, these and any of the other observed associations could also have been due to chance.

The limitations of our study are similar to those of previous cohort and case-control studies of diet and risk of lymphoid malignancies. We performed only one dietary assessment, preventing us from accounting for dietary changes over time. We lacked biological measures of dietary intake among all cohort members, although our questionnaire-based measures of isoflavone and lignan intake correlated well with excreted urinary levels in a small subset of the cohort [(17) and unpublished data]. Future studies would be strengthened by including measures of phytocompounds in urine or plasma, which should be collected repeatedly over time, as these biomarkers reflect only recent dietary intake (27). Finally, we lacked sufficient statistical power for detecting weak effects or associations with less common lymphoid malignancies, including most NHL subtypes, MM, and HL. A further limitation in our study, as well as many other studies of isoflavones in US populations, is that our baseline food frequency questionnaire included only limited soy-based foods and excluded soy milk, an important source of isoflavones in western populations. We did assess soy milk consumption in our follow-up questionnaire in 1997-98, but found no inverse associations with risk of any lymphoid malignancies (data not shown).

These limitations are countered by the strengths of our study, including its detailed dietary assessment, estimation of isoflavone intake based not only on soy-based foods, such as tofu, but also common foods in the US diet that contain soy flour and soy protein, investigation of novel measurements of antioxidants, complete ascertainment of incident cancer through linkage to the California Cancer Registry, and prospective design, which minimized the problems of selection, recall, and survival bias that often invalidate retrospective studies.

In summary, we found that a range of dietary phytocompounds were not related to risk of overall B-cell NHL, common NHL subtypes, MM, or HL, although we detected modest inverse associations of isothiocyanate intake and the antioxidant index measuring hydroxyl radical absorbance capacity with DLBCL risk. Despite our generally null results, we cannot

exclude the possibility that isoflavones, lignans, isothiocyanates, or antioxidants exert a protective effect against lymphoid malignancies when consumed in early life, in greater amounts, or by persons with particular genetic or other host characteristics. Furthermore, our finding of no association between total fruits and vegetables and risk of B-cell NHL, MM, or HL does not rule out a beneficial effect of specific types of fruits, vegetables, or unmeasured components in some of these foods. Nevertheless, our findings do not support increasing dietary intake of isoflavones, lignans, isothiocyanates, antioxidants, and foods rich in these compounds as a promising strategy for decreasing risk of lymphoid malignancies overall.

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Table 1

Demographic characteristics of 110,215 eligible California Teachers Study cohort members at baseline (1995-1996), stratified by average vegetable and fruit intake

	<1 serving/day of vegetables		≥1 serving/day of vegetables		<1 serving/day of fruit		≥1 serving/day of fruit		Total	
Characteristic	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Age (years)										
20-29	2,664	6%	1,543	2%	2,443	5%	1,765	3%	4,229	4%
30-39	7,764	17%	7,067	11%	7,177	16%	7,647	12%	14,908	14%
40-49	14,480	31%	15,507	25%	13,834	31%	16,147	25%	30,170	27%
50-59	11,536	25%	16,256	26%	10,966	25%	16,845	26%	27,991	25%
60-69	6,172	13%	12,339	20%	6,079	14%	12,444	19%	18,676	17%
70-79	3,409	7%	7,990	13%	3,248	7%	8,134	13%	11,536	10%
80-84	786	2%	1,852	3%	779	2%	1,867	3%	2,705	2%
Race and birthplace										
White non-Hispanic, born in North America	38,599	82%	53,256	85%	36,511	82%	55,372	85%	92,551	84%
Other race and/or birthplace	7,546	16%	8,379	13%	7,374	17%	8,534	13%	16,054	15%
Missing	666	1%	919	1%	641	1%	943	1%	1,610	1%
Body mass index (kg/m^2)										
<30	38,486	82%	51,955	83%	36,225	81%	54,216	84%	91,117	83%
≥30	6,839	15%	8,283	13%	6,881	15%	8,248	13%	15,224	14%
Missing	1,486	3%	2,316	4%	1,420	3%	2,385	4%	3,874	4%
Total daily caloric intake										
<1,500	25,962	55%	27,175	43%	24,775	56%	28,378	44%	53,583	49%
≥1,500	20,849	45%	35,379	57%	19,751	44%	36,471	56%	56,632	51%
Alcohol drinking status										
Consistent non-drinker	8,354	18%	11,914	19%	8,012	18%	12,284	19%	20,468	19%
Former drinker	5,803	12%	7,495	12%	5,223	12%	8,093	12%	13,400	12%
Current drinker	28,668	61%	37,963	61%	27,589	62%	39,011	60%	67,075	61%
Missing	3,986	9%	5,182	8%	3,702	8%	5,461	8%	9,272	8%

Subjects with missing vegetable intake (*N*=850) or fruit intake (*N*=840) are shown only in the “Total” columns.

Table 2

Incidence rate ratios (RRs) with 95% confidence intervals (CI) for associations between baseline intake of phytoestrogens, isothiocyanates, and antioxidants and risk of B-cell non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma

	Overall B-cell non-Hodgkin lymphoma			Diffuse large B-cell lymphoma			Follicular lymphoma		
Daily dietary intake	**Cases (*N*)**	**RR***	**95% CI***	**Cases (*N*)**	**RR**	**95% CI**	**Cases (*N*)**	**RR**	**95% CI**
Isoflavones (mcg)									
<720	164	1.00	(reference)	35	1.00	(reference)	33	1.00	(reference)
720-<1100	140	0.99	(0.78, 1.24)	41	1.30	(0.83, 2.04)	33	1.08	(0.67, 1.75)
1100-<1800	118	0.97	(0.75, 1.24)	35	1.25	(0.78, 2.01)	27	0.96	(0.57, 1.59)
≥1800	114	1.06	(0.82, 1.37)	34	1.37	(0.85, 2.21)	22	0.85	(0.49, 1.46)
P_{trend}			0.58			0.30			0.44
Lignans (mcg)									
<350	134	1.00	(reference)	37	1.00	(reference)	28	1.00	(reference)
350-<760	120	0.88	(0.69, 1.12)	33	0.86	(0.54, 1.38)	24	0.83	(0.48, 1.42)
760-<1340	136	0.90	(0.71, 1.15)	41	0.96	(0.61, 1.49)	29	0.93	(0.55, 1.56)
≥1340	146	0.97	(0.76, 1.24)	34	0.77	(0.48, 1.22)	34	1.07	(0.65, 1.77)
P_{trend}			0.91			0.33			0.55
Isothiocyanates (mcM)									
<2.7	134	1.00	(reference)	41	1.00	(reference)	32	1.00	(reference)
2.7-<6.4	126	0.80	(0.63, 1.02)	30	0.61	(0.38, 0.98)	25	0.68	(0.41, 1.16)
6.4-<12.1	129	0.78	(0.61, 1.00)	39	0.75	(0.49, 1.17)	26	0.67	(0.40, 1.13)
≥12.1	147	0.89	(0.70, 1.13)	35	0.67	(0.43, 1.05)	32	0.81	(0.50, 1.32)
P_{trend}			0.77			0.27			0.73
Total antioxidant score (mM Trolox equiv/g)									
<9.4	105	1.00	(reference)	25	1.00	(reference)	25	1.00	(reference)
9.4-<14.9	128	1.04	(0.80, 1.35)	38	1.27	(0.77, 2.11)	24	0.84	(0.48, 1.47)
14.9-<22.6	139	1.03	(0.80, 1.34)	34	1.03	(0.61, 1.73)	33	1.07	(0.63, 1.80)
≥22.6	164	1.11	(0.86, 1.44)	48	1.30	(0.80, 2.12)	33	0.99	(0.58, 1.68)
P_{trend}			0.40			0.42			0.80
Peroxyl radical absorbance capacity (μM Trolox equiv/g)									
<2.4	120	1.00	(reference)	31	1.00	(reference)	28	1.00	(reference)

	Overall B-cell non-Hodgkin lymphoma			Diffuse large B-cell lymphoma			Follicular lymphoma		
Daily dietary intake	**Cases (*N*)**	**RR***	**95% CI***	**Cases (*N*)**	**RR**	**95% CI**	**Cases (*N*)**	**RR**	**95% CI**
2.4-<3.9	137	0.99	(0.78, 1.27)	46	1.27	(0.81, 2.01)	25	0.78	(0.45, 1.33)
3.9-<6.3	139	0.95	(0.74, 1.22)	36	0.92	(0.57, 1.50)	29	0.85	(0.50, 1.43)
≥6.3	140	0.96	(0.74, 1.24)	32	0.82	(0.50, 1.34)	33	0.95	(0.57, 1.58)
P_{trend}			0.72			0.15			0.88
Antioxidant capacity against transition metals (μM Trolox equiv/g)									
<0.4	128	1.00	(reference)	34	1.00	(reference)	27	1.00	(reference)
0.4-<0.6	135	0.93	(0.73, 1.18)	42	1.07	(0.68, 1.68)	28	0.90	(0.53, 1.53)
0.6-<1.0	128	0.86	(0.67, 1.10)	36	0.87	(0.55, 1.40)	22	0.68	(0.39, 1.20)
≥1.0	145	0.96	(0.75, 1.23)	33	0.79	(0.49, 1.27)	38	1.14	(0.70, 1.88)
P_{trend}			0.85			0.20			0.46
Hydroxyl radical absorbance capacity (μM Trolox equiv/g)									
<0.9	128	1.00	(reference)	37	1.00	(reference)	29	1.00	(reference)
0.9-<1.5	134	0.96	(0.75, 1.22)	39	0.95	(0.60, 1.49)	26	0.82	(0.48, 1.40)
1.5-<2.2	134	0.88	(0.69, 1.13)	38	0.84	(0.53, 1.32)	27	0.77	(0.46, 1.31)
≥2.2	140	0.92	(0.72, 1.19)	31	0.68	(0.42, 1.10)	33	0.94	(0.57, 1.55)
P_{trend}			0.53			0.08			0.97

	Chronic lymphocytic leukemia/small lymphocytic lymphoma			Multiple myeloma			Hodgkin lymphoma		
Daily dietary intake	Cases (*N*)	RR†	95% CI†	Cases (*N*)	RR	95% CI	Cases (*N*)	RR‡	95% CI‡
Isoflavones (mcg)									
<720	48	1.00	(reference)	32	1.00	(reference)	19	1.00	(reference)
720-<1100	25	0.57	(0.35, 0.93)	26	0.92	(0.55, 1.55)			
1100-<1800	18	0.48	(0.28, 0.82)	23	0.94	(0.55, 1.60)	15	0.77	(0.39, 1.53)
≥1800	26	0.89	(0.55, 1.45)	23	1.11	(0.64, 1.90)			
P_{trend}			0.98			0.63			
Lignans (mcg)									
<350	29	1.00	(reference)	24	1.00	(reference)	12	1.00	(reference)
350-<760	25	0.79	(0.46, 1.34)	25	1.00	(0.57, 1.75)			
760-<1340	30	0.83	(0.50, 1.38)	30	1.04	(0.61, 1.79)	22	1.74	(0.86, 3.53)
≥1340	33	0.89	(0.54, 1.48)	25	0.83	(0.48, 1.46)			

	Overall B-cell non-Hodgkin lymphoma			Diffuse large B-cell lymphoma			Follicular lymphoma		
Daily dietary intake	**Cases (*N*)**	**RR***	**95% CI***	**Cases (*N*)**	**RR**	**95% CI**	**Cases (*N*)**	**RR**	**95% CI**
P_{trend}			0.90			0.49			
Isothiocyanates (mcM)									
<2.7	28	1.00	(reference)	22	1.00	(reference)	18	1.00	(reference)
2.7-<6.4	28	0.80	(0.47, 1.35)	18	0.66	(0.36, 1.24)			
6.4-<12.1	27	0.72	(0.43, 1.23)	23	0.80	(0.45, 1.44)	16	0.93	(0.47, 1.84)
≥12.1	34	0.89	(0.54, 1.47)	41	1.40	(0.83, 2.34)			
P_{trend}			0.93			0.02§			
Total antioxidant score (mM Trolox equiv/g)									
<9.4	20	1.00	(reference)	19	1.00	(reference)	17	1.00	(reference)
9.4-<14.9	26	1.01	(0.56, 1.81)	24	1.03	(0.57, 1.89)			
14.9-<22.6	29	0.98	(0.55, 1.73)	26	0.98	(0.54, 1.78)	17	0.99	(0.50, 1.96)
≥22.6	42	1.25	(0.73, 2.13)	35	1.14	(0.65, 2.01)			
P_{trend}			0.32			0.61			
Peroxyl radical absorbance capacity (μM Trolox equiv/g)									
<2.4	26	1.00	(reference)	25	1.00	(reference)	21	1.00	(reference)
2.4-<3.9	24	0.75	(0.43, 1.30)	20	0.67	(0.37, 1.21)			
3.9-<6.3	33	0.92	(0.55, 1.54)	23	0.71	(0.40, 1.25)	13	0.64	(0.32, 1.30)
≥6.3	34	0.94	(0.56, 1.57)	36	1.08	(0.65, 1.80)			
P_{trend}			0.84			0.34			
Antioxidant capacity against transition metals (μM Trolox equiv/g)									
<0.4	28	1.00	(reference)	25	1.00	(reference)	22	1.00	(reference)
0.4-<0.6	26	0.76	(0.45, 1.31)	20	0.68	(0.38, 1.23)			
0.6-<1.0	30	0.81	(0.49, 1.36)	25	0.81	(0.46, 1.40)	12	0.56	(0.28, 1.14)
≥1.0	33	0.87	(0.52, 1.44)	34	1.07	(0.64, 1.79)			
P_{trend}			0.82			0.42			
Hydroxyl radical absorbance capacity (μM Trolox equiv/g)									
<0.9	26	1.00	(reference)	24	1.00	(reference)	19	1.00	(reference)
0.9-<1.5	26	0.86	(0.50, 1.49)	22	0.81	(0.46, 1.45)			
1.5-<2.2	31	0.90	(0.53, 1.51)	24	0.79	(0.45, 1.39)	15	0.81	(0.41, 1.61)
≥2.2	34	0.98	(0.59, 1.63)	34	1.10	(0.65, 1.85)			

	Overall B-cell non-Hodgkin lymphoma			Diffuse large B-cell lymphoma			Follicular lymphoma		
Daily dietary intake	**Cases (*N*)**	**RR***	**95% CI***	**Cases (*N*)**	**RR**	**95% CI**	**Cases (*N*)**	**RR**	**95% CI**
P_{trend}			0.90			0.49			

All models adjusted for age (as time-scale) and calendar-year effects

*Adjusted for total daily energy intake

†Adjusted for race/birthplace and alcohol consumption

‡Adjusted for body mass index

§$P_{non\text{-}linearity}$=0.19

Table 3

Incidence rate ratios (RRs) with 95% confidence intervals (CI) for associations between baseline intake of major food sources of phytoestrogens, isothiocyanates, and antioxidants and risk of B-cell non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma

	Overall B-cell non-Hodgkin lymphoma			Diffuse large B-cell lymphoma			Follicular lymphoma		
Daily dietary intake (medium servings)	**Cases (*N*)**	**RR***	**95% CI***	**Cases (*N*)**	**RR**	**95% CI**	**Cases (*N*)**	**RR**	**95% CI**
Tofu/bean curd									
0	459	1.00	(reference)	118	1.00	(reference)	105	1.00	(reference)
>0	77	0.95	(0.75, 1.21)	27	1.29	(0.85, 1.96)	10	0.51	(0.27, 0.98)
Dark/whole grain breads§									
<0.04	115	1.00	(reference)	30	1.00	(reference)	23	1.00	(reference)
0.04-<0.25	132	1.00	(0.78, 1.28)	37	1.07	(0.66, 1.73)	27	1.05	(0.60, 1.83)
0.25-<0.50	105	0.92	(0.70, 1.20)	33	1.09	(0.66, 1.79)	23	1.07	(0.60, 1.91)
≥0.50	184	0.92	(0.73, 1.17)	45	0.83	(0.52, 1.32)	42	1.11	(0.66, 1.85)
P_{trend}			0.41			0.30			0.69
Cruciferous vegetables#									
<0.1	105	1.00	(reference)	33	1.00	(reference)	25	1.00	(reference)
0.1-<0.2	127	0.92	(0.71, 1.19)	34	0.78	(0.48, 1.26)	24	0.75	(0.43, 1.32)
0.2-<0.4	145	0.97	(0.75, 1.25)	36	0.76	(0.47, 1.23)	33	0.99	(0.59, 1.67)
≥0.4	159	0.90	(0.70, 1.16)	42	0.75	(0.47, 1.21)	33	0.84	(0.50, 1.43)
P_{trend}			0.49			0.39			0.78
Vegetables									
≥0.6	138	1.00	(reference)	37	1.00	(reference)	29	1.00	(reference)
0.7-0.9	71	0.83	(0.63, 1.11)	18	0.77	(0.44, 1.36)	17	1.01	(0.55, 1.84)
1.0-1.5	159	0.84	(0.66, 1.05)	47	0.90	(0.58, 1.39)	29	0.78	(0.46, 1.31)
≥2.0	167	0.82	(0.65, 1.03)	43	0.76	(0.49, 1.19)	40	1.02	(0.63, 1.67)
P_{trend}			0.21			0.30			0.73
Fruits									
≤0.6	127	1.00	(reference)	30	1.00	(reference)	30	1.00	(reference)
0.7-0.9	55	0.91	(0.67, 1.25)	19	1.34	(0.76, 2.39)	10	0.73	(0.36, 1.50)
1.0-1.5	150	0.98	(0.77, 1.24)	45	1.23	(0.77, 1.96)	32	0.93	(0.57, 1.54)
≥2.0	204	1.05	(0.84, 1.32)	51	1.09	(0.69, 1.73)	43	1.02	(0.64, 1.64)

Daily dietary intake (medium servings)	Overall B-cell non-Hodgkin lymphoma Cases (*N*)	RR*	95% CI*	Diffuse large B-cell lymphoma Cases (*N*)	RR	95% CI	Follicular lymphoma Cases (*N*)	RR	95% CI
P_{trend}			0.44			0.93			0.68
Vegetables and fruits									
<1.3	102	1.00	(reference)	23	1.00	(reference)	26	1.00	(reference)
1.3-<2.2	119	0.77	(0.59, 1.00)	30	0.85	(0.49, 1.47)	29	0.78	(0.46, 1.32)
2.2-<3.5	127	1.02	(0.78, 1.32)	41	1.43	(0.86, 2.40)	16	0.54	(0.29, 1.01)
≥3.5	187	0.91	(0.71, 1.17)	51	1.07	(0.65, 1.77)	44	0.93	(0.56, 1.52)
P_{trend}			0.73			0.39			0.94

Daily dietary intake (medium servings)	Chronic lymphocytic leukemia/ small lymphocytic lymphoma Cases (*N*)	RR†	95% CI†	Multiple myeloma Cases (*N*)	RR	95% CI	Hodgkin lymphoma Cases (*N*)	RR‡	95% CI‡
Tofu/bean curd									
0	101	1.00	(reference)	88	1.00	(reference)	29	1.00	(reference)
>0	16	1.02	(0.60, 1.74)	16	1.05	(0.62, 1.79)	5	0.96	(0.37, 2.50)
Dark/whole grain breads§									
<0.04	30	1.00	(reference)	23	1.00	(reference)	10	1.00	(reference)
0.04-<0.25	22	0.59	(0.34, 1.02)	22	0.82	(0.46, 1.48)			
0.25-<0.50	23	0.68	(0.40, 1.18)	24	0.98	(0.55, 1.75)	24	2.22	(1.06, 4.68)
≥0.50	42	0.72	(0.45, 1.15)	35	0.80	(0.47, 1.36)			
P_{trend}			0.51			0.55			
Cruciferous vegetables#									
<0.1	21	1.00	(reference)	17	1.00	(reference)	21	1.00	(reference)
0.1-<0.2	25	0.75	(0.43, 1.32)	23	0.98	(0.52, 1.83)			
0.2-<0.4	35	0.99	(0.59, 1.67)	20	0.76	(0.40, 1.46)	13	0.64	(0.32, 1.30)
≥0.4	36	0.84	(0.50, 1.43)	44	1.35	(0.76, 2.37)			
P_{trend}			0.74			0.12			
Vegetables									
≤0.6	27	1.00	(reference)	20	1.00	(reference)	14	1.00	(reference)
0.7-0.9	15	0.83	(0.44, 1.57)	15	1.15	(0.59, 2.25)			
1.0-1.5	35	0.83	(0.50, 1.38)	25	0.85	(0.47, 1.53)	19	1.05	(0.52, 2.13)

	Overall B-cell non-Hodgkin lymphoma			Diffuse large B-cell lymphoma			Follicular lymphoma		
Daily dietary intake (medium servings)	**Cases (*N*)**	**RR***	**95% CI***	**Cases (*N*)**	**RR**	**95% CI**	**Cases (*N*)**	**RR**	**95% CI**
≥2.0	39	0.85	(0.52, 1.39)	42	1.27	(0.74, 2.17)			
P_{trend}			0.69			0.25			
Fruits									
≤0.6	27	1.00	(reference)	20	1.00	(reference)	15	1.00	(reference)
0.7-0.9	14	1.05	(0.55, 2.00)	11	1.14	(0.55, 2.39)			
1.0-1.5	29	0.82	(0.48, 1.38)	28	1.11	(0.62, 1.98)	18	0.82	(0.41, 1.65)
≥2.0	47	1.01	(0.62, 1.62)	41	1.22	(0.71, 2.10)			
P_{trend}			0.82			0.49			
Vegetables and fruits									
<1.3	19	1.00	(reference)	15	1.00	(reference)	15	1.00	(reference)
1.3-<2.2	26	0.81	(0.45, 1.47)	27	1.13	(0.60, 2.13)			
2.2-<3.5	30	1.12	(0.63, 2.00)	16	0.82	(0.40, 1.66)	18	1.22	(0.61, 2.46)
≥3.5	41	0.90	(0.52, 1.56)	42	1.23	(0.68, 2.24)			
P_{trend}			0.96			0.57			

All models adjusted for age (as time-scale) and calendar-year effects

*Adjusted for total daily energy intake

†Adjusted for race/birthplace and alcohol consumption

‡Adjusted for body mass index

§1 medium serving = 2 slices

#Broccoli, cauliflower, brussels sprouts, cabbage, and coleslaw