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# Antioxidant Intake from Fruits, Vegetables and Other Sources and Risk of Non-Hodgkin Lymphoma: The Iowa Women's Health Study

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## Abstract

Antioxidant nutrients found in fruits, vegetables, and other foods are thought to inhibit carcinogenesis and to influence immune status. We evaluated the association of these factors with risk of NHL overall and for diffuse large B-cell (DLBCL) and follicular lymphoma specifically in a prospective cohort of 35,159 Iowa women aged 55–69 years when enrolled at baseline in 1986. Diet was ascertained using a validated semi-quantitative food frequency questionnaire. Through 2005, 415 cases of NHL (including 184 DLBCL and 90 follicular) were identified. Relative risks (RRs) and 95% confidence intervals (CI) were estimated using Cox regression, adjusting for age and total energy. The strongest associations of antioxidants with risk of NHL (RR for highest versus lowest quartile; p for trend) were observed for dietary vitamin C (RR=0.78; p=0.044), α-carotene (RR=0.71; p=0.015), proanthocyanidins (RR=0.70; p=0.0024), and dietary manganese (RR=0.62; p=0.010). There were no associations with multivitamin use or supplemental intake of vitamins C, E, selenium, zinc, copper or manganese. From a food perspective, greater intake of total fruits and vegetables (RR=0.69; p=0.011), yellow/orange (RR=0.72; p=0.015) and cruciferous (RR=0.82; p=0.017) vegetables, broccoli (RR=0.72; p=0.018), and apple juice/cider (RR=0.65; p=0.026) were associated with lower NHL risk; there were no strong associations for other antioxidant-rich foods, including whole grains, chocolate, tea or nuts. Overall, these associations were mainly observed for follicular lymphoma, and were weaker or not apparent for DLBCL. In conclusion, these results support a role for vegetables and perhaps fruits, and associated antioxidants from food sources, as protective factors against the development of NHL and follicular lymphoma in particular.

### Keywords

antioxidants; cohort studies; fruits; non-Hodgkin lymphoma; vegetables

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## Introduction

The incidence rate of non-Hodgkin lymphoma (NHL) increased rapidly over the later half of the 20th century in the United States, and only in the later part of 1990s did the rate of increase level off in developed countries. However, among women aged 55 years and older, incidence rates continued to increase, albeit at a slower pace. The most well-established risk factor for the development of NHL is immunosuppression, including primary immunodeficiency diseases, HIV infection, or iatrogenic immunosuppression (e.g., for organ transplantation or treatment of certain disorders),[1] but these factors account only for a small proportion of patients.[2] Thus, the etiology of a majority of cases of NHL remains unknown, and diet has been proposed to play a role in the development of NHL, including a protective role for fruits and vegetables.[3, 4]

Reactive oxygen species (ROS) production, including superoxide radicals, hydrogen peroxide, and hydroxyl radicals, can alter DNA and lipid membrane structures, particularly in proliferating cells such as those in the immune system. Cells of the immune system tend to have higher concentrations of nutrients with antioxidant activities,[5] and lower intakes of antioxidants have been linked to a compromised immune system.[5–7] This raises the hypothesis that nutrients involved in antioxidant activities may protect against the development of NHL. The major dietary sources of antioxidants are fruits and vegetables, although other foods rich in antioxidants include whole grains, nuts, chocolate, and tea. There is growing evidence that higher intake of fruits or vegetables may be inversely associated with risk of NHL,[8–16] although this evidence has not been universal.[17–19] While associations with specific types of fruits and vegetables have varied, an inverse associations with cruciferous vegetables and α- or β-carotene are the most consistent findings to date.[3] Epidemiologic data are sparse for NHL and trace elements with antioxidant activities (e.g., selenium and zinc), although one study reported an inverse association with zinc among women.[15] The major limitations of this literature include lack of comprehensive assessment of antioxidant nutrients, a limited number of prospective cohort studies[9, 11, 19] and the relatively small number of studies of any design that have assessed the risk of NHL by subtypes,[13–15, 18, 19] which may have unique etiologies.

We report the association of selected antioxidant micronutrients from food and supplement intake, as well as selected food groups and foods with high levels of antioxidants, with the risk of NHL in the Iowa Women's Health Study (IWHS) cohort. This analysis is based on 20 years of follow-up and 415 cases of NHL, and updates and expands on our initial report from the IWHS cohort based on seven years of follow-up and 104 cases of NHL.[9] We also report for the first time associations for the two most common subtypes of NHL, diffuse large B-cell (DLBCL) and follicular lymphoma. Chronic lymphocytic leukemia (CLL) was not included in this analysis, as it was not historically presented with the NHL data from this cohort,[9] and dietary associations with CLL have been reported separately.[20]

## Material and methods

### The Iowa Women's Health Study Cohort

Study design details for the overall cohort and NHL analyses specifically have been previously published.[9, 21] Briefly, in 1986, 41,836 randomly selected women who were aged 55–69 years and had a valid Iowa driver's license returned a mailed questionnaire (42.7% response rate). There were only minor demographic differences between respondents and non-respondents to the baseline survey, and compared to non-respondents, respondents have had somewhat lower cancer incidence and mortality rates for smoking related cancers.[22] Self-reported items on the baseline 1986 questionnaire included demographics, anthropometrics, medical history, and other lifestyle factors.

### Dietary assessment

Diet was assessed on the 1986 baseline survey using a 127 item semi-quantitative food frequency questionnaire (FFQ).[23] For each food, a commonly used portion size or unit was specified, and respondents were asked how often on average over the last year they had consumed that amount of each food item. There were nine possible responses, ranging from "never or less than once per month," to "six or more times per day." Women were also asked if they used a multivitamin (including the brand name and frequency of use) as well as whether they regularly used the following supplements, not counting multivitamins: vitamin C, vitamin E, selenium, zinc, copper, and beta-carotene. Except for the latter two supplements, the daily dose used was also collected. However, no data on duration of supplement use were collected.

The daily intake of nutrients was calculated by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions.[23, 24] This dietary instrument was found to be reliable and valid in this population.[24] For example, the correlation for energy-adjusted intakes between the FFQ estimate and five 24-hour dietary recalls were quite good for vitamins E (0.55) and C (0.76). Calculation of dietary flavonoid intakes were determined from three flavonoid food composition databases developed by the USDA Nutrient Data Laboratory; full details have been previously published.[25]

### Follow-up

Vital status and NHL incidence in the cohort were ascertained from the 1986 baseline through 2005. Follow-up questionnaires were mailed in 1987, 1989, 1992, 1997 and 2004 to ascertain vital status and address changes. Deaths were also ascertained by annual linkage to a database of Iowa death certificates, supplemented by linkage to the National Death Index for survey non-respondents and emigrants from Iowa. Migration out of Iowa has been low for this cohort, and is estimated at approximately 1% per year.

NHL incidence was ascertained by annual linkage to the Iowa Cancer Registry, which is part of the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program.[26] Participants were linked by a combination of social security number; first, last, and maiden name; birth date; and zip code. The Iowa Cancer Registry collects cancer data including identifying information, primary site, morphology and other data. All tumor site and morphology data were derived from pathology reports of the diagnosing pathologist, and there was no centralized pathology review. Topographic and morphologic data were coded using the International Classification of Diseases for Oncology ($2^{nd}$ and $3^{rd}$ editions).[27, 28] These codes were grouped into the two most common subtypes of DLBCL and follicular lymphoma, according to the approach advocated by the InterLymph Consortium.[29]

### Data analysis

Women with a self-reported history of cancer or cancer chemotherapy from the 1986 baseline questionnaire (n=3,904) were excluded prior to data analysis to provide a cancer-free at-risk cohort. An additional 2,773 women who left 30 or more food items blank on the food frequency questionnaire or who had implausible daily energy intakes (i.e., less than 600 k/cal or ≥ 5000 k/cal) were excluded. Therefore, 35,159 women remained eligible for analysis.

Each woman accumulated person-years of follow-up from the date of receipt of the 1986 baseline questionnaire to the date of NHL diagnosis, date of emigration from Iowa, or date of death; if none of these events occurred, person-years were accumulated through December 31, 2005.

Dietary variables were categorized into approximate quartiles based on their distribution of consumption among all women included in the analysis. Relative risks (RR), along with 95% confidence intervals (CI), were calculated as a measure of association between the dietary factor of interest and NHL incidence, and were estimated using Cox proportional hazards regression.[30] Analyses were conducted for all NHL, as well as for the two most common subtypes of DLBCL and follicular lymphoma. For the subtype analyses, women diagnosed with NHL not of the subtype of interest were censored at their diagnosis date. Relative risks were estimated using age as the time variable.[31] A one-degree of freedom trend test was also conducted using the ordinal scoring of the consumption quartiles, and statistical significance was declared for $p<0.05$. Basic models accounted for age and total energy, and full models accounted for education, marital status, farm residence, adult-onset diabetes, history of blood transfusion, hormone replacement therapy, red meat consumption, alcohol use, body mass index, and smoking. Total energy was modeled as a continuous covariate in the Cox model, and was included to adjust for systematic over- and under-reporting of food intake.[32] The other factors have previously been found to be associated with NHL risk in this cohort.[21, 33–36] In secondary analyses, we also evaluated all associations for the most common NHL subtypes of DLBCL and follicular lymphoma; due to the small sample sizes and exploratory nature of these analyses, no formal statistical test of differences by subtypes was conducted. All statistical tests were two-sided, and all analyses were carried out using the SAS (SAS Institute, Inc., Cary, NC) and S-Plus (Insightful, Inc., Seattle, WA) software systems.

## Results

The mean baseline age of the 35,159 women in the at-risk cohort was 62.0 years and over 99% were Caucasian. During 597,941 person years of follow-up (1986–2005), 415 women developed NHL, 184 of which were DLBCL and 90 were follicular NHL. The mean age at diagnosis was 73.5 years (range, 57.8 – 88.2).

Women with the greatest intake of fruit and vegetables, which is the major source of antioxidants, had slightly higher red meat consumption and were slightly more likely to use any alcohol and report adult onset diabetes, but the magnitudes of these differences were small (Table I). In contrast, women in the highest quartile of intake were more likely to have greater than a high school education and to have never smoked compared to women in lowest quartile. There was little difference with respect to age, body mass index, farm residence, marital status, use of hormone replacement therapy, and prior blood transfusion across categories of fruit and vegetable intake.

After adjustment for age and total energy, total intake of vitamins C and E (i.e., from food and supplements) were not associated with NHL risk, while intake of total carotenoids was inversely associated with risk (RR=0.78 for highest versus lowest quartile; p-trend=0.033) (Table II). However, dietary intake of vitamin C (RR=0.78; p-trend=0.044) and dietary intake of carotenoids (RR=0.78; p-trend=0.048) were inversely associated with NHL risk, while supplemental intake of these nutrients were not. In more detailed evaluation of specific types of dietary carotenoids (Table III), there were inverse associations with α-carotene (RR=0.71; p-trend=0.015), and suggestive inverse associations with β-carotene (RR=0.80; p-trend=0.072) and lutein+zeaxanthin (RR=0.81; p-trend=0.068). β-cryptoxanthin was weakly and inversely associated with risk (RR=0.82), but none of the RRs were statistically significant and there was no evidence for a trend with intake (p-trend=0.21). There was no association with lycopene. Alpha-carotene, β-cryptoxanthin, and lutein+zeaxanthin were moderately correlated (Spearman r's 0.3–0.5), and when these factors were included in the same model, estimates attenuated modestly, but overall trends in the RRs still held (data not shown).

The associations with antioxidant nutrients observed for all NHL in Tables II and III were much more striking for follicular lymphoma compared to DLBCL, which showed either weak inverse or no associations. However, for follicular lymphoma the associations were only statistically significant for dietary intake of vitamin C (RR=0.55; p-trend=0.032), lutein +zeaxanthin (RR=0.56; p-trend=0.007), and β-cryptoxanthin (RR=0.57; p-trend=0.040). As observed for all NHL, simultaneous adjustment for α-carotene, β-cryptoxanthin, and lutein +zeaxanthin modestly attenuated the RR estimates (but all trends held) for risk of follicular lymphoma.

We observed no association of total flavonoids with risk of NHL (Table IV). For all NHL, there were no clear associations with isoflavones, flavonols, and anthocyanidins, while there was an inverse association with proanthocyanidins (RR=0.70; p-trend=0.0024). The associations for proanthocyanidins were stronger for follicular lymphoma (RR=0.52; p-trend=0.013) than for DLBCL (RR=0.78; p-trend=0.071). While there were no overall associations for isoflavones and flavonols, there were inverse associations for follicular lymphoma for each of these (RR=0.53 for isoflavones, p-trend=0.022; RR=0.52 for flavonols, p-trend=0.030). There were no associations for flavones, flavanones, flavan-3-ols, overall or for either subtype (data not shown).

Multivitamin use, as well as intakes of selenium, zinc, and copper, was not associated with risk of NHL, either overall or by subtype (Table V). However, there was an inverse association of total manganese intake and risk of NHL (RR=0.73; p-trend=0.016), and this was specific to manganese from food sources (RR=0.62; p-trend=0.010) and not manganese from multivitamin use. This inverse trend was observed for follicular lymphoma but not for DLBCL.

Finally, we evaluated food groups and foods high in antioxidants, including manganese and flavonoids, with risk of NHL (Table VI). We observed inverse associations for intake of all fruits and vegetables (RR=0.69; p-trend=0.011), all vegetables (RR=0.84; p-trend=0.041), apple juice/cider (RR=0.65; p-trend=0.026), yellow/orange vegetables (RR=0.72; p-trend=0.015) and cruciferous vegetables (RR=0.82; p-trend=0.017), as well as broccoli (RR=0.72; p-trend=0.018). Although many of the point estimates were below unity, there were no consistent associations observed for DLBCL, and none of the trend tests approached statistical significance. In contrast, for follicular lymphoma, inverse associations were similar to those observed for all NHL, although the trend tests were statistically significant only for intake of all fruits and vegetables (RR=0.59; p-trend=0.038), all vegetables (RR=0.56; p-trend=0.013), and cruciferous vegetables (RR=0.64; p-trend=0.016). We did not observe any associations with intake of whole grains or nuts (Table VI); there were also no associations with intake of refined grains or peanut butter (data not shown). Furthermore, there were no associations for risk of NHL overall, or for DLBCL and follicular lymphoma, with intake of citrus fruit, oranges, orange juice, grapefruit, grapefruit juice, fresh apples/pears, tomatoes/tomato juice/tomato sauce, green leafy vegetables, spinach, legumes, chocolate, tea (excluding herbal tea), or red wine (data not shown).

Further adjustment of all results for education, marital status, farm residence, body mass index, adult-onset diabetes, history of blood transfusion, hormone replacement therapy, red meat consumption, alcohol use, and smoking did not substantially alter these associations (data not shown).

## Discussion

In this prospective study of older Iowa women, we observed an overall inverse association for intakes of both fruits and vegetables with risk of NHL, as well as dietary intakes of carotenoids, vitamin C, proanthocyanidins, and manganese. For vegetables, the associations were strongest for yellow/orange and cruciferous vegetables; for fruits, the strongest association was for apple juice/cider; and for the carotenoids, the strongest association was for α-carotene. Other foods with strong antioxidant properties, including whole grains, nuts, chocolate, tea, and red wine, were not associated with NHL risk. All associations held after multivariate adjustment for a variety of NHL risk factors, and the associations were strongest for follicular lymphoma. This analysis is an update of a previous IWHS report based on seven years of follow-up and 104 cases of NHL.[9] In the earlier report, there was a trend (highest versus lowest tertile of intake) for a lower risk of NHL with greater intake of fruits (RR=0.67; 95% CI 0.41–1.08) and yellow/orange vegetables (RR=0.84; 95% CI 0.53–1.33), but there were no associations for intake of total vegetables, cruciferous vegetables, total vitamin C, and total carotene; results for other foods and food groups, antioxidant nutrients, flavonoids, and NHL subtypes were not assessed.

### Vegetables

Our finding of an inverse association of total vegetable intake with risk of NHL is consistent with five studies.[11, 13–16] In contrast, five other studies did not observe an overall association,[8, 12, 17–19] although some of these studies reported inverse associations with specific vegetables.[8, 12] Of the null studies, three[8, 12, 17] had only a very limited assessment of diet (≤30 food items), one[18] had a modest assessment (69 food items), and the fifth[19] combined several cohorts that were a part of the European Investigation of Cancer (EPIC) study, each using a different dietary instrument. Of the studies reporting an inverse association, all but one had robust dietary assessment (≥100 food items),[16] four (including this study) were population based,[13–15] and two (including this study) used a prospective cohort study design,[11] all characteristics of studies associated with greater internal validity.

While on balance there is modest support for an inverse association of vegetable intake with NHL risk, a role for specific types of vegetables is not well-defined. Our finding of an inverse association with yellow/orange vegetables is supported by two other studies[8, 10] but not most others.[11–13, 18] Three studies[10, 14, 15] have reported an inverse association with green leafy vegetables, which was not observed here. Our findings of no association for tomatoes/tomato-based products and legumes agrees with the limited evaluation of these factors and NHL risk,[13, 15, 18] although an inverse association with cooked tomatoes was reported in one study.[13] Our findings of an inverse association for cruciferous vegetables (or broccoli specifically) is consistent with most,[8, 11–15] but not all[18, 19] previous studies, and this is probably one of the most robust dietary associations for NHL. Mechanistically, cruciferous vegetables might be protective against NHL due to their antioxidant properties as well as their high levels of glucosinolates, which are converted *in vivo* to isothiocyanates and are potent inducers of carcinogen-detoxifying enzymes.[37]

Of the studies evaluating vegetables and NHL risk by subtype,[11, 14, 15, 18, 19] there has been little evidence for etiologic heterogeneity across the major subtypes, although somewhat stronger associations were reported for vegetable intake and follicular lymphoma in one study,[14] while null[14] or even positive[18] associations were reported for CLL and small lymphocytic lymphoma (SLL) in other studies. Intake of all vegetables (RR=0.72, p-trend=0.39), cruciferous (RR=1.73, p-trend=0.15) and carotene-rich (RR=1.00, p-trend=0.99) vegetables were not associated with CLL in this cohort.[20]

## Fruit

Our finding of a suggestive inverse association of total fruit with NHL risk is consistent with one prior study that reported a statistically significant result[16] while other studies reported a suggestive inverse association,[10–12, 14] no association,[13, 15, 18, 19] or a positive[17] association. In our study, citrus fruit was only weakly and inversely associated with NHL risk, which is consistent with multiple reports,[8, 11, 13–15, 19] although this association was specific to men in one study[8] and women in another.[14] No other particular class of fruits has specifically been identified with risk of NHL. Of the studies evaluating NHL subtypes,[11, 14, 15, 18, 19] there has been little evidence for etiologic heterogeneity, with the exception of a suggestive protective association for fruit intake with DLBCL but not follicular lymphoma in one study[15] and an inverse association with fruit intake for both DLBCL and follicular lymphoma but not CLL/SLL in another study.[14] In this cohort, fruit intake was inversely associated with CLL risk at a similar magnitude as seen for NHL (RR=0.72), although this estimate lacked precision (95% CI 0.35–1.49).[20]

## Antioxidant nutrients

From a nutrient perspective, our strongest findings were for dietary vitamin C, carotenoids (particularly α-carotene), proanthocyanidins, and dietary manganese. Dietary vitamin C was inversely associated with NHL risk at the same magnitude as this study (~ 20% lower risk, although not statistically significant) in two studies[11, 15] and among men in a third study;[8] a fourth study found no association.[13] Specific dietary carotenoids have not been evaluated as extensively, but two prior studies have found a non-significant 20% lower risk for α-carotene but not β-carotene,[11, 13] a third found a similar reduction for both cartenoids,[15] and a fourth found a reduction for β-carotene (α-carotene not evaluated).[10] While we observed a very weak inverse association for lutein+zeaxanthin, one prior study found a strong inverse association[15] and two others reported no association.[11, 38]

Only a single prior study has evaluated flavonoids and risk of NHL.[39] In that study, total flavonoid intake was associated with a lower risk of NHL (OR=0.47 for the highest versus lowest quartile; 95% CI 0.31–0.73; p-trend<0.01), as were higher intakes of flavonols, epicatechins, anthocyanidins, and proanthocyanidins; similar associations were observed for DLBCL and follicular lymphoma. We observed a weaker and not statistically significant inverse association with total flavonoids in the IWHS (RR=0.82; 95% CI 0.61–1.10; p-trend=0.18), and our only statistically significant inverse association was for the proanthocyanidins. Our results were somewhat stronger for follicular lymphoma compared to DLBCL, and we also observed inverse associations for isoflavones and flavonols that were specific to follicular lymphoma. Of foods rich in flavonoids and proanthocyanidins in particular, we observed a significant inverse association for apple juice/cider but not fresh apples/pears, chocolate, tea, or red wine. While not completely consistent, these two studies do provide some support for an inverse association of flavonoids, particularly proanthocyanidins, with NHL risk. Proanthocyanidins are an important if overlooked class of polyphenolic compounds, and could inhibit lymphomagenesis through antioxidant mechanisms (most importantly free radical scavenging, chelation of transition metals, and inhibition of enzymes) as well as anti-inflammatory effects (including down regulation of TNFα and blocking of NF-κB activation), or impacts on apoptosis.[40]

To our knowledge, an inverse association with manganese has not been previously evaluated for NHL, and thus this will require replication. Foods rich in manganese include whole grains, nuts, and leafy vegetables. However, we observed no clear association with foods that are major sources of manganese. Manganese is an essential component of manganese superoxide dismutase, a metalloprotease enzyme that serves to protect mitochondrial components from superoxide, a potent free radical. It has also been shown that a polymorphism of the manganese superoxide dismutase gene moderately increases risk of NHL,[41] raising the potential for a diet-gene interaction that should be evaluated in future studies.

We did not observe an association of NHL with selenium, zinc or copper intake. Zinc intake that was inversely associated with NHL risk one prior study among women,[15] but showed no association in another study.[38]

We observed no associations for multivitamin use or supplemental intake of vitamins C, E, or any of the micronutrients, although we did not have duration of use. While one prior report suggested elevated NHL risk with use of multivitamins, particularly over 10 year's duration,[42] results from two other cohorts did not confirm this initial observation.[42, 43]

## Strengths and Limitations

This study has several strengths. It is only one of three cohort studies that have published data on diet and risk of NHL,[11, 19] and the only one that is population-based. Dietary and other data were prospectively collected, eliminating the potential for recall bias inherent in case-control studies. Dietary assessment was comprehensive (over 120 food items), and was found to be valid and reliable in the study population.[24] Cancer cases were identified through linkage to a SEER registry, and there were over 400 cases, making it one of the larger studies published to date. We were also able to evaluate the two most common NHL subtypes, although with limited statistical power for detecting weak associations and for formally evaluating differences between DLBCL and follicular lymphoma. Lastly, we were able to adjust for total energy and adjust for a variety of potential confounding factors.

An important limitation of this study is that the dietary assessment was based on a single self-report at study baseline in 1986, which will introduce measurement error. This would likely attenuate associations. There are also unmeasured dietary changes since 1986. However, remote diet is more likely to be of etiologic significance than diet near the time of diagnosis in NHL,[11] and the latency period for development of NHL, while unknown, is likely to be more than 5 years, if not decades. While this study accounted for many confounding factors, there are other potential risk factors for which we were not able to adjust, including exposure to pesticides, occupational status, and hair dye use. We also conducted many statistical tests, and some of the findings will represent false positive associations. The cases in this study were not reviewed by a central pathologist, although SEER registry report versus central review for follicular lymphoma and DLBCL is excellent.[29] Finally, the cohort consists of an older population of women in one geographic location, and results may not readily generalize to other populations.

## Conclusions

In summary, these data support a role for antioxidant nutrients from vegetables and perhaps some fruits, as protective factors against the development of NHL. Manganese intake from food sources also showed a protective association which has not previously been reported and requires replication. Associations were strongest and most consistent for follicular lymphoma, although, overall in the literature there has been fairly limited evidence for any etiologic heterogeneity by NHL subtype for these dietary factors, mainly due to a limited number of studies with subtype data as well as small sample sizes. Whether differences in biology and outcome between follicular lymphoma and DLBCL extend to etiologic differences is an area of active investigation. The field is rapidly reaching a critical mass of studies on diet and NHL risk, and pooling efforts, for example through the InterLymph consortium,[44] would be very useful to more precisely define associations and fully evaluate whether there are NHL subtype-specific associations. Finally, most studies have not shown an association with supplemental intake of antioxidant nutrients, suggesting that any association is likely to be mediated through foods. This has mechanistic implications (potential synergies between antioxidants; other anti-carcinogenic compounds in these foods) and also suggests that prevention approaches will likely need to be targeted towards foods and food groups and not individual nutrients, particularly taken as supplements.

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## Abbreviations

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| **DLBCL** | Diffuse large B-cell lymphoma |
| **RR** | relative risk |
| **CI** | confidence interval |
| **NHL** | non-Hodgkin lymphoma |
| **IWHS** | Iowa Women's Health Study |
| **FFQ** | food frequency questionnaire |

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## TABLE I

DISTRIBUTION OF BASELINE (1986) FACTORS BY LEVEL OF FRUIT AND VEGETABLE CONSUMPTION

| | Fruit and Vegetable Consumption (servings/month) | | | |
|---|---|---|---|---|
| **Variable** | **Quartile 1 (<106) N=8813** | **Quartile 2 (106 – 150) N=8979** | **Quartile 3 (151 – 204) N=8707** | **Quartile 4 (>204) N=8660** |
| | Mean ± SD | | | |
| Age (years) | 61.7 ± 4.2 | 61.9 ± 4.2 | 62.2 ± 4.2 | 62.2 ± 4.2 |
| BMI (kg/m$^2$) | 26.7 ± 5.0 | 27.0 ± 5.1 | 27.0 ± 5.0 | 27.2 ± 5.3 |
| Red Meat Consumption (servings/ week) | 7.1 ± 5.0 | 7.6 ± 4.9 | 8.1 ± 5.1 | 9.0 ± 6.2 |
| | Percent Distribution | | | |
| Greater than High School Education | 30.9 | 39.0 | 43.9 | 46.2 |
| Martial Status | | | | |
| Current | 74.5 | 78.3 | 78.9 | 77.8 |
| Former | 23.2 | 19.2 | 18.5 | 19.8 |
| Never | 2.4 | 2.5 | 2.5 | 2.4 |
| Live on a Farm | 17.3 | 20.1 | 20.7 | 20.4 |
| No alcohol use | 58.1 | 54.8 | 53.3 | 53.1 |
| Smoking Status | | | | |
| Never | 59.3 | 66.0 | 69.0 | 68.5 |
| Current | 22.3 | 14.6 | 11.9 | 10.8 |
| Past | 18.5 | 19.4 | 19.1 | 20.7 |
| Ever Used Hormone Replacement Therapy | 37.4 | 38.9 | 39.5 | 39.3 |
| Adult Onset Diabetes | 4.4 | 5.8 | 6.1 | 7.4 |
| Ever had a Blood transfusion | 25.6 | 24.4 | 25.5 | 26.9 |

## TABLE II

RELATIVE RISK OF NHL, DLBCL AND FOLLICULAR NHL ACCORDING TO INTAKE OF ANTIOXIDANT VITAMINS FROM FOOD AND SUPPLEMENTS, IOWA WOMEN'S HEALTH STUDY, 1986–2005

| | | All NHL | | | DLBCL | | | Follicular lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Vitamin** | **Person Years** | **Cases** | **RR (95% CI)*** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** |
| Vitamin C (mg/day) | | | | | | | | | | |
| Total | | | | | | | | | | |
| <127 | 150007 | 110 | 1.00 (reference) | 0.65 | 48 | 1.00 (reference) | 0.72 | 25 | 1.00 (reference) | 0.54 |
| 127–191 | 150846 | 96 | 0.84 (0.64, 1.11) | | 45 | 0.90 (0.60, 1.35) | | 20 | 0.75 (0.42, 1.37) | |
| 192–325 | 150206 | 109 | 0.95 (0.72, 1.25) | | 46 | 0.91 (0.60, 1.38) | | 25 | 0.93 (0.52, 1.64) | |
| >325 | 146882 | 100 | 0.90 (0.68, 1.18) | | 45 | 0.92 (0.60, 1.39) | | 20 | 0.76 (0.42, 1.40) | |
| Diet only | | | | | | | | | | |
| <101 | 149020 | 117 | 1.00 (reference) | 0.044 | 46 | 1.00 (reference) | 0.36 | 34 | 1.00 (reference) | 0.032 |
| 101–142 | 150372 | 108 | 0.87 (0.67, 1.14) | | 52 | 1.07 (0.72, 1.60) | | 17 | 0.46 (0.26, 0.83) | |
| 143–191 | 149915 | 89 | 0.71 (0.53, 0.94) | | 42 | 0.85 (0.55, 1.31) | | 16 | 0.41 (0.22, 0.76) | |
| >191 | 148634 | 101 | 0.78 (0.58, 1.05) | | 44 | 0.87 (0.55, 1.37) | | 23 | 0.55 (0.30, 1.00) | |
| Supplements only | | | | | | | | | | |
| Nonusers | 330696 | 223 | 1.00 (reference) | 0.79 | 104 | 1.00 (reference) | 0.57 | 47 | 1.00 (reference) | 0.77 |
| <334 | 181966 | 135 | 1.09 (0.88, 1.35) | | 57 | 0.99 (0.72, 1.36) | | 35 | 1.35 (0.87, 2.09) | |
| >334 | 85278 | 57 | 0.99 (0.74, 1.33) | | 23 | 0.86 (0.55, 1.35) | | 8 | 0.67 (0.31, 1.41) | |
| Vitamin E (IU/day) | | | | | | | | | | |
| Total | | | | | | | | | | |
| <7.7 | 149787 | 107 | 1.00 (reference) | 0.97 | 46 | 1.00 (reference) | 0.85 | 23 | 1.00 (reference) | 0.60 |
| 7.7–11 | 150370 | 95 | 0.87 (0.65, 1.16) | | 45 | 0.94 (0.61, 1.44) | | 17 | 0.69 (0.36, 1.33) | |
| 12–33 | 149994 | 109 | 0.98 (0.72, 1.33) | | 44 | 0.89 (0.56, 1.43) | | 25 | 0.98 (0.51, 1.87) | |
| >33 | 147790 | 104 | 0.96 (0.73, 1.27) | | 49 | 1.04 (0.68, 1.58) | | 25 | 1.04 (0.57, 1.87) | |
| Diet only | | | | | | | | | | |
| <6.7 | 152254 | 105 | 1.00 (reference) | 0.60 | 41 | 1.00 (reference) | 0.54 | 24 | 1.00 (reference) | 0.55 |
| 6.7–8.6 | 147272 | 107 | 1.03 (0.78, 1.36) | | 50 | 1.27 (0.83, 1.95) | | 19 | 0.76 (0.41, 1.41) | |
| 8.7–11.0 | 151829 | 100 | 0.91 (0.67, 1.24) | | 44 | 1.09 (0.68, 1.75) | | 26 | 0.94 (0.50, 1.76) | |
| >11.0 | 146586 | 103 | 0.94 (0.65, 1.36) | | 49 | 1.28 (0.74, 2.22) | | 21 | 0.70 (0.32, 1.56) | |
| Supplements only | | | | | | | | | | |

| Vitamin | Person Years | All NHL | | | DLBCL | | | Follicular lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Cases | RR (95% CI)* | *p*-trend | Cases | RR (95% CI) | *p*-trend | Cases | RR (95% CI) | *p*-trend |
| Nonusers | 330696 | 223 | 1.00 (reference) | 0.79 | 119 | 1.00 (reference) | 0.78 | 53 | 1.00 (reference) | 0.34 |
| <40 | 181966 | 135 | 1.09 (0.88, 1.35) | | 38 | 0.93 (0.64,1.34) | | 21 | 1.16 (0.70, 1.92) | |
| >40 | 85278 | 57 | 1.07 (0.74, 1.33) | | 27 | 0.97 (0.64, 1.47) | | 16 | 1.29 (0.74, 2.26) | |
| Carotenoids (IU/day) | | | | | | | | | | |
| Total | | | | | | | | | | |
| <4693 | 148770 | 109 | 1.00 (reference) | 0.033 | 49 | 1.00 (reference) | 0.52 | 23 | 1.00 (reference) | 0.075 |
| 4693–7107 | 149222 | 119 | 1.05 (0.81, 1.37) | | 43 | 0.85 (0.56, 1.29) | | 32 | 1.31 (0.77, 2.25) | |
| 7108–12159 | 149414 | 93 | 0.80 (0.61, 1.07) | | 47 | 0.91 (0.60, 1.37) | | 16 | 0.63 (0.33, 1.21) | |
| >12159 | 150535 | 94 | 0.78 (0.58, 1.05) | | 45 | 0.84 (0.55, 1.30) | | 19 | 0.70 (0.37, 1.33) | |
| Diet only | | | | | | | | | | |
| <4541 | 148476 | 109 | 1.00 (reference) | 0.048 | 48 | 1.00 (reference) | 0.60 | 25 | 1.00 (reference) | 0.16 |
| 4541–6789 | 149482 | 115 | 1.01 (0.78, 1.32) | | 43 | 0.86 (0.57, 1.31) | | 25 | 0.94 (0.54, 1.65) | |
| 6790–11838 | 149504 | 97 | 0.84 (0.63, 1.11) | | 48 | 0.95 (0.63, 1.43) | | 20 | 0.72 (0.40, 1.32) | |
| >11838 | 150478 | 94 | 0.78 (0.58, 1.05) | | 45 | 0.86 (0.56, 1.33) | | 20 | 0.68 (0.36, 1.28) | |
| Supplements only | | | | | | | | | | |
| Nonusers | 538118 | 372 | 1.00 (reference) | 0.85 | 128 | 1.00 (reference) | 0.72 | 83 | 1.00 (reference) | 0.48 |
| Users | 59823 | 43 | 1.03 (0.75, 1.41) | | 20 | 1.09 (0.69, 1.73) | | 7 | 0.76 (0.35, 1.64) | |

*Relative risk (RR) and 95% confidence interval (CI), adjusted for age and total energy intake.

## TABLE III

RELATIVE RISK OF NHL, DLBCL, AND FOLLICULAR NHL ACCORDING TO INTAKE OF SELECTED CAROTENOIDS, IOWA WOMEN'S HEALTH STUDY, 1986–2005

| | | All NHL | | | DLBCL | | | Follicular lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Carotenoid | Person Years | Cases | RR (95% CI)* | p-trend | Cases | RR (95% CI) | p-trend | Cases | RR (95% CI) | p-trend |
| α-carotene (μg/day) | | | | | | | | | | |
| <323 | 146502 | 111 | 1.00 (reference) | 0.015 | 45 | 1.00 (reference) | 0.38 | 26 | 1.00 (reference) | 0.077 |
| 323–499 | 149661 | 114 | 0.98 (0.76, 1.28) | | 50 | 1.06 (0.71, 1.59) | | 25 | 0.90 (0.52, 1.57) | |
| 500–1318 | 150442 | 103 | 0.87 (0.66, 1.14) | | 48 | 1.00 (0.66, 1.51) | | 21 | 0.73 (0.41, 1.31) | |
| >1318 | 151336 | 87 | 0.71 (0.53, 0.95) | | 41 | 0.83 (0.53, 1.29) | | 18 | 0.59 (0.31, 1.11) | |
| β-carotene (μg/day) | | | | | | | | | | |
| <2603 | 148991 | 112 | 1.00 (reference) | 0.072 | 47 | 1.00 (reference) | 0.99 | 25 | 1.00 (reference) | 0.085 |
| 2603–3989 | 149691 | 111 | 0.96 (0.74, 1.25) | | 41 | 0.85 (0.56,1.30) | | 28 | 1.07 (0.62, 1.83) | |
| 3990–6173 | 149469 | 95 | 0.81 (0.61, 1.07) | | 49 | 1.00 (0.67, 1.51) | | 18 | 0.66 (0.36, 1.22) | |
| >6173 | 149790 | 97 | 0.80 (0.60, 1.07) | | 47 | 0.94 (0.61, 1.45) | | 19 | 0.65 (0.35, 1.23) | |
| β-crytoxanthin (μg/day) | | | | | | | | | | |
| <30 | 151173 | 120 | 1.00 (reference) | 0.21 | 51 | 1.00 (reference) | 0.95 | 29 | 1.00 (reference) | 0.040 |
| 30–64 | 158321 | 100 | 0.77 (0.59, 1.01) | | 43 | 0.79 (0.52, 1.18) | | 26 | 0.82 (0.48, 1.39) | |
| 65–106 | 139727 | 94 | 0.82 (0.63, 1.08) | | 37 | 0.76 (0.50, 1.17) | | 17 | 0.60 (0.33, 1.09) | |
| >106 | 148720 | 101 | 0.82 (0.62, 1.08) | | 53 | 1.02 (0.68, 1.51) | | 18 | 0.57 (0.31, 1.05) | |
| Lycopene (μg/day) | | | | | | | | | | |
| <2209 | 149015 | 106 | 1.00 (reference) | 0.72 | 38 | 1.00 (reference) | 0.10 | 24 | 1.00 (reference) | 0.45 |
| 2209–3591 | 149360 | 99 | 0.94 (0.72, 1.24) | | 48 | 1.29 (0.84, 1.97) | | 21 | 0.86 (0.48, 1.55) | |
| 3592–5540 | 150729 | 98 | 0.93 (0.70, 1.22) | | 41 | 1.09 ( 0.70, 1.71) | | 27 | 1.08 (0.62, 1.89) | |
| >5540 | 148838 | 112 | 1.06 (0.80, 1.40) | | 57 | 1.54 (1.00, 2.37) | | 18 | 0.70 (0.37, 1.33) | |
| Lutein + zeaxanthin (μg/day) | | | | | | | | | | |
| <1426 | 149968 | 121 | 1.00 (reference) | 0.068 | 47 | 1.00 (reference) | 0.67 | 34 | 1.00 (reference) | 0.007 |
| 1426–2344 | 150557 | 104 | 0.84 (0.64, 1.09) | | 42 | 0.88 (0.58, 1.33) | | 24 | 0.66 (0.39, 1.13) | |
| 2345–3661 | 149503 | 88 | 0.70 (0.53, 0.93) | | 43 | 0.90 (0.59, 1.37) | | 10 | 0.27 (0.13, 0.54) | |
| >3661 | 147914 | 102 | 0.81 (0.61, 1.07) | | 52 | 1.09 (0.72, 1.65) | | 22 | 0.56 (0.32, 0.99) | |

*Relative risk (RR) and 95% confidence interval (CI), adjusted for age and total energy intake.

## TABLE IV

RELATIVE RISK OF NHL, DLBCL, AND FOLLICULAR NHL ACCORDING TO INTAKE OF SELECTED FLAVONOIDS, IOWA WOMEN'S HEALTH STUDY, 1986–2005

| | | All NHL | | | DLBCL | | | Follicular lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Flavonoid** | **Person Years** | **Cases** | **RR (95% CI)*** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** |
| Total Flavonoids (mg/day) | | | | | | | | | | |
| <150.8 | 148502 | 105 | 1.00 (reference) | 0.18 | 40 | 1.00 (reference) | 0.44 | 28 | 1.00 (reference) | 0.14 |
| 150.8–239.3 | 149351 | 109 | 1.00 (0.76,1.31) | | 56 | 1.35 (0.89, 2.03) | | 19 | 0.64 (0.35, 1.14) | |
| 239.4–376.7 | 150520 | 108 | 0.96 (0.73, 1.27) | | 50 | 1.16 (0.76, 1.79) | | 24 | 0.76 (0.43, 1.34) | |
| >376.7 | 149568 | 93 | 0.82 (0.61, 1.10) | | 38 | 0.88 (0.55, 1.40) | | 19 | 0.58 (0.31, 1.08) | |
| Isoflavones (mg/day) | | | | | | | | | | |
| <0.15 | 148068 | 107 | 1.00 (reference) | 0.42 | 40 | 1.00 (reference) | 0.68 | 32 | 1.00 (reference) | 0.022 |
| 0.15–0.25 | 150184 | 106 | 0.95 (0.73, 1.25) | | 52 | 1.26 (0.83, 1.90) | | 21 | 0.61 (0.35, 1.06) | |
| 0.26–0.36 | 150294 | 101 | 0.90 (0.68, 1.19) | | 43 | 1.03 (0.67, 1.61) | | 17 | 0.47 (0.26, 0.86) | |
| >0.36 | 149396 | 101 | 0.90 (0.67, 1.20) | | 49 | 1.19 (0.76, 1.84) | | 20 | 0.53 (0.29, 0.97) | |
| Flavonols (mg/day) | | | | | | | | | | |
| <6.1 | 148627 | 117 | 1.00 (reference) | 0.23 | 43 | 1.00 (reference) | 0.92 | 33 | 1.00 (reference) | 0.030 |
| 6.1–8.9 | 150363 | 93 | 0.77 (0.59, 1.02) | | 47 | 1.07 (0.70, 1.62) | | 18 | 0.51 (0.28, 0.91) | |
| 9.0–13.2 | 150349 | 107 | 0.87 (0.66, 1.14) | | 52 | 1.16 (0.76, 1.76) | | 19 | 0.51 (0.29, 0.91) | |
| >13.2 | 148602 | 98 | 0.80 (0.60, 1.07) | | 42 | 0.95 (0.60, 1.49) | | 20 | 0.52 (0.29, 0.94) | |
| Proanthocyanidins (mg/day) | | | | | | | | | | |
| <78.4 | 147925 | 118 | 1.00 (reference) | 0.0024 | 50 | 1.00 (reference) | 0.071 | 32 | 1.00 (reference) | 0.013 |
| 78.5–124.8 | 149520 | 118 | 0.95 (0.73, 1.23) | | 56 | 1.06 (0.72, 1.56) | | 22 | 0.63 (0.37, 1.09) | |
| 124.9–189.4 | 149897 | 84 | 0.65 (0.49, 0.87) | | 33 | 0.61 (0.39, 0.95) | | 15 | 0.41 (0.22, 0.76) | |
| >189.4 | 150600 | 95 | 0.70 (0.52, 0.94) | | 45 | 0.78 (0.50, 1.21) | | 21 | 0.52 (0.28, 0.95) | |
| Anthocyanidins (mg/day) | | | | | | | | | | |
| 0 | 203864 | 151 | 1.00 (reference) | 0.22 | 69 | 1.00 (reference) | 0.38 | 32 | 1.00 (reference) | 0.25 |
| <0.02 | 130894 | 96 | 0.98 (0.76, 1.27) | | 39 | 0.87 (0.59, 1.29) | | 24 | 1.15 (0.68, 1.96) | |
| 0.02–0.79 | 115757 | 71 | 0.83 (0.62, 1.10) | | 33 | 0.84 (0.55, 1.27) | | 17 | 0.92 (0.51, 1.66) | |
| >0.79 | 147426 | 97 | 0.88 (0.68, 1.14) | | 43 | 0.85 (0.58, 1.26) | | 17 | 0.71 (0.39, 1.29) | |

* Relative risk (RR) and 95% confidence interval (CI), adjusted for age and total energy intake.

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**TABLE V**

RELATIVE RISK OF NHL, DLBCL, AND FOLLICULAR NHL ACCORDING TO INTAKE OF MULTIVITAMIN SUPPLEMENT AND ANTIOXIDANT MICRONUTRIENTS, IOWA WOMEN'S HEALTH STUDY, 1986–2005

| | | All NHL | | | DLBCL | | | Follicular lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Supplement** | **Person Years** | **Cases** | **RR (95% CI)*** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** |
| Multi vitamin | | | | | | | | | | |
| Nonuser | 394275 | 266 | 1.00 (reference) | 0.50 | 123 | 1.00 (reference) | 0.81 | 54 | 1.00 (reference) | 0.35 |
| User | 195610 | 142 | 1.07 (0.87, 1.31) | | 59 | 0.96 (0.71, 1.31) | | 33 | 1.23 (0.80, 1.90) | |
| Selenium supplements | | | | | | | | | | |
| Nonusers | 552949 | 388 | 1.00 (reference) | 0.26 | 175 | 1.00 (reference) | 0.25 | 81 | 1.00 (reference) | 0.33 |
| User | 18658 | 9 | 0.69 (0.35, 1.33) | | 3 | 0.51 (0.17, 1.60) | | 1 | 0.39 (0.06, 2.64) | |
| Zinc (mg/day) | | | | | | | | | | |
| Total | | | | | | | | | | |
| <9.4 | 147781 | 109 | 1.00 (reference) | 0.82 | 51 | 1.00 (reference) | 0.98 | 22 | 1.00 (reference) | 0.63 |
| 9.4–12 | 149942 | 91 | 0.81 (0.61, 1.09) | | 38 | 0.71 (0.46, 1.11) | | 17 | 0.75 (0.39, 1.44) | |
| 13–18 | 151379 | 104 | 0.91 (0.67, 1.24) | | 44 | 0.80 (0.50, 1.26) | | 27 | 1.16 (0.61, 2.20) | |
| >18 | 148838 | 111 | 0.99 (0.72, 1.35) | | 51 | 0.93 (0.58, 1.49) | | 24 | 1.04 (0.52, 2.07) | |
| Diet only | | | | | | | | | | |
| <8.8 | 147447 | 106 | 1.00 (reference) | 0.53 | 46 | 1.00 (reference) | 0.48 | 23 | 1.00 (reference) | 0.35 |
| 8.8–11 | 149463 | 93 | 0.88 (0.66, 1.18) | | 41 | 0.90 (0.58, 1.41) | | 17 | 0.76 (0.39, 1.46) | |
| 12–15 | 150198 | 101 | 0.96 (0.70, 1.32) | | 44 | 0.98 (0.61, 1.58) | | 20 | 0.91 (0.46, 1.80) | |
| >15 | 150833 | 115 | 1.12 (0.76, 1.64) | | 53 | 1.23 (0.69, 2.16) | | 30 | 1.42 (0.65, 3.13) | |
| Supplements only | | | | | | | | | | |
| Nonusers | 490273 | 337 | 1.00 (reference) | 0.66 | 153 | 1.00 (reference) | 0.67 | 73 | 1.00 (reference) | 0.84 |
| ≤27 | 83245 | 59 | 1.02 (0.77, 1.34) | | 24 | 0.92 (0.60, 1.41) | | 13 | 1.04 (0.58, 1.88) | |
| >27 | 24423 | 19 | 1.12 (0.71, 1.78) | | 7 | 0.91 (0.43, 1.94) | | 4 | 1.09 (0.40, 2.98) | |
| Copper (mg/day) | | | | | | | | | | |
| Total | | | | | | | | | | |
| <1.1 | 152239 | 116 | 1.00 (reference) | 0.21 | 52 | 1.00 (reference) | 0.63 | 24 | 1.00 (reference) | 0.32 |
| 1.1–1.4 | 149123 | 109 | 0.92 (0.70, 1.21) | | 46 | 0.87 (0.58, 1.31) | | 25 | 0.97 (0.54, 1.74) | |
| 1.5–2.0 | 149470 | 80 | 0.66 (0.48, 0.90) | | 33 | 0.61 (0.38, 0.98) | | 19 | 0.70 (0.36, 1.35) | |
| >2.0 | 147109 | 110 | 0.89 (0.65, 1.22) | | 53 | 0.97 (0.61, 1.54) | | 22 | 0.77 (0.38, 1.55) | |

| Supplement | Person Years | All NHL | | | DLBCL | | | Follicular lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Cases | RR (95% CI)* | *p*-trend | Cases | RR (95% CI) | *p*-trend | Cases | RR (95% CI) | *p*-trend |
| Diet only | | | | | | | | | | |
| <1.1 | 150286 | 106 | 1.00 (reference) | 0.15 | 44 | 1.00 (reference) | 0.58 | 23 | 1.00 (reference) | 0.25 |
| 1.1–1.3 | 148991 | 115 | 1.04 (0.79, 1.38) | | 55 | 1.23 (0.81, 1.86) | | 23 | 0.89 (0.49, 1.64) | |
| 1.4–1.7 | 149075 | 94 | 0.84 (0.62, 1.13) | | 37 | 0.82 (0.51, 1.31) | | 25 | 0.91 (0.48, 1.71) | |
| >1.7 | 149589 | 100 | 0.83 (0.58, 1.19) | | 48 | 1.01 (0.59, 1.74) | | 19 | 0.58 (0.26, 1.30) | |
| Supplements only | | | | | | | | | | |
| Nonusers | 522245 | 367 | 1.00 (reference) | 0.49 | 166 | 1.00 (reference) | 0.23 | 80 | 1.00 (reference) | 0.65 |
| User | 75696 | 48 | 0.90 (0.67, 1.21) | | 18 | 0.74 (0.46, 1.21) | | 10 | 0.86 (0.45, 1.66) | |
| Manganese (mg/day) | | | | | | | | | | |
| Total | | | | | | | | | | |
| <1.9 | 149267 | 112 | 1.00 (reference) | 0.016 | 44 | 1.00 (reference) | 0.29 | 31 | 1.00 (reference) | 0.070 |
| 1.9–2.6 | 150870 | 118 | 0.98 (0.75, 1.28) | | 56 | 1.19 (0.79, 1.80) | | 19 | 0.53 (0.30, 0.96) | |
| 2.7–3.6 | 149619 | 89 | 0.70 (0.52, 0.95) | | 41 | 0.84 (0.53, 1.34) | | 16 | 0.41 (0.21, 0.79) | |
| >3.6 | 148185 | 96 | 0.73 (0.53, 1.01) | | 43 | 0.86 (0.52, 1.41) | | 24 | 0.56 (0.29, 1.09) | |
| Diet only | | | | | | | | | | |
| <1.9 | 148514 | 114 | 1.00 (reference) | 0.010 | 44 | 1.00 (reference) | 0.43 | 31 | 1.00 (reference) | 0.026 |
| 1.9–2.5 | 149964 | 105 | 0.84 (0.64, 1.11) | | 48 | 1.02 (0.67, 1.56) | | 18 | 0.49 (0.27, 0.90) | |
| 2.6–3.3 | 150947 | 107 | 0.81 (0.60, 1.08) | | 52 | 1.06 (0.68, 1.65) | | 20 | 0.49 (0.26, 0.91) | |
| >3.3 | 148516 | 89 | 0.62 (0.44, 0.88) | | 40 | 0.78 (0.46, 1.32) | | 21 | 0.43 (0.21, 0.89) | |
| Supplements only | | | | | | | | | | |
| Nonusers | 540406 | 377 | 1.00 (reference) | 0.70 | 169 | 1.00 (reference) | 0.47 | 81 | 1.00 (reference) | 0.92 |
| User | 57535 | 38 | 0.94 (0.67, 1.31) | | 15 | 0.82 (0.49, 1.40) | | 9 | 1.04 (0.52, 2.06) | |

*Relative risk (RR) and 95% confidence interval (CI), adjusted for age and total energy intake.

## TABLE VI

RELATIVE RISK OF NHL, DLBCL, AND FOLLICULAR NHL ACCORDING TO INTAKE OF SELECTED FOOD GROUPS AND FOODS RICH IN ANTIOXIDANTS, IOWA WOMEN'S HEALTH STUDY, 1986–2005

| | | All NHL | | | DLBCL | | | Follicular lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Food or Food Group (servings per month)** | **Person Years** | **Cases** | **RR (95% CI)*** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** | **Cases** | **RR (95% CI)** | ***p*-trend** |
| All fruits and vegetables | | | | | | | | | | |
| <107 | 148916 | 120 | 1.00 (reference) | 0.011 | 45 | 1.00 (reference) | 0.43 | 31 | 1.00 (reference) | 0.038 |
| 107–150 | 153363 | 107 | 0.83 (0.64, 1.08) | | 51 | 1.06 (0.71, 1.59) | | 22 | 0.65 (0.37, 1.12) | |
| 151–204 | 149235 | 96 | 0.74 (0.56, 0.97) | | 47 | 0.97 (0.64, 1.49) | | 15 | 0.43 (0.23, 0.80) | |
| >204 | 146426 | 92 | 0.69 (0.51,0.94) | | 41 | 0.84 (0.53, 1.34) | | 22 | 0.59 (0.32,1.08) | |
| All fruits | | | | | | | | | | |
| <45 | 149262 | 119 | 1.00 (reference) | 0.066 | 46 | 1.00 (reference) | 0.58 | 30 | 1.00 (reference) | 0.16 |
| 45–68 | 155346 | 103 | 0.80 (0.61, 1.04) | | 50 | 1.00 (0.67, 1.49) | | 17 | 0.51 (0.28, 0.93) | |
| 69–96 | 151475 | 96 | 0.74 (0.57, 0.98) | | 44 | 0.88 (0.58, 1.34) | | 23 | 0.69 (0.39, 1.20) | |
| >96 | 141858 | 97 | 0.78 (0.58, 1.04) | | 44 | 0.92 (0.59, 1.42) | | 20 | 0.60 (0.33, 1.10) | |
| Citrus fruits | | | | | | | | | | |
| <11 | 149575 | 128 | 1.00 (reference) | 0.10 | 55 | 1.00 (reference) | 0.30 | 31 | 1.00 (reference) | 0.17 |
| 11–26 | 149310 | 88 | 0.68 (0.52, 0.89) | | 40 | 0.71 (0.47, 1.07) | | 18 | 0.57 (0.32, 1.01) | |
| 27–38 | 164936 | 102 | 0.70 (0.54, 0.90) | | 47 | 0.74 (0.50, 1.10) | | 20 | 0.56 (0.32, 0.98) | |
| >38 | 134120 | 97 | 0.81 (0.62, 1.06) | | 42 | 0.80 (0.53, 1.21) | | 21 | 0.70 (0.40, 1.23) | |
| Apple juice/cider | | | | | | | | | | |
| 0 | 409960 | 301 | 1.00 (reference) | 0.026 | 133 | 1.00 (reference) | 0.15 | 65 | 1.00 (reference) | 0.28 |
| 1–2 | 100219 | 71 | 0.96 (0.74, 1.24) | | 32 | 0.97 (0.66, 1.43) | | 16 | 0.99 (0.57, 1.71) | |
| >2 | 87762 | 43 | 0.65 (0.47, 0.90) | | 19 | 0.65 (0.40, 1.06) | | 9 | 0.62 (0.31, 1.26) | |
| All vegetables | | | | | | | | | | |
| <53 | 156243 | 122 | 1.00 (reference) | 0.041 | 51 | 1.00 (reference) | 0.82 | 34 | 1.00 (reference) | 0.013 |
| 53–78 | 151786 | 118 | 0.98 (0.76, 1.26) | | 51 | 1.02 (0.69, 1.51) | | 23 | 0.66 (0.39, 1.13) | |
| 79–112 | 144390 | 74 | 0.63 (0.47, 0.85) | | 28 | 0.59 (0.37, 0.94) | | 12 | 0.34 (0.18, 0.68) | |
| > 112 | 145522 | 101 | 0.84 (0.63, 1.12) | | 54 | 1.11 (0.73, 1.68) | | 21 | 0.56 (0.31, 1.01) | |
| Yellow/orange vegetables | | | | | | | | | | |
| <5 | 227508 | 168 | 1.00 (reference) | 0.015 | 70 | 1.00 (reference) | 0.49 | 36 | 1.00 (reference) | 0.16 |
| 5–6 | 90519 | 75 | 1.08 (0.82, 1.42) | | 34 | 1.18 (0.78, 1.78) | | 18 | 1.20 (0.68, 2.12) | |

| Food or Food Group (servings per month) | Person Years | All NHL Cases | All NHL RR (95% CI)* | All NHL p-trend | DLBCL Cases | DLBCL RR (95% CI) | DLBCL p-trend | Follicular lymphoma Cases | Follicular lymphoma RR (95% CI) | Follicular lymphoma p-trend |
|---|---|---|---|---|---|---|---|---|---|---|
| 7–14 | 160476 | 103 | 0.83 (0.65, 1.06) | | 43 | 0.83 (0.57, 1.23) | | 22 | 0.81 (0.47, 1.39) | |
| >14 | 119437 | 69 | 0.72 (0.54, 0.97) | | 37 | 0.94 (0.62, 1.42) | | 14 | 0.66 (0.35, 1.25) | |
| Green leafy vegetables | | | | | | | | | | |
| <5 | 150472 | 114 | 1.00 (reference) | 0.17 | 45 | 1.00 (reference) | 0.95 | 26 | 1.00 (reference) | 0.24 |
| 5–12 | 162415 | 119 | 0.96 (0.74, 1.24) | | 55 | 1.13 (0.76, 1.67) | | 26 | 0.91 (0.53, 1.57) | |
| 13–22 | 143276 | 87 | 0.79 (0.60, 1.05) | | 36 | 0.84 (0.54, 1.30) | | 19 | 0.74 (0.41, 1.35) | |
| >22 | 141777 | 95 | 0.87 (0.66, 1.15) | | 48 | 1.12 (0.74, 1.69) | | 19 | 0.73 (0.40, 1.35) | |
| Cruciferous vegetables | | | | | | | | | | |
| <7 | 210277 | 163 | 1.00 (reference) | 0.017 | 66 | 1.00 (reference) | 0.95 | 39 | 1.00 (reference) | 0.016 |
| 7–10 | 147255 | 116 | 1.01 (0.80, 1.29) | | 48 | 1.04 (0.72, 1.51) | | 29 | 1.05 (0.65, 1.70) | |
| 11–16 | 105930 | 48 | 0.58 (0.42, 0.80) | | 23 | 0.69 (0.43, 1.11) | | 5 | 0.25 (0.10, 0.63) | |
| >16 | 134479 | 88 | 0.82 (0.63, 1.07) | | 47 | 1.10 (0.75, 1.61) | | 17 | 0.64 (0.36, 1.14) | |
| Broccoli | | | | | | | | | | |
| 0 | 107419 | 85 | 1.00 (reference) | 0.018 | 35 | 1.00 (reference) | 0.64 | 18 | 1.00 (reference) | 0.12 |
| 1–2 | 183579 | 141 | 0.97 (0.74, 1.27) | | 58 | 0.97 (0.64, 1.48) | | 35 | 1.14 (0.65, 2.02) | |
| 3–4 | 193665 | 124 | 0.81 (0.62, 1.07) | | 57 | 0.91 (0.60, 1.38) | | 23 | 0.71 (0.38, 1.31) | |
| >4 | 113279 | 65 | 0.72 (0.52, 1.00) | | 34 | 0.92 (0.57, 1.48) | | 14 | 0.72 (0.36, 1.45) | |
| Whole grains (servings per week) | | | | | | | | | | |
| <4.6 | 148525 | 105 | 1.00 (reference) | 0.28 | 42 | 1.00 (reference) | 0.90 | 23 | 1.00 (reference) | 0.34 |
| 4.6–9.0 | 161146 | 118 | 1.02 (0.78, 1.32) | | 50 | 1.08 (0.71, 1.62) | | 29 | 1.14 (0.66, 1.96) | |
| 9.1–17.0 | 140828 | 96 | 0.92 (0.70, 1.22) | | 48 | 1.15 (0.76, 1.75) | | 17 | 0.73 (0.39, 1.38) | |
| >17.0 | 147443 | 96 | 0.88 (0.66, 1.17) | | 44 | 1.01 (0.65, 1.56) | | 21 | 0.85 (0.46, 1.55) | |
| Nuts | | | | | | | | | | |
| < 1/month | 247626 | 159 | 1 .00 (reference) | 0.85 | 70 | 1.00 (reference) | 0.79 | 26 | 1.00 (reference) | 0.26 |
| < 1 time/week | 206536 | 164 | 1.24 (0.99, 1.54) | | 74 | 1.27 (0.91, 1.76) | | 43 | 1.97 (1.21, 3.21) | |
| 1–4 times/week | 126709 | 81 | 0.99 (0.76, 1.3) | | 33 | 0.92 (0.60, 1.40) | | 19 | 1.40 (0.77, 2.56) | |
| 5+ times/week | 17069 | 11 | 0.97 (0.52, 1.81) | | 7 | 1.40 (0.64, 3.10) | | 2 | 1.05 (0.25, 4.52) | |

*Relative risk (RR) and 95% confidence interval (CI), adjusted for age and total energy intake.