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Intake of vitamins D and A, and calcium and risk of non-Hodgkin lymphoma: San Francisco Bay Area population-based case-control study

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Abstract

Several nutrients identified as potentially cancer protective have been inconsistently associated with non-Hodgkin lymphoma (NHL) risk. Dietary history data, including use of vitamin supplements, were collected using a semi-quantitative food frequency questionnaire administered during in-person interviews with 4,133 participants (2052 cases, 2081 controls) in a San Francisco Bay Area population-based case-control. Data were used to determine the association of intake levels of vitamins D, A and calcium with risk of NHL and NHL subtypes. Odds ratios (OR) and 95% confidence intervals (CI) were computed as estimates of relative risk using adjusted unconditional logistic regression. Increasing vitamin D intake from food and supplements was positively associated with NHL risk in men (5^{th} quintile: OR=1.6, 95% CI= 1.0-2.4, P_{trend}=0.07) and with diffuse large B-cell lymphoma (DLBCL) in women and men (5^{th} quintile: OR=1.6, 95% CI=1.0-2.5, P_{trend}=0.02), that was largely due to the effect in men (P_{trend}=0.03). These results do not support a strong role for vitamin D intake with NHL risk with the exception of a potential association for DLBCL risk in men. Our results should be interpreted conservatively until further investigation in larger pooled studies can be conducted to better assess the role of vitamin D intake in lymphomagenesis.

Keywords

lymphoma, non-Hodgkin; case-control studies; vitamin D; vitamin A; calcium

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a heterogeneous cancer of B- and T-cells with B-cell lymphomas comprising the majority of NHL diagnosed in U.S. adults. Incidence has increased worldwide over the past several decades[1-4] and the U.S. Surveillance. Epidemiology and End Results (SEER) data show that the increase in incidence rates vary by age, sex, race and NHL subtype.[5] Although a link between immune-deficiency, especially severe immunosuppression such as that for human immunodeficiency virus (HIV) infection and NHL risk has been established,[6,7] the HIV epidemic only partly explains the increased incidence in the pre-HAART (Highly Active Anti-Retroviral Therapy) era.[8] Other known factors include family history and other immune-related factors including infection with human T-lymphotropic virus-1 (HTLV-I), Epstein-Barr Virus (EBV), hepatitis C and *helicobacter pylori*, immunosuppression related to graft-host disease, autoimmune

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conditions and several rare inherited immunosuppressive disorders.[2,4,9,10] Despite the challenges associated with identifying risk factors and underlying disease mechanisms for such a heterogeneous cancer, scientific and technological advances over the past decade have contributed to an increased understanding of NHL and to NHL subtype differences in prognosis, genetic characteristics and etiology,[11-13] especially for the most common subtypes, diffuse large B-cell (DLBCL), follicular (FL) and chronic lymphocytic leukemia/ small lymphocytic lymphomas(CLL/SLL).[11-13]

Initial support for a potential association between vitamin D and NHL risk came from studies of NHL risk and sun exposure (the primary source for vitamin D in humans). The initial hypothesis for the sun-NHL association was based on ecological data showing an NHL geographic incidence pattern similar to melanoma and non-melanoma skin cancers.[44,45] The sun-related results from subsequent independent studies of NHL have been inconsistent, however, a large pooled analysis of 10 case-control studies from North America, Europe and Australia showed an inverse association between personal recreational sun exposure and NHL risk.[45] To help elucidate the potential association subsequent studies have focused on the association with vitamin D levels, mainly as intake from diet and supplements.

The association between NHL and vitamin D is of particular interest because of the potential effect that vitamin D has on immune function. Intake of some nutrients, including vitamin D, has been associated with immunosuppressive and immune enhancing effects on innate and adaptive immune responses.[15,16] These findings have led to subsequent hypotheses that nutrients from food and taken as supplements might play a role in the development of NHL and other cancers by increasing risk via their immunosuppressive effects or by decreasing risk via their immune enhancing effects.[17,18] However, thus far the overall results have been inconclusive from studies of NHL that evaluated risk associated with intake of foods that are rich sources of vitamin D and other nutrients that can affect vitamin D levels and metabolism, vitamin A and calcium.[19-37] Results also have been inconsistent across epidemiologic studies that analyzed NHL risk and nutrient intake levels of vitamin D,[19,38,40-42] vitamin A (and/or retinol)[19,26,34,35,38,39] and calcium.[19,38] In contrast, a recent population-based, randomized, double-blind, placebo-controlled intervention trial of vitamin D and calcium reported that compared with the placebo group, all-cancer risk was substantially reduced among postmenopausal women in the treatment arm who received calcium plus vitamin D.[43]

Recently the Institute of Medicine (IOM) encouraged continued research on the role of vitamin D in health and disease based on a comprehensive review of the published research that showed current data were inadequate to determine the relationship with health conditions other than bone health.[46] Here we present new findings from detailed analyses of risk of NHL and common NHL subtypes associated with diet and supplement intake of vitamin D and nutrients that can influence vitamin D levels, vitamin A and calcium, among participants in a large San Francisco Bay Area population-based case-control study of NHL.

MATERIALS AND METHODS

Study Population

Incident cases were identified shortly after diagnosis by the Northern California Cancer Center (now the Cancer Prevention Institute of California) using rapid case ascertainment (RCA) methods. Surveillance, Epidemiology and End Results abstracts also were obtained to identify new cases diagnosed in Bay Area hospitals that did not participate in rapid case ascertainment and to confirm NHL diagnoses. Eligible patients were diagnosed with incident NHL from 2001 to 2006, were 20 to 85 years of age, were a resident of one of six

San Francisco Bay Area counties, were able to complete an interview in English, and had no physician indicated contraindications to contact. Of the 3,850 patients identified during the study period, a total of 2,052 eligible patients completed in-person interviews. Reasons for non-participation included: death before initial contact (12%), too ill (5%), unable to complete an interview in English (9%), could not be located or had moved (5%), had physician indicated contraindications to contact (2%), refused to participate (12%) and other miscellaneous reasons (<1%). No proxy interviews were conducted.

Random digit dial (RDD) methods supplemented by random sampling of the Center for Medicare and Medicaid Services (CMS) lists for those ≥65 years of age (includes approximately 98% of the population ≥65 years of age)[47] were used to identify control participants from the same target population as the cases. Eligibility criteria were the same as for cases, except that controls could have no history of a lymphoma diagnosis. Controls were frequency matched to cases by age in 5-year groups, sex and county of residence. A one-stage RDD approach resulted in a total of 29,053 telephone numbers dialed to 4,149 household and 24,904 non-residential numbers (*i.e.*, businesses, pay phones, disconnected numbers, data/tech lines, fax machines etc.). Of the residential telephone calls, reasons for non-participation included no eligible adult at the residence (33%), refused (13%), did not speak English (20%) and were too ill (2%). Among the controls who were randomly selected from the CMS list, reasons for non-participation included refused (27%), did not speak English (8%), too ill (4%), could not be located/moved out-of-area (21%), died (4%), were deaf or had dementia (2%) and were not available for other reasons (<1%). A total of 2081 eligible controls completed in-person interviews (1,313 RDD and 768 CMS).

Diagnostic materials were requested from the diagnosing facility for the 97% of the NHL cases who provided consent. Materials were re-reviewed by the study hematopathologist to confirm the initial NHL diagnosis (98%) and for consistent classification of NHL subtypes using the WHO classification.[48]

In-person interviews were conducted by trained interviewers at a time and a place convenient to the participants, usually in their homes. The median duration from diagnosis to interview for cases was 150 days (interquartile range 269 days). Demographic and immune-related exposures and conditions that occurred prior to diagnosis (cases) or interview (controls) were obtained in the main questionnaire and a detailed dietary history was collected using a validated, multiethnic, scannable, semi-quantitative food-frequency questionnaire (FFQ) developed by the Cancer Research Center (CRC) at the University of Hawaii.[49,50] Twelve participants (11 cases, 1 control) for whom dietary and/or nutrient data were missing are not included in these analyses.

Assessment of Dietary Intake

The FFQ included questions about consumption of more than 180 foods and beverages, food preparation methods, and use of vitamin and mineral supplements. Participants were asked to report their average frequency of intake and usual serving size of food items as well as vitamin supplement use in the year before diagnosis (cases) or interview (controls). Pictures of food on a dinner plate were provided to help responders estimate their usual food serving size e.g. ≤1/2 c, about 1 c, or ≥2 c. Respondents reported frequency of food intake from among eight categories that ranged from never or hardly ever to ≥ 2/day and reported usual food serving size *e.g.* ≤1/2 c, about 1 c, or ≥2 c with the help of photos depicting food portion sizes.

Frequency (1-3/week, 4-6/week, 1/day, 2/day or ≥3/day) and duration (≤1 year, 2-4 year, ≥5 year) of use were obtained for vitamins and minerals taken at least once per week. Supplemental vitamin D intake was assessed from multivitamins (Stress-tabs ™ type,

Therapeutic, Theragran-M type, and One-a-day® type) whereas supplemental vitamin A and calcium were based on use of multivitamins and individual supplements (vitamin A: 4 doses from 5000 - ≥25,000 international units; calcium: 4 doses from 250 - ≥1,250 mg). Average daily nutrient intake from food and supplements was computed using the food and supplement composition tables developed and maintained at the University of Hawaii CRC for items recorded on the multiethnic FFQ[51].

All participants provided informed consent for interview. In addition, cases provided informed consent to access their diagnostic pathology materials. Protocols and procedures were approved by the University of California San Francisco Committee on Human Research.

Statistical Analysis

All statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, North Carolina). Unconditional logistic regression models were used to obtain odds ratios (OR) and 95% confidence intervals (CI) as estimates of the relative risk of NHL, hereafter referred to as risk. All models were adjusted for the frequency-matched variables of age in 5-year groups, sex and county, and for total caloric intake in quintiles.[52] Participants with implausible total energy intake as measured by the FFQ (<500 kcal or >5000 kcal) were excluded from analyses. Mutual effects of nutrient intake were assessed in adjusted multivariable models and were retained in the final model if their inclusion altered the effect estimates for the specific nutrient of interest by greater than 10% as noted in the table footnotes. In our analyses, calcium intake was adjusted for vitamin D intake in quintiles and vitamin D intake was adjusted for vitamin A intake in quintiles. In the event of small sample size and non-convergence, age was modeled as a continuous variable. Cells with five or fewer exposed participants are not presented in the tables. Analyses of NHL and by the NHL subtypes, DLBCL, FL, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone lymphoma (MZL) and T-cell NHL, were conducted stratified by sex and for men and women combined.

Total nutrient intake (food and supplements) and intake from food only were categorized into quintiles based on the control distribution. In all analyses, the referent group was those whose nutrient intake was in the 1st quintile. Tests for trend were based on the chi-square statistic from adjusted logistic regression where median values in each quintile were modeled as an ordinal variable. Individual statistically significant ORs are included in the text only when a statistically significant linear trend was observed.

Main effect ORs were not confounded by race, ethnicity, education, physical activity, body-mass index (weight in kg/height in m^2), and previous history of a primary invasive cancer in multivariable models All statistical tests were two-sided and were considered statistically significant for P<0.05 and somewhat significant for P between 0.05 and 0.1.

RESULTS

The distribution of demographic factors was similar between cases and controls (Table 1). Study participants were predominantly of white non-Hispanic race/ethnicity with a slightly greater ratio of men to women. Median age at diagnosis for all cases was 61 years, with men somewhat younger than women at diagnosis (median age: men=60 years, women=62 years). Median daily total energy intake was 1942.8 kcal among NHL cases and 1849.5 kcal among controls. A total of 1448 (63%) men and 1310 (76%) women reported multivitamin or individual vitamin supplement use (data not in table).

Risk of NHL was not associated with vitamin A from food and supplements with all ORs near unity and with similar estimates in men and women (Table 2). An increased risk of NHL associated with increasing vitamin D intake was observed among men and women combined that in stratified analyses was found mainly to be due to the effect among men. The ORs for vitamin D were further increased when models also were adjusted for vitamin A intake but were not altered when adjusted for calcium intake. Specifically, men in the highest quintile of vitamin D intake had an increased risk of NHL (OR=1.6, 95% CI 1.0-2.4) with a weak suggestion of a dose-response effect (P_{trend} =0.07, Table 2). Intake of calcium from food and supplements was not associated with NHL risk.

Results from analyses of intake of vitamins A and D from food alone were consistent with those from food and supplements combined (Table 2) and were not altered in models that included mutual adjustment for nutrient intake from food alone. Calcium intake from food alone also was not associated with NHL risk and among men, the ORs were attenuated when quintiles of vitamin D intake was included in the model. .

In NHL subtype analyses, there was some evidence that risk of DLBCL increased with increased levels of vitamin D intake from food and supplements (5^{th} quintile: OR=1.6, 95% CI 1.0-2.5; P_{trend} =0.02, Table 3). There was some evidence that risk of FL increased with increasing vitamin D intake from food alone (P_{trend}=0.05), although individual ORs were not different from unity. Risks of CLL/SLL, MZL and T-cell lymphoma were not associated with intake of vitamins A and D, and of calcium (Table 3).

Results from further analyses of NHL subtype stratified by sex (data not shown) were consistent with subtype analyses of men and women combined, although small sample sizes constrained analyses by sex. No linear trends in risk were observed and ORs were not different from unity for FL, CLL/SLL, MZL and T-cell lymphoma subtypes or for vitamin A and for calcium intake (data not shown) whereas there was some suggestion of an association between DLBCL risk and vitamin D intake. Consistent with the effects for all NHL, an increased risk of DLBCL with increasing intake of vitamin D from food and supplements was observed among men (additionally adjusted for vitamin A intake; 5^{th} quintile: OR=1.6, 95% CI:1.0-2.4; P_{trend} =0.06; data not shown in tables) but not among women (P_{trend} =0.33).

DISCUSSION

In this large population-based case-control study, our results did not provide evidence that risk of NHL or of common NHL subtypes was associated with increased intake of vitamin A or calcium from food and supplements, or with intake of vitamins A and of calcium from food alone. Our results also do not provide strong support for a role of vitamin D from food and supplements in NHL development although, among men, there was some suggestion of an increased risk of NHL and of DLBCL with increasing intake of vitamin D from food and supplements. Approximately one-half of our study participants had average daily intake levels for vitamin D and calcium that were below the new IOM recommended intake levels (600 or 800 IU for vitamin D and 1000 or 1200 mg for calcium[46]). Our results should be interpreted conservatively until validated in further studies.

The active form of vitamin D, 1,25-dihydroxyvitamin D_3, has immunomodulatory, antiproliferative, apoptotic and B-cell regulatory effects that are important in lymphomagenesis.[53,54] The effect of vitamin D on risk of NHL and NHL subtypes has been assessed in earlier published studies through dietary intake in food and supplements,[19,23,35,38,40,55] by the proxy exposure of sunlight[40-42,45,55] (UV exposure is the primary source of vitamin D) and through direct measure of circulating 25-hydroxyvitamin

D (25(OH)D) in serum/plasma.[56-59] Each measure has known strengths and weaknesses that are likely to account for the inconsistencies in the results across studies but integration of these findings provides insights that have increased our understanding of the role of vitamin D in NHL risk.

Several studies have investigated NHL risk associated with dietary vitamin D intake from food and supplements.[19,23,35,38,40,55] To our knowledge, the increasing trend in risk of all NHL and DLBCL associated with increased vitamin D from food and supplements in men is unique to our study. Other studies have reported statistically non-significant increased risk of NHL with increased vitamin D intake that was similar by sex.[19,40] No associations between NHL risk and dietary vitamin D intake were reported in the other population-based studies.[19,40,42,55] Among the few studies that assessed risk by NHL subtypes, increased risk of T-cell lymphoma has been reported in two studies[19,42] although the association could have been due to chance in one study.[42] In comparison, a 70% reduced risk has been reported for FL[38] and no studies reported an association with DLBCL. Consistent with our results several studies also showed that calcium did not confound the association between NHL risk and vitamin D intake[19] or 25(OH)D levels.[58,59] Some of the inconsistency in results across studies may be related to a low overall estimated vitamin D intake from food in many study populations. In our analyses that used quintiles of vitamin D intake based on the frequency distribution in controls, the moderately increased risk among men reflects a comparison of “adequate” relative to “inadequate” levels of vitamin D intake (based on IOM report recommendations[46]). Further, the ORs in the top quintile groups were similar, making it difficult to infer a relationship between “high” vitamin D intake (*i.e.* greater than the new recommended intake) and NHL risk.

Few studies that assessed vitamin D also provided data specific to the effect of related nutrients, calcium and vitamin A. Our results showing no association between calcium intake and risk of NHL and common NHL subtypes were consistent with those from a previous study, although that study did not adjust for vitamin D intake.[38] In contrast, authors of a study that showed an increased risk of NHL, DLBCL and CLL with increased calcium intake (from vitamin D adjusted models) but no association with vitamin D intake, suggested that the ability of high levels of calcium to inhibit bioavailability of vitamin D may have explained their findings.[19]

A greater number of studies have assessed the effect of vitamin A[19,34,35,39] or retinol[19,35,38] on NHL risk. Similar to our results most reports show no association between NHL risk and intake of vitamin A from food and supplements or from food alone.[34,35,38,39] However, increased risk of NHL has been reported among women in the Nurses’ Health Study who used vitamin A supplements[39] and among women with higher retinol intake from food.[35] Vitamins A and D may be mutual confounders due to retinol and some vitamin D metabolites binding to the same receptors.[60] Results from the one study that mutually adjusted for vitamin D and vitamin A/retinol showed an increased risk of NHL, DLBCL and T-cell lymphoma with increased vitamin A and retinol intake from food but no association between NHL risk and vitamin D intake.[19] However, as retinol and vitamin A were combined, it was not possible to elucidate a potential effect of competitive binding by retinol.

Studies of sunlight exposure were among the first to implicate a possible vitamin D association and in general have suggested a slight decreased risk of NHL with increased sunlight exposures.(as reviewed in[61]) Results from a recent pooled analysis of 10 case-control studies within the InterLymph Consortium showed decreased risk of all NHL with increasing recreational sunlight exposure that was similar in women and men, and largely due to associations in B-cell lymphomas, specifically, FL, DLBCL and Mantle cell

lymphomas.[45] Our mostly null results for vitamin D from diet and NHL risk differ from results reported for sun exposure. The generally low levels of vitamin D intake from foods and supplements in our study population may partly explain this inconsistency or it also may be that vitamin D does not completely explain the sun-NHL associations.

Measure of circulating 25(OH)D in epidemiological studies is considered to be a better measure of vitamin D status as it reflects vitamin D level due to sun exposure and to dietary sources. The results from prospective cohort studies that investigated this association have been mixed with a suggestive somewhat increased risk with increased 25(OH)D level reported in women,[59] a statistically non-significant inverse association in men[57] and among men in the ATBC study, a reduced risk of NHL diagnosed within 7 years of baseline in men with the highest 25(OH)D levels.[58] From these same studies, overall results by common NHL subtypes were null[58,59] although reduced risk estimates for FL, DLBCL and CLL/SLL were reported among women and men with high 25(OH)D levels.[59] A recent study further assessed vitamin D insufficiency based on 25(OH)D levels and outcomes among NHL patients.[56] In analyses that included clinical prognostic factors, insufficient vitamin D was associated with poorer outcomes (event free survival, overall survival, and lymphoma-specific survival) for DLBCL and T-cell lymphomas.[56]

Investigation of possible biologic pathways for vitamin D and NHL risk have focused on stimulatory and suppressive effects of vitamin D on the immune response.[16,53,62] The ability of vitamin D to shift T-helper cell activity from a Th1-mediated response to a Th2-mediated anti-inflammatory cytokine profile[63,64] has been suggested as a possible mechanism. Furthermore, vitamin D and conversion of vitamin D to its active metabolites are integrally related to calcium levels and absorption.[64,65] Low dietary calcium levels have been associated with diminished vitamin D effects *in vivo*.[64,65] High calcium intake has been associated with suppressed production of active vitamin D metabolites, 1,25-dihydroxyvitamin D_3.[66] These data may partly explain our results for vitamin D and calcium and NHL risk. However this mechanism has been investigated more extensively in studies of prostate cancer[67,68] with data showing a complex relationship among vitamin D receptors, calcium and vitamin D metabolite levels that is tissue specific. Interestingly, one NHL study to investigate vitamin D receptor (VDR) polymorphisms showed some evidence that sun exposure and vitamin D intake may increase risk of FL among carriers of a variant allele in VDR.[69]

The difference in results between our study and others could be due to several factors: multiple testing may have resulted in chance associations, differences in adjustment for potential confounders, variation in levels of vitamin D intake including the intake level of the referent group, and the geographic location of the study populations. Vitamin D is one of the most challenging nutrients to investigate in diet studies because it is largely produced through cutaneous exposure to UVB radiation. We did not have information on UV exposure to present a more comprehensive assessment of vitamin D and NHL development. However, our study was completed prior to the recent publicity about vitamin D and cancer. Therefore, it is less likely that participants with low UV exposure were more likely to compensate by taking vitamin D supplements or increasing consumption of foods rich in vitamin D, or that this would be differential between cases and controls. Also, there are few dietary sources rich in vitamin D, vitamin D levels in food can be seasonally dependent, variable and unstable, and data in food-composition databases that are critical for FFQ nutrient assessment, are limited.[70] Thus, dietary vitamin D intake assessed from FFQs may be inaccurate although unlikely to be directly biased by disease status. These inherent limitations in assessing vitamin D from cutaneous and dietary intake factors has prompted studies that evaluate serum 25-hydroxyvitamin D concentration as a surrogate marker for *in vivo* levels of vitamin D .[71] However, the active form of vitamin D, 1,25-dihydroxyvitamin

D_3, has a very short half-life and levels can provide misleading information about vitamin D status because compensatory biologic activity maintains levels of 1,25-dihydroxyvitamin D within the normal range even when vitamin D levels are low.[54] Also, as these measures are seasonally dependent for most geographic regions, a single measure may not provide an accurate evaluation of individual usual vitamin D status.

The large sample size and the extent of data collected in our population-based study (2052 cases, 2081 controls) allowed us to examine potential confounding factors and to evaluate main effects by major NHL subtypes. RCA was used to identify patients shortly after diagnosis to help diminish survival bias in our study population. However, as not all hospitals participate in RCA (accounting for most of the 12% who died before contact due to delayed case-reporting), the effect of survival bias cannot be eliminated completely. To diminish possible reporting biases related to disease status, many exposures, including dietary history, pertained to a time one year before diagnosis (cases) or interview (controls). A general assessment of specific dietary changes relative to an individual's diet 10 years ago and found that disease status was independent of an overall change in diet or in most foods high in nutrients investigated in these analyses including consumption of fish, milk and vegetables. Further, given the large number of dietary items assessed in the FFQ that are included in the assessment of individual nutrient levels, it is unlikely that recall of a specific food(s) would influence our results unless the food was a high source of the nutrient of interest. It is unlikely that dietary history was differentially assessed within the population or that nutrient intake would be affected by participation bias as the FFQ was developed in a multiethnic population that reflects that of the San Francisco Bay Area, cases and controls had a similar race/ethnicity distribution, and race/ethnicity was not a confounder in our analyses. Finally, although our analyses were based on *a priori* hypotheses, nutrient intake from diet and supplements is complex and further study including controlled trials are needed to elucidate the role of vitamin D and related nutrients in lymphomagenesis.

In conclusion, our study does not support a strong role for vitamin D intake or an overall role for intake of vitamin A and calcium from food and supplements or from food alone in risk of all NHL and common NHL subtypes. The increased risk of NHL, particularly among men, and DLBCL with increased intake of vitamin D could have been due to chance and should be interpreted conservatively. Further study is warranted in large pooled analyses, such as those facilitated in the InterLymph Consortium[72] (an international collaborative consortium of investigators conducting epidemiological case-control studies of NHL), to increase statistical power needed to investigate the complex association between genetic susceptibility, diet and circulating nutrient levels that will help to clarify the role of nutrients in the vitamin D pathway on risk of NHL and NHL subtypes.

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REFERENCES

1. Altekruse, SF.; Kosary, CL.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975-2007 SEER Cancer Statistics Review. Vol. 2010. National Cancer Institute, based on November 2009 SEER data submission, posted to the SEER web site; Bethesda, MD: 2010.
2. Baris D, Zahm SH. Epidemiology of lymphomas. Curr Opin Oncol. 2000; 12(5):383–394. [PubMed: 10975544]

3. Hartge, P.; Wang, SS.; Bracci, PM.; Devesa, SS.; Holly, EA. Non-Hodgkin Lymphoma. In: Schottenfeld, D.; Fraumeni, JF., Jr., editors. Cancer Epidemiology and Prevention. Oxford University Press; New York, NY: 2006. p. 898-918.
4. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55(2):74–108. [PubMed: 15761078]
5. Howlader, N.; Noone, A.; Krapcho, M., et al. SEER Cancer Statistics Review. Vol. National Cancer Institute, based on November 2010 SEER data submission, posted to the SEER web site; Bethesda, MD: 2011. SEER Cancer Statistics Review, 1975-2008.
6. Melbye M, Adami HO, Hjalgrim H, Glimelius B. Ultraviolet light and non-Hodgkin's lymphoma. Acta Oncol. 1996; 35(6):655–657. [PubMed: 8938209]
7. Streilein JW, Taylor JR, Vincek V, et al. Relationship between ultraviolet radiation-induced immunosuppression and carcinogenesis. J Invest Dermatol. 1994; 103(5 Suppl):107S–111S. [PubMed: 7963670]
8. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011; 103(9):753–762. Prepublished on 2011/04/13 as DOI 10.1093/jnci/djr076. [PubMed: 21483021]
9. Evans LS, Hancock BW. Non-Hodgkin lymphoma. Lancet. 2003; 362(9378):139–146. [PubMed: 12867117]
10. Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. Oncogene. 2004; 23(38): 6524–6534. [PubMed: 15322522]
11. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000; 403(6769):503–511. [PubMed: 10676951]
12. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol. 2003; 158(4):316–327. [PubMed: 12915497]
13. Macintyre E, Willerford D, Morris SW. Non-Hodgkin's Lymphoma: Molecular Features of B Cell Lymphoma. Hematology Am Soc Hematol Educ Program. 2000:180–204. [PubMed: 11701542]
14. Calder PC, Kew S. The immune system: a target for functional foods? Br J Nutr. 2002; 88(Suppl 2):S165–177. [PubMed: 12495459]
15. Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. Am J Clin Nutr. 1997; 66(2):464S–477S. [PubMed: 9250134]
16. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab. 2007; 51(4):301–323. [PubMed: 17726308]
17. Philpott M, Ferguson LR. Immunonutrition and cancer. Mutat Res. 2004; 551(1-2):29–42. [PubMed: 15225579]
18. Valdes-Ramos R, Benitez-Arciniega AD. Nutrition and immunity in cancer. Br J Nutr. 2007; 98(Suppl 1):S127–132. [PubMed: 17922950]
19. Chang ET, Balter KM, Torrang A, et al. Nutrient intake and risk of non-Hodgkin's lymphoma. Am J Epidemiol. 2006; 164(12):1222–1232. [PubMed: 17005624]
20. Chang ET, Smedby KE, Zhang SM, et al. Dietary factors and risk of non-hodgkin lymphoma in men and women. Cancer Epidemiol Biomarkers Prev. 2005; 14(2):512–520. [PubMed: 15734980]
21. Chiu BC, Cerhan JR, Folsom AR, et al. Diet and risk of non-Hodgkin lymphoma in older women. Jama. 1996; 275(17):1315–1321. [PubMed: 8614116]
22. De Stefani E, Fierro L, Barrios E, Ronco A. Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. Leuk Res. 1998; 22(5):445–452. [PubMed: 9652731]
23. Erber E, Maskarinec G, Lim U, Kolonel LN. Dietary vitamin D and risk of non-Hodgkin lymphoma: the multiethnic cohort. Br J Nutr. 2010; 103(4):581–584. [PubMed: 19781122]
24. Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. Am J Clin Nutr. 1999; 70(1):85–90. [PubMed: 10393143]
25. Fritschi L, Ambrosini GL, Kliewer EV, Johnson KC. Dietary fish intake and risk of leukaemia, multiple myeloma, and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2004; 13(4): 532–537. [PubMed: 15066916]

26. Kelemen LE, Cerhan JR, Lim U, et al. Vegetables, fruit, and antioxidant-related nutrients and risk of non-Hodgkin lymphoma: a National Cancer Institute-Surveillance, Epidemiology, and End Results population-based case-control study. Am J Clin Nutr. 2006; 83(6):1401–1410. [PubMed: 16762953]
27. Matsuo K, Hamajima N, Hirose K, et al. Alcohol, smoking, and dietary status and susceptibility to malignant lymphoma in Japan: results of a hospital-based case-control study at Aichi Cancer Center. Jpn J Cancer Res. 2001; 92(10):1011–1017. [PubMed: 11676850]
28. Pan SY, Mao Y, Ugnat AM. Physical activity, obesity, energy intake, and the risk of non-Hodgkin's lymphoma: a population-based case-control study. Am J Epidemiol. 2005; 162(12): 1162–1173. [PubMed: 16269580]
29. Purdue MP, Bassani DG, Klar NS, Sloan M, Kreiger N. Dietary factors and risk of non-Hodgkin lymphoma by histologic subtype: a case-control analysis. Cancer Epidemiol Biomarkers Prev. 2004; 13(10):1665–1676. [PubMed: 15466985]
30. Talamini R, Polesel J, Montella M, et al. Food groups and risk of non-Hodgkin lymphoma: a multicenter, case-control study in Italy. Int J Cancer. 2006; 118(11):2871–2876. [PubMed: 16385566]
31. Tavani A, Pregnolato A, Negri E, et al. Diet and risk of lymphoid neoplasms and soft tissue sarcomas. Nutr Cancer. 1997; 27(3):256–260. [PubMed: 9101555]
32. Ward MH, Zahm SH, Weisenburger DD, et al. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). Cancer Causes Control. 1994; 5(5):422–432. [PubMed: 7999964]
33. Zhang S, Hunter DJ, Rosner BA, et al. Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. J Natl Cancer Inst. 1999; 91(20):1751–1758. [PubMed: 10528026]
34. Zhang SM, Hunter DJ, Rosner BA, et al. Intakes of fruits, vegetables, and related nutrients and the risk of non-Hodgkin's lymphoma among women. Cancer Epidemiol Biomarkers Prev. 2000; 9(5): 477–485. [PubMed: 10815692]
35. Zheng T, Holford TR, Leaderer B, et al. Diet and nutrient intakes and risk of non-Hodgkin's lymphoma in Connecticut women. Am J Epidemiol. 2004; 159(5):454–466. [PubMed: 14977641]
36. Rohrmann S, Linseisen J, Jakobsen MU, et al. Consumption of meat and dairy and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2011; 128(3): 623–634. Prepublished on 2010/05/18 as DOI 10.1002/ijc.25387. [PubMed: 20473877]
37. Rohrmann S, Becker N, Linseisen J, et al. Fruit and vegetable consumption and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control. 2007; 18(5):537–549. Prepublished on 2007/04/20 as DOI 10.1007/s10552-007-0125-z. [PubMed: 17443415]
38. Polesel J, Talamini R, Montella M, et al. Linoleic acid, vitamin D and other nutrient intakes in the risk of non-Hodgkin lymphoma: an Italian case-control study. Ann Oncol. 2006; 17(4):713–718. [PubMed: 16556850]
39. Zhang SM, Giovannucci EL, Hunter DJ, et al. Vitamin supplement use and the risk of non-Hodgkin's lymphoma among women and men. Am J Epidemiol. 2001; 153(11):1056–1063. [PubMed: 11390323]
40. Hartge P, Lim U, Freedman DM, et al. Ultraviolet radiation, dietary vitamin D, and risk of non-Hodgkin lymphoma (United States). Cancer Causes Control. 2006; 17(8):1045–1052. [PubMed: 16933055]
41. Purdue MP, Hartge P, Davis S, et al. Sun exposure, vitamin D receptor gene polymorphisms and risk of non-Hodgkin lymphoma. Cancer Causes Control. 2007; 18(9):989–999. [PubMed: 17653830]
42. Soni LK, Hou L, Gapstur SM, Evens AM, Weisenburger DD, Chiu BC. Sun exposure and non-Hodgkin lymphoma: a population-based, case-control study. Eur J Cancer. 2007; 43(16):2388–2395. [PubMed: 17686627]
43. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007; 85(6): 1586–1591. [PubMed: 17556697]

44. Armstrong BK, Kricker A. Sun exposure and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2007; 16(3):396–400. Prepublished on 2007/03/06 as DOI 10.1158/1055-9965.epi-06-1068. [PubMed: 17337644]
45. Kricker A, Armstrong BK, Hughes AM, et al. Personal sun exposure and risk of non Hodgkin lymphoma: a pooled analysis from the Interlymph Consortium. Int J Cancer. 2008; 122(1):144–154. [PubMed: 17708556]
46. Ross, AC.; Taylor, CL.; Yaktine, AL.; Del Valle, HB., editors. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Dietary reference intakes for calcium and vitamin D. Institute of Medicine; Washington, DC: 2011.
47. Petrie JT, Silverman HA. Medicare enrollment. Health Care Financ Rev Annu Suppl. 1992:13–22. [PubMed: 10171785]
48. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999; 17(12):3835–3849. [PubMed: 10577857]
49. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol. 2000; 151(4):346–357. [PubMed: 10695593]
50. Stram DO, Hankin JH, Wilkens LR, et al. Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. Am J Epidemiol. 2000; 151(4):358–370. [PubMed: 10695594]
51. Sharma S, Murphy SP, Wilkens LR, Au D, Shen L, Kolonel LN. Extending a multiethnic food composition table to include standardized food group servings. Journal of Food Composition and Analysis. 2003; 16(4):485–495. 10.1016/s0889-1575(03)00015-2.
52. Willett, W.; Stampfer, M. Implications of Total Energy Intake for Epidemiologic Analysis. In: WW, editor. Nutritional Epidemiology. Vol. 30. Oxford University Press; New York (NY): 1998. p. 273
53. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol. 2007; 179(3):1634–1647. [PubMed: 17641030]
54. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004; 80(6 Suppl):1678S–1688S. [PubMed: 15585788]
55. Chang ET, Canchola AJ, Cockburn M, et al. Adulthood residential ultraviolet radiation, sun sensitivity, dietary vitamin D, and risk of lymphoid malignancies in the California Teachers Study. Blood. 2011 Prepublished on 2011/05/31 as DOI 10.1182/blood-2011-02-336065.
56. Drake MT, Maurer MJ, Link BK, et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. J Clin Oncol. 2010; 28(27):4191–4198. [PubMed: 20713849]
57. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst. 2006; 98(7):451–459. [PubMed: 16595781]
58. Lim U, Freedman DM, Hollis BW, et al. A prospective investigation of serum 25-hydroxyvitamin D and risk of lymphoid cancers. Int J Cancer. 2009; 124(4):979–986. [PubMed: 19035445]
59. Purdue MP, Freedman DM, Gapstur SM, et al. Circulating 25-hydroxyvitamin D and risk of non-hodgkin lymphoma: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Am J Epidemiol. 2010; 172(1):58–69. [PubMed: 20562184]
60. Rowe A. Retinoid X receptors. Int J Biochem Cell Biol. 1997; 29(2):275–278. [PubMed: 9147128]
61. Negri E. Sun exposure, vitamin D, and risk of Hodgkin and non-Hodgkin lymphoma. Nutr Cancer. 2010; 62(7):878–882. Prepublished on 2010/10/07 as DOI 10.1080/01635581.2010.509535. [PubMed: 20924963]
62. Yang S, Smith C, Prahl JM, Luo X, DeLuca HF. Vitamin D deficiency suppresses cell-mediated immunity in vivo. Arch Biochem Biophys. 1993; 303(1):98–106. [PubMed: 8489269]
63. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. Am J Clin Nutr. 2004; 80(6 Suppl):1717S–1720S. [PubMed: 15585793]

64. Griffin MD, Xing N, Kumar R. Vitamin D and its analogs as regulators of immune activation and antigen presentation. Annu Rev Nutr. 2003; 23:117–145. Epub 2003 Mar 2019. [PubMed: 12651965]

65. Gorman S, Kuritzky LA, Judge MA, et al. Topically applied 1,25-dihydroxyvitamin D3 enhances the suppressive activity of CD4+CD25+ cells in the draining lymph nodes. J Immunol. 2007; 179(9):6273–6283. [PubMed: 17947703]

66. Dusso AS, Brown AJ, Slatopolsky E, Vitamin D. Am J Physiol Renal Physiol. 2005; 289(1):F8–28. [PubMed: 15951480]

67. Chan JM, Pietinen P, Virtanen M, et al. Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus (Finland). Cancer Causes Control. 2000; 11(9):859–867. [PubMed: 11075876]

68. Giovannucci E. Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. Cancer Causes Control. 1998; 9(6):567–582. [PubMed: 10189042]

69. Purdue MP, Lan Q, Kricker A, Vajdic CM, Rothman N, Armstrong BK. Vitamin D receptor gene polymorphisms and risk of non-Hodgkin's lymphoma. Haematologica. 2007; 92(8):1145–1146. [PubMed: 17650449]

70. Brannon PM, Yetley EA, Bailey RL, Picciano MF. Overview of the conference "Vitamin D and Health in the 21st Century: an Update". Am J Clin Nutr. 2008; 88(2):483S–490S. [PubMed: 18689388]

71. Haddad JG Jr. Hahn TJ. Natural and synthetic sources of circulating 25-hydroxyvitamin D in man. Nature. 1973; 244(5417):515–517. [PubMed: 4621128]

72. Boffetta P, Armstrong B, Linet M, Kasten C, Cozen W, Hartge P. Consortia in cancer epidemiology: lessons from InterLymph. Cancer Epidemiol Biomarkers Prev. 2007; 16(2):197–199. Prepublished on 2007/02/16 as DOI 10.1158/1055-9965.epi-06-0786. [PubMed: 17301250]

Table 1

Characteristics of study participants[a] in a population-based case-control study of non-Hodgkin lymphoma (NHL), San Francisco Bay Area, California, 2001-2006

Characteristics	Cases N=2052		Controls N=2081	
	n	%	n	%
Age				
< 40	187	9	211	10
40-49	303	15	313	15
50-59	478	23	433	21
60-69	491	24	493	23
70-79	434	21	474	23
80-85	159	8	157	8
Age, mean years (SD)	60 (14.1)		60 (14.5)	
Sex				
Men	1201	58	1164	56
Women	851	42	917	44
Race				
White	1709	83	1757	84
Black or African American	79	4	83	4
Asian	199	10	164	8
Other/Mixed	65	3	77	4
Hispanic/Latino				
No	1874	91	1900	91
Yes	177	9	181	9
Education				
High School Degree or less	454	22	380	18
Technical school/some college	563	27	588	28
College graduate	566	28	598	29
Graduate Degree	469	23	515	25
Previous primary invasive cancer other than lymphoma				
No	1691	82	1781	86
Yes	360	18	300	14
Total caloric intake (median values for quintiles (kcal))				
Q1 (1044)	369	19	409	20
Q2 (1499)	334	17	409	20
Q3 (1851)	411	21	409	20
Q4 (2299)	419	21	409	20
Q5 (3256)	435	22	410	20
NHL subtypes [b]				
DLBCL	732	36		
FL	397	19		

Characteristics	Cases N=2052		Controls N=2081	
	n	%	n	%
CLL/SLL	404	20		
MZL	192	9		
T-cell	144	6		

[a]Total number of study participants may vary because of missing values, 12 individuals did not complete a diet questionnaire, and 73 cases and 34 controls with extreme total caloric intake (<500 or >5000 kcal) were excluded. .

[b]Diffuse large B-cell lymphoma (DLBCL); Follicular lymphomas (FL); Chronic lymphocytic leukemia / Small lymphocytic lymphoma (CLL/SLL); Marginal zone lymphoma (MZL); T-cell lymphomas include ICDO 9700-9702, 9705, 9708, 9709, 9714, 9716-9719, 9727-9729, 9760, 9761, 9764, 9766-9768, and T-cell NHL not otherwise specified

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for risk of non-Hodgkin lymphoma (NHL) associated with intake of vitamins A, D and calcium from food and supplements, and from food alone; San Francisco Bay Area population-based case-control study, California, 2001-2006

Quintiles (Q) of Nutrient Intake (Median)[a]	Men and Women						Men		Women	
	Cases	%	Controls	%	OR[b]	95% CI[b]	OR[b]	95% CI[b]	OR[b]	95% CI[b]
Vitamin A from food and supplements (mcg)										
Q1 (485)	346	18	409	20	1.0		1.0		1.0	
Q2 (886)	395	20	409	20	1.0	0.82,1.3	1.1	0.83,1.4	0.90	0.64,1.2
Q3 (1690)	400	20	409	20	1.0	0.82,1.2	1.1	0.84,1.5	0.86	0.62,1.2
Q4 (2285)	394	20	409	20	1.1	0.87,1.3	1.2	0.89,1.5	0.91	0.67,1.2
Q5 (3004)	433	22	410	20	1.0	0.84,1.3	1.1	0.82,1.5	0.94	0.67,1.3
P trend						0.57		0.44		0.86
Vitamin D from food and supplements (IU) [c]										
Q1 (65)	320	16	409	20	1.0		1.0		1.0	
Q2 (155)	438	22	409	20	1.4	1.1,1.7	1.3	0.99,1.7	1.5	1.1,2.1
Q3 (318)	372	19	409	20	1.2	0.94,1.6	1.1	0.82,1.6	1.3	0.89,2.0
Q4 (495)	401	20	409	20	1.4	1.0,1.9	1.5	1.0,2.2	1.3	0.84,2.1
Q5 (626)	437	22	410	20	1.5	1.1,2.1	1.6	1.0,2.4	1.5	0.91,2.4
P trend						0.05		0.07		0.33
Calcium from food and supplements (mg) [d]										
Q1 (501)	346	18	409	20	1.0		1.0		1.0	
Q2 (780)	395	20	409	20	1.1	0.89,1.4	1.2	0.88,1.6	0.84	0.59,1.2
Q3 (1036)	400	20	409	20	1.1	0.88,1.4	0.97	0.71,1.3	1.2	0.82,1.6
Q4 (1367)	394	20	409	20	1.1	0.87,1.4	1.2	0.81,1.6	0.89	0.63,1.2
Q5 (2017)	433	22	410	20	1.2	0.95,1.5	1.2	0.79,1.7	1.1	0.77,1.5
P trend						0.17		0.53		0.49
Vitamin A from food (mcg)										
Q1 (352)	160	18	193	20	1.0		1.0		1.0	
Q2 (560)	190	21	193	20	1.1	0.80,1.5	1.0	0.70,1.6	1.2	0.72,1.9
Q3 (759)	191	21	193	20	1.0	0.74,1.4	1.2	0.76,1.8	0.80	0.46,1.4
Q4 (1005)	176	19	193	20	0.93	0.65,1.3	0.98	0.62,1.6	0.80	0.46,1.3

Quintiles (Q) of Nutrient Intake (Median)[a]	Men and Women						Men		Women	
	Cases	%	Controls	%	OR[b]	95% CI[b]	OR[b]	95% CI[b]	OR[b]	95% CI[b]
Q5 (1417)	194	21	194	20	0.99	0.68,1.4	1.1	0.65,1.8	0.81	0.45,1.4
P trend						0.72		0.97		0.31
Vitamin D from food (IU)										
Q1 (43)	157	17	199	20	1.0		1.0		1.0	
Q2 (83)	153	16	199	20	0.97	0.71,1.3	0.99	0.66,1.5	0.91	0.57,1.5
Q3 (124)	202	21	200	20	1.3	0.93,1.7	1.2	0.78,1.8	1.4	0.88,2.2
Q4 (179)	221	24	199	20	1.3	0.98,1.3	1.4	0.95,2.1	1.3	0.76,2.1
Q5 (280)	211	22	200	20	1.3	0.92,1.8	1.3	0.87,2.0	1.2	0.70,2.1
P trend						0.06		0.09		0.35
Calcium from food (mg) [e]										
Q1 (390)	142	18	166	20	1.0		1.0		1.0	
Q2 (597)	116	15	167	20	0.68	0.45,1.0	0.70	0.42,1.2	0.62	0.30,1.3
Q3 (783)	185	23	166	20	0.99	0.64,1.5	1.2	0.67,2.0	0.74	0.35,1.6
Q4 (1025)	165	21	167	20	0.78	0.47,1.3	0.89	0.48,1.6	0.67	0.27,1.6
Q5 (1435)	184	23	167	20	0.88	0.50,1.5	1.0	0.52,2.1	0.68	0.25,1.8
P trend						0.94		0.66		0.73

[a] Analyses of nutrients from food and supplements included: Men (1147 cases, 1144 controls), Women (821 cases, 902 controls). Analyses of nutrients from food sources excluded participants who reported the use of specific vitamin; Vitamin A: Men (558 cases, 591 controls), Women (353 cases, 375 controls); Vitamin D: Men (578 cases, 604 controls), Women (366 cases, 393 controls); Calcium: Men (540 cases, 560 controls), Women (252 cases, 273 controls)

[b] Adjusted for age, sex, county and total caloric intake in quintiles.

[c] Vitamin D from food and supplements also adjusted for vitamin A from food and supplements in quintiles

[d] Among men, calcium from food and supplements also adjusted for vitamin D from food and supplements in quintiles.

[e] Calcium from food also adjusted for vitamin D from food in quintiles

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for risk of non-Hodgkin lymphoma (NHL) histologic subtypes[a] associated with intake of vitamins A, D and calcium from food and supplements, and from food alone among women and men combined, San Francisco Bay Area, California, 2001-2006

Quintiles (Q) of Nutrient Intake (Median)[b]	DLBCL			FL			CLL/SLL			MZL			T-cell			Controls
	n	OR[c]	95%CI[c]	n	OR[c]	95%CI[c]	n	OR[c]	95%CI[c]	n	OR[c]	95%CI[c]	n	OR[c]	95%CI[c]	n
Vitamin A from food and supplements (mcg)																
Q1 (485)	132	1.0		63	1.0		76	1.0		29	1.0		31	1.0		409
Q2 (886)	122	0.84	0.62,1.1	91	1.5	1.0,2.2	87	1.0	0.72,1.5	39	1.3	0.77,2.2	29	0.88	0.50,1.5	409
Q3 (1690)	130	0.88	0.66,1.2	77	1.2	0.85,1.8	67	0.84	0.58,1.2	36	1.3	0.75,2.1	35	1.1	0.63,1.8	409
Q4 (2285)	164	1.2	0.93,1.6	70	1.1	0.77,1.6	77	0.92	0.64,1.3	45	1.4	0.85,2.3	18	0.60	0.32,1.1	409
Q5 (3004)	149	1.0	0.74,1.4	85	1.4	0.93,2.0	84	0.90	0.62,1.3	35	1.2	0.66,2.0	26	0.91	0.50,1.6	410
P trend			0.15			0.70			0.38			0.64			0.46	
Vitamin D from food and supplements (IU) [d]																
Q1 (65)	117	1.0		60	1.0		57	1.0		29	1.0		28	1.0		409
Q2 (155)	142	1.3	0.92,1.7	88	1.4	0.92,2.2	96	1.7	1.2,2.6	37	1.2	0.71,2.1	35	1.2	0.72,2.2	409
Q3 (318)	116	1.0	0.69,1.4	82	1.3	0.86,2.0	74	1.6	0.99,2.5	37	1.3	0.70,2.4	27	0.92	0.47,1.8	409
Q4 (495)	151	1.4	0.93,2.2	68	1.2	0.69,1.7	74	1.7	0.98,3.0	46	1.5	0.71,3.1	29	1.4	0.61,3.0	409
Q5 (626)	171	1.6	1.0, 2.5	88	1.6	0.88,2.2	90	1.9	1.0,3.4	35	1.2	0.56,2.7	20	0.94	0.38,2.3	410
P trend			0.02			0.38			0.14			0.44			0.56	
Calcium from food and supplements (mg) [e]																
Q1 (501)	125	1.0		73	1.0		67	1.0		28	1.0		26	1.0		409
Q2 (780)	124	0.87	0.63,1.2	65	0.84	0.57,1.2	77	1.2	0.82,1.7	50	1.6	0.91,2.6	31	0.97	0.55,1.7	409
Q3 (1036)	149	0.97	0.70,1.3	73	0.89	0.59,1.4	82	1.2	0.82,1.8	29	0.90	0.49,1.7	36	1.1	0.63,2.0	409
Q4 (1367)	140	0.86	0.60,1.2	83	1.0	0.67,1.6	72	1.1	0.71,1.6	42	1.3	0.73,2.5	23	0.74	0.39,1.4	409
Q5 (2017)	159	0.94	0.65,1.3	92	1. 1	0.73,1.8	93	1.4	0.91,2.0	35	1.1	0.58,2.1	23	0.82	0.42,1.6	410
P trend			0.94			0.24			0.23			0.81			0.38	
Vitamin A from food (mcg)																
Q1 (352)	58	1.0		25	1.0		35	1.0		11	1.0		13	1.0		193
Q2 (560)	69	1.1	0.72,1.7	34	1.3	0.72,2.3	35	0.93	0.53,1.6	17	1.4	0.60,3.2	17	1.2	0.52,2.6	193
Q3 (759)	60	0.84	0.52,1.4	44	1.7	0.91,3.0	46	1.1	0.61,1.9	17	1.3	0.54,3.1	14	0.99	0.41,2.4	193

Quintiles (Q) of Nutrient Intake (Median)[b]	DLBCL			FL			CLL/SLL			MZL			T-cell			Controls
	n	OR[C]	95%CI[C]	n	OR[C]	95%CI[C]	n	OR[C]	95%CI[C]	n	OR[C]	95%CI[C]	n	OR[C]	95%CI[C]	n
Q4 (1005)	56	0.73	0.44,1.2	40	1.6	0.86,3.0	38	0.86	0.47,1.6	17	1.3	0.52,3.2	14	0.94	0.38,2.3	193
Q5 (1417)	73	0.86	0.51,1.4	35	1.4	0.70,2.8	27	0.60	0.30,1.2	17	1.4	0.53,3.6	18	1.2	0.46,3.0	194
P trend			0.36			0.49			0.11			0.69			0.82	
Vitamin D from food (IU)																
Q1 (43)	55	1.0		28	1.0		30	1.0		16	1.0		13	1.0		199
Q2 (83)	58	1.0	0.68,1.6	29	0.99	0.56,1.8	25	0.86	0.48,1.5	12	0.66	0.30,1.5	15	1.1	0.48,2.4	199
Q3 (124)	65	1.2	0.75,1.8	41	1.4	0.81,2.4	45	1.5	0.87,2.6	16	0.83	0.39,1.8	17	1.2	0.55,2.7	200
Q4 (179)	73	1.2	0.78,1.9	43	1.5	0.86,2.6	50	1.6	0.94,2.8	20	1.1	0.53,2.4	17	1.2	0.54,2.7	199
Q5 (280)	73	1.1	0.71,1.8	46	1.6	0.91,2.9	39	1.3	0.69,2.3	17	1.0	0.45,2.3	15	1.0	0.42,2.4	200
P trend			0.59			0.05			0.26			0.51			0.99	
Calcium from food (mg) [f]																
Q1 (390)	53	1.0		23	1.0		29	1.0		9	1.0		12	1.0		166
Q2 (597)	39	0.55	0.31,1.0	24	0.96	0.46,2.0	23	0.65	0.31,1.4	10	1.5	0.51,4.7	13	0.79	0.30,2.1	167
Q3 (783)	62	0.71	0.38,1.3	36	1.5	0.67,3.2	34	0.89	0.40,2.0	24	4.1	1.3,13.0	9	0.48	0.15,1.6	166
Q4 (1025)	53	0.50	0.24,1.0	37	1.6	0.67,3.8	34	0.80	0.33,1.9	9	1.6	0.40,6.4	18	0.96	0.28,3.2	167
Q5 (1435)	69	0.56	0.25,1.3	33	1.7	0.63,4.7	35	0.84	0.31,2.3	13	2.6	0.56,11.6	15	0.76	0.18,3.2	167
P trend			0.43			0.22			0.97			0.60			0.99	

[a] Diffuse large B-cell lymphoma (DLBCL); Follicular lymphomas (FL); Chronic lymphocytic leukemia /Small lymphocytic lymphoma (CLL/SLL); Marginal zone lymphoma (MZL); T-cell lymphomas include ICDO 9700-9702, 9705, 9708, 9709, 9714, 9716-9719, 9727-9729, 9760, 9761, 9764, 9766-9768, and T-cell NHL not otherwise specified

[b] Analyses of nutrients from food and supplements included: DLBCL n=697; FL, n=386; CLL/SLL, n=391; MZL, n=184; T-cell, n=139; Controls, n=2046;. Analyses of nutrients from food sources excluded participants who reported the use of specific vitamin; Vitamin A: DLBCL, n=316; FL, n=178; CLL/SLL, n=181; MZL, n=78; T-cell, n=76; Controls, n=966. Vitamin D: DLBCL, n=324; FL, n=187; CLL/SLL, n=189; MZL, n=81; T-cell, n=77; Controls, n=997. Calcium: DLBCL, n=276; FL, n=153; CLL/SLL, n=155; MZL, n=65; T-cell, n=67; Controls, n=833.

[c] Adjusted for age, sex, county and total caloric intake (quintiles)

[d] Vitamin D from food and supplements also adjusted for vitamin A from food and supplements (quintiles)

[e] Calcium from food and supplements also adjusted for vitamin D from food and supplements (quintiles).for DLBCL, FL, and MZL

[f] Calcium from food also adjusted for vitamin D from food (quintiles).