Published in final edited form as:

Cancer Causes Control. 2008 June ; 19(5): 491–503. doi:10.1007/s10552-008-9111-3.

Vegetables- and antioxidant-related nutrients, genetic susceptibility, and non-Hodgkin lymphoma risk

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Abstract

Genetic susceptibility to DNA oxidation, carcinogen metabolism, and altered DNA repair may increase non-Hodgkin lymphoma (NHL) risk, whereas vegetables-and antioxidant-related nutrients may decrease risk. We evaluated the interaction of a priori-defined dietary factors with 28 polymorphisms in these metabolic pathways. Incident cases ($n = 1,141$) were identified during 1998–2000 from four cancer registries and frequency-matched to population-based controls ($n = 949$). We estimated diet-gene joint effects using two-phase semi-parametric maximum-likelihood methods, which utilized genotype data from all subjects as well as 371 cases and 311 controls with available diet information. Adjusted odds ratios (95% confidence intervals) were lower among common allele carriers with higher dietary intakes. For the *GSTM3* 3-base insertion and higher total vegetable intake, the risk was 0.56 (0.35–0.92, p interaction = 0.03); for *GSTP1* A114V and higher cruciferous vegetable intake, the risk was 0.52 (0.34–0.81, p interaction = 0.02); for *OGGI* S326C and higher daily zinc intake, the risk was 0.71 (0.47–1.08, p interaction = 0.04) and for *XRCC3* T241M and higher green leafy vegetable intake, the risk was 0.63 (0.41–0.97, p interaction = 0.03). Calculation of the false positive report probability determined a high likelihood of falsely positive associations. Although most associations have not been examined previously with NHL, our results suggest the examined polymorphisms are not modifiers of the association between vegetable and zinc intakes and NHL risk.

Keywords

Brassicaceae; Zinc; *GST*; *OGGI*; *XRCC*

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Electronic supplementary material: The online version of this article (doi:10.1007/s10552-008-9111-3) contains supplementary material, which is available to authorized users.

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies characterized by proliferation of T or B cells, with the majority of these cancers originating from B cells. Age-adjusted incidence of NHL increased from 11.1 per 100,000 in 1975 to 19.3 per 100,000 in 2002 and was one of the fastest rising cancers during this time period [1]. The reason for this increase is largely unknown. Studies have consistently shown strong associations with factors related to altered immunologic responses [2]. Reactive oxygen species (ROS) production, such as superoxide radical, hydrogen peroxide, and hydroxyl radical, could alter DNA and lipid membrane structures, particularly in cells with rapid turn-over rates such as those involved in the immune system [3], suggesting a possible protective effect of NHL from nutrients involved in antioxidant activities.

Epidemiologic investigations provide evidence that intake of foods and nutrients with antioxidant properties interact with genetic susceptibility for developing some solid tumors [4–8]. We previously reported inverse associations with NHL from increased intake of all, green leafy, and cruciferous vegetables and the nutrients lutein/zeaxanthin and zinc in a multi-centered population-based case–control study of incident NHL [9]. In separate analyses, we also examined NHL risk by inherited differences in polymorphic genes in pathways of ROS neutralization and detoxification [10–12] and DNA repair [13]. In these reports [10–13], allelic variants of the genes encoding nitric oxide synthase 2A (*NOS2A*), manganese superoxide dismutase (*SOD2*), N-acetyltransferases (*NAT1*, *NAT2*), and X-Ray repair cross-complementing proteins (*XRCC1*, *XRCC3*, *XRCC4*) were associated with increased NHL risk and a variant in the gene encoding myeloperoxidase (*MPO*) was associated with decreased risk. No significant and independent associations were observed between NHL and variation in the genes glutathione-S-transferases (*GSTM3*, *GSTP1*), NAD(P)H dehydrogenase quinone 1 (*NQO1*), *CYP1A1*, *CYP1A2*, and glutathione peroxidase 1 (*GPX1*), 8-oxoguanine DNA glycosylase 1 (*OGG1*), *NOS3* and *XRCC2*. The role of the proteins encoded by these genes in ROS neutralization and detoxification and DNA repair is summarized in Table 1.

In this report, we hypothesize that our previously observed inverse associations with NHL of specific vegetables and nutrients with antioxidant-related activities may interact with host genetic variability for enzymes that rely on these vegetable components or nutrients as cofactors or substrates in antioxidant-related pathways.

Materials and methods

Study design and population

Between 1998 and 2000, 1,321 of 2,248 potentially eligible incident cases of NHL (59% response) without evidence of HIV infection and aged 20–74 years were enrolled from National Cancer Institute (NCI)-sponsored Surveillance, Epidemiology and End Results (SEER) registries in Iowa, Seattle, Los Angeles and Detroit. Population controls without history of NHL aged <65 years were identified by random-digit-dialing and those aged ≥65, from Medicare files. Controls were frequency matched to cases by age (within 5 years), center, race, and sex. Of 2,409 potentially eligible controls, 1,057 (44%) were enrolled. Response among eligible subjects was highest among women and in Iowa for both cases and controls; among controls, response ranged from 46% in Detroit to 63% in Iowa. Full details of the study are presented elsewhere [9,24]. All respondents gave their informed consent prior to interview and each center's Institutional Review Board approved the study protocol. An overview of subject participation and data collection relevant to the current report is shown in Fig. 1 and described in detail below.

Genetic analysis

Study participants provided a venous blood or mouthwash buccal cell sample. We obtained blood samples from 773 cases and 668 controls and buccal cells from 399 cases and 314 controls (1,172 cases and 982 controls, Fig. 1), representing 89% of enrolled cases and 93% of enrolled controls. Of SNPs evaluated in the present analysis, we successfully genotyped 1,141 cases and 949 controls. Genotype frequencies for individuals who provided blood compared to buccal cells were not statistically different [25]. A priori, we selected 29 single nucleotide polymorphisms (SNPs) in 17 genes involved in pathways of ROS neutralization and detoxification and DNA repair based on functional evidence of the polymorphism, supportive literature for a role in NHL or from previously published associations with other cancers. DNA was extracted from blood clots or buffy coats using a standard protocol [26]. All genotyping was conducted at the NCI Core Genotyping Facility (CGF, Advanced Technology Corporation, Gaithersburg, MD) using the Taqman platform. Sequence data and assay conditions are provided at <http://snp500cancer.nci.nih.gov> [27]. Genotyping and quality control procedures are detailed elsewhere [10]. Successful genotyping was achieved for 96–100% of DNA samples for all SNPs and agreement between replicate and duplicate samples was >99% for all assays. For each genotype, we tested Hardy–Weinberg equilibrium among African-American and non-Hispanic White controls: HWE was observed for each SNP in the control group. Two *XRCC4* SNPs (rsID 1805377 and 1056503) were found to be in linkage disequilibrium among the non-Hispanic White controls in our sample ($r^2 = 0.99$, Haploview version 3.32, <http://www.broad.mit.edu/mpg/haploview>); therefore, data are presented on *XRCC4* rsID 1805377 only, leaving 28 SNPs for analysis. Four of these 28 SNPs were used to determine the NAT1*10 genotype and another six were used to determine the NAT2 phenotype [11].

Dietary assessment

As previously described [9], participants were assigned to one of two study arms: each group received a different version of a computer-assisted personal interview with common questions on demographic characteristics, personal, medical, and environmental exposure history. One study arm consisted of all African-Americans ($n = 215$) and a random sample of 50% of non-Hispanic White Americans, while the “diet” study arm consisted of the remaining 50% of non-Hispanic White Americans (552 cases and 462 controls, Fig. 1). Among the latter group, diet was assessed using a mailed self-administered modified version of the Block 1995 Revision of the Health Habits and History Questionnaire [28,29]. In addition, the questionnaire asked about the regular use of multivitamins and eight single vitamin and mineral supplements, defined as ≥ 1 pill per week, over the past year. Estimation of micronutrients from vitamin supplements has been described [9]. Briefly, standard doses were applied to each of four broad categories of multivitamins and for some individual micronutrient supplements. For example, 50 mg was assigned to zinc supplement use, whereas information on usual dose of vitamins A and C was elicited from participants. The questionnaire was validated against multiple diet records (correlations were 0.5–0.6 for most nutrients) [28,30]. We used the updated US Department of Agriculture–National Cancer Institute Carotenoid Database (www.nal.usda.gov/fnic/foodcomp/Data/Carot) to evaluate the α - and β -carotene, lycopene, β -cryptoxanthin and lutein and zeaxanthin content of fruit, vegetables and multicomponent foods that contained fruits and vegetables [9]. Daily intakes of nutrients were calculated by summing across all food items the product of the frequency of consumption of the serving of each food by the nutrient content of that serving of food. We excluded subjects if the daily number of reported foods on the questionnaire was <4 or >30 for males and <3 or >30 for females, or if the number of food items missing or left blank exceeded 20% (18 cases and 28 controls) leaving 466 cases and 391 controls with complete dietary data.

Statistical analysis

Monthly servings of food groups and daily intake of individual nutrients were adjusted for total energy by taking the residual from a linear regression model in which total energy intake was the independent variable and the dietary variable was the dependent variable [31].

We calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression to estimate gene–environment joint effects. We estimated parameters of the logistic model using two-phase design, semi-parametric maximum-likelihood methods [32,33] that utilized genotype data from the entire sample of genotyped subjects (phase I: 1,141 cases and 949 controls), including those who were not part of the diet study arm and hence lacked data on vegetable and antioxidant intake. The phase II sample (371 cases and 311 controls) in this analysis involved subjects who were included in the diet arm and had both genotype and exposure data (Fig. 1). The method, in essence, involves estimation of the distribution of the dietary exposures given genotypes in an empirical (non-parametric) fashion from the subjects in the diet study arm and then uses the estimated distribution to “impute” the exposure data for the remaining subjects given their genotypes. By utilizing the marginal disease-gene association from the entire sample, the method can produce more efficient estimates of gene-exposure joint effects than those that would be obtained using a standard logistic regression analysis of the data from subjects in the diet arm only.

The presence or absence of effect modification was evaluated using indicator variables to represent the effect of each exposure in the absence of the other, as well as the joint effect of both exposures, using the group not exposed to either factor as the referent [34]. Exposure categories were classified as above-median intake of the dietary variable using the control group’s distribution [9] and as genotypes with ≥ 1 copies of the variant allele, depending on the genetic model from previous analyses [10–13]. Statistical significance of effect modification was evaluated with the Wald test in models that included a product term for the dietary variable and the genotype. The false positive probability report (FPRP) was assessed as recommended by Wacholder et al. [35].

All models were adjusted for the matching factors: age in years (<45 , $45-64$, ≥ 65), sex, race (White, other), and study center (Detroit, Iowa, Los Angeles, Seattle) as well as smoking in pack years (non-smoker, <17 , $17-34$, ≥ 35), body mass index (BMI) in kg/m^2 (<25 , $25-29$, ≥ 30), exercise in weekly metabolic equivalents (METs: no exercise, $30-675$, ≥ 676) and alcohol consumption in grams per day ($0, >0$). These covariates were chosen from a larger number of confounders from our dietary analysis [9] after examining their distributions in the control group across strata of genotypes for each of the 17 genes, and across strata of the five dietary exposures of interest in the present analysis. Descriptive analyses were performed using SAS (version 8, SAS Institute, Cary, NC) and the two-phase analysis was performed using Splus statistical software (Insightful Corp, Seattle, WA, Version 7.05, 2005) and “tps” package freely available from StatLib (<http://lib.stat.cmu.edu>).

Results

We hypothesized that specific dietary variables would interact with specific polymorphisms (Table 1). For those polymorphisms where the associations with NHL interacted significantly with diet, we show the distribution of covariates for the control group across strata of genotypes for each gene (Supplementary Table A) and across strata of the dietary exposures of interest (Supplementary Table B).

A priori-hypothesized associations among NHL, genetic polymorphisms involved in detoxification pathways, and the influence of dietary variables are shown in Tables 2 and 3. Three associations had significant or suggestive p values. Collectively, lower risks of 23–44%

were observed with higher total vegetable intake among individuals with the *GSTM3* 3-base insertion (AGG/AGG genotype, p interaction = 0.03) and *GSTP1* (I105V) AG or GG genotypes (p interaction = 0.07). Lower risks of 48–46% were observed with higher cruciferous vegetable intake among individuals with the *GSTP1* (A114V) CC genotype and also with lower cruciferous vegetable intake among individuals with the *GSTP1* (A114V) CT or TT genotypes (p interaction = 0.02), respectively.

A priori-hypothesized associations among NHL, genetic polymorphisms involved in DNA repair pathways, and the influence of dietary variables are shown in Table 4. Four associations had significant or suggestive p values. A 29% lower risk was observed with higher total zinc intake among individuals with the *OGG1* (S326C) CC genotype (p interaction = 0.04). Higher green leafy vegetable intake was associated with a 37% lower risk among individuals with the *XRCC3* (T241M) CC or CT genotypes (p interaction = 0.03). A 2.1-fold higher risk was seen from lower zinc intake among individuals with the *XRCC1* (R194W) CT or TT genotypes (p interaction = 0.06) and a 1.7-fold higher risk was seen from higher zinc intake among individuals with the *XRCC4* (N298S) GA or AA genotypes (p interaction = 0.08).

Supplementary Table C shows the risk estimates for the above associations performed using unconditional logistic regression among the 371 cases and 311 controls of non-Hispanic White ancestry for whom both dietary and genotype data were available. No appreciable differences in estimates with the imputation method (Tables 2–4) were observed.

In order to account for chance associations from multiple tests of individual SNPs with NHL, we calculated the false positive report probability (FPRP) [35], which depends on the prior probability that the polymorphism under investigation is associated with NHL, the power of the present study and the observed p value. In the absence of previous reports of interactions between the specific polymorphisms and dietary variables under study for risk of NHL, we used associations of the main effects of the dietary variables from a previous analysis [9] as a reasonable estimate of the expected magnitude of joint effects (Supplementary Table D). We also considered whether the function of the polymorphisms was conclusive and whether epidemiologic data from other cancer types supported our findings. Assigning a “moderate” prior probability of 0.01 and a FPRP < 0.5 (e.g., less than 50% probability that the study hypotheses were false positives), the associated FPRPs were all >0.63, indicating the likelihood that our findings were falsely positive.

Discussion

This multi-centered case–control study found associations with NHL between vegetables and nutrients with antioxidant properties and polymorphisms within *GSTM3* and *GSTP1* in detoxification pathways and within *OGG1* and *XRCC3* involved in DNA repair. However, the likelihood that these associations are falsely positive or attributable to chance is high and should be interpreted accordingly.

A priori, we hypothesized that specific dietary variables would interact with genetic polymorphisms based on the putative function of the polymorphism and the role of the gene product in biologic processes that may benefit from higher intake of antioxidants. For example, the GST enzymes are phase 2 detoxification enzymes that can deactivate carcinogens and products of oxidative stress by conjugation with glutathione [36]. Vegetables, particularly cruciferous vegetables, contain glucinolates, that are converted in vivo to isothiocyanates, compounds that are potent inducers and substrates of carcinogen-detoxifying enzymes. The 3-base deletion in *GSTM3* may decrease transcript expression [37] and reduce ability of the enzyme to neutralize ROS. An independent effect of the 3-base deletion was not associated with NHL risk in our study population [12] although higher intake of vegetables and,

specifically, cruciferous vegetables was associated with lower risk [9]. The 3-base deletion in *GSTM3* has not been well studied and appears to be in linkage disequilibrium with the *GSTM1* null allele in exon 4 [37], which we did not investigate. Inheritance of both the *GSTM3* 3-base deletion and the *GSTM1* null allele has been reported to confer increased cancer susceptibility [12]. The functional effect of the *GSTP1* (A114V) SNP is unclear [38] and also was not independently associated with NHL risk in our sample [12]. Published findings between diet and the *GSTP1* (A114V) polymorphism with cancer are few although, like us, another study found lower colorectal cancer risk among higher vegetable consumers who carried the common A114V allele [39].

The *OGG1* and *XRCC3* genes are involved in DNA repair. *OGG1* encodes an enzyme with lyase activity for chain cleavage of mutagenic base by-products in DNA that occurs as a result of exposure to reactive oxygen [40]. The S326C polymorphism in the 3' untranslated region (UTR) may decrease enzymatic activity in the DNA base excision repair pathway (reviewed in [40]). The SNP was not independently associated with NHL in our study population [13], but interacted jointly with zinc intake in the present analyses. This association is plausible: zinc can physically displace DNA-bound iron and reduce the extent of iron-catalyzed hydroxyl radical production (OH $\cdot$) and OH $\cdot$ -driven DNA damage [41]. Others have also reported dietary effects with the *OGG1* common allele: Le Marchand and colleagues [7] observed a 50% lower risk (95% CI, 0.3–0.8) of lung cancer among homozygous or heterozygous carriers of the common C allele with higher compared to lower vegetable intake. Though not significant, we also observed decreases of 21% and 29% of higher intakes of green leafy and cruciferous vegetables, respectively, with NHL risk among homozygous carriers of the common C allele in the present analyses (data not shown), supporting the direction of the findings by Le Marchand et al [7].

XRCC3 participates in DNA double-strand break/recombinational repair through homologous recombination to maintain chromosome stability. NHL risk was not significantly associated with ≥ 1 copies of the *XRCC3* (T241M) variant T allele among Whites in this population [13] nor in another study of follicular lymphoma [42]. Others found no significant association of this polymorphism by plasma folate level for breast cancer risk [23], by vegetable intake for gastric cancer [43] or by vegetable/fruit intake for colorectal cancer [44]. Furthermore, this polymorphism was recently associated non-significantly with abnormal repair of DNA strand breaks in lymphocytes following X-ray exposure in vitro [45], questioning the certainty of its functional impact.

It is unlikely that the use of the two-phase design, semi-parametric maximum-likelihood method [32,33], which utilized data from all subjects with genotypes including 215 African-Americans, to produce estimates of gene-exposure joint effects threatened the internal validity of our study. First, there were no deviations from HWE for genotypes for which we observed significant interactions with diet when examined by race. Second, the subjects in the subsample were chosen randomly from among all non-Hispanic White subjects in the study and we have no reason to believe their diet was systematically different from those who didn't receive the FFQ. Similar distributions in demographic characteristics between the cases and controls in the subsample compared with all eligible cases and controls were observed [9]. Third, although diet was not assessed among African-Americans, they comprised the same sampling frame as non-Hispanic Whites (mostly from the Detroit region) and would have received the same comprehensive Block FFQ. If food selection was different among African-Americans, our imputation estimates would be biased. However, the common dietary exposures of interest in this study (vegetables, zinc) are unlikely to be specific to one racial group, suggesting any differences between races would be due to intake frequency. Several studies support this and report that the distribution of vegetable intake between racial groups in the US does vary, but not greatly, with African-Americans consuming slightly fewer servings, on average, of

vegetables than Whites [46,47]. National surveys of individual diets also show that the differences in dietary patterns among racial and socioeconomic groups have narrowed over time, and that similar intakes of fruits and vegetables are reported by Whites and African-Americans across socioeconomic gradients [48]. Fourth, ORs and 95% CIs were inappreciably changed when estimated among the subsample of non-Hispanic Whites with both diet and gene information. For these reasons, we believe imputation of diet to African-Americans does not impart bias in the risk estimates.

The strengths of our study include ascertainment using SEER tumor registries, which ensured few cases were missed; the use of population controls, which minimized some biases associated with hospital-based case-control studies; the administration of a validated FFQ to assess diet, and adherence to standardized protocols for genotyping.

Our study also has potential limitations. Although we identified a priori associations of interest, multiple testing can produce false positive findings and application of the conservative Bonferroni correction would have clearly weakened all significant results. We also report a somewhat low response among cases and controls in this study; however, the magnitude of the responses is similar to those reported by other population-based studies, particularly those with in-home interviews [49]. The impact of low response on associations with NHL was investigated by us in a related manuscript [50] by restricting analyses to the Iowa population and to women, the two groups with the highest participation. Similar associations were observed among these high-response groups although with wider confidence intervals. This suggests that the influence of response on our associations is likely to be modest at best. We cannot exclude the possibility that other unassayed SNPs in the genes under study may be associated with NHL, given our limited knowledge of the genetics of NHL and the relevance of environmental factors and their interactions with these polymorphisms. Thus, these genes should not be dismissed without comprehensive examination of all polymorphisms in the genes. As with any case-control study design, recall bias of dietary intake is a concern. Studies, especially those from prospectively collected exposure data, can help to clarify these relationships further.

In summary, although we provide the first data of potentially lower risk for NHL from the effects of higher intakes of vegetables and dietary zinc with polymorphisms in the genes *GSTM3*, *GSTP1*, *OGG1* and *XRCC3*, the probability of false positive findings is high.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Jane Curtin and Adam Risch of Information Management Services, Inc. for assisting with data analysis and Nilanjan Chatterjee for guidance with the two-phase design, semi-parametric maximum-likelihood method implementation.

Financial support: Supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute and contracts with the National Cancer Institute (N01-CP-67010, N01-PC-67008, N01-PC-67009, N01-PC-65064 and N02-PC-71105). LEK was supported by National Institutes of Health Grant R25 CA92049-03.

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Table 1
Genetic polymorphisms and a priori-hypothesized interactions with foods or nutrients for risk of NHL

Gene name/Gene product function	Gene	Chromosome	Polymorphic region or amino acid change	rsID	A priori hypothesized gene—food or nutrient interaction
<i>Glutathione-S-transferase enzyme</i> Phase 2 detoxification enzymes that can deactivate carcinogens, drugs, environmental toxins and products of oxidative stress by conjugation with glutathione	<i>GSTM3</i> <i>GSTP1</i> <i>GSTP1</i>	1p 11q	-/ACG I105V A114V	1799735 947894 1799811	All vegetables, cruciferous vegetables are inducers and substrates for GSTs [14,15]
<i>NAD(P)H dehydrogenase, quinone 1</i> Phase 2 detoxification enzyme that catalyzes the two- or four-electron reduction of quinones to prevent redox cycling, which leads to the generation of free radicals	<i>NQO1</i>	16q	P187S	1800566	All vegetables, cruciferous vegetables are inducers and substrates for NQO1 [14,15]
<i>N-acetyltransferase-1</i> Phase 2 enzyme that catalyzes the N- or O-acetylation of various arylamine and heterocyclic amine substrates and bioactivates several known carcinogens	<i>NAT1</i>	8p	V149I R187Q	4987076 13249533 1057126 15561	All vegetables, cruciferous vegetables may induce NAT1 & NAT2
<i>N-acetyltransferase-2</i> Encodes the 'acetylator phenotype' that has been associated with DNA damage by chemicals that undergo N-acetylation	<i>NAT2</i>	8p	Y94Y I114T L161L R197Q R268K G286E	1041983 1801280 1799929 1799930 1208 1799931	All vegetables, cruciferous vegetables may decrease bio-activation of carcinogens by inhibiting CYP450 enzymes [15,16]
<i>Cytochrome 450 enzymes</i> : Phase 1 enzymes that metabolize procarcinogens to carcinogenic intermediates	<i>CYP1A1</i> (also known as m2) <i>CYP1A2</i> (also known as CYP1A1*1F)	15q 15q	I462V -154A > C	1048943 762551	Zinc is a component of the cytosolic enzyme and may stabilize it [17,18]
<i>Superoxide dismutases</i> Catalyze conversion/neutralization of superoxide radicals to hydrogen peroxide	<i>SOD2</i>	6q	V16A	1799725	↑Zinc may disrupt balance between SOD2/GPX1 activities [19]
<i>Glutathione peroxidase</i> Catalyzes hydrogen peroxide conversion to water using selenium as a cofactor	<i>GPX1</i>	3p	P200L	1050450	↑HOCL production can oxidize SOD2 [20]; zinc may act as a modifier
<i>Myeloperoxidase</i> Catalytic conversion/neutralization of hydrogen peroxide to the pro-oxidant, hypochlorous acid (HOCL)	<i>MPO</i>	17q	-642G > A promoter	2333227	All vegetables, green leafy vegetables and lutein/zeaxanthin may protect against ROS over-production [21]; Zinc is required for optimal iNOS function and activity [18]; diet may modify NOS3 associations with non-cancer phenotypes [22]
<i>Nitric Oxide Synthase 2A (inducible)</i> Synthesizes nitric oxide, a reactive free radical with anti-microbial and antitumoral activities. Unchecked	<i>NOS2A</i>	17q	S608L	2297518	

Gene name/Gene product function	Gene	Chromosome	Polymorphic region or amino acid change	rsID	A priori hypothesized gene—food or nutrient interaction
production can cause DNA damage and oxidative stress					
<i>Nitric Oxide Synthase 3 (endothelial)</i>	<i>NOS3</i> <i>NOS3</i>	7q	E298D -762C > T promoter	1799983 2070744	
<i>8-Oxoguanine DNA glycosylase</i> Lyase activity for chain cleavage of mutagenic base byproducts in DNA which occurs as a result of exposure to reactive oxygen	<i>OGG1</i>	3p	S326C	1052133	All vegetables, green leafy vegetables, lutein/zeaxanthin, zinc intakes; vegetables may modify <i>OGG1</i> associations with other cancers [7]
<i>X-ray repair cross-complementing</i> genes are involved in DNA repair	<i>XRCC1</i>	19q	Q399R	25487	All vegetables, green leafy vegetables, lutein/zeaxanthin, and zinc may play a role in DNA repair [23]
<i>XRCC1</i> is involved in base-excision repair	<i>XRCC1</i>		R280H	25489	
<i>XRCC2</i> and <i>XRCC3</i> are involved in homologous recombinational repair	<i>XRCC1</i>		R194W	1799782	
<i>XRCC4</i> is involved in non-homologous end-joining repair	<i>XRCC2</i> <i>XRCC3</i> <i>XRCC4</i> <i>XRCC4</i>	7q 14q 5q	R188H T241M N298S S307S	3218536 861539 1805377 1056503	

Table 2

Associations^{ab} between NHL and *GSTM3*, *GSTP1*, *NQO1*, *CYP1A1*, *CYP1A2* and *NAT1* polymorphisms and the NAT2 phenotype across categories of dietary exposures

	All vegetables ^c , svgs/mo		Cruciferous vegetables ^d , svgs/mo	
	≤57	>57	≤6.25	>6.25
<i>GSTM3</i> 3-b deletion				
AGG/AGG	1.00 (ref.)	0.56 (0.35–0.92)	1.00 (ref.)	0.56 (0.35–0.90)
AGG/– or –/–	0.70 (0.44–1.09)	0.99 (0.57–1.72)	0.86 (0.53–1.40)	0.74 (0.45–1.23)
<i>p</i> interaction		0.03		0.31
Cases–Controls, <i>n</i>	118/85	61/84	115/86	64/83
Cases–Controls, <i>n</i>	48/45	37/28	46/36	39/37
<i>GSTP1</i> (I105V)				
AA	1.00 (ref.)	1.12 (0.61–2.07)	1.00 (ref.)	0.71 (0.40–1.27)
AG or GG	1.39 (0.91–2.13)	0.77 (0.48–1.24)	1.16 (0.75–1.78)	0.67 (0.42–1.06)
<i>p</i> interaction		0.07		0.60
Cases–Controls, <i>n</i>	77/65	43/41	76/59	42/47
Cases–Controls, <i>n</i>	92/66	55/71	87/63	60/74
<i>GSTP1</i> (A114V)				
CC	1.00 (ref.)	0.75 (0.48–1.18)	1.00 (ref.)	0.52 (0.34–0.81)
CT or TT	0.89 (0.53–1.50)	0.67 (0.34–1.31)	0.54 (0.30–0.95)	0.89 (0.48–1.65)
<i>p</i> interaction		0.99		0.02
Cases–Controls, <i>n</i>	140/105	82/92	142/95	80/102
Cases–Controls, <i>n</i>	28/25	16/19	21/26	23/18
<i>NQO1</i> (P187S)				
CC	1.00 (ref.)	0.76 (0.51–1.14)	1.00 (ref.)	0.80 (0.54–1.18)
CT or TT	0.81 (0.55–1.17)	0.76 (0.49–1.18)	0.94 (0.63–1.40)	0.67 (0.44–1.01)
<i>p</i> interaction		0.53		0.74
Cases–Controls, <i>n</i>	156/107	95/105	146/107	106/105
Cases–Controls, <i>n</i>	68/54	51/45	68/47	51/52
<i>NAT1</i>				
Any/Any	1.00 (ref.)	0.88 (0.56–1.40)	1.00 (ref.)	0.75 (0.48–1.16)
Any/*10 or *10/*10	1.17 (0.77–1.79)	0.78 (0.48–1.27)	1.07 (0.68–1.67)	0.77 (0.49–1.20)
<i>p</i> interaction		0.46		0.92
Cases–Controls, <i>n</i>	111/87	78/85	111/84	78/88
Cases–Controls, <i>n</i>	74/42	44/40	65/38	53/44
<i>NAT2</i> phenotype				
Slow	1.00 (ref.)	0.90 (0.56–1.45)	1.00 (ref.)	0.76 (0.48–1.20)
Intermediate or rapid	1.21 (0.81–1.79)	0.90 (0.58–1.40)	1.08 (0.71–1.63)	0.88 (0.58–1.34)
<i>p</i> interaction		0.60		0.83
Cases–Controls, <i>n</i>	101/87	73/78	100/81	74/84
Cases–Controls, <i>n</i>	97/56	62/53	86/52	73/57
AA	1.00 (ref.)	0.75 (0.49–1.13)	1.00 (ref.)	0.59 (0.39–0.88)

	All vegetables ^c , svgs/mo		Cruciferous vegetables ^d , svgs/mo	
	≤57	>57	≤6.25	>6.25
AG or GG	0.97 (0.47–2.03)	0.75 (0.28–2.0)	0.62 (0.29–1.35)	1.01 (0.40–2.57)
<i>p</i> interaction		0.97		0.15
Cases–Controls, <i>n</i>	153/120	89/103	151/110	91/113
Cases–Controls, <i>n</i>	15/11	8/9	12/12	11/8
AA	1.00 (ref.)	0.76 (0.43–1.36)	1.00 (ref.)	0.56 (0.32–0.98)
AC or CC	1.02 (0.67–1.56)	0.74 (0.45–1.20)	0.87 (0.56–1.35)	0.63 (0.38–1.03)
<i>p</i> interaction		0.89		0.51
Cases–Controls, <i>n</i>	79/71	44/54	76/59	47/66
Cases–Controls, <i>n</i>	87/59	53/58	85/62	55/55

^a Odds ratios (95% confidence intervals) are adjusted for age in years (<45, 45–64, ≥65), gender, race (white, other), study site (Detroit, Iowa, Los Angeles, Seattle), smoking in pack years (non-smoker, <7, 7–34, ≥35), BMI in kg/m² (<25, 25–29, ≥30), Physical activity in METS per week (none, 30–675, >676), alcohol intake (none, any)

^b Estimates are imputed and use genotype data from 1,141 cases and 949 controls; however, reported numbers of cases and controls are based on non-Hispanic White subjects for whom we had both dietary and genotype data. The sample varies by genotyping success rate for each SNP

^c Includes alfalfa sprouts, beets, broccoli, carrots, cauliflower/Brussels sprouts, celery, corn, green beans, mustard greens, green salad, other vegetables, peas, radish, rhubarb, coleslaw, spinach, sweet potatoes and tomatoes/tomato juice

^d Includes broccoli, cauliflower/Brussels sprouts, coleslaw, mustard greens and radish

Table 3Associations^{ab} between NHL and *SOD2*, *GPX1*, *MPO* polymorphisms across categories of dietary zinc

	Total zinc, mg/d	
	≤15	>15
<i>SOD2</i> (V16A)		
TT or TC	1.00 (ref.)	1.02 (0.71–1.46)
CC	1.23 (0.81–1.87)	0.90 (0.54–1.52)
<i>p</i> interaction		0.41
Cases–Controls, <i>n</i>	141/123	137/122
Cases–Controls, <i>n</i>	58/36	33/29
<i>GPX1</i> (P200L)		
CC	1.00 (ref.)	1.22 (0.68–2.19)
CT or TT	0.97 (0.62–1.52)	1.19 (0.74–1.93)
<i>p</i> interaction		0.99
Cases–Controls, <i>n</i>	58/59	55/49
Cases–Controls, <i>n</i>	79/74	72/59
<i>MPO</i> (-642 promoter)		
GG	1.00 (ref.)	0.90 (0.60–1.35)
GA or AA	1.08 (0.73–1.60)	1.21 (0.81–1.82)
<i>p</i> interaction		0.51
Cases–Controls, <i>n</i>	123/102	98/96
Cases–Controls, <i>n</i>	69/54	70/50

^a Odds ratios (95% confidence intervals) are adjusted for age in years (<45, 45–64, ≥65), gender, race (white, other), study site (Detroit, Iowa, Los Angeles, Seattle), smoking in pack years (non-smoker, <7, 7–34, ≥35), BMI in kg/m² (<25, 25–29, ≥30), Physical activity in METS per week (none, 30–675, >676), alcohol intake (none, any)

^b Estimates are imputed and use genotype data from 1,141 cases and 949 controls; however, reported numbers of cases and controls are based on non-Hispanic White subjects for whom we had both dietary and genotype data. The sample varies by genotyping success rate for each SNP

Table 4

Associations^{ab} between NHL and NOS polymorphisms and polymorphisms involved in DNA repair pathways across categories of dietary exposures

	All vegetables ^c , svgs/mo		Green leafy vegetables ^d , svgs/mo		Lutein/zeaxanthin, mcg/d		Total zinc, mg/d	
	≤57	>57	≤14.6	>14.6	≤1,914	>1,914	≤15	>15
<i>NOS2A</i> (S608L)								
CC	1.00 (ref.)	0.67 (0.45–1.02)	1.00 (ref.)	0.64 (0.42–0.98)	1.00 (ref.)	1.01 (0.67–1.51)	1.00 (ref.)	0.84 (0.57–1.25)
CT or TT	0.88 (0.60–1.31)	1.03 (0.66–1.60)	0.88 (0.60–1.30)	1.02 (0.66–1.59)	1.09 (0.73–1.61)	1.17 (0.76–1.80)	0.95 (0.64–1.41)	1.14 (0.73–1.79)
<i>p</i> interaction		0.12		0.10		0.85		0.31
Cases–Controls, <i>n</i>	154/100	93/106	161/104	86/102	141/106	106/100	131/100	116/106
Cases–Controls, <i>n</i>	61/54	50/41	60/52	51/43	59/52	52/43	61/54	50/41
<i>NOS3</i> (E298D)								
GG	1.00 (ref.)	0.91 (0.51–1.62)	1.00 (ref.)	0.97 (0.54–1.72)	1.00 (ref.)	1.15 (0.66–2.01)	1.00 (ref.)	1.65 (0.94–2.90)
GT or TT	1.15 (0.76–1.75)	0.78 (0.47–1.31)	1.21 (0.80–1.83)	0.75 (0.44–1.27)	1.10 (0.72–1.69)	1.09 (0.66–1.82)	1.38 (0.87–2.19)	1.29 (0.78–2.14)
<i>p</i> interaction		0.47		0.26		0.71		0.15
Cases–Controls, <i>n</i>	72/62	48/50	73/62	47/50	66/60	54/52	52/60	68/52
Cases–Controls, <i>n</i>	91/65	48/54	93/66	46/53	84/68	55/51	82/66	57/53
<i>NOS3</i> (IVS1–762)								
TT	1.00 (ref.)	0.96 (0.52–1.79)	1.00 (ref.)	0.68 (0.37–1.27)	1.00 (ref.)	1.15 (0.62–2.12)	1.00 (ref.)	1.45 (0.79–2.64)
CT or TT	1.35 (0.87–2.11)	0.69 (0.40–1.18)	1.0 (0.64–1.55)	0.75 (0.43–1.30)	1.20 (0.76–1.88)	1.05 (0.63–1.77)	1.21 (0.76–1.92)	1.37 (0.83–2.26)
<i>p</i> interaction		0.12		0.81		0.51		0.54
Cases–Controls, <i>n</i>	56/52	42/46	59/49	39/49	53/54	45/44	47/54	51/44
Cases–Controls, <i>n</i>	106/72	44/63	103/78	47/57	95/74	55/61	80/73	70/62
<i>OGG1</i> (S326C)								
CC	1.00 (ref.)	0.85 (0.56–1.31)	1.00 (ref.)	0.81 (0.52–1.25)	1.00 (ref.)	0.93 (0.61–1.42)	1.00 (ref.)	0.71 (0.47–1.08)
CG or GG	1.19 (0.83–1.71)	0.94 (0.61–1.44)	1.21 (0.85–1.73)	0.81 (0.51–1.29)	1.08 (0.75–1.55)	1.17 (0.74–1.84)	0.83 (0.57–1.21)	1.18 (0.79–1.78)
<i>p</i> interaction		0.81		0.57		0.65		0.04
Cases–Controls, <i>n</i>	122/98	85/94	119/93	88/99	109/88	98/104	120/95	87/97
Cases–Controls, <i>n</i>	101/62	61/54	110/65	52/51	99/71	63/45	79/64	83/52
<i>XRCC1</i> (Q399R)								
AA	1.00 (ref.)	0.85 (0.59–1.22)	1.00 (ref.)	0.77 (0.53–1.11)	1.00 (ref.)	1.02 (0.72–1.45)	1.00 (ref.)	0.99 (0.70–1.40)
AG or GG	1.06 (0.58–1.93)	0.71 (0.39–1.31)	1.24 (0.67–2.28)	0.57 (0.30–1.07)	1.35 (0.74–2.48)	0.64 (0.34–1.22)	1.13 (0.61–2.09)	0.78 (0.44–1.40)

	All vegetables ^c , svgs/mo		Green leafy vegetables ^d , svgs/mo		Lutein/zeaxanthin, mcg/d		Total zinc, mg/d	
	≤57	>57	≤14.6	>14.6	≤1,914	>1,914	≤15	>15
<i>p</i> interaction		0.63		0.30		0.13		0.46
Cases–Controls, <i>n</i>	197/138	128/123	203/139	122/122	182/139	143/122	178/139	147/122
Cases–Controls, <i>n</i>	22/18	18/24	24/16	16/26	25/17	15/25	21/18	19/24
<i>XRCC1</i> (R280H)								
GG	1.00 (ref.)	0.73 (0.51–1.05)	1.00 (ref.)	0.68 (0.47–0.98)	1.00 (ref.)	0.92 (0.65–1.32)	1.00 (ref.)	1.01 (0.72–1.43)
GA or AA	0.69 (0.41–1.16)	1.14 (0.56–2.31)	0.83 (0.48–1.42)	0.79 (0.40–1.53)	0.93 (0.53–1.64)	0.92 (0.48–1.75)	1.16 (0.66–2.03)	0.77 (0.40–1.47)
<i>p</i> interaction		0.12		0.51		0.90		0.42
Cases–Controls, <i>n</i>	194/136	125/135	200/137	119/134	180/139	139/132	169/140	150/131
Cases–Controls, <i>n</i>	28/22	20/12	29/19	19/15	28/18	20/16	29/18	19/16
<i>XRCC1</i> (R194W)								
CC	1.00 (ref.)	0.83 (0.58–1.20)	1.00 (ref.)	0.73 (0.50–1.07)	1.00 (ref.)	0.96 (0.66–1.38)	1.00 (ref.)	1.10 (0.77–1.56)
CT or TT	1.47 (0.88–2.46)	1.12 (0.62–2.04)	1.48 (0.89–2.46)	0.99 (0.55–1.79)	1.48 (0.87–2.51)	1.28 (0.73–2.26)	2.13 (1.22–3.71)	0.98 (0.55–1.74)
<i>p</i> interaction		0.85		0.86		0.83		0.06
Cases–Controls, <i>n</i>	182/138	126/128	189/136	119/130	172/137	136/129	160/142	148/124
Cases–Controls, <i>n</i>	39/20	21/20	39/20	21/20	35/20	25/20	38/17	22/23
<i>XRCC2</i> (R188H)								
GG	1.00 (ref.)	0.76 (0.49–1.19)	1.00 (ref.)	0.70 (0.45–1.10)	1.00 (ref.)	1.04 (0.68–1.59)	1.00 (ref.)	1.13 (0.76–1.70)
GA or AA	0.87 (0.48–1.61)	0.58 (0.28–1.23)	0.69 (0.37–1.27)	0.77 (0.38–1.58)	0.82 (0.46–1.47)	0.87 (0.40–1.90)	0.64 (0.35–1.17)	1.41 (0.64–3.15)
<i>p</i> interaction		0.81		0.40		0.98		0.24
Cases–Controls, <i>n</i>	145/115	85/96	151/115	79/96	132/115	98/96	118/111	112/100
Cases–Controls, <i>n</i>	23/16	13/16	20/17	16/15	23/19	13/13	19/22	17/10
<i>XRCC3</i> (T241M)								
CC or CT	1.00 (ref.)	0.73 (0.48–1.13)	1.00 (ref.)	0.63 (0.41–0.97)	1.00 (ref.)	0.95 (0.62–1.44)	1.00 (ref.)	1.30 (0.87–1.96)
TT	1.02 (0.55–1.88)	0.94 (0.44–2.03)	0.66 (0.35–1.22)	1.52 (0.67–3.46)	0.86 (0.46–1.60)	1.55 (0.70–3.43)	1.26 (0.66–2.41)	1.31 (0.64–2.70)
<i>p</i> interaction		0.69		0.03		0.28		0.69
Cases–Controls, <i>n</i>	147/113	82/99	153/111	76/101	136/114	93/98	117/118	112/94
Cases–Controls, <i>n</i>	21/17	16/11	18/19	19/9	19/18	18/10	20/15	17/13
<i>XRCC4</i> (N298S)								
GG	1.00 (ref.)	0.76 (0.48–1.19)	1.00 (ref.)	0.65 (0.41–1.03)	1.00 (ref.)	0.90 (0.58–1.39)	1.00 (ref.)	1.01 (0.66–1.55)
GA or AA	1.15 (0.69–1.90)	0.79 (0.44–1.42)	0.89 (0.54–1.47)	0.95 (0.53–1.70)	0.85 (0.52–1.39)	1.34 (0.74–2.45)	0.77 (0.46–1.28)	1.74 (0.95–3.20)

	All vegetables ^c , svgs/mo		Green leafy vegetables ^d , svgs/mo		Lutein/zeaxanthin, mcg/d		Total zinc, mg/d	
	≤57	>57	≤14.6	>14.6	≤1,914	>1,914	≤15	>15
<i>p</i> interaction								
Cases–Controls, <i>n</i>	127/103	69/82	133/102	63/83	119/101	77/84	103/95	93/90
Cases–Controls, <i>n</i>	41/28	28/30	38/30	31/28	36/33	33/25	34/38	35/20

^aOdds ratios (95% confidence intervals) are adjusted for age in years (<45, 45–64, ≥65), gender, race (white, other), study site (Detroit, Iowa, Los Angeles, Seattle), smoking in pack years (non-smoker, <7, 7–34, ≥35), BMI in kg/m² (<25, 25–29, ≥30), Physical activity in METS per week (none, 30–675, >676), alcohol intake (none, any)

^bEstimates are imputed and use genotype data from 1,141 cases and 949 controls; however, reported numbers of cases and controls are based on non-Hispanic White subjects for whom we had both dietary and genotype data. The sample varies by genotyping success rate for each SNP

^cIncludes alfalfa sprouts, beets, broccoli, carrots, cauliflower/Brussels sprouts, celery, corn, green beans, mustard greens, green salad, other vegetables, peas, radish, rhubarb, coleslaw, spinach, sweet potatoes and tomatoes/tomato juice

^dIncludes mustard greens, green salad and spinach