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Genetic polymorphisms in nitric oxide synthase genes modify the relationship between vegetable and fruit intake and risk of non-Hodgkin lymphoma

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Abstract

Oxidative damage caused by reactive oxygen species (ROS) and other free radicals is involved in carcinogenesis. It has been suggested that high vegetable and fruit intake may reduce the risk of non-Hodgkin lymphoma (NHL) as vegetables and fruit are rich in antioxidants. The aim of this study is to evaluate the interaction of vegetable and fruit intake with genetic polymorphisms in oxidative stress pathway genes and NHL risk. This hypothesis was investigated in a population-based case-control study of NHL and NHL histological subtype in Connecticut women including 513 histologically confirmed incident cases and 591 randomly selected controls. Gene-vegetable/fruit joint effects were estimated using unconditional logistic regression model. The false discovery rate method was applied to adjust for multiple comparisons. Significant interactions with vegetable and fruit intake were **mainly** found for genetic polymorphisms on nitric oxide synthase (*NOS*) genes among those with diffuse large B-cell lymphoma (DLBCL) and Follicular lymphoma (FL). Two single nucleotide polymorphisms (SNPs) in the *NOS1* gene were found to significantly modify the association between total vegetable and fruit intake and risk of NHL overall, as well as the risk of follicular lymphoma (FL). When vegetables, bean vegetables, cruciferous vegetables, green leafy vegetables, red vegetables, yellow/orange vegetables, fruit, and citrus fruit were examined separately, strong interaction effects were narrowed to vegetable intake among DLBCL patients. Our results suggest that genetic polymorphisms in oxidative stress pathway genes, especially in the nitric oxide synthase genes, modify the association between vegetable and fruit intake and risk of NHL.

Keywords

oxidative stress pathway; vegetable and fruit intake; non-Hodgkin lymphoma; nitric oxide synthase; genetic polymorphisms

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Introduction

Non-Hodgkin lymphoma (NHL) presents a heterogeneous group of malignancies arising from lymphocytes throughout the body. It has been estimated that 66,120 individuals will be diagnosed with NHL and 19,160 will die from NHL in the United States in 2008. Although established risk factors such as immunodeficiency and viral infection may be responsible for a portion of the cases, the vast majority of the NHL cases remain unexplained.

Reactive oxygen species (ROS) and other free radicals can cause oxidative damage to all components of the cell (i.e., proteins, lipids, and DNA) and have been demonstrated to be involved in a number of pathological conditions including cancer (1-7). Vegetables and fruit are rich in antioxidants that protect cells from such damage. As such, high vegetable and fruit intake has been hypothesized to reduce the risk of NHL. However, results from epidemiologic studies have been inconsistent (8-22). Variation in genetic susceptibility within these populations under study could, in part, account for some of the conflicting findings in previous investigation into the role of fruit and vegetable intake.

It is biologically plausible that the role of antioxidant-rich vegetable and fruit intake in lymphomagenesis is modified by common genetic variation in oxidative stress pathway genes. Oxidative stress pathway genes can modify the impact of oxidative damage at many stages of carcinogenesis (4), including tumor initiation due to genotoxicity of ROS, tumor promotion by oxidants and free radicals, inflammatory responses mediated by oxide synthase and oxygenase, inhibition of intercellular communication regulating cellular proliferation and differentiation, and alteration of the extracellular matrix involved in tumor invasion and metastasis. We therefore investigated NHL risk in general and by subtype in relation to common genetic variation in the oxidative stress pathway in conjunction with vegetable and fruit intake in a population-based case-control study of females in Connecticut.

Materials and methods

Study population

The study population has been described in detail elsewhere (8,23). Briefly, cases were histologically confirmed, incident NHL patients diagnosed in Connecticut between 1996 and 2000, restricted to women aged 21-84 at diagnosis, without previous diagnosis of cancer except nonmelanoma skin cancer, and alive at the time of interview. **Out of 832 eligible NHL cases, 601 (72%**) cases completed in-person interviews. Participants were slightly older than non-participants, with mean ages of 67 and 62, respectively. The race distribution was similar between participants and non-participants. Out of 601 cases, 518 provided a biosample (461 provided a blood sample and 57 provided a buccal cell sample); excluding 5 cases with dietary information missing, **yielding 513 cases for final analysis**.

Pathology slides or tissue blocks were obtained from the hospitals where the cases were diagnosed. The specimens were reviewed by two independent study pathologists. All NHL cases were classified according to the World Health Organization (WHO) classification system (24,25), including 160 cases of diffuse large B-cell lymphoma (DLBCL), 117 cases of follicular lymphoma (FL), 59 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 35 cases of marginal zone B-cell lymphoma (MZBL), 39 cases of T/NK-cell lymphoma (T-cell), and 103 cases of other rare and unspecified subtypes.

Population-based controls with Connecticut addresses were recruited using random digit dialing methods (RDD) for those below age 65 years and files provided by the Centers for Medicare and Medicaid Service (CMS) were used to recruit those aged 65 years or older, and were frequency matched to cases by age (±5 years). The participation rates were 69% for RDD

controls and 47% for CMS controls. The distribution of age and race between participants and non-participants was similar. Out of 717 controls, 597 provided a biosample (535 provided a blood sample and 62 provided a buccal cell sample); excluding 6 controls with dietary information missing, yielding **591 controls for final analysis**.

The study was approved by the Human Subjects Research Review Committee at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. Written and informed consent was obtained from all subjects.

Exposure assessment

In-person interviews were conducted by trained personnel using a standardized questionnaire to collect demographic information and other major known or suspected NHL risk factors, such as family history of cancer, pesticide exposure, medical history, smoking, alcohol consumption, UV radiation and hair-coloring products use. Diet was assessed using a mailed self-administered semiquantitative food frequency questionnaire (FFQ) developed by the Fred Hutchinson Cancer Research Center (Seattle, Washington), in which subjects were asked to characterize their usual diet in the year prior to being interviewed. Reproducibility and validity studies indicated that fruits and vegetables on the FFQ reasonably reflect long-term dietary intake (26). Following completion, the FFQ was sent to the Fred Hutchinson Cancer Research Center for analysis. Average daily nutrient intakes were calculated using the University of Minnesota Nutrition Coding Center Nutrient Data System database.

The FFQ collects data on consumption frequency and portion size for approximately 120 foods including 19 vegetables and 11 fruits (Table 1). Besides overall vegetable intake, we individually analyzed bean vegetables, cruciferous vegetables, green leafy vegetables, red vegetables, and yellow/orange vegetables. In addition to total fruit intake, we individually analyzed citrus fruits.

The methods for evaluating genotypes in our study population have been described previously by Lan et al. (27). Briefly, DNA was extracted for blood or buccal cell samples using phenol-chloroform extraction. 137 Tag SNPs from 18 candidate genes (Table **2**) involved in oxidative stress pathway were chosen from the designable set of common SNPs (minor allele frequency >5%) genotyped in the Caucasian (CEU) population sample of the HapMap Project (Data Release 20/Phase II, NCBI Build 35 assembly, dpSNPb125) using the software Tagzilla (http://tagzilla.nci.nih.gov/), which implements a tagging algorithm based on the pairwise binning method of Carlson et al. (28). For each gene, SNPs within the region 20kb 5' of the ATG-translation initiation codon and 10kb 3' of the end of the last exon were binned using a binning threshold of $r^2 > 0.80$. When there were multiple transcripts available for genes, the primary transcript was assessed. Genotyping was conducted at the National Cancer Institute Core Genotyping Facility (Advanced Technology Center, Gaithersburg, MD; http://snp500cancer.nci.nih.gov) (29) using a real-time PCR assay (18 SNPs) and a custom-designed GoldenGate assay (Illumina, www.illumina.com) (129 SNPs). Duplicate samples and replicate samples were genotyped for quality control, and blinded to laboratory personnel. The concordance rates were 99-100% for all assays.

Statistical analysis

Intake of vegetables and fruit, all vegetables, bean vegetables, cruciferous vegetables, green leafy vegetables, red vegetables, yellow/orange vegetables, fruit, and citrus fruits was dichotomized into high and low levels according to the median daily consumption (servings of medium portions per day) in controls. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the relative risk of NHL and NHL subtypes in relation to the SNP genotype using unconditional logistic regression models in different vegetable and/or fruit

strata (high and low). The homozygote of the most common allele was used as the referent group. Significance of gene-vegetable and/or fruit intake interaction was assessed by adding an interaction term in the logistic models. The reference groups with a homozygote wild-type genotype were coded as 0, and the heterozygote and homozygote variant genotypes were grouped together **to increase power** and coded as 1. Statistical analyses were performed using the SAS system, version 9.1 (SAS Institute, Cary, NC).

Haplotype analyses were conducted for all genes in which more than one SNP was genotyped. Haplotype block structure was evaluated with the program HaploView (Whitehead Institute, Cambridge, MA) in controls using the 4-gamete rule with a minimum frequency of 0.005 for the fourth gamete. Haplotypes were estimated using the estimation-maximization algorithm (30) in SAS Genetics (SAS Institue, Cary, NC). An unconditional logistic regression model was used to estimate the effect of individual haplotypes in different vegetable and/or fruit intake level strata.

All models were adjusted for age, race (white and other), family history of NHL, total energy intake (kcal), smoking (never/ever), alcohol consumption (gm/day), and body mass index (BMI) (kg/m^2). Total energy intake was examined for extreme values and exclusion of these subjects did not result in material changes for the observed associations.

The false discovery rate (FDR) method (31) was applied to adjust for multiple comparisons. The FDR provides the expected ratio of erroneous rejections of the null hypothesis compared to the total number of rejected hypotheses. FDR values were calculated separately for each vegetable and/or fruit category from the results of the 137 tests (i.e. total number of SNPs studied) evaluating the association between each SNP-vegetable and/or fruit interaction and the risk of NHL. Interactions were deemed significant at an FDR level of 0.20.

Results

Selected demographic characteristics of cases and controls were compared (Table **3**). Cases and controls were similar with respect to age, race, reported family history of NHL, smoking status and total energy intake. However, cases tended to consume less alcohol and have a higher BMI.

Significant effect modification was identified for **8** SNPs in nitric oxide synthase (*NOS*) genes, 1 SNP in Myeloperoxidase (*MPO*) gene and 1 SNP in Superoxide dismutase 3 (*SOD3*) gene, with total vegetable and fruit intake, vegetable intake, red vegetable intake, or yellow/orange vegetable intake among either NHL overall or the three most common subtypes DLBCL, FL and CLL/SLL (Table 4). No significant result was found for MZBL or T-cell lymphoma (data not shown).

Significant effect modification was identified for SNPs in ***MPO*** and *NOS1* genes, with total vegetable and fruit intake, were found for NHL overall and FL. Carriers of the variant allele for *MPO* (rs4401102) (CT or TT) had a 1.9-fold increased risk of NHL overall and FL in the high vegetable and fruit intake group, but not in the low intake group. Carriers of the variant allele for *NOS1* (rs2293054) (AG or AA) had a 50% reduced risk of NHL and a 60% reduced risk of FL in the high vegetable and fruit intake group, while a 2.7-fold increased risk of FL in the low intake group. Carriers of the variant allele for another *NOS1* (rs7298903) (CT or CC) had a 1.7-fold increased risk of NHL and a 3.0-fold increased risk of FL in the low vegetable and fruit intake group but a 60% reduced risk of FL in the low intake group.

When vegetable intake was investigated alone, significant interactions with SNPs in *NOS1* and *SOD3* genes were found for DLBCL and CLL/SLL. Carriers of the variant allele for *NOS1* (rs545654) (CT or TT) had a 60% reduced risk of DLBCL in the low vegetable intake groups

but not in high intake group. Carriers of the variant allele for *SOD3* (rs2284659) (GT or TT) had a 4.6-fold increased risk of CLL/SLL in the low intake group while a 60% reduced risk of CLL/SLL was observed in the high intake group.

When different types of vegetables were investigated separately, no significant interaction was found for bean vegetables, cruciferous vegetables or green leafy vegetables after adjusting for multiple comparisons. For red vegetable intake, significant interactions with five SNPs in the *NOS1* gene and one SNP in the *NOS2A* gene were found for DLBCL. Those with variant alleles for *NOS1* (rs11068446) (CT or TT), *NOS1* (rs3782221) (AG or AA), *NOS1* (rs7298903) (CT or CC) and *NOS2A* (rs3729508) (CT or TT) had a 1.7-2.2-fold increased risk of DLBCL in the low red vegetable intake group, while those in the high intake group had a 30%-60% reduced risk of DLBCL. Those with variant alleles for *NOS1* (rs545654) (CT or TT) and *NOS1* (rs12424669) (CT or TT) had a 60% reduced risk of DLBCL in the low red vegetable intake group and a 1.7-2.4-fold increased risk of DLBCL in the high intake group.

For yellow/orange vegetable intake, significant interactions with three SNPs in the *NOS1* gene were found for DLBCL. Those with variant alleles for *NOS1* (rs11068446) (CT or TT), *NOS1* (rs1552227) (CT or TT) and *NOS1* (rs7298903) (CT or CC) had a 2.1-2.3 fold increased risk of DLBCL in the low yellow/orange vegetable intake group though it reduces the risk by 40%-70% in the high intake group.

No significant interaction was found when fruit intake overall, or citrus fruit was investigated.

There were a total of 26 haplotype structures identified in the investigated genes (16 2-SNP haplotypes, 7 3-SNP haplotypes, 1 4-SNP haplotype, and 2 5-SNP haplotypes). No significant interaction with haplotype was found for NHL overall or for any histological subtype.

The results were similar when the analyses were limited to Caucasian subjects.

Discussion

Our study offers the first comprehensive analysis of the interaction between vegetable and fruit intake, genetic polymorphisms in oxidative stress pathway genes and NHL risk overall and by histological subtype. We observed that the risk of NHL differs by vegetable and fruit intake when considered in conjunction with genetic variation in *NOS1*, *NOS2A*, ***MPO*** **and** ***SOD3*** **with majority findings in** ***NOS1***, especially for the most prevalent histological subtypes DLBCL and FL.

The interaction between vegetable intake and polymorphisms in 28 genes and the risk of NHL overall recently studied (32). We shared 6 common SNPs (GPX P200L rs1050450, NOS2A S608L rs2297518, NOS3 D298E rs1799983, NOS3-762C>T rs2070744, OGG S326C rs1052133 and SOD2V16A rs4880). Our results are consistent with the previous findings as no interaction was observed for any of overlapping SNPs and vegetable intake.

High vegetable and fruit intake is believed to be protective for many types of cancers as vegetables and fruit are good sources of vitamins and minerals, carotenoids and other antioxidants, and various phytochemicals, each of which may play a role in reducing cancer risk. It is likely a combination of these factors, and other factors not yet explored, that confers protection (33). Vegetable and fruit intake have been previously examined as protective factors for NHL (8-22). Although the majority of studies indicate that a protective effect is found when vegetables and fruit are combined, or for specific types of vegetables and fruits, the evidence from prospective data has been weak (10,19,22), and inconsistencies have been observed. Potential explanations for the inconsistency in findings may be due to gender differences (34), lack of examination by NHL histological subtypes, and the issue of multiple comparisons.

However, the gene-diet interactions identified in our multiple comparison-adjusted analyses by NHL subtype could address the inconsistencies observed in previous epidemiological studies.

The gene-diet interactions identified in our study confer support for prior findings that oxidative stress pathway genes and alter NHL risk (27,35,36). The genes with polymorphisms shown to impact risk include *AKR1A1* and *CYBA* (27), *CPX1* (35), *NOS2A* and *SOD2* (35,36). However, in an investigation of the same study population, Lan et al. (27) did not find an association between genetic polymorphisms in *MPO* or *NOS2A* and susceptibility to NHL and its major subtypes. Our results suggest that the dietary differences in vegetables and fruit might have masked the role of these genes in the susceptibility of NHL in the previous analyses.

We observed vegetable and/or fruit intake interactions with 8 SNPs in *NOS* genes (7 in *NOS1* and 1 in *NOS2A*). NOS are isoenzymes that catalyze the synthesis of nitric oxide (NO), a free radical whose role in tumor biology is still controversial (37). On the one hand, NO can favor tumor growth and development by stimulating angiogenesis (38) and cause immunosuppression (39,40); on the other hand, NO could play a role in tumor regression through its ability to induce apoptosis (41) and facilitate an immune response/rejection of the tumor (42). Studies have showed that certain antioxidants in vegetables and fruits regulate NOS expression and NO production. For example, polyphenols(43-46), which are widely distributed in fruit and vegetables, lutein (47), primarily found in dark-green leafy vegetables and fruits, and tomatoes, inhibit NOS expression and decrease NO production. Soyasaponins (48), which are found in soybeans, garlic and its derivatives (49,50), dietary soy isoflavones (51), and onion (52) activate NOS expression leading to an increase in NO. Sulforaphane, which is rich in cruciferous vegetables, inhabits Hypoxia-inducible factor 1 which regulates NOS2 expression in cancer cells (53).

In addition to the components of vegetables and fruit, other factors such as contamination during cooking or processing, could also modulate NOS expression and impact NHL risk. For example, 3-monochloro-1,2-propanediol, a contaminant of acid-hydrolyzed vegetables can be formed during the cooking process, was recently found to inhabit NOS1 expression and increase NOS2 expression (54). Our finding of an interaction between *NOS1* and *NOS2A* SNPs and red vegetables (including fresh tomato, cooked tomatoes and tomato sauce) support this explanation.

Our finding of the risk associated with *NOS1* SNPs suggests that in addition to the known role of NOS1 in cellular communication, it may be also involved in lymphomagenesis and development, and its role could be strongly modified by the intake of vegetables, especially tomatoes, carrots and other yellow/orange vegetables. NOS1 are constitutively expressed in neurons and endothelial cells (37) and polymorphisms in *NOS1* have previously been associated with many diseases and disorders in nervous system, such as Parkinson's disease (55), achalasia (56), restless legs syndrome (57), depression (58), schizophrenia (59), and suicidal behavior (60), while demonstrating few associations with cancer. Moreover, none of the risk *NOS1* polymorphisms we identified were functional, implying a need for further exploration on this gene's role in tumor biology. There is, however, evidence of an association between the NOS2 isoform and NHL. Investigators have previously shown that the isoform NOS2 is inducible and expressed in many cell types including macrophage (61), B-lymphocytes (39), lymphoid neoplasms (62-64) and other tumor cells (65-68).

To our knowledge, there is no functional evidence for any of the risk SNPs we identified. *NOS1* (rs2293054) is a synonymous mutation on Exon13, although theoretically, this type of mutation may impact splicing and protein structure and function, no evidence is shown for this specific SNP. All the other SNPs are intron variations or found in the cap or tail; which was

generally thought to be “junk DNA”. Our findings support the dispute against it, and suggest that more exploration and investigation is needed for these mutations. Specifically, our results suggest that these mutations might affect human health by interacting with common environmental exposure or lifestyle factors such as diet, and were subsequently maintained through evolution.

We did not include specific antioxidant nutrients in our analysis, since the major source of antioxidant for human beings is natural plants other than supplements. And more likely, it is the combination of the antioxidants in vegetables and fruits confer a protection against cancer.

Although we adjusted for multiple comparisons, it is still possible that some of the interactions we identified are due to chance. Our results should be confirmed in future studies with large sample sizes. Three *NOS1* SNPs (rs545654, rs7298903 and rs11068446) were significant in the multiple vegetable and/or fruit comparison groups, suggesting a strong likelihood that the association is true and should be investigated in future studies.

In summary, our study support a role for the modification from oxidative stress pathway genetic variations on the association between vegetable and fruit intake and NHL subtypes. Our results warrant replication in further studies and suggest that future research on the role of nonfunctional variants in lymphoma tumor biology should be explored.

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References

1. Olinski R, Gackowski D, Foksinski M, Rozalski R, Roszkowski K, Jaruga P. Oxidative DNA damage: assessment of the role in carcinogenesis, atherosclerosis, and acquired immunodeficiency syndrome. Free Radic Biol Med 2002;33:192–200. [PubMed: 12106815]
2. Wan J, Winn LM. In utero-initiated cancer: the role of reactive oxygen species. Birth Defects Res C Embryo Today 2006;78:326–32. [PubMed: 17315246]
3. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44–84. [PubMed: 16978905]
4. Lee KW, Lee HJ. Biphasic effects of dietary antioxidants on oxidative stress-mediated carcinogenesis. Mech Ageing Dev 2006;127:424–31. [PubMed: 16519920]
5. Kawanishi S, Hiraku Y, Oikawa S. Mechanism of guanine-specific DNA damage by oxidative stress and its role in carcinogenesis and aging. Mutat Res 2001;488:65–76. [PubMed: 11223405]
6. Arakaki N, Kajihara T, Arakaki R, et al. Involvement of oxidative stress in tumor cytotoxic activity of hepatocyte growth factor/scatter factor. J Biol Chem 1999;274:13541–6. [PubMed: 10224123]
7. Guyton KZ, Kensler TW. Oxidative mechanisms in carcinogenesis. Br Med Bull 1993;49:523–44. [PubMed: 8221020]
8. 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;159:454–66. [PubMed: 14977641]
9. 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;83:1401–10. [PubMed: 16762953]
10. 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;9:477–85. [PubMed: 10815692]

11. 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;14:512–20. [PubMed: 15734980]
12. 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;92:1011–7. [PubMed: 11676850]
13. Ward MH, Zahm SH, Weisenburger DD, et al. Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). Cancer Causes Control 1994;5:422–32. [PubMed: 7999964]
14. 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;118:2871–6. [PubMed: 16385566]
15. Chiu BC, Dave BJ, Ward MH, et al. Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma. Cancer Causes Control 2008;19:859–67. [PubMed: 18386141]
16. Tavani A, Pregnolato A, Negri E, et al. Diet and risk of lymphoid neoplasms and soft tissue sarcomas. Nutr Cancer 1997;27:256–60. [PubMed: 9101555]
17. Franceschi S, Serraino D, Carbone A, Talamini R, La Vecchia C. Dietary factors and non-Hodgkin's lymphoma: a case-control study in the northeastern part of Italy. Nutr Cancer 1989;12:333–41. [PubMed: 2608538]
18. 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;13:1665–76. [PubMed: 15466985]
19. Chiu BC, Cerhan JR, Folsom AR, et al. Diet and risk of non-Hodgkin lymphoma in older women. Jama 1996;275:1315–21. [PubMed: 8614116]
20. 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;22:445–52. [PubMed: 9652731]
21. Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F. Vegetable and fruit consumption and cancer risk. Int J Cancer 1991;48:350–4. [PubMed: 2040528]
22. 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;18:537–49. [PubMed: 17443415]
23. Morton LM, Holford TR, Leaderer B, et al. Cigarette smoking and risk of non-Hodgkin lymphoma subtypes among women. Br J Cancer 2003;89:2087–92. [PubMed: 14647142]
24. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997;89:3909–18. [PubMed: 9166827]
25. 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;17:3835–49. [PubMed: 10577857]
26. Willett, W.; Lenart, E. Nutritional epidemiology. 2nd ed.. Oxford University Press; New York, NY: 1998. Reproducibility and validity of food-frequency questionnaires..
27. Lan Q, Zheng T, Shen M, et al. Genetic polymorphisms in the oxidative stress pathway and susceptibility to non-Hodgkin lymphoma. Hum Genet 2007;121:161–8. [PubMed: 17149600]
28. Carlson CS, Eberle MA, Rieder MJ, Yi Q, Kruglyak L, Nickerson DA. Selecting a maximally informative set of single-nucleotide polymorphisms for association analyses using linkage disequilibrium. Am J Hum Genet 2004;74:106–20. [PubMed: 14681826]
29. Packer BR, Yeager M, Burdett L, et al. SNP500Cancer: a public resource for sequence validation, assay development, and frequency analysis for genetic variation in candidate genes. Nucleic Acids Res 2006;34:D617–21. [PubMed: 16381944]
30. Excoffier L, Slatkin M. Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population. Mol Biol Evol 1995;12:921–7. [PubMed: 7476138]
31. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Statist Soc B 1995;57:289–300.
32. Kelemen LE, Wang SS, Lim U, et al. Vegetables- and antioxidant-related nutrients, genetic susceptibility, and non-Hodgkin lymphoma risk. Cancer Causes Control 2008;19:491–503. [PubMed: 18204928]

33. Heimendinger, J.; Stables, G.; Foerster, SB. 5 a day: a national program to increase fruit and vegetable intake. National 5 a Day Program Office, National Cancer Institute; Bethesda, MD: 1998. Chapter 1. The scientific, policy, and theoretical foundation for the National 5 A day for better health program.; p. 3
34. Cross AJ, Lim U. The role of dietary factors in the epidemiology of non-Hodgkin's lymphoma. Leuk Lymphoma 2006;47:2477–87. [PubMed: 17169793]
35. Lightfoot TJ, Skibola CF, Smith AG, et al. Polymorphisms in the oxidative stress genes, superoxide dismutase, glutathione peroxidase and catalase and risk of non-Hodgkin's lymphoma. Haematologica 2006;91:1222–7. [PubMed: 16956821]
36. Wang SS, Davis S, Cerhan JR, et al. Polymorphisms in oxidative stress genes and risk for non-Hodgkin lymphoma. Carcinogenesis 2006;27:1828–34. [PubMed: 16543247]
37. Forstermann U, Gath I, Schwarz P, Closs EI, Kleinert H. Isoforms of nitric oxide synthase. Properties, cellular distribution and expressional control. Biochem Pharmacol 1995;50:1321–32. [PubMed: 7503779]
38. Gallo O, Masini E, Morbidelli L, et al. Role of nitric oxide in angiogenesis and tumor progression in head and neck cancer. J Natl Cancer Inst 1998;90:587–96. [PubMed: 9554441]
39. Mannick JB, Asano K, Izumi K, Kieff E, Stamler JS. Nitric oxide produced by human B lymphocytes inhibits apoptosis and Epstein-Barr virus reactivation. Cell 1994;79:1137–46. [PubMed: 7528106]
40. Lejeune P, Lagadec P, Onier N, Pinard D, Ohshima H, Jeannin JF. Nitric oxide involvement in tumor-induced immunosuppression. J Immunol 1994;152:5077–83. [PubMed: 7513729]
41. Atik E, Ergin M, Erdogan S, Tuncer I. Inducible nitric oxide synthase and apoptosis in human B cell lymphomas. Mol Cell Biochem 2006;290:205–9. [PubMed: 16924421]
42. Hu DE, Dyke SO, Moore AM, Thomsen LL, Brindle KM. Tumor cell-derived nitric oxide is involved in the immune-rejection of an immunogenic murine lymphoma. Cancer Res 2004;64:152–61. [PubMed: 14729619]
43. Biesalski HK. Polyphenols and inflammation: basic interactions. Curr Opin Clin Nutr Metab Care 2007;10:724–8. [PubMed: 18089954]
44. Lomnitski L, Foley JE, Grossman S, et al. Effects of apocynin and natural antioxidant from spinach on inducible nitric oxide synthase and cyclooxygenase-2 induction in lipopolysaccharide-induced hepatic injury in rat. Pharmacol Toxicol 2000;87:18–25. [PubMed: 10987211]
45. Suh N, Paul S, Hao X, et al. Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats. Clin Cancer Res 2007;13:350–5. [PubMed: 17200374]
46. Pergola C, Rossi A, Dugo P, Cuzzocrea S, Sautebin L. Inhibition of nitric oxide biosynthesis by anthocyanin fraction of blackberry extract. Nitric Oxide 2006;15:30–9. [PubMed: 16517190]
47. Rafi MM, Shafaie Y. Dietary lutein modulates inducible nitric oxide synthase (iNOS) gene and protein expression in mouse macrophage cells (RAW 264.7). Mol Nutr Food Res 2007;51:333–40. [PubMed: 17340577]
48. Xiao JX, Huang GQ, Zhang SH. Soyasaponins inhibit the proliferation of Hela cells by inducing apoptosis. Exp Toxicol Pathol 2007;59:35–42. [PubMed: 17582751]
49. Aquilano K, Filomeni G, Baldelli S, et al. Neuronal nitric oxide synthase protects neuroblastoma cells from oxidative stress mediated by garlic derivatives. J Neurochem 2007;101:1327–37. [PubMed: 17298386]
50. Rahman K. Effects of garlic on platelet biochemistry and physiology. Mol Nutr Food Res 2007;51:1335–44. [PubMed: 17966136]
51. Mahn K, Borras C, Knock GA, et al. Dietary soy isoflavone induced increases in antioxidant and eNOS gene expression lead to improved endothelial function and reduced blood pressure in vivo. Faseb J 2005;19:1755–7. [PubMed: 16107535]
52. Sakai Y, Murakami T, Yamamoto Y. Antihypertensive effects of onion on NO synthase inhibitor-induced hypertensive rats and spontaneously hypertensive rats. Biosci Biotechnol Biochem 2003;67:1305–11. [PubMed: 12843658]
53. Yao H, Wang H, Zhang Z, Jiang BH, Luo J, Shi X. Sulforaphane inhibited expression of hypoxia-inducible factor-1alpha in human tongue squamous cancer cells and prostate cancer cells. Int J Cancer 2008;123:1255–61. [PubMed: 18561315]

54. Kim K. Differential expression of neuronal and inducible nitric oxide synthase in rat brain after subchronic administration of 3-monochloro-1,2-propanediol. Food Chem Toxicol 2008;46:955–60. [PubMed: 18063462]
55. Levecque C, Elbaz A, Clavel J, et al. Association between Parkinson's disease and polymorphisms in the nNOS and iNOS genes in a community-based case-control study. Hum Mol Genet 2003;12:79–86. [PubMed: 12490535]
56. Mearin F, Garcia-Gonzalez MA, Strunk M, Zarate N, Malagelada JR, Lanas A. Association between achalasia and nitric oxide synthase gene polymorphisms. Am J Gastroenterol 2006;101:1979–84. [PubMed: 16848803]
57. Winkelmann J, Lichtner P, Schormair B, et al. Variants in the neuronal nitric oxide synthase (nNOS, NOS1) gene are associated with restless legs syndrome. Mov Disord 2008;23:350–8. [PubMed: 18058820]
58. Yu YW, Chen TJ, Wang YC, Liou YJ, Hong CJ, Tsai SJ. Association analysis for neuronal nitric oxide synthase gene polymorphism with major depression and fluoxetine response. Neuropsychobiology 2003;47:137–40. [PubMed: 12759556]
59. Shinkai T, Ohmori O, Hori H, Nakamura J. Allelic association of the neuronal nitric oxide synthase (NOS1) gene with schizophrenia. Mol Psychiatry 2002;7:560–3. [PubMed: 12140778]
60. Rujescu D, Giegling I, Mandelli L, et al. NOS-I and -III gene variants are differentially associated with facets of suicidal behavior and aggression-related traits. Am J Med Genet B Neuropsychiatr Genet 2008;147B:42–8. [PubMed: 17579350]
61. van Straaten JF, Postma DS, Coers W, Noordhoek JA, Kauffman HF, Timens W. Macrophages in lung tissue from patients with pulmonary emphysema express both inducible and endothelial nitric oxide synthase. Mod Pathol 1998;11:648–55. [PubMed: 9688186]
62. Mendes RV, Martins AR, de Nucci G, Murad F, Soares FA. Expression of nitric oxide synthase isoforms and nitrotyrosine immunoreactivity by B-cell non-Hodgkin's lymphomas and multiple myeloma. Histopathology 2001;39:172–8. [PubMed: 11493334]
63. Li HL, Sun BZ, Ma FC. Expression of COX-2, iNOS, p53 and Ki-67 in gastric mucosa-associated lymphoid tissue lymphoma. World J Gastroenterol 2004;10:1862–6. [PubMed: 15222024]
64. Mori N, Nunokawa Y, Yamada Y, Ikeda S, Tomonaga M, Yamamoto N. Expression of human inducible nitric oxide synthase gene in T-cell lines infected with human T-cell leukemia virus type-I and primary adult T-cell leukemia cells. Blood 1999;94:2862–70. [PubMed: 10515890]
65. Sherman PA, Laubach VE, Reep BR, Wood ER. Purification and cDNA sequence of an inducible nitric oxide synthase from a human tumor cell line. Biochemistry 1993;32:11600–5. [PubMed: 7692964]
66. Ambs S, Merriam WG, Bennett WP, et al. Frequent nitric oxide synthase-2 expression in human colon adenomas: implication for tumor angiogenesis and colon cancer progression. Cancer Res 1998;58:334–41. [PubMed: 9443414]
67. Cobbs CS, Brenman JE, Aldape KD, Bredt DS, Israel MA. Expression of nitric oxide synthase in human central nervous system tumors. Cancer Res 1995;55:727–30. [PubMed: 7531613]
68. Rosbe KW, Prazma J, Petrusz P, Mims W, Ball SS, Weissler MC. Immunohistochemical characterization of nitric oxide synthase activity in squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg 1995;113:541–9. [PubMed: 7478643]
69. Cascorbi I, Henning S, Brockmoller J, et al. Substantially reduced risk of cancer of the aerodigestive tract in subjects with variant--463A of the myeloperoxidase gene. Cancer Res 2000;60:644–9. [PubMed: 10676648]
70. Taioli E, Benhamou S, Bouchardy C, et al. Myeloperoxidase G-463A polymorphism and lung cancer: a HuGE genetic susceptibility to environmental carcinogens pooled analysis. Genet Med 2007;9:67–73. [PubMed: 17304047]
71. Li D, Diao Y, Li H, Fang X. Association of the polymorphisms of MTHFR C677T, VDR C352T, and MPO G463A with risk for esophageal squamous cell dysplasia and carcinoma. Arch Med Res 2008;39:594–600. [PubMed: 18662591]
72. Hsu PI, Jwo JJ, Yang CL, et al. Association of the myeloperoxidase polymorphism with the risk of gastric cancer. Anticancer Res 2008;28:1317–23. [PubMed: 18505072]

73. He C, Tamimi RM, Hankinson SE, Hunter DJ, Han J. A prospective study of genetic polymorphism in MPO, antioxidant status, and breast cancer risk. Breast Cancer Res Treat 2009;113:585–94. [PubMed: 18340529]
74. Choi JY, Neuhouser ML, Barnett MJ, et al. Iron intake, oxidative stress-related genes (MnSOD and MPO) and prostate cancer risk in CARET cohort. Carcinogenesis 2008;29:964–70. [PubMed: 18296681]
75. Wheatley-Price P, Asomaning K, Reid A, et al. Myeloperoxidase and superoxide dismutase polymorphisms are associated with an increased risk of developing pancreatic adenocarcinoma. Cancer 2008;112:1037–42. [PubMed: 18205184]
76. Ahn J, Gammon MD, Santella RM, et al. Myeloperoxidase genotype, fruit and vegetable consumption, and breast cancer risk. Cancer Res 2004;64:7634–9. [PubMed: 15492293]
77. Gitenay D, Lyan B, Rambeau M, Mazur A, Rock E. Comparison of lycopene and tomato effects on biomarkers of oxidative stress in vitamin E deficient rats. Eur J Nutr 2007;46:468–75. [PubMed: 18026867]
78. Bobek P, Galbavy S, Mariassyova M. The effect of red beet (Beta vulgaris var. rubra) fiber on alimentary hypercholesterolemia and chemically induced colon carcinogenesis in rats. Nahrung 2000;44:184–7. [PubMed: 10907240]
79. Verma N, Vinayak M. Effect of Terminalia arjuna on antioxidant defense system in cancer. Mol Biol Rep. 2008
80. Jiang ZY, Jiang SQ, Lin YC, Xi PB, Yu DQ, Wu TX. Effects of soybean isoflavone on growth performance, meat quality, and antioxidation in male broilers. Poult Sci 2007;86:1356–62. [PubMed: 17575182]
81. Diniz YS, Cicogna AC, Padovani CR, et al. Dietary restriction and fibre supplementation: oxidative stress and metabolic shifting for cardiac health. Can J Physiol Pharmacol 2003;81:1042–8. [PubMed: 14719039]
82. Rauma AL, Torronen R, Hanninen O, Verhagen H, Mykkanen H. Antioxidant status in long-term adherents to a strict uncooked vegan diet. Am J Clin Nutr 1995;62:1221–7. [PubMed: 7491884]
83. Agte VV, Chiplonkar SA, Tarwadi KV. Factors influencing zinc status of apparently healthy indians. J Am Coll Nutr 2005;24:334–41. [PubMed: 16192257]
84. Avci A, Atli T, Erguder IB, et al. Effects of garlic consumption on plasma and erythrocyte antioxidant parameters in elderly subjects. Gerontology 2008;54:173–6. [PubMed: 18463427]

Table 1

Vegetables and fruit in Food Frequency Questionnaire

Category of food	Composition of food categories
Vegetable	Bean vegetables; cruciferous vegetables; green leafy vegetables; red vegetables; yellow/orange vegetables; avocado or guacamole; corn; summer squash such as zucchini; onions, leeks, including in cooking; mixed lettuce salad with vegetables, such as carrots, tomatoes, etc.
Fruit	Apples, pears; bananas; peaches, nectarines or plums; cantaloupes; other melon, watermelon, honeydew, etc.; apricots; other dried fruit, raisins, prunes, etc.; strawberries; any other fruit (fruit cocktail, berries, applesauce, grapes, pineapple, etc.); citrus fruits.
Bean vegetables	String beans, green beans; peas; beans, such as baked beans, pinto, kidney, lima beans, lentils.
Cruciferous vegetables	Broccoli; coleslaw; cabbage, sauerkraut, brussel sprouts; cauliflower.
Green leafy vegetables	Cooked greens (spinach, mustard greens, tuinip greens, collards, etc.); lettuce, plain lettuce salad.
Red vegetables	Tomatoes, fresh or juice; tomatoes cooked, tomato sauce, salsa.
Yellow/orange vegetables	Carrots, including in mixed dishes; winter squash, such as acorn, butternut; sweet potatoes, yams.
Citrus fruits	Oranges, grapefruit or tangerines; orange juice, grapefruit juice, or vitamin C enriched fruit drinks.

Table 2

Candidate genes in oxidative stress pathway

Candidate gene* (N=18)	Chromosomal location*	Gene name (aliases)*	Total SNPs (N=137)	SNP500 Alias** (dbSNP ID)
AKR1A1	1p33-p32	Aldo-keto reductase family 1, member A1(aldehyde reductase)	1	AKR1A1_02 (rs2088102)
AKR1C1	10p15-p14	Aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	1	AKR1C1_02 (rs8483)
AKR1C3	10p15-p14	Aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II)	2	AKR1C3_01 (rs12529), AKR1C3_08 (rs2245191)
ATG9B	7q36.1	ATG9 autophagy related 9 homolog B (S. cerevisiae)	1	ATG9B_01 (rs2373929)
CYBA	16q24	Cytochrome b-245, alpha polypeptide	5	CYBA_01 (rs4673), CYBA_02 (rs1049255), CYBA_07 (rs7195830), CYBA_08 (rs12709102), CYBA_14 (rs3794624)
GPX1	3p21.3	Glutathione peroxidase 1	1	GPX1_01 (rs1050450)
MPO	17q23.1	Myeloperoxidase	5	MPO_02 (rs2333227), MPO_03 (rs2243828), MPO_04 (rs2071409), MPO_17 (rs12452417), MPO_18 (rs4401102)
NCF2	1q25	Neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2)	7	NCF2_27 (rs10797888), NCF2_28 (rs11588654), NCF2_29 (rs12753665), NCF2_30 (rs3843293), NCF2_31 (rs3845466), NCF2_34 (rs11579965), NCF2_35 (rs2333686)
NCF4	22q13.1	Neutrophil cytosolic factor 4, 40kDa	18	NCF4_12 (rs3788523), NCF418 (rs729749), NCF4_33 (rs2072711), NCF4_34 (rs2075938), NCF4_35 (rs4821544), NCF4_36 (rs741998), NCF4_37 (rs746713), NCF4_38 (rs760519), NCF4_39 (rs10854693), NCF4_41 (rs1883113), NCF4_42 (rs4821542), NCF4_43 (rs5750326), NCF4_44 (rs5756372), NCF4_45 (rs5756381), NCF4_46 (rs5995355), NCF4_47 (rs6000462), NCF4_48 (rs8137602), NCF4_49 (rs9680849)
NOS1	12q24.2-q24.31	Nitric oxide synthase 1 (neuronal)	31	NOS1_01 (rs10850803), NOS1_02 (rs11068446), NOS1_03 (rs1123425), NOS1_04 (rs11611788), NOS1_05 (rs12578547), NOS1_06 (rs1353939), NOS1_07 (rs1552227), NOS1_08 (rs2291908), NOS1_09 (rs2293054), NOS1_10 (rs2293055), NOS1_12 (rs3782218), NOS1_13 (rs3782221),

Candidate gene* (N=18)	Chromosomal location*	Gene name (aliases)*	Total SNPs (N=137)	SNP500 Alias** (dbSNP ID)
				NOS1_14 (rs483589), NOS1_15 (rs532967), NOS1_16 (rs545654), NOS1_17 (rs6490121), NOS1_18 (rs7295972), NOS1_19 (rs7298903), NOS1_20 (rs816293), NOS1_21 (rs816351), NOS1_22 (rs816353), NOS1_23 (rs816361), NOS1_24 (rs884847), NOS1_25 (rs9658354), NOS1_26 (rs9658490), NOS1_27 (rs11068458), NOS1_28 (rs12424669), NOS1_29 (rs1879417), NOS1_30 (rs4767535), NOS1_31 (rs816347), NOS1_32 (rs9658282)
NOS2A	17q11.2-q12	Nitric oxide synthase 2A (inducible, hepatocytes)	22	NOS2A_01 (rs944722), NOS2A_02 (rs2297518), NOS2A_03 (rs9282799), NOS2A_07 (rs9282801), NOS2A_09 (rs12944039), NOS2A_11 (rs2255929), NOS2A_12 (rs2297516), NOS2A_13 (rs3729508), NOS2A_14 (rs3794763), NOS2A_15 (rs3794766), NOS2A_16 (rs4795067), NOS2A_17 (rs8072199), NOS2A_18 (rs944725), NOS2A_19 (rs9797244), NOS2A_20 (rs11080358), NOS2A_21 (rs12150211), NOS2A_22 (rs2248814), NOS2A_23 (rs2531863), NOS2A_25 (rs2779248), NOS2A_26 (rs2779252), NOS2A_28 (rs8081248), NOS2A_29 (rs9901734)
NOS3	7q36	Nitric oxide synthase 3 (endothelial cell)	8	NOS3_01 (rs1799983), NOS3_07 (rs1007311), NOS3_11 (rs2070744), NOS3_23 (rs743507), NOS3_38 (rs3918227), NOS3_39 (rs12703107), NOS3_40 (rs2373961), NOS3_41 (rs4496877)
OGG1	3p26.2	8-Oxoguanine DNA glycosylase	1	OGG1_04 (rs1052133)
RAC1	7p22	Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)	7	RAC1_05 (rs3729790), RAC1_06 (rs6463554), RAC1_07 (rs6967221), RAC1_08 (rs702484), RAC1_09 (rs4720672), RAC1_10 (rs836551), RAC1_11 (rs836554)
RAC2	22q13.1	Ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	15	RAC2_01 (rs1476002), RAC2_05 (rs6572), RAC2_06 (rs7390410, RAC2_09, RAC2_14 (rs2213430), RAC2_15 (rs2239773), RAC2_16 (rs2239774), RAC2_17 (rs2239775), RAC2_18 (rs5756573), RAC2_19 (rs8135343), RAC2_20

Candidate gene* (N=18)	Chromosomal location*	Gene name (aliases)*	Total SNPs (N=137)	SNP500 Alias** (dbSNP ID)
				(rs9607432), RAC2_21 (rs12484031), RAC2_22 (rs4820274), RAC2_23 (rs7288979), RAC2_24 (rs739043)
SOD1	21q22.11	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	3	SOD1_03 (rs10432782), SOD1_08 (rs202445), SOD1_16 (rs1041740)
SOD2	6q25.3	Superoxide dismutase 2, mitochondrial	5	SOD2_01 (rs4880), SOD2_16 (rs2758352), SOD2_20 (rs5746136), SOD2_29 (rs2758331), SOD2_30 (rs5746151)
SOD3	4p16.3-q21	Superoxide dismutase 3, extracellular	4	SOD3_16 (rs2695234), SOD3_26 (rs13434451), SOD3_27 (rs2284659), SOD3_28 (rs758946)

Abbreviations: single nucleotide polymorphism (SNP).

* As defined by Entrez gene (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene).

** SNP500 (http://snp500cancer.nci.nih.gov).

Table 3

Selected characteristics of NHL cases and controls among women from Connecticut

Characteristic		Case (N=513)	Control (N=591)	P-value
Age (years)		61.8 (± 13.6)	62.1 (± 14.2)	0.71[a]
Race				0.11[b]
	White	492 (95.9)	554 (93.7)	
	Other	21 (4.1)	37 (6.3)	
Family history of NHL				0.08[c]
	Yes	9 (1.8)	3 (0.5)	
	No	504 (98.2)	588 (99.5)	
Smoking				0.33[b]
	Never	227 (44.2)	279 (47.2)	
	Ever	286 (55.8)	312 (52.8)	
Alcohol consumption (gm/day)		3.4 (± 9.6)	4.7 (± 8.5)	0.05[a]
Total energy intake (kcal)		1708.3 (± 592.3)	1642.3 (± 596.4)	0.07[a]
Body mass index (Kg/m2)		26.1 (± 5.7)	25.4 (± 5.0)	0.03[a]

Table values are mean±SD for continuous variables and n (column%) for categorical variables.

[a] P-value is for T-test.

[b] P-value is for Chi-Square test.

[c] P-value is for Fisher's Exact test.

Table 4

Associations between genetic polymorphisms and NHL overall and histological subtypes risks by vegetable and fruit intake (svgs/d).

	NHL overall				DLBCL				FL				CLL/SLL			
	Low		High		Low		High		Low		High		Low		High	
	ca\co	OR (95% CI)	ca\co	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)
Vegetable and fruit																
MPO (rs4401102)																
CC	126 \ 141	1	108 \ 165	1	43	1	37	1	23	1	29	1	20	1	12	1
CT + TT	86 \ 115	0.9(0.6- 1.3)	121 \ 95	*1.9(1.3- 2.8)*	22	0.7(0.4- 1.3)	41	*2.0(1.2- 3.4)*	17	0.9(0.5- 1.8)	33	*1.9 (1.1-3.5)*	10	0.6(0.3- 1.3)	10	1.5(0.6- 3.7)
P-interaction				***0.0026***				*0.0052*				0.1173				0.1243
NOS1 (rs2293054)																
GG	108 \ 144	1	130 \ 108	1	35	1	42	1	13	1	39	1	17	1	10	1
AG + AA	103 \ 112	1.2(0.8- 1.7)	98 \ 152	*0.5(0.4- 0.8)*	30	1.1(0.6- 1.9)	36	*0.6(0.4- 1.0)*	26	*2.7(1.3- 5.6)*	23	*0.4(0.2- 0.7)*	13	1.0(0.5- 2.1)	11	0.7(0.3- 1.9)
P-interaction				***0.0024***				0.1467				***0.0001***				0.6042
NOS1 (rs7298903)																
TT	161 \ 215	1	187 \ 200	1	50	1	65	1	26	1	55	1	24	1	13	1
CT + CC	51 \ 41	*1.7(1.1- 2.8)*	42 \ 60	0.8(0.5- 1.2)	15	1.7(0.8- 3.4)	13	0.7(0.3- 1.3)	14	*3.0(1.4- 6.3)*	7	*0.4(0.2- 1.0)*	6	1.3(0.5- 3.5)	9	2.6(1.0- 6.7)
P-interaction				*0.0121*				*0.0459*				***0.0003***				0.3442
Vegetables																
NOS1 (rs545654)																
CC	68 \ 68	1	63 \ 66	1	30	1	12	1	11	1	22	1	10	1	7	1
CT + TT	153 \ 183	0.8(0.5- 1.2)	151 \ 192	0.8(0.6- 1.3)	42	*0.4(0.2- 0.8)*	57	1.9(0.9- 3.8)	31	1.0(0.4- 2.1)	37	0.6(0.3- 1.1)	19	0.8(0.3- 1.8)	16	0.8(0.3-2.0)
P-interaction				0.8548				***0.0028***				0.3679				0.9955
SOD3 (rs2284659)																
GG	75 \ 103	1	87 \ 95	1	22	1	21	1	19	1	25	1	4	1	14	1
GT + TT	147 \ 148	*1.5(1.0- 2.2)*	126 \ 164	0.8(0.6- 1.2)	50	1.6(0.9- 2.9)	48	1.4(0.8- 2.4)	24	1.0(0.5- 2.0)	34	0.8(0.5-1.5)	25	*4.6(1.5-13.7)*	9	*0.4(0.2-0.9)*
P-interaction				*0.0463*				0.578				0.7281				***0.0007***
Red vegetables																
NOS1 (rs11068446)																
CC	174 \ 196	1	149 \ 185	1	51	1	57	1	38	1	37	1	23	1		1
CT + TT	66 \ 53	*1.5(1.0- 2.3)*	44 \ 73	0.8(0.5- 1.2)	22	1.7(0.9- 3.1)	10	*0.4(0.2- 0.9)*	17	*1.9(1.0- 3.8)*	9	0.6(0.3- 1.4)	10	1.7(0.7-3.8)		1.2(0.4- 3.5)
P-interaction				*0.0353*				***0.0057***				*0.0377*				0.7181

Cancer Epidemiol Biomarkers Prev. Author manuscript, available in PMC 2010 October 28.

	NHL overall				DLBCL				FL				CLL/SLL			
	Low		High		Low		High		Low		High		Low		High	
	ca\co	OR (95% CI)	ca\co	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)
NOS1 (rs3782221)																
GG	126 \ 154	1	113 \ 134	1	31	1	43	1	29	1	28	1	18	1	3	1
AG + AA	112 \ 96	1.4(1.0- 2.1)	80 \ 121	0.8(0.5- 1.2)	42	*2.2(1.3- 3.9)*	24	0.6(0.3- 1.1)	24	1.5(0.8- 2.8)	18	0.7(0.4- 1.3)	14	1.3(0.6- 2.8)	15	6.3(1.7-22.7)
P-interaction				*0.0243*				***0.0011***				0.1128				*0.0448*
NOS1 (rs545654)																
CC	80 \ 63	1	50 \ 70	1	31	1	10	1	17	1	16	1	10	1	7	1
CT + TT	158 \ 183	*0.6(0.4- 0.9)*	140 \ 185	1.1(0.7- 1.7)	41	*0.4(0.2- 0.7)*	56	*2.4(1.1- 5.0)*	37	0.6(0.3- 1.2)	30	0.8(0.4- 1.5)	23	0.8(0.4- 1.8)	11	0.7(0.2- 1.8)
P-interaction				*0.0593*				***0.0002***				0.718				0.6200
NOS1 (rs7298903)																
TT	186 \ 210	1	158 \ 197	1	53	1	60	1	40	1	40	1	25	1	12	1
CT + CC	55 \ 40	*1.6(1.0- 2.6)*	35 \ 61	0.7(0.5- 1.2)	20	*2.1(1.1- 3.9)*	7	*0.4(0.2- 0.9)*	15	*2.3(1.1- 4.7)*	6	0.5(0.2- 1.2)	8	1.9(0.8- 4.5)	6	1.7(0.6-4.7)
P-interaction				*0.0172*				***0.0015***				*0.0101*				0.9399
NOS1 (rs12424669)																
CC	201 \ 194	1	149 \ 202	1	64	1	47	1	40	1	35	1	29	1	16	1
CT + TT	39 \ 55	0.6(0.4- 1.0)	44 \ 55	1.1(0.7- 1.7)	9	*0.4(0.2- 0.9)*	20	1.7(0.9- 3.2)	15	1.2(0.6- 2.3)	11	1.2(0.5- 2.5)	3	0.4(0.1- 1.2)	2	0.5(0.1- 2.3)
P-interaction				0.0961				***0.0073***				0.9057				0.7909
NOS2A (rs3729508)																
CC	76 \ 103	1	82 \ 94	1	20	1	30	1	13	1	19	1	14	1	7	1
CT + TT	161 \ 145	*1.5(1.0- 2.2)*	111 \ 161	0.8(0.5- 1.2)	53	*2.0(1.1- 3.7)*	37	0.7(0.4- 1.2)	40	*2.2(1.1- 4.4)*	27	0.8(0.4- 1.6)	18	0.9(0.4- 1.9)	11	0.9(0.3- 2.5)
P-interaction				*0.021*				***0.0086***				*0.0445*				0.9647
								Yellow/orange vegetables								
NOS1 (rs11068446)																
CC	155 \ 205	1	166 \ 183	1	49	1	59	1	34	1	40	1	22	1	12	1
CT + TT	60 \ 50	1.7(1.1- 2.7)	49 \ 75	0.7(0.5- 1.1)	23	*2.1(1.1- 3.8)*	10	*0.4(0.2- 0.9)*	12	1.6(0.8- 3.4)	13	0.9(0.4- 1.7)	9	1.9(0.8- 4.5)	7	1.5(0.5- 4.0)
P-interaction				*0.0068*				***0.001***				0.2339				0.709
NOS1 (rs1552227)																
CC	93 \ 128	1	113 \ 117	1	25	1	40	1	20	1	25	1	12	1	12	1
CT + TT	122 \ 128	1.3(0.9- 2.0)	103 \ 141	0.8(0.5- 1.1)	47	*2.1(1.2- 3.7)*	29	*0.6(0.3- 1.0)*	26	1.4(0.7- 2.6)	28	1.0(0.5- 1.8)	19	1.4(0.6- 3.1)	7	0.5(0.2- 1.3)
P-interaction				*0.0195*				***0.0014***				0.3022				
NOS1 (rs7298903)																

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2010 October 28.

	NHL overall				DLBCL				FL				CLL/SLL			
	Low		High		Low		High		Low		High		Low		High	
	ca\co	OR (95% CI)	ca\co	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)	ca	OR (95% CI)
TT	163 \ 213	1	179 \ 200	1	50	1	63	1	36	1	43	1	23		13	
CT + CC	52 \ 43	*1.7(1.1- 2.8)*	37 \ 58	0.7(0.5- 1.2)	22	*2.3(1.2- 4.3)*	6	*0.3(0.1- 0.8)*	10	1.5(0.7- 3.3)	10	0.8(0.4- 1.8)	8	2.1(0.8- 5.2)	6	1.8(0.6- 4.9)
P-interaction				*0.0104*				***0.0005***				0.3115				0.8504

Abbreviations: non-Hodgkin lymphoma (NHL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); marginal zone B-cell lymphoma (MZBL); T/NK-cell lymphoma (T-cell); odd ratio (OR); confidence interval (CI); cases (ca); controls (co).

OR (95% CI) were adjusted for age, race (white, other), family history of NHL, total energy intake (kcal), smoking (ever/never), alcohol consumption (gm/day) and body mass index.

Italic P-values <0.05, and *italic* odd ratios' 95% confidence intervals do not include 1; ***Bold*** P-values are significant after FDR adjustment for multiple comparisons.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2010 October 28.