HHS Public Access

Author manuscript

*Cancer Causes Control*. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

*Cancer Causes Control*. 2017 July ; 28(7): 791–799. doi:10.1007/s10552-017-0905-z.

# Dietary Inflammatory Index and Non-Hodgkin Lymphoma risk in an Italian case-control study

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## Abstract

**Background—**While dietary factors have been shown to play an important etiologic role in non-Hodgkin lymphoma (NHL), little is known about the association between inflammatory properties of diet and NHL risk.

**Methods—**We explored the association between the dietary inflammatory index (DII) and NHL risk in a multicentric Italian case-control study conducted between 1999 and 2014. Cases were 536 subjects with incident, histologically confirmed NHL from 3 areas in Italy. Controls were 984 subjects admitted to the same network of hospitals as the cases for acute, non-malignant conditions, unrelated to diet. DII scores were computed based on 30 nutrients and food items assessed using a reproducible and validated 78-item food frequency questionnaire. Odds ratios (ORs) were estimated through logistic regression models adjusting for age, total energy intake and other recognised or likely confounding factors.

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**Disclosure:** Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

**Results—**Subjects in the highest quartile of DII scores (i.e., with the most pro-inflammatory diets) had a higher risk of NHL compared to subjects in the lowest quartile (i.e., with the most anti-inflammatory diets) ($OR_{Quartile4vs1}$= 1.61, 95% confidence interval, CI, 1.07, 2.43; *p*-trend=0.01). Stratified analyses produced stronger associations between DII and NHL among males ($OR_{Quartile4vs1}$= 2.14; 95%CI=1.25, 3.67) with significant heterogeneity (p-value=0.02); when analysed by histological subtype, a significant association was observed with diffuse large B-cell lymphoma ($OR_{Quartile4vs1}$= 1.84; 95%CI=1.09, 3.10).

**Conclusion—**A pro-inflammatory diet, as indicated by higher DII scores, is associated with elevated odds of NHL, especially among males.

### Keywords

diet; inflammatory index; NHL; risk factor

## INTRODUCTION

Non-Hodgkin lymphomas (NHLs) represent 3% of all new cancer cases worldwide and are the most frequent hematological malignancies (1). Among European countries, Italy shows one of the highest age-standardized incidence rates in both men and women (2). The etiology of NHL is poorly understood. Infections with HIV, hepatitis B (HBV) and C (HCV) viruses, Epstein-Barr virus (EBV), human herpes virus 8, and perhaps Helicobacter *pylori* are among the few established risk factors for specific NHL histological subtypes (3). There also is growing evidence indicating a possible role of diet in the development of NHL (4–6). Increased trans-fatty acid intake was associated with increased risk, whereas increased omega-3 fatty acid intake was associated with decreased NHL risk (4). Increased dietary intake of fruit and vegetables also has been associated with reduced NHL risk (5). There are several studies that have linked inflammation to NHL (7–9). An association between plasma levels of IL2, ICAM, IFN-gamma, and TNF-alpha with NHL risk was observed in a nested case-control study in Europe (9). Although a link has been established between diet and inflammation (10, 11), to date there has been no research on the role that inflammatory potential of diet plays in NHL risk.

The dietary inflammatory index (DII) is a literature-derived tool developed to assess the inflammatory potential of an individual's diet (10). The DII has been validated in a variety of longitudinal and cross-sectional studies using various inflammatory markers, including C-reactive protein (CRP) (10), interleukin-6 (IL-6) (12), and tumor necrosis factor (TNF)-α (13). The DII has been associated with risk of various chronic inflammatory conditions such as colorectal cancer (14–18) and cardiovascular diseases (19, 20). In Italy, the DII has been shown to be associated with various cancers ranging from those of the digestive tract (15, 21, 22) to hormone-sensitive cancers (23–26).

Using a multi-center case-control study conducted in Italy, this is the first attempt to examine the association between the DII and NHL risk. Our working hypothesis is that subjects with NHL are more likely to have consumed a pro-inflammatory diet compared to subjects without NHL.

# METHODS

## Design and Participants

The data in the present study were derived from two case-control studies on lymphomas, conducted with similar study protocols in the periods 1999–2002 and 2003–2014.

## First Study, 1999–2002

Between 1999 and 2002, we conducted a multi-cancer case-control study on the association between HBV/HCV infections and lymphomas and hepatocellular carcinoma (HCC) in the province of Pordenone, in northeastern Italy, and the city of Naples, in southern Italy. The study design and previous findings are described elsewhere (27). Briefly, the study included 231 cases with incident, histologically confirmed NHL aged 18–84 years (median age: 59 years). Controls were 547 inpatients aged 18–84 years (median age: 62 years) admitted for a wide spectrum of acute conditions to the same hospitals as cases. They were frequency-matched according to center (Pordenone, Naples), sex, and age (in 5-year age groups) based on the distribution of overall study cases, which also included Hodgkin lymphomas (HL and HCCs). As already reported (27), controls were younger and more likely to be male than NHL cases. Specifically excluded from the control group were patients admitted for malignant diseases, conditions related to alcohol and tobacco consumption or hepatitis viruses as well as any chronic hematologic, allergic, and autoimmune diseases or other diseases that might have changed lifestyle habits,. However, comorbidity for the above-listed diseases was not an exclusion criterion.

## Second Study, 2003–2014

Between 2003 and 2014, we extended the previous study, focusing only on NHL, and maintaining the same study design, inclusion and exclusion criteria, and questionnaire. Cases for the present analysis were 353 patients aged 18–84 years (median age: 56 years) with incident, histologically confirmed NHL. They were admitted to two National Cancer Institutes located in Aviano (“Centro di Riferimento Oncologico”) and in Naples (“Fondazione G. Pascale”), and to the general hospitals located in Catania. The control group included 537 patients aged 18–83 years (median age: 50 years), admitted for a wide spectrum of acute conditions to the same hospitals as lymphomas cases. Cases and controls were frequency matched by center (Pordenone, Naples, and Catania), gender, and age (in 5-year age groups) based on the distribution of both HL and NHL cases. In order to guarantee a sufficient statistical power, particularly with respect to NHL subtypes and different combinations of viral markers, the two studies were combined. Overall, a total of 584 NHL cases and 1084 controls participated in the present study. Thirteen cases were interviewed but could not give blood samples, leaving 571 NHL cases (median age: 56 years) with available questionnaires and blood samples. Histological diagnoses were centrally revised, and cases were classified according to the International Classification of Diseases for Oncology (third edition). Blood samples were available for 1004 controls (median age: 57 years) of whom, 20.4% were admitted to the hospital for trauma, 39.4% for non-traumatic orthopedic diseases, 20.9% for acute surgical conditions, 9.2% for eye diseases, and 10.1% for a variety of other illnesses. All NHL cases were tested for HIV as part of their routine management, and they were all HIV-negative. To the best of our knowledge, no control

subjects had a history of HIV infection or AIDS. After excluding participants with missing data on diet, the final study sample consisted of 536 cases and 984 controls (28). Each case and each control provided a 15 ml sample of blood the day that the interview took place. Sera were screened for antibodies against HCV using a third-generation chemiluminescent microparticle immunoassay (CMIA Architect anti-HCV assay, Abbott Diagnostic Division, Wiesbaden, Germany). Positive samples were tested for serum HCV RNA using the Abbott HCV RNA RealTime PCR (Abbott Diagnostic Division, Wiesbaden, Germany) with a limit of detection of 12 IU/mL.

All study participants signed an informed consent, according to the recommendations of the Board of Ethics of each study center, which had approved the study. Trained interviewers administered a structured questionnaire to cases and controls during their hospital stay. The questionnaire included information on socio-demographic indicators, tobacco smoking, alcohol drinking, dietary habits, behaviours, and exposures that entailed risk of HCV transmission. A validated food frequency-questionnaire (FFQ) was employed to assess the usual diet during the 2 years before diagnosis, or hospital admission for the controls. Briefly, the FFQ included 63 foods, food groups or recipes divided into seven sections: (i) milk, hot beverages and sweeteners; (ii) bread, cereals and first courses; (iii) second courses (e.g. meat and other main dishes); (iv) side dishes (i.e. vegetables); (v) fruits; (vi) sweets, desserts and soft drinks; (vii) alcoholic beverages. For vegetables and fruit subject to seasonal variation, consumption in season, and the corresponding duration, were elicited. Serving size was defined in ‘natural’ units (e.g. 1 teaspoon of sugar, 1 egg) or as an average in the Italian diet. Nutrient and total energy intake was determined using an Italian food composition database (29). The FFQ was successfully tested for validity (30) and reproducibility (31, 32).

In order to compute the DII score, dietary information for each study participant was first linked to the regionally representative database that provided a robust estimate of a mean and a standard deviation for each of the 45 items (i.e., foods, nutrients, and other food components) considered in the DII definition (10). These then were used to derive each subject’s exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter’s standard deviation. The purpose of deriving z-scores was to alleviate problems with using actual units of measurements as multipliers, as doing so in the original DII formulation resulted in over- or under-weighting of variables in an effort to place them into an arbitrary “reasonable” range. For example, $\mu$g and mg differ by three orders of magnitude and some parameters, such as vitamin A and β-carotene, had to be divided by 100 and others, such as *n*-3 and *n*-6 fatty acids, multiplied by 10 in order to place them in a ‘reasonable’ range so as not to over- or underestimate their influence on the overall score. The use of z-scores solved this problem entirely by eliminating problems with right-skewing of the data. By converting z-scores to percentiles, and then centering them fixes “null” values to zero, arbitrary weighting is avoided. The resulting value was then multiplied by the corresponding food parameter effect score (derived from a literature review on the basis of 1943 articles (10). All of these food-specific DII scores were then summed to create the overall DII score for every subject in the study. Higher scores indicate a pro-inflammatory diet while lower scores indicate a more anti-inflammatory diet. The DII computed on this study’s FFQ includes data on 30 of the 45 possible food parameters

comprising the DII: carbohydrates, proteins, fats, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, niacin, thiamin, riboflavin, vitamin B6, iron, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, anthocyanidins, flavan3ols, flavonols, flavanones, flavones, isoflavones, caffeine, and tea. Because we adjusted for energy and alcohol in the analyses, we did not use them for DII calculation. The remaining 13 missing food parameters are pepper, saffron, turmeric, garlic, ginger, onion, eugenol, trans fat, selenium, magnesium, vitamin B12, thyme and rosemary.

### Statistical analysis

The DII was analysed both as a continuous variable and by quartiles of exposure computed among controls. Distributions of characteristics across quartiles of DII for controls were computed and differences were analyzed using the chi-square test. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression models adjusted for quinquennia of age, sex, total energy intake (quintiles among both cases and controls), years of education, (<7, 7–11, >11 years), place of birth (North-Center and South), seropositivity for HCV, smoking (Never, Former, Current <15 cigs/day, Current ≥15 cigs/day), alcohol consumption (Never, Former, Current <8 drk/week, Current ≥8 drk/week). Tests of linear trend between DII and NHL risk adjusted for covariates were computed by assigning the median value of each quartile to each participant in the quartile, and this variable was entered into models as ordinal values. To investigate whether the effect of the DII was homogeneous across strata of selected covariates, we carried out stratified analyses according to sex, age (<60, ≥ 60 years) and smoking (Never, former/current). To test heterogeneity across strata, we computed the difference in the −2 log likelihood of the models with and without the interaction terms. Analyses were also carried out by histological type. Statistical analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC).

## RESULTS

The distribution of NHL cases and controls according to selected factors is given in Table 1. Cases and controls had a similar distribution by study centre, sex, and education. Cases were younger, more likely to be female, born in South Italy, heavy smokers, non-drinkers and HCV RNA+ than controls. All of these factors were adjusted in subsequent analyses.

Characteristics of control subjects across quartiles of DII are provided in Table 2. Compared to controls in the lowest quartile of DII, those in the highest quartile was more likely to be younger, female, reside in Aviano and Catania, currently smoke, and never drink. Table 3 shows adjusted ORs of NHL according to the DII quartiles and continuous DII. Subjects in the highest quartile of DII had a 61% excess risk of NHL compared to subjects in the lowest quartile ($OR_{Quartile4vs1}$= 1.61, 95% CI, 1.07, 2.43; *p*-trend=0.01). Also, when analyses were carried out using continuous DII, a significant positive association with NHL was observed; the OR corresponding to a one-unit increment in the DII score was 1.14 (95% CI=1.02, 1.27). Table 4 shows multivariable ORs of NHL according to the DII quartiles in strata of selected covariates. No heterogeneity in risks emerged across strata of age, and smoking

status. A modifying effect of sex was observed: the NHL risk was significantly elevated only among males ($OR_{Quartile4vs1}$= 2.14; 95%CI=1.25, 3.67; *p*-heterogeneity =0.02). When analysed by histological subtypes, significant association was observed with Diffuse large B-cell lymphoma (DLBCL) (ORQuartile4vs1= 1.84; 95%CI=1.09, 3.10). Sensitivity analyses carried out by additionally adjusting for BMI did not materially change any of the results (data not shown).

## DISCUSSION

In this case-control study, we observed a positive association between inflammatory potential of diet as measured by increasing DII scores and NHL with stronger association observed among males. This is the first study to examine the association between the DII and NHL. Results from the first case-control study (1999–2002) analyses showed significant trends of increasing risk for pasta and cheese; whereas inverse associations for high consumption of vegetables, fruits and eggs (33). When nutrients were analyzed previously in the same case-control study, lower risk of NHL was observed for diets rich in polyunsaturated fatty acids and vitamin D (34). Interestingly, an inverse association of folate, vitamin B2, vitamin B6 and methionine with NHL risk emerged among never/former drinkers alone (35). Several of these anti-inflammatory components that are involved in DII calculation include vitamin D, linoleic acid and components of fruits and vegetables like flavonoids. By contrast, carbohydrate and saturated fat contribute to the pro-inflammatory of diet and therefore increase DII scores (10).

Results from other studies exploring dietary components that contribute to the DII score and NHL have been inconsistent. In a case-control study conducted in the USA, dietary intake of α-tocopherol, β-carotene, zinc was inversely associated with NHL risk (36). In another case-control study conducted in Nebraska, USA; a higher intake of green leafy vegetables and cruciferous vegetables was associated with a lower risk of NHL overall, particularly follicular lymphoma and DLBCL (5). Diets high in trans-fatty acids, processed meats, and higher fat dairy products were positively associated with NHL risk; whereas diets high in n3 fatty acids and total seafood were inversely associated with risk (4). In a meta-analyses conducted from 9 studies (8 case-control and 1 cohort), it was reported that higher vitamin D status does not play a protective role in risk of NHL or common NHL subtypes (6). Several studies have also shown diet to be associated with inflammation(11, 12).

Despite the somewhat equivocal evidence on specific dietary components, there is strong evidence suggesting the role of inflammation in the development of NHL (9, 37). In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, elevated levels of IL-10, TNF-α and sTNF-R2 were associated with increased risk of NHL overall (37). Results from a case-control study nested within the Italian subset of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, suggested a possible association between plasma levels of I-2, ICAM, IFN-γ, and TNF-α and NHL risk (9). In another study, NHL was associated with selected inflammatory cytokines such as TNF–α, IL-5 and sTNF-R2 (7). Those results support our hypothesis that inflammation is associated with NHL and that diet plays a role in this association. In relation to inflammatory markers, the DII has been shown to be associated with CRP (10), IL-6 (13), TNF-α (13) and homocysteine (12).

A possible mechanism could be through up-regulation of pro-inflammatory and anti-apoptotic signals, via the nuclear transcription factor (NF)-κB pathway, thereby promoting lymphomagenesis (8).

A potential limitation of the present study is the use of hospital controls, which may differ from the general population in relation to their dietary habits. However, in the comparison group, we included subjects admitted for a wide spectrum of acute, non-neoplastic, non-immunological diseases, unrelated to chronic conditions (e.g., diabetes mellitus, cardiovascular diseases, etc.), which could have modified dietary habits. As in most case-control studies, potential information bias due to disease-differential recall is a possibility (e.g., cases may recall their diet differently than healthy controls; for example, overestimating the consumption of foods considered unhealthy in an attempt to explain the cause of their disease). The comparability of recall between cases and controls was improved by interviewing all subjects in a hospital setting. Repetition of interviews in out of hospital setting for a sub-sample of controls confirmed the reproducibility of diet information (38). With reference to other potential source of recall bias in the present study, awareness of any particular dietary hypothesis in NHL etiology was very limited in the Italian public at the time that this investigation was undertaken (33–35). Moreover, the dietary questionnaire was tested for reproducibility (31, 32) and validity (30), giving satisfactory results. The almost complete participation of both cases and controls (97% of cases, 95% of controls) in this large study indicates that selection bias is unlikely to be a major concern. A limitation of the study may be the use of a FFQ that, with respect to the DII, did not include 14 food factors for complete calculation. However, some missing food parameters such as saffron, ginger and turmeric are consumed infrequently in this population; so, non-availability of these parameters may not have had a major impact. However, food items such as rosemary, thyme, garlic, magnesium, selenium are more likely to be consumed in higher quantities; so, inclusion of these food parameters could have influenced our results. Further to this issue of non-availability, we have found little drop off in predictability in other studies, such as the SEASONS Study (10), in which we compared multiple (up to 15) 24-hour recall interviews to five 7-Day Dietary Recalls (7DDR) and the Women's Health Initiative (13), which compared multiple 24-hour recall interviews to an FFQ. In the SEASONS study, DII scores were calculated from 44 food parameters using the 24-hour recalls and from 27 food parameters using 7DDR. With CRP (>3 mg/l) as the outcome, we did not observe any drop off in the effect of the DII in the 7DDR subset (10). Similarly, robust results based on a limited list of food parameters available for computing the DII were observed with the WHI FFQ (13). Despite the relatively large sample size of the current study, there still was limited power to detect associations for specific NHL subtypes. Non availability of data on other important risk factors such as physical activity(39) could be another potential limitation.

In conclusion, our study suggests that subjects with NHL were more likely to have a pro-inflammatory diet, as shown by higher DII scores. However, this finding requires replication in other studies, including prospective cohorts.

## Acknowledgments

**Funding:** This study was supported by the Italian Association for the Research on Cancer (AIRC; Grant #10447) and the Italian Foundation for Research on Cancer (FIRC). Drs. Shivappa and Hébert were supported by grant number R44DK103377 from the United States National Institute of Diabetes and Digestive and Kidney Diseases.

## References

1. Ferlay, JSI., Ervik, M., Dikshit, R., Eser, S., Mathers, C., et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No 11. Lyon, France: 2013.
2. Ferlay, JBF., Steliarova-Foucher, E., Forman, D. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No 9. Lyon, France: 2014.
3. Non-Hodgkin Lymphoma. Atlanta: American Cancer Society; 2016. http://www.cancer.org/cancer/non-hodgkinlymphoma/detailedguide/non-hodgkin-lymphoma-risk-factors
4. Charbonneau B, O'Connor HM, Wang AH, Liebow M, Thompson CA, Fredericksen ZS, et al. Trans fatty acid intake is associated with increased risk and n3 fatty acid intake with reduced risk of non-hodgkin lymphoma. The Journal of nutrition. 2013 May; 143(5):672–81. [PubMed: 23486982]
5. Chiu BC, Kwon S, Evens AM, Surawicz T, Smith SM, Weisenburger DD. Dietary intake of fruit and vegetables and risk of non-Hodgkin lymphoma. Cancer causes & control: CCC. 2011 Aug; 22(8): 1183–95. [PubMed: 21695384]
6. Lu D, Chen J, Jin J. Vitamin D status and risk of non-Hodgkin lymphoma: a meta-analysis. Cancer causes & control: CCC. 2014 Nov; 25(11):1553–63. [PubMed: 25148916]
7. Gu Y, Shore RE, Arslan AA, Koenig KL, Liu M, Ibrahim S, et al. Circulating cytokines and risk of B-cell non-Hodgkin lymphoma: a prospective study. Cancer causes & control: CCC. 2010 Aug; 21(8):1323–33. [PubMed: 20373009]
8. Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. The Lancet Oncology. 2006 Jan; 7(1):27–38. [PubMed: 16389181]
9. Saberi Hosnijeh F, Krop EJ, Scoccianti C, Krogh V, Palli D, Panico S, et al. Plasma cytokines and future risk of non-Hodgkin lymphoma (NHL): a case-control study nested in the Italian European Prospective Investigation into Cancer and Nutrition. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010 Jun; 19(6):1577–84.
10. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public health nutrition. 2014 Aug; 17(8): 1689–96. [PubMed: 23941862]
11. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public health nutrition. 2014 Aug; 17(8):1825–33. [PubMed: 24107546]
12. Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. The British journal of nutrition. 2015 Feb; 113(4):665–71. [PubMed: 25639781]
13. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, et al. Construct validation of the dietary inflammatory index among postmenopausal women. Annals of epidemiology. 2015 Jun; 25(6): 398–405. [PubMed: 25900255]
14. Zamora-Ros R, Shivappa N, Steck SE, Canzian F, Landi S, Alonso MH, et al. Dietary inflammatory index and inflammatory gene interactions in relation to colorectal cancer risk in the Bellvitge colorectal cancer case-control study. Genes & nutrition. 2015 Jan.10(1):447. [PubMed: 25488145]
15. Shivappa N, Zucchetto A, Montella M, Serraino D, Steck SE, La Vecchia C, et al. Inflammatory potential of diet and risk of colorectal cancer: a case-control study from Italy. The British journal of nutrition. 2015 Jul 14; 114(1):152–8. [PubMed: 26050563]

16. Tabung FK, Steck SE, Ma Y, Liese AD, Zhang J, Caan B, et al. The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. Cancer causes & control: CCC. 2015 Mar; 26(3):399–408. [PubMed: 25549833]
17. Wirth MD, Shivappa N, Steck SE, Hurley TG, Hebert JR. The dietary inflammatory index is associated with colorectal cancer in the National Institutes of Health-American Association of Retired Persons Diet and Health Study. The British journal of nutrition. 2015 Jun 14; 113(11): 1819–27. [PubMed: 25871645]
18. Shivappa N, Prizment AE, Blair CK, Jacobs DR Jr, Steck SE, Hebert JR. Dietary inflammatory index and risk of colorectal cancer in the Iowa Women's Health Study. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2014 Nov; 23(11):2383–92.
19. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, Salas-Salvado J, Corella D, Shivappa N, et al. Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the PREDIMED Study. Nutrients. 2015 Jun; 7(6):4124–38. [PubMed: 26035241]
20. Ramallal R, Toledo E, Martinez-Gonzalez MA, Hernandez-Hernandez A, Garcia-Arellano A, Shivappa N, et al. Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the SUN Cohort. PloS one. 2015; 10(9):e0135221. [PubMed: 26340022]
21. Shivappa N, Hebert JR, Polesel J, Zucchetto A, Crispo A, Montella M, et al. Inflammatory potential of diet and risk for hepatocellular cancer in a case-control study from Italy. The British journal of nutrition. 2015 Nov.11:1–8.
22. Shivappa N, Zucchetto A, Serraino D, Rossi M, La Vecchia C, Hebert JR. Dietary inflammatory index and risk of esophageal squamous cell cancer in a case-control study from Italy. Cancer causes & control: CCC. 2015 Oct; 26(10):1439–47. [PubMed: 26208592]
23. Shivappa N, Hébert JR, Zucchetto A, Montella M, Serraino D, La Vecchia C, et al. Dietary inflammatory index and endometrial cancer risk in an Italian case–control study. British Journal of Nutrition. 2015 FirstView: 1–9.
24. Shivappa N, Bosetti C, Zucchetto A, Montella M, Serraino D, La Vecchia C, et al. Association between dietary inflammatory index and prostate cancer among Italian men. The British journal of nutrition. 2015 Jan 28; 113(2):278–83. [PubMed: 25400225]
25. Shivappa N, Hébert JR, Rosato V, Montella M, Serraino D, La Vecchia C. Association between the dietary inflammatory index and breast cancer in a large Italian case-control study. Molecular nutrition & food research. 2016:n/a–n/a.
26. Shivappa N, Hebert JR, Rosato V, Rossi M, Montella M, Serraino D, et al. Dietary inflammatory index and ovarian cancer risk in a large Italian case-control study. Cancer causes & control: CCC. 2016 Jul; 27(7):897–906. [PubMed: 27262447]
27. Talamini R, Montella M, Crovatto M, Dal Maso L, Crispo A, Negri E, et al. Non-Hodgkin's lymphoma and hepatitis C virus: a case-control study from northern and southern Italy. International journal of cancer Journal international du cancer. 2004 Jun 20; 110(3):380–5. [PubMed: 15095303]
28. Taborelli M, Polesel J, Montella M, Libra M, Tedeschi R, Battiston M, et al. Hepatitis B and C viruses and risk of non-Hodgkin lymphoma: a case-control study in Italy. Infectious agents and cancer. 2016; 11:27. [PubMed: 27340429]
29. Gnagnarella P, Parpinel M, Salvini S, Franceschi S, Palli D, Boyle P. The update of the Italian Food Composition Database. Journal of Food Composition and Analysis. 2004; 17(3–4):509–22. 6//.
30. Decarli A, Franceschi S, Ferraroni M, Gnagnarella P, Parpinel MT, La Vecchia C, et al. Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. Annals of epidemiology. 1996 Mar; 6(2):110–8. [PubMed: 8775590]
31. Franceschi S, Negri E, Salvini S, Decarli A, Ferraroni M, Filiberti R, et al. Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. European journal of cancer. 1993; 29A(16):2298–305. [PubMed: 8110502]
32. Franceschi S, Barbone F, Negri E, Decarli A, Ferraroni M, Filiberti R, et al. Reproducibility of an Italian food frequency questionnaire for cancer studies. Results for specific nutrients. Annals of epidemiology. 1995 Jan; 5(1):69–75. [PubMed: 7728288]

33. Talamini R, Polesel J, Montella M, Dal Maso L, Crovatto M, Crispo A, et al. Food groups and risk of non-Hodgkin lymphoma: a multicenter, case-control study in Italy. International journal of cancer Journal international du cancer. 2006 Jun 1; 118(11):2871–6. [PubMed: 16385566]

34. Polesel J, Talamini R, Montella M, Parpinel M, Dal Maso L, Crispo A, et al. Linoleic acid, vitamin D and other nutrient intakes in the risk of non-Hodgkin lymphoma: an Italian case-control study. Annals of oncology: official journal of the European Society for Medical Oncology/ESMO. 2006 Apr; 17(4):713–8.

35. Polesel J, Dal Maso L, La Vecchia C, Montella M, Spina M, Crispo A, et al. Dietary folate, alcohol consumption, and risk of non-Hodgkin lymphoma. Nutrition and cancer. 2007; 57(2):146–50. [PubMed: 17571947]

36. Holtan SG, O'Connor HM, Fredericksen ZS, Liebow M, Thompson CA, Macon WR, et al. Food-frequency questionnaire-based estimates of total antioxidant capacity and risk of non-Hodgkin lymphoma. International journal of cancer Journal international du cancer. 2012 Sep 1; 131(5): 1158–68. [PubMed: 22038870]

37. Purdue MP, Lan Q, Bagni R, Hocking WG, Baris D, Reding DJ, et al. Prediagnostic serum levels of cytokines and other immune markers and risk of non-hodgkin lymphoma. Cancer research. 2011 Jul 15; 71(14):4898–907. [PubMed: 21632552]

38. B DA, La Vecchia C, Katsouyanni K, Negri E, Trichopoulos D. Reliability of information on cigarette smoking and beverage consumption provided by hospital controls. Epidemiology. 1996 May; 7(3):312–5. [PubMed: 8728449]

39. Boyle T, Gallagher RP, Gascoyne RD, Connors JM, Le ND, Spinelli JJ. Lifetime physical activity and the risk of non-Hodgkin lymphoma. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2015 May; 24(5):873–7.

## Table 1

Distribution cases of Non Hodgkin Lymphoma (NHL) and controls according to selected covariates. Italy, 1999–2014.

| Characteristics | Cases (536) | Controls (984) | *p* value[a] |
|---|---|---|---|
| | N (%) | N (%) | |
| Age (years) | | | 0.006 |
| <45 | 133 (24.8) | 303 (30.8) | |
| 45–54 | 106 (19.8) | 149 (15.1) | |
| 55–64 | 138 (25.7) | 211 (21.4) | |
| ≥65 | 159 (29.7) | 321 (32.6) | |
| Sex | | | 0.02 |
| Male | 299 (55.8) | 611 (62.1) | |
| Female | 237 (44.2) | 373 (37.9) | |
| Center | | | 0.02 |
| Aviano | 240 (44.8) | 507 (51.5) | |
| Napoli | 212 (39.5) | 359 (36.5) | |
| Catania | 84 (15.7) | 118 (12.0) | |
| Place of birth[b] | | | <0.01 |
| North Central | 195 (36.4) | 467 (47.5) | |
| South | 340 (63.4) | 515 (52.3) | |
| Education (years) | | | 0.27 |
| <7 | 175 (32.7) | 355 (36.1) | |
| 7–11 | 177 (33.0) | 297 (30.2) | |
| ≥12 | 183 (34.1) | 332 (33.7) | |
| Smoking[b] | | | 0.05 |
| Never | 225 (42.0) | 414 (42.1) | |
| Former | 136 (25.4) | 292 (29.7) | |
| Current <15 cigs/day | 72 (13.4) | 139 (14.1) | |
| Current ≥15 cigs/day | 103 (19.2) | 137 (13.9) | |
| Drinking[b] | | | 0.001 |
| Never | 168 (31.3) | 236 (24.0) | |
| Former | 47 (8.8) | 62 (6.3) | |
| Current <8drinks/wk | 143 (26.7) | 272 (41.4) | |
| Current ≥ 8drinks/wk | 177 (33.0) | 407 (41.4) | |
| HCV test[b] | | | <0.001 |
| AntiHCV- or HCV RNA- | 477 (89.0) | 948 (96.3) | |
| HCV RNA+ | 57 (10.6) | 34 (3.5) | |

[a] *p* value for Chi-square test.

[b] The sum does not add up to the total because of some missing values.

**Table 2**

Distribution of 984 controls across quartiles of dietary inflammatory index (DII). Italy, 1999–2014.

| Characteristics | DII quartiles | | | | |
|---|---|---|---|---|---|
| | < −1.36 | −1.36, −0.39 | −0.38,0.72 | >0.72 | *p* value[a] |
| | N (%) | N (%) | N (%) | N (%) | |
| Age (years) | | | | | 0.02 |
| <45 | 60 (24.4) | 73 (29.7) | 83 (33.7) | 87 (35.4) | |
| 45–54 | 33 (13.4) | 35 (14.2) | 41 (16.7) | 40 (16.3) | |
| 55–64 | 65 (26.4) | 52 (21.1) | 53 (21.5) | 41 (16.7) | |
| ≥65 | 88 (35.8) | 86 (35.0) | 69 (28.1) | 78 (31.7) | |
| Sex | | | | | <0.01 |
| Male | 186 (75.6) | 148 (60.2) | 151 (61.4) | 126 (51.2) | |
| Female | 60 (24.4) | 98 (39.8) | 95 (38.6) | 120 (48.8) | |
| Center | | | | | <0.01 |
| Aviano | 126 (51.2) | 107 (43.5) | 130 (52.8) | 144 (58.5) | |
| Napoli | 102 (41.5) | 109 (44.3) | 79 (32.1) | 69 (28.1) | |
| Catania | 18 (7.3) | 30 (12.2) | 37 (15.1) | 33 (13.4) | |
| Place of birth[b] | | | | | 0.03 |
| North Central | 116 (47.3) | 97 (39.4) | 119 (48.4) | 135 (55.1) | |
| South | 129 (52.7) | 149 (60.6) | 127 (51.6) | 110 (44.9) | |
| Education (years) | | | | | 0.36 |
| <7 | 96 (39.0) | 92 (37.4) | 76 (30.9) | 91 (37.0) | |
| 7–11 | 73 (29.7) | 66 (26.8) | 87 (35.4) | 71 (28.9) | |
| ≥12 | 77 (31.3) | 88 (35.8) | 83 (33.7) | 84 (34.1) | |
| Smoking[b] | | | | | <0.01 |
| Never | 100 (41.0) | 96 (39.0) | 91 (37.0) | 127 (51.6) | |
| Former | 87 (35.7) | 86 (35.0) | 68 (27.6) | 51 (20.7) | |
| Current <15 cigs/day | 23 (9.4) | 38 (15.4) | 43 (17.5) | 35 (14.2) | |
| Current ≥15 cigs/day | 34 (13.9) | 26 (10.6) | 44 (17.9) | 33 (13.4) | |

| Characteristics | DII quartiles | | | | |
|---|---|---|---|---|---|
| | < −1.36 | −1.36, −0.39 | −0.38,0.72 | >0.72 | *p* value[a] |
| | N (%) | N (%) | N (%) | N (%) | |
| Drinking[b] | | | | | <0.01 |
| Never | 32 (13.1) | 60 (24.7) | 67 (27.2) | 77 (31.6) | |
| Former | 12 (4.9) | 16 (6.6) | 11 (4.5) | 23 (9.4) | |
| Current <8drinks/wk | 55 (22.5) | 73 (30.0) | 67 (27.2) | 77 (31.6) | |
| Current ≥ 8drinks/wk | 145 (59.4) | 94 (38.7) | 101 (41.1) | 67 (27.5) | |
| HCV test[b] | | | | | 0.85 |
| AntiHCV- or HCV RNA- | 239 (97.2) | 238 (96.7) | 235 (95.9) | 236 (96.3) | |
| HCV RNA+ | 7 (2.8) | 8 (3.3) | 10 (4.1) | 9 (3.7) | |

[a] *p* value for Chi-square test.

[b] The sum does not add up to the total because of some missing values.

**Table 3**

Odds ratios (ORs) of Non-Hodgkin Lymphoma and corresponding 95% confidence intervals (CIs) according to dietary inflammatory index (DII) among 536 cases and 984 controls. Italy, 1999–2014.

| | DII quartiles, OR (95% CI) | | | | *p* value for trend[a] | DII continuous[b] |
|---|---|---|---|---|---|---|
| | **< −1.36** | **−1.36, −0.39** | **−0.38,0.72** | **>0.72** | | |
| Cases/Controls | 140/246 | 106/246 | 133/246 | 157/246 | | 536/984 |
| Model 1[d] | 1 [c] | 0.88 (0.63, 1.24) | 1.24 (0.87, 1.76) | 1.74 (1.17, 2.61) | 0.002 | 1.17 (1.05, 1.31) |
| Model 2[e] | 1 [c] | 0.86 (0.61, 1.21) | 1.17 (0.82, 1.68) | 1.61 (1.07, 2.43) | 0.007 | 1.14 (1.02, 1,27) |

[a] Test for linear trend was carried out using the median approach by assigning the median value of each quartile to each participant in the quartile, and this variable was entered into models as ordinal values.

[b] One-unit increase equals 13% increase of DII in the current study (+3.62 to −4.32).

[c] Reference category.

[d] Adjusted for quinquennia of age, sex, center, years of education, (<7, 7–11, >11 years), place of birth (North-Center and South), and energy intake.

[e] Adjusted as in Model 1 and additionally adjusted for seropositivity for HCV, smoking (Never, Former, Current <15 cigs/day. Current ≥ 15 cigs/day) and alcohol consumption (Never, Former, Current <8 drk/week, Current ≥8 drk/week).

**Table 4**

Odds ratios (ORs) of Non-Hodgkin Lymphoma and corresponding 95% confidence intervals (CIs) according to dietary inflammatory index (DII) by selected strata, among 536 cases and 984 controls. Italy, 1999–2014.

| | Cases/Controls | DII quartiles, OR (95% CI)[a] | | | | *p* value for trend[b] | DII continuous[c] | *p* value for heterogeneity |
|---|---|---|---|---|---|---|---|---|
| | | < −1.36 | −1.36, −0.39 | −0.38,0.72 | >0.72 | | | |
| Sex | | | | | | | | 0.02 |
| Males | 299/611 | 1 [d] | 1.09 (0.71, 1.68) | 1.12 (0.70, 1.77) | 2.14 (1.25, 3.67) | 0.007 | 1.24 (1.08, 1.44) | |
| Females | 237/373 | 1 [d] | 0.58 (0.32, 1.02) | 1.24 (0.68, 2.25) | 1.22 (0.62, 2.39) | 0.20 | 1.04 (0.87, 1.24) | |
| Age (years) | | | | | | | | 0.17 |
| <60 | 317/552 | 1 [d] | 0.78 (0.50, 1.22) | 0.75 (0.47, 1.20) | 1.06 (0.63, 1.78) | 0.63 | 1.01 (0.88, 1.11) | |
| ≥60 | 219/432 | 1 [d] | 0.93 (0.55, 1.58) | 1.90 (1.08, 3.34) | 2.60 (1.30, 5.21) | <0.01 | 1.34 (1.11, 1.61) | |
| Smoking | | | | | | | | 0.14 |
| Never | 225/414 | 1 [d] | 1.16 (0.67, 2.00) | 1.89 (1.05, 3.41) | 1.64 (0.84, 3.20) | 0.12 | 1.07 (0.89, 1.27) | |
| Former/Current | 311/568 | 1 [d] | 0.69 (0.44, 1.08) | 0.86 (0.54, 1.36) | 1.78 (1.04, 3.03) | <0.01 | 1.23 (1.06, 1.42) | |
| Histological subtype | | | | | | | | |
| Follicular | 98/984 | 1 [d] | 0.49 (0.25, 0.97) | 0.61 (0.31, 1.18) | 0.69 (0.32, 1.49) | 0.80 | 0.96 (0.78, 1.18) | |
| DLBCL | 272/984 | 1 [d] | 0.82 (0.52, 1.28) | 1.52 (0.97, 2.39) | 1.84 (1.09, 3.10) | <0.01 | 1.19 (1.04, 1.37) | |
| Other | 149/984 | 1 [d] | 1.19 (0.69, 2.06) | 0.80 (0.43, 1.51) | 1.87 (0.96, 3.67) | 0.62 | 1.11 (0.93, 1.33) | |

DLBCL, Diffuse large B-cell lymphoma.

[a] Adjusted for quinquennia of age, sex, energy intake, center, years of education, (<7, 7–11, >11 years), place of birth (North-Center and South), seropositivity for HCV, alcohol consumption (Never, Former, Current <8 drk/week, Current ≥8 drk/week), when appropriate.

[b] Test for linear trend was carried out using the median approach by assigning the median value of each quartile to each participant in the quartile, and this variable was entered into models as ordinal values.

[c] One unit increase equals 13% increase of DII in the current study (+3.62 to −4.32).

[d] Reference category.