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ORIGINAL PAPER

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 multicenter Italian case–control study conducted between 1999 and 2014. Cases were 536 subjects with incident, histologically confirmed NHL from three areas in Italy. Controls were 984 subjects admitted to the same network of hospitals as the cases for acute, nonmalignant 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 recognized confounding factors.

Results Subjects in the highest quartile of DII scores (i.e., with the most pro-inflammatory diets) had a higher risk of NHL compared with 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 analyzed by histologic 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

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Introduction

Non-Hodgkin lymphomas (NHLs) represent 3% of all new cancer cases worldwide and are the most frequent hematologic 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 *Helicobacter pylori* are among the few established risk factors for specific NHL histologic subtypes (IARC 2009). There is growing evidence indicating a possible role of diet in the development of NHL [3–5]. Increased trans-fatty acid has been associated with increased risk whereas increased omega-3 was associated

with decreased risk of NHL [3]. In a case–control study, increased dietary intake of fruit and vegetables was associated with reduced risk of non-Hodgkin lymphoma [4]. There are several studies that have linked inflammation to NHL [6–8]—a possible 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 [8], and there are studies that examined the association between diet and inflammation [9, 10]. However, 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 that was developed to assess the inflammatory potential of an individual's diet [9]. The DII has been validated in a variety of longitudinal and cross-sectional studies using various inflammatory markers, including C-reactive protein (CRP) [9], interleukin-6 (IL-6) [11], and tumor necrosis factor (TNF)-α [12]. The DII has been associated with risk of various chronic inflammatory conditions such as colorectal cancer [13–17] and cardiovascular diseases [18, 19]. In Italy, the DII has been shown to be associated with various cancers ranging from digestive those of the tract [14, 20, 21] to hormone-sensitive cancers [22]. Using a multicenter 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 with subjects with no NHL.

Methods

Design and participants

The data in the present study were derived from two consecutive 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 multicenter case–control study on the association between HBV/HCV infections and lymphomas and hepatocellular carcinoma (HCC) in the province of Pordenone, northeastern Italy, and the cities of Naples and Catania, southern Italy. The study design and findings are described elsewhere [23]. In brief, 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). Consequently, as already reported [23], controls were younger and more likely to be male than were NHL cases. Specifically excluded from the control group were patients admitted for malignant diseases, conditions related to risk factors for NHL such as alcohol and tobacco consumption, or hepatitis viruses as well as any chronic diseases that might have changed lifestyle habits, hematologic, allergic, and autoimmune diseases. However, a previous history of comorbidity for the above-listed diseases was not an exclusion criterion. We also included controls who were admitted for other diseases, but had been treated for them.

Second study, 2003–2014

Between 2003 and 2014, we extended the previous study, focusing only on lymphomas, 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), sex, 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 in respect of 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 questionnaire-derived data and blood samples. Histologic 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 nontraumatic orthopoedic 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 [24]. Each case and each control provided a 15-ml sample of blood the day 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 sociodemographic indicators, tobacco smoking, alcohol drinking, dietary habits, other health-related behaviors, 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. In brief, 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; and (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., one teaspoon of sugar, one egg) or as an average in the Italian diet. Nutrient and total energy intake was determined using an Italian food composition database [25]. The FFQ was successfully tested for validity [26] and reproducibility [27, 28]. Supplements are rarely used in Italy [29], and hence questions on supplements were not asked about their intake.

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 parameters (i.e., foods, nutrients, and other food components) considered in the DII definition [9]. These parameters then were used to derive the 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 faced while using actual units of measurements as multipliers, as doing so in the original DII formulation resulted in over- or under-weighting of parameters in an effort to place them into an arbitrary "reasonable" range. For example, μg 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. Clinical interpretation remains clear with these additional steps as inappropriate weighting is avoided and higher (i.e., more positive) DII scores still represent more pro-inflammatory diets. The resulting value was then multiplied by the corresponding food parameter effect score (derived from a literature review on the basis of 1943 articles [9]. All of these food parameter-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 analyzed 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 χ^2 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), and 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 histologic subtype. 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 were younger, more likely female, born in the South of Italy, be heavy smokers, nondrinker, and HCV RNA+ than controls.

Characteristics of control subjects across quartiles of DII are provided in Table 2. Compared with controls in the lowest quartile of DII, those in the highest one were 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 with 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, with the OR for one-unit increment in the DII score being 1.14 (95% CI 1.02–1.27). Table 3 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. Table 4 shows results stratified by certain study characteristics and histology type. 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 analyzed by histologic subtypes, significant association was observed with diffuse large B-cell lymphoma (DLBCL) ($OR_{Quartile4vs1}$ 1.84; 95% CI 1.09–3.10).

Discussion

In this case–control study, we observed a significant positive association between inflammatory potential of diet as measured by increasing DII scores and NHL, with a stronger association observed among males. This is the first study to examine 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 [30]. When nutrients were analyzed previously in the same case–control study, lower risk of NHL for diet rich in polyunsaturated fatty acids and vitamin D—but for other macro- or micronutrients—were reported [31]. Interestingly, an inverse association of folate, vitamin B2, vitamin B6 and methionine with NHL risk emerged among never/former drinkers alone [32]. Several of these anti-inflammatory components that are involved in DII calculation include vitamin D, linoleic acid and components of fruits and vegetables such as flavonoids. By contrast, carbohydrate and saturated fatty intake contribute to the pro-inflammatory of diet and therefore increase DII scores [9].

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 [33]. In another case–control study conducted in Nebraska, USA; a higher intake of green leafy vegetables and cruciferous vegetables is associated with a lower risk of NHL overall, particularly follicular lymphoma and DLBCL [4]. 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 [3]. In a recent meta-analyses conducted from nine studies (eight case–control and one cohort), it was reported that higher vitamin D status does not play a protective role in risk of NHL or common NHL subtypes [5]. Several studies have also shown diet to be associated with inflammation [10, 11].

Despite the somewhat equivocal evidence on specific dietary components, there is strong evidence suggesting the role of inflammation in the incidence of NHL [8, 34]. In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, elevated levels of IL-10, TNF-α and sTNF-R2 were significantly associated with increased risk of NHL overall [34]. 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 [8]. In another study, NHL was associated with selected inflammatory cytokines such as TNF-α, IL-5 and sTNF-R2 [6]. These previous results support our hypotheses 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 [9], IL-6 [12], TNF-α [12] and homocysteine [11]. The exact mechanism for this association is not known and is yet to be investigated. A possible mechanism could be through up-regulation of pro-inflammatory and anti-apoptotic signals, via the nuclear

Table 1 Distribution of cases of non-Hodgkin lymphoma (NHL) and controls according to selected covariates

Characteristics	Cases (536) *n* (%)	Controls (984) *n* (%)	*p* Value[a]
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/week	143 (26.7)	272 (41.4)	
Current ≥ 8drinks/week	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)	

Italy 1999–2014

[a] *p* Value for χ^2 test

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

transcription factor (NF)-κB pathway thereby promoting lymphomagenesis [7].

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, nonimmunologic 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, 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 probably was improved by interviewing all subjects in a hospital setting. 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. Moreover, the dietary questionnaire was tested for reproducibility [27, 28] and validity [26], giving satisfactory results. The almost complete participation of both cases and controls in this large study

Table 2 Distribution of 984 controls across quartiles of dietary inflammatory index (DII)

Characteristics	DII quartiles				p Value[a]
	<−1.36 *n* (%)	−1.36, −0.39 *n* (%)	−0.38, 0.72 *n* (%)	>0.72 *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)	
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/week	55 (22.5)	73 (30.0)	67 (27.2)	77 (31.6)	
Current ≥ 8drinks/week	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)	

Italy 1999–2014

[a] p value for χ^2 test

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

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 food parameters such as saffron, ginger and turmeric are consumed infrequently in this population; so, nonavailability of these parameters may not have had a major impact. However, food parameters 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 nonavailability, we have found little drop off in predictability in other studies, such as the SEASONS Study [9], in which we compared multiple (up to 15) 24 h recall interviews to five 7 day Dietary Recalls (7DDR) and the Women's Health Initiative [12], which compared multiple 24 h recall interviews to an FFQ. In the SEASONS study, DII scores were calculated from 44 food parameters using the 24 h 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 [9]. Similarly, robust results were observed with the WHI FFQ [12]. Despite the relatively

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

	DII quartiles, OR (95% CI)				*p* Value for trend[a]	DII continuous[b]
	<−1.36	−0.36, −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)

Italy 1999–2014

[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

	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)	
Histologic 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)	

Italy 1999–2014

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

large sample size, the study has still limited power to detect associations for specific NHL subtypes. Another limitation of this study is the nonavailability of data on other important covariates like BMI and physical activity which are also known risk factors for NHL.

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.

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Compliance with ethical standards

Conflict of interest Though this is not thought to represent a conflict, Dr. James R. Hébert wishes to disclose that he 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.

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