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ORIGINAL CONTRIBUTION

Inflammatory potential of diet and risk of lymphoma in the European Prospective Investigation into Cancer and Nutrition

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Abstract

Introduction Chronic inflammation plays a critical role in lymphomagenesis and several dietary factors seem to be involved its regulation. The aim of the current study was to assess the association between the inflammatory potential of the diet and the risk of lymphoma and its subtypes in the European Investigation into Cancer and Nutrition (EPIC) study.

Methods The analysis included 476,160 subjects with an average follow-up of 13.9 years, during which 3,136 lymphomas (135 Hodgkin lymphoma (HL), 2606 non-Hodgkin lymphoma (NHL) and 395 NOS) were identified. The dietary inflammatory potential was assessed by means of an inflammatory score of the diet (ISD), calculated using 28 dietary components and their corresponding inflammatory weights. The association between the ISD and lymphoma risk was estimated by hazard ratios (HR) and 95% confidence intervals (CI) calculated by multivariable Cox regression models adjusted for potential confounders.

Results The ISD was not associated with overall lymphoma risk. Among lymphoma subtypes, a positive association between the ISD and mature B-cell NHL (HR for a 1-SD increase: 1.07 (95% CI 1.01; 1.14), p trend = 0.03) was observed. No statistically significant association was found among other subtypes. However, albeit with smaller number of cases, a suggestive association was observed for HL (HR for a 1-SD increase = 1.22 (95% CI 0.94; 1.57), p trend 0.13).

Conclusions Our findings suggested that a high ISD score, reflecting a pro-inflammatory diet, was modestly positively associated with the risk of B-cell lymphoma subtypes. Further large prospective studies on low-grade inflammation induced by diet are warranted to confirm these findings.

Keywords Chronic inflammation · Inflammatory score of the diet · Lymphoma · Nutrition · Prospective studies

Background

Lymphomas are a heterogeneous group of malignancies that arise from the lymphatic system. Their etiology remains largely unknown, with few well-established risk factors including immunosuppression, certain infections and other chronic inflammatory conditions [1–3]. In addition, several individual dietary factors have been linked to lymphoma risk, although to the date, no conclusive associations have been reported [4].

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Chronic inflammation is known to play an important role in carcinogenesis [5] and several lines of evidence suggest that this process may be influenced by specific dietary factors [6]. Indeed, several food components have an impact on blood concentrations of inflammatory markers, including cytokines, chemokines, acute-phase proteins, soluble adhesion molecules and cytokine receptors [6, 7]. Recently, promising tools have emerged to assess the inflammatory potential of diet—the dietary inflammatory index (DII) [8] and the inflammatory score of diet (ISD) [9], scores combining the intake of dietary constituents and their association with well-known inflammatory markers. Epidemiological studies have assessed the association between the DII/ISD and several solid neoplasms, such as breast [10], gastric [9], oral and pharyngeal [11], renal [12] or colorectal [13] cancers. To date, however, evidence on hematological malignancies is scarce, with no prospective data and only two case–control studies reporting a positive association between a pro-inflammatory diet and NHL [14] and no associations for HL [15].

The aim of this study is to investigate the association between the inflammatory potential of diet, measured by means of the ISD, and lymphoma risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) population.

Methods

Study population

EPIC is an ongoing prospective cohort study involving 23 centers from ten European countries (Denmark, France, Germany, Greece, the Nederland's, Italy, Norway, United Kingdom, Spain and Sweden). The rationale, full methods and study design have been described previously [16, 17]. In brief, 521,324 subjects, mostly aged 30–70 years, were recruited between 1992 and 2000. Written informed consent was provided by all participants. The ethical review boards from the International Agency for Research on Cancer (IARC) and from all local centers approved the study. Prior to analysis, the following exclusions were made: participants with a prevalent cancer ($n = 25{,}184$), with missing follow-up information ($n = 4148$), with incomplete/ no dietary information ($n = 6259$), or those in the highest and lowest 1% of the distribution for the ratio of energy intake to estimate energy requirement ($n = 9573$). Thus, our final study population included 476,160 EPIC participants among whom 3,136 incident lymphoma cases occurred during an average follow-up of 13.9 years.

Data collection

Validated country-specific questionnaires were used to record the usual diet during the previous year [17, 18]; namely through quantitative or semi-quantitative food frequency questionnaires (FFQs) (administered through a personal interview or self-administered), although few countries used semi-quantitative FFQs combined with a food record. Information on dietary supplements was not collected. Lifestyle questionnaires were used to obtain information on sociodemographic characteristics, physical activity, reproductive history, use of oral contraceptives and hormone replacement therapy, medical history and alcohol and tobacco consumption. Anthropometric measures were also ascertained at recruitment.

Exposure assessment: ISD

The inflammatory potential of diet was assessed using the ISD. Its scoring system has been described elsewhere [9]. In brief, 28 components (e.g. carbohydrates, fats, vitamins or flavonoids) available in the EPIC databases for all centers were selected. Only dietary data (not dietary supplementation) were used. The intake of each food parameter was standardized using the mean and standard deviation of our study population (Online Resource 1, Table S1). These z-scores were then converted to percentile scores to avoid the right skewness of data, and then centred on 0 by doubling each percentile score and subtracting 1. The centred percentile values were then multiplied by its respective inflammatory weight, also used to construct the DII, obtained after a literature review according to the pro- or anti-inflammatory effect of the food parameter, the level of evidence of the studies and the number of articles reviewed [8]. The food parameter-specific inflammatory score was then summed to obtain the overall ISD for each individual. Overall, the ISD is a relative index that allows categorizing individuals' diets on a continuum from maximally anti-inflammatory (corresponding to lower scores) to maximally pro-inflammatory (higher scores).

The procedure of construct the ISD is similar to the DII [8] with a few modifications. First, we used 28 food parameters instead of the 45 included in the DII (Online Resource 1, Table S1). Information on total fats was dismissed because its inflammatory effect is likely to be represented by the weights of all separate components of fats (i.e. saturated, mono-unsaturated, and polyunsaturated fats), and thus including them in the scoring calculation could imply an overestimation of its inflammatory effect. For the remaining food parameters, information was not available or not specific enough to be used (e.g. type of

tea, green/black). Second, in the DII, alcohol is considered to be anti-inflammatory for all levels of consumption (it has a negative weight: − 0.278), but this property has only been reported in literature for low/moderate consumers (less than 30–40 g/day) [19, 20]. Therefore, for subjects with intake > 40 g/day the weight for alcohol was set to 0 (Online Resource 1, Table S1). Finally, each individual item intake was standardized using the mean and standard deviation (SD) of our study population (Online Resource 1, Table S1), whereas the DII used data from a regional worldwide database taken as "referent" population. Given that comparing the inflammatory potential of diet was not the aim of this study, but assessing whether the inflammatory potential of diet was associated with cancer risk, we gave priority to internal validity and used our own population to standardize the intakes of the ISD components.

Follow-up and outcome assessment

Incident lymphoma cancer cases were identified by population cancer registries for Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. A combination of methods was used in France, Germany and Greece, as detailed previously [17]. Mortality data were also obtained from regional or national mortality registries. The follow-up period was defined from the age at recruitment to the age at first cancer diagnosis, death or last complete follow-up, whichever occurred first. Censoring dates for the last complete follow-up ranged from June 2008 to December 2013, depending on the EPIC center.

Initially, the diagnosis of lymphoma cases was based on the second revision of the International Classification of Diseases for Oncology (ICD-O-2). Later, all cases were reclassified into the ICD-O-3 using a conversion program available on the web site of the Surveillance Epidemiology and End Results (SEER) program (http://seer.cancer.gov/tools/conversion/ICD02- 3manual.pdf) and involving a pathology expert and experts from the EPIC centers. Because not all ICD-O-2 diagnostics can be translated unequivocally into the ICD-O-3 classification, we left the respective lymphomas unclassified (not otherwise specified ''NOS'') when further detailed specification failed. Finally, the InterLymph Pathology Working Group classification, which is based on the 2008 WHO classification, was used to categorize lymphoma histologic subtypes [21].

In the current analysis, the following groups were considered: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL); within NHL, mature B-cell lymphoma and mature T/NK-cell lymphoma; and among mature B-cell lymphoma, the following entities: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) (all grades), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), multiple myeloma/plasma cell neoplasm (MM/PCN), and other B-cell lymphoma (i.e. those cases in which the B-cell lymphoma subtype is unknown or does not fall within the above mentioned subtypes). Other entities were not considered due to small numbers (Table 1). Overall, during an average follow-up of 13.9 years, 3,136 lymphoma cases were diagnosed.

Statistical analysis

Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) to examine the association between the ISD and lymphoma risk. Two models with two levels of adjustment were used: a basic model, stratified by center, sex and age at recruitment (in 1-year categories), and a multivariable model, further adjusted for body mass index (BMI) (< 25, 25–30, ≥ 30 kg/m^2), total energy intake (continuous, kcal/day), education level (no formal education, primary school, secondary school, technical or professional training, university, unknown [3.6%]), height (continuous, cm), physical activity level based on the Cambridge Physical Activity Index (inactive, moderately inactive, moderately active, active, unknown [1.9%]), smoking status (never, former, current and, unknown [2.0%]), and alcohol intake at recruitment (continuous, g/day).

The ISD was analysed both as a continuous variable (1-standard deviation [SD] increase) and as a categorical variable (in quartiles). The ISD categorical variable was scored from 1 to 4, and trend tests were performed using these categories. In addition, we tested for interaction between the ISD score (continuous) and age, sex, BMI, smoking status and alcohol intake in the multivariable Cox model using a likelihood ratio test.

Sensitivity analyses were performed by repeating the models after the exclusion of cases diagnosed during the first 2 years of follow-up ($n = 259$), since participants may have changed their diets in the pre-diagnostic period. We also conducted analysis excluding participants without complete data ($n = 226$), and restricted HL analysis to classical HL cases. Moreover, given that alcohol has been shown to be inversely associated with several lymphoma subtypes [22], we excluded it from the ISD construction to confirm it was not the only element driving the association. Schoenfeld residuals were assessed to ensure that the proportional hazard assumption was satisfied in all models. Two-sided p values were reported with statistical significance set at $p < 0.05$. All analyses were performed using STATA statistical software, version 14 (Stata Corporation, College Station, Texas).

Table 1 Distribution of lymphoma cases in the EPIC study

	Total cohort	Person-years	Overall	Lymphoma subgroups			NHL subgroups[a]		Mature B-cell subgroups					ISD mean[b] (SD)
				NHL	HL	NOS	Mature B-cell	Mature T/NK-cell	DLBCL	FL	CLL/SLL	MM/PCN	Other B-cell	
Denmark	55,014	815,096.8	631	538	29	64	506	23	121	78	118	123	66	0.20 (0.92)
France	67,403	869,362.5	228	216	11	1	205	8	40	44	44	45	32	0.11 (0.91)
Germany	48,557	504,479.0	231	190	13	28	170	12	30	20	39	55	26	0.54 (0.84)
Greece	26,048	281,283.6	62	44	3	15	38	2	3	3	13	15	4	− 0.19 (0.95)
Italy	44,545	630,951.3	298	241	15	42	218	11	38	33	44	73	30	0.56 (0.86)
Norway	33,975	452,171.1	163	147	5	11	129	14	26	31	26	24	22	0.97 (0.75)
Spain	39,989	637,947.4	241	211	14	16	194	10	35	27	51	51	30	0.26 (1.00)
Sweden	48,674	801,130.2	517	381	13	123	344	20	57	48	74	132	33	0.77 (0.83)
The Netherlands	36,539	524,670.7	201	186	7	8	172	10	43	26	41	43	19	0.47 (0.76)
United Kingdom	75,416	1,122,765	564	452	25	87	426	20	95	71	87	115	58	− 0.53 (1.00)
Total	476,160	6,639,857.5	3,136	2,606	135	395	2,402	130	488	381	537	676	320	0.26 (1.00)

NHL non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *NOS* not otherwise specified, DLBCL diffuse large B-cell lymphoma, FL follicular lymphoma, CLL/SLL chronic lymphocytic leukemia/small lymphocytic lymphoma, *MM/PCN* multiple myeloma/ plasma cell neoplasm, Other B-cell (those cases for which the mature B-cell NHL subtype is unknown or does not fall within the above mentioned subtypes, *ISD* inflammatory score of diet, *SD* standard deviation

[a]Three individuals with NHL without B- or T-cell information

[b]ISD: positive values indicate a more pro-inflammatory diet and negative values correspond to a more anti-inflammatory diet

Results

Distributions of all the EPIC participants and lymphoma cases by country are displayed in Table 1. The inflammatory potential of diet in the whole cohort, measured by the ISD, had a mean of 0.26 with SD of 1.00 and a ranged from − 3.52 (the maximum anti-inflammatory value) to 2.76 (the maximum pro-inflammatory value). Lower ISD means were observed in the UK and Greece whereas higher ISD means were seen in Norway and Sweden.

Baseline characteristics of the study participants according to the ISD are detailed in Table 2. In general, participants with higher values of the ISD (more pro-inflammatory diet) were more likely to be women, ever smokers, and physically inactive, with a lower education level, and lower alcohol intake compared with those with a lower ISD score (more anti-inflammatory diet). Surprisingly, total energy intake (although associated with a pro-inflammatory weight: 0.180), appeared to be inversely related to the ISD.

The association of the inflammatory potential of the diet with lymphoma and its subtypes is presented in Table 3. Overall, the ISD was not associated with risk of lymphoma (HR_{Q4vsQ1}= 1.07 (95% CI 0.93; 1.22, *p* trend = 0.34); HR for a 1-SD increase = 1.05 (95% CI 1.00; 1.11), *p* trend = 0.06). Among lymphoma subtypes, each SD increase in the ISD was associated with a 6% higher risk of having NHL (95% CI 1.00; 1.13, *p* trend = 0.04), and within them, there were modest positive associations for mature B-cell NHL (HR for a 1-SD increase = 1.07 (95% CI 1.01; 1.14), *p* trend = 0.03) and other B-cell neoplasms (HR_{Q4vsQ1}= 1.54 (1.01; 2.34), *p* trend = 0.07). No statistically significant associations where found among other lymphoma subtypes; however, albeit with smaller number of cases, high HR were observed for HL (HR_{Q4vsQ1} = 1.90 (95% CI 0.97; 3.71; *p* trend = 0.08); HR for a 1SD increase = 1.22 (95% CI 0.94; 1.57), *p* trend = 0.13). Following the exclusion of non-classical HL (*n* = 8) risk showed similar results (HR_{Q4vsQ1}= 1.98 (95% CI 0.99; 3.97), *p* trend = 0.09; HR for a 1-SD increase = 1.23 (95% CI 0.94; 1.59), *p* trend = 0.13). Neither age, sex, BMI, smoking status nor alcohol consumption modified the associations of the ISD and risk of lymphoma, HL, NHL or mature B-cell NHL (Online Resource 1, Table S2). Likewise, no statistically significant interactions were detected for the rest of mature B-cell NHL subtypes (*data not shown*). Similarly, no significant differences in the association of lymphoma and its subtypes were observed by country, with the exception of DLBCL (Online Resource 1, Figure S1).

In sensitivity analyses, excluding alcohol from the ISD construction (Online Resource 1, Table S3), excluding cases diagnosed during the first 2 years of follow-up (Online Resource 1, Table S4) or those individuals with no information on adjustment variables from the analyses (Online Resource 1, Table S5) did not substantially alter the observed associations.

Discussion

In this large European prospective study, the inflammatory potential of diet, measured by means of the ISD, was not associated with overall lymphoma risk and showed a modest positive association with B-cell lymphoma subtypes.

During the last decades, most nutritional epidemiological studies have shifted from studying individual foods

Table 2 Baseline characteristics of participants in the EPIC study according to the ISD

	Total cohort	ISD			
		Q1 (mean = − 1.09, range − 3.52; − 0.43)	Q2 (mean = − 0.02, range: − 0.43; 0.34)	Q3 (mean = 0.68, range: 0.34; 1.02)	Q4 (mean = 1.47, range: 1.02; 2.76)
Total cohort, n	476,160	119,040	119,040	119,040	119,040
Females (%)	70.1	64.8	67.5	71.4	76.8
Age at recruitment (mean [SD], years)	51.2 (9.9)	50.7 (11.1)	51.5 (9.9)	51.5 (9.5)	51.2 (9.2)
Energy intake (mean [SD], kcal/day)	2,075.1 (619.2)	2,523.2 (640.3)	2,198.1 (540.9)	1,954.7 (468.9)	1,624.3 (421.4)
Alcohol intake (median [25th–75th percentiles], g/day)	5.3 (0.9; 14.9)	7.4 (1.6; 17.9)	6.4 (1.3; 16.7)	5.3 (0.9; 14.9)	2.8 (0.4; 10.6)
BMI (mean [SD], kg/m^2)	25.4 (4.3)	25.4 (4.3)	25.4 (4.3)	25.4 (4.2)	25.5 (4.3)
Height (mean [SD], cm)	166.0 (8.9)	166.9 (9.0)	166.4 (9.1)	165.8 (8.9)	164.9 (8.7)
Smoking status (% ever)	49.0	45.8	48.2	49.9	52.3
Physical activity (% inactive)	21.0	19.2	20.5	21.0	23.2
Educational level (% ≤ primary school)	30.0	23.8	28.3	31.0	36.9

ISD inflammatory score of diet, *Q* quartile, *n* total number, *SD* standard deviation, *BMI* body mass index

Table 3 Association between the ISD and risk of lymphoma and its subtypes in the EPIC study

	ISD						
	Q1	Q2	Q3	Q4	*p* trend[c]	1-SD increase	*p* trend[d]
Lymphoma, *n*	784	783	786	783			
HR[a] (95% CI)	Ref	0.99 (0.89; 1.09)	0.99 (0.89; 1.10)	1.00 (0.89; 1.11)	1.00	1.01 (0.97; 1.05)	0.56
HR[b] (95% CI)	Ref	1.01 (0.91; 1.13)	1.04 (0.92; 1.16)	1.07 (0.93; 1.22)	0.34	1.05 (1.00; 1.11)	0.06
HL, *n*	25	35	35	40			
HR[a] (95% CI)	Ref	1.51 (0.89; 2.55)	1.64 (0.96; 2.80)	**1.99 (1.15; 3.43)**	**0.02**	**1.25 (1.03; 1.52)**	**0.02**
HR[b] (95% CI)	Ref	1.48 (0.86; 2.57)	1.60 (0.88; 2.90)	1.90 (0.97; 3.71)	0.08	1.22 (0.94; 1.57)	0.13
NHL, *n*	658	659	647	642			
HR[a] (95% CI)	Ref	0.98 (0.88; 1.10)	0.97 (0.86; 1.09)	0.98 (0.87; 1.11)	0.72	1.00 (0.96; 1.05)	0.88
HR[b] (95% CI)	Ref	1.03 (0.91; 1.15)	1.04 (0.92; 1.19)	1.10 (0.94; 1.27)	0.24	**1.06 (1.00; 1.13)**	**0.04**
Mature T/ NK-cell, *n*	34	35	31	30			
HR[a] (95% CI)	Ref	0.93 (0.57; 1.51)	0.79 (0.47; 1.33)	0.72 (0.42; 1.25)	0.20	0.99 (0.81; 1.20)	0.91
HR[b] (95% CI)	Ref	0.86 (0.51; 1.43)	0.70 (0.39; 1.25)	0.61 (0.31; 1.19)	0.12	0.99 (0.76; 1.29)	0.95
Mature B-cell, *n*	603	608	596	595			
HR[a] (95% CI)	Ref	1.00 (0.89; 1.12)	0.99 (0.88; 1.12)	1.02 (0.90; 1.16)	0.79	1.01 (0.96; 1.06)	0.67
HR[b] (95% CI)	Ref	1.05 (0.93; 1.19)	1.08 (0.94; 1.23)	1.15 (0.99; 1.35)	0.08	**1.07 (1.01; 1.14)**	**0.03**
DLBCL, *n*	126	121	118	123			
HR[a] (95% CI)	Ref	1.00 (0.77; 1.29)	1.00 (0.77; 1.31)	1.12 (0.85; 1.47)	0.46	1.05 (0.95; 1.16)	0.38
HR[b] (95% CI)	Ref	1.03 (0.78; 1.34)	1.06 (0.78; 1.42)	1.21 (0.86; 1.70)	0.29	1.09 (0.96; 1.25)	0.20
FL, *n*	98	95	98	90			
HR[a] (95% CI)	Ref	0.98 (0.73; 1.31)	1.00 (0.74; 1.35)	0.91 (0.66; 1.25)	0.62	0.99 (0.89; 1.11)	0.89
HR[b] (95% CI)	Ref	1.05 (0.78; 1.43)	1.13 (0.81; 1.58)	1.10 (0.74; 1.62)	0.58	1.09 (0.94; 1.27)	0.25
CLL/SLL, *n*	129	149	135	124			
HR[a] (95% CI)	Ref	1.13 (0.89; 1.44)	1.05 (0.81; 1.35)	1.02 (0.78; 1.34)	0.97	1.00 (0.91; 1.10)	0.99
HR[b] (95% CI)	Ref	1.13 (0.88; 1.46)	1.07 (0.80; 1.42)	1.04 (0.75; 1.45)	0.95	1.01 (0.89; 1.15)	0.88
MM/PCN, *n*	170	160	171	175			
HR[a] (95% CI)	Ref	0.90 (0.72; 1.12)	0.94 (0.75; 1.18)	0.96 (0.76; 1.21)	0.85	0.99 (0.91; 1.08)	0.84
HR[b] (95% CI)	Ref	0.94 (0.75; 1.19)	1.02 (0.79; 1.31)	1.08 (0.81; 1.45)	0.48	1.05 (0.93; 1.17)	0.43
Other B-cell, *n*	80	83	74	83			
HR[a] (95% CI)	Ref	1.05 (0.77; 1.44)	0.96 (0.69; 1.34)	1.16 (0.83; 1.62)	0.51	1.03 (0.91; 1.17)	0.64
HR[b] (95% CI)	Ref	1.18 (0.85; 1.65)	1.17 (0.80; 1.69)	**1.54 (1.01; 2.34)**	0.07	1.16 (0.98; 1.37)	0.08

ISD inflammatory score of diet, *HR* hazard ratio, *CI* confidence interval, *HL* Hodgkin lymphoma, *NHL* non-Hodgkin lymphoma, DLBCL diffuse large B-cell lymphoma, *FL* follicular lymphoma, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, MM/PCN multiple myeloma/ plasma cell neoplasm, Other B-cell (those cases for which the mature B-cell NHL subtype is unknown or does not fall within the above mentioned subtypes

In bold: $p < 0.05$

[a]Basic model: Cox proportional hazard model stratified by age (in 1-year categories), center and sex

[b]Multivariate model: Cox proportional hazard model stratified by age (in 1-year categories), center and sex and further adjusted for body mass index, total energy intake, education, height, physical activity, smoking status, and alcohol intake

[c]*p* value of Cox proportional model fitter with the ISD ordinal variable as continuous to test for lineal trend

[d]*p* value of Cox proportional model fitted with the ISD continuous variable

or nutrients to dietary pattern analysis, which represents a broader picture of subject's diet, and may thus be more predictive of disease risk [23]. Among them, the ISD and DII represent a promising tool to evaluate a set of dietary exposures with cumulative and interactive effects on both low-grade inflammation and health outcomes [8]. While it has been largely studied in solid neoplasms [9–13, 24, 25], studies on hematological malignancies are utterly scarce, mostly arising from case–control studies restricted to NHL patients without detailed information for specific subtypes.

To the best of our knowledge, this is the first prospective study to investigate the link between the inflammatory potential of diet and risk of lymphoma and its subtypes. Our results are in line with those reported in a multicenter

case–control Italian study with 536 NHL cases and 934 matched controls [14]. The adjusted odds ratio (OR) comparing the highest to the lowest quartile of the DII for NHL was 1.61 (95% CI 1.07; 2.43); p trend = 0.01)) and when analyses were carried out using continuous DII, the OR for 1-unit increment in the score was 1.14 (95% CI 1.02; 1.27). Stratified analyses revealed stronger associations between DII and NHL among males and an association between a pro-inflammatory diet and DLBCL was also reported. By contrast, no associations between the DII and HL (n = 179) were reported in the same case–control study [15]. However, although the DII and ISD have been shown to highly correlate in the EPIC population (Pearson's correlation coefficient: 0.91; p value < 0.001) [9], data from both studies cannot be directly compared with ours, since they are based upon different indexes and study designs. In addition, the Italian case–control study lacked information on potential confounders (e.g. BMI or physical activity) as well as on NHL entities other than DLBCL or FL. In the EPIC study, a positive association between the ISD and other B-cell neoplasms (which included Burkitt lymphoma, hairy cell leukemia, lymphoplasmatic lymphoma, mantle cell lymphoma, marginal zone lymphoma, primary effusion lymphoma, and B-cell prolymphocytic lymphoma) was observed, but unfortunately a limited sample size did not allow further specific subtype analyses. In addition, we observed suggestive inverse associations with HL albeit statistically non significant. Given the small number of HL (n = 135), we may have lacked statistical power to detect associations within this subgroup. Thus, more prospective studies with larger sample size and with detailed lymphoma classification schemes are needed to shed light into this relationship.

The role of inflammation, mediated by dietary factors, in the pathogenesis of lymphoma has a strong biological plausibility. Certain autoimmune and chronic inflammatory conditions characterized by severe immune dysregulation such as immunosuppression, Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis have been established as strong risk factors for lymphoma [1, 2, 26]. In addition, several infectious agents have been specifically linked to certain subtypes of lymphoma, including the Human immunodeficiency virus, Epstein-Bar virus (EBV), human T-cell lymphotrophic virus-1, human herpes virus-8, and hepatitis C virus, and the bacteria *Helicobacter pylori, Borrelia burgdorferi ,Chlamydia psittaci* and *Campylobacter jejunei* [1–3, 26]. Most of these agents are believed to exert their lymphomagenic mechanisms primarily or partially through chronic immune stimulation [2, 3, 26]. In particular for HL, it is widely believed that its clinical and histological features are primarily due to the effects of a plethora of cytokines and chemokines produced by Reed-Sternberg cells and their surrounding cellular infiltrate in response to inflammatory signals triggered by etiological factors such as EBV [27]. Moreover, it is unclear whether subclinical immunologic perturbations influence lymphoma risk. However, recent studies within general population cohorts incorporating serologic measurements of cytokines, chemokines, and other immune markers have provided important evidence supporting a role for subtle immunologic effects in lymphomagenesis [28–37]. The modest associations between the ISD and B-cell lymphoma subtypes suggest that inflammation induced by diet may be also implied in this process and merits further research.

Incidence of lymphoid neoplasms exhibits a marked geographical variability, with the highest incidence rates in western countries, and the lowest found in Asia and Eastern Europe [38, 39]. In addition, incidence patterns of both HL and NHL vary with migration and nativity, suggesting an influence of acculturation on lymphoma risk [40, 41]. Indeed, markedly lowered rates of lymphoid malignancies among Asians relative to other racial/ethnic groups in the United States and among foreign-born Asians compared to United states-born Asians [40] have suggested some kind of protection from lymphomagenic processes, but it is still unclear whether this protection relies genetic, environmental differences or a combination. In addition, a Western dietary pattern, characterized by higher intakes of red and processed meats, sweets, desserts, French fries, and refined grains, has been positively associated with inflammatory biomarkers [42]. Thus, a westernization of diet, characterized by the inclusion of foods and nutrients with a pro-inflammatory profile, could partly explain these incidence trends.

Limitations of our study should be considered when interpreting the results, including potential measurement errors derived from dietary questionnaires, which could lead to systematic and random errors when estimating the ISD. Although our adjustment for total energy intake and exclusion of subjects with implausible diets (those in the highest and lowest 1% of the distribution of the ratio between energy intake and estimated energy requirement) would partly remove some of these errors [43, 44] we cannot rule out that they have modified risk estimates. However, since dietary information was collected on healthy individuals at the beginning of the study, measurement errors would be expected to be non-differential and thus, their effect would most likely dilute the true association. In addition, we were unable to take into account any possible changes in dietary and lifestyle habits over time. In particular, cases might have modified their diet during the early pre-diagnostic period of the disease, although sensitivity analyses excluding incident cases diagnosed in the first 2 years of follow-up did not alter the estimates. Moreover, despite adjusting for risk factors associated with lymphomas, residual confounding by other unmeasured (such as immunosuppressive conditions) or unknown exposure cannot be dismissed. In addition, because of the high number of comparisons performed,

we cannot exclude chance findings. Despite the large number of enrolled subjects at baseline, the number of observed incident cases of some lymphoma subtype was low (e.g. 135 HL). Therefore, the study might not have sufficient power to detect significant associations within those subgroups. Finally, we lacked information on the usual consumption of anti-inflammatory drugs or supplements. All these factors could have influenced the inflammatory potential of diet. Information on several parameters previously considered in the DII score was not available or not sufficiently specific in EPIC to be included in the ISD score (i.e. type of tea, green/black). However, a study reported that seven components explained 91% of the inter-individual variance in DII [45]. All of them were included in the ISD and, therefore, we can assume that the components that were not included into the ISD score did not have a major impact on the estimation of the inflammatory potential of diet.

The strengths of our study are its prospective design and high statistical power, owing to a large number of cases, an accurate case-ascertainment, and the ability to carry out specific analyses according to lymphoma subtypes. The latter is particularly relevant since there is growing evidence that lymphoma subtypes have different pathological and epidemiological features [1]. In addition, its multi-centric European design allowed the inclusion of a geographically diverse population, covering a wide range of dietary patterns and lifestyle habits.

Conclusions

In summary, our results suggest that a high ISD score, reflecting a pro-inflammatory diet, may be modestly positively associated with B-cell lymphomas. Further research including biomarkers of inflammation would help to better understand the underlying mechanisms between diet-related inflammation and lymphomagenesis, in particular for B-cell lymphoma subtypes.

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Availability of data and material. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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