Adherence to the Western, Prudent, and Mediterranean dietary patterns and chronic lymphocytic leukemia in the MCC-Spain study

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ABSTRACT

Diet is a modifiable risk factor for several neoplasms but evidence for chronic lymphocytic leukemia (CLL) is sparse. Previous studies examining the association between single-food items and CLL risk have yielded mixed results, while few studies have been conducted on overall diet, reporting inconclusive findings. This study aimed to evaluate the association between adherence to three dietary patterns and CLL in the multicase-control study (MCC-Spain) study. Anthropometric, sociodemographic, medical and dietary information was collected for 369 CLL cases and 1605 controls. Three validated dietary patterns, Western, Prudent and Mediterranean, were reconstructed in the MCC-Spain data. The association between adherence to each dietary pattern and CLL was assessed, overall and by Rai stage, using mixed logistic regression models adjusted for potential confounders. High adherence to a Western dietary pattern (i.e. high intake of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, and convenience food) was associated with CLL [ORQ4 *vs.* Q1=1.63 (95%CI 1.11; 2.39); *P*-trend=0.02; OR 1-SD increase=1.19 (95%CI: 1.03; 1.37)], independently of Rai stages. No differences in the association were observed according to sex, Body Mass Index, energy intake, tobacco, physical activity, working on a farm, or family history of hematologic malignancies. No associations were observed for Mediterranean and Prudent dietary patterns and CLL. This study provides the first evidence for an association between a Western dietary pattern and CLL, suggesting that a proportion of CLL cases could be prevented by modifying dietary habits. Further research, especially with a prospective design, is warranted to confirm these findings.

Introduction

Chronic lymphocytic leukemia (CLL) is the commonest leukemia among the adult population in Western countries, with an annual incidence rate of around 5 per 100,000 person-years in Europe,[1] but its etiology is still poorly understood. A pooled analysis of 2440 CLL cases and 15,186 controls from the InterLymph consortium showed significant inverse associations with atopic conditions, smoking, blood transfusion history, and recreational sun exposure, and positive associations with height, hepatitis C virus seropositivity, living or working on a farm, working as a hairdresser, and family history of hematologic malignancies.[2]

Diet is a modifiable risk factor for several neoplasms,[3] but evidence for CLL is inconclusive. Epidemiological data on the association of diet and CLL are heterogeneous, and mainly arise from studies on nutrients or single food items. While most prospective studies[4-12] did not find any association with a wide range of dietary factors, case-control studies[13-25] have yielded contradictory results for items such as meat, dairy or vegetable intake. Some authors argue that focusing on overall dietary patterns instead of on individual foods or nutrients may better capture dietary variability in the population's diet while allowing the evaluation of interactions between dietary factors.[26] However, the few studies that have been conducted on overall diet and CLL[25,27,28] reported inconclusive findings, mainly due to small sample size.

A population-based multicase-control study (MCC-Spain) was launched to evaluate the influence of environmental exposures and their interaction with genetic factors in CLL, among other cancers.[29] The aim of the present study was to evaluate the association between adherence to three validated dietary patterns,[30] Western, Prudent and Mediterranean, and CLL in the MCC-Spain study.

Methods

Study population

MCC-Spain is a multicentric case-control study with population controls and cases with common tumors (prostate, breast, colorectal, gastroesophageal and CLL) in Spain. Between 2010 and 2013, CLL cases aged 20-85 years were recruited in 11 Spanish hospitals from 5 Spanish provinces (Asturias, Barcelona, Cantabria, Girona and Granada). Simultaneously, population-based controls frequency-matched to cases according to age (5-year intervals), sex, and province of recruitment were randomly selected from primary care centers within the hospitals' catchment areas. Participation rates were 87% in cases and 53% in controls, with variability among geographical regions. After applying specific diet exclusion criteria (excluding participants with no dietary data or with missing or implausible energy intakes under 750 or over 4500 kcal/day), a total of 1605 controls and 369 CLL cases were included in the study. All participants gave informed consent. Approval for the study was obtained from the ethical review boards of all recruiting centers. Additional information regarding the study design has been provided elsewhere.[29]

Outcome definition

Chronic lymphocytic leukemia cases were diagnosed according to the International Workshop on CLL criteria: presence of an absolute count ≥5 x10^9 B cells/L for three or more months in peripheral blood and a clonal population of $CD5^+$, $CD19^+$, and $CD23^+$ B cells.[31] All diagnoses were morphologically and immunologically confirmed using flow cytometry immunophenotype and complete blood cell count. CLL and small lymphocytic lymphoma were considered the same underlying disease. Given the indolent course of the disease, CLL cases were recruited and interviewed within three years from diagnosis. Disease severity at interview was evaluated using the Rai staging system obtained from medical records and verified by local hematologists. CLL subjects were then categorized into two groups based on Rai stage: a) low-risk category including asymptomatic patients with lymphocytosis only (Rai 0); and b) intermediate/high-risk category including patients with either lymphadenopathy, hepatomegaly, splenomegaly, anemia and/or thrombocytopenia (Rai I-IV).

Data collection

Data on socio-demographic factors, lifestyle and personal/family medical history were collected through face-to-face interviews performed by trained personnel. Height and weight at different ages were self-reported. The questionnaire in Spanish is available at *www.mccspain.org*.

In addition, subjects were provided a semi-quantitative Food Frequency Questionnaire (FFQ), which was a modified version from a previous tool validated in Spain to include regional products.[32] The FFQ was self-administered and returned by mail or filled out face-to-face. It included 140 food items with portion sizes specified for each item, and assessed usual dietary intake during the previous year. Cross-check questions on aggregated food group consumption were used to adjust the frequency of food consumption and reduce misreporting of food groups with large numbers of items.[33] Nutrient intakes were estimated using food composition tables published for Spain, and other sources.[34] The response rate of the FFQ was slightly lower in cases (82%) than in controls (87%). Overall, responsiveness was not associated with age, and individuals from Granada were less likely to answer the FFQ than those from Barcelona. Those individuals who did not answer the diet questionnaire had a lower level of education and, in controls, were also more likely to be women.

Dietary patterns

Three validated dietary patterns identified in a Spanish case-control study (EpiGEICAM)[30] were reconstructed in the MCC-study: a) a Western dietary pattern characterized by high intake of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food and sauces; b) a Prudent pattern, with high intake of low-fat dairy products, vegetables, fruits, whole grains and juices; and c) a Mediterranean pattern, defined by a high intake of fish, vegetables, legumes, boiled potatoes, fruits, olives, and vegetable oil. Further information on identification of the dietary patterns can be found elsewhere.[30] In brief, dietary information extracted from a semi-quantitative questionnaire in the EpiGEICAM study was converted to mean daily intake in grams and grouped into 26 food categories. Major existing dietary patterns were identified in the control population by applying principal components analysis (PCA) without rotation of the variance-covariance matrix over the 26 inter-correlated food groups. The set of loadings obtained represent the correlation between the consumption of each food group and the component/pattern score, and can be used to apply such patterns to other populations.[35] In the MCC-study, we grouped the FFQ items into the same 26 food groups (*Online Supplementary Table S1*), and calculated the score of adherence to the Western, Prudent and Mediterranean dietary patterns as a linear combination of the loads described in the EpiGEICAM study and the log-transformed centered food group consumption reported by the participants of MCC-Spain study.

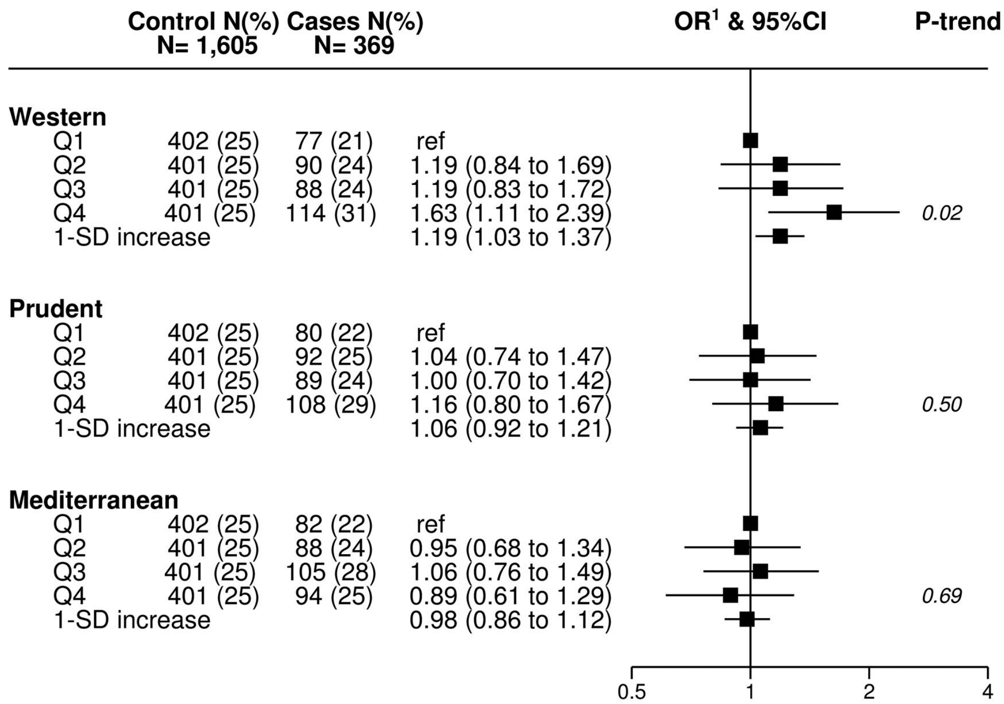

Figure 1. Association between adherence to dietary patterns and chronic lymphocytic leukemia in the multicase-control (MCC-Spain) study. OR: Odds Ratio; 95%CI: 95% confidence interval; Q: quartile; SD: standard deviation. Black squares indicate OR and horizontal lines represent 95%CI. [1]Logistic regression models adjusted for age, sex, education, energy intake (kcal/day) with province of residence as random effect.

Statistical analysis

As descriptive analyses, we compared anthropometric, sociodemographic and lifestyle characteristics between cases and controls. χ^2 test was used to evaluate the level of significance of the differences observed in categorical variables, Student *t*-test for normally distributed continuous variables, and Wilcoxon rank-sum test for non-normally distributed continuous variables. In addition, we analyzed the distribution of each dietary pattern (continuous) across categories of descriptive variables. Student *t*-test was used to assess differences observed in variables with two categories and ANOVA for those with more than two categories.

The association between the dietary patterns and CLL was evaluated using mixed logistic regression models with random province-specific intercepts. The exposure variables (adherence to Western, Prudent or Mediterranean patterns) were included in the model both as continuous variables [1-standard deviation (SD) increase in the controls' scores] and as categorical variables (according to the quartile distribution in all controls). All models were adjusted for age (years, continuous), sex, education (no formal education, primary school, secondary school, university), and energy intake (kcal/day, continuous) as fixed effects and province of residence as a random effect term. Height (cm, continuous), waist-to-hip ratio (continuous), Body Mass Index (BMI in kg/m^2, continuous), experience working on a farm (yes, no), family history of hematologic malignancies (yes, no), alcohol consumption (g/day, continuous), smoking status (never, past, current), and physical activity [in the last 10 years, measured in Metabolic Equivalent of Task (METs)/week: inactive (0), low (0.1-8), moderate (8-15.9) and very active (≥16)] were examined as potential confounders, but were not included in the final models as they were not found alone, or in combination, to affect the estimates. Interaction terms were modeled between each of these separate variables and the dietary score (continuous), and tested using log-likelihood ratio tests. A possible effect modification of sex, BMI, energy intake, tobacco, physical activity, working on a farm, and family history of hematologic malignancies was tested including an interaction term between each of the patterns and such variables. The estimation of the effects according to Rai stage (0 *vs.* I-IV) was calculated with multinomial logistic regression models adjusted by the set of variables described above plus province of residence as random effect term. Finally, sensitivity analyses were performed to examine how the inclusion of: i) cases with longer period of time from diagnosis to recruitment (<1 year *vs.* ≥ 1 year); and ii) cases treated before the interview affected the overall estimates. Odds Ratios (OR) and 95% confidence intervals (CI) were also obtained with multinomial logistic regression models. The *P*-value for heterogeneity of effects across Rai stage and for sensitivity analyses was obtained with the Wald test. All analyses were performed using STATA/MP (v.14.1, 2015, StataCorp LP) and statistical significance was set at two-sided $P<0.05$.

Results

Distribution of baseline characteristics between cases and controls is shown in Table 1. Compared with controls, cases were more adherent to the Western pattern, while no differences in level of adherence to the Prudent and Mediterranean patterns were observed in bivariate analyses. CLL cases were also slightly older, had a higher waist-to-hip ratio, and were more likely to have a family history of hematologic malignancy and to have worked on a farm. No other differences were observed for any of the other pre-selected variables.

The distribution of key characteristics of controls according to level of adherence to each dietary pattern is shown in *Online Supplementary Figure S1.* Controls with greater adherence to a Western pattern were more likely to be men, younger, taller, current smokers, less prone to have worked in farming or agriculture, had a lower BMI and waist-to-hip ratio, and a higher level of education, energy and alcohol intake. Those with a higher adherence to a Prudent pattern were more likely to be women, younger, taller, physically active, never/former smokers,

Table 1. Baseline characteristics of chronic lymphocytic leukemia for cases and controls in the multicase-control (MCC-Spain) study.

	Controls (n=1605)	Cases (n=369)	P^1
Western, mean (SD)	5.88 (1.46)	6.06 (1.40)	0.03
Prudent, mean (SD)	6.55 (1.12)	6.66 (1.03)	0.07
Mediterranean, mean (SD)	7.08 (1.00)	7.16 (0.88)	0.20
Province, n(%)			**<0.001**
Barcelona	900 (56)	242 (66)	
Asturias	211 (13)	51 (14)	
Cantabria	281 (18)	21 (6)	
Granada	144 (9)	27 (7)	
Girona	69 (4)	28 (8)	
Age (years), mean (SD)	64.30 (10.54)	66.19 (10.12)	**0.002**
Sex, n(%)			0.95
Male	936 (58)	217 (59)	
Female	669 (42)	152 (41)	
Energy intake (kcal/day), mean (SD)	1901.15 (585.88)	1937.91 (612.06)	0.28
Current alcohol intake (g/day), median (IQI)[2]	8.80 (0.58;27.32)	8.82 (0.83;24.47)	0.75
BMI (kg/m^2), mean (SD)[2]	26.99 (4.50)	27.32 (4.43)	0.21
Height (cm), mean(SD)[2]	165.63 (8.51)	165.97 (9.11)	0.50
Waist-to-hip ratio[3], n(%)			**0.004**
Low	460 (29)	77 (21)	
Moderate	449 (28)	98 (27)	
High	682 (42)	192 (52)	
Unknown	14 (1)	2 (1)	
Smoking status, n(%)			0.39
Never	696 (43)	165 (45)	
Former	602 (38)	134 (36)	
Current	303 (19)	67 (18)	
Unknown	4 (0)	3 (1)	
Education, n(%)			0.54
No formal education	357 (22)	94 (25)	
Primary	502 (31)	106 (29)	
Secondary	461 (29)	107 (29)	
University	285 (18)	62 (17)	
Physical activity[4], n(%)			0.50
Inactive	656 (41)	136 (37)	
Low	219 (14)	55 (15)	
Moderate	190 (12)	47 (13)	
Very active	502 (31)	118 (32)	
Unknown	38 (2)	13 (4)	
Ever worked in farming or agriculture, n(%)			**<0.001**
No	1257 (78)	258 (70)	
Yes	323 (20)	108 (29)	
Unknown	25 (2)	3 (1)	
Family history of hematologic malignancy, n(%)			**<0.001**
No	1551 (97)	333 (90)	
Yes	54 (3)	36 (10)	
Rai stage			
0	–	199 (54)	
I-IV	–	150 (41)	
Unknown	–	20 (5)	

SD: standard deviation; IQI: interquartile interval; BMI: Body Mass Index. [1]*P*-value for heterogeneity calculated with the Student *t*-test for comparison of normally distributed continuous variables, with the Wilcoxon rank-sum test for comparison of non-normally distributed continuous variables (alcohol intake), and with the χ^2 test for categorical variables. [2]% of missing values in continuous variables: alcohol intake (2%), BMI (4%), height (3%). [3]Waist-to-hip ratio risk categories according to WHO criteria. [4]Physical activity, in the last ten years, measured in METs/week: inactive (0), low (0.1-8), moderate (8-15.9), and very active (≥16). In bold: $P<0.05$.

Table 2. Association between adherence to dietary patterns and chronic lymphocytic leukemia by severity of the disease, in the multicase-control (MCC-Spain) study.

	Controls N(%) (n=1605)	Rai 0 Cases N(%) (n=199)	Rai 0 OR[1] (95% CI)	Rai I-IV Cases (n=150)	Rai I-IV OR[1] (95% CI)	*P*-het[2]
Western						
Q1	402 (25)	45 (23)	1	26 (17)	1	
Q2	401 (25)	47 (24)	1.11 (0.71;1.74)	39 (26)	1.40 (0.82;2.38)	
Q3	401 (25)	47 (24)	1.17 (0.73;1.87)	37 (25)	1.32 (0.76;2.30)	
Q4	401 (25)	60 (30)	1.60 (0.97;2.65)	48 (32)	1.71 (0.95;3.06)	
P-trend			0.07		0.11	
1-SD increase			1.15 (0.95;1.39)		1.26 (1.02;1.56)	0.50
Prudent						
Q1	402 (25)	42 (21)	1	30 (20)	1	
Q2	401 (25)	53 (27)	1.09 (0.70;1.70)	37 (25)	1.16 (0.69;1.93)	
Q3	401 (25)	52 (26)	1.07 (0.68;1.69)	32 (21)	0.97 (0.56;1.66)	
Q4	401 (25)	52 (26)	1.01 (0.62;1.64)	51 (34)	1.47 (0.86;2.51)	
P-trend			0.98		0.23	
1-SD increase			0.99 (0.83;1.18)		1.18 (0.96;1.45)	0.17
Mediterranean						
Q1	402 (25)	48 (24)	1	29 (19)	1	
Q2	401 (25)	51 (26)	0.88 (0.57;1.36)	29 (19)	0.94 (0.55;1.62)	
Q3	401 (25)	55 (28)	0.88 (0.57;1.37)	46 (31)	1.39 (0.83;2.30)	
Q4	401 (25)	45 (23)	0.65 (0.40;1.06)	46 (31)	1.32 (0.76;2.27)	
P-trend			0.11		0.17	
1-SD increase			0.88 (0.74;1.04)		1.15 (0.93;1.41)	**0.04**

OR: Odds Ratio; 95% CI: 95% Confidence Interval; Q: quartile; SD: Standard Deviation. [1]Multinomial logistical regression models adjusted for age, sex, education, energy intake (kcal/day) with province of residence as a random effect. [2]*P*-value for the heterogeneity of effects. In bold: *P*<0.05.

more highly educated, less prone to have worked in farming or agriculture, and with a higher energy intake and lower alcohol consumption. Finally, controls with a greater adherence to a Mediterranean pattern were more likely to be men, physically active, showing a lower proportion of ever smokers and having worked in farming or agriculture, and a higher energy intake.

Figure 1 summarizes the adjusted ORs for the association between CLL and level of adherence to the Western, Prudent and Mediterranean dietary patterns. Individuals in the highest quartile of the Western score had an OR for CLL of 1.63 (95%CI: 1.11; 2.39) compared with individuals with low adherence (*P* for trend 0.02). Each SD increment in the score was associated with a 19% higher OR of having CLL (95%CI: 1.03; 1.37). No associations were observed for Mediterranean and Prudent diet patterns. The impact of each individual covariate (region, age, sex, education, and energy intake) in the association of the three dietary patterns and CLL is provided in *Online Supplementary Figure S2.*

Since CLL is more prevalent in men, who are also more likely to adhere to a Western dietary pattern (Table 1 and *Online Supplementary Figure S1*), all analyses were stratified according to sex. No differences across sexes were observed for any of the dietary patterns [*P*-heterogeneity (*P*-het): Western (0.79), Prudent (0.11) and Mediterranean (0.17); *data not shown*]. In addition, no differences were observed according to BMI, energy intake, tobacco, physical activity, working on a farm, and family history of hematologic malignancies (all *P* for interaction >0.05; *data not shown*).

Analyses according to Rai-stage did not show significant heterogeneity of effects for the Western or Prudent dietary patterns (*P*-het=0.50 and 0.17, respectively). However, weak opposite trends in relation to a Mediterranean diet pattern were observed; it was inversely associated (although not statistically significant) with Rai 0 CLL [OR 1-SD increase= 0.88 (95%CI: 0.74; 1.04)] and positively related with Rai I-IV CLL [OR 1-SD increase= 1.15 (95%CI: 0.93; 1.41)] (*P*-het=0.04) (Table 2).

Sensitivity analyses according to time from diagnosis to recruitment yielded similar results for the three dietary patterns (*Online Supplementary Table S2*). Similarly, excluding cases treated prior to consent (n=79) did not materially modify the results [*P*-het in trends: Western (0.25), Prudent (0.32) and Mediterranean (0.33)], but higher ORs for a Western dietary pattern were observed in cases treated prior to consent in comparison to those not treated (*Online Supplementary Table S3*).

Discussion

This study provides, for the first time, evidence of an association between adherence to a Western dietary pattern and CLL. By contrast, no associations were found for a Prudent or Mediterranean pattern.

There is limited evidence linking extrinsic-risk factors, and particularly diet, with non-Hodgkin lymphoma (NHL). In the 2007 report by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR),[3] the Panel decided not to make any judgements regarding the causality of associations between specific dietary factors and NHL, but pointed out a suggestive inverse association with vegetables, fruit, and alcoholic beverages, and a positive association with meat, total fat, body fatness, and dairy. Recent meta-analyses further support these associations,[36,37] but there is still not sufficient evidence to establish a causal role. Similarly, data on the association of diet and CLL are inconclusive and mainly arise from studies on nutrients or single food items. To our knowledge, 9 prospective studies[4-12] and 13 case-control studies[13-25] have been published on this topic. With the exception of a few studies that found positive associations with consumption of processed meat and poultry,[4] total carbohydrate[8] or fat (in women)[11] intake, and inverse associations with isoflavones consumption,[10] generally large prospective studies found no associations between a wide range of dietary factors and CLL. By contrast, case-control studies have yielded contradictory results for meat,[13,14,16,24,25] dairy products,[13-17] fish[15,18] or vegetables and fruit[14,16,19,22,23,25] intake.

Inconsistencies in previous epidemiological nutritional studies in part reflect the difficulty in disentangling the influence of single food items that, when consumed in combination, may be highly correlated and exert synergistic or antagonistic effects on CLL risk. The examination of dietary patterns, which better reflect the complexity of dietary intake, has been used to address such limitations.[26] So far, only a few studies have examined associations of dietary patterns and risk of CLL,[25,27,28] reporting inconclusive findings, mainly due to small sample size. Ollberding *et al*.[28] pointed out that a high adherence to a 'Meat, Fat and Sweets' dietary pattern, characterized by a high intake of French fries, red meat, processed meat, pizza, salty snacks, sweets and desserts, was associated with an increased risk of overall NHL (ORQ4 *vs.* Q1=3.6; 95%CI: 1.9, 6.8) in a Nebraska case-control study. This association was maintained when stratifying according to lymphoma subtypes but sub-analyses did not include CLL cases due to sample size (n=25). By contrast, a large prospective cohort in the US did not find associations with 'Fat and Meat' pattern and CLL etiology.[27] However, this pattern did not include sweets and deserts, sweetened beverages, or convenience foods, which may be important contributing factors of these associations. Thus, not only differences in the study design and setting, but also in food groups loaded in these data-driven analyses, should be carefully considered when comparing results. In line with our findings, no associations with overall NHL[25,27,28] or CLL[25,27] were detected for a 'healthy' dietary pattern characterized by high intake of fruit and vegetables.

We observed opposite trends in relation to a Mediterranean diet pattern and Rai stages, with stronger adherence among cases with higher disease severity (*P*-het=0.04). We hypothesize that reverse causality could partly explain these results. While Rai 0 patients are usually diagnosed in a routine blood test and present an indolent course, Rai I-IV are more prone to be symptomatic (e.g. night sweat, fatigue, weight loss or fever) and to receive active treatment. Thus, those patients with a more severe disease (and probably more concerned about their illness) would be more prone to shift towards a healthier dietary pattern. However, these results have to be taken with caution since none of the trends showed statistically significant associations.

Chronic lymphocytic leukemia is the most common leukemia in Western countries while its incidence is much lower in Eastern countries, where it accounts for only 1-3% of NHL in most series.[38] While genetic backgrounds may be responsible for some of the differences in the CLL incidence, some studies have suggested that environmental factors also play an important role. A dramatic increase in CLL incidence in Taiwan in recent years was associated with a strong birth-cohort effect, that corresponded to the Westernization of lifestyle in Taiwan since 1960.[39] In addition, a higher incidence of CLL has been reported among US-born Asians compared to foreign-born Asians, pointing out the influence of environmental factors that change with immigration and acculturation to a Westernized lifestyle.[40] Our results further support the view that adopting a Western diet could partly explain these incidence patterns.

A Western diet has been associated with obesity phenotypes,[41] including a higher waist-to-hip ratio, which has in turn been recently linked to higher OR of CLL, particularly in women, in the MCC-Spain study.[42] Despite the fact that CLL cases showed a higher waist-to-hip ratio than controls in our study, waist-to-hip ratio and BMI were not included as covariates in the final multiple-adjusted model since they did not change risk estimates. Hence, an independent effect of the Western dietary pattern may be contributing to CLL lymphomagenesis, which seems plausible from a mechanistic point of view. On one hand, it has been well-established that dietary changes, and particularly switching from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar Western diet, can induce alterations in microbiota composition.[43] Beyond its role in the biosynthesis of key components (e.g. vitamins, essential amino acids or short chain fatty acid byproducts), several studies using germ-free mice suggest that microbiota also plays a fundamental role on the induction, training, and function of the host immune system.[44] Exposure to a Western diet may have selected for a microbiota that lack the resilience and diversity required to establish balanced immune responses, and this phenomenon is proposed to account for some of the dramatic rise in autoimmune and chronic inflammatory disorders found in high-income countries. On the other hand, a diet high in fat, refined grains, red and processed meats, and sweets has been largely associated with higher levels of inflammatory markers[45] and with inflammation-related chronic diseases.[46] In particular in CLL, the strong production of inflammatory cytokines and chemokines accompanied by activation of intra-cellular pro-inflammatory pathways, and the presence of somatic mutations that activate pro-inflammatory signaling pathways, suggest that chronic inflammation plays a pathophysiological role in this disease.[47] Thus, an inflammation-related mechanism may in part underlie the observed associations with CLL, although no research on the inflammatory potential of diet and CLL risk has yet been conducted.

The dietary patterns used in this study were identified using the control population of a multicentric case-control study on female breast cancer in Spain.[30] By contrast, the MCC-Spain study included male participants, who may have different dietary habits. However, this difference does not preclude the application of the original scoring system over the current sample. Scores of adherence to dietary patterns can be calculated following the exact same rules over different populations, resulting in different levels of adherence while still being valid, as has been recently proved.[35] As a matter of fact, the current dietary patterns had previously been constructed in the MCC-study and a Western dietary pattern was positively associated with gastric,[48] breast[49] and colorectal[50] cancers.

One of the main limitations is the study design since case-control studies are prone to selection and recall biases. Measurement errors in the estimation of food intake due to the use of self-reported FFQ are also of some concern. However, the FFQ was validated in the Spanish population and included regional products.[32] Moreover, some questions about general dietary habits were included in the questionnaire and were used to adjust the responses to the FFQ following the methodology described in Calvert *et al*.[33] The inclusion of prevalent cases might be another cause for concern since patients who survived might have a very different etiology than those who died soon after diagnosis. In addition, diet can be influenced by many external factors and patients who survive longer might have substantially modified their diet. However, results of the sensitivity analysis suggested that the use of prevalent cases might not have introduced selective survival bias or reverse causation. We may have been limited by the small sample size and lack of statistical power to detect significant associations when evaluating certain subgroups. Finally, although we adjusted for a range of potential confounders, residual confounding factors cannot be totally ruled out.

The strengths of the study include the substantial sample size of CLL cases, with specific information on clinical presentation. We were able to collect detailed information on demographics and disease stage, and statistically adjust for a number of potential confounding factors. This allowed the evaluation of potential interactions of diet with numerous covariates and the exploration of the associations by stage. Finally, the multi-centric nature of the study, including both rural and urban areas, provided a wide geographic variability of dietary intake data.

In conclusion, in this Spanish population-based case-control study, greater adherence to a Western dietary pattern was associated with CLL. These novel results suggest that a proportion of CLL cases could be prevented by modifying dietary patterns. Further research, especially with a prospective design, is warranted to confirm these findings.

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