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Dietary factors and risk of chronic lymphocytic leukemia and small lymphocytic lymphoma: a pooled analysis of two prospective studies

Huei-Ting Tsai^{1,2}, Amanda J. Cross¹, Barry I. Graubard¹, Martin Oken³, Arthur Schatzkin¹, and Neil E. Caporaso¹

¹ Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892

² Cancer Control Program, Georgetown University Medical Center, Washington, DC 20007

³ Hubert H. Humphrey Cancer Center, North Memorial Medical Center, 3300 Oakdale Ave. N, Plaza 100, Robbinsdale, MN 55422

Abstract

Background—Other than male sex, family history, advanced age, and race, risk factors for chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) are unknown. Very few studies have investigated diet in relation to these leukemias, and no consistent associations are known.

Methods—Using two large prospective population-based studies, we evaluated the relationship between diet and CLL/SLL risk. Among 525,982 men and women free of cancer at enrollment, we identified 1,129 incident CLL/SLL cases during 11.2 years of follow-up.

Results—We found no associations between total fat, saturated fat, fiber, red meat, processed meat, fruit or vegetable intake and risk of CLL/SLL. We noted a suggestive positive association between body mass index (BMI) and CLL/SLL (hazard ratio =1.30; 95% confidence interval= 0.99-1.36).

Conclusion—We did not find any associations between foods or nutrients and CLL/SLL.

Impact—Our large prospective study indicates that diet may not play a role in CLL/SLL development.

Keywords

diet; chronic lymphocytic leukemia; body mass index; cohort study

Background

Chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) are the most common leukemias in the western hemisphere; because they share very similar demographic features and no decisive evidence supports differences in risk factors, many etiologic studies combine them. Advanced age, race (Caucasian>African American> Asian) and male gender are established risk factors for CLL/SLL; and familial and migration studies support a

genetic component. However, no environmental risk factors have been reproducibly identified.

Several studies have suggested associations between some dietary factors and CLL/SLL, but the findings are inconsistent due to small sample size and retrospective study designs (1-6). Given that fruits and vegetables contain antioxidants, and diets high in fat and animal protein may alter immunocompetence, we hypothesize that diet may play a role in CLL/SLL. We conducted an analysis in a pooled dataset of two large prospective studies.

Material and Methods

Study population

We pooled data from the National Institutes of Health (NIH)-AARP Diet and Health study and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial; details of their design have previously been described (7-8). Briefly, the NIH-AARP Diet and Health study is a cohort of 567,169 men and women aged 50-71 years from 8 US states. PLCO is a cancer screening trial of 155,000 men and women aged 55-74 years from 10 centers throughout the US. We restricted our analyses to Caucasians, without a personal history of cancer (except basal skin cancer) and excluded outliers for energy intake (top and bottom 1%) and body mass index (BMI) under 18.5 or over 50 kg/m².

Exposure assessment and endpoint ascertainment

Diet was assessed in both cohorts at baseline by a self-administered food frequency questionnaire – Diet History Questionnaire (DHQ), which has been validated using 24-hour dietary recalls (9). The DHQ assessed the usual frequency of consumption and portion size of foods and beverages over the previous 12 months. Dietary variables were energy adjusted by the nutrient density method. Incident CLL/SLL cases were identified by linkage to state cancer registries in the NIH-AARP Diet and Health study and through study screening centers and annual study questionnaires in the PLCO trial.

Statistical analysis

We used Wilcoxon rank-sum test to investigate intake distributions between cases and controls. Dietary variables were categorized into quartiles and the median of each quartile was used to compute p-trend values. We used Cox proportional hazards regression, with age as the underlying time metric, to estimate hazard ratios (HR) and 95% confidence intervals (CIs). Follow-up began from date of randomization or completion of questionnaire and ended at diagnosis of CLL/SLL, moving out of study areas, or through 2006 for the NIH-AARP Diet and Health study, or 2007 for the PLCO trial. We conducted sensitivity analyses that only included cases diagnosed after the first year of follow-up.

Results

We identified 1,129 incident CLL/SLL cases among 525,982 participants (median age: 63 years; 59% male) from the two cohorts during up to 11.2 years of follow-up (median: 10.5 years). Men had an increased risk of CLL/SLL (HR=1.67, 95% CI= 1.46, 1.90) compared with women (Table 1). In addition, there was a suggestive positive association for BMI and CLL/SLL (HR=1.30, 95% CI= 0.99, 1.69 for a BMI >35kg/m² compared to 25kg/m²). However, education, smoking, alcohol, or multivitamin use was not associated with CLL/SLL (Table 1).

Comparing those in the highest intake quartile to those in the lowest, we found no associations for total fat (HR=0.87, 95% CI= 0.73, 1.03), saturated fat (HR=0.87, 95% CI=

0.73, 1.03), fiber (HR=1.03, 95% CI= 0.87, 1.23), red meat (HR=0.90, 95% CI= 0.76, 1.08), processed meat (HR=0.88, 95% CI= 0.74, 1.05), vegetables (HR=0.93, 95% CI= 0.78, 1.11), or fruit (HR=0.93, 95% CI= 0.78, 1.12) with CLL/SLL (Table 2). Furthermore, we found no association between intake of foods with a high glycemic index or high glycemic load and CLL/SLL. Conducting a one-year lag analysis did not alter our findings.

Discussion

In this pooled analyses of over half a million people from two prospective studies, we found no associations between diet and CLL/SLL. The suggestive increased risk for CLL/SLL for those with a BMI over 25kg/m² requires further investigation.

Limited sample size and recall bias are major issues when investigating diet and non-Hodgkin lymphoma. Case-control studies report positive associations between fried red meat (4), processed meat (1), rice or pasta (2), fat and saturated fat (1, 5) and risk of CLL/SLL, findings not replicated in our study.

Although no foods or nutrients were associated with risk for CLL/SLL, we identified a suggestive positive association between BMI and CLL/SLL. Obesity can lead to decreased immune response and changes in endogenous hormone metabolism, which may increase risk of CLL/SLL. Studies with appropriate molecular markers, particularly relevant to immune and metabolic function, are desirable to further explore the association between BMI and CLL/SLL.

The strengths of our study include its large size and prospective dietary assessment. Nevertheless, our study was limited by having dietary data from a single time point and potential measurement error associated with self-reported assessment. In summary, we did not find any associations between foods or nutrients and CLL/SLL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Population characteristic and lifestyle factors in relation to risk of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) among 525,982 men and women from two cohort studies.

Factors	non-CLL/SLL (n= 524,853, %)	CLL/SLL (n=1,129, %)	Adjusted HR (95% CI)*
Age at baseline, years (median, range and interquartile range)	63 (50- 83, 9)	65 (51- 79, 8)	--
Male	308,916 (59)	791 (70) [‡]	1.67 (1.46, 1.90) [‡]
Current body mass index (BMI, kg/m ²) [‡]			
23.1 (18.5< BMI 25)	182,263 (35)	333 (30)	1.0
27.1 (25< BMI 30)	226,861 (43)	541 (48)	1.18 (1.03, 1.36) [§]
31.8 (30< BMI 35)	84,059 (16)	188 (17)	1.17 (0.98, 1.41)
37.7 (35<BMI 50)	31,670 (6)	67 (6)	1.30 (0.99, 1.69)
P for trend			0.56
Education			
Up to high school	135,699 (26)	297 (26)	1.0
Post high school other than college	55,026 (10)	141 (13)	1.21 (0.99, 1.48)
Some college	120,323 (23)	229 (20)	0.93 (0.78, 1.10)
College and post graduate	203,291 (39)	443 (39)	1.00 (0.86, 1.16)
missing	15,014 (2)	19 (2)	
P for trend			0.42
Smoking status			
Never	193,792 (37)	410 (36)	1.0
Former	256,833 (49)	598 (53)	1.04 (0.91, 1.20)
Current	59,341 (11)	94 (8)	0.94 (0.78, 1.13)
missing	14,887 (3)	27 (2)	
Alcohol consumption (g/day) [‡]			
0	33,129 (6)	64 (6)	1.0
1.2 (0< alcohol 15)	379,627 (72)	813 (72)	1.05 (0.81, 1.36)
28.3 (>15)	112,097 (21)	252 (22)	1.01 (0.77, 1.33)
P for trend			0.65
Multivitamin use			
No	81,528 (16)	177 (16)	1.0
Yes	317,095 (60)	685 (61)	1.04 (0.88, 1.23)
Missing	126,230 (24)	267 (24)	

* adjusted for age, sex, body mass index

[‡] median (range)

[‡] p<0.001

[§] p<0.05

Table 2

Diet in relation to risk of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) among 525,982 men and women from two cohort studies.

Dietary factors	CLL/SLL (n=1,129, %)	Adjusted HR (95% CI)*
Total fat (g/1000 kcal) [†]		
24.0 (0.8, 28.2)	294 (26)	1.0
31.3 (28.2, 34.1)	305 (27)	1.01 (0.86, 1.19)
36.8 (34.1, 39.8)	263 (23)	0.85 (0.72, 1.01)
43.6 (39.8, 80.7)	267 (24)	0.87 (0.73, 1.03)
P for trend		0.04
Saturated fat (g/1000 kcal) [†]		
6.9 (0.2, 8.3)	284 (25)	1.0
9.4 (8.3, 10.5)	311 (28)	1.04 (0.89, 1.23)
11.5 (10.5, 12.7)	276 (24)	0.93 (0.79, 1.10)
14.4 (12.7, 35.8)	258 (23)	0.87 (0.73, 1.03)
P for trend		0.06
Fiber CSFII (g/1000 kcal) [†]		
6.8 (0.3, 8.1)	274 (24)	1.0
9.2 (8.1, 10.2)	291 (26)	1.04 (0.88, 1.23)
11.4 (10.2, 12.8)	292 (26)	1.08 (0.91, 1.28)
15.0 (12.8, 57.2)	272 (24)	1.03 (0.87, 1.23)
P for trend		0.70
Red meat (g/1000 kcal) [†]		
12.4 (0.0, 19.6)	274 (24)	1.0
25.8 (19.6, 31.8)	295 (26)	1.01 (0.85, 1.19)
38.5 (31.8, 46.7)	288 (26)	0.96 (0.81, 1.14)
59.0 (46.7, 250.5)	272 (24)	0.90 (0.76, 1.08)
P for trend		0.22
Processed meat (g/1000 kcal) [†]		
2.1 (0.0, 3.8)	262 (23)	1.0
5.6 (3.8, 7.6)	282 (25)	0.98 (0.83, 1.17)
10.1 (7.6, 13.8)	313 (28)	1.04 (0.87, 1.23)
20.2 (13.8, 256.4)	272 (24)	0.88 (0.74, 1.05)
P for trend		0.14
Vegetables (g/1000 kcal) [†]		
80.5 (0, 106.3)	276 (24)	1.0
128.6 (106.3, 151.6)	303 (27)	1.08 (0.92, 1.28)
177.7 (151.6, 211.8)	314 (28)	1.17 (0.99, 1.38)
268.9 (211.8, 2138.5)	236 (21)	0.93 (0.78, 1.11)
P for trend		0.48
Fruit (g/1000 kcal) [†]		

Dietary factors	CLL/SLL (n=1,129, %)	Adjusted HR (95% CI)[*]
45.1 (0.0, 79.8)	266 (24)	1.0
112.5 (79.8, 146.9)	317 (28)	1.14 (0.97, 1.35)
185.2 (146.9, 234.8)	299 (26)	1.08 (0.91, 1.28)
314.9 (234.8, 1895.2)	247 (22)	0.93 (0.78, 1.12)
P for trend		0.24
Glycemic index [†]		
49.8 (33.0, 51.5)	254 (23)	1.0
52.7 (51.5, 53.8)	299 (26)	1.13 (0.95, 1.33)
54.9 (53.8, 56.1)	288 (26)	1.07 (0.90, 1.27)
57.7 (56.1, 84.1)	288 (26)	1.08 (0.91, 1.28)
P for trend		0.50
Glycemic load [‡]		
50.4 (4.1, 56.2)	275 (24)	1.0
60.4 (56.2, 64.2)	271 (24)	0.99 (0.84, 1.17)
67.9 (64.2, 72.1)	281 (25)	1.03 (0.87, 1.22)
78.0 (72.1, 151.2)	302 (27)	1.15 (0.98, 1.36)
P for trend		0.08

^{*} adjusted for age, sex, body mass index

[†] median (range)

[‡] p<0.001

[§] p<0.05