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Malignant Lymphomas

Family clustering of blood cancers as a risk factor for lymphoid neoplasms

Family aggregation of cancer was significantly more common among 588 incident cases with lymphoid neoplasms than among 631 controls (OR: 1.4; 95%CI= 1.1-1.8, *p* value=0.004). This association was of particular relevance among cases of multiple myeloma and chronic lymphocytic leukemia, with a 2-fold increased risk, the latter also showing an almost 4-fold increased risk of family aggregation of hematologic cancers.

haematologica 2005; 90:416-417
(*http://www.haematologica.org/journal/2005/03/416.html*)

A 2- to 4-fold increased risk of lymphoma has been identified in patients with a family history of hematologic disease or lymphoma in first-degree relatives,[1-3] with chronic lymphocytic leukaemia (CLL),[4,5] multiple myeloma (MM)[6] and Hodgkin's lymphoma (HL)[7-9] being the three entities more consistently reported. The purpose of this study was to evaluate the risk of lymphoid neoplasms and its association with a family history of cancer.

The study was conducted in four Spanish hospitals during the period from 1998 to 2002.[10] Cases were 588 consecutive patients newly diagnosed with a lymphoid neoplasm according to the WHO classification. Simultaneously, 631 controls were randomly selected from hospitalized patients and frequency-matched to cases by age (±5 years), gender and study center. Personal interviews were conducted in order to collect data on demographics, environmental exposure to risk factors, medical and family history, including cancer. The site of cancer age at diagnosis, and status of any affected relatives with cancer were requested. Informed consent was obtained from all subjects prior to enrollment, and the Institutional Review Boards from each of the participating centers approved the study. Odds ratio and 95% confidence intervals were calculated from logistic regression analysis (OR, 95%CI) in order to estimate the degree of association between lymphoid neoplasms and family history. Table 1 shows that cases and controls were comparable for age, sex, recruitment area and educational level. The probability of having a first-degree relative with cancer was significantly higher among the patients with lymphoid neoplasm (252/588) than among the control subjects (218/631) (43% vs.35%, $p<0.05$). The cases also tended to have a higher number of affected relatives than did the controls (more than 1 affected relative: 23.8% vs. 19.3%, respectively; $p>0.05$) (*data not shown*) but this difference was not statistically significant. All-lymphoma patients, B-cell lymphoma, CLL and MM patients were significantly more likely to report a first-degree relative with any cancer, with a risk increase ranging from 1.4 up to 2.1 among CLL patients (Table 2). A family history of hematologic cancer was statistically associated only with CLL patients, based on the fact that 10 out of 125 cases with CLL reported at least 1 relative with a hematologic cancer. Of these, 4 affected relatives had been diagnosed as having acute leukemia, 3 with CLL (2 out of 3 confirmed by medical records), 2 with lymphoma and 1 with MM. The average age at diagnosis was 54 years for CLL patients and 52 for the affected relatives ($p>0.05$). Only one CLL case had an affected relative who was diagnosed with cancer at a younger age. One patient reported more than 1 affected relative with a hematologic cancer: the father, at the age of 85 years, and a sister at the age of 56 years. In one family of a case patient with HL, the father and a brother were diagnosed with the same histology as the index case. The data presented shows a significant familial aggregation of cancer cases among subjects with CLL and MM. Cases were at least 40% more likely than controls to report a first degree relative with cancer. This proportion reached over 200% among CLL patients. Furthermore, 8% of CLL patients show a significant familial aggregation of hematologic cancers. These results are in agreement with the existing literature on the magnitude of the association and with the identification of CLL and MM as the most likely histologies to show fam-

Table 1. Characteristics of the study population.

	Cases (n=588)	*Controls (n=631)*	*p*
Median age (range)	64 (17-89)	63 (17-96)	0.12
Gender			
Male	330 (56%)	328 (52%)	0.15
Female	258 (44%)	303 (48%)	
Recruitment area			
Barcelona	465 (79%)	527 (83%)	0.12
Madrid	70 (12%)	55 (9%)	
Tarragona	53 (9%)	49 (8%)	
Educational level attained			
Never attended school	76 (13%)	68 (11%)	
No degree reached	124 (21%)	150 (24%)	0.51
Primary school	240 (41%)	243 (38%)	
Secondary school and higher	109 (18%)	120 (19%)	
Other	39 (7%)	50 (8%)	
First-degree relatives with cancer			
No	336 (57%)	413 (65%)	0.004
Yes	252 (43%)	218 (35%)	
Number of relatives			
1	192 (33%)	176 (28%)	0.5
2	47 (8%)	33 (5%)	
3	11 (2%)	6 (1%)	
4	2 (0%)	3 (1%)	

Table 2. Risk of a specific lymphoid neoplasm category being associated with a family history of any cancer and with a family history of hematologic cancer.

		Any Type of Cancer			Hematologic Cancer		
	N Total Subjects	N[1]	OR (IC 95%)	p	N	OR (IC 95%)	p
Controls	631	218	Reference		22	Reference	
Cases	588	252	1.4 (1.1-1.8)	0.004	27	1.6 (0.9-2.9)	0.140
B-cell	476	217	1.5 (1.2-2.0)	0.001	23	1.7 (0.9-3.1)	0.106
Chronic lymphocytic leukemia	125	68	2.1 (1.4-3.2)	< 0.001	10	3.7 (1.6-8.8)	0.003
Multiple myeloma	84	45	1.9 (1.2-3.1)	0.006	5	1.8 (0.6-5.2)	0.262
Marginal zone B-cell	57	24	1.3 (0.7-2.3)	0.389	0	–	
Follicular lymphoma	43	19	1.4 (0.7-2.7)	0.290	0	–	
Diffuse large-cell	101	40	1.3 (0.8-2.0)	0.239	4	1.3 (0.4-4.1)	0.610
Other B-cell lymphoma[2]	66	21	0.9 (0.5-1.6)	0.684	4	1.7 (0.5-5.2)	0.373
Hodgkin's lymphoma	66	17	0.9 (0.6-1.7)	0.828	2	1.2 (0.3-5.8)	0.799
T-Cell	46	18	1.1 (0.6-2.1)	0.749	2	1.3 (0.3-5.9)	0.764
Mycosis fungoides/Sézary's syndrome	23	8	0.8 (0.3-2)	0.657	0	–	
Other T-cell lymphoma[3]	23	10	1.5 (0.6-3.5)	0.383	2	2.7 (0.5-13.9)	0.249

[1]At least one relative with any type of cancer (hematologic cancer included); [2]Other B-cell lymphoma includes: lymphoplasmacytic lymphoma (n=5), mantle cell lymphoma (n=4), B lymphoblastic lymphoma/leukemia (n=4), Burkitt's lymphoma (n=1), Burkitt's-like lymphoma (n= 2), B-cell NOS lymphoma (n=5); [3]other T-cell lymphoma includes: large granular lymphocytic leukemia (n=1), peripheral T-cell lymphoma (n=2), angioimmunoblastic T-cell lymphoma (n=2), angiocentric lymphoma (n=2), anaplastic large cell lymphoma (n=2), anaplastic large cell lymphoma Hodgkin-like (n=1).

ily aggregation.[1-6] The large Swedish family-cancer database[5] identified a similar risk of CLL in parents, offspring and siblings of CLL patients suggesting a potential effect of a dominant or co-dominant gene against a recessive gene. The design and size of our study did not allow these estimations. However, in agreement with Goldin *et al.*,[5] we could not identify an association of family risk with the age at diagnosis. One of the main limitations when requesting a family history of cancer is that information may be affected by a recall bias, since cases are more likely than controls to report an affected relative with a similar disease. Although this type of bias cannot be precluded with certainty, we aimed to reduce its magnitude by requesting only the family history of first-degree relatives and enquiring about any malignancies, as well as other medical conditions.

We conclude that familial aggregation of cancer was identified in a small proportion of lymphoma cases. Within all categories of lymphoid neoplasms, inherited genetic pathways are probable among CLL and MM subjects, although shared environmental factors cannot be ruled out. Given the few families affected in an average sized study, large collaborative studies are needed in order to further evaluate family aggregation as a marker of an inherited genetic etiology of lymphomas.

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Funding: this work was supported by the Spanish Ministry of Health grant 98-0066/04, FIS_RCSP and 5th frame Quality of Life Program QLK4-CT-2000-00422. This case-control study was undertaken within the framework of the EPILYMPH international study. We thank R. Font for data collection, data management and statistical analysis and Dr. A. Domingo-Clarós for her valuable comments.

Key words: family history, lymphoma, heritability.

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