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Influence of familial cancer history on lymphoid neoplasms risk validated in the large European case-control study epilymph

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ABSTRACT

Lymphomas have a potentially important familial component; large studies using recent classification systems are lacking. Based on a multicentre case-control study in seven European countries, we recruited 2480 cases of lymphoid neoplasms (LN) and 2540 controls, matched by country, age and sex. Diagnoses were established according to the World Health Organisation (WHO) classification. We estimated odds ratios (OR) and 95% confidence intervals (CI) for cancer in first-degree relatives and for the kind of relative affected. The OR of LN for a family history of haematological cancer was 1.6 (OR = 1.2–2.1). The OR was particularly high for chronic lymphocytic leukaemia (CLL) (OR = 2.9 [1.9–4.5]). A familial case of lymphoma increased the risk of Hodgkin's lymphoma (HL) (OR = 3.4 [1.5–7.8]). No increased risk was observed for diffuse large B-cell and follicular lymphomas. For CLL and HL, the risk was similar in parents, offspring and siblings. Our study suggests familial aggregation of CLL with a family history of haematological cancer and of HL with a family history of lymphoma. The transmission pattern suggests a dominant model of heredity.

1. Introduction

Lymphoid neoplasms (LN) represent a heterogeneous group of tumours sensitive to immunosuppression. Previous studies investigating familial aggregation have tended to ignore the biological heterogeneity of these diseases and have focused on major groups such as non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM).[1–10] Few studies have evaluated separately familial aggregation in sub-entities such as diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).[11–15]

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The lack of specificity in the characterisation of LN might explain why results of previous studies have been inconsistent; several reports have provided evidence for a dominant transmission of susceptibility to alleles whereas others suggested a recessive mode of inheritance.

We estimated the risk of LN associated with a family history of cancer among first-degree relatives, paying special attention to haematological cancers.

2. Materials and methods

2.1. Study design

Epilymph is a multicentre case-control study of LN conducted in seven European countries between 1998 and 2004: Czech Republic, Finland, France, Germany, Ireland, Italy and Spain. It included a standardised questionnaire-based interview on lifestyle and professional activities and the collection of clinical and biological data. All cases and controls were informed about the aim of the study and agreed to participate upon signature of an informed consent form, and the Institutional Review Boards of participating centres approved the study.

Eligible patients were aged 18 or more and represented a consecutive series of newly diagnosed (⩽3 months) cases of LN according to the World Health Organisation (WHO) classification.[16] All diagnoses were confirmed by pathological reports and their validity was ascertained by an expert panel of eight pathologists from the different countries. A total of 2480 cases were included, with an overall refusal rate of 12.4% (ranging from 7.0% in Italy to 17.9% in Spain).

Control recruitment was population-based in two countries (Germany and Italy), and hospital-based in the other countries. In population-based centres, controls were selected from the same geographical regions as the cases, based on random selection of the population register. In the other countries, controls were selected in the same hospitals as the index cases from a pre-selected list of diseases, excluding autoimmune or infection-related conditions. No single disease was diagnosed in more than 10% of controls. Matching was either frequency- or individual-based, depending on the centre, and included area of residence, age and sex. A total of 2540 controls were included, with an overall refusal rate of 20.8% (ranging from 3.6% to 40.0%) for hospitalised controls and 49.8% for population controls (ranging from 34.0% to 55.6%).

2.2. Questionnaire

Personal interviews were conducted with all subjects by trained interviewers. The interview provided information on the subject's demographic history, and potential risk factors including multiple environmental and occupational exposures, a complete medical history, reproductive history and familial history of cancer.

With respect to familial history of cancer, respondents were asked about numbers of children, brothers and sisters with their year of birth, and about cases of cancer among first-degree relatives, including age at diagnosis, current age and type of cancer for each case. The cancers among relatives were classified according to the ICD-10 classification.

2.3. Statistical analyses

Cancers in family members were grouped as follows: haematological cancer (C81, C83, C85, C90–C92, C95 and C96.9), upper aero-digestive tract (C00, C02–C06, C14, C15, C30 and C32), digestive tract (C16–C26), urinary tract (C64, C67 and C68), respiratory system (C34, C38, C39 and C45), gynaecological (C53–C57), breast (C50), brain (C71), prostate (C61), skin and bone (C40, C41, C43 and C44). In further analyses, leukaemias (C91, C92 and C95) and lymphomas (with no distinction between Hodgkin's and non-Hodgkin's lymphomas) (C81, C83, C85 and C96.9 with "lymphoma" specified) of relatives were separated.

The initial analysis focused on the report of at least one familial cancer among first-degree relatives. Subsequently, we compared the occurrence of cancer in siblings with this risk in parents and offspring, since transmission through a recessive gene would imply a higher risk if siblings of the index case were affected compared to parents and offspring, whereas a dominant gene would imply equal risks.[4] Regression models were adjusted for number of relevant relatives.

Furthermore, the analysis for haematological cancers was subdivided by the median age of the study participants, i.e. 60 years old. We compared age at diagnosis between sporadic and familial cases.

A total of 33 cases and 27 controls were excluded due to various reasons including adoption and incomplete information on family history.

The odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated using unconditional logistic regression, with adjustment for age (continuous), sex, educational level (low, median and high) and country. We assigned 21 cases and 14 controls with no information on an educational level to the median class of educational level of the relevant country. Exposure covariates were categorised based upon their distribution among the controls. For all cancers, we subdivided the analysis by gender and type of controls, whether hospital or population controls, to explore for any possible difference in risk. All the analyses were conducted using R 2.0.0 software.

3. Results

3.1. Cases

Socio-demographic characteristics of cases are reported in Table 1. Cases were similar to controls according to educational level ($\chi^2 = 1.53$, $df = 2$, $p = 0.47$). Table 2 shows the number of cases by pathological entities defined according to the *International Classification of Diseases for Oncology, Third Edition* (ICD-O3). The three principal entities were B-NHL (79.6%), HL (14.4%) and T-NHL (5.8%). Among mature B-NHL, the most frequently represented LN sub-type was DLBCL (24.0%) followed by CLL (16.7%), MM (11.3%) and FL (11.0%).

3.2. Family history of cancer

Cases were similar to controls according to the number of first-degree relatives with a family history of cancer (χ^2= 1.43, $df = 3$, $p = 0.70$). Even though the numbers were small,

Table 1 – Characteristics of cases and controls

	Controls		Cases	
	N	%	N	%
Age (years)				
⩽30	236	9.3	242	9.8
31–40	269	10.6	252	10.2
41–50	333	13.1	316	12.7
51–60	543	21.4	509	20.5
61–70	661	26.0	676	27.3
⩾71	498	19.6	485	19.5
Sex				
Males	1341	52.8	1399	56.4
Females	1199	47.2	1081	43.6
Education level				
Low	1132	44.6	1101	44.4
Medium	1004	39.5	949	38.3
High	390	15.4	409	16.5
NA	14	0.6	21	0.8
Country				
Czech Republic	304	12.0	293	11.8
Finland	75	3.0	118	4.8
France	276	10.9	298	12.0
Germany	710	28.0	710	28.6
Ireland	208	8.2	208	8.4
Italy	336	13.2	262	10.6
Spain	631	24.8	591	23.8
Number of relatives with family history of cancer				
1	737	29.0	744	30.0
2	204	8.0	184	7.4
3	40	1.6	41	1.7
⩾4	13	0.5	10	0.4
Number of relatives with family history of haematological cancer				
1	87	3.4	120	4.8
2	0	0.0	8	0.3
Number of affected family members with a haematological disease by relationship to the proband				
Parents	45		65	
Siblings	35		56	
Offspring	7		14	
NA	0		1	
Total	2540		2480	

cases seemed to have more first-degree relatives with a family history of haematological cancer than controls ($\chi^2 = 14.80$, $p = 0.001$ estimated by Monte Carlo simulation with 2000 replicates). After grouping parents and offspring, cases were similar to controls according to number of affected family members with a haematological disease by relationship to the proband ($\chi^2 = 0.45$, $df = 1$, $p = 0.50$) (Table 1).

A family history of haematological cancer among first-degree relatives increased the risk of LN by 60% (OR = 1.60, 95% CI 1.21–2.12) (Table 3). Risk did not vary according to whether the family history occurred among parents/offspring or siblings, or whether age at diagnosis in the proband was lower/equal or greater than 60. Risk did not vary by main pathological entity of LN in the proband, although the number of cases of HL and T-cell lymphoma was small. Instead, there was some evidence of a stronger association with lymphoma as opposed to leukaemia among family members (p for difference = 0.25). This was most apparent among HL cases (p for difference = 0.021).

Regarding B-NHL sub-types, a family history of haematological cancer strongly increased CLL risk (OR = 2.94, 95% CI 1.94–4.45), which was higher among probands with an age at onset lower or equal to 60 (OR = 4.10, 95% CI 2.29–7.37) (Table 4). Whether lymphoma or leukaemia was the previous haematological cancer among first-degree relatives did not affect CLL risk. No such increase in risk was observed for DLBCL, FL or MM. We observed an important increase in the risk of acute lymphoblastic leukaemia with a family history of haematological cancer (OR = 5.33, 95% CI 1.92–14.78). However, this result was based on only five analysed cases (not shown in the tables).

Age at diagnosis of familial CLL cases seemed to be younger (57.6 years) than sporadic CLL cases (64.1 years) ($p = 0.04$). Conversely, sporadic and familial cases of lymphoma revealed the same age at diagnosis (54.0 versus 52.9, $p = 0.78$).

Risks of LN with a family history of haematological cancer did not vary by type of controls, whether hospital-based or population-based, or by gender.

A family history of solid tumours did not increase the risk of LN overall or by sub-type (Table 5). Nevertheless, we observed a few associations with specific B-cell sub-entities: a family history of breast cancer, and skin and bone cancer

Table 2 – Cases by lymphoid neoplasm sub-types, according to the ICD-O3 classification

Groups	ICD-O3[a]	Male	Female	Total (%)
Malignant lymphoma, Not otherwise specified (Nos)	9590	3	3	6 (0.2)
Non-Hodgkin's B-cell lymphoma				
Nos	9591	52	35	87 (3.5)
Precursor B-cell lymphoblastic lymphoma/leukaemia	9835, 9728, 9836	23	26	49 (2.0)
Mature				
Diffuse large B-cell lymphoma	9679, 9680, 9683, 9684, 9687, 9826	323	271	594 (24.0)
Follicular lymphoma	9690, 9691, 9695, 9698	124	148	272 (11.0)
Multiple myeloma	9731, 9732, 9734	160	121	281 (11.3)
B-cell CLL/B prolympocytic leukaemia	9670, 9823, 9833	263	152	415 (16.7)
Others				
Hairy cell leukaemia	9940	15	2	17 (0.7)
LPL/Waldenstrom disease/ IPD	9671, 9761	28	16	44 (1.8)
Mantle cell lymphoma	9673	51	20	71 (2.9)
Marginal zone B-cell lymphoma, Nos	9699	53	49	102 (4.1)
Splenic marginal zone B-cell lymphoma	9689	18	21	39 (1.6)
Hodgkin's lymphoma	9596, 9650, 9651, 9652, 9653, 9659, 9663, 9665, 9667	197	161	358 (14.4)
Non-Hodgkin's NK- and T-cell lymphoma	9700, 9701, 9702, 9705, 9714, 9716, 9717, 9718, 9719, 9729, 9831, 9834, 9837	89	56	145 (5.8)
Total		1399	1081	2480 (100)

a All codes are malignant diseases (/3).

Table 3 – Odds ratio (OR) and 95% confidence limits for subjects with lymphoid neoplasms, B-NHL, T-NHL and HL and family history of haematological cancers

	Controls	LN		B-NHL		HL		T-NHL	
	N	N	OR	N	OR	N	OR	N	OR
All haematological cancers	**87**	**128**	**1.60 [1.21–2.12]**	**111**	**1.67 [1.25–2.24]**	**12**	**1.57 [0.82–3.03]**	**5**	**1.12 [0.44–2.82]**
Parents/Offspring	52	77	1.54 [1.08–2.21]	70	1.75 [1.21–2.52]	5	1.06 [0.41–2.76]	2	0.73 [0.17–3.03]
Siblings	35	53	1.72 [1.11–2.65]	42	1.56 [0.99–2.47]	8	2.92 [1.22–6.96]	3	1.81 [0.54–6.09]
Age at diagnosis of proband									
Early onset (⩽60)	48	69	1.62 [1.11–2.37]	55	1.59 [1.06–2.38]	11	1.84 [0.90–3.75]	3	1.30 [0.39–4.36]
Late onset (>60)	39	59	1.62 [1.07–2.46]	56	1.70 [1.11–2.59]	1	0.75 [0.10–5.67]	2	0.93 [0.22–4.02]
Leukaemia	**61**	**84**	**1.48 [1.06–2.08]**	**78**	**1.65 [1.17–2.33]**	**3**	**0.67 [0.20–2.24]**	**3**	**0.98 [0.30–3.18]**
Parents/Offspring	40	54	1.41 [0.93–2.13]	51	1.64 [1.07–2.50]	1	0.30 [0.04–2.24]	2	0.96 [0.23–4.04]
Siblings	21	30	1.64 [0.93–2.88]	27	1.66 [0.93–2.97]	2	1.86 [0.40–8.79]	1	1.09 [0.14–8.29]
Age at diagnosis of proband									
Early onset (⩽60)	32	41	1.45 [0.90–2.32]	37	1.61 [0.99–2.62]	2	0.57 [0.13–2.51]	2	1.37 [0.32–5.98]
Late onset (>60)	29	43	1.56 [0.96–2.52]	41	1.64 [1.00–2.67]	1	0.99 [0.13–7.58]	1	0.67 [0.09–5.03]
Lymphoma	**23**	**41**	**1.93 [1.15–3.23]**	**30**	**1.72 [0.99–2.99]**	**9**	**3.36 [1.45–7.78]**	**2**	**1.63 [0.37–7.12]**
Parents/Offspring	10	20	2.06 [0.96–4.42]	16	2.09 [0.94–4.65]	4	3.76 [1.13–12.54]	0	–
Siblings	13	22	1.86 [0.93–3.73]	14	1.41 [0.65–3.03]	6	3.86 [1.30–11.47]	2	2.95 [0.64–13.65]
Age at diagnosis of proband									
Early onset (⩽60)	15	27	2.00 [1.05–3.79]	17	1.51 [0.74–3.08]	9	4.19 [1.72–10.24]	1	1.25 [0.16–9.93]
Late onset (>60)	8	14	1.94 [0.81–4.67]	13	1.97 [0.81–4.80]	0	–	1	2.25 [0.27–19.14]

All results were adjusted for age, sex, socio-economic level and centre.

increased the risk of MM (OR = 1.53, 95% CI 1.00–2.34 and OR = 2.08, 95% CI 1.09–3.99, respectively); a family history of upper aero-digestive tract cancer increased the risk of lymphoplasmocytic lymphoma (OR = 3.38, 95% CI 1.22–9.33); a family history of brain cancer increased the risk of mycosis fungoides (OR = 4.50, 95% CI 1.24–16.33) and a family history of lung/bronchus cancer increased the risk of HL, mixed-cellularity sub-type (OR = 3.30, 95% CI 1.53–7.15). The risk of LN with a family history of solid tumours did not vary by type of controls, whether hospital-based or population-based, or by gender.

4. Discussion

This report from the Epilymph multicentre case-control study identifies an association between a family history of haematological cancer and the risk of LN. These results confirm a number of previous studies based either on case-control design[1–3,10,12,17] or on linkage of cancer registries data.[4,5,8,14,15]

We found a risk of CLL associated with a family history of haematological cancer. As these results have already been reported for the Spanish series,[3] we specifically checked that the risk was still present without these data (OR = 3.07, 95%

Table 4 – Odds ratio (OR) and 95% confidence limits for subjects with B-NHL sub-types and family history of haematological cancers

	DLBCL		FL		MM		CLL	
	N	OR	N	OR	N	OR	N	OR
All haematological cancers	**22**	**1.12 [0.69–1.81]**	**10**	**0.99 [0.50–1.95]**	**14**	**1.45 [0.80–2.61]**	**37**	**2.94 [1.94–4.45]**
Parents/Offspring	13	1.11 [0.60–2.07]	6	0.97 [0.41–2.30]	9	1.63 [0.79–3.39]	24	3.35 [2.00–5.60]
Siblings	8	1.01 [0.46–2.21]	4	1.03 [0.36–2.96]	6	1.39 [0.57–3.40]	14	2.44 [1.27–4.69]
Age at diagnosis of proband								
Early onset (⩽60)	11	1.01 [0.51–1.99]	6	0.87 [0.36–2.10]	3	0.61 [0.18–2.02]	21	4.10 [2.29–7.37]
Late onset (>60)	11	1.35 [0.68–2.69]	4	0.98 [0.34–2.84]	11	2.16 [1.06–4.39]	16	1.92 [1.04–3.54]
Leukaemia	**16**	**1.18 [0.67–2.08]**	**7**	**1.03 [0.46–2.29]**	**11**	**1.49 [0.77–2.91]**	**26**	**2.74 [1.68–4.47]**
Parents/Offspring	11	1.24 [0.63–2.45]	5	1.10 [0.42–2.84]	5	1.11 [0.43–2.86]	18	3.06 [1.70–5.51]
Siblings	5	1.09 [0.40–2.95]	2	0.88 [0.20–3.81]	6	2.07 [0.81–5.31]	8	2.14 [0.92–5.00]
Age at diagnosis of proband								
Early onset (⩽60)	11	1.61 [0.79–3.29]	4	0.84 [0.29–2.47]	2	0.53 [0.12–2.28]	14	3.72 [1.86–7.45]
Late onset (>60)	5	0.82 [0.31–2.14]	3	1.11 [0.32–3.77]	9	2.28 [1.04–5.01]	12	1.97 [0.98–3.98]
Lymphoma	**5**	**0.92 [0.34–2.47]**	**3**	**1.02 [0.30–3.48]**	**4**	**1.81 [0.61–5.38]**	**9**	**3.19 [1.41–7.19]**
Parents/Offspring	2	0.84 [0.18–3.97]	1	0.72 [0.09–5.78]	4	4.09 [1.23–13.57]	4	3.84 [1.15–12.83]
Siblings	3	0.95 [0.27–3.41]	2	1.31 [0.29–6.02]	0	–	5	2.80 [0.95–8.32]
Age at diagnosis of proband								
Early onset (⩽60)	0	–	2	0.98 [0.21–4.50]	2	1.66 [0.36–7.66]	6	4.91 [1.74–13.89]
Late onset (>60)	5	3.07 [0.99–9.56]	1	0.89 [0.11–7.43]	2	2.02 [0.41–9.99]	3	1.67 [0.43–6.51]

All results were adjusted for age, sex, socio-economic level and centre.

Table 5 – Odds ratio (OR) and 95% confidence limits for subjects with lymphoid neoplasms, B-NHL, T-NHL and HL and family history of solid cancers

	Controls	LN		B-NHL		HL		T-NHL	
	N	N	OR	N	OR	N	OR	N	OR
Brain	42	31	0.75 [0.47–1.20]	26	0.75 [0.45–1.23]	2	0.55 [0.13–2.40]	3	1.26 [0.38–4.17]
Upper aero-digestive tract	82	68	0.88 [0.63–1.23]	57	0.88 [0.62–1.25]	6	0.92 [0.38–2.22]	5	1.19 [0.47–3.03]
Digestive tract	356	343	0.99 [0.84–1.17]	306	1.05 [0.89–1.24]	20	0.64 [0.40–1.05]	17	0.84 [0.50–1.43]
Lung and bronchus	157	149	1.00 [0.79–1.26]	121	0.98 [0.76–1.25]	21	1.64 [0.98–2.73]	7	0.84 [0.39–1.85]
Urology	47	37	0.82 [0.53–1.27]	32	0.83 [0.53–1.32]	2	0.60 [0.14–2.56]	3	1.20 [0.37–3.95]
Gynaecology	83	77	0.94 [0.68–1.29]	66	0.95 [0.68–1.33]	9	1.14 [0.55–2.38]	2	0.44 [0.11–1.83]
Breast	163	150	0.96 [0.76–1.21]	129	0.99 [0.78–1.26]	15	1.01 [0.57–1.80]	6	0.69 [0.30–1.59]
Prostate	77	84	1.10 [0.80–1.51]	71	1.12 [0.80–1.56]	6	0.93 [0.39–2.23]	7	1.64 [0.73–3.65]
Skin and bone	61	58	1.00 [0.70–1.45]	49	1.05 [0.72–1.55]	5	0.72 [0.28–1.87]	4	1.25 [0.44–3.51]

All results were adjusted for age, sex, socio-economic level, centre and family size.

CI 1.89–4.98). The risk of CLL did not vary with a familial history of leukaemia or lymphoma. This contrasts with the Swedish Family–Cancer Database in which the CLL risk was higher with a family history of leukaemia compared with lymphoma.[5]

The strong association observed between a familial history of lymphoma (but not of leukaemia) and HL confirms the results reported from Israel[8] and Sweden and Denmark.[4] We could not assess the effect of family history of lymphoma on age at diagnosis of HL in our study because of the great difference between the age distribution of HL cases and that of controls, selected to match the age distribution of LN overall. The median age among HL cases was 33 years, and using this age as a cutoff resulted in one control only with a familial history of lymphoma, consequently yielding unstable results (data not shown).

We did not observe an increase in the risk of DLBCL and FL. In contrast to two population-based case-control studies in the USA, where a 5.4-fold increase in the risk of diffuse NHL was estimated among subjects who had a sibling with lymphoma,[11] and a 4.5-fold increased risk was observed for FL among subjects who had a relative with NHL.[12] Also, another study observed a two- to three-fold increased risk for FL and DLBCL with a familial history of haematological cancer.[13] In two other studies, using the Swedish Cancer Registry database,[14,15] a familial aggregation of DLBCL and FL were observed. Nevertheless, three of these studies were smaller than ours and were thus likely to represent false-positive associations, and two studies used older classification systems. Therefore, the hypothesis requires further testing with the necessary statistical power and the most updated classification system.

In two case-control studies conducted in the USA, an increased risk of 2.4[1] and 1.7[2] was observed for MM with a family history of haematological cancer: we did not confirm this observation.

For other sub-entities, we observed a significant increase in acute lymphoblastic leukaemia risk with a familial history of haematological cancer, but not in T-NHL risk, although only five T-NHL cases had a family history of haematological cancer.

Results from family studies can help elucidate whether the relationship between a familial history of haematological cancer and occurrence of LN is connected with a dominant or recessive heredity. If a dominant mechanism is involved, we would expect the risk to be similar in different first-degree relatives. On the contrary, a recessive mechanism would generate a greater risk in siblings than in parents and offspring.[4] Our results are in favour of a dominant mechanism for CLL and HL, in agreement with studies in Sweden,[5] the UK[18] and the USA.[10] In some studies, no dominant mechanism was observed,[4] so we can put forward the hypothesis that if a dominant process exists and if it is very rare in the population, it was not likely to be found. Moreover, the prevalence of this sort of genetic alteration may be predominant in one geographical area compared to others.

Our results showed that the association of LN with familial haematological cancer is similar for cases occurring early- versus late-onset, according to Chatterjee et al.,[12] except for CLL, where the association is higher for cases occurring before the age of 60. Also, age at diagnosis of CLL, but not lymphoma, seems to be younger in familial cases compared to sporadic cases. An earlier age at diagnosis of familial CLL compared to sporadic CLL has been reported in a previous study; however CLL cases occurring in relatives of controls were similar to the familial cases as regards age at diagnosis.[5] It was not possible in our study to test this effect in relatives because a high number of leukaemia patients lacked specific information.

A familial history of solid tumours does not seem to increase the risk of LN, according to previous studies.[2,10,12] We observed, nevertheless, five cancer sites which increased the risk of specific LN sub-entities. As far as we know, these associations have not been previously reported except between breast cancer and MM.[1] Despite the fact that these results could be false-positive resulting from multiple comparisons, it was particularly interesting to note that, in three out of five cancer sites, an association was found with a proliferation that had developed from a mature lymphoid cell, which could be due to a peculiar physiopathological mechanism. This observation requires confirmation using larger-scale studies.

Regarding study limitations and potential biases, a major concern was the quality of the diagnosis reported by probands: people are generally not able to make a precise distinction between different types of haematological disease and even between lymphoma and leukaemia. Within the Spanish series, some attempts were made to request confirmation of the diagnosis and when this was possible, many so-called leukaemias were in fact lymphomas. Thus, caution is advised in analysing results regarding leukaemias. Nevertheless this factor did not affect the pooled analysis that showed an increased risk. Furthermore, to limit misclassification of cancers reported by probands, the cancers were grouped by anatomical systems or site such as gynaecological cancers, upper aero-digestive tract cancers, etc. Nevertheless, any such misclassification would probably affect cases and controls in a similar way, so the consequence of this misclassification would only underestimate the associations.

Another possible source of bias is the difference in the reporting of familial cancers between cases and controls. Cases with a family history of haematological cancer may be more likely to recall haematological cancers than controls which may account for part of our results. The study conducted by Kerber and Slattery[19] showed that any significant differences between cases and controls were found in self-reported cases. Nevertheless, in a more recent study conducted in Sweden,[20] the authors compared validated, registry-based data with self-reported data on familial cancer. They showed that for the haematopoietic system, sensitivity of response was higher for participants with lymphoid neoplasms (cases) than for other participants (controls). They observed a 25 to 30% higher OR for haematopoietic cancer and lymphoma in families with self-reported questionnaire data compared to register data. Thus, there was a risk of OR overestimation with our data. Another study showed that male and clinic-based probands were respectively more likely to overreport familial cancers as compared to female and population-based probands.[21] The consistency of our results by type of controls across all cancer sites provided some degree of confidence in our findings. In the same way, the rate of non-response in controls needs to be mentioned; where there is substantial non-response in controls, the remainder who do participate typically have more of a family history, causing a biais towards nil. The hospitalised controls had a better rate of response than the population controls, so if there was a bias, this would cause a lower risk in population controls. Here too, the consistency of our results by type of controls provides some degree of confidence in our findings.

Our findings need to be confirmed in two ways. The first one, by largest epidemiologic studies with up-to-date clasification system. The second one, and with no doubt the most important knowing that the familial aggregation of LN is now well established in a number of epidemiologic studies, by biologic studies. In the framework of the Epilymph study, biological data were collected. In the Epilymph study and the International Lymphoma Epidemiology Consortium (Interlymph),[22] genetic susceptibility is studied.

In summary, our results confirm familial aggregation of LN due to a dominant genetic mechanism in relatives of CLL cases with a family history of haematological cancer, and in relatives of HL cases with a family history of lymphoma. No familial aggregation was found in DLBCL and FL cases.

Conflict of interest statement

None declared.

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