Increased frequency of hematopoietic malignancies in relatives of patients with lymphoid neoplasms: a French case-control study.

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INCREASED FREQUENCY OF HEMATOPOIETIC MALIGNANCIES IN RELATIVES OF PATIENTS WITH LYMPHOID NEOPLASMS: A FRENCH CASE-CONTROL STUDY

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Short title: Familial aggregation in hematopoietic malignancy

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Abstract

Lymphoid neoplasms (LN), including non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), lymphoproliferative syndrome (LPS) and multiple myeloma (MM), are among the most frequent cancers (approximately 17,000 new cases per year in France), after those related to smoking. LN were investigated using the data from the ENGELA study. ENGELA is a multicenter hospital-based case-control study that was carried out in France over the period September 2000 – December2004. In all, 822 cases (397 NHL, 149 LH, 168 SLP and 108 MM) and 752 controls were included and described 5481 and 5188 first degree relatives, respectively. A positive association with a familial history of hematopoietic cancer was observed for LN (OR = 1.7 [1.0-2.8]) overall and for LPS (OR = 3.2 [1.4-6.8]). The associations with HL (OR = 10.4 [2.0-53.8]) and NHL (OR = 2.4 [1.0-5.9]) were stronger for men. The associations were also stronger when the disease had been diagnosed before the relatives were aged 45 years. The results mainly support the involvement of genetic factors and suggest that at least some of those factors may be sex-linked. However, the slight overrepresentation of affected spouses among the cases might also support the responsibility of environmental factors.

INTRODUCTION

Lymphoid neoplasm (LN), including Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) and lymphoproliferative syndromes (LPS) are among the most common cancers in France after smoking-related cancers. According to data from French registries, there were approximately 17,000 new cases of LN in 2000 and almost 9,000 deaths [1]. In the last two decades (1978-2000), the yearly incidence rate for NHL has increased by more than 3% (3.8% for men and 3.5% for women), for reasons that have yet to be elucidated [1].

A few risk factors for lymphoid neoplasms have been identified. They include congenital and acquired immunodeficiencies[2-3-4-5], chromosomal instability syndromes [6-7], Epstein-Barr Virus (EBV) infection [8-9-10] for some Burkitt's [11-10] and Hodgkin's lymphomas, *Helicobacter pylori* infection for gastric lymphoma [12-13] and some autoimmune disorders for non-Hodgkin lymphoma[14-15-16-17]. Farming and exposure to pesticides [18-19-20] have also been consistently associated with LN.

Several studies have investigated the relationships between familial hematopoietic cancer aggregation and hematopoietic cancer and suggest a two-fold increase in the risk of NHL [21-22-23-24], and HL [25] with a history of NHL in first degree relatives.

This study analyzed the association between LN and familial history of cancer in the first-degree relatives of the subjects included in a large case-control study designed to investigate for environmental and genetic risk factors for LN.

MATERIALS AND METHODS

The ENGELA study is a French multicenter hospital-based case-control study that was conducted in the main hospitals of Bordeaux, Brest, Caen, Nantes, Lille and Toulouse from September 2000 to December 2004 in order to investigate for environmental, infectious and genetics risk factors for LN. The LN types considered in the study were LPS, which included chronic lymphoid leukaemia (CLL) and hairy cell leukaemia (HCL), NHL, HL and MM.

Cases and controls ascertainment

The eligible cases were subjects aged between 18 and 75 years old, recently diagnosed with LN, and residing in the catchment area of each hospital. The diagnosis of LN was documented by cytology and histology, and reviewed by a team of pathologists. All the cases were coded using the WHO classification (ICD-O-3). Cases with AIDS or treated with immunosuppressant drugs were not eligible. The inclusion of the cases took place within 6 months of diagnosis, except for LPS cases, who could be included up to 18 months post-diagnosis, in view of their good prognosis.

The controls were patients with no prior history of LN, recruited in the same hospital as the cases, mainly in orthopaedic and rheumatologic departments. The patients admitted for cancer or a disease directly related to occupation, smoking or alcohol consumption were not eligible as controls in order to avoid over-representation of some factors of interest. The controls were matched with cases by centre, age (± 3 years) and gender.

Out of the 872 eligible cases, 48 (5.5%) refused to participate. In addition, 2 cases who had been adopted were excluded from the analysis. Out of the 853 eligible controls, 100 refused the interview (11.7%) and one subject whose interview was incomplete was excluded *a posteriori*.

The study sample finally comprised 822 cases of LN, classified using ICD-O-3, and further subdivided into four categories: HL (n = 149, ICD-O-3 codes (9650-9655/3, 9659/3, 9661-9665/3, 9667/3)), NHL (n = 397 consisting of 172 cases of diffuse large B cell-lymphoma (DLCL) (9679/3, 9680/3), 101 cases of follicular lymphoma (FL) (9690/3, 9691/3, 9695/3, 9698/3), 21 cases of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (9671/3, 9761/3), 17 cases of marginal zone B-cell lymphoma of the MALT type (9699/3), 3 cases of splenic marginal zone B-cell lymphoma (9689/3), 25 cases of T-cell lymphoma (9702/3, 9705/3, 9714/3, 9729/3), 25 cases of mantle-cell lymphoma (9673/3), and 33 cases of other lymphoma (9728/3, 9687/3, 9826/3, 9591/3)), MM (n = 108, (9731-9732/3)) and LPS (n = 168, 132 cases of chronic lymphocytic leukemia (CLL) (9823/3, 9670/3) and 36 cases of hairy cell leukemia (HCL) (9940/3)) and 752 controls.

Data collection

The data were collected in two stages. First, the cases and controls completed a standardized self-administered questionnaire eliciting information on their socioeconomic characteristics, familial medical history and lifetime residential and occupational histories. The patients were asked to describe each of their first-degree relatives (gender, year of birth and, if applicable, year of death) and report each relative's history of cancer, leukemia or lymphoma, with details of cancer sites and years of occurrence. Each relative's age was considered to be that at the time of interview or death.

Each patient then underwent a face-to-face interview by a trained interviewer using a standardized questionnaire addressing personal medical history, lifestyle characteristics (smoking and alcohol, tea and coffee consumption), outdoor leisure activities and non-occupational exposure. The self-administered questionnaire was also checked by the interviewer.

Blood samples were obtained from the cases and controls after consent form signature and biological specimens (constitutional DNA, tumor tissue) were placed on storage.

The blood samples and interviews were rendered anonymous.

Statistical analysis

Analyses were carried out for all LN taken together, for LN types LPS, NHL, HL and MM separately, and for the LPS (CLL and HCL) and NHL (DLCL and FL) subtypes.

The pair-matching used as a basis for the recruitment was broken in order to enable the whole control group to be used for the analysis of all LN. For each subgroup, the control group consisted in all controls that could be included in one of the age-gender-centre strata covered by the corresponding subgroup of cases.

Unconditional logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (95% CI). The analyses were systematically adjusted for the stratification variables: age, centre and gender. Additional analyses including familial structure and socioeconomic category (blue collar, white collar, unemployed) in the models were also conducted.

The relatives' malignancies were considered overall (any cancer), by large group (solid cancer or hematopoietic cancer) and by disease site. The analysis also took into account the type of relative

(parent, child, sibling), the age at onset of the earliest cancer in the family, the gender of the relatives with cancer, and the total number of relatives with cancer in the family.

Sensitivity analyses were also conducted to evaluate the robustness of the results. Each centre and each category of the controls' reasons for admission was excluded in turn. Additional analyses restricted to the matched samples were also carried out using conditional logistic regression models. The SAS® software package (version 9, Cary, NC) was used for the analyses. All *p* values were two-tailed.

RESULTS

Case and control comparability

The distribution of the 822 cases and 752 controls by the stratification variables, centre, age and gender, is shown in Table 1. Significant differences between centre were observed, mainly because the Caen hospital had higher LPS recruitment than the others. The use of the whole control group assigned more than 2 controls to each case in most strata, except in the youngest categories, in which HL predominated. The MM cases differed from the controls with regard to gender since they did not show the male predominance observed in other lymphoid neoplasms. The cases of HL were more educated and had higher socioeconomic status than the controls (Table 2). The cases and controls described 5481 (6.5 per subject on average) and 5188 (6.7 per subject on average) first degree relatives, respectively, and did not differ in terms of the number of relatives or the relatives' mean age. (Table 1 and Table 2 here)

Family history of cancer

Having at least one relative with a history of cancer was reported by 44.8% of the cases and 42.2% of the controls. None of the LN types was associated with a history of cancer in relatives (Table 3). However, having had at least 2 relatives with cancer was associated with LPS.

In contrast, having at least one relative with a history of hematopoietic cancer was reported by 5.8% of the cases and 3.5% of the controls. A family history of hematopoietic cancer was significantly

associated with LN overall (OR = 1.7 [1.0-2.8]), and with LPS in particular (OR = 3.2 [1.4-6.8]). An elevated OR of 2.4 ([0.8-7.1]) was also observed for HL, but was not statistically significant. The association with LN and with LN subtypes was rather weak for the younger patients and stronger for the age group, 45-60 years.

The analyses stratified by gender showed that some associations were restricted to men. Among men, HL and NHL were significantly related to a familial history of hematopoietic cancer, with OR of 10.4 [2.0-53.8] and 2.4 [1.0-5.9], respectively (Table 4), while no association was observed for women.

The associations were stronger when the relatives' disease had been diagnosed before the age of 45 years. The same pattern was observed for MM, although it was not significant, but not for LPS. Most frequently, the relatives' hematopoietic cancer had occurred at least 10 years before the diagnosis (cases) or interview (controls).

The associations between LPS subtypes, CLL and HCL, and a family history of hematopoietic cancer were close to those observed for the whole LPS group (Table 5). Similar associations were also observed for the FL and DLCL NHL subtypes.

More detailed information on the relatives' cancers showed that HL and NHL were only associated with a family history of lymphoma, while LPS was related to a history of lymphoma and leukemia (Table 6). Some positive associations with specific solid cancer sites, particularly kidney cancer for NHL (OR = 4.1 [1.0-16.8]) and HL (OR = 18.2 [1.3-251]), breast cancer for LPS (OR = 1.9 [1.1-3.7]), colon cancer for NHL (OR = 2.7 [1.6-4.6]) and melanoma for MM (OR = 13.6 [1.1-162]) were also observed (Table 6).

In order to investigate for potential familial anticipation, the 30 cases (12 LPS (11 CLL, 1 HCL), 9 NHL, 6 HL and 3 MM) who reported parents' hematopoietic cancer were considered separately.

The 6 cases of CLL with a parent who had had leukemia (not otherwise specified) were diagnosed at ages ranging from 43 to 64 years (average: 55 years), while their parents were 56 to 83 years old at the time of diagnosis (average: 70 years). Only 3 NHL cases had parent who had had NHL. The cases were also younger than their affected parent (56 years [52 to 59] *vs* 65 years [59 to 71]). Lastly, 4 LH cases had parents who had had LH. The cases did not seem to be younger at the time of diagnosis than

their affected parent (36 years [21 to 51] *vs* 26 years [20 to 32]). Within those pairs, the parents were diagnosed at an early age in 4 out of 6 pairs of CLL (not otherwise specified for the parent), 3 out of 3 pairs of NHL and 2 out of 4 pairs of HL. The numbers were too small for other combinations of cases and parents diagnoses to be investigated.

Seven cases (4 NHL, 1 HL, 1 LPS, 1 MM) reported that their spouses (5 husbands and 2 wives) had been diagnosed with a hematopoietic cancer, but no control did. Only 3 couples had concordant diagnoses of NHL (as a whole). Interestingly, for 5 of the 7 affected spouses, including the 3 NHL-NHL couples, the disease was diagnosed 5 years or less before the case diagnosis. The small numbers preclude accurate OR estimation. The spouses of 58 cases and 53 controls (OR = 1.0 [0.7-1.5]) had had cancer (any type). (Tables 3, 4, 5, 6 here).

Additional adjustments and sensitivity analyses

The results were unchanged after adjustment for the number and age of the relatives, and for educational level and socioeconomic category. Conditional logistic regression models using the initial matching instead of age, gender and centre strata yielded similar results. The results did not change when each centre was excluded in turn or when the reason for admission of each group of controls was excluded in turn.

DISCUSSION

The present study showed that LN, and particularly LPS, was associated with a history of hematopoietic cancer in first-degree relatives. For HL and NHL, the associations seemed to be restricted to men, particularly when the hematopoietic cancer had occurred in relatives before the age of 45 years.

The inclusion of the cases was independent of their family history. The cases were recruited in main hospitals that were unlikely to attract specific patient categories. All eligible cases hospitalized in the department on the interviewers' working days were systematically contacted and the high participation rate (94.5%) made high self-selection on family history unlikely. In addition, the cases were included

just after diagnosis to prevent survival bias that might have overrepresented cases with a family history in the event that the history was related, directly or indirectly, to a factor for a superior prognosis.

The cases and controls were hospitalized in the same center and resided in its catchment area. The controls were mainly recruited in orthopedic and rheumatologic departments, and were not to have been admitted for a disease directly related to smoking, alcohol intake or occupation, although they could have had those diseases in the past. Those precautions were taken to avoid artificial over- or under-representation of certain risk factors or socioeconomic categories that might be related to a family history of cancer or history reporting by the controls. In addition, the participation rate was quite high (88.3%), making self-selection on family history more improbable.

Over- or under-reporting was more possible in that the information was obtained by interview and not documented by medical reports. The cases were more conscious of their disease and perhaps more prone to having obtained information on their family history and relatives' cancer. However, the study focused on first-degree relatives (parents, siblings, children), whose medical history is less likely to be different for cases and controls. Moreover, the questionnaires were standardized and the cases and controls were interviewed under the same conditions in order to reduce the opportunity for differential misclassifications. Non-differential misclassifications were also reduced by those measures, but could not be completely prevented since it was not possible to access objective information (anonymous data). The misclassifications are probably stronger for specific types of cancer than for broad categories. In addition, some LH or NHL diagnoses in relatives may have been confused: cases may have been influenced by their own diagnosis when they reported a history of lymphoma in their relatives

Several studies have quantified misclassifications by comparing the reported family history of cancer with the relatives' medical files. Strong concordances were observed for cancer in first-degree relatives [26,27,28,29,30,31]. Differences were observed for some cancer sites [26,28,32,30,31,32]. The greatest differences were reported for hepatic, uterine and cervical disease sites [26,27,33,31].

The reporting of cancer in offspring and, to a lesser extent, siblings was hampered by censoring by age. This probably reduced the power of the study, particularly for HL. The power was also weak for women and for multiple myeloma, due to small numbers.

Socioeconomic category is a strong potential confounder since it is usually related to the risk of smoking-related cancer in the family and to the quality of the report, assumed to be more accurate in more educated subjects. However, analyses were adjusted for socioeconomic category and the results were very similar.

The Epilymph study [34] also showed a significant and positive association between lymphoid neoplasm taken as a whole and a history of hematopoietic cancer in first degree relatives. Several studies have shown specific associations between a familial history of hematopoietic cancer and LPS [35-34-36-37-38], NHL[34-39-33-40], and HL [41]. However, in the present study, the latter two relationships were not significant when both genders were considered together. The OR were higher for men, which has also been observed in two other studies [25-33]. The associations were not only stronger in males, but they were also mostly due to hematopoietic cancers in male relatives. These results suggest a sex-linked genetic susceptibility to hematopoietic cancers. Stronger associations between hematopoietic cancer in male relatives were also reported for HL and NHL in a study in the US [22] and for CLL in the Swedish Family-Cancer Database [37].

Two studies on MM showed associations with parental history of MM [21-42]. The present study did not evidence any such association. HL and NHL were mainly associated with lymphomas in relatives, which supports the results of previous studies [21-34-41-37-25-23-39-33].

Anticipation of CLL diagnosis in CLL case families, which implies that CLL presents earlier than in the preceding generation, has been suggested in a few studies [37-43-44-45] but not that of the Swedish Family-Cancer Database [37-46]. The finding in the present study, based on 6 CLL-CLL parent-case pairs is compatible with anticipation. The cases were more conscious of their disease and perhaps more prone to having obtained information on their family history and relatives' cancer, which may induce a recall bias. However, the study focused on first-degree relatives (parents, siblings, children), whose medical history is less likely to be differentially reported for cases and controls.

Daugherty et al (2005)[46], using data from the Swedish Family-Cancer Database and the Danish registry, showed that the secular trends in incidence and diagnosis of NHL could give rise to apparent anticipation. They did not evidence any anticipation of HL, CLL and MM cases. . Secular trends and censoring of the youngest parents may result in false anticipation. Moreover, in CLL, anticipation was assumed to be due to an increase in genomic instability over succeeding generations, but studies of nucleotides repeats did not support that hypothesis (Auer et al, 2001)[47].

The study showed associations between both NHL and HL and a family history of kidney and digestive tract cancers, between LPS and a family history of breast cancer, and between MM and a family history of melanoma. The analysis was not hypothesis-driven. The numbers were small and resulted in wide confidence intervals. Multiple tests increased the risk that an association may have occurred by chance. Therefore, the results are to be considered exploratory. A few studies have reported associations between LN and solid tumors, but no clear consistency has emerged. Associations between NHL and kidney cancer[33] or colorectal cancers[41]-[38], and between breast cancer and LPS[38] have been reported and are in line with the results of the present study. In contrast, to the authors' knowledge, the association between MM and a family history of melanoma has never been reported.

The study also showed a slight trend toward cases reporting hematopoietic cancer in the spouse more frequently than controls. Spouses may be assumed to be aware of each other's health; recall bias is thus rather unlikely. However, the numbers are small and the trend may be a chance finding. Out of the three studies that investigated cancer among spouses [48]-[49]-[50], a Japanese study [50] showed an increase in all malignant neoplasm in spouses and an American study [48] showed an increase in NHL. As they stand, the results of the present study do not strongly support an increase in hematopoietic cancer in spouses similar to that in first degree relatives. Nonetheless, it is still possible that a part of familial aggregation results from an environmental exposure – possibly to an infectious agent – shared by the family. However, the predominance of the association with a history of hematopoietic cancer in men, particularly for HL, suggests a sex-linked genetic predisposition.

CONCLUSION

In conclusion, the results mainly support the involvement of genetic factors in the aetiology of NHL, and suggest that at least some of those factors could be sex-linked. However, the slight overrepresentation of affected spouses among the cases may also support the responsibility of environmental factors.

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Table 1: Distribution of cases and controls by stratification variable: age, gender and centre.

	LPS			NHL			HL			MM		
	Cases n = 168	Controls n = 464	Controls per case	Cases n = 397	Controls n = 701	Controls per case	Cases n = 149	Controls n = 417	Controls per case	Cases n = 108	Controls n = 478	Controls per case
Centre		***			*			*ns*			*ns*	
Brest	22	111	5.0	86	140	1.6	22	73	3.3	21	107	5.1
Caen	64	90	1.4	24	84	3.5	16	51	3.2	10	54	5.4
Nantes	26	71	2.7	76	117	1.5	40	106	2.7	12	57	4.8
Lille	29	60	2.1	30	65	2.2	5.5	8	1.6	13	47	3.6
Toulouse	9	54	6.0	77	137	1.8	34	90	2.6	21	91	4.3
Bordeaux	16	75	4.7	104	158	1.5	32	89	2.8	26	117	4.5
Paris	2	3	1.5	-	-	-	-	-	-	5	5	1.0
Age (year)		*ns*			*ns*			***			*ns*	
< 25	-	-	-	10	28	2.8	35	38	1.1	-	-	-
[25-29]	-	-	-	9	22	2.4	20	32	1.6	-	-	-
[30-34]	-	-	-	16	28	1.8	16	26	1.7	1	2	2.0
[35-39]	5	19	3.8	22	41	1.9	16	35	2.2	2	11	5.5
[40-44]	8	17	2.1	31	56	1.8	18	38	2.1	3	13	4.3
[45-49]	14	46	3.3	40	66	1.7	14	53	3.8	9	42	4.7
[50-54]	22	63	2.9	69	121	1.8	10	74	7.4	19	113	5.9
[55-59]	35	85	2.5	66	91	1.4	4	38	9.5	15	73	4.9
[60-64]	28	94	3.4	46	102	2.2	5	33	6.6	24	93	3.9
[65-69]	33	74	2.2	45	75	1.7	10	42	4.2	22	72	3.3
≥ 70	23	66	2.9	45	71	1.6	1	6	6.0	13	59	4.5
Mean age (SD)	60(9)	59(9)		54(12)	53(12)		34(14)	46(14)		59(9)	59(9)	
Gender		*ns*			*ns*			*ns*			**	
Female	64	159	2.5	155	265	1.7	62	152	2.5	52	165	3.2
Male	104	305	2.9	244	436	1.8	87	265	3.0	56	313	5.6

LPS: lymphoproliferative syndrome, NHL: non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: multiple myeloma, ns: not significant, SD: standard deviation
* p<0.05, **p<0.01, ***p<0.0001,

Table 2: Comparability of cases and controls by familial structure and socioeconomics characteristic

	LPS				NHL				HL				MM			
	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI
Education			*ns*				*ns*				*				*ns*	
< high school	126	348	**1.0**	*ref*	270	484	**1.0**	*ref*	65	260	**1.0**	*ref*	76	349	**1.0**	*ref*
≥ high school	42	116	**1.3**	[0.8-1.9]	129	217	**1.1**	[0.8-1.4]	84	157	**1.5**	[1.1-2.3]	32	129	**1.2**	[0.8 -2.0]
Socioeconomic category			*ns*				*ns*				*				*ns*	
Unemployed	1	8	**0.5**	[0.1-3.7]	11	26	**0.8**	[0.3-1.6]	21	26	**0.8**	[0.4-1.8]	3	14	**0.9**	[0.2 -.3.2]
White collar	85	207	**1.0**	*ref*	188	311	**1.0**	*ref*	82	179	**1.0**	*ref*	50	208	**1.0**	*ref*
Blue collar	82	249	**0.8**	[0.5-1.1]	200	364	**0.9**	[0.7-1.2]	46	212	**0.5**	[0.3-0.8]	55	256	**0.9**	[0.2 -3.2]
Number of relatives			*ns*				*ns*				*ns*				*ns*	
2 to 3	9	25	**1.0**	[0.4-2.3]	48	74	**1.7**	[1.1-2.8]	40	68	**1.5**	[0.7-3.3]	10	34	**1.4**	[0.6 -3.2]
4 to 5	46	116	**1.2**	[0.8-1.5]	122	186	**1.4**	[1.0-2.0]	41	109	**1.5**	[0.8-3.0]	28	121	**1.2**	[0.7 -2.1]
6 to 7	43	135	**1.0**	[0.6-1.5]	114	199	**1.2**	[0.9-1.7]	48	116	**2.2**	[1.2-4.1]	34	34	**1.2**	[0.7 -2.2]
8 and more	70	188	**1.0**	*ref*	113	242	**1.0**	*ref*	20	124	**1.0**	*ref*	36	180	**1.0**	*ref*
Relatives' mean age (SD)	55(8)	54(8)		*ns*	52(10)	51(10)		*ns*	43(11)	47(10)		*ns*	56(9)	54(9)		*ns*

LPS: lymphoproliferative syndrome, NHL: non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: multiple myeloma, ns: not significant, SD: standard deviation
OR estimated by unconditional logistic regression adjusted for gender, age and centre.

*$p \leq 0.05$

Table 3: Relationships between lymphoid neoplasm (LN) and family history of any cancer in first-degree relatives

	All LN				LPS				NHL				HL				MM			
	Ca n = 822	Co n = 752	OR	95% CI	Ca n = 168	Co n = 464	OR	95% CI	Ca n = 397	Co n = 701	OR	95% CI	Ca n = 149	Co n = 417	OR	95% CI	Ca n = 108	Co n = 478	OR	95% CI
Any cancer																				
At any age	368	317	**1.1**	[0.9-1.3]	97	227	**1.3**	[0.9-1.9]	176	303	**1.0**	[0.8-1.3]	45	147	**1.3**	[0.8-2.0]	50	228	**1.0**	[0.6-1.5]
< 45 years	61	49	**0.7**	[0.5-1.2]	3	11	**2.1**	[0.4-11.2]	31	44	**0.6**	[0.4-1.1]	26	38	**0.8**	[0.4-1.4]	1	9	**3.3**	[0.3-44.7]
45-60 years	199	181	**1.0**	[0.7-1.4]	47	139	**2.0**	[1.1-3.6]	112	179	**0.9**	[0.6-1.3]	18	124	**0.9**	[0.4-2.1]	22	157	**0.5**	[0.3-1.1]
≥ 60 years	156	133	**1.1**	[0.8-1.6]	48	120	**1.1**	[0.7-1.9]	66	126	**1.0**	[0.6-1.5]	7	34	**1.0**	[0.3-3.0]	35	109	**1.6**	[0.9-2.9]
Number of relatives with cancer																				
1	257	233	**1.0**	[0.8-1.3]	60	168	**1.2**	[0.7-1.7]	126	224	**1.0**	[0.7-1.3]	35	120	**1.2**	[0.7-2.0]	36	164	**1.0**	[0.6-1.5]
≥ 2	111	84	**1.2**	[0.9-1.7]	37	59	**1.9**	[1.1-3.2]	50	79	**1.2**	[0.8-1.7]	10	27	**1.6**	[0.7-3.7]	14	64	**1.0**	[0.5-1.9]
Gender of relatives with cancer																				
Male	244	217	**1.0**	[0.8-1.3]	75	155	**1.6**	[1.0-2.5]	105	207	**0.8**	[0.6-1.1]	27	97	**1.1**	[0.6-2.0]	37	157	**1.1**	[0.7-1.9]
Female	205	155	**1.3**	[1.0-1.6]	53	114	**1.3**	[0.8-2.0]	104	148	**1.3**	[0.9-1.8]	25	70	**1.5**	[0.8-2.7]	23	114	**0.9**	[0.5-1.5]
Age of relatives at cancer onset																				
< 45 years	51	35	**1.5**	[0.9-2.3]	9	24	**1.6**	[0.7-3.8]	26	35	**1.4**	[0.8-2.4]	11	17	**2.1**	[0.9-5.1]	5	20	**1.3**	[0.5-3.8]
≥ 45 years	209	177	**1.1**	[0.9-1.4]	54	129	**1.3**	[0.8-1.9]	104	168	**1.1**	[0.8-1.4]	25	77	**1.4**	[0.8-2.5]	26	136	**0.8**	[0.5-1.3]
Hematopoietic cancer																				
At any age	48	26	**1.7**	[1.0-2.8]	16	15	**3.2**	[1.4-6.8]	19	25	**1.3**	[0.7-2.5]	8	10	**2.4**	[0.8-7.1]	5	19	**1.2**	[0.4-3.3]
< 45 years	10	5	**0.5**	[0.2-1.5]	1	1	**0.7**	[0.01-15.8]	4	4	**0.4**	[0.1-1.9]	5	4	**0.5**	[0.12-2.0]	0	1	**-**	-
45-60 years	199	181	**2.1**	[1.0-4.3]	47	139	**3.4**	[1.1-10.8]	112	179	**1.9**	[0.8-4.5]	18	124	**3.5**	[0.6-22.2]	22	157	**1.9**	[0.5-7.9]
≥ 60 years	12	10	**1.0**	[0.4-2.5]	7	8	**2.8**	[0.9-8.6]	2	10	**0.3**	[0.1-1.6]	1	2	**2.6**	[0.2-38.4]	2	9	**0.8**	[0.2-3.9]
Number of relatives with hematopoietic cancer																				
1	46	23	**1.8**	[1.1-3.1]	15	13	**3.7**	[1.6-8.3]	19	22	**1.5**	[0.8-2.8]	8	9	**2.9**	[1.0-8.5]	4	17	**1.1**	[0.3-3.4]
≥ 2	2	3	**0.6**	[0.1-3.6]	1	2	**0.8**	[0.1-9.9]	0	3	**-**	-	0	1	**-**	-	1	2	**2.0**	[0.2-24.2]
Gender of relatives with cancer																				
Male	31	18	**1.5**	[0.8-2.8]	10	9	**3.1**	[1.2-8.5]	12	17	**1.2**	[0.6-2.6]	4	6	**2.1**	[0.5-8.6]	5	12	**2.2**	[0.7-7.1]
Female	19	9	**1.8**	[0.8-4.1]	7	6	**2.7**	[0.8-8.6]	7	9	**1.3**	[0.4-3.3]	4	5	**2.3**	[0.5-10.6]	1	7	**0.6**	[0.1-5.1]
Age of relatives at cancer onset																				
< 45 years	16	7	**2.2**	[0.9-5.3]	2	6	**1.0**	[0.2-5.4]	8	7	**2.2**	[0.8-6.3]	5	1	**15.6**	[1.6-154]	1	5	**0.9**	[0.1-8.7]
≥ 45 years	19	11	**1.5**	[0.7-3.3]	7	8	**2.4**	[0.8-7.4]	9	11	**1.4**	[0.5-3.4]	1	3	**1.0**	[0.1-11.7]	2	10	**0.8**	[0.5-3.9]

LPS: lymphoproliferative syndrome, NHL: non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: multiple myeloma,
OR estimated by unconditional logistic regression adjusted for gender, age, centre, socioeconomic category

Table 4: Associations between lymphoid neoplasms (LN) and family history of hematopoietic cancer in first-degree relatives by gender

		All LN		LPS		NHL		HL		MM	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Both	Any hematopoietic cancer in relatives	**1.7**	[1.0-2.8]	**3.2**	[1.4-6.8]	**1.3**	[0.7-2.5]	**2.4**	[0.8-7.1]	**1.2**	[0.4-3.3]
	Characteristics of relatives										
	Men	**1.5**	[0.8-2.8]	**3.1**	[1.2-8.5]	**1.2**	[0.6-2.6]	**2.1**	[0.5-8.6]	**2.2**	[0.7-7.1]
	Women	**1.8**	[0.8-4.1]	**2.7**	[0.8-8.6]	**1.3**	[0.4-3.3]	**2.3**	[0.5-10.6]	**0.6**	[0.1-10.0]
	< 45 years at onset	**2.2**	[0.9-5.3]	**1.0**	[0.2-5.4]	**2.2**	[0.8-6.3]	**15.6**	[1.6-154]	**0.9**	[0.1-8.7]
	≥ 45 years at onset	**1.5**	[0.7-3.3]	**2.4**	[0.8-7.4]	**1.4**	[0.5-3.4]	**1.0**	[0.1-11.7]	**0.8**	[0.5-3.9]
Men	Any hematopoietic cancer in relatives	**3.0**	[1.4-6.5]	**3.5**	[1.1-10.5]	**2.4**	[1.0-5.9]	**10.4**	[2.0-53.8]	**1.7**	[0.3-9.0]
	Characteristics of relatives										
	Men	**3.2**	[1.0-10.2]	**4.8**	[0.9-25.8]	**2.1**	[0.6-7.8]	**26.2**	[1.6-438]	**5.9**	[0.9-40.6]
	Women	**1.8**	[0.6-5.4]	**1.7**	[0.3-8.2]	**1.6**	[0.4-5.8]	**8.3**	[1.0-70.5]	0 ca/5 co	
	< 45 years at onset	**3.8**	[1.1-14.0]	0 ca /2 co		**5.2**	[1.3-21.2]	3 ca/0 co		**2.2**	[0.2-23.7]
	≥ 45 years at onset	**1.1**	[0.3-37.0]	**1.6**	[0.3-10.0]	**1.2**	[0.3-4.6]	0 ca/2 co		0 ca/5 co	
Women	Any hematopoietic cancer in relatives	**1.1**	[0.6-2.3]	**2.8**	[0.9-8.4]	**0.7**	[0.2-1.9]	**0.9**	[0.2-4.3]	**0.9**	[0.2-3.7]
	Characteristics of relatives										
	Men	**1.2**	[0.5-2.7]	**2.2**	[0.5-9.1]	**0.6**	[0.2-2.3]	**1.1**	[0.1-7.8]	0 ca/2 co	
	Women	**1.7**	[0.5-6.2]	**3.7**	[0.7-31]	**0.5**	[0.0-4.6]	**0.6**	[0.0-9.3]	**1.0**	[0.2-6.1]
	< 45 years at onset	**0.8**	[0.2-3.6]	**1.2**	[0.2-8.0]	0 ca/4 co		**5.6**	[0.3-97.7]	0 ca/2 co	
	≥ 45 years at onset	**2.2**	[0.7-5.5]	**2.8**	[0.6-12]	**1.4**	[0.4-5.1]	**2.8**	[0.1-74.2]	**1.0**	[0.2-6.1]

LPS: lymphoproliferative syndrome, NHL: non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: multiple myeloma,
OR estimated by unconditional logistic regression adjusted for gender, age, centre, socioeconomic category

Table 5 : Associations between LPS and NHL subtypes and family history of hematopoietic cancer in first degree relatives by gender

		LPS				NHL			
		CLL (n=132)		HCL (n=36)		FL (n=101)		DLCL (n=172)	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Both	Any hematopoietic cancer in relatives	**3.3**	[1.4-7.4]	**3.4**	[0.8-13.5]	**1.0**	[0.3-2.9]	**1.7**	[0.8-3.7]
	Characteristics of relatives								
	Men	**3.1**	[1.1-9.1]	**5.9**	[1.0-35.9]	**1.4**	[0.4-4.4]	**1.1**	[0.4-3.2]
	Women	**2.9**	[0.9-9.9]	**2.1**	[0.2-20.5]	0 ca /9 co		**2.3**	[0.7-7.3]
	< 45 years at onset	**1.1**	[0.2-5.8]	**-**	-	**2.0**	[0.4-10.2]	**2.9**	[0.8-10.8]
	≥ 45 years at onset	**2.3**	[0.7-8.2]	**3.9**	[0.8-22.0]	**1.1**	[0.2-5.4]	**1.4**	[0.4-4.5]
Men	Any hematopoietic cancer in relatives	**3.5**	[1.0-12.8]	**2.9**	[0.4-19.3]	**2.0**	[0.4-8.6]	**2.5**	[0.8-7.7]
	Characteristics of relatives								
	Men	**3.2**	[0.5-21.9]	**20.1**	[1.7-240.8]	**5.1**	[0.8-33.0]	**1.2**	[0.1-7.9]
	Women	**2.2**	[0.4-12.1]	0 ca /4 co		0 ca /5 co		**2.5**	[0.6-10.5]
	< 45 years at onset	0 ca /2 co		0 ca /2 co		**5.7**	[0.7-44.7]	**5.7**	[1.1-30.2]
	≥ 45 years at onset	**1.4**	[0.1-14.8]	**1.5**	[0.1-18.0]	**1.1**	[0.1-10.6]	**0.8**	[0.1-6.7]
Women	Any hematopoietic cancer in relatives	**2.5**	[0.8-8.2]	**11.9**	[0.2-613.5]	**0.4**	[0.0-3.6]	**1.1**	[0.3-4.1]
	Characteristics of relatives								
	Men	**2.2**	[0.5-9.0]	0 ca /6 co		**0.3**	[0.0-3.6]	**1.0**	[0.2-5.1]
	Women	**2.6**	[0.3-23.0]	1 ca /2 co		**0.5**	[0.0-4.6]	**0.8**	[0.1-8.6]
	< 45 years at onset	**1.4**	[0.2-9.6]	0 ca /4 co		0 ca/4 co		0 ca/4 co	
	≥ 45 years at onset	**2.2**	[0.4-11.7]	**28.6**	[0.6-∞]	**0.8**	[0.1-11.2]	**2.0**	[0.4-9.3]

CLL: chronic lymphoid leukemia, HCL : hairy cell leukemia, FL: follicular lymphoma, DLCL: diffuse large B cell lymphoma, OR estimated by unconditional logistic regression adjusted for gender, age, centre, socioeconomic category

Table 6: Associations between lymphoid neoplasm (LN) and family history of cancer by site of cancer in first degree relative

	All LN				LPS				NHL				HL				MM			
	Ca n = 822	Co n = 752	**OR**	95% CI	Ca n = 168	Co n = 464	**OR**	95% CI	Ca n = 397	Co n = 701	**OR**	95% CI	Ca n = 149	Co n = 417	**OR**	95% CI	Ca n = 108	Co n = 478	**OR**	95% CI
Solid cancer	314	267	**1.1**	[0.9-1.3]	86	200	**1.3**	[0.9-1.9]	148	258	**1.0**	[0.8-1.3]	35	121	**1.3**	[0.8-2.0]	45	195	**1.1**	[0.7-1.7]
Head & neck	30	26	**1.0**	[0.6-1.7]	16	21	**2.0**	[1.0-4.1]	9	25	**0.6**	[0.3-1.3]	2	11	**0.7**	[0.2-3.7]	3	16	**0.9**	[0.2-3.2]
Lung	54	44	**1.2**	[0.8-1.8]	10	37	**0.7**	[0.3-1.6]	29	43	**1.3**	[0.8-2.1]	6	19	**1.6**	[0.6-4.4]	9	38	**1.2**	[0.5-2.6]
Digestive	128	94	**1.3**	[0.9-1.7]	32	76	**1.1**	[0.7-1.7]	62	90	**1.3**	[0.9-1.9]	15	35	**2.1**	[1.0-4.2]	19	71	**1.2**	[0.7-2.2]
Colon	50	27	**1.0**	[0.5-2.0]	1	7	**0.4**	[0.0-3.6]	35	25	**2.7**	[1.6-4.6]	6	12	**1.8**	[0.6-5.4]	0	19	-	-
Breast	77	59	**1.2**	[0.8-1.7]	25	41	**1.9**	[1.1-3.7]	37	59	**1.1**	[0.7-1.7]	5	29	**0.7**	[0.2-1.8]	10	44	**0.9**	[0.4-2.0]
Skin	13	9	**1.3**	[0.5-3.0]	3	4	**1.9**	[0.4-9.3]	4	8	**0.9**	[0.3-3.2]	4	6	**1.6**	[0.4-6.6]	2	4	**2.7**	[0.5-15.6]
Melanoma	7	4	**1.5**	[0.4-5.3]	2	1	**4.1**	[0.3-51.8]	2	3	**1.2**	[0.2-7.4]	1	3	**0.8**	[0.1-8.9]	2	1	**13.6**	[1.1-162]
Bone	2	6	**0.3**	[0.1-1.4]	1	6	**0.5**	[0.1-4.5]	0	6	**-**	-	0	4	**-**	-	1	4	**1.0**	[0.1-12.0]
Genitourinary	75	67	**1.0**	[0.7-1.4]	22	47	**1.3**	[0.7-2.2]	33	65	**0.8**	[0.5-1.3]	7	32	**0.8**	[0.3-1.9]	13	47	**1.2**	[0.6-2.4]
Kidney	11	3	**2.9**	[0.8-10.6]	0	2	**-**	-	7	3	**4.1**	[1.0-16.8]	2	1	**18.2**	[1.3-251]	2	2	**5.6**	[0.7-46.2]
CNS	14	10	**1.3**	[0.6-2.9]	3	5	**1.4**	[0.3-6.4]	9	9	**1.8**	[0.7-4.6]	1	6	**0.5**	[0.1-4.5]	1	5	**1.5**	[0.2-13.3]
Thyroid	5		**1.1**	[0.3-4.2]	1	4	**0.4**	[0.0-4.3]	3	4	**1.4**	[0.3-6.7]	0	1	**-**	-	1	2	**1.6**	[0.1-19.5]
Hematopoietic cancer	48	26	**1.7**	[1.0-2.8]	16	15	**3.2**	[1.4-6.8]	19	25	**1.3**	[0.7-2.5]	8	10	**2.4**	[0.8-7.1]	5	19	**1.2**	[0.4-3.4]
Lymphoma	19	6	**3.0**	[1.2-7.7]	3	2	**9.9**	[1.4-71.5]	7	6	**1.8**	[0.6-5.4]	8	2	**14.0**	[2.6-74.3]	1	5	**0.5**	[0.1-4.6]
HL	9	2	**4.6**	[1.0-21.9]	1	1	**9.1**	[0.4-214]	2	2	**1.6**	[0.2-11.9]	5	1	**18.0**	[1.8-184]	1	1	**4.0**	[0.2-73.7]
NHL	11	4	**2.4**	[0.8-7.7]	2	1	**10.2**	[0.8-128]	5	4	**1.8**	[0.5-6.9]	3	1	**9.1**	[0.8-102]	1	4	**0.6**	[0.1-5.5]
Leukemia	29	20	**1.3**	[0.7-2.3]	13	12	**2.8**	[1.2-6.5]	12	19	**1.1**	[0.5-2.4]	0	9	**-**	-	4	13	**1.9**	[0.6-6.1]
Myeloma	1	1	**0.9**	[0.1-15.1]	1	1	**1.5**	[0.1-2.7]	0	1	**-**	-	-	-	**-**	-	0	1	**-**	-

LPS: lymphoproliferative syndrome, NHL: non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma, MM: multiple myeloma,
OR estimated by unconditional logistic regression adjusted for gender, age, centre and socioeconomic category