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Abbreviations used: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; CI, confidence interval; OR, odds ratio; ENT, ear, nose or throat.

Novelty and impact of our paper: This paper investigated in detail family history of cancer in children with leukemia and lymphoma in France at a national scale. We report that cancers were more frequent in the first and second-degree relatives of lymphoma cases than in population controls, and the associations were stronger for a family history of Hodgkin's lymphoma.

Abstract

The role of a family history of cancer in the etiology of childhood hematopoietic malignancies was investigated using the data from the ESCALE study. ESCALE, a population-based case-control study, was carried out in France over the period, 2003-2004. A total of 773 cases of acute leukemia (AL), 130 of Hodgkin's lymphoma (HL), 163 of non-Hodgkin's lymphoma (NHL) and 1681 population-based controls were included. The controls were randomly selected from the French population and were frequency matched with the cases on age and gender. Cancer history in first- and second-degree relatives was reported by the mothers in a structured telephone questionnaire which was the same for the cases and controls. Odds ratios (ORs) were estimated using an unconditional regression model taking into account the stratification variables and potential confounders. A family history of cancer was associated with an increased risk of HL (OR = 1.5 [1.0-2.2]) and NHL (OR = 1.8 [1.3-2.5]), but not AL (OR = 1.0 [0.9-1.2]). The ORs were higher when at least two relatives had a history of cancer or when one case occurred before age 46 years. Only HL was significantly associated with a family history of hematopoietic malignancies (OR = 2.0 [1.0-3.8]), mainly because of a significant association with a history of Hodgkin's lymphoma (OR = 5.4 [1.3-22]). In conclusion, the study findings support the hypothesis of familial susceptibility to childhood lymphoma, but do not suggest familial susceptibility to childhood acute leukemia.

Introduction

Specific genetic syndromes play a role in the etiology of only a very small proportion of hematopoietic malignancies in children [1, 2]. The syndromes include familial neoplastic syndromes, inherited immunodeficiency and bone marrow failure syndromes [1]. The potential role of inherited susceptibility in childhood acute leukemia and lymphoma has yet to be elucidated. Large population-based registry-linked studies have investigated the familial aggregation of Hodgkin's lymphoma, non-Hodgkin's lymphoma or leukemia [3-7]. In children, few population-based registry-linked studies have been published [8-13], most of them relating to first-degree relatives [8-12]. The estimated relative risks for a positive family history of cancer ranged from 0.8 to 1.0 for childhood leukemia [8, 10-13] and from 1.0 to 1.8 for childhood lymphoma taken as a whole [8, 10-12]. A number of case-control studies have addressed the association between history of cancer in first and second degree relatives of children with leukemia and observed OR from 1.1 to 1.6 [14-18]. Only one case-control study has been published for childhood Hodgkin's lymphoma and non-Hodgkin's lymphoma [15]. Overall the number of published studies in children is weak, particularly for lymphomas. The aim of the present study was to investigate the association between childhood acute leukemia (AL), Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) and a family history of cancer in the first- and second-degree relatives of the index children.

Patient and methods

The ESCALE study was a French national population-based case-control study conducted in 2003 and 2004 to investigate the role of infectious, environmental and genetic factors in four childhood neoplastic diseases. The present paper focuses on acute leukemia (AL), Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL).

Case and control ascertainment

The cases were identified directly by the investigators assigned to each French pediatric oncology hospital department, with the support of the French National Registry of Childhood Blood Malignancies [19]. In order for the cases to be eligible, leukemia or lymphoma was to have been newly diagnosed between January 1, 2003, and December 31, 2004. The cases were also required to be aged less than 15 years and resident in France at the time of diagnosis. Cases who had been adopted, or whose biological mother had died, or whose mother did not speak French or whose mother presented with a psychiatric disorder were not eligible. For ethical reasons, the mothers of children who had died or who were receiving hospital palliative care were not eligible. Out of the 1321 cases (945 AL, 169 HL, 207 NHL) of childhood hematopoietic malignancies identified during the study period, 1188 (851 AL, 151 HL, 186 NHL) cases were eligible. The reasons for non-eligibility consisted in the child's death (34 AL, 3 HL, 7 NHL), hospital palliative care (7 AL), biological mother's death (10 AL, 3 NHL), non-French-speaking mother (29 AL, 11 HL, 8 NHL) or mother with serious psychiatric disorders (14 AL, 4 HL, 3 NHL).

The participation rates were 91, 86 and 88% for acute leukemia, Hodgkin's lymphoma and non-Hodgkin's lymphoma, respectively.

The controls were randomly selected from the French population using a quota sampling method. A first sample of 60,000 addresses representative of the French population in terms of region and degree of urbanization was constituted from the French national telephone directory (plus randomly generated unlisted numbers). The quotas were designed to make the controls similar to all the cases of all types of cancer in term of age and gender, using the French National Registry of Childhood Blood Malignancies [19] and the Regional Childhood cancer Registries [20] as reference. Additional quotas were used to ensure that the control group was also representative of the French general population in terms of the number of children aged under 15 years living in the household, conditionally on age, based on the 1999 population census. Like the cases, the controls were not to have been adopted and were to have a biological mother who could be interviewed (alive, not presenting with a serious psychiatric disorder and French- speaking).

Out of the 50,217 phone numbers dialed, 22,584 did not connect to a home number, 24,410 were ineligible, and, for 862, the respondent hung up before eligibility could be checked. For

the 2,361 remaining numbers, there were 679 refusals to participate. Thus, 1,682 mothers were interviewed (71.2%). One control with a history of neuroblastoma was excluded and 1681 children were included as controls.

Data collection

The telephone interviews with the cases' and controls' biological mothers were carried out by the same trained interviewers using structured questionnaires. The cases' mothers were interviewed at least 2 months after the diagnosis. The telephone questionnaire elicited information on demographic and socioeconomic characteristics, country of birth of each grand-parent, parental occupational history, childhood environment, and personal and familial medical history. The first- (parents and siblings) and second-degree (grandparents, uncles, aunts, half-brothers and half-sisters, but not the nephews and nieces of index children) genealogy was elicited and, for each relative, the mother was asked whether he or she had ever had a diagnosis of leukemia, Hodgkin's disease, lymphoma, myeloma or a solid tumor in any of the following disease sites: oral cavity or ENT (ear, nose or throat); lung; esophagus or stomach; liver; colon, rectum or anus; breast; thyroid; skin; melanoma; bone; kidney; bladder; uterus or ovary; prostate; or brain. An open question targeted other or unclearly-specified disease sites. The date of, or age at, diagnosis was also elicited.

Statistical analysis

Separate analyses by childhood hematopoietic malignancy and leukemia subtype (i.e., acute lymphoblastic leukemia [ALL] and acute myeloblastic leukemia [AML]) were carried out. Unconditional logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (CI), with adjustment for the stratification variables, age and gender. The analyses were restricted to children aged 5 years or more for Hodgkin's lymphomas and 2 years or more for non-Hodgkin's lymphomas because of the small numbers of cases in the lowest age groups. Family history was analyzed for all family members and separately for first- and second-degree relatives. The malignancies in relatives were considered by disease site, by group of disease sites and as a whole. Further analyses investigated the role of the relative's relationship to the case-control status (paternal or maternal relative), the age at onset of the earliest cancer in the family, and the total number of relatives with a cancer in the family. Investigation for and taking account of potential confounding by the age and number of relatives were conducted. The relative's age was his/her age at the time of interview or death. The analyses were repeated after excluding the children with Down's syndrome. A sensitivity analysis was also conducted to evaluate the extent of a potential survival bias by allocating a positive family history of cancer to cases excluded because of death or hospital palliative care. Additional analyses by hematopoietic malignancy (AL, HL, NHL) and leukemia subtype (ALL, AML) were carried out using the polytomous logistic

regression model. Additional analyses were also carried out by HL and NHL subtypes. The SAS® software package (version 9, Cary, North Carolina) was used for all the analyses. All *p* values were two-tailed.

Results

The cases consisted in 1066 children with an incident hematopoietic malignancy: 773 cases of acute leukemia (654 ALL, 101 AML, and 18 unspecified or biphenotypic AL), 130 of Hodgkin's lymphoma, of whom 128 aged more than 4 years (19 mixed cell, 79 nodular sclerosis, 17 lymphocyte predominant, 1 lymphocyte depleted and 12 not other specified HL), and 163 of non-Hodgkin's lymphoma, of whom 162 aged more than 1 year (73 Burkitt, 20 anaplastic large cell, 37 B-cell lymphoblastic and 27 T-cell lymphoblastic, and 5 unspecified NHL).

Case and control comparability

The distribution of the cases and controls by the quota variable combining age and gender is shown in table 1. The cases and controls were similar with respect to that variable for the study as a whole, but not for each hematopoietic malignancy. In particular, the lymphoma cases were significantly older than the controls. All the strata contained more than one control per case for adjustment, with more controls per lymphoma case in the youngest strata. The controls' parents were slightly more educated and had a higher professional status than the parents of the leukemia and Hodgkin's lymphoma cases (table 2). There was no significant difference between the cases and controls in terms of the mothers' or grand-parents' ages and the number of family members, after controlling for child age and gender. Consanguinity within first and second degree relatives was observed in none of the cases or controls.

Family history of cancer

The ORs associated with a positive family history of cancer in first-degree relatives, second-degree relatives and first- and second-degree relatives are shown in table 3. A family history of cancer was positively associated with childhood Hodgkin's lymphoma and non-Hodgkin's lymphoma (HL: OR = 1.5 [1.0-2.2]; NHL: OR = 1.8 [1.3-2.5]). No association with acute leukemia was observed (AL: OR = 1.0 [0.9-1.2]). A positive family history of cancer was reported for 42% of the acute leukemia, 61% of the Hodgkin's lymphoma and 61% of the non-Hodgkin's lymphoma cases and 42% of the controls. For each childhood hematopoietic malignancy, the ORs were higher when at least two relatives had had a cancer or when at least one family member had experienced a malignancy before age 46 years. The ORs associated with a history of malignancy in a paternal relative were higher than those for a history of malignancy in a maternal relative for acute leukemia, but not for either type of lymphoma.

Table 4 shows the results by disease site and group of sites. A family history of hematopoietic malignancy was only associated with Hodgkin's lymphoma (AL: OR = 1.0 [0.6-1.5]; HL: OR = 2.0 [1.0-3,8]; NHL: OR = 1.0 [0.5-2.1]). Hodgkin's lymphoma was statistically

significantly associated with a family history of lymphoma (OR = 3.2 [1.2-8.0]) and, more particularly, with a history of Hodgkin's lymphoma (OR = 5.4 [1.3-22]). There were significant associations between childhood acute leukemia and a family history of uterine or ovarian cancer (OR = 1.6 [1.1-2.4]). Family history of cancer of the colon, rectum or anus was statistically significantly associated with both childhood Hodgkin's (OR = 2.4 [1.0-5.4]) and non-Hodgkin's (OR = 2.4 [1.2-4.7]) lymphomas. Non-Hodgkin's lymphoma was also statistically significantly associated with a family history of testicular (OR = 6.3 [1.4-29]), uterine/ovarian (OR = 2.6 [1.4-4.8]), and pancreas cancer (OR = 3.4 [1.0-11]).
The analyses by lymphoma subtypes were based on small numbers. A family history of cancer was significantly associated with anaplastic large cell lymphoma (OR = 4.4 [1.4-13.3]) and T cell lymphoblastic lymphoma (OR = 3.0 [1.3-6.9]), while ORs of 1.5 (95%CI: [0.9-2.4]) and 1.4 (95%CI: [0.7-2.7]) were observed for Burkitt's lymphoma and B-cell lymphoblastic lymphoma, respectively. With respect to Hodgkin's lymphoma, ORs were of 2,1 (95%CI: [0.8-5.5]), 1.2 (95%CI: [0.7-1,9]), 1.8 (95%CI: [0.7-5.0]) for mixed cellularity, nodular sclerosis and lymphocyte predominant subtypes, respectively. The lymphocyte predominant subtype was significantly related to family history of Hematopoietic malignancy (OR = 5.1 [1.6-16.5]).

The results were unchanged after exclusion of the children with Down's syndrome. The use of polytomous logistic regression models for ALL and AML, for AL and NHL (restricted to age greater than or equal to 2 years), and for AL, HL and NHL (restricted to age greater than or equal to 5 years) did not alter the results. With regard to potential confounders, no variable was statistically significantly associated with both a childhood hematopoietic malignancy and a family history of cancer, after controlling for child age and gender. Neither parental professional category nor educational level was associated with a family history of cancer in the control group. The results were also unchanged when the analyses were adjusted for familial structure (mother's and father's ages, mean ages of grand-parents and of uncles and aunts, number of relatives), socioeconomic status (professional category, educational level, degree of urbanization of the place of residence), breast-feeding and early infections, which have been previously shown to be related to leukemia in the literature and were also related in this study [21]. The results were unchanged after exclusion of the children who had at least one grandparent born in Africa or Asia.

Discussion

A positive association with a family history of cancer was observed for non-Hodgkin's lymphoma and Hodgkin's lymphoma, but not for acute leukemia. Only Hodgkin's lymphoma was associated with a positive family history of hematopoietic malignancy, mainly due to the high OR for family history of Hodgkin's lymphoma. Significant positive associations were also observed with a family history of solid tumor in the following disease sites: colon/rectum/anus with Hodgkin's and non-Hodgkin's lymphoma; uterine/ovarian with non-Hodgkin's lymphoma and acute leukemia; and testicular and pancreas with non-Hodgkin's lymphoma. The numbers were too small to allow the analysis of leukemia or lymphoma aggregation separately for the first and second degrees.

Genetic susceptibility could be reflected by an increased familial incidence and earlier onset of malignancies. Indeed, for lymphoma, the ORs were higher when at least two relatives had presented with cancer or when the age at diagnosis of a single case was less than 46 years. This tendency was also observed, at a lesser extent, for leukemia; a weak genetic susceptibility to leukemia cannot be then excluded with regard to our results.

With an alpha error of 5%, the statistical power of the study to evidence an OR of 1.5, which was the order of magnitude of the relationship between childhood AL and family history of cancer in three previous case-control studies [15-17], was greater than 99%.
The relatives were quite young: the mean age of the parents at the time of the interview was about 40 years; that of the grand-parents about 65 years. A lack of statistical power for specific types of cancer with a high age of onset is therefore probable. The positive results for cancers with lower ages of onset were less censored.

The cases were identified through the data collection system of the French National Registry of Childhood Blood Malignancies, making case selection at the identification stage unlikely. Cases who had died or were receiving palliative care (41 AL, 3 HL and 7 NHL) were not eligible. However, the absence of a relationship between leukemia and family history of cancer is unlikely to result from a survival bias. The severity of leukemia is not known to be related to family history, and, in the present study, the leukemia cases who died during the year following the telephone interview had an even less frequently positive family history of cancer than the survivors (35% vs 42%). All of the 41 ineligible leukemia cases who had died or were receiving palliative care would have had to have a positive family history of cancer in order for cases selection to have masked a slight association, with a corresponding OR of 1.2 (95%CI: [1.0-1.4]), instead of the observed one of 1.0 (95%CI: [0.9-1.2]). None of the lymphoma cases eligible during the study period had a known ataxia telangiectasia or any other genetic syndrome reported in the French National Registry of Childhood Blood

Malignancies. Therefore, a selection by survival of cases related to these familial rare diseases is unlikely.

The controls were randomly selected from the overall population. The national telephone directory was used as the basis for random selection. Selection of controls with listed numbers only was avoided by randomly generating unlisted numbers. There were no differences between the cases and controls with regard to gender or age (considering all types of cancer), or between the controls and overall population with regard to birth order. The quota recruitment process was thus successful. The refusals to take part could have been related to the parental socioeconomic status or educational level which appeared higher among controls than among Hodgkin's lymphoma and, to a lesser extent, leukemia cases. The control mothers educational levels were very similar to those of the French population, but the control fathers' educational levels were higher [22-24]. However, parental socioeconomic status and educational level were not associated with a family history of cancer in the control group and the results were unchanged after adjustment for these variables. We collected no direct information on ethnicity, which might be related to the risk of childhood cancer and to history of cancer in relatives. However, excluding the children whose any grand-parent was born in Africa or Asia had no influence on the results.

Non-differential misclassification bias was probable since the cancer history data only consisted in the mothers' reports. However, bias was limited by the use of specific closed questions and by the fact that the mothers were asked about her and the father's close family, i.e. children, siblings and parents. Adults with cancer have been shown to report their family history of cancer in first degree relatives quite accurately [25-33]. Bondy et al. studied the accuracy of data on family history of cancer obtained by interviewing the mothers of children and adolescents with sarcoma [34] and reported positive predictive values (PPV) of 88 and 71% for first- and second-degree relatives of children, respectively. For Perillat et al [17], the PPV of mothers' reports on first-degree relatives of children with leukemia was 100%. The sensitivity and specificity of those two studies could not be determined since the negative reports were not analyzed.

Differential recall between cases and controls cannot be excluded. Studies on adults have reported no or few differential errors between cancer cases and their controls with respect to cancer in relatives [27-31]. To our knowledge, no study of accuracy with respect to children has been conducted.

Misclassification may be more marked for paternal than maternal family history of cancer, given that mothers were interviewed. However, the ORs associated with the paternal and maternal histories were very similar for HL and NHL. This may suggest that the recall bias

was weak for lymphomas. Differences were observed for leukemia only, but there would appear to be no obvious reason for a recall bias for leukemia and not for lymphoma.

Five previous case-control studies have estimated the association between childhood leukemia and family history of cancer [14-18]. One study only addressed acute lymphoblastic leukemia [18] and a second targeted children aged less than 19 months [14]. A positive association was found in all the studies. Three reported significant cancer ORs of 1.5 (95%CI: [1.0-2.1]) [15], 1.5 (95%CI: [1.0-2.2]) [17] and 1.6 (95%CI: [1.2-2.1]) [16]; two reported significant ORs for a family history of hematopoietic malignancy of 2.7 (95%CI: [1.1-6.9]) [17] and 2.1 (95%CI: [1.2-3.6]) [18]. Six population-based studies on childhood leukaemia linked Cancer Registry data with a family database [8-13]. One of these studies only addressed childhood acute lymphoblastic leukemia [9] and another, acute myeloblastic leukemia [13]. With the exception of the study by Hasle & Olsen [13], all the registry studies considered first-degree relatives only. None of these studies detected a positive association between childhood leukemia and family history of cancer, with observed standardized incidence rate ratio from 0.8 to 1.0. Three of the registry studies [8, 12, 13] did not consider cancer that occurred in relatives before the index child's birth in order to avoid survival bias. Consequently they may have failed to detect early-onset malignancies and may have underestimated associations, if an earlier onset age was particularly associated with familial cancers.

Fewer studies have addressed the association between family history of cancer and childhood lymphoma [8, 10-12, 15, 35]. One of the previous case-control studies reported quite similar ORs for childhood leukemia, Hodgkin's lymphoma and non-Hodgkin's lymphoma (LA: OR = 1.5 [1.0-2.1]; LH: OR = 1.4 [0.7-2.9]; LNH: OR = 1.8 [1.0-3.3]) [15]. Four of the previous registry studies [8, 10-12] also addressed childhood lymphoma, without distinguishing between Hodgkin's and non-Hodgkin's lymphoma. The association with family history of cancer was always stronger for lymphoma than for leukemia, with observed standardized incidence rate ratio ranging from 1.0 to 1.8. Le Bihan et al. [35] did not observe an increased frequency of cancer in the relatives of children with non-Hodgkin's lymphoma in a familial study.

With regard to associations with specific types of malignancy in relatives, the literature is relatively heterogeneous and chance may explain some of the associations. Significant positive associations between childhood acute leukemia and a family history of cancer in the following disease sites was observed: oral cavity [16]; esophagus or stomach [17], colon [16, 17], uterus or ovary [16]; breast [18]; brain [16]; melanoma [17]; testis [9]; and kidney [12]. Childhood lymphoma, taken as a whole, was shown to be significantly associated with a family history of any lymphoma [10, 11] and brain tumor [12].

In conclusion, our results support the hypothesis of a familial susceptibility to childhood lymphoma but not to childhood leukemia. Besides genetic factors, they may also reflect the existence of environmental or infectious risk factors shared by the family members.

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Appendix (SFCE Investigators of the ESCALE study)

Principal Investigator	Degree	Hospital	City (France)
André Baruchel	MD	Saint-Louis / Robert Debré	Paris
Claire Berger	MD	Centre Hospitalier Universitaire	Saint-Etienne
Christophe Bergeron	MD	Centre Léon Bérard	Lyon
Jean-Louis Bernard	MD	La Timone	Marseille
Yves Bertrand	MD	Debrousse	Lyon
Pierre Bordigoni	MD	Centre Hospitalier Universitaire	Nancy
Patrick Boutard	MD	Centre Hospitalier Régional Universitaire	Caen
Gérard Couillault	MD	Hôpital d'Enfants	Dijon
Lionel De Lumley	MD	Centre Hospitalier Régional Universitaire	Limoges
Anne-Sophie Defachelles	MD	Centre Oscar Lambret	Lille
François Demeocq	MD	Hôtel-Dieu	Clermont-Ferrand
Alain Fischer	MD	Hôpital des Enfants Malades	Paris
Virginie Gandemer	MD	Centre Hospitalier Universitaire – Hôpital Sud	Rennes
Olivier Hartmann	MD	Institut Gustave Roussy	Villejuif
Jean-Pierre Lamagnere	MD	Centre Gatien de Clocheville	Tours
Françoise Lapierre	MD	Centre Hospitalier Universitaire Jean Bernard	Poitiers
Guy Leverger	MD	Trousseau	Paris
Patrick Lutz	MD	Hôpital de Hautepierre	Strasbourg
Geneviève Margueritte	MD	Arnaud de Villeneuve	Montpellier
Françoise Mechinaud	MD	Hôpital Mère et Enfants	Nantes
Gérard Michel	MD	La Timone	Marseille
Frédéric Millot	MD	Centre Hospitalier Universitaire Jean Bernard	Poitiers
Martine Münzer	MD	American Memorial Hospital	Reims
Brigitte Nelken	MD	Jeanne de Flandre	Lille
Hélène Pacquement	MD	Institut Curie	Paris
Brigitte Pautard	MD	Centre Hospitalier Universitaire	Amiens
Yves Perel	MD	Pellegrin Tripode	Bordeaux
Alain Pierre-Kahn	MD	Enfants Malades	Paris
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Xavier Rialland	MD	Centre Hospitalier Universitaire	Angers
Alain Robert	MD	Hôpital des Enfants	Toulouse
Hervé Rubie	MD	Hôpital des Enfants	Toulouse
Nicolas Sirvent	MD	L'Archet	Nice
Christine Soler	MD	Fondation Lenval	Nice
Danièle Sommelet	MD	Centre Hospitalier Universitaire	Nancy
Jean-Pierre Vannier	MD	Charles Nicolle	Rouen

Table 1: Distribution of cases and controls by the stratification variable, age x gender (16 categories) used for quota sampling.

	Controls		Acute leukemia				Hodgkin's lymphoma		Non-Hodgkin's lymphoma	
			ALL	AML	All					
Age (year)	n=1681		n=654	n=101	n=773		n=130		n=163	
Boys										
0-1	201	*12%*	35	17	54	*7%*	-		1	*1%*
2	79	*5%*	50	5	55	*7%*	-		2	*1%*
3	87	*5%*	57	2	60	*8%*	1	*1%*	9	*6%*
4	89	*5%*	42	4	48	*6%*	-		11	*7%*
5-6	126	*7%*	51	6	61	*8%*	7	*5%*	24	*15%*
7-8	96	*6%*	31	5	37	*5%*	11	*8%*	18	*11%*
9-11	137	*8%*	49	9	59	*8%*	22	*17%*	23	*14%*
12-14	117	*7%*	35	6	45	*6%*	21	*16%*	26	*16%*
Girls										
0-1	168	*10%*	44	19	63	*8%*	-		-	
2	74	*4%*	45	3	48	*6%*	-		2	*1%*
3	79	*5%*	47	2	50	*6%*	-		5	*3%*
4	56	*3%*	35	3	38	*5%*	1	*1%*	5	*3%*
5-6	102	*6%*	57	5	62	*8%*	1	*1%*	7	*4%*
7-8	67	*4%*	33	5	39	*5%*	2	*2%*	9	*6%*
9-11	88	*5%*	27	7	35	*5%*	10	*8%*	8	*5%*
12-14	115	*7%*	16	3	19	*2%*	54	*42%*	13	*8%*

ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia

Table 2: Socioeconomic and familial characteristics of cases and controls. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated by unconditional regression, adjusted for stratification variable, age x gender. Analyses were restricted to children aged more than 4 years for HL and more than 1 year for NHL.

	Acute leukemia				**Hodgkin's lymphoma**				**Non-hodgkin's lymphoma**			
	Cases n=773	Controls n=1681	OR	95%CI	Cases n=128	Controls n=848	OR	95%CI	Cases n=162	Controls n=1312	OR	95%CI
Maternal educational level												
≤ high-school	470	979	**1.0**	-	91	532	**1.0**	-	95	795	**1.0**	-
> high-school	303	701	**0.9**	[0.8 - 1.1]	33	315	**0.7**	[0.4 - 1.0]	66	516	**1.2**	[0.8 - 1.6]
Missing data	-	1			4	1			1	1		
Paternal educational level			**				**					
≤ high-school	531	1063	**1.0**	-	102	569	**1.0**	-	110	851	**1.0**	-
> high-school	234	601	**0.8**	[0.6 – 0.9]	22	270	**0.5**	[0.3 - 0.8]	50	445	**1.0**	[0.7 - 1.4]
Missing data	8	17			4	9			2	16		
Professional category[a]			*				*					
Intellectual and scientific jobs, managers and inter-mediate professions	282	713	**1.0**	-	38	360	**1.0**	-	66	556	**1.0**	-
Administrative and sales workers	226	477	**1.2**	[1.0 - 1.5]	33	221	**1.5**	[0.9 - 2.5]	41	356	**1,0**	[0.7 - 1.5]
Service workers	97	215	**1.2**	[0.9 - 1.5]	29	133	**1.9**	[1.1 - 3.3]	30	179	**1.2**	[0.7 - 2.1]
Factory and agricultural workers, unemployed	168	274	**1.5**	[1.2 - 1.9]	28	134	**2.1**	[1.2 - 3.7]	25	220	**1,0**	[0.6 - 1.7]
Missing data	-	2			-	-			-	1		
Maternal age at interview (year)												
<35	338	654	**1,0**	-	16	136	**1.0**	-	34	393	**1.0**	-
[35-40[	245	562	**0.8**	[0.7 - 1.0]	42	337	**0.6**	[0.3 - 1.2]	59	480	**1.1**	[0.7 - 1.8]
[40-45[	140	335	**0.9**	[0.7 - 1.2]	36	260	**0.5**	[0.2 - 1.0]	45	311	**1.2**	[0.7 - 2.1]
≥ 45	50	128	**0.9**	[0.6 - 1.4]	34	114	**0.9**	[0.4 - 1.8]	24	126	**1.5**	[0.8 - 2.9]
Missing data		2				1				2		
mean (sd)	*36 (6)*	*36 (6)*			*41 (6)*	*39 (5)*			*39 (6)*	*37 (5)*		
Grand-parents' mean age (year)												
<60	257	550	**1.0**	-	11	153	**1.0**	-	34	331	**1,0**	-
[60-65[	216	406	**1.1**	[0,9 - 1,4]	33	199	**2.0**	[0,9 - 4.1]	32	324	**0.8**	[0,5 - 1,4]
[65-70[	164	373	**0.9**	[0,7 - 1,2]	40	243	**1.8**	[0,9 - 3.7]	47	329	**1.1**	[0,7 - 1.8]
[70-75[	98	238	**0.9**	[0,6 - 1,2]	22	162	**1.2**	[0,6 - 2.7]	37	219	**1.3**	[0.8 - 2.3]
≥ 75	36	96	**0.9**	[0,6 - 1,5]	22	78	**1.9**	[0.8 - 4.3]	11	92	**0.9**	[0,4 - 1.9]
Missing data	2	18			-	13			1	17		
mean (sd)	*63 (7)*	*63 (7)*			*68 (7)*	*66 (7)*			*66 (7)*	*65 (7)*		
Number of family members												
6 to 9	182	366	**1,0**	-	15	140	**1.0**	-	25	255	**1.0**	-
10 to 12	313	699	**0.9**	[0.7 - 1.1]	43	347	**1.1**	[0.6 - 2.1]	73	547	**1.3**	[0.8 - 2.0]
13 to 15	130	337	**0.8**	[0.6 - 1.1]	35	200	**1.4**	[0.7 - 2.8]	33	282	**1.0**	[0.6 - 1.8]
16 and more	148	279	**1.1**	[0.8 - 1.4]	35	161	**1.9**	[1.0 - 3.7]	31	228	**1.2**	[0.7 - 2.1]
mean (sd)	*12 (4)*	*12 (4)*			*14 (4)*	*13 (4)*			*13 (3)*	*12 (4)*		

[a] Professional category = best occupational activity of child's mother or father.

* : $10^{-2} \leq p < 0.05$; **: $10^{-3} \leq p < 10^{-2}$; ***: $p < 10^{-3}$

Table 3: Family history of cancer and childhood hematopoietic malignancies. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated by unconditional regression, adjusted for stratification variable, age x gender. Analyses were restricted to children aged more than 4 years for HL and more than1 year for NHL.

	Acute leukemia									Hodgkin's lymphoma				Non-Hodgkin's lymphoma			
	ALL			AML			All										
	Cases n=654	OR	95%CI	Cases n=101	OR	95%CI	Cases n=773	OR	95%CI	Controls n=1681	Cases n=128	Controls n=848	OR	95%CI	Cases n=162	Controls n=1312	OR	95%CI
Family history of cancer																		
First-degree relatives																		
No	640	**1.0**	-	100	**0.9**	-	758	**1.0**	-	1640	120	819	**1.0**	-	155	1275	**1.0**	-
Yes	14	**0.9**	[0.5 - 1.6]	1	**0.4**	[0.1 - 3.0]	15	**0.8**	[0.4 - 1.4]	41	8	29	**2.2**	[0.9 - 5.1]	7	37	**1.4**	[0.6 - 3.1]
Second-degree relatives																		
No	381	**1.0**	-	62	**1.0**	-	451	**1.0**	-	993	53	457	**1.0**	-	66	748	**1.0**	-
Yes	273	**1.1**	[0.9 - 1.3]	39	**0.8**	[0.6 - 1.4]	322	**1.1**	[0.9 - 1.3]	688	75	391	**1.4**	[1.0 - 2.1]	96	564	**1.8**	[1.3 - 2.5] **
First- and second-degree relatives																		
No	374	**1.0**	-	62	**1.0**	-	444	**1.0**	-	968	50	438	**1.0**	-	62	726	**1.0**	-
Yes	280	**1.1**	[0.9 - 1.3]	39	**0.9**	[0.6 - 1.3]	329	**1.0**	[0.9 - 1.2]	713	78	410	**1.5**	[1.0 - 2.2]	100	586	**1.8**	[1.3 - 2.5] ***
Number of relatives with cancer																		
0	374	**1.0**	-	62	**1.0**	-	444	**1.0**	-	968	50	438	**1.0**	-	62	726	**1.0**	-
1	192	**0.9**	[0.7 - 1.1]	27	**0.8**	[0.5 - 1.3]	226	**0.9**	[0.8 - 1.1]	548	47	310	**1.2**	[0.8 - 1.8]	71	451	**1.7**	[1.2 - 2.4] **
2 and more	88	**1.5**	[1.1 - 2.0] **	12	**1.1**	[0.6 - 2.2]	103	**1.4**	[1.1 - 1.9] **	165	31	100	**2.5**	[1.4 - 4.2] ***	29	135	**2.2**	[1.4 - 3.6] **
Earliest cancer onset age in family																		
No cancer in family	374	**1.0**	-	62	**1.0**	-	444	**1.0**	-	968	50	438	**1.0**	-	62	726	**1.0**	-
> 60 years	69	**0.9**	[0.7 - 1.2]	9	**0.6**	[0.2 - 1.2]	81	**0.9**	[0.7 - 1.2]	200	18	121	**1.0**	[0.6 - 1.9]	28	171	**1.7**	[1.1 - 2.8] *
]45 - 60 years]	91	**0.9**	[0.7 - 1.2]	21	**1.3**	[0.8 - 2.2]	116	**1.0**	[0.8 - 1.3]	259	23	148	**1.2**	[0.7 - 2.1]	34	211	**1.7**	[1.1 - 2.6] *
≤ 45 years	94	**1.3**	[1.0 - 1.7]	7	**0.7**	[0.4 - 1.5]	104	**1.2**	[0.9 - 1.6]	196	27	111	**2.0**	[1.2 - 3.5] *	32	156	**2.2**	[1.4 - 3.4] **
Missing data	26	-	-	2	-	-	28	-	-	58	10	30	-	-	6	43	-	-
Side of family with cancer																		
No cancer in family	374	**1.0**	-	62	**1.0**	-	444	**1.0**	-	968	50	438	**1.0**	-	62	726	**1.0**	-
Only paternal relatives	131	**1.2**	[0.9 - 1.5]	12	**0.7**	[0.4 - 1.3]	150	**1.2**	[0.9 - 1.5]	290	29	166	**1.3**	[0.8 - 2.2]	38	238	**1.7**	[1.1 - 2.6] *
Only maternal relatives	87	**0.7**	[0.6 - 1.0] *	20	**1.1**	[0.6 - 1.8]	108	**0.8**	[0.6 - 1.0]	305	27	171	**1.2**	[0.7 - 2.0]	43	251	**1.8**	[1.2 - 2.8] **
Both sides	62	**1.4**	[1.0 - 2.0] *	7	**0.9**	[0.4 - 2.1]	71	**1.4**	[1.0 - 1.9]	118	22	73	**2.5**	[1.4 - 4.5] **	19	97	**2.0**	[1.1 - 3.5] *

ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia

* : $10^{-2} \leq p < 0.05$; **: $10^{-3} \leq p < 10^{-2}$; ***: $p < 10^{-3}$

Table 4: Family history of specific types of cancer (first- and second-degree relatives) and childhood hematopoietic malignancies. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated by unconditional regression, adjusted for stratification variable, age x gender. Analyses were restricted to children aged more than 4 years for HL and more than 1 year for NHL.

	Acute leukemia									Hodgkin's lymphoma				Non-Hodgkin's lymphoma			
	ALL			AML			All										
Cancer in relatives	Cases n=654	OR	95%CI	Cases n=101	OR	95%CI	Cases n=773	OR	95%CI	Controls n=1681	Cases n=128	Controls n=848	OR	95%CI	Cases n=162	Controls n=1312	OR	95%CI
Hematopoietic malignancies	29	**1.0**	[0.6 - 1.5]	6	**1.1**	[0.5 - 2.6]	37	**1.0**	[0.7 - 1.5]	85	15	48	**2.0**	[1.0 - 3.8] *	9	62	**1.0**	[0.5 - 2.1]
Leukemia	16	**0.8**	[0.5 - 1.5]	3	**0.9**	[0.3 - 3.0]	20	**0.9**	[0.5 - 1.5]	52	8	32	**1.6**	[0.7 - 3.7]	6	39	**1.0**	[0.4 - 2.5]
Lymphoma	10	**1.1**	[0.5 - 2.2]	2	**1.1**	[0.2 - 4.6]	13	**1.1**	[0.6 - 2.5]	28	8	15	**3.2**	[1.2 - 8.0] *	3	20	**1.0**	[0.3 - 3.6]
Hodgkin's	4	**1.0**	[0.3 - 3.0]	1	**1.2**	[0.1 – 9.3]	5	**1.0**	[0.3 - 3.0]	12	4	5	**5.4**	[1.3 - 22] *	3	9	**2.6**	[0.7 - 10]
Non-Hodgkin's	7	**1.1**	[0.5 - 2.8]	1	**0.9**	[0.1 - 6.6]	9	**1.2**	[0.5 - 3.0]	18	4	11	**2.0**	[0.6 - 6.7]	-	13	**-**	-
Myeloma	4	**2.1**	[0.6 - 7.9]	1	**2.3**	[0.3 - 20]	5	**2.1**	[0.6 - 5.0]	6	-	2	-	-	-	4	**-**	-
Solid cancers	257	**1.0**	[0.8 - 1.2]	35	**0.9**	[0.6 - 1.3]	301	**1.0**	[0.8 - 1.3]	662	74	383	**1.5**	[1.0 - 2.2] *	94	550	**1.8**	[1.3 - 2.6] ***
Oral cavity, ENT	36	**1.4**	[0.9 - 2.2]	5	**1.2**	[0.5 - 3.2]	42	**1.4**	[1.0 - 2.0]	67	8	34	**1.6**	[0.7 - 3.7]	11	52	**1.8**	[0.9 - 3.6]
Lung	38	**0.7**	[0.5 - 1.1]	6	**0.8**	[0.3 - 1.9]	46	**0.7**	[0.5 - 1.1]	135	18	84	**1.3**	[0.7 - 2.3]	20	118	**1.3**	[0.8 - 2.2]
Digestive	73	**1.2**	[0.9 - 1.6]	9	**1.0**	[0.5 - 1.9]	83	**1.1**	[0.8 - 1.6]	163	20	96	**1.5**	[0.9 - 2.6]	28	139	**1.7**	[1.1 - 2.7] *
Esophagus, stomach	20	**1.2**	[0.7 - 2.0]	-	**-**	-	20	**1.0**	[0.6 - 1.9]	43	5	24	**1.4**	[0.5 - 3.9]	5	39	**1.0**	[0.4 - 2.7]
Liver	22	**1.4**	[0.8 - 2.3]	3	**1.3**	[0.4 - 4.2]	26	**1.4**	[0.8 - 2.3]	43	4	29	**0.8**	[0.3 - 2.5]	8	38	**1.6**	[0.7 - 3.5]
Colon, rectum, anus	23	**1.1**	[0.7 - 1.8]	3	**0.9**	[0.3 - 2.8]	26	**1.0**	[0.6 - 1.7]	56	9	30	**2.4**	[1.0 - 5.4] *	12	44	**2.4**	[1.2 - 4.7] *
Pancreas	8	**1.4**	[0.6 - 3.4]	2	**2.6**	[0.6 - 12]	11	**1.7**	[0.7 - 4.0]	14	4	7	**3.2**	[0.8 - 13]	4	12	**3.4**	[1.0 - 11] *
Other or NOS	9	**1.6**	[0.7 - 3.7]	1	**1.2**	[0.2 - 9.7]	10	**1.5**	[0.7 - 3.5]	15	2	10	**1.6**	[0.3 - 8.0]	-	13	**-**	-
Breast	63	**1.1**	[0.8 - 1.5]	7	**0.7**	[0.3 - 1.6]	73	**1.0**	[0.8 - 1.5]	157	17	92	**1.1**	[0.6 - 2.0]	21	124	**1.3**	[0.8 - 2.2]
Thyroid	8	**2.4**	[0.9 - 6.3]	1	**1.7**	[0.2 - 14]	9	**2.3**	[0.9 - 6.4]	9	2	6	**3.0**	[0.6 - 15]	1	7	**1.0**	[0.1 - 8.1]
Skin	10	**0.9**	[0.4 - 1.9]	1	**0.7**	[0.1 - 5.2]	11	**0.9**	[0.4 - 1.9]	26	2	17	**0.8**	[0.2 - 3.5]	3	24	**0.9**	[0.3 - 3.0]
Melanoma	2	**0.7**	[0.1 - 3.5]	1	**2.0**	[0.2 - 17]	3	**0.9**	[0.2 - 3.5]	8	1	5	**1.2**	[0.1 - 11]	2	7	**2.0**	[0.3 - 10]
Other or NOS	8	**0.9**	[0.4 - 2.2]	1	**1.0**	[0.1 - 7.3]	9	**0.9**	[0.4 - 2.1]	19	1	13	**0.6**	[0.1 - 4.6]	1	18	**0.4**	[0.1 - 2.9]
Bone	5	**0.6**	[0.2 - 1.5]	-	**-**	-	5	**0.5**	[0.2 - 1.3]	20	3	11	**2.0**	[0.5 - 8.3]	-	17	**-**	-
Genitourinary	74	**1.2**	[0.9 - 1.6]	13	**1.4**	[0.7 - 2.5]	91	**1.2**	[0.9 - 1.6]	164	21	97	**1.4**	[0.8 - 2.4]	31	133	**1.9**	[1.2 - 3.0] **
Kidney	5	**0.9**	[0.3 - 2.4]	-	**-**	-	6	**0.9**	[0.3 - 2.1]	16	5	10	**3.2**	[1.0 - 10]	2	14	**1.1**	[0.2 - 4.8]
Bladder	10	**1.3**	[0.6 - 2.7]	1	**0.8**	[0.1 - 5.8]	11	**1.2**	[0.6 - 2.5]	20	1	15	**0.5**	[0.1 - 4.1]	-	18	**-**	-
Uterus, ovary	33	**1.5**	[0.9 - 2.3]	7	**2.1**	[0.9 - 4.8]	42	**1.6**	[1.1 - 2.4] *	57	6	34	**1.1**	[0.4 - 2.8]	16	48	**2.6**	[1.4 - 4.8] **
Prostate	28	**1.0**	[0.7 - 1.7]	6	**1.5**	[0.6 - 3.5]	35	**1.1**	[0.7 - 1.7]	71	9	38	**1.3**	[0.6 - 2.8]	11	54	**1.6**	[0.8 - 3.1]
Testis	2	**0.8**	[0.2 - 4.3]	1	**3.0**	[0.4 - 26]	3	**1.0**	[0.3 - 4.1]	6	-	3	**-**	-	3	5	**6.3**	[1.4 - 29] *
Brain	17	**1.4**	[0.8 - 2.6]	2	**1.1**	[0.3 - 4.8]	19	**1.3**	[0.7 - 2.4]	32	4	19	**1.2**	[0.4 - 3.7]	6	27	**1.6**	[0.6 - 4.0]
Other or NOS	22	**0.9**	[0.5 - 1.5]	1	**0.2**	[0.0 - 1.8]	23	**0.8**	[0.5 - 1.5]	65	10	35	**2.2**	[1.0 - 4.8] *	9	52	**1.3**	[0.6 - 2.7]

ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia; ENT = Ear Nose Throat; NOS = site not otherwise specified

* : $10^{-2} \leq p < 0.05$; **: $10^{-3} \leq p < 10^{-2}$; ***: $p < 10^{-3}$