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Key words: Case-control study; childhood; leukemia; familial history

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Abstract

Objective: A case-control study was conducted to investigate the role of a familial history of cancer in the etiology of childhood acute leukemia (AL).

Methods: The history of cancer in the relatives of 472 cases was compared to that of 567 population-based controls. Recruitment was frequency matched on age, gender and region. The familial history of cancer in each child's relatives was reported by the mother in response to a standardized self-administered questionnaire.

Results: A familial history of solid tumor in first- or second-degree relatives was associated with an increased risk of ALL (OR=1.6 [1.2-2.1]), while a familial history of hematopoietic malignancies in first- or second-degree relatives was associated with an increased risk of AML (OR=4.3 [1.4-13]). The ORs for the histories of cancer increased with the number of relatives with cancer (OR=1.5 [1.1-2.0] for one relative and OR=2.3 [1.3-3.8] for two relatives or more; $p_{trend}<0.0001$). Significant associations between childhood AL and familial history of genital cancers and brain tumor were also observed (OR=2.7 [1.2-5.8], OR=10.7 [1.3-86], respectively).

Conclusion: This study supports the hypothesis that a familial history of cancer may play a role in the etiology of childhood acute leukemia. It also evidences some specific associations that require further investigation.

Introduction

Leukemia is the most common cancer in childhood with an incidence rate of 43.1 per 1,000,000 per year in France [1]. With the exception of ionizing radiation, certain rare genetic syndromes and cancer chemotherapy, its etiology remains largely unknown.

The hypothesis of a relationship between a familial history of cancer and a risk of childhood acute leukemia (AL) was suggested by the reports of familial clusters of leukemia [2], especially for acute myeloid leukemia (AML) [3, 4] and chronic lymphocytic leukemia [5], and by several case-control studies. To the authors' knowledge, only four case-control studies and one cohort study have been published to date. A study in the USA by the Children's Oncology Group found a non-significant relationship between AL in children aged less than 18 months and a history of cancer in first degree relatives [6]. A Russian study evidenced an association between AL and a familial history of cancer in relatives of any degree [7]. A French study also showed a positive and significant association between AL and a history of solid tumor or hematopoietic malignancy in first or second degree relatives [8]. Finally, a Canadian study evidenced an association between ALL and a history of hematopoietic malignancies only, in first or second degree relatives [9]. All four studies reported estimated ORs between 1.5 and 2. Conversely, the Danish cohort study did not show any increase in leukemia risk in the parents of child cancer patients [10].

The main objective of the present study was to assess the role of genetic and environmental factors in the etiology of childhood acute leukemia. This paper investigated the relationship between a familial history of cancer and childhood AL in a population-based case-control study.

Material and Methods

Study population

The cases were identified through the National Registry of Childhood Leukemia and Lymphoma (NRCL), which has registered all the cases of leukemia in children aged less than 15 years in mainland France since 1990 [1]. All the leukemia cases were confirmed by bone marrow analysis. The eligible cases were all the children for whom AL was diagnosed between January 1, 1995, and December 31, 1998, who were aged not more than 15 years and who were residing in mainland France at the time of diagnosis. The cases from four regions already involved in a hospital-based case-control study [8] and those from four other regions whose oncology departments were unable to contribute to the study for practical reasons were excluded. Out of the 651 eligible cases, 472 (73%) were included in the study.

The controls were randomly selected from the general population using a sample of 30,000 phone numbers representative of the French population with respect to area of residence and municipality size category. The controls were frequency matched with the cases on the basis of age at diagnosis, gender and region. Out of the 805 eligible controls, 567 (70%) were included in the study.

Data collection

The case and control mothers answered a standardized self-administered questionnaire, given to them by the child's physician for cases, and sent to them by mail, with their agreement, for controls.

The questionnaire elicited information on socio-demographic characteristics, the occupational history of the parents, parental smoking habits, maternal alcohol and

coffee consumption during pregnancy, familial history of cancer and the medical history of the index child.

The familial history of cancer was collected for the first (siblings and parents) and second (grand-parents, uncles, aunts, half brothers and sisters) degree relatives of the index child. For each relative with a history of cancer, the mother reported the specific type of cancer, the age at diagnosis and the kinship with the index child. The type of cancer was coded using the International Classification of Diseases, ninth revision (ICD-9).

Study power

With a power of 80% and alpha = 5%, the size of the study enables detection of a minimum OR of 1.5, 1.7 and 2.0 for exposure prevalences among controls of 30%, 10% and 5%, respectively.

Statistical analysis

All the analyses were performed using the SAS® software package (version 8.1, Cary North Carolina). Statistical analyses were performed using unconditional logistic regression models including the stratification variables (age, gender and region). Family size was systematically included in the regression models. Separate analyses and polytomous regressions were also used to estimate specific odds ratios for ALL and AML. Adjustments for potential socio-demographic confounders were also incorporated in the various analyses.

Results

Out of the 472 cases, 407 had a diagnosis of ALL, 62 had a diagnosis of AML and 3 consisted in unspecified leukemia.

The cases and controls were very similar with regard to age, gender, region of residence at diagnosis, parental education and socio-professional category (Table 1). Forty-eight percent of the cases and 45% of the controls were in age group 2-6 years, corresponding to the incidence peak of leukemia.

There was a small but significant difference between cases and controls with regard to the total number of family members (12.5 members on average for the controls *vs.* 13.3 members for the cases; p = 0.001) (Table 2). However, the cases and controls were similar for the ages of the first degree relatives, parents and siblings at the time of the child's birth.

Twelve mothers reported a personal history of cancer (3 cases of breast cancer, 4 of uterine cancer, 1 of ovarian cancer, 1 of thyroid cancer, 1 of lung cancer and 2 of cancer at other sites). Among the fathers, 13 had a personal history of cancer (3 cases of thyroid cancer, 1 of pancreas cancer, 1 of liver cancer, 1 of brain tumor, 1 of kidney cancer, 1 of melanoma, 1 of bone tumor, 1 of stomach tumor and 3 of hematopoietic malignancies). Only one case had a sibling with cancer (osteosarcoma).

As shown in table 3, AL was significantly associated with a history of solid tumor with an OR of 4.1 [1.5-11.6] for the first degree relatives and an OR of 1.5 [1.1-1.9] for the

second degree relatives. There was a non-significant excess of hematopoietic malignancies among the relatives of the cases, compared to the controls (OR = 1.6 [0.8-3.4]). The ORs for the histories of cancer, solid tumors or hematopoietic malignancies, increased with the number of relatives with cancer (OR = 1.5 [1.1-2.0] for one relative and OR = 2.3 [1.3-3.8] for two relatives or more; $p_{trend}<0.0001$). The associations were similar for maternal and paternal relatives.

The association with a familial history of solid tumor, for relatives of both degrees, were similar for ALL and AML, but non-significant for AML (Table 4). Only AML was positively and significantly associated with a history of hematopoietic malignancy, for both first and second degree relatives.

Significant associations between childhood AL and a familial history of genital cancer and brain tumor were observed (OR = 2.7 [1.2-5.8], OR = 10.7 [1.3-86], respectively). Colonic/rectal and genital tumors were significantly more frequent in relatives of AML cases (OR = 3.9 [1.1-13], OR = 4.2 [1.3-14], respectively), while lip/mouth and brain tumors were significantly more frequent in the relatives of ALL cases (OR = 3.5 [1.2-10], OR = 11.5 [1.3-91], respectively). Among the children with more than one relative with cancer, no specific cancer aggregation was observed.

The inclusion of birth order and history of early common infection, previously found to be associated with leukemia in this study [11], did not modify the results.

Similar findings were obtained after the exclusion of 12 children with Down's syndrome (10 cases and 2 controls).

Discussion

A familial history of cancer in first- or second-degree relatives was associated with childhood acute leukemia with an OR of 1.6 [1.2-2.1]. The ORs increased with the number of relatives with cancer, in a similar manner for maternal and paternal relatives. A familial history of hematopoietic malignancies was only observed for AML (OR = 4.3 [1.4-13]).

The study was able to detect a minimum OR of 2.4 for exposures with 3% prevalence for a history of hematopoietic malignancies and 1.3 for a familial history of cancer, for relatives of both degrees, for all AL. The study may therefore have suffered from a lack of power with respect to the study of hematopoietic malignancies in relatives. The prevalence of cancer — especially hematopoietic malignancies — in the first- and second-degree relatives (0.5% and 2% respectively) was very low, in part due to the fact that the parents were young.

All the cases were selected from the NRCL, which has an exhaustiveness of 99% [1]. Thus, a selection bias related to the case identification process seems unlikely.

The response rates for the cases and controls were very similar (73% for the cases and 70% for the controls) and the nonrespondents controls dit not differ from the respondents controls in terms of age, gender and region of residence. More-over, the non-respondent and respondent cases did not differ in terms of age, gender and type of leukemia. Nevertheless, a difference between the respondents and non-respondents in terms of the number of relatives having had cancer could be possible. Case mothers with several relatives with cancer may have had a higher response

rate. But, in order to explain the study findings, the non-respondents would have had to have no familial history of cancer, which is very unlikely.

Using the vital status data from the NCRL, the cases who died after their inclusion in the study were compared to the survivors. There was no difference with respect to familial history of cancer. A survival bias therefore seems unlikely.

The cases and controls were comparable in terms of their socio-demographic characteristics and parental age. The size of the family was slightly smaller for controls than for cases and all the analyses were therefore adjusted on the size of the family. However, the results were unchanged.

Differential misclassification of cancer history in first-degree relatives, over-declaration by case mothers and under-declaration by control mothers are unlikely since the medical histories in question are those of the mother herself, her child's father and her children. Such bias could not be ruled out for the history of cancer in second degree relatives. However, the prevalence of cancer in the family members of the control group was similar to that in the authors' hospital-based case-control study [8]. Nevertheless, non-differential misclassifications could not be ruled out.

The results remained unchanged when potential confounding factors were taken into account. Exclusion of children with Down's syndrome did not modify the results. They were also unchanged after adjustment for birth order and early common infections, which had been previously found to be associated with AL in the study [11].

Only a few epidemiological studies have investigated the association between childhood acute leukemia and a familial history of cancer. A Danish cohort study found no excess of cancer in the parents of leukemia cases under the age of 15

years [10]. An American case-control study, conducted on infants aged less than 18 months found a non-significant positive association between AML and a history of cancer in first degree relatives [6]. This study suffered from lack of power because of the very young age of the children's relatives. The study conducted by Smulevich *et al*. evidenced an association between AL and a familial history of cancer for relatives of all degrees [7]. In France, Perrillat *et al*. obtained similar results [8] with, in particular, associations with a history of colonic and rectal cancer, melanoma and genital cancer. In that study, a history of hematopoietic malignancy was associated with both ALL and AML. Finally, in Canada, Infante-Rivard *et al*. observed a relationship between a history of hematopoietic malignancy in second degree relatives and ALL [9].

In conclusion, this study supports the hypothesis that a familial history of cancer may play a role in the etiology of childhood acute leukemia. Our results suggest a possible responsibility of genetic factors. However, it is also compatible with the existence of environmental and/or infectious factors shared by the index child and his/her relatives, especially for the associations observed in first-degree relatives.

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Table 1: Sample description for the cases and controls

	Cases (%) n = 472		Controls (%) n = 567		p
Gender*					**0.37**
Male	260	(55)	326	(58)	
Age at diagnosis (year)*					**0.16**
< 2	44	(9)	78	(14)	
2-3	115	(24)	148	(26)	
4-5	110	(23)	109	(19)	
6-9	113	(24)	130	(23)	
≥ 10	90	(19)	102	(18)	
Region of residence at diagnosis*					**0.26**
Aquitaine	59	(13)	42	(7)	
Bretagne	45	(10)	70	(12)	
Centre	51	(11)	62	(11)	
Franche-Comté / Alsace	56	(12)	60	(11)	
Languedoc-Roussillon	31	(7)	48	(8)	
Midi-Pyrénées	32	(7)	42	(7)	
Haute et Basse Normandie	58	(12)	55	(10)	
Pays de Loire	48	(10)	75	(13)	
Picardie / Champagne Ardennes	53	(11)	69	(12)	
Poitou-Charentes / Limousin	39	(8)	44	(8)	
Parental socio-professional category					**0.08**
Professionals, technical workers, administrators, managers	196	(42)	228	(41)	
Clerical, sales and services workers	86	(18)	134	(24)	
Factory and agricultural workers	186	(40)	200	(36)	
Maternal education					**0.80**
≤ High school	336	(74)	415	(74)	
> High school	120	(26)	144	(26)	
Paternal education					**0.38**
≤ High school	336	(77)	424	(79)	
> High school	102	(23)	113	(21)	
Place of residence at diagnosis (population)					**0.76**
< 2,000	165	(37)	223	(39)	
2,000 – 9,999	75	(17)	100	(18)	
10,000 – 49,999	58	(13)	62	(11)	
50,000 – 199,999	64	(14)	82	(15)	
≥ 200,000	86	(19)	98	(17)	

* Stratification variables

Table 2: Familial characteristics of the cases and controls

	Controls n = 567 (mean ± SD)		Cases n = 472 (mean ± SD)		p
Number of family members					
First-degree	3.0	(±1.0)	3.2	(±1.1)	0.001
Second-degree	9.5	(±3.4)	10.1	(±3.9)	0.03
First- and second-degree	12.5	(±3.8)	13.3	(±4.3)	0.001
Average age of first-degree relatives (years)					
Parents	35.8	(±5.5)	36.1	(±6.0)	0.38
Siblings	8.8	(±4.9)	8.2	(±5.6)	0.18

SD: standard deviation

Table 3: Familial history of solid tumor or hematopoietic malignancy and childhood acute leukemia

	Controls n = 567 (%)		Cases n = 472 (%)		OR[a]	95% CI[b]
History of cancer						
First-degree relative						
No	561	(99)	453	(96)	**1.0**	reference
Yes	6	(1)	19	(4)	**3.8**	[1.5-9.8]
Second-degree relative						
No	424	(76)	307	(68)	**1.0**	reference
Yes	143	(24)	165	(32)	**1.5**	[1.1-2.0]
First- or second-degree relative						
No	420	(76)	298	(66)	**1.0**	reference
Yes	147	(24)	174	(34)	**1.6**	[1.2-2.1]
History of solid tumor						
First-degree relative						
No	562	(99)	454	(96)	**1.0**	reference
Yes	5	(1)	17	(4)	**4.1**	[1.5-11.6]
Second-degree relative						
No	432	(76)	319	(68)	**1.0**	reference
Yes	134	(24)	152	(32)	**1.5**	[1.1-1.9]
First- or second-degree relative						
No	429	(76)	309	(66)	**1.0**	reference
Yes	137	(24)	162	(34)	**1.6**	[1.2-2.1]
History of hematopoietic malignancy						
First-degree relative						
No	548	(99.5)	445	(99)	**1.0**	reference
Yes	1	(0.5)	2	(1)	**2.0**	[0.1-23]
Second-degree relative						
No	553	(98)	455	(97)	**1.0**	reference
Yes	13	(2)	16	(3)	**1.6**	[0.7-3.4]
First- or second-degree relative						
No	552	(97)	453	(96)	**1.0**	reference
Yes	14	(3)	18	(4)	**1.6**	[0.8-3.4]
Number of relatives with cancer						
0	420	(74)	297	(63)	**1.0**	reference
1	122	(22)	131	(28)	**1.5**	[1.1-2.0]
≥ 2	25	(4)	43	(9)	**2.3**	[1.3-3.8]
Number of mother's relatives with cancer						
0	420	(84)	297	(75)	**1.0**	reference
1	71	(14)	85	(22)	**1.6**	[1.1-2.3]
≥ 2	10	(2)	13	(3)	**1.8**	[0.7-4.2]
Number of father's relatives with cancer						
0	420	(85)	297	(75)	**1.0**	reference
1	68	(14)	83	(21)	**1.7**	[1.2-2.5]
≥ 2	7	(1)	16	(4)	**2.9**	[1.1-7.5]

[a] OR: Odds ratios were derived from an unconditional logistic model, adjusted for age, gender, region of residence and family size.

[b] 95% CI: 95% confidence interval

Table 4: Familial history of solid tumor or hematopoietic malignancy by type of childhood acute leukemia

	Controls		ALL[a]				AML[b]			
	n = 567 (%)		n = 407 (%)		OR[c]	95% CI[d]	n = 62 (%)		OR[c]	95% CI[d]
History of cancer										
First-degree relative										
No	561	(99)	392	(96)	**1.0**	reference	58	(94)	**1.0**	reference
Yes	6	(1)	15	(4)	**3.6**	[1.4- 12]	4	(6)	**4.7**	[1.2- 18]
Second-degree relative										
No	424	(75)	266	(66)	**1.0**	reference	38	(61)	**1.0**	reference
Yes	143	(25)	141	(34)	**1.5**	[1.1-2.0]	24	(39)	**1.6**	[0.9-2.8]
First- or second-degree relative										
No	420	(74)	259	(64)	**1.0**	reference	36	(58)	**1.0**	reference
Yes	147	(26)	148	(36)	**1.6**	[1.0-3.0]	26	(42)	**1.7**	[1.0- 30]
History of solid tumor										
First-degree relative										
No	562	(99)	392	(97)	**1.0**	reference	59	(95)	**1.0**	reference
Yes	5	(1)	14	(3)	**4.5**	[1.5- 12]	3	(5)	**4.5**	[1.0- 20]
Second-degree relative										
No	432	(76)	275	(54)	**1.0**	reference	42	(68)	**1.0**	reference
Yes	134	(24)	131	(46)	**1.5**	[1.1-2.0]	20	(32)	**1.4**	[0.8-2.5]
First- or second-degree relative										
No	429	(76)	267	(66)	**1.0**	reference	40	(65)	**1.0**	reference
Yes	137	(24)	139	(34)	**1.6**	[1.2-2.1]	22	(35)	**1.6**	[0.9-2.0]
History of hematopoietic malignancy										
First-degree relative										
No	548	(99.5)	382	(99)	**1.0**	reference	60	(98)	**1.0**	reference
Yes	1	(0.5)	1	(1)	**1.2**	[0.1- 20]	1	(2)	**6.4**	[0.4-113]
Second-degree relative										
No	553	(98)	394	(97)	**1.0**	reference	58	(94)	**1.0**	reference
Yes	13	(2)	12	(3)	**1.4**	[0.6-3.1]	4	(6)	**3.8**	[1.2- 13]
First- or second-degree relative										
No	552	(97)	393	(97)	**1.0**	reference	57	(92)	**1.0**	reference
Yes	14	(3)	13	(3)	**1.4**	[0.6-2.9]	5	(8)	**4.3**	[1.4- 13]

[a] ALL: Acute Lymphoblastic Leukemia. [b] AML : Acute Myeloblastic Leukemia. [c] OR: Odds ratios adjusted for age, gender, region of residence and family size. [d] 95% CI: 95% confidence interval

TABLE 5: associations between a familial history of specific types of cancer in first and second degree relatives and childhood acute leukemia

	ICD- 9 [a]	Controls	AL [b]			ALL [c]			AML [d]		
		n = 567	n = 472	OR [e]	95%CI [f]	n = 407	OR [e]	95%CI [f]	n = 62	OR [e]	95%CI [f]
Lip, oral cavity	140-149	5	12	**2.8**	(0.9-8.0)	12	**3.5**	(1.2-10)	0	**-**	
Esophagus, stomach	150-152	7	11	**1.8**	(0.9-1.6)	10	**1.9**	(0.7-5.1)	1	**1.3**	(0.1- 11)
Colon, rectum	153-154	10	12	**1.5**	(0.6-3.4)	8	**1.1**	(0.4-2.9)	4	**3.9**	(1.1- 13)
Liver, gallbladder	155-157	11	13	**1.2**	(0.5-2.8)	12	**1.4**	(0.6-3.2)	1	**0.5**	(0.1-4.2)
Lung	162	17	17	**1.2**	(0.6-2.4)	15	**1.3**	(0.6-2.7)	2	**0.9**	(0.2-4.1)
Melanoma	172	2	6	**4.4**	(0.8- 22)	4	**3.5**	(0.6- 19)	2	**9.0**	(0.6- 19)
Breast	174	34	30	**1.1**	(0.6-1.8)	27	**1.1**	(0.6-1.9)	3	**0.7**	(0.2-2.6)
Uterus, ovary	179-184	10	23	**2.7**	(1.2-5.8)	18	**2.4**	(1.1-5.4)	5	**4.2**	(1.3- 14)
Prostate	185	5	3	**0.7**	(0.1-3.2)	2	**0.5**	(0.1-2.9)	1	**2.7**	(0.3- 27)
Kidney, bladder	188-189	4	4	**1.0**	(0.2-4.1)	4	**1.2**	(0.3-4.9)	0	**-**	
Thyroid	193	2	4	**2.6**	(0.4- 15)	4	**3.3**	(0.6- 19)	0	**-**	
Brain	191	1	9	**10.7**	(1.3- 86)	8	**11.5**	(1.3- 91)	1	**8.6**	(0.5-140)
Hematopoietic malignancy	200-208	14	18	**1.6**	(0.8-3.4)	13	**1.4**	(0.6-2.9)	5	**4.3**	(1.4- 13)
Others sites		48	46	**1.1**	(0.7-1.7)	40	**1.1**	(0.7-1.7)	6	**1.3**	(0.5- 3.0)

[a] ICD-9 = Ninth International Classification of Diseases. [b] AL: Acute Leukemia. [c] ALL: Acute Lymphoblastic Leukemia. [d] AML: Acute Myeloblastic Leukemia. [e] OR: Odds ratios adjusted for age, gender, region of residence and family size. [f] 95% CI: 95% confidence interval.