

Childhood Hodgkin's lymphoma, non-Hodgkin's lymphoma and factors related to the immune system: The Escale Study (SFCE)

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The study investigated the role of factors considered related to the early stimulation of the immune system in the aetiology of childhood lymphoma. The national registry-based case-control study, Escale, was carried out in France over the period 2003–2004. Population controls were frequency matched with the cases on age and gender. Data were obtained from structured telephone questionnaires administered to mothers. Odds ratios (ORs) were estimated using unconditional regression models adjusted for potential confounders. Data from 128 cases of Hodgkin's lymphoma (HL) aged 5–14 years, 164 cases of non-Hodgkin's lymphoma (NHL) aged 2–14 years and 1,312 controls were analyzed. Negative associations were observed between HL and day care attendance [OR = 0.5 (0.2–1.2)] and between HL and repeated early common infections among non-breastfed children [OR = 0.3 (.2–0.7), $p = 0.003$] [OR for breastfed children: 1.0 (.5–2.1)], but not for the other factors investigated. Negative associations were observed between NHL and birth order 3 or more [OR = 0.7 (0.4–1.1)], prolonged breastfeeding [OR = 0.5 (0.3–1.0)], regular contact with farm animals [OR = 0.5 (0.3–1.0)], frequent farm visits in early life [OR = 0.6 (0.4–1.1)] and history of asthma [OR = 0.6 (0.3–1.1)]. In conclusion, the results partly support the hypothesis that an abnormal maturation of the immune system may play a role in childhood HL or NHL, and call for further investigations.

In developed countries, childhood Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) present with incidences of about 7 and 10 cases per million person-years, respectively.¹ Immune deficiencies and some genetic disorders

are known risk factors that explain a few cases of childhood lymphomas. Epstein-Barr virus (EBV) is present in around 20% of Burkitt's lymphoma and 40% of Hodgkin's lymphoma cases in France. In African Burkitt's lymphoma, malaria acts

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as a cofactor for lymphoma genesis after EBV infection but in western countries, cofactors have yet to be identified. Early exposure to EBV protects against mononucleosis, which is an established risk factor for HL, in young adults. With regard to children, very few studies have investigated the role of late exposure to common infections in childhood lymphoma. Early life exposure to infections is fundamental to the development and modulation of the immune system² and a lack of infections may predispose to immune-mediated disorders, such as atopy³ and acute lymphoblastic leukemia.⁴ Other factors inducing early immune system stimulation, such as prolonged breastfeeding and exposure to farm animal, may also be protective with respect to such diseases.^{5–7} The aim of this study was to test these hypotheses for childhood lymphomas.

The national population-based case-control study, Escale, investigated the relationship between the risk of childhood lymphoma and factors known to be related, or suspected of being related, to the early stimulation of the immune system: repeated early common infections and markers of early exposure to infection, *i.e.*, high birth order, daycare centre attendance, breastfeeding, contact with farm animals, farm visits in early life and a history of allergy.

The cases had been reliably documented by the French National Registry of Childhood Blood Malignancies (RNHE),⁸ enabling investigation of the associations with HL and NHL, and also with HL and NHL subtypes.

Material and Methods

The Escale study [French Society to Combat Cancer in Children and Adolescents (SFCE)] was conducted in 2003 and 2004 to investigate the role of infectious, environmental and genetic factors in four childhood neoplastic diseases (acute leukemia, lymphoma, neuroblastoma and brain tumor). This article focuses on lymphoma.

Case and control ascertainment

Cases. The cases were identified directly by the investigators of the RNHE⁸ assigned to each pediatric oncology hospital department. In order for the cases to be eligible, they had to have been newly diagnosed between January 1, 2003 and December 31, 2004, to be less than 15 years old, and to be resident in mainland France at the time of diagnosis. Cases who had been adopted, whose biological mother had died, whose mother did not speak French, or whose mother presented with a serious psychiatric disorder were not eligible. For ethical reasons, the mothers of children who had died or who were receiving hospital palliative care were not contacted. Out of the 171 cases of HL and 207 cases of NHL identified during the study period, 152 cases of HL and 186 cases of NHL were eligible. The reasons for noneligibility consisted in the child's death, hospital palliative care, biological mother's death, non-French-speaking mother and mother with a serious psychiatric disorder. In all, 130 (HL) and 165 (NHL) of the eligible households consented to participate (86 and 89%). The histological subtypes of HL and NHL were obtained from the RNHE.

Controls. Population controls were randomly selected over the years 2003 and 2004, using a quota sampling method. A base of 60,000 addresses representative of the population in terms of the administrative regions and urbanization was randomly extracted from the national telephone directory (plus randomly generated unlisted numbers). The quotas were designed to make the age and gender distribution of the controls similar to that of all Escale cases, based on estimates from the RNHE⁸ and the Regional Childhood Cancer Registries,⁹ with age group quotas: 0–1, 2, 3, 4, 5–6, 7–8, 9–11, 12–14 years. Additional quotas ensured that the control group had the same number of children aged less than 15 years living in the household as the French general population of the same age (1999 population census¹⁰). The controls were selected among children free from cancer, who had not been adopted, and whose biological mother was alive, free from serious psychiatric disorders and French-speaking. Out of the 50,217 phone numbers dialed, 22,584 did not connect to a home number, 24,411 were ineligible, and for 862, the respondent hung up before eligibility could be checked. The 2,360 remaining numbers were considered to be those of eligible households, 679 of which refused to participate. Thus, 1,681 mothers were interviewed (71.2%).

Data collection

The same trained interviewers carried out the telephone interviews with the cases' and controls' biological mothers using structured questionnaires. Half of the cases' mothers were interviewed less than 5 months after the diagnosis. The telephone questionnaire elicited information on demographic and socio-economic characteristics, childhood environment, lifestyle and familial history of cancer. The interviews detailed the number and age of the siblings, childcare history, duration of breastfeeding, history of asthma, eczema and wheezing bronchitis, history of surgical procedures for early ear-nose-throat (ENT) infections, history of tonsillitis, otitis, upper respiratory tract infections, gastroenteritis, bronchiolitis and other lower respiratory tract infections as well as urinary tract infections. "Repeated early common infections" was defined as 4 or more episodes of infection of at least one given site, or 1–3 episodes of infection of at least 4 sites in infancy. Mothers were also asked how often their child visited a farm in infancy and whether the child had been in contact with cats, dogs, rodents, birds, cows, sheep, horses, pigs, rabbits and poultry at least once a week in infancy. The questionnaire also elicited the following specific infections in infancy: measles, German measles, mumps, chickenpox, infectious mononucleosis and whooping-cough.

Statistical analysis

Separate analyses were carried out for HL and NHL. The analyses were restricted to cases and controls 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 lymphoma cases in the lowest age groups. Odds ratios (ORs)

and their 95% confidence intervals (CIs) were estimated using unconditional logistic regression models including the stratification variable age/gender used for quota sampling. Systematic adjustment was conducted for parental professional category, degree of urbanization of the place of residence (1999 census¹⁰) and maternal age. Models including animal contacts were also adjusted for housing during the 1st year of life (only apartment vs. house). The stability of the results was tested after additional adjustments for maternal and paternal education (complete high school vs. less), paternal smoking, household exposure to pesticides and family history of cancer.^{11–13}

Analyses were also carried out by HL subtype (nodular sclerosis HL, mixed cell HL and lymphocyte predominant HL) and by NHL subtype (Burkitt NHL, non-Burkitt B-cell lymphoma, anaplastic large cell NHL and T-cell lymphoma other than anaplastic) using polytomous logistic regression models.

The SAS[®] software package (version 9, Cary, NC) was used for all the analyses. All *p* values were two-tailed.

Results

A total of 130 incident cases of HL, of whom 128 aged 2 years or more (79 nodular sclerosis, 19 mixed cell, 18 lymphocyte predominant and 12 unspecified HL) and 165 incident cases of NHL, of whom 164 aged 5 years or more (77 Burkitt, 35 non-Burkitt B-cell lymphoma, 21 anaplastic large cell, 27 T-cell lymphoma other than anaplastic and four unspecified NHL) were included. In all 848 and 1,312 out of the 1,681 controls included were aged 5 years or more and 2 years or more, respectively.

Case-control comparability

The age and gender distribution of the cases and controls is shown in Table 1. The controls were similar to the whole case group (data not shown), but not to the HL and NHL cases considered separately, due to the over-representation of older girls for HL and older boys for NHL. Nevertheless, all the strata included at least one control per case.

The control parents were more educated and had a more qualified job than the HL case parents, but they were similar with regard to the urban/rural status of their place of residence (Table 1). HL case mothers were more often aged 25 years or less at the child's birth than control mothers. In contrast, the control parents and NHL case parents were similar with regard to educational level, professional category and maternal age at the child's birth, but the NHL cases lived in urban areas more often than the controls. The number of children aged less than 15 years in the household at the time of diagnosis was similar for the controls and HL and NHL cases (Table 1).

Early common infections, birth order, daycare attendance, breastfeeding, farm visiting and childhood Hodgkin's lymphoma

Overall, repeated early common infections were significantly negatively associated with HL [OR = 0.5 (0.3–0.9), *p* = 0.01], and, in particular, with the nodular sclerosis [OR =

0.5 (0.3–0.9), *p* = 0.03] and lymphocyte predominant [OR = 0.2 (0.0–1.0), *p* = 0.05] subtypes (Table 2). A history of surgical operations for ENT infections before age 3 years was also linked negatively with HL [OR = 0.6 (0.3–1.5)], but not significantly. Full-time daycare centre attendance in infancy was slightly negatively associated with HL [OR = 0.5 (0.2–1.2)], but birth order was positively associated with HL [OR = 1.5 (0.9–2.4) for birth order 2 versus 1, and OR = 1.2 (0.7–2.2) for birth order 3 and more versus 1]. Prolonged breastfeeding for at least 6 months was not significantly associated with HL [OR = 1.4 (0.8–2.9)]. Regular contacts with cats [OR = 0.9 (0.3–1.3)], dogs [OR = 0.7 (0.5–1.1)] or farm animal [OR = 1.0 (0.5–1.7)] and farm visits [OR = 1.0 (0.5–1.8)] in infancy were not associated with HL. The results were quite similar for the various HL subtypes. HL and the various HL subtypes were not associated with a history of asthma [OR = 1.0 (0.5–1.9)], bronchitis with wheezing [OR = 1.1 (0.7–1.8)] or eczema [OR = 1.1 (0.7–1.8)].

Early common infections, birth order, daycare attendance, breastfeeding, farm visiting and childhood non-Hodgkin's lymphoma

Repeated early common infections [OR = 0.9 (0.7–1.3)], surgical operations for ENT infections [OR = 1.2 (0.6–2.2)] and daycare attendance [OR = 0.9 (0.5–1.6)] were not associated with NHL (Table 3). Birth order three or more [OR = 0.7 (0.4–1.1)], prolonged breast-feeding [OR = 0.5 (0.3–1.0), *p* = 0.06], regular contact with farm animals [OR = 0.5 (0.3–1.0), *p* = 0.04] and farm visits [OR = 0.6 (0.4–1.1)] in early life were negatively associated with NHL. The negative associations were observed for all the NHL subtypes, except the association with prolonged breast-feeding which was restricted to Burkitt B-cell lymphoma. NHL was negatively associated, albeit not significantly, with a history of asthma [OR = 0.6 (0.3–1.1)].

Types of infection

HL was negatively associated, albeit not significantly, with early repeated episodes of each type of common infection (Table 4). NHL was negatively associated with early repeated tonsillitis, bronchiolitis and gastroenteritis (Table 4). A history of any specific infection before the age of 1 year was not significantly associated with HL [OR = 0.7 (0.2–2.1)] or NHL [OR = 0.7 (0.3–1.7)], but those infections are rare in the age group considered.

Multivariate analysis and sensitivity analyses

The associations were very similar when the analysis was stratified by parental socioeconomic status or degree of urbanization, and after adjustment for educational level, maternal age at birth, paternal tobacco smoking and household exposure to pesticides.

The results for birth order, daycare attendance, breastfeeding, repeated early common infections, farm visits, animal contacts and history of allergy were not substantially changed after mutual adjustment. However, stratification on

Table 1. Comparability of cases and controls—distribution of the cases and controls by the stratification variable age × gender (16 categories) used for quota sampling and socioeconomic characteristics

	Hodgkin's lymphoma						Non-Hodgkin's lymphoma					
	Cases (<i>n</i> = 128)		Controls (<i>n</i> = 848)		OR ¹	95% CI	Cases (<i>n</i> = 164)		Controls (<i>n</i> = 1,312)		OR ¹	95% CI
	<i>N</i>	%	<i>N</i>	%			<i>N</i>	%	<i>N</i>	%		
Quota variable gender/age												
Boy/2 years	–		–				3	2	79	6		
Boy/3 years	–		–				9	6	87	7		
Boy/4 years	–		–				11	7	89	7		
Boy/5–6 years	7	5	126	15			25	16	126	10		
Boy/7–8 years	11	8	96	11			18	11	96	7		
Boy/9–11 years	22	17	137	16			24	15	137	10		
Boy/12–14 years	21	17	117	14			26	16	117	9		
Girl/2 years	–		–				2	1	74	6		
Girl/3 years	–		–				5	3	79	6		
Girl/4 years	–		–				5	3	56	4		
Girl/5–6 years	1	1	102	12			7	4	102	8		
Girl/7–8 years	2	2	67	8			8	5	67	5		
Girl/9–11 years	10	8	88	10			8	5	88	7		
Girl/12–14 years	54	43	115	14			13	8	115	9		
Maternal educational level												
≤High-school	91	71	532	63	1.0	–	96	59	795	61	1.0	–
>High-school	33	26	315	37	0.7	(0.4–1.0)	67	41	516	39	1.2	(0.8–1.6)
Missing	4	3	1	0.1			1	1	1	0		
Parental professional category at interview ²												
Intellectual jobs, managers and intermediate professions	38	30	360	42	1.0	–	67	41	557	42	1.0	–
Administrative and sales workers	33	26	221	26	1.5	(0.9–2.5)	41	25	356	27	1.0	(0.6–1.5)
Service workers	29	23	133	16	1.9	(1.1–3.3)	32	20	179	14	1.3	(0.8–2.0)
Factory and agricultural workers, unemployed	28	22	134	16	2.1	(1.2–3.7)	24	15	220	17	0.9	(0.6–1.6)
Place of residence at the time of diagnosis												
Rural	44	34	294	35	1.0	–	44	27	459	35	1.0	–
Semi-urban	34	27	200	24	1.1	(0.7–1.8)	52	32	305	23	1.8	(1.2–2.8)
Urban	50	39	354	42	1.0	(0.6–1.6)	68	41	548	42	1.3	(0.9–2.0)
Maternal age at child's birth (year)												
<25	29	23	89	10	2.2	(1.3–3.8)	17	10	134	10	1.1	(0.6–2.0)
25–29	53	41	392	46	1.0	–	68	41	541	41	1.0	–
30–34	31	24	255	30	1.1	(0.7–1.9)	51	31	436	33	1.1	(0.7–1.6)
35 and more	15	12	112	13	1.1	(0.6–2.1)	28	17	201	15	1.2	(0.8–2.0)
Number of children aged less than 15 years in the household at the time of diagnosis												
1	52	41	240	28	1.0	–	46	28	390	30	1.0	–
2	45	35	374	44	0.8	(0.5–1.2)	75	46	576	44	1.1	(0.7–1.6)
3 and more	31	24	234	28	0.8	(0.5–1.4)	43	26	346	26	1.0	(0.6–1.6)

Only the controls aged more than 4 years for the Hodgkin's lymphoma cases and more than 1 year for the non-Hodgkin's lymphoma cases were used for the analyses.

¹Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by unconditional logistic regression, adjusted for stratification variable, age × gender. ²Professional category = higher of maternal and paternal professional categories.

Table 2. Repeated common infections in the 1st year of life, birth order, daycare attendance, breastfeeding, animal contacts, farm visits and childhood Hodgkin's lymphoma

	Controls <i>n</i> = 848	All HL <i>n</i> = 128		NoSc <i>n</i> = 79		MixC <i>n</i> = 19		LyPr <i>n</i> = 18	
		OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI
Repeated early common infections									
No	214	37	1.0 –	58	1.0 –	10	1.0 –	14	1.0 –
Yes	288	26	0.5 (0.3–0.9)	15	0.5 (0.3–1.0)	6	0.9 (0.3–2.6)	2	0.2 (0.0–0.9)
Missing	48	11		6		3		2	
Surgical operation for ear-nose-throat infections before age 3 years									
No	789	121	1.0 –	77	1.0 –	16	1.0 –	18	1.0 –
Yes	57	6	0.6 (0.3–1.5)	1	0.2 (0.0–1.3)	3	2.0 (0.5–7.4)	0	–
Missing	2	1		1		0		0	
Birth order									
1	350	53	1.0 –	31	1.0 –	8	1.0 –	8	1.0 –
2	319	51	1.5 (0.9–2.4)	32	1.5 (0.8–2.7)	6	0.9 (0.3–2.8)	7	1.1 (0.4–3.3)
≥3	179	24	1.2 (0.7–2.2)	16	1.4 (0.6–2.9)	5	1.2 (0.34–4.6)	3	0.8 (0.2–3.8)
Full-time daycare centre in the 1st year of life									
No	767	122	1.0 –	75	1.0 –	18	1.0 –	17	1.0 –
Yes	81	6	0.5 (0.2–1.3)	4	0.7 (0.2–2.0)	1	0.5 (0.1–4.2)	1	0.5 (0.1–4.0)
Breast feeding									
No	450	70	1.0 –	47	1.0 –	8	1.0 –	8	1.0 –
<6 months	308	43	1.1 (0.7–1.7)	23	0.9 (0.5–1.6)	8	1.6 (0.6–4.6)	8	1.5 (0.5–4.1)
≥6 months	85	14	1.4 (0.7–2.8)	8	1.3 (0.6–3.1)	3	2.5 (0.6–10.3)	2	1.5 (0.3–7.6)
Regular contacts with animals before 1-year old (at least once a week)									
Cats	281	40	0.9 (0.6–1.3)	22	0.6 (0.4–1.1)	6	1.1 (0.4–3.0)	8	1.7 (0.7–4.5)
Dogs	368	49	0.7 (0.5–1.1)	29	0.6 (0.4–1.1)	7	0.9 (0.3–2.5)	7	0.8 (0.3–2.2)
Farm animals ²	123	18	1.0 (0.5–1.7)	12	1.0 (0.5–1.9)	2	0.7 (0.2–3.3)	3	1.2 (0.3–4.5)
Farm visits before 2 years old									
No	729	112	1.0 –	55	1.0 –	13	1.0 –	16	1.0 –
Several days/year	116	18	1.1 (0.6–2.0)	13	1.5 (0.8–2.9)	2	0.9 (0.2–3.9)	1	0.3 (0.0–2.6)
More often	119	16	1.0 (0.5–1.8)	11	1.1 (0.5–2.2)	4	2.1 (0.6–7.3)	1	0.3 (0.0–2.6)
Asthma									
No	759	115	1.0 –	70	1.0 –	17	1.0 –	17	1.0 –
Yes	88	13	1.0 (0.5–1.9)	9	1.1 (0.5–2.5)	2	1.0 (0.2–4.4)	1	0.4
Bronchitis with wheezing									
No	661	98	1.0 –	61	1.0 –	14	1.0 –	12	1.0 –
Yes	185	29	1.1 (0.7–1.8)	18	1.1 (0.6–2.0)	4	1.1 (0.4–3.5)	6	1.8 (0.6–4.8)
Eczema									
No	674	101	1.0 –	61	1.0 –	16	1.0 –	14	1.0 –
Yes	171	26	1.1 (0.7–1.8)	17	1.2 (0.7–2.2)	3	0.9 (0.2–3.1)	4	1.2 (0.4–3.9)

Analyses were restricted to children aged more than 4 years.

¹Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by unconditional logistic regression, adjusted for stratification variables, age, gender, parental professional category, degree of urbanization, maternal age at child birth and housing, for contact with animals. ²Farm animals: cows, sheep, horses, pigs, rabbits and poultry.

Abbreviations: HL: Hodgkin's lymphoma; NoSc: nodular sclerosis HL; MixC: mixed cell HL; LyPr: lymphocyte predominant HL.

breastfeeding status showed that the association between HL and repeated early common infections only occurred among non-breastfed children [OR = 0.3 (0.2–0.7), *p* =

0.003] [OR for breastfed children: 1.0 (0.5–2.1)]. For NHL, no change was observed after stratification on breastfeeding status.

Table 3. Number of common infections in the 1st year of life, birth order, daycare attendance, breastfeeding, animal contacts, farm visits and childhood non-Hodgkin's lymphoma

	Controls <i>n</i> = 1,312			All NHL			Burkitt			Other B-cell			Anaplastic			Other T-cell		
	<i>n</i> = 164	OR ¹	95% CI	<i>n</i> = 77	OR ¹	95% CI	<i>n</i> = 35	OR ¹	95% CI	<i>n</i> = 21	OR ¹	95% CI	<i>n</i> = 27	OR ¹	95% CI			
Repeated early common infections																		
No	316	30	1.0	–	50	1.0	–	21	1.0	–	12	1.0	–	15	1.0	–		
Yes	465	56	0.9	(0.7–1.3)	23	0.7	(0.4–1.3)	13	1.1	(0.6–2.4)	8	1.2	(0.5–2.9)	11	1.3	(0.6–2.8)		
Missing	57	7			4			1			1			1				
Surgical operation for ear-nose-throat infections before age 3 years																		
No	1,228	149	1.0	–	67	1.0	–	32	1.0	–	20	1.0	–	26	1.0	–		
Yes	82	13	1.2	(0.6–2.2)	9	1.7	(0.8–3.6)	2	0.8	(0.2–3.6)	1	0.7	(0.1–5.3)	1	0.5	(0.1–3.9)		
Missing	2	2			1			1			0			0				
Birth order																		
1	549	68	1.0	–	36	1.0	–	14	1.0	–	7	1.0	–	10	1.0	–		
2	478	69	1.1	(0.7–1.6)	24	0.7	(0.4–1.2)	17	1.4	(0.6–2.9)	13	2.3	(0.8–6.0)	12	1.3	(0.5–3.0)		
≥3	285	27	0.7	(0.4–1.1)	17	0.8	(0.4–1.6)	4	0.4	(0.1–1.4)	1	0.2	(0.0–2.2)	5	0.9	(0.3–2.9)		
Full-time daycare centre in the 1st year of life																		
No	1,181	148	1.0	–	66	1.0	–	32	1.0	–	21	1.0	–	25	1.0	–		
Yes	131	15	0.9	(0.5–1.6)	10	1.2	(0.6–2.5)	3	0.9	(0.3–3.2)	0	–	–	2	0.7	(0.2–3.1)		
Breastfeeding																		
No	672	90	1.0	–	40	1.0	–	18	1.0	–	14	1.0	–	15	1.0	–		
<6 months	473	63	1.0	(0.7–1.5)	32	1.0	(0.6–1.7)	13	1.2	(0.6–2.5)	5	0.5	(0.2–1.5)	12	1.2	(0.5–2.6)		
≥6 months	161	11	0.5	(0.3–1.0)	5	0.5	(0.2–1.2)	4	1.4	(0.4–4.4)	2	0.7	(0.2–3.3)	0	–	–		
Regular contacts with animals before 1-year old (at least once a week)																		
Cats	432	47	0.9	(0.6–1.2)	18	0.7	(0.4–1.2)	9	0.7	(0.3–1.5)	8	1.2	(0.5–3.0)	10	1.3	(0.6–3.0)		
Dogs	591	76	1.1	(0.8–1.5)	37	1.3	(0.8–2.1)	16	1.0	(0.5–2.1)	9	0.9	(0.4–2.3)	11	0.8	(0.4–1.9)		
Farm animals ²	162	13	0.5	(0.3–1.0)	6	0.6	(0.2–1.4)	3	0.6	(0.2–1.9)	2	0.6	(0.1–2.6)	1	0.2	(0.0–1.9)		
Farm visits before 2 years old																		
No	931	130	1.0	–	62	1.0	–	26	1.0	–	16	1.0	–	23	1.0	–		
Several days/year	180	18	0.7	(0.4–1.2)	8	0.6	(0.3–1.4)	5	1.1	(0.4–3.0)	2	0.7	(0.2–3.1)	3	0.7	(0.2–2.3)		
More often	201	16	0.6	(0.4–1.1)	7	0.6	(0.3–1.4)	4	0.8	(0.3–2.5)	3	0.9	(0.3–3.3)	1	0.2	(0.0–1.7)		
Asthma																		
No	1,191	154	1.0	–	73	1.0	–	33	1.0	–	20	1.0	–	24	1.0	–		
Yes	120	10	0.6	(0.3–1.1)	4	0.5	(0.2–1.3)	2	0.5	(0.1–2.3)	1	0.4	–	3	1.2	(0.4–4.1)		

Table 3. Number of common infections in the 1st year of life, birth order, daycare attendance, breastfeeding, animal contacts, farm visits and childhood non-Hodgkin's lymphoma (Continued)

	Controls n = 1,312	All NHL		Burkitt		Other B-cell		Anaplastic		Other T-cell						
		n = 164	OR ¹	95% CI	n = 77	OR ¹	95% CI	n = 35	OR ¹	95% CI	n = 27	OR ¹	95% CI			
Bronchitis with wheezing																
No	1,040	130	1.0	-	64	1.0	-	29	1.0	-	16	1.0	-			
Yes	269	33	0.9	(0.6-1.4)	12	0.7	(0.3-1.2)	6	0.8	(0.3-2.1)	5	1.0	(0.4-2.9)	10	2.3	(1.0-5.1)
Eczema																
No	1,019	129	1.0	-	59	1.0	-	31	1.0	-	16	1.0	-	20	1.0	-
Yes	289	35	1.0	(0.6-1.4)	18	1.1	(0.6-1.9)	4	0.5	(0.2-1.6)	5	1.2	(0.4-3.3)	7	1.2	(0.5-3.0)

Analyses were restricted to children aged more than 1 year.

¹Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by unconditional logistic regression, adjusted for stratification variables, age, gender, parental professional category, degree of urbanization, maternal age at child birth and housing, for contact with animals. ²Farm animals: cows, sheep, horses, pigs, rabbits and poultry.

Abbreviations: NHL: non-Hodgkin's lymphoma; Burkitt: Burkitt lymphoma; Other B-cell: non-Burkitt B-cell NHL; anaplastic: anaplastic large cell NHL; Other T-cell: T-cell lymphoma other than anaplastic.

Discussion

In the study, factors considered to stimulate the immune system were negatively associated with childhood NHL: high birth order, breastfeeding for at least 6 months, and frequent farm visits or regular contacts with farm animals in infancy. NHL was also negatively related to childhood history of asthma. Childhood HL was only negatively linked with repeated early common infections.

For NHL, significant two-tailed negative minimum ORs of 0.6 and 0.4 for exposure prevalence in controls of 30 and 10%, respectively, were evidenced with a statistical power of 80% and an alpha error of 5%. For HL, the corresponding ORs were 0.5 and 0.3. Even though the study may have suffered from a lack of power for low-prevalence exposure, a relatively high number of cases was included, compared to previous studies that investigated childhood NHL or childhood HL.

The cases were identified in all the pediatric cancer units in France through the data collection system of the RNHE, which has a high degree of exhaustiveness (>97% of NHL diagnosed in mainland France).⁸ Thus, very few cases diagnosed in France in 2003 and 2004 may have escaped inclusion due to nonidentification. Moreover, the case-mother participation rate was very high, close to 90%.

Regarding control selection, the quota sampling process successfully ensured that responding controls had the same distribution as the entire case group with regard to gender and age, and the same distribution as the overall population with regard to birth order and region, as shown by comparison with the French national perinatal surveys carried out in 1995, 1998 and 2003.¹⁴⁻¹⁶ The overall birth order distribution in those 3 surveys, each including 15,000 women, was: 42.6% first-born, 34.3% second-born and 22.6% third-born and subsequent, whereas the rates were 40.9%, 36.8% and 22.3%, respectively, for the controls born in France between 1995 and 2003. Maternal education was very similar in the control group and in the French population.¹⁴⁻¹⁶ However, the refusals to take part could have been related to parental socioeconomic status or education, which seemed higher for the controls than for the HL cases. Nonetheless, the results were unchanged when the analyses were stratified by, or adjusted for, those factors. Moreover, in our study, the mothers of 11.1% of the controls aged 11-14 years reported asthma in their child. The frequency was very similar to the 12.7% history of asthma events in 11-14-year-old children reported in a French survey carried out in 2003.¹⁷

Misclassifications are likely to have occurred since the exposures were described retrospectively and reported by maternal interviews. The UKCCS study showed that mothers tended to underreport that their child had had at least one infection before 1 year of age as recorded by the general practitioner, and that the misclassification was slightly more frequent for leukemia cases than for controls.^{18,19} Some studies on maternal recall errors in severe childhood diseases were also reviewed in a validation paper on a Quebec study,

Table 4. Childhood Hodgkin's and non-Hodgkin's lymphoma and common sites of infections in the 1st year of life

	HL				NHL			
	Controls <i>n</i> = 848	Cases <i>n</i> = 128	OR ¹	95% CI	Controls <i>n</i> = 1,312	Cases <i>n</i> = 164	OR ¹	95% CI
Tonsillitis								
No infection	718	114	1.0	–	1,128	145	1.0	–
1–3	83	8	0.7	(0.3–1.6)	120	7	0.4	(0.2–1.0)
≥4	31	2	0.5	(0.1–2.2)	44	5	0.8	(0.3–2.2)
Otitis								
No infection	610	90	1.0	–	957	110	1.0	–
1–3	130	26	1.4	(0.8–2.3)	190	41	1.9	(1.3–2.8)
≥4	95	10	0.8	(0.4–1.7)	150	12	0.7	(0.4–1.2)
Upper respiratory tract infections								
No infection	358	57	1.0	–	537	55	1.0	–
1–3	265	49	1.2	(0.8–1.8)	415	60	1.5	(1.0–2.2)
≥4	209	17	0.5	(0.2–1.0)	341	46	1.3	(0.9–2.0)
Bronchiolitis and other lower respiratory tract infections								
No infection	689	111	1.0	–	1,026	139	1.0	–
1–3	110	12	0.9	(0.5–1.8)	206	23	0.9	(0.6–1.5)
≥4	39	2	0.4	(0.1–1.6)	65	1	0.1	–
Gastroenteritis								
No infection	699	98	1.0	–	1,046	135	1.0	–
1–3	110	21	1.4	(0.8–2.5)	211	23	0.9	(0.6–1.5)
≥4	18	1	0.4	–	29	1	0.2	–
Urinary tract infections								
No infection	819	123	1.0	–	1,268	156	1.0	–
≥1	25	3	0.9	(0.3–1.5)	39	6	1.3	(0.6–3.3)

Analyses were restricted to children aged more than 1 year for NHL to children aged more than 4 years for HL.

¹Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by unconditional logistic regression, adjusted for stratification variables, age, gender, parental professional category, degree of urbanization and maternal age at child birth.

Abbreviations: HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma.

which estimated the bias to be relatively small overall.²⁰ In this study, the association between HL and repeated early common infections was of the same order of magnitude as that with ENT surgery before age 3 years, assumed to follow a history of repeated infections, and with daycare attendance, considered to increase the risk of early exposure to infection, both events that were likely to be less prone to recall bias than a history of early common infections itself. Similarly, the association between NHL and repeated early common infections was of the same order of magnitude as that with high birth order or daycare attendance. In addition, the case and control interviews were conducted in the same manner, by the same interviewers, using closed questions which would have generated less differential error between cases and controls.^{21–23} However, the possibility of differential recall of historical allergic or infectious events by cases and controls in this study cannot be ruled out.

There is no known strong potential confounding factor for HL and NHL. Parental professional category, urbanization and

maternal age, which could have influenced exposures and exposure reports, and the factors related to HL or NHL in the authors' previous analyses, were taken into account. With the exception of the modifying effect of breastfeeding on the relationship between early infections and HL, none of the main exposures of interest in this article was confounded by the others, or was a substantial confounder or modifier of the others.

The parents of children with HL were less educated and had a less qualified job than the control parents. Although it has been frequently and consistently observed that HL in young adults is more prevalent in people with higher socioeconomic status, few studies have reported relationships between socioeconomic status and childhood HL. In two studies, one conducted in the US and the other in the UK, children with HL tended to belong to lower social-class categories,^{24,25} whereas a Greek study found the opposite relationship,²⁶ albeit based on small numbers. People more willing to participate in epidemiologic studies appear to have higher socioeconomic status,^{27–32} which could partly explain the

fact that the controls had higher socio-economic status than the HL cases in this study. However, that was not the case for NHL. The finding may be explained by the presence of undetermined risk factors associated with both HL and socioeconomic status. Exposures linked to the early stimulation of the immune system could theoretically be such factors since those exposures are probably influenced by socioeconomic status. Yet, in this study, they were not associated with childhood HL.

Three studies have reported associations between a history of early severe infections and childhood lymphoma. Adami *et al.*³³ and McKinney *et al.*³⁴ reported nonsignificant odds ratios of 0.5 and 0.8, respectively, for a history of neonatal infection. Paltiel *et al.*³⁵ reported relative risks of childhood HL and NHL of 3.7 (0.4–36) and 5.6 (0.5–61), respectively, for children hospitalized for infection before age 1 year, compared to nonhospitalized children in an Israeli cohort. The questionnaire used in the present study was designed to identify children with the highest frequency of common infections in early life.

More studies have investigated birth order.^{26,33,34,36–41} Birth order may be of importance for the age at exposure to common infections, assuming that children of later birth order are more likely to be exposed to infectious agents at an earlier age *via* older siblings. Most studies reported odds ratios lower than one for the highest birth order, but rarely significantly, for HL^{36,39–41} and NHL.^{33,37,41} In contrast, two studies found an increased risk of HL with increasing birth order.^{26,38} Birth order may be biased if the probability of a control being selected is lower when he/she belongs to a larger sibship, which may happen if the statistical unit for control sampling is the family rather than the individual.⁴² In this study, a telephone call procedure was used to select controls, but bias linked to family size was avoided by basing the quotas on the number of children aged less than 15 years in the household. Most of the published studies of adults aged less than 40 years have also shown that earlier exposure to common infections may decrease the risk of HL.³⁶ The results reported herein are consistent with this hypothesis for HL diagnosed before age 15 years old. Sixty percent of the cases in this study were aged 12–14 years.

No study has reported results for daycare attendance in early childhood and childhood lymphoma, even though daycare is associated with the transmission of infectious agents.⁴³

With regard to breastfeeding, Martin *et al.*⁷ included 7 studies on LH and 7 studies on LNH in a meta-analysis carried out in 2005. The authors reported meta-odds ratios of 0.9 (0.6–1.0) for HL and 1.0 (0.6–1.7) for NHL. The associations were more marked when breastfeeding lasted 6 months or more [OR = 0.7 (0.6–0.7) for HL and OR = 0.7 (0.3–1.4) for NHL]. In a

study published since then, slightly less of the cases of HL and NHL than the controls were breastfed for 6 months or more.⁴⁴

Interestingly, in our study, the negative relationship between HL and frequent early common infections was observed only in children who had not been breastfed and was not even discernible in children breastfed for more than 6 months, as if a child could not benefit fully from both breast-feeding and early infections.

To the authors' best knowledge, this study is the first to report on contacts with pets, farms and farm animals during infancy. Such exposures may enable effective maturation of the immune system and thus prevent childhood lymphoma, as has been hypothesized for allergies, for which epidemiologic studies have shown a lower risk in children exposed to animals in infancy^{6,45,46} and children living on farms.⁵ In this study, the negative associations between NHL and farm animal contacts and farm visits in early life are consistent with the preventive hypothesis. Petridou *et al.*²⁶ reported that cat ownership was more frequent in cases of childhood HL than in the controls, but did not specifically investigate infancy.

Allergy has also been investigated as a possible modulating factor in childhood leukemia development,⁴⁷ and most studies have reported negative links. In this study, only a weak negative association between NHL and asthma was observed. Magnani *et al.*⁴⁸ also reported a negative association between asthma and childhood NHL, but based on small samples (1 child out of 19 affected with NHL and 37 controls out of 307 had a history of asthma).

Overall, early viral or bacterial infections may decrease the occurrence of pediatric HL and NHL by enhancing maturation of T-helper cells (Th1 immunity).⁴⁹ In this study, negative associations were observed between HL and repeated early common infections and between NHL and high birth order, prolonged breast-feeding, farm animal contact in infancy and history of asthma. The findings only partly support the hypothesis that some conditions promoting the maturation of the immune system may play a protective role with respect to the risk of HL and NHL.

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APPENDIX

Table A1. SFCE Investigators of the Escalé study

Principal investigator	Hospital	City (France)
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Claire Berger	Centre Hospitalier Universitaire	Saint-Etienne
Christophe Bergeron	Centre Léon Bérard	Lyon
Jean-Louis Bernard	Hôpital La Timone	Marseille
Yves Bertrand	Hôpital Debrousse	Lyon
Pierre Bordigoni	Centre Hospitalier Universitaire	Nancy
Patrick Boutard	Centre Hospitalier Régional Universitaire	Caen
Gérard Couillault	Hôpital d'Enfants	Dijon
Christophe Piguet	Centre Hospitalier Régional Universitaire	Limoges
Anne-Sophie Defachelles	Centre Oscar Lambret	Lille
François Demeocq	Hôpital Hôtel-Dieu	Clermont-Ferrand
Alain Fischer	Hôpital des Enfants Malades	Paris
Virginie Gandemer	Centre Hospitalier Universitaire—Hôpital Sud	Rennes
Dominique Valteau-Couanet	Institut Gustave Roussy	Villejuif
Jean-Pierre Lamagnere	Centre Gatien de Clocheville	Tours
Françoise Lapiere	Centre Hospitalier Universitaire Jean Bernard	Poitiers
Guy Leverger	Hôpital Armand-Trousseau	Paris
Patrick Lutz	Hôpital de Haute pierre	Strasbourg
Geneviève Margueritte	Hôpital Arnaud de Villeneuve	Montpellier
Françoise Mechinaud	Hôpital Mère et Enfants	Nantes
Gérard Michel	Hôpital La Timone	Marseille
Frédéric Millot	Centre Hospitalier Universitaire Jean Bernard	Poitiers
Martine Münzer	American Memorial Hospital	Reims
Brigitte Nelken	Hôpital Jeanne de Flandre	Lille
Hélène Pacquement	Institut Curie	Paris
Brigitte Pautard	Centre Hospitalier Universitaire	Amiens
Yves Perel	Hôpital Pellegrin Tripode	Bordeaux

Table A1. SFCE Investigators of the Escalé study (continued)

Principal investigator	Hospital	City (France)
Alain Pierre-Kahn	Hôpital Enfants Malades	Paris
Emmanuel Plouvier	Centre Hospitalier Régional	Besançon
Xavier Rialland	Centre Hospitalier Universitaire	Angers
Alain Robert	Hôpital des Enfants	Toulouse
Hervé Rubie	Hôpital des Enfants	Toulouse
Nicolas Sirvent	L'Archet	Nice
Christine Soler	Fondation Lenval	Nice
Jean-Pierre Vannier	Hôpital Charles Nicolle	Rouen