Number of Siblings and the Risk of Lymphoma, Leukemia, and Myeloma by Histopathology

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Abstract

Epidemiologic evidence indicates that several markers of exposure to childhood infections are inversely associated with the risk of childhood leukemia and lymphomas. We used the Swedish Family-Cancer Database to assess the effects of number of siblings on the risk of non-Hodgkin's (n = 7,007) and Hodgkin's lymphomas (n = 3,115), leukemias (n = 7,650), and multiple myeloma (n = 1,492) by histopathology. Poisson regression models included terms for age, sex, family history, period, and socioeconomic index. Having four or more siblings compared with none was associated with an excess risk of childhood acute lymphoblastic leukemia [ALL; rate ratio (RR), 2.11; P_{trend} = 0.001], acute monocytic leukemia (RR, 2.51; P_{trend} = 0.002), and multiple myeloma (RR, 1.34; P_{trend} = 0.006). Having three or more older siblings compared with none decreased the risk of acute monocytic leukemia (RR, 0.35; P_{trend} = 0.001) and childhood ALL (RR, 0.69; P_{trend} = 0.01). The risk of Hodgkin's lymphoma for five or more older siblings compared with none was 0.41 (P_{trend} = 0.003). Acute myeloid leukemia, chronic lymphocytic leukemia, and other lymphoproliferative malignancies were not associated with number of siblings. In conclusion, we found an excess risk of childhood ALL and acute monocytic leukemia in large families. However, for ALL, acute monocytic leukemia, and Hodgkin's lymphoma, younger siblings were strongly protected compared with older siblings. The remarkable protective effect of number of older siblings on acute monocytic leukemia is a novel finding of potential interest. Possible interpretations of our findings in the context of a putative infectious etiology are discussed. (Cancer Epidemiol Biomarkers Prev 2006; 15(7):1281–6)

Introduction

Several indirect markers of exposures to infectious agents, including birth order, day care attendance, and socially unprivileged environments, have been found to be inversely associated with leukemia and Hodgkin's lymphoma (1-4). Large families and number of older siblings are possible indicators of early-life exposure to infections because children come in close contact with each other, thereby sharing exposures to many infectious agents. Previous work on the association between sibship size and birth order and the risk of leukemia has produced mixing results (5). Some studies reported an excess risk for acute lymphoblastic leukemia (ALL) for firstborns, but other studies found no association or a decreased risk (5, 6-13). For lymphomas, later-born children and those with many siblings have been found to have a low risk of Hodgkin's lymphoma (1, 14-16), whereas for non-Hodgkin's lymphoma (NHL), the epidemiologic evidence points toward an increased risk or no association (14, 16, 17). The effects of sibship size and birth order on other subtypes of lymphohematopoietic malignancies, including acute monocytic leukemia and subtypes of NHL, are unknown. Possible reasons for the apparently conflicting results could be that most studies considered all leukemias and lymphomas together and failed to stratify by age at diagnosis.

Viral infections have traditionally been associated with an increased risk of lymphomas and leukemias (5, 18, 19). Yet, specific agents have been identified only for a relatively small proportion of cases. EBV is found in about 50% of B-cell lymphomas, in the endemic form of Burkitt lymphomas, and in a consistent proportion of Hodgkin's lymphoma. Human herpes virus 8 has been associated with Kaposi sarcoma, HIV with Kaposi's sarcoma, Hodgkin's lymphoma and NHL (20-22), and hepatitis C with B-cell NHL (23). An infective etiology in childhood leukemia has been suggested for nearly 70 years (19). However, with the exception of the human T-cell lymphotropic virus type-1, associated with adult T-cell leukemia, no other specific pathogen has yet been implicated consistently (24-26). The importance of genetic events, including recurrent chromosome translocations, is clearly shown in acute myeloid leukemias, mature B-cell neoplasms, and Hodgkin's lymphoma. For childhood leukemia, and in particular for ALL, the evidence from molecular genetic and population-based family studies suggest that chromosome translocations are the initiating event of the disease that seems to arise per-natally (19, 27). One or more postnatal genetic alterations, possibly caused by abnormal immune responses to infections, are also thought to be needed for ALL development (19). According to the infection hypothesis, diminished or delayed exposure to common viral or bacterial infections in infancy is a risk factor for childhood leukemia and possibly Hodgkin's lymphoma (19, 20). Because critical characteristics of the adult immune system are believed to be shaped by environmental exposures in early life, the timing, the type, and the number of episodes of infection may play a pivotal role, which cannot be assessed without a proper age stratification (7, 28, 29).

Lymphohematopoietic neoplasms encompass an extremely heterogeneous group of malignancies with markedly different histologic and epidemiologic features and likely different etiologies. We investigate here the effect of sibship size and number of siblings, as markers of childhood infections, on the risk of leukemias, lymphomas, and myelomas using data from the Swedish Family-Cancer Database. The availability of

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Note: The Family Cancer Database was created by linking registries maintained by Statistics Sweden and the Swedish Cancer Register.

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detailed histopathology-specific data on a uniquely large data set allows to distinguish reliably between the effects of younger and older sibling numbers on specific tumor types in different periods of life. Such data may provide further insights into disease etiology (30).

Materials and Methods

The Swedish Family-Cancer Database was created in the mid-1990s by linking census information, death notifications, and the administrative family register at Statistics Sweden to the Swedish Cancer Registry (31). The Database was updated at the end of 2004 to include persons born in Sweden after 1931 with their biological parents, totalling over 10.5 million individuals. Each person has been assigned a unique technical identification number. For each child, there are data on both parents at the time of birth, allowing construction of families. The Database is organized in >3.6 million nuclear families, with parents and offspring. Neoplasms have been retrieved from the Swedish Cancer Registry from 1958 to 2002. The Swedish Cancer Registry is based on compulsory reports of individual cases provided by clinicians and pathologist/cytologists and is considered to be now almost 100% complete (32). Pathologists or cytologists report every cancer diagnosis on surgically removed tissues, biopsies, cytologic specimens, bone marrow aspirates, and autopsies. The incidence of tumors in the Database has been validated previously (31). Data on parity are complete, and data on socioeconomic index and area of residence are based on population censuses from the years 1960, 1970, 1980, and 1990.

Four-digit diagnostic codes from the seventh revision of the International Statistical Classification of Diseases and subsequent International Statistical Classification of Diseases classifications are available. Cancer site grouping were NHL (200 and 202) and leukemias (204-209). NHL subtypes classified according to the SNOMED system are available starting 1993 and consisted of diffuse large B-cell, follicular NHL, T-cell, B-cell NOS, NHL NOS, and rare lymphomas grouped as ''others.'' Different subtypes of leukemias classified according to seventh revision of the International Statistical Classification of Diseases included ALL (2040), chronic lymphocytic leukemia (2041), acute myeloid leukemia (2050), acute monocytic leukemia (2060), polycythemia vera (208), myelofibrosis (209), and other leukemias (2061, 2069, and 207).

Thus, the analyses considered diagnoses recorded between 1958 and 2002 and included a total of 19,264 cancer patients. The age of parents was not limited, but the maximum age of offspring was 70 years. In our population, 13% of the offspring were singletons; 39% had one sibling; 40% had two or three siblings; and 21% had four or more siblings. The mean age of older siblings at the time of diagnosis of the index case was 32 years (range, 1-70 years) for leukemia, 32 years (range, 4-68 years) for Hodgkin's lymphoma, 45 years (range, 1-70 years) for NHL, and 56 years (range, 5-70 years) for multiple myeloma. The mean age difference between older siblings was ~5 years with a range between 0 and 20 years for the different types of malignancies. Birth order is expressed for each individual as the number of older and younger siblings. In case of divorce, we had no possibility to verify which children remained with the same family. However, we assumed that all children have lived with the mother.

Statistical Methods. Follow-up was started on the date of birth, date of immigration, or 1st of January 1958, whichever occurred last. Follow-up ended on the date of diagnosis of the first primary neoplasm, date of death, date of emigration, or the closing date of the study (31st December 2002), whichever occurred first.

Person-years and cancer cases were counted and grouped by the study explanatory variables during the follow-up period for the child. Poisson regression models (multiplicative model and logarithm of person years as offset) were applied to the data using the GENMOD-procedure of the SAS-system V.9.1. The term rate ratio (RR) was used for the $\exp(\beta)$, where β is the estimated variable value; this was interpreted as an incidence rate ratio (e.g., RR is the incidence rate ratio for sibship size 2 compared with sibship size 1 as the reference category).

Table 1. RRs for sibship size

Cancer site	Sibship size									
	1*		2		3		≥4			
	Cases	RR	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	P_{trend}	Total
Leukemias	1,041	1.00	2,594	1.04 (0.97-1.12)	2,172	**1.14 (1.04-1.25)**	1,843	**1.13 (1.00-1.27)**	0.016	7,650
ALL	209	1.00	888	1.09 (0.94-1.28)	810	**1.29 (1.08-1.55)**	506	1.29 (1.02-1.63)	0.003	2,413
Chronic lymphocytic leukemia	256	1.00	352	0.97 (0.83-1.13)	266	1.08 (0.88-1.33)	283	1.01 (0.76-1.35)	0.842	1,157
Acute myeloid leukemia	354	1.00	857	1.07 (0.94-1.21)	671	1.08 (0.92-1.27)	626	1.08 (0.87-1.33)	0.456	2,508
Acute monocytic leukemia	9	1.00	29	1.48 (1.00-2.19)	24	**2.02 (1.24-3.29)**	21	**2.51 (1.37-4.60)**	0.002	83
Other leukemias	71	1.00	238	1.17 (0.89-1.71)	224	1.24 (0.89-1.71)	233	1.43 (0.96-2.14)	0.115	766
Polycythemia vera	88	1.00	159	1.17 (0.93-1.47)	114	1.16 (0.84-1.60)	106	1.01 (0.66-1.56)	0.757	467
Myelofibrosis	54	1.00	71	0.81 (0.56-1.18)	63	0.92 (0.56-1.52)	68	0.91 (0.47-1.77)	0.713	256
Hodgkin's lymphoma	412	1.00	1,124	1.17 (0.94-1.45)	878	1.09 (0.93-1.29)	701	1.17 (0.94-1.45)	0.119	3,115
NHL†	1,247	1.00	2,287	0.96 (0.89-1.04)	1,656	0.96 (0.87-1.06)	1,817	1.06 (0.92-1.21)	0.665	7,007
Diffuse large B cell	98	1.00	185	0.98 (0.70-1.36)	119	0.94 (0.61-1.46)	139	1.06 (0.60-1.88)	0.950	541
Diffuse lymphoblastic	8	1.00	31	1.16 (0.59-2.27)	33	2.02 (0.91-4.51)	17	1.10 (0.37-3.28)	0.289	89
Follicular	173	1.00	267	0.82 (0.68-1.00)	187	**0.76 (0.58-0.98)**	237	0.85 (0.61-1.20)	0.207	864
B cell, NOS	133	1.00	235	1.07 (0.82-1.39)	145	0.94 (0.65-1.35)	179	0.93 (0.58-1.51)	0.765	692
NHL, NOS	142	1.00	276	1.03 (0.87-1.24)	196	0.94 (0.75-1.19)	209	0.90 (0.66-1.23)	0.489	823
T cell	54	1.00	126	1.03 (0.67-1.59)	76	0.76 (0.44-1.33)	89	0.80 (0.39-1.67)	0.380	345
Others	139	1.00	283	1.13 (0.92-1.38)	206	1.24 (0.95-1.62)	187	1.33 (0.93-1.90)	0.097	815
Multiple myeloma	280	1.00	496	**1.24 (1.10-1.39)**	316	**1.19 (1.01-1.40)**	400	**1.34 (1.08-1.66)**	0.006	1,492

NOTE: RR and 95% CI are adjusted for age, sex, number of older and younger siblings, residential area, birth cohort, parity, age at first birth, family history of cancer, and socioeconomic index.

*Reference category.

†The total number of NHL subtypes does not add up to the total number of NHLs because the histologic information was available starting from 1993.

Table 2. RRs for number of older siblings

Cancer site	No. older siblings									
	None*		1 or 2		3 or 4		≥5			
	Cases	RR	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	P_{trend}	Total
Leukemias	3,941	1.00	3,238	0.97 (0.91-1.03)	410	0.95 (0.83-1.10)	61	0.81 (0.62-1.07)	0.180	7,650
ALL	1,111	1.00	1,149	0.93 (0.84-1.02)	153	0.86 (0.68-1.08)	—	—	0.112	2,413
Chronic lymphocytic leukemia	703	1.00	404	1.06 (0.91-1.24)	50	1.03 (0.70-1.52)	—	—	0.540	1,157
Acute myeloid leukemia	1,278	1.00	1,070	1.03 (0.94-1.14)	160	1.02 (0.81-1.29)	—	—	0.586	2,508
Acute monocytic leukemia	44	1.00	34	**0.62 (0.46-0.85)**	5	**0.35 (0.17-0.74)**	—	—	0.001	83
Other leukemias	375	1.00	324	0.93 (0.76-1.13)	67	1.05 (0.68-1.62)	—	—	0.710	766
Polycythemia vera	282	1.00	164	0.88 (0.68-1.13)	21	0.76 (0.40-1.44)	—	—	0.285	467
Myelofibrosis	148	1.00	93	1.03 (0.74-1.43)	15	1.03 (0.49-2.17)	—	—	0.870	256
Hodgkin's lymphoma	1,526	1.00	1,398	0.91 (0.82-1.00)	170	**0.69 (0.54-0.89)**	21	**0.41 (0.25-0.69)**	0.003	3,115
NHL†	3,733	1.00	2,831	1.05 (0.98-1.12)	368	0.95 (0.81-1.12)	75	1.01 (0.77-1.34)	0.464	7,007
Diffuse large B cell	278	1.00	219	1.05 (0.78-1.41)	44	1.14 (0.59-2.22)	—	—	0.699	541
Diffuse lymphoblastic	38	1.00	43	0.87 (0.50-1.49)	8	1.96 (0.62-6.25)	—	—	0.862	89
Follicular	464	1.00	346	1.13 (0.95-1.34)	54	0.99 (0.66-1.48)	—	—	0.367	864
B cell, NOS	396	1.00	247	1.02 (0.80-1.30)	49	1.63 (0.94-2.81)	—	—	0.381	692
NHL, NOS	444	1.00	333	1.01 (0.86-1.17)	46	0.71 (0.49-1.02)	—	—	0.464	823
T cell	169	1.00	151	1.26 (0.88-1.82)	25	1.26 (0.54-2.92)	—	—	0.262	345
Others	455	1.00	318	0.87 (0.73-1.05)	42	0.72 (0.46-1.12)	—	—	0.103	815
Multiple myeloma	883	1.00	524	0.95 (0.86-1.06)	75	1.04 (0.80-1.35)	10	0.77 (0.46-1.30)	0.471	1,492

NOTE: RR and 95% CI are adjusted for age, sex, total number of siblings, number of younger siblings, residential area, birth cohort, parity, age at first birth, family history of cancer, and socioeconomic index.
*Reference category.
†The total number of NHL subtypes does not add up to the total number of NHLs because the histologic information was available starting from 1993.

The main explanatory variables were total number of siblings and number of older and younger siblings. Other explanatory variables included in the statistical models were sex, socioeconomic status (four categories: agriculture, professional, worker, and other), area of residence (five categories: Stockholm area, Götebörg-Malmö area, the two largest cities in south of Sweden; Götaland, Svealand, and Norrland), family history of cancer in first-degree relatives, and, for women, parity (no child, 1-2, 3-4, and ≥5 children) and age at first birth (no child, ≤20, 21-29, 30-39, and ≥40 years of age). Details of socioeconomic factors were extracted from censuses of 1960, 1970, 1980, and 1990 of Statistics Sweden. All the models also included the following other variables: age at diagnosis (quinquennia, 0-70 years), year of birth (birth cohort, four categories: <1970, 1970-1979, 1980-1989, and ≥1990), and total number of siblings and number of younger and older siblings, when appropriate. Further adjustment for parental age did not substantially influence the risk estimates.

Results

Table 1 shows the effects of total number of siblings on the risk of leukemia, lymphoma, and multiple myeloma. Overall, leukemias, Hodgkin's lymphoma and NHL were not associated with total number of siblings. Compared with singletons, the RRs for individuals with four or more siblings were 1.13 [95% confidence interval (95% CI), 1.00-1.27] for leukemia, 1.29 (95% CI, 1.02-1.63; P_{trend} = 0.003) for ALL, 2.51 (95% CI, 1.37-4.60; P_{trend} = 0.002) for acute monocytic leukemia, 1.17 (95% CI, 0.94-1.45) for Hodgkin's lymphoma, 1.06 (95% CI, 0.92-1.21) for NHL, and 1.34 (95% CI, 1.08-1.66, P_{trend} = 0.006) for multiple myeloma. No significant association was observed for any other histologic subtype of leukemia or NHL.

Table 2 gives the RRs for the number of older siblings. Compared with individuals with no older siblings, the risk of leukemia for persons with five or more older siblings was 0.81 (95% CI, 0.62-1.07). Hodgkin's lymphoma showed a remarkable inverse association with the number of older siblings, the RR being 0.41 (95% CI, 0.25-0.69, P_{trend} = 0.003) for five or more older siblings. NHL and multiple myeloma showed no significant association with number of older siblings. For the histologic subtypes, due to the lower number of cases, we limited the analyses to three or more older siblings. Acute monocytic leukemia showed the strongest inverse association (RR, 0.35; 95% CI, 0.17-0.74 for three or more older siblings compared with none) with a significant trend in risk (P_{trend} = 0.001). ALL showed a nonsignificant inverse association; the

Table 3. RRs of Hodgkin's lymphoma for number of older siblings in strata of age

Age at diagnosis (Years)	No. older siblings									
	None*		1 or 2		3 or 4		≥5			
	Cases	RR	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	P_{trend}	Total
≤15	138	1.00	128	0.79 (0.47-1.32)	19	0.76 (0.22-2.58)	3	0.62 (0.07-5.33)	0.426	288
16-39	1,065	1.00	1,055	0.97 (0.83-1.04)	118	**0.69 (0.53-0.90)**	12	0.35 (0.19-0.64)	0.008	2,250
≥40	323	1.00	215	0.86 (0.66-1.11)	33	0.69 (0.38-1.24)	6	0.57 (0.21-1.58)	0.152	577

NOTE: RR and 95% CI are adjusted for age, sex, total number of siblings, number of younger siblings, residential area, birth cohort, parity, age at first birth, family history of cancer, and socioeconomic index.
*Reference category.

Table 4. RRs of ALL for sibship size in strata of age

Age	Sibship size									
	1*		2		3		≥4			
	Cases	RR	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	P_{trend}	Total
≤5	233	1.00	346	**1.29 (1.07-1.55)**	391	**1.56 (1.26-1.93)**	73	**2.11 (1.62-2.75)**	0.001	1063
6-14	122	1.00	254	0.96 (0.72-1.28)	275	1.04 (0.74-1.46)	57	0.81 (0.52-1.27)	0.640	708
≥15	151	1.00	210	1.01 (0.79-1.29)	222	1.22 (0.90-1.66)	79	0.98 (0.65-1.46)	0.661	662

NOTE: RR and 95% CI are adjusted for age, sex, total number of siblings, number of younger siblings, residential area, birth cohort, parity, age at first birth, family history of cancer, and socioeconomic index.
*Reference category.

RR was 0.86 (95% CI, 0.68-1.08). Chronic lymphocytic leukemia, acute myeloid leukemia, and NHL subtypes were not associated with number of older siblings. When the analyses were repeated according the number of younger siblings as proof of concept, no significant association emerged for lymphoma, leukemia, or multiple myeloma in strata of histologic subtype, except for ''other leukemias'' that showed an increased risk of borderline significance (RR, 1.75; 95% CI, 1.04-2.96 for three or more younger siblings; data not shown).

Table 3 shows the effect of number of older siblings on the risk of Hodgkin's lymphoma for ages at diagnosis of ≤15, 16-39, and ≥40 years. A pattern of decreasing risk was evident in each strata of age. For age at diagnosis between 16 and 39 years, the RRs were 0.97 (95% CI, 0.83-1.04) for one or two older siblings, 0.69 (95% CI, 0.53-0.90) for three or four older siblings, and 0.35 (95% CI, 0.19-0.64) for five or more older siblings (P_{trend} = 0.008).

Tables 4 and 5 give the risk of sibship size and the number of older siblings for ALL in strata of age. For age at diagnosis of ≤5 years, the RR of ALL for total number of siblings of four or more compared with none was 2.11 (95% CI, 1.62-2.75, P_{trend} = 0.001). For the number of older siblings, the RR for age at diagnosis of ≤5 years was 0.69 (95% CI, 0.52-0.91) for three or more older siblings compared with none (P_{trend} = 0.01). Total number of siblings and number of older siblings were not associated with ALL in the older age groups.

Discussion

Two main hypotheses have attempted to explain the protective effect consistently reported for markers of childhood infections on the risk of childhood leukemia and lymphomas (19, 33). The ''delayed infection'' hypothesis suggests that the risk of childhood leukemia, and possibly Hodgkin's lymphoma, is initiated by a lack of exposure to childhood infections and a failure of the immune system modulation in infancy (19). Later in childhood, an abnormal immune response occurs to one or more common bacterial or viral infections. At a molecular level, common chromosomal translocations that occur early in prenatal life followed by one or more postnatal genetic alteration caused be abnormal immune responses to infections would be responsible for the onset of the disease (19). The other hypothesis assumes that the risk of childhood leukemia is increased by population mixing as a result of the increased level of exposure to new infections (33, 34). The two hypotheses differ in the rational and hypothetical mechanism, but they both consider childhood leukemia as ''rare response to one or more common infections'' (19). A novel hypothesis, proposed by zur Hausen and de Villiers, attempts to explain the epidemiologic associations with new virological evidence (20). The theory assumes that persistent lymphohematopoietic cell infections acquired in the first years of life by newly discovered TT viruses could increase the risk of specific chromosomal translocations in several types of lymphohematopoietic cell lines, thereby predisposing to malignant transformation (20, 35). According to this theory, frequent infections in early childhood with other common viruses, such as influenza, measles, rubella, and mumps, should reduce, by IFN release, the TT viral load and the level of virus persistence in lymphohematopoietic cells (20).

The strengths of the present study include the population-based design, the nationwide coverage, and the complete ascertainment of family structures and medical diagnoses. Some of the novel findings on rare malignancies were only possible because of the uniquely large Database with histopathology-specific information. The large data set allows also to distinguish reliably between the effects of younger and older siblings and between different periods of life. The associations found persisted after adjustment for several potential confounding covariates. Due to the rarity of these malignancies, the exclusion of families with multiple cases did not change the risk estimates. Individuals with lower socioeconomic index tended to belong to larger families. However, we observed no substantial difference in the risks estimates for different birth cohorts or socioeconomic index. The characteristics of the Swedish population in terms of day care practices and schooling are similar to other Western societies, including North America. In Sweden, most children stay at home until about 18 months of age (36). A recent study reported that 87.2% of children 1 to 6 years old were in current day care or had attended day care earlier in life. In the youngest group of children (ages 1-2 years), 71.2% were currently or had earlier been in day care, whereas the corresponding frequency for the older children (ages 5-6 years) was 92.6% (36). Sweden, like the other Scandinavian countries and the United Kingdom, has high vaccination rates, including diphtheria, tetanus, whooping cough, polio, haemophilus influenzae, measles, mumps, and rubella, that started in the 1940s to 1950s (37). However, the evidence on the effect of immunization on the risk of lymphoproliferative malignancies is inconclusive (5).

The major weakness of our study is the lack of availability of more and direct markers of exposure to infections, such as number and type of infections, age at infection, and serologic data. The availability of such data from at least a subset of individuals of our population could add further evidence to the hypothesis. However, they are not likely to confound or modify the effect of sibship size or number of siblings.

Despite the fact that many studies have investigated the effect of birth order on the risk of leukemias and lymphomas, only a few have investigated the effect of total number of siblings, reporting no substantial association (38-41). We found a 2-fold increased risk of childhood ALL and acute monocytic leukemia for individuals with five or more siblings, with a significant trend in risk. The age-specific pattern of risk for ALL suggests that the effect is evident only in early childhood. A study from Denmark reported a risk of 2.5 (95% CI, 1.5-4.4) in large families for acute myeloid leukemia for age at diagnosis of ≤2 years (15). No published study reported specifically on total number of siblings and acute monocytic leukemia. Large families may involve close contacts between family members, increasing the probability of sharing a viral

Table 5. RRs of ALL for number of older siblings in strata of age

No. older siblings							
None*		1 or 2		≥3			
Cases	RR	Cases	RR (95% CI)	Cases	RR (95% CI)	P_{trend}	Total
382	1.00	425	**0.88 (0.78-0.99)**	52	**0.69 (0.52-0.91)**	0.010	1,043
321	1.00	347	1.00 (0.86-1.16)	40	0.96 (0.65-1.43)	0.927	708
329	1.00	288	0.90 (0.75-1.10)	45	1.01 (0.64-1.59)	0.475	662

*Reference category.

or bacterial infection (5). These data support the hypothesis that, overall, an increased exposure to common infective agents may increase the risk of ALL and acute monocytic leukemia. Molecular studies have failed so far to identify a specific agent. However, our results suggest that a good candidate would be an infection that runs in families. Infections with *Mycoplasma pneumonie* (42, 43) and more recently, with *Helicobacter pylori*, both pathogens that have been reported to be transmitted within families and from mother to child, have been reported to be associated with adult ALL (44). Specific agents associated with acute myeloid leukemia include human herpes virus 6 (24, 25) and, possibly, varicella zoster for acute monocytic leukemia (26). Other subtypes of leukemia, including chronic lymphocytic leukemia, acute myeloid leukemia, and Hodgkin's lymphoma and NHL, were not associated with total number of siblings. Our finding that multiple myeloma was more frequent in larger families has not been previously reported. This finding support a role for a viral infection which runs in families, such as human herpes virus 8 (45-48) or hepatitis C virus (49-51).

The inverse association of all leukemia and particularly ALL with birth order is not a new finding (1, 4, 5, 7, 8, 10, 15, 28). However, our study provides novel data on other histologic subtypes of leukemia. The strong inverse association found between number of older siblings and ALL diagnosed before age 5 lends particular support to the Greaves hypothesis, suggesting that only children with a large number of older siblings, presumably exposed to infections at earlier ages, are protected (19). The finding that the pattern of risk for ALL varies in different strata of age could also explain some of the inconsistent findings of previous studies that did not have the power to properly stratify by age (5-13). Our data suggest that the risk of ALL may be affected by postnatal events, such as number, timing, and, possibly, type of common infections. However, these results are not in contradiction with the hypothesis that some ALL arise in the fetal period, as supported by molecular studies (19, 27, 52, 53) and previous results from this Database (54).

Acute myeloid leukemia was not associated with any familial characteristics, in agreement with two published studies (55, 56). Two studies reported an increased risk for acute myeloid leukemia for high birth order compared with firstborns, but acute monocytic leukemia was not analyzed (15, 57). The strong inverse association that we found between acute monocytic leukemia and the number of older siblings is a novel finding. Acute monocytic leukemia is a distinct subtype of myeloid leukemia in which ≥80% of the leukemic cells are of monocytic lineage, which play a key role in acute innate immune responses (58). Somatic genetic alterations, deletions, and translocations, mainly in chromosomes 8 and 11, are common in monocytic leukemia, similar to other acute myeloid leukemias (58). Seasonal variations in the diagnosis of monocytic leukemia have been reported in England and Wales, suggesting a potential role for infections (3). However, no specific infectious agent has yet been identified. Chronic lymphocytic leukemia, which shares several histopathologic features with NHL, showed no significant association with any family characteristics, nor did polycytemia vera or myelofibrosis.

Our results add to the epidemiologic evidence of an inverse association between Hodgkin's lymphoma and number of older siblings (1, 14-16, 59). Hodgkin's lymphoma was not associated with other familial characteristics, such as total number of siblings and number of younger siblings. Thus, the association can not be attributed to overall sibship size. Our results are in partial agreement with a case-control study from Sweden conducted on a subset of cases included in our Database, which found an inverse association between Hodgkin's lymphoma and number of older siblings only in young adults ages 16 to 39 years (14). In our Database, most diagnoses of Hodgkin's lymphoma were also made in the strata of age 16 to 39 years, and the association seemed to follow a dose-response pattern with a 65% reduction of risk for five or more older siblings. However, the pattern of risk in the childhood and adult groups, although not significant, seemed to follow a similar course. EBV has been postulated to play a role in the onset of Hodgkin's lymphoma. Immunodeficiency status, such as HIV infection or milder forms of immune dysfunction, may predispose to EBV-associated Hodgkin's lymphoma (22). Thus, our findings are compatible with the hypothesis that a delayed viral infection in childhood may be one of the triggering events of Hodgkin's lymphoma onset. The effect is strong in young adults, but other age groups may also be at risk (14, 16).

A population-based case-control study from Australia, including 704 cases, found that the risk of NHL was reduced in singletons and first-born children, and that the risk increased linearly with the number of older siblings (17). Our null results on NHL with number of siblings, based on >7,000 cases, are in broad agreement with a case-control study from Italy that reported no association of family characteristics with NHL (16). It has been suggested that a high number of younger siblings may be associated with a higher probability of EBV infection, independent of number of older siblings (30, 60). In our Database, the number of younger siblings showed no significant effect.

The nonsignificant associations found for the number of younger or older siblings with multiple myeloma are consistent with a previous case-control study from Italy (16).

The current investigation represents the first population-based study, providing reliable quantification of the effects number of siblings according to histologic subtypes of lymphohematopoietic malignancies. The major novel finding is a high risk in large families and an inverse dose-response association of the number of older siblings with acute monocytic leukemia. Similar strong associations were also confirmed and further quantified for childhood ALL. For Hodgkin's lymphoma, only the protective effect of the number of older siblings was noted. In the context of a putative infectious etiology of childhood leukemia and lymphomas, our data suggest that the pool of infectious agents is large in large families, thus explaining the excess risk for acute monocytic leukemia and early onset ALL. Probably because of immunologic adaptation, younger siblings are protected compared with older siblings. However, any interpretation of this data in the context of an infectious hypothesis remains speculative until the effect of direct markers of infections and pattern of are clarified.

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