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 sibling 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 sibling 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 sibling 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...
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 diffusely 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 Hodkin’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 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(β), 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**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>1*</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P trend</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>209</td>
<td>1.00</td>
<td>888</td>
<td>1.09</td>
<td>(0.94-1.28)</td>
<td>810</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>256</td>
<td>1.00</td>
<td>352</td>
<td>0.97</td>
<td>(0.83-1.13)</td>
<td>266</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>354</td>
<td>1.00</td>
<td>857</td>
<td>1.07</td>
<td>(0.94-1.21)</td>
<td>671</td>
</tr>
<tr>
<td>Acute monocytic leukemia</td>
<td>9</td>
<td>1.00</td>
<td>29</td>
<td>1.48</td>
<td>(1.00-2.19)</td>
<td>24</td>
</tr>
<tr>
<td>Other leukemias</td>
<td>71</td>
<td>1.00</td>
<td>238</td>
<td>1.17</td>
<td>(0.89-1.71)</td>
<td>224</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>88</td>
<td>1.00</td>
<td>159</td>
<td>1.17</td>
<td>(0.93-1.47)</td>
<td>114</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>54</td>
<td>1.00</td>
<td>71</td>
<td>0.81</td>
<td>(0.56-1.18)</td>
<td>63</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>412</td>
<td>1.00</td>
<td>1,124</td>
<td>1.17</td>
<td>(0.94-1.45)</td>
<td>878</td>
</tr>
<tr>
<td>NHL*</td>
<td>1,247</td>
<td>1.00</td>
<td>2,287</td>
<td>0.96</td>
<td>(0.89-1.04)</td>
<td>1,656</td>
</tr>
<tr>
<td>Diffuse large B cell</td>
<td>98</td>
<td>1.00</td>
<td>185</td>
<td>0.98</td>
<td>(0.70-1.36)</td>
<td>119</td>
</tr>
<tr>
<td>Diffuse lymphoblastic</td>
<td>38</td>
<td>1.00</td>
<td>51</td>
<td>1.16</td>
<td>(0.59-2.27)</td>
<td>33</td>
</tr>
<tr>
<td>Follicular</td>
<td>173</td>
<td>1.00</td>
<td>267</td>
<td>0.82</td>
<td>(0.68-1.00)</td>
<td>187</td>
</tr>
<tr>
<td>B cell, NOS</td>
<td>133</td>
<td>1.00</td>
<td>235</td>
<td>1.07</td>
<td>(0.82-1.39)</td>
<td>145</td>
</tr>
<tr>
<td>NHL, NOS</td>
<td>142</td>
<td>1.00</td>
<td>276</td>
<td>1.03</td>
<td>(0.87-1.24)</td>
<td>196</td>
</tr>
<tr>
<td>T cell</td>
<td>54</td>
<td>1.00</td>
<td>126</td>
<td>1.03</td>
<td>(0.67-1.59)</td>
<td>76</td>
</tr>
<tr>
<td>Others</td>
<td>139</td>
<td>1.00</td>
<td>283</td>
<td>1.13</td>
<td>(0.92-1.38)</td>
<td>196</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>280</td>
<td>1.00</td>
<td>496</td>
<td>1.24</td>
<td>(1.10-1.39)</td>
<td>316</td>
</tr>
</tbody>
</table>

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.

1The 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                  | Cases | RR    | Cases | RR (95% CI)                  | Cases | RR (95% CI)                  | 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)              | 1,065 | 1.00                         | —      | 7,650                         |
| ALL                          | 1,111 | 1.00  | 1,149 | 0.93 (0.84-1.02)              | 153   | 0.86 (0.68-1.08)              | —     | —                            | 1,055 | 0.97 (0.83-1.10)              | —      | 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 (0.86-1.24)              | —     | —                            | —     | —                            | 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                       | 435   | 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.

Results

Table 3 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 RR for individuals with four or more siblings was 1.13 (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).

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

<table>
<thead>
<tr>
<th>Age at diagnosis (Years)</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>P_trend</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>128</td>
<td>1.00</td>
<td></td>
<td>0.79</td>
<td>(0.47-1.32)</td>
<td>0.76</td>
<td>(0.22-2.58)</td>
<td>0.62</td>
<td>(0.07-5.33)</td>
<td>0.426</td>
<td>288</td>
</tr>
<tr>
<td>1,055</td>
<td>1.00</td>
<td></td>
<td>0.97</td>
<td>(0.83-1.04)</td>
<td>0.69</td>
<td>(0.53-0.90)</td>
<td>0.35</td>
<td>(0.19-0.64)</td>
<td>0.008</td>
<td>2,250</td>
</tr>
<tr>
<td>215</td>
<td>1.00</td>
<td></td>
<td>0.86</td>
<td>(0.66-1.11)</td>
<td>0.69</td>
<td>(0.38-1.24)</td>
<td>0.57</td>
<td>(0.21-1.58)</td>
<td>0.152</td>
<td>577</td>
</tr>
</tbody>
</table>

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.
Twomainhypotheseshaveattemptedtoexplaintheprotective
8.6(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 RR 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 0.37 (95% CI, 0.19-0.64) for five or more older
siblings (P<0.001).

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<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=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
on 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 lymphohema-
topoietic cell lines, thereby predisposing to malignant trans-
formation (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 histopa-
thology-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 con-
founding 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, whoop-
ing 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 monomy-
cytic 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 monomy-
cytic leukemia. Large families may involve close contacts between
family members, increasing the probability of sharing a viral

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Sibship size</th>
<th>Cases</th>
<th>RR</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>P&lt;sup&gt;trend&lt;/sup&gt;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>1*</td>
<td>233</td>
<td>1.00</td>
<td>346</td>
<td>1.29 (1.07-1.55)</td>
<td>391</td>
<td>1.56 (1.26-1.93)</td>
<td>73</td>
<td>2.11 (1.62-2.75)</td>
<td>1063</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-14</td>
<td>122</td>
<td>3.00</td>
<td>254</td>
<td>0.96 (0.72-1.28)</td>
<td>275</td>
<td>1.04 (0.74-1.46)</td>
<td>57</td>
<td>0.81 (0.52-1.27)</td>
<td>708</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td>151</td>
<td>1.00</td>
<td>210</td>
<td>1.01 (0.79-1.29)</td>
<td>222</td>
<td>1.22 (0.90-1.66)</td>
<td>79</td>
<td>0.98 (0.65-1.46)</td>
<td>662</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.
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 pneumoniae (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). Somatic variants in the diagnosis of monocytic leukemias 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 polycythemia 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.

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

<table>
<thead>
<tr>
<th>No. older siblings</th>
<th>Cases</th>
<th>RR</th>
<th>Cases</th>
<th>RR (95% CI)</th>
<th>P_trend</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None*</td>
<td>362</td>
<td>1.00</td>
<td>425</td>
<td>0.88 (0.78-0.99)</td>
<td>0.010</td>
<td>1,043</td>
</tr>
<tr>
<td>1 or 2</td>
<td>321</td>
<td>1.00</td>
<td>347</td>
<td>1.00 (0.86-1.16)</td>
<td>0.927</td>
<td>708</td>
</tr>
<tr>
<td>≥3</td>
<td>329</td>
<td>1.00</td>
<td>288</td>
<td>0.90 (0.75-1.10)</td>
<td>0.475</td>
<td>662</td>
</tr>
</tbody>
</table>

*Reference category.
References

Cancer Epidemiology, Biomarkers & Prevention

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

Andrea Altieri, Felipe Castro, Justo Lorenzo Bermejo, et al.


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