

Research Article

Parental Age, Family Size, and Offspring's Risk of Childhood and Adult Acute Leukemia

Gunnar Larfors^{1,2}, Helene Hallböök², and Bengt Simonsson²

Abstract

Background: An association between childhood acute leukemia and advanced parental age was observed more than 50 years ago, and the association has been repeated in several, but not all, subsequent studies. In contrast to the many studies addressing childhood leukemia, few have included adult patients.

Methods: In this register-based case-control study, we examined the association between parental age and incidence of acute leukemia in 2,660 childhood cases and 4,412 adult cases of acute leukemia, compared with 28,288 age-matched controls selected from a population-based register. Relative risks were estimated with conditional logistic regression.

Results: We found a small increased risk of childhood acute lymphoblastic leukemia with increasing paternal age (adjusted OR, 1.05 per 5-year increase in age). Risk estimates were similar for childhood acute myeloid leukemia (AML), whereas no association was found with adult leukemia. Meanwhile, we observed a decreased risk of adult AML with increasing number of siblings, both older and younger.

Conclusions: The results support the idea of a prenatal etiology of leukemia but indicate that parental age effects are limited to childhood cases.

Impact: This is the first large study on parental age and leukemia risk, which includes adult cases. The finding on family size and risk of adult AML needs to be validated in future studies. *Cancer Epidemiol Biomarkers Prev*; 21(7); 1185–90. ©2012 AACR.

Introduction

The etiology of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) is largely unknown. Few risk factors have been described, and taken together, they can only account for a minor proportion of incident cases. Both diseases occur during all ages but with very different age distributions. ALL has a peak during childhood and thereafter remains at a low incidence during adulthood (1), whereas AML is relatively uncommon in childhood and gradually increases with age (2), similar to most other malignancies.

Down syndrome was first linked to childhood ALL in 1930 (3) and is today one of the few established risk factors for both childhood AML and ALL (4). The only established risk factor for Down syndrome is advanced maternal age, and accordingly, an association between maternal age and risk of childhood leukemia was observed more than 50 years ago (5). Both maternal and paternal age have been linked to genetic aberrations

in the offspring. In small retrospective studies on blood samples taken from newborns who later developed childhood leukemia, the majority of cases also had genetic lesions already at birth (6), indicating that the malignant process starts *in utero* or even in germ cells.

Results from previous studies on parental age and leukemia are conflicting. Several of the more than 30 published studies are insufficiently small and some are outdated. However, among recent studies with more than 1,000 cases, there are examples where increasing maternal and/or paternal age have been linked to risk of childhood leukemia (7–11) and others who have failed to find such an association (12–14). Some have further argued that the relationship is modified by an inverse relationship between birth order and leukemia risk (8, 13, 15–17).

We proposed a study of AML and ALL risk in relation to parental age with adjustment for number of siblings and other potential confounders and stratified by age at diagnosis.

Materials and Methods

Data sources

Data was collected from 5 Swedish nation-wide registers. The registers are kept by The National Board of Health and Welfare and by Statistics Sweden. As all Swedish citizens at birth or immigration are assigned a unique identification number, all Swedish registers can be cross-linked.

Authors' Affiliations: ¹Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm; and ²Unit of Hematology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Corresponding Author: Gunnar Larfors, Department of Medicine, Unit of Clinical Epidemiology (T2), Karolinska Institutet, Stockholm SE-171 71, Sweden. Phone: 46-18-6110000; Fax: 46-8-51779304; E-mail: gunnar.larfors@ki.se

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The Swedish Cancer Register was founded in 1958 and covers all incident cancers in Sweden. Reporting is mandatory for both clinician and pathologist, resulting in a near total completeness (18). The register contains data on malignant diagnoses but not clinical data as laboratory findings, tumor characteristics, or genetic analyses.

The Multi-Generation Register is derived from Swedish population statistics and contains linkages and birth dates for parents and siblings of all Swedish citizens born in 1932 or later and resident in Sweden at some point after January 1, 1961. Overall completeness for citizens born in Sweden is 98% (mother's identity) and 95% (father's identity), but as the completeness for citizens born abroad (16% of the registered individuals) is much lower, the total completeness is 84% and 82%, respectively (19). The completeness is also lower for deceased subjects; among citizens born in Sweden who died between 1961 and 2009, the completeness is 82% and 73%, respectively. Information on all immigration and emigration in Sweden is also derived from population statistics and recorded as the Swedish Migration Register.

Two more registries were used for ascertainment of potential confounders. The Swedish Medical Birth Register contains data on all pregnancies and births from 1973 and onwards, and the National Patient Register includes ICD-coded diagnoses from all admissions to hospital. Whereas the former is nearly 100% complete (20), the latter has gradually expanded from the start in 1964 to cover all Sweden in 1987. Since 2001, also diagnoses from outpatient care have been recorded (21).

Ascertainment of outcome and exposure

All patients born in 1932 or later with a diagnosis of acute leukemia between 1962 and 2008 were retrieved from the cancer registry. Cases of acute promyelocytic leukemia (APL; ICD10 = C92.4) were excluded from analysis of AML cases, as it cannot readily be assumed that the etiology of APL is shared with other subtypes of AML (2). Childhood leukemia was defined as leukemia diagnosed before age 15, as this cutoff point has been most frequently used in previous studies, and by WHO/IARC (22). To each case, 4 controls were matched from population statistics. Controls were randomly selected among all citizens born in the same calendar year as the case and resident in Sweden at the date of diagnosis. Apart from year of birth and residency at time of diagnosis, no further matching was conducted (such as sex or birth place). For both cases and controls, information on years of birth of parents and siblings was retrieved from the multigeneration registry. This resulted in information on mother's year of birth for 87% of cases and 91% of controls, and father's year of birth for 83% of cases and 90% of controls.

Data on chromosomal aberrations were retrieved both from the birth registry and the patient registry. Chromosomal aberrations were divided into Down syndrome and other, whereas the latter category included Klinefelter

(47XXY), Turner (45X), fragile X, triple X, unspecified trisomy, unspecified monosomy, unspecified balanced translocation, and unspecified chromosomal aberration.

Statistical analysis

The data were analyzed with conditional logistic regression for matched case-control studies. Relative risks were estimated by OR with 95% confidence intervals (CI). As an increased risk of leukemia in some previous studies has been observed for the youngest and oldest parents, parental age was analyzed both as a categorized (<20, 20–34, and ≥ 35 years of age) and as a continuous variable. Birth order and number of younger siblings were also analyzed both as categorical and continuous variables. In analyses of younger siblings, only siblings born in the year before diagnosis of the case or earlier were considered, to avoid reverse causality. All analyses were conducted with SAS 9.2 statistical software (SAS Institute Inc.).

Ethical considerations

The study was approved by the regional research ethics committee at Karolinska Institutet (Stockholm, Sweden; 2009/513 31). All data was cross-linked at the registries and delivered to researchers de-identified.

Results

Between 1962 and 2008, we could identify 3,249 cases of ALL and 3,823 cases of AML. Of these, 2,199 cases of ALL and 461 cases of AML were below 15 years of age at diagnosis. Ninety-nine additional cases of APLs were excluded from analysis.

Baseline characteristics are shown in Table 1. ALL among both children and adults had a predominance of males, whereas no significant association with sex was noted for AML. Down syndrome was associated with both AML and ALL risk during childhood, but the oldest leukemia case with a diagnosis of Down syndrome was 41 years of age and only 8 cases were diagnosed after 14 years of age. Also, other chromosomal aberrations appeared in higher frequency among cases than among controls. Twins were more common among cases than controls in all subgroups, but the association only reached statistical significance for cases with childhood ALLs.

In a univariate analysis, increasing birth order was associated with a significantly decreased risk of adult AML, and there was also a tendency toward lower risk of childhood and adult ALL among later-born than among first-born offspring (Table 2). Increasing number of younger siblings was associated with lower risk of adult AML but showed no association to childhood leukemia. After mutual adjustment, both birth order and number of younger siblings remained significantly associated with lower risk of adult AML with an OR of 0.96 for each additional older sibling (95% CI, 0.92–1.00; $P = 0.02$) and 0.95 for each additional younger sibling (95% CI, 0.93–0.98; $P < 0.001$).

Table 1. Baseline characteristics

	Percentage of cases and controls											
	Childhood ALL			Childhood AML			Adult ALL			Adult AML		
	Cases (N = 2,199)	Controls (N = 8,796)	<i>P</i> ^a	Cases (N = 461)	Controls (N = 1,844)	<i>P</i> ^a	Cases (N = 1,050)	Controls (N = 4,200)	<i>P</i> ^a	Cases (N = 3,362)	Controls (N = 13,448)	<i>P</i> ^a
Sex			<0.0001			0.39			0.001			0.11
Male	54.9	50.1		49.0	51.3		57.7	52.1		51.6	50.0	
Female	45.1	49.9		51.0	48.7		42.3	47.9		48.4	50.0	
Down syndrome			<0.0001			<0.0001			<0.0001			—
Yes	1.8	0.1		11.1	0.05		0.8	0.02		0	0.05	
No	98.2	99.99		88.9	99.95		99.2	99.98		100	99.95	
Other chromosomal aberrations			0.002			0.80			0.0008			0.003
Yes	0.3	0.05		0.2	0.2		0.4	0.02		0.2	0.06	
No	99.7	99.95		99.8	99.8		99.6	99.98		99.8	99.94	
Twin ^b			0.03			0.59			0.16			0.90
Yes	3.0	2.2		2.8	2.4		2.5	1.8		1.7	1.7	
No	97.0	97.8		97.2	97.6		97.5	98.2		98.3	98.3	

^aThe χ^2 test (2-sided) of association between outcome and characteristic.

^bIncluding triplets, quadruplets, etc.

Regarding parental age, a statistically significant association was noted between increasing paternal age and childhood ALL, with an unadjusted OR of 1.04 per 5-year increase in age (Table 3). The risk increase remained after

adjustment for maternal age and for potential confounders (listed in Table 3) but no longer statistically significant (OR, 1.05; 95% CI, 0.99–1.11). When analyzing the youngest and oldest among parents, no significant risk

Table 2. Birth order and number of siblings in relationship to leukemia risk (unadjusted data)

	Childhood ALL			Childhood AML			Adult ALL			Adult AML		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Birth order												
First	894	3,428	1 ^a (—)	168	722	1 ^a (—)	563	2,150	1 ^a (—)	2,078	8,070	1 ^a (—)
Second	709	2,988	0.91 (0.82–1.02)	166	605	1.18 (0.93–1.50)	268	1,189	0.85 (0.72–1.01)	779	3,248	0.92 (0.84–1.01)
Third	367	1,465	0.96 (0.84–1.10)	78	321	1.05 (0.78–1.41)	129	543	0.90 (0.73–1.12)	315	1,258	0.96 (0.84–1.10)
≥Fourth	229	915	0.96 (0.82–1.13)	49	196	1.07 (0.75–1.54)	90	318	1.07 (0.83–1.39)	190	872	0.83 ^b (0.70–0.99)
For each increase by 1			0.99 (0.95–1.03)			1.01 (0.93–1.09)			1.02 (0.96–1.08)			0.96 ^b (0.92–1.00)
Birth order												
First	894	3,428	1 ^a (—)	168	722	1 ^a (—)	563	2,150	1 ^a (—)	2,078	8,070	1 ^a (—)
Later	1,305	5,368	0.93 (0.85–1.03)	293	1,122	1.12 (0.91–1.39)	487	2,050	0.90 (0.78–1.04)	1,284	5,378	0.92 ^b (0.84–1.00)
Number of younger siblings												
0	1,335	5,327	1 ^a (—)	309	1,181	1 ^a (—)	489	1,922	1 ^a (—)	1,738	6,522	1 ^a (—)
1	681	2,768	0.98 (0.88–1.09)	108	469	0.86 (0.66–1.11)	275	1,224	0.88 (0.75–1.04)	815	3,425	0.89 ^b (0.81–0.98)
2	147	553	1.06 (0.87–1.30)	32	141	0.84 (0.55–1.27)	149	583	1.00 (0.82–1.23)	454	1,831	0.93 (0.83–1.05)
≥3	36	148	0.97 (0.67–1.42)	12	53	0.83 (0.43–1.58)	137	471	1.15 (0.92–1.42)	355	1,670	0.80 ^c (0.70–0.90)
For each increase by 1			1.00 (0.94–1.08)			0.93 (0.80–1.07)			1.02 (0.97–1.07)			0.95 ^c (0.93–0.98)

^aReference category.

^b*P* < 0.05.

^c*P* < 0.001.

Table 3. Parental age in relationship to leukemia risk in offspring

	Childhood ALL			Childhood AML			Adult ALL			Adult AML		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
<i>Unadjusted</i>												
Maternal age, y												
<20	82	206	1.17 (0.90–1.50)	19	60	1.30 (0.77–2.21)	47	203	0.92 (0.66–1.28)	120	527	0.88 (0.72–1.08)
20–34	1,801	7,307	1 ^a (–)	369	1,530	1 ^a (–)	704	3,005	1 ^a (–)	2,054	8,915	1 ^a (–)
≥35	293	1,113	1.07 (0.93–1.23)	65	233	1.15 (0.85–1.55)	137	553	0.99 (0.80–1.21)	434	2,072	0.81 ^b (0.72–0.90)
Per 5-y increase			1.02 (0.98–1.07)			1.03 (0.94–1.14)			1.00 (0.94–1.07)			0.99 (0.95–1.03)
Paternal age, y												
<20	14	50	1.15 (0.63–2.09)	1	15	0.27 (0.04–2.02)	8	43	0.71 (0.33–1.52)	17	84	0.76 (0.45–1.28)
20–34	1,544	6,394	1 ^a (–)	317	1,312	1 ^a (–)	595	2,603	1 ^a (–)	1,633	7,327	1 ^a (–)
≥35	591	2,214	1.10 (0.99–1.22)	121	484	0.99 (0.78–1.26)	225	1,061	0.80 ^c (0.68–0.94)	805	3,837	0.78 ^c (0.72–0.86)
Per 5-y increase			1.04 ^c (1.00–1.09)			1.08 (0.99–1.17)			0.99 (0.94–1.05)			1.00 (0.96–1.03)
<i>Adjusted^d</i>												
Maternal age, y												
<20	82	206	1.17 (0.89–1.53)	19	60	1.63 (0.88–3.03)	47	203	0.85 (0.59–1.25)	120	527	1.00 (0.79–1.26)
20–34	1,801	7,307	1 ^a (–)	369	1,530	1 ^a (–)	704	3,005	1 ^a (–)	2,054	8,915	1 ^a (–)
≥35	293	1,113	0.98 (0.83–1.16)	65	233	0.94 (0.64–1.39)	137	553	1.12 (0.86–1.47)	434	2,072	0.89 (0.77–1.03)
Per 5-y increase			1.00 (0.93–1.07)			0.90 (0.77–1.06)			1.04 (0.93–1.16)			1.01 (0.95–1.07)
Paternal age, y												
<20	14	50	1.19 (0.65–2.18)	1	15	0.30 (0.04–2.34)	8	43	0.70 (0.32–1.53)	17	84	0.90 (0.52–1.57)
20–34	1,544	6,394	1 ^a (–)	317	1,312	1 ^a (–)	595	2,603	1 ^a (–)	1,633	7,327	1 ^a (–)
≥35	591	2,214	1.08 (0.95–1.23)	121	484	0.89 (0.65–1.22)	225	1,061	0.79 ^c (0.64–0.98)	805	3,837	0.83 ^c (0.74–0.94)
Per 5-y increase			1.05 (0.99–1.11)			1.10 (0.96–1.26)			0.97 (0.88–1.06)			0.99 (0.94–1.04)

^aReference category.^b $P < 0.001$.^c $P < 0.05$.^dAdjusted for sex, Down syndrome, other chromosomal aberrations, multiple birth, birth order, number of younger siblings, and mutually adjusted for maternal/paternal age.

increases were found. On the contrary, the risk of adult AML was significantly reduced among offspring both to the oldest mothers and fathers.

Discussion

We found a small, but statistically significant, increase in risk for childhood ALLs with increasing paternal age. The same risk increase was not observed with maternal age, in contrast to some previous studies. Maternal and paternal age both affect risk of offspring genetic lesions but in different manners. Increasing maternal age is linked to trisomy, perhaps through oxidative stress, and to mitochondrial disorders, whereas X-linked diseases naturally are linked to paternal age (23). Risk of germ cell sporadic mutations are more closely linked to paternal age, according to earlier assumptions as male germ cells undergo more cell divisions than female (24). Recent data intriguingly suggest that such mutations are in fact rare, but mutant sperms can in certain cases be positively selected and their mutations thereby amplified (25). Furthermore,

paternal age has been linked to leukocyte telomere length, which in turn is linked to cancer risk (26, 27). If we have succeeded to statistically control for presence of Down syndrome and other chromosomal aberrations, it can be speculated that remaining parental age effect predominantly would be paternal.

For childhood AML, the OR for increasing paternal age was higher than for childhood ALLs but due to smaller numbers did not reach statistical significance. For adult acute leukemia, no linear effect of increasing parental age was found. The results support the hypothesis of germ line sporadic mutations in the etiology of childhood acute leukemia but meanwhile suggest that the impact of such perinatal risk factors is smaller or nonexistent for adult leukemia.

Few previous studies have included adult patients. Hemminki and Kyyronen included 118 cases of nonspecified leukemia, 15 to 53 years old at diagnosis (28), and found a borderline significant increased relative risk of 1.36 for mothers ages 40 to 49 compared with mothers younger than 20 years. More recently, Lu and colleagues

included 89 cases of adult AML but found no excess risk among offspring to older parents (29).

Some previous authors have found an excess risk of childhood leukemia among offspring of the youngest parents (12, 30) or a U-shaped association with risk increases both in offspring of the youngest and the oldest parents (31, 32). Such associations could obscure a true relationship when analyzing linear trends, but in the present data, we did not find any such association.

We did not find a statistically significant association between birth order and acute leukemia in childhood, but there was a borderline significant decrease in risk for adult AML in subjects with older siblings compared with first-borns (Table 2). Adult AML was further significantly negatively associated with number of younger siblings. Exposure to common infections in early childhood has repeatedly been suggested as protective against childhood leukemia, possibly by strengthening the immune defense against leukemogenic viruses (33). Supporting epidemiologic data include protective effects of day-care attendance and increasing birth order (34–36). Our findings on adult AML should be considered explorative but could suggest importance of early infections also in adult leukemia.

As expected, Down syndrome was overrepresented among childhood cases, and multivariate analyses were adjusted for presence of Down syndrome. Among those diagnosed with other chromosomal aberrations, 6 cases and 3 controls had Klinefelter syndrome (47XXY), making it 8 times more common among cases than controls. However, the majority of patients with Klinefelter syndrome remain undiagnosed throughout life, and data from screening studies suggest that the expected number of Klinefelter among cases and controls would be 6.5 and 24.8, respectively (37). In 4 of 6 leukemia cases with Klinefelter syndrome, the diagnosis of Klinefelter was recorded during the same year or later than the diagnosis of leukemia, suggesting that surveillance bias may be responsible for the observed association.

Data on parental age were missing to a higher extent for cases than controls. The reason is presumably the lower completeness for deceased subjects. The discrepancy

could have a modest impact on generalizability, as more cases with mortal disease had missing data. The data concerning siblings were backward truncated at 1932, as the multigeneration registry contains no records of earlier births. This causes a nondifferential misclassification, which leads to an underestimation of potential effects of birth order for cases and controls with siblings born before 1932. However, since the subjects were born between 1932 and 2008, the bias is likely to be small.

The strengths of this study include the size, the population-based approach without self-reported data, and most importantly that it includes adult cases. Although a number of large studies in this field have been carried out before, this study adds to the previous knowledge on childhood leukemia and brings new insights to the etiology of adult leukemia. A major limitation in this study is that we had no access to data on cytogenetics or other prognostic markers, which could indicate the severity of disease.

In summary, we have found an effect of parental age on acute leukemia incidence among children but meanwhile showed that this association cannot be extrapolated to adults.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G. Larfors, H. Hallböök, B. Simonsson
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. Larfors
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Larfors, B. Simonsson
Writing, review, and/or revision of the manuscript: G. Larfors, H. Hallböök, B. Simonsson

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Gunnar Larfors, Helene Hallböök and Bengt Simonsson

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