

Age- and Sex-Specific Incidence of Childhood Leukemia by Immunophenotype in the Nordic Countries

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Background: Studies from various countries have found an increasing incidence of childhood leukemia in recent decades. To characterize time trends in the age- and sex-specific incidence of childhood acute leukemia during the last 20 years in the Nordic countries, we analyzed a large set of population-based data from the Nordic Society of Paediatric Haematology and Oncology (NOPHO) in their acute leukemia database covering a population of approximately 5 million children aged 0–14 years. **Methods:** Temporal trends in acute myeloid leukemia and acute lymphoblastic leukemia incidence rates overall and for acute lymphoblastic leukemia immunophenotypes and for specific age groups were analyzed by Poisson regression adjusting for age, sex, and country. All statistical tests were two-sided. **Results:** We identified 1595 girls and 1859 boys diagnosed with acute lymphoblastic leukemia between January 1, 1982, and December 31, 2001, and 260 girls and 224 boys diagnosed with *de novo* acute myeloid leukemia between January 1, 1985, and December 31, 2001. No statistically significant change was seen in the overall incidence rate for acute lymphoblastic leukemia during the 20-year study (annual change = 0.22%, 95% confidence interval [CI] = -0.36% to 0.80%). The incidence rate of B-precursor acute lymphoblastic leukemia remained unchanged (annual change = 0.30%, 95% CI = -0.57% to 1.18%) from January 1, 1986, through December 31, 2001. A somewhat lower incidence in the first years of the study period indicated an early increasing incidence of B-precursor acute lymphoblastic leukemia that corresponded to a simultaneous decreasing incidence of unclassified acute lymphoblastic leukemia. Incidences of T-cell acute lymphoblastic leukemia (annual change = 1.55%, 95% CI = -1.14% to 4.31%) and acute myeloid leukemia (annual change = 0.58%, 95% CI = -1.24% to 2.44%) were stable during the study period. **Conclusion:** Incidences of acute myeloid leukemia overall, acute lymphoblastic leukemia overall, and specific acute lymphoblastic leukemia immunophenotypes have been stable in the Nordic countries over the past two decades. [J Natl Cancer Inst 2003;95:1539–44]

The etiology of childhood leukemia remains incompletely understood. It is concerning, therefore, that studies from different parts of the world have indicated an increase in recent decades in the incidence of childhood leukemia (1–4), in particular its most common subtype, B-precursor acute lymphoblastic leukemia (5–7). Leukemias in childhood are rare diseases, and trends in incidence are, therefore, sensitive to changes in registration procedures. For the few studies (5–7) that have examined trends in incidence of childhood leukemia by immunophenotype, misclassification between leukemia subtypes may be a matter of concern, because the leukemia subtype classification

rests on immunologic and cytologic techniques that have become readily accessible within only the past two decades (8).

We took advantage of a unique and complete register of all cases of leukemia diagnosed in a population of approximately 5 million children aged 0–14 years in Sweden, Denmark, Norway, Finland, and Iceland over a 20-year period to characterize time trends in incidence of acute lymphoblastic leukemia, including acute lymphoblastic leukemia subtypes, and of *de novo* acute myeloid leukemia. The combination of ethnic homogeneity, free and easily accessible public health care, and this unparalleled registration of all children diagnosed with leukemia make the Nordic countries a unique setting to assess incidence trends in childhood acute leukemia.

SUBJECTS AND METHODS

Study Subjects

The Nordic Society of Paediatric Haematology and Oncology (NOPHO) was established in 1981 to create uniform diagnostic, treatment, and clinical follow-up procedures for the major subgroups of childhood cancers within the five Nordic countries (Sweden, Denmark, Norway, Finland, and Iceland). As a corollary of this initiative, a unique register (the NOPHO acute leukemia database) was created to include all cases of acute lymphoblastic leukemia (complete since 1982) and acute myeloid leukemia (complete since 1985) diagnosed in the Nordic child population.

For each patient, registered information includes personal data such as personal identification number (which includes date of birth) (9), nationality, sex, information on diagnosis of Down syndrome (yes/no), and data pertaining to the leukemia diagnosed, including information on the date of diagnosis, histology, immunophenotype, karyotype, and history of previous malignancies. Specifically, cases of acute lymphoblastic leukemia are

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classified according to their immunophenotype as follows: B precursor, mature B cell, T cell, or not otherwise specified, if registered information does not allow proper classification. Cases of acute myeloid leukemia are grouped according to the modified French/American/British classification (10). In addition, one subtype of leukemia is classified according to age of diagnosis, i.e., infant leukemia (children diagnosed with leukemia between 0 and 12 months), because of the special cytogenetic, clinical, and prognostic features of this group of patients (10).

We identified all children (aged 0–14 years) registered with acute lymphoblastic leukemia or acute myeloid leukemia in the NOPHO database who resided in a Nordic country on the date of diagnosis. All records of both acute lymphoblastic leukemia and acute myeloid leukemia patients were scrutinized to exclude patients with previous cancers ($n = 0$ for acute lymphoblastic leukemia and $n = 17$ for acute myeloid leukemia) and patients with myelodysplastic syndrome ($n = 27$).

Statistical Analyses

We obtained precise information on the composition of the child populations (aged 0–14 years) of each of the five Nordic countries by sex and 1-year age strata for each year from 1982 through 2001 from the national statistics bureaus in the Nordic countries. We estimated age, sex, and country incidence rates for acute myeloid leukemia and acute lymphoblastic leukemia overall and for specific subtypes of acute lymphoblastic leukemia in 4-year calendar periods. We evaluated temporal trends in annual incidence rates by Poisson regression analysis (11,12), adjusting for age (categorized in 1-year intervals), sex, and country, modeling the effect of calendar time as a linear trend. Accordingly, the number of events in any cell cross-classified by age a , sex s , calendar year y , and country c , Y_{asye} was assumed to be Poisson-distributed with mean $\mu_{asye} = \exp(\alpha + \beta_a + \gamma_s + \kappa_c + \tau \times [y - 1991] + \log[PYRS])$, where β_a represents the effect of age group a , γ_s represents the effect of sex s , κ_c represents the effect of country c , and $\log[PYRS]$ was entered as an offset ($PYRS =$ person-years at risk). Temporal trends were then estimated as the annual change in percent, i.e., $(\exp(\hat{\tau}) - 1) \times 100\%$, where $\hat{\tau}$ is the maximum-likelihood estimate of τ . Confidence intervals were based on Wald's tests, and statistical significance tests were likelihood ratio tests. All statistical tests were two-sided. We used SAS PROC GENMOD (version 6.12) for the estimation (13).

For some outcomes, we further modeled the age-specific incidence rate, $r(a)$, as $\exp\{\beta_0 + \exp(\beta_1 + \beta_2 \log[a] - \beta_3 a)\}$, with β_0 through β_3 as the parameters to be estimated, providing a very flexible family of positively skewed incidence patterns. This particular family of models was based on viewing age parameter estimates on a logarithmic scale (which is the natural parameter scale for a Poisson regression analysis) and then modeling the age parameter curve in a simple parametric way $\{\exp(\beta_1 + \beta_2 \log[a] - \beta_3 a)\}$, resembling a γ density (14) providing a shape parameter (β_2), a vertical scaling parameter (β_1), and a horizontal scaling parameter ($\psi = \beta_2/\beta_3$). Again, we assumed the number of events in age group a , Y_a , to be Poisson distributed with mean $r(a) \times PYRS_a$. We used maximum-likelihood estimation, with the midpoints of the 1-year age intervals as age and sometimes made further adjustments or stratifications as indicated in the text. When fitting this model for T-cell acute lymphoblastic leukemia for girls or for T cells overall adjusting for sex, convergence was questionable. To overcome this problem, β_2 was set to 0.5 ($\beta_{2, boys} = 0.65$) when modeling $r(a)$ for T-cell acute lymphoblastic leukemia. We used SAS PROC NLIN (version 6.12) for the estimation (15).

RESULTS

Acute Lymphoblastic Leukemia

Overall, 1595 girls and 1859 boys were registered with acute lymphoblastic leukemia in the NOPHO acute leukemia database from January 1, 1982, through December 31, 2001, with the subtype distribution shown in Table 1. Diagnosis of Down syndrome was registered for 80 (2.3%) children with acute lymphoblastic leukemia. Table 1 shows standardized incidence rates, adjusted for age, sex, and country, for acute lymphoblastic leukemia and its subtypes, including infant acute lymphoblastic leukemia, in five 4-year calendar periods. The incidence rate of acute lymphoblastic leukemia overall remained stable during the 20-year study period (annual change = 0.22%, 95% confidence interval [CI] = -0.36% to 0.80%; Fig. 1). The incidence rate of acute lymphoblastic leukemia not otherwise specified decreased during the study period (Table 1). Though statistically consistent with a constant rate of decreasing incidence throughout the study period (annual change = -15.00%, 95% CI = -17.79% to -12.15%), the reduction in proportion of acute lymphoblastic leukemia not otherwise specified was particularly pronounced early in the study period (Table 1), constituting 13.8% of all

Table 1. Incidence of acute lymphoblastic leukemia (ALL) in the Nordic countries*

ALL by sex and subtype	Incidence rate per 100 000 person-years (No. of cases)				
	1982–1985	1986–1989	1990–1993	1994–1997	1998–2001
ALL by sex					
Boys	3.96 (348)	4.04 (344)	4.22 (374)	4.15 (392)	4.32 (401)
Girls	3.74 (312)	3.71 (301)	3.68 (312)	3.86 (348)	3.67 (322)
Overall	3.84 (660)	3.87 (645)	3.94 (686)	4.03 (740)	4.00 (723)
ALL subtype†					
B-precursor	2.92 (501)	3.36 (560)	3.39 (590)	3.46 (638)	3.59 (647)
T-cell	0.30 (54)	0.31 (53)	0.38 (64)	0.38 (68)	0.36 (66)
NOS	0.53 (91)	0.14 (23)	0.13 (23)	0.10 (19)	0.03 (5)
Infant	1.98 (21)	2.05 (23)	1.41 (18)	2.32 (28)	1.37 (15)

*All incidence rates are standardized by age (in 1-year strata), sex, and country to the Nordic child population. NOS = ALL not otherwise specified; Infant ALL = children diagnosed between 0 and 12 months of age.

†Numbers of ALL subtype cases do not add up to the number of cases of ALL overall because of the exclusion of 52 mature B-cell ALL cases.

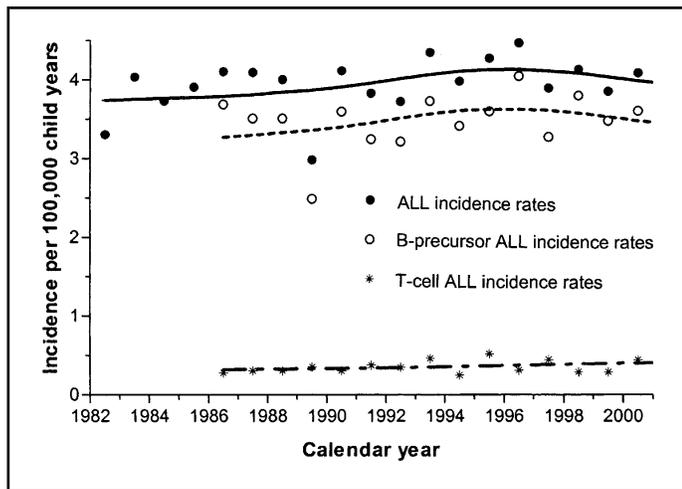


Fig. 1. Incidence rates of acute lymphoblastic leukemia (ALL) overall (January 1, 1982, through December 31, 2001), B-precursor ALL (January 1, 1986, through December 31, 2001), and T-cell ALL (January 1, 1986, through December 31, 2001) in the Nordic countries. A Poisson regression model was used to estimate the effect of calendar time as a linear trend, adjusting for age (in 1-year strata), sex, and country. The lines represent predicted values from the model, and the curvature of the lines is caused mainly by changes in the composition of the child populations.

acute lymphoblastic leukemia cases in the first 4-year calendar period, as opposed to less than 5% in the subsequent study period. The incidence rate of B-precursor acute lymphoblastic leukemia increased between January 1, 1982, and December 31, 2001 (annual change = 0.93%, 95% CI = 0.30% to 1.57%). However, when we restricted analyses to the period from January 1, 1986, through December 31, 2001, the incidence rate of B-precursor acute lymphoblastic leukemia remained constant (annual change = 0.30%, 95% CI = -0.57% to 1.18%; Fig. 1). The incidence rate of infant acute lymphoblastic leukemia was also stable between January 1, 1982, and December 31, 2001 (annual change = -1.16%, 95% CI = -4.48% to 2.27%).

No differences in incidence trend estimates in the period from January 1, 1986, throughout 2001 for B-precursor acute lymphoblastic leukemia were observed between the five countries (P for homogeneity = .99, adjusted for age and sex), between girls and boys (P for homogeneity = .95, adjusted for age and country), or between 1-year age groups (P for homogeneity = .41, adjusted for sex and country). In particular, no increase in incidence rate was observed for the peak age group of 2- to 5-year-olds (annual change = -0.08%, 95% CI = -1.23% to 1.08%) or in the age group of 1- to 4-year-olds (annual change = 0.08%, 95% CI = -1.07% to 1.25%). Age-specific incidence rates for B-precursor acute lymphoblastic leukemia from 1986 through 2001, stratified by country and period, are presented in Figs. 2 and 3. Both the overall incidence rate (P for homogeneity = .32, adjusted for age and country) and age-specific incidence rates (P for homogeneity = .50, adjusted for country) were similar between boys and girls.

The incidence rate of T-cell acute lymphoblastic leukemia remained constant during the period from January 1, 1986, throughout 2001 (annual change = 1.55%, 95% CI = -1.14% to 4.31%). This was true for all countries, both sexes, and all age groups (data not shown). Fig. 4, A and B, demonstrates sex- and age-specific incidence rates for T-cell acute lymphoblastic leukemia in the five Nordic countries combined. The age distribu-

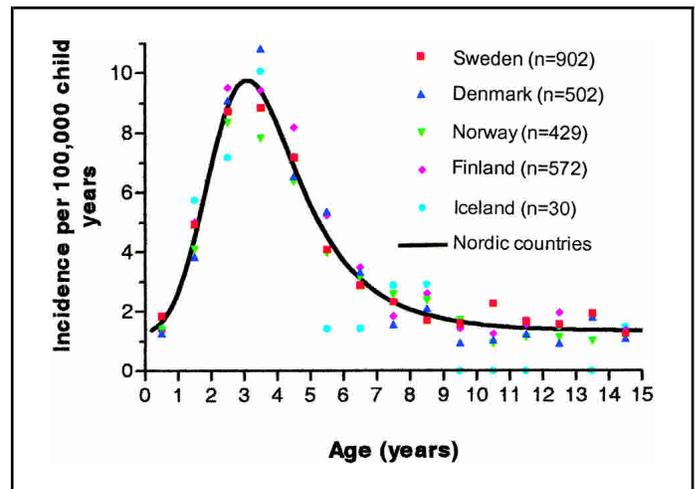


Fig. 2. Age-specific incidence rates of B-precursor acute lymphoblastic leukemia in the Nordic countries from January 1, 1986, through December 31, 2001 (P for homogeneity = .43, adjusted for sex). **Solid line** = model-predicted, age-specific incidence rate in the Nordic countries combined.

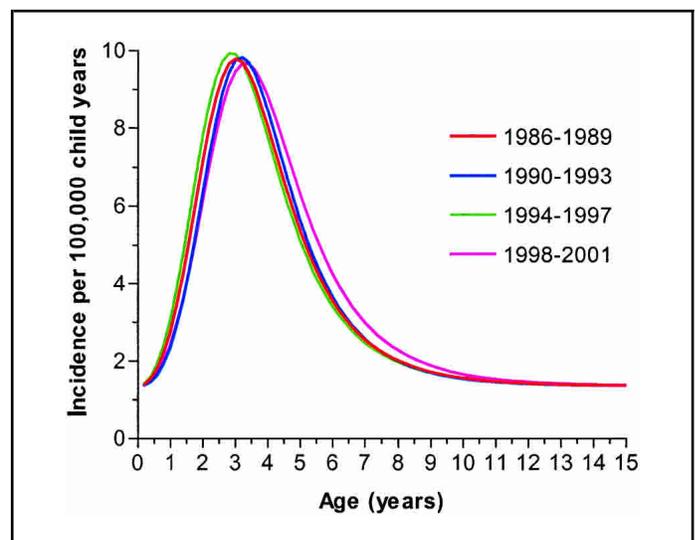


Fig. 3. Model-predicted, age-specific incidence rates of B-precursor acute lymphoblastic leukemia in the Nordic countries stratified in four calendar periods (P for homogeneity = .33, adjusted for sex).

tion was the same in all five Nordic countries (P for homogeneity = .57). The overall male/female incidence rate ratio was 2.19 for T-cell acute lymphoblastic leukemia and was constant for all age groups (P for homogeneity = .15, adjusted for country).

Excluding children with Down syndrome from the acute lymphoblastic leukemia analyses did not change the results substantially (data not shown). The small number ($n = 52$) of registered cases of mature B-cell acute lymphoblastic leukemia prevented meaningful analyses.

Acute Myeloid Leukemia

Overall, 260 girls and 224 boys were registered with acute myeloid leukemia in the period from January 1, 1985, through December 31, 2001. Down syndrome was registered for 67 (13.8%) of the children with acute myeloid leukemia (45 girls and 22 boys). The incidence rate of acute myeloid leukemia was

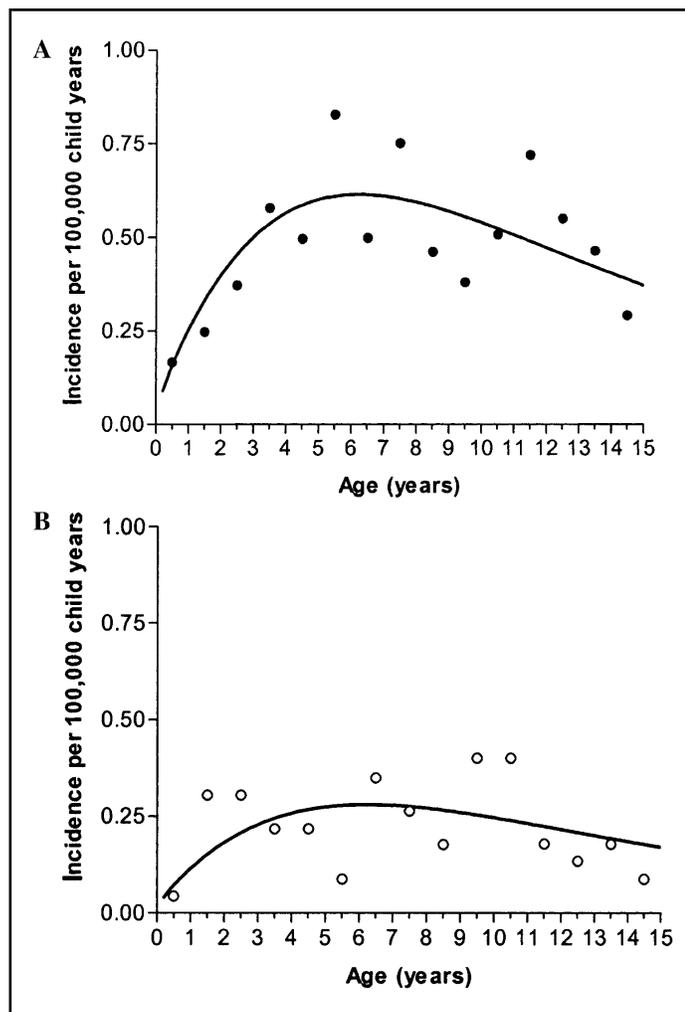


Fig. 4. Age-specific incidence rates of T-cell acute lymphoblastic leukemia for boys (A) and girls (B) in the Nordic countries from January 1, 1986, through December 31, 2001. **Solid line** = the model-predicted, age-specific incidence rate.

constant throughout the period from January 1, 1985, through December 31, 2001 (annual change = 0.58%, 95% CI = -1.24% to 2.44%; Table 2). Excluding patients with Down syndrome from the analyses did not change the observed trend estimates (annual change = 0.95%, 95% CI = -1.02 to 2.96%). No difference in incidence trend estimates was observed among the five countries (P for homogeneity = .35, adjusted for age and sex), between girls and boys (P for homogeneity = .24,

adjusted for age and country), or among age groups (P for homogeneity = .64, adjusted for sex and country).

The age-specific pattern for acute myeloid leukemia incidence changed when children with Down syndrome were excluded (Fig. 5). This reflected that Down syndrome children exclusively were diagnosed with acute myeloid leukemia before the age of 5 years. The female/male case ratio for acute myeloid leukemia was 1.16 among children without Down syndrome and 2.05 among children with Down syndrome. The age-specific incidence patterns were similar in all Nordic countries for children without Down syndrome (P for homogeneity = .94, adjusted for sex).

DISCUSSION

The present analysis demonstrated that incidence rates of childhood leukemias, whether acute myeloid leukemia or acute lymphoblastic leukemia, have been remarkably stable during the last 20 years in the Nordic countries. These findings extend previous incidence surveys from the population-based Nordic Cancer Registries (16–21) also reporting constant incidence rates, thus, suggesting that the incidence of childhood leukemia has been stable for more than 40 years.

Incidence surveys have revealed a 10-fold variation in the incidence of childhood acute lymphoblastic leukemia worldwide, and studies (22–24) have indicated a geographic correlation between socioeconomic status and childhood acute lymphoblastic leukemia incidence. The higher acute lymphoblastic leukemia incidence in developed countries reflects a high incidence of B-precursor acute lymphoblastic leukemia that makes up the conspicuous acute lymphoblastic leukemia incidence peak in children 2–5 years old in industrialized countries (Fig. 2) (22). Accordingly, earlier studies have indicated that this characteristic incidence peak emerges with socioeconomic development (22). These observations are consistent with the hypothesis that the risk of childhood acute lymphoblastic leukemia can be modified by exogenous factors (25).

It is interesting that recent studies from the United Kingdom (5,6) and Northern Italy (7) have pointed toward increases in B-precursor acute lymphoblastic leukemia incidence, suggesting changes in the prevalence of risk factors for childhood acute lymphoblastic leukemia. A number of methodologic issues, however, need to be considered in the interpretation of these investigations, including the limited number of observations, diagnostic misclassification, imprecise information about the population at risk, and annual fluctuations in incidence, which could create artificially increasing (or decreasing) trends in in-

Table 2. Incidence of *de novo* acute myeloid leukemia (AML) in the Nordic countries*

AML overall and by sex	Incidence rate per 100 000 person years (No. of cases)			
	1985–1988	1989–1992	1993–1996	1997–2001
AML by sex				
Boys	0.52 (45)	0.61 (53)	0.54 (50)	0.67 (76)
Girls	0.79 (65)	0.70 (59)	0.60 (53)	0.77 (83)
AML overall	0.66 (110)	0.65 (112)	0.57 (103)	0.72 (159)
AML overall exclusive of Down syndrome	0.54 (92)	0.58 (100)	0.49 (87)	0.62 (138)
Infant AML	1.30 (14)	1.54 (19)	1.20 (15)	1.20 (17)

*All incidence rates are standardized by age (in 1-year strata), sex, and country to the Nordic child population. Infant AML = children diagnosed between 0 and 12 months of age.

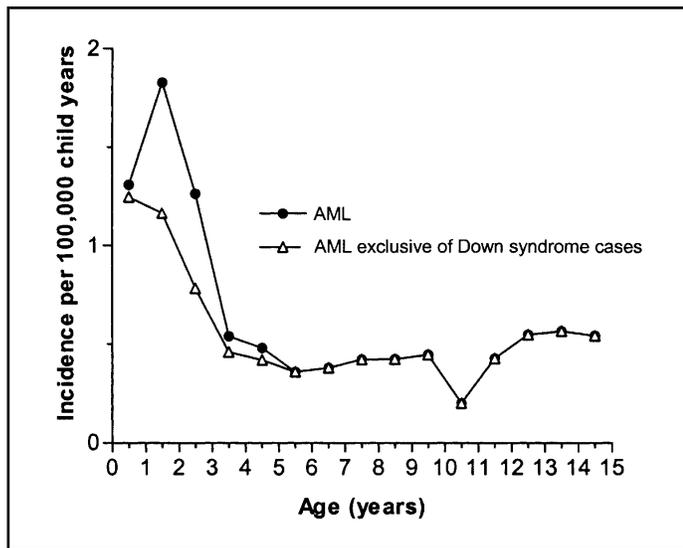


Fig. 5. Age-specific incidence rates of *de novo* acute myeloid leukemia (AML) in the Nordic countries from January 1, 1985, through 2001. Incidence rates for AML overall and AML exclusive of Down syndrome are shown.

idence, if the study period were set to start or end around a given calendar year (e.g., 1989 in our data).

In the present study, we took advantage of complete and detailed registration of all cases of childhood leukemia diagnosed in a 20-year period in the homogeneous populations of the Nordic countries, combined with detailed information on the annual age and sex composition of the Nordic child population of 5 million. Throughout the 1960s, civil registration systems were established in the Nordic countries; since then, these systems have continuously monitored the vital status of all residents by use of unique person-number systems (9). All patients in the Nordic countries have free and easy access to public health care, and children with leukemia are treated according to common Nordic protocols. Therefore, registration of patients in the NOPHO acute leukemia database is considered complete and misclassification of cases is negligible. In addition, follow-up of each patient with respect to treatment and disease status ensures a high degree of validity of all registered diagnoses. This system allowed us to accrue a large number of leukemia cases to provide relatively precise incidence estimates and also to perform detailed incidence trend analyses.

At first glance, our analyses indicated that a modest increase in the incidence of B-precursor acute lymphoblastic leukemia might have occurred during the study period. However, comparison with trends in the incidence of other acute lymphoblastic leukemia subgroups strongly indicated that the observed increase in B-precursor acute lymphoblastic leukemia is an artifact that reflects insufficient leukemia classification in the early part of the study period. Thus, the increasing incidence of B-precursor acute lymphoblastic leukemia that occurred early in the study period (i.e., between 1982 and 1985) was conspicuously mirrored by the decreasing incidence of unspecified acute lymphoblastic leukemia. In analyses restricted to the period from 1986 through 2001, no changes were observed in the incidence of B-precursor acute lymphoblastic leukemia overall or in the incidence of B-precursor acute lymphoblastic leukemia in specific age groups. Importantly, the peak age of B-precursor acute lymphoblastic leukemia did not change from 1986 through 2001,

and the shape of the age-specific incidence curve did not change (Fig. 3).

As shown in Fig. 1, the incidence rate of acute lymphoblastic leukemia in calendar year 1989 was very low. This rate could not be explained by any systematic mistakes in the recording of cases. The case distribution in 1989 did not differ statistically significantly between sexes, countries, age groups, or subtypes compared with the rest of the study period (data not shown). Therefore, we believe that the low incidence in this year is a phenomenon brought about by coincident low incidence rates in all the Nordic countries.

We found a stable incidence of T-cell acute lymphoblastic leukemia between 1985 and 2001. The annual incidence of T-cell acute lymphoblastic leukemia of approximately 0.36 case per 100 000 child-years corresponds to what has been found in other developed countries (7,22,26,27). Not surprisingly, we found that twice as many boys as girls were diagnosed with this disease (26–28). Our analyses indicated that the age-specific incidence pattern for boys followed a bell-shaped curve with a peak age of approximately 6 years (Fig. 4, A). Although the low number of girls with T-cell acute lymphoblastic leukemia prevented statistical assessment of variation in age-specific incidences, there was no indication that the age-specific incidence pattern in girls should be any different from that in boys (Fig. 4, B).

The observed incidence of acute lymphoblastic leukemia in the Nordic countries (approximately 4.0 cases per 100 000 child-years; Table 1) is among the highest in the world (24). If exogenous factors are involved in the development of childhood acute lymphoblastic leukemia, the constant incidence rates observed in the Nordic countries over a 40-year period indicate that the prevalence of these elusive risk factors has been constant or that they may have counterbalanced over a similar period of time. An alternative explanation is that the relatively high childhood leukemia incidence in the Nordic countries might reflect a saturation phenomenon, i.e., the number of susceptible individuals and prevalence of risk factors are at their maximum. Thus, the increasing incidence rates of B-precursor acute lymphoblastic leukemia reported from the United Kingdom and Northern Italy need not conflict with our findings but could reflect the fact that a similar saturation phenomenon has not yet occurred in these countries.

In comparison with acute lymphoblastic leukemia, the incidence rate of acute myeloid leukemia is more uniform across the world, and there is no clear geographic pattern in incidence rates (24). Trend analyses from different parts of the world have provided different and inconsistent results, but two recent reports (5,6) from the United Kingdom have suggested an increase of up to 3% per year for this leukemia subtype. In contrast, we observed no change in incidence of acute myeloid leukemia in the Nordic countries from January 1, 1985, through December 31, 2001. Importantly, the annual incidence rate of acute myeloid leukemia in our material did not include children with Down syndrome, secondary acute myeloid leukemia, or myelodysplastic syndrome.

To our knowledge, this study is the largest so far to analyze change in incidence pattern of childhood leukemia by age and immunophenotype. We found that incidences of acute myeloid leukemia overall, acute lymphoblastic leukemia overall, and specific acute lymphoblastic leukemia immunophenotypes have been remarkably stable in the Nordic countries over the past two decades.

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NOTES

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