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Quality of Health in Survivors of Childhood Acute Myeloid Leukemia Treated With Chemotherapy Only: A NOPHO-AML Study

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Background. More than 60% of children with acute myeloid leukemia (AML) become long-term survivors, and approximately 50% are cured with chemotherapy only. Limited data exist about their long-term morbidity and social outcomes. The aim of the study was to compare the self-reported use of health care services, health experience, social outcomes, and lifestyle behavior of AML survivors with that of their sibling controls. ***Methods.*** This population-based study included 138 children treated for AML according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO)-AML-84, -88, and -93 trials, and alive by June 30, 2007. Patients treated with hematopoietic stem cell transplantation (HSCT) or relapse were not included. Altogether, 102 (74%) survivors and 91% of their siblings completed a questionnaire. ***Results.*** The median follow-up was 11 (range 4–25) years after diagnosis. AML survivors had no increased rate of hospitalization compared with sibling controls, but were more often receiving prescription drugs, especially for asthma (23% vs. 9%, $P = 0.03$). Self-reported health experience was excellent or very good in 77% and comparable with that of siblings. Educational achievement, employment, and marital status were comparable in the two groups. Among surviving AML patients, 23% were current smokers and 24% of their siblings were current smokers. ***Conclusions.*** The self-reported health of children treated on NOPHO-AML protocols without HSCT was good, and their use of health care services was limited. Reported health and social outcomes were comparable to those of their siblings. Many survivors were smoking which may increase the risk of late effects. Pediatr Blood Cancer 2011;57:1222–1229.

Key words: acute myeloid leukemia; children; late effects; late mortality; social outcomes

INTRODUCTION

Acute myeloid leukemia (AML) represents 20% of the acute leukemia cases in children and adolescents. In the Nordic countries, AML is diagnosed in approximately 30 children annually in a total child population of 4.5 million below the age of 15 years. The past two decades have seen a marked improvement in survival. The results of the NOPHO-AML studies (Nordic Society of Pediatric Hematology and Oncology) are among the best in the world with a 5-year survival rate of 65% [1,2]. The late morbidity and mortality after the very intensive treatment therefore deserve attention.

Long-term survivors of childhood cancer are at risk of developing several adverse outcomes including early death, second neoplasms, organ dysfunction (e.g., cardiac and pulmonary), growth disturbance, reduced fertility, impaired intellectual function, difficulties in obtaining employment and insurance, and reduced quality of life [3–5]. Previous studies have reported common late effects after childhood AML [6–15]. In the Childhood Cancer Survivor Study (CCSS), 62% of AML survivors reported a chronic medical condition [6]. However, most previous studies included rather few AML survivors whose therapy varied considerably. Cranial irradiation had been given to 9–100% of patients, and hematopoietic stem cell transplantation (HSCT) had been used in 0–60%. Many of the late effects reported in previous studies were probably caused by these treatments [7,9,10]. From 1984 to 2003, approximately 50% of Nordic children with AML were cured with chemotherapy only. Cranial irradiation was not used, and cumulative doses of anthracyclines were lower than in most other protocols [1,2]. However, the chemotherapy used to cure AML remained very intensive and its use was associated with major acute toxicity, including a high frequency of both early (6%) and late toxic death (7%) [2]. Limited data exist about the long-term mortality, morbidity, and social outcomes of AML patients treated with chemotherapy only.

The objective of the Nordic AML Late Effect Study was to investigate the spectrum, frequency and possible risk factors for late effects of childhood AML cured by chemotherapy only. This study compared the self-reported use of health care services, health experience, social outcomes, and lifestyle behavior of AML survivors with those of their sibling controls.

METHODS

Eligibility

Since July 1984, all children diagnosed with AML in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) have been registered and treated according to the NOPHO-AML protocols. Enrolment is population-based for patients below 15 years, and in accordance with local practice for patients 15–18-years-old.

Patients diagnosed from July 1, 1984 to December 31, 2003 were identified in the database. All patients completing the treatment according to the NOPHO-AML-84, -88, or -93 protocols and alive by June 30, 2007 were eligible for this study. We excluded

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patients with myeloid leukemia of Down syndrome, Fanconi anemia, Kostmann syndrome, preceding myelodysplastic syndrome, therapy-related AML, patients receiving allogeneic or autologous HSCT, and patients who had experienced relapse or had a secondary malignancy by June 30, 2007. A total of 138 survivors fulfilled the inclusion criteria for the Nordic AML Late Effect Study. They were diagnosed in 21 hospitals in Denmark (n = 33), Finland (n = 27), Iceland (n = 3), Norway (n = 33), and Sweden (n = 42). A sibling of each survivor was included in the study whenever available. If a survivor had several siblings, the one closest in age was selected.

A previous study of all deaths on the NOPHO-AML-84, -88, and -93 protocols identified five children in first complete remission (CR1) who died more than 3 months after termination of AML treatment due to disease- or treatment-related complications [16]. The results from this study are included to obtain a comprehensive description of the long-term mortality.

Follow-up Procedures

AML survivors or their parents received written information about the study and were asked to participate in a follow-up. A reminder letter was sent to those, who did not respond within 2 weeks. If consent was obtained, the survivor underwent a clinical evaluation at the treating department, including a physical examination and specified blood tests of which most were analyzed locally. Additional serum samples were frozen for later central analysis. Pure-tone audiometry, electrocardiography, and transthoracic echocardiography were also performed. Results concerning hearing, endocrine function, fertility, cardiac, renal, gastrointestinal, and hepatic complications are reported separately.

At the clinical evaluation, the AML survivors (or parents of survivors <15 years of age) completed a questionnaire. It contained 124 questions about hospitalization after end of AML treatment, use of prescription drugs during the past 2 years, medical conditions diagnosed by a doctor, development of subsequent neoplasms, pregnancy history, offspring, tobacco use, education, employment, and marital status. All questions were part of the CCSS questionnaire [17]. We added questions about parental height and weight. Questions concerning education were adapted to Nordic conditions. The questionnaire was translated from English into each of the Nordic languages.

The AML survivors (or parents of survivors <15 years of age) were asked for permission to contact one of the siblings. If approved, a questionnaire was sent to adult siblings or to the parents of siblings <15 years of age. A reminder letter was sent to those who did not respond within 2 weeks. The questionnaire for siblings was identical to the one filled in by AML survivors, except for the nine AML-related questions which were omitted.

Information from the NOPHO-AML database was used to assess whether disease-related or demographic factors differed between respondents and non-respondents. Furthermore, using information from medical records, the doctor at the local treating department completed a registration form for both respondents and non-respondents.

NOPHO-AML-84/88/93 Treatment

The cumulative drug doses of the NOPHO-AML-84, -88, and -93 protocols are summarized in Table I. Intrathecal methotrexate was the only central nervous system therapy given. Details concerning treatment elements, patient characteristics, and clinical outcome have been reported previously [2].

Statistics

Included survivors were classified as *respondents* and *non-respondents* depending on whether they completed the questionnaire or not. Demographics, leukemia- and treatment-related characteristics in respondents and non-respondents were compared using multiple logistic regression analysis adjusted for sex and age.

Rates of hospitalization, surgical procedures, medication consumption, tobacco use, educational achievement, employment status, marital status, and experience of health status in responding AML survivors and their sibling controls were compared using polytomous and binary logistic regression adjusted for sex and age. To adjust for within-family correlations, standard errors of the estimates were obtained by bootstrapping, based on resampling of families [18].

The *P*-values reported were two-tailed, and *P*-values less than 0.05 were considered significant. The statistical analyses were performed using Stata Statistical Software, Release 10 (College Station, TX, USA: StataCorp 2007).

Ethics

The study was approved by Nordic national ethics committees according to national regulations. Written informed consent was obtained from the AML survivor and/or parents/guardians. For

TABLE I. NOPHO-AML-84/88/93 Cumulative Doses of Cytarabine, Etoposide, and Anthracyclines

	Cytarabine	Etoposide	Doxorubicin/mitoxantrone cumulative dose of anthracyclines[a]
	(g/m^2)	(mg/m^2)	(mg/m^2)
NOPHO-AML-84	50.4	0	225/0 Cum. dose = 225
NOPHO-AML-88	50.1	1600	150/60 Cum. dose = 450
NOPHO-AML-93	GR: 49.6 PR: 61.3	GR: 1600 PR: 1600	GR: 150/30 PR: 75/60 Cum. dose GR = 300, PR = 375

GR, good responders; PR, poor responders. [a]Calculated applying the following conversion factors to daunorubicin-equivalents: doxorubicin 1 x, mitoxantrone 5 x.

siblings, a returned questionnaire was considered as written informed consent.

RESULTS

Characteristics of the Respondents

The questionnaire was completed by 102 (74%) of 138 AML survivors a median of 10.6 (range 4.4–25.0) years after diagnosis. The respondents did not differ from the non-respondents concerning demographics, leukemia- or treatment-related characteristics (Table II). Eight respondents had no siblings. The questionnaire was completed by 86 (91%) of 94 eligible siblings.

Pre-existing disease, hospitalization, and medication. Eight respondents had a chronic disease when AML was diagnosed. This included one patient each with Turner syndrome, Marfan syndrome, congenital heart disease, epilepsy, asthma, and severe learning disability of unknown origin; and two patients had undergone surgery for bilateral cataract. The two patients with epilepsy and asthma received medication at the time of AML diagnosis.

Among the 102 respondents, 23 reported having taken prescription drugs for ≥1 month, or ≥30 days in a year, within the past 2 years. More respondents than sibling controls used medication (23% vs. 9%, $P = 0.03$) (Table III). In particular, survivors more often received prescription drugs for respiratory diseases, including bronchodilators for asthma (16% vs. 6%, $P = 0.04$).

Forty (39%) respondents had been admitted to a hospital after end of AML treatment. Nineteen had been admitted once, ten had been admitted twice, and 11 had been admitted three to six times. Five respondents had been admitted due to a late side effect. One had undergone surgery for necrosis of the femoral head. One had plastic surgery of a scar caused by a gastrostomy tube. One respondent had been diagnosed with a chronic hepatitis C infection without signs of disease activity. One patient suffered a cerebral bleeding after the first consolidation course causing spastic quadriplegia and several hospital

TABLE II. Characteristics of AML Survivors Who Completed the Questionnaire vs. Non-responders

	Respondents		Non-respondents		OR for responding
	n = 102	%	n = 36	%	(95%CI)
Sex					
Female	58	57	19	53	1.2 (0.6–2.5)
Male	44	43	17	47	1.0
Age at diagnosis (years)					
0–4	57	55	14	39	1.0
5–9	22	22	9	25	0.6 (0.2–1.6)
10–14	22	22	9	25	0.6 (0.2–1.6)
15–20	1	1	4	11	0.06 (0.01–0.6)
Leukocytes at diagnosis ($\times 10^9$/L)					
<20	66	65	16	45	1.0
20–99	25	24	12	33	0.5 (0.2–1.2)
≥100	11	11	8	22	0.3 (0.1–1.0)
CNS leukemia at diagnosis					
Yes	4	4	3	8	0.5 (0.1–2.1)
No	97	95	33	92	1.0
No data	1	1	0	0	—
FAB-type					
M0	4	4	0	0	—
M1	10	10	3	8	1.0
M2	23	22	7	19	1.0 (0.2–4.6)
M3	7	7	2	6	1.1 (0.1–8.0)
M4	22	21	13	36	0.5 (0.1–2.2)
M5	24	24	7	19	1.0 (0.2–4.8)
M6	6	6	1	3	1.8 (0.2–21.5)
M7	4	4	1	3	1.2 (0.1–15.3)
Others/no data	2	2	2	6	0.2 (0.01–2.3)
Cytogenetics					
Normal	19	19	5	14	2.0 (0.6–6.2)
Cytogenetic favorable[a]	31	30	16	44	1.0
Other MLL aberration than t(9;11)	7	7	3	8	1.2 (0.3–5.3)
Others	29	28	7	20	2.1 (0.8–6.0)
No data	16	16	5	14	1.7 (0.5–5.3)
Protocol					
NOPHO-AML-84	11	11	8	22	1.0
NOPHO-AML-88	16	16	4	11	2.9 (0.7–12.1)
NOPHO-AML-93	75	73	24	67	2.3 (0.8–6.3)

OR, odds ratio; 95%CI, 95% confidence interval. [a]Favorable cytogenetics: t(15;17)(q22;q12-21), t(8;21)(q22;q22), inv16(p13q22)/t(16;16)(p13;q22) and t(9;11)(p22;q23).

admissions after termination of AML treatment. The fifth patient had been admitted due to reduced muscle strength, bowel and bladder dysfunction caused by an epidural hematoma after spinal puncture when AML was diagnosed. No significant differences in rate of hospitalization were found between AML survivors and their siblings.

Only 1% of respondents needed help concerning personal care due to health problems, and 2% needed assistance to perform activities of daily living. This was comparable with sibling controls (0 and 2%).

Experience of health status and previous illness. The experienced health status did not differ significantly between respondents ≥10 years of age and their sibling controls (Table IV). Most survivors ≥10 years reported having no or limited anxiety regarding the previous cancer or treatment, whereas 2% reported having very much anxiety (Table V). AML survivors were most concerned about their fertility whereas parents were mainly concerned about their child's risk of relapse or developing a new cancer (Table VI).

Education, employment, and marriage. AML survivors did not participate in a learning-disability programme in elementary school more frequently than their siblings (29% vs. 20%, $P = 0.1$) (Table III). Sixty-seven percent of the respondents ≥20 years of age and 73% of their siblings reported to be undertaking or having completed an education, defined as vocational training or academic education lasting at least 3 years ($P = 0.8$).

TABLE III. Self-reported Characteristics of AML Survivors and Their Siblings

	AML survivors		Siblings		Adjusted OR[a] (95%CI)
	n = 102	%	n = 86	%	Multiple regression
Sex					
Female	57	56	51	59	0.8 (0.4–1.5)
Male	45	44	35	41	1.0
Age at questionnaire (y)					
0–9	16	16	15	18	1.0
10–14	30	29	25	29	0.9 (0.3–2.4)
15–19	20	20	20	23	0.6 (0.1–2.8)
20–29	27	26	20	23	0.6 (0.1–4.1)
≥30	9	9	6	7	0.5 (0.05–5.5)
Median (range)	16.2 (5.2–35.4)	15.7 (2.0–42.2)			
Hospitalization[b]					
Admitted to hospital					
Yes	40	39	34	40	1.0 (0.5–1.9)
No	62	61	52	60	1.0
Surgery					
Yes	33	32	20	23	1.8 (0.8–4.4)
No	69	68	66	77	1.0
Medication[c]					
Yes	23	23	8	9	3.1 (1.1–8.6)
No	79	77	78	91	1.0
Hormones[d]					
Yes	2	2	1	1	2.7 (0.2–33.2)
No	100	98	85	99	1.0
Blood pressure and heart medication					
Yes	1	1	1	1	1.1 (0.1–20.9)
No	101	99	85	99	1.0
Drugs for respiratory diseases					
Yes	16	16	5	6	4.9 (1.1–22.3)
No	86	84	81	94	1.0
Antiepileptic drugs					
Yes	2	2	0	0	—
No	100	98	86	100	1.0
Antidepressant medication					
Yes	5	5	2	2	2.0 (0.2–11.6)
No	97	95	84	98	1.0
Smoking (age ≥15 y)					
Ever smoker[e]					
Yes	23	41	13	28	2.0 (0.5–8.0)
No	33	59	33	72	1.0
Current smoker					
Yes	13	23	11	24	1.0 (0.3–3.4)
No	43	77	35	76	1.0
Education					
Learning-disability program (age ≥5 y)					
Yes	29	29	16	20	2.2 (0.9–5.3)

(*Continued*)

Table III. (*Continued*)

	AML survivors		Siblings		Adjusted OR[a] (95%CI)
	n = 102	%	n = 86	%	Multiple regression
No	72	71	65	80	1.0
Education (age ≥20 y)[f]					
Yes	24	67	19	73	1.0
No	12	33	7	27	1.2 (0.2–6.8)
Employment status (age ≥20 y)[g]					
Working full time					
Yes	14	39	16	62	1.0
No	22	61	10	38	11.0 (1.3–91.7)
Turned down[h]					
Yes	3	8	3	12	1.6 (0.2–10.7)
No	33	92	23	88	1.0
Married or cohabitant (age ≥20 y)					
Yes	22	61	14	54	1.0
No	14	39	12	46	1.2 (0.3–4.8)

OR, odds ratio; 95%CI, 95% confidence interval; y, years. [a]AML survivors without siblings excluded; adjusted for sex and age; [b]For AML survivors, hospitalization including surgery after end of AML treatment; [c]Prescription drugs taken during the past 2 years before answering the questionnaire. The drug should have been taken ≥30 days in a year. Includes hormones, medication for blood pressure, heart or respiratory conditions, antiepileptic drugs, and antidepressants; [d]Including estrogens, progesterone, testosterones and others, thyroid medications, medication for diabetes. Not birth control pills; [e]Having smoked at least 100 cigarettes in one's lifetime; [f]Completed or undertaking an education; [g]During the past 12 months before

TABLE IV. AML Survivors' and Siblings' Experience of Their Own Health Status. Age ≥10 years

Health status	AML survivors		Siblings		Adjusted OR[a] (95% CI)
	n = 86	%	n = 71	%	Multiple regression
Excellent/very good	66	77	55	77	1.8 (0.6–5.6)
Good	12	14	12	17	1.0
Fair/poor	8	9	4	6	2.1 (0.5–10.1)

OR, odds ratio; 95% CI, 95% confidence interval. [a]AML survivors without siblings excluded; adjusted for sex and age.

The number of full-time employees defined as ≥30 hr per week within the past 12 months, was significantly lower among respondents ≥20 years of age than among siblings (39% vs. 62%, $P = 0.03$). An explanation could be that more AML survivors than siblings tended to be students (33% vs. 15%, $P = 0.07$). The survivors not working full-time included persons working <30 hr per week (n = 4), caring for family (n = 3), unemployed (n = 1), and students (n = 12). Two survivors were retired due to illness or disability; one because of a severe learning-disability unrelated to the AML diagnosis. No significant difference was observed between the number of survivors ≥20 years of age and siblings who had to retire or were unable to work due to illness or disability (6% vs. 8%, $P = 0.2$). No difference was seen between the survivors and siblings regarding being turned down when applying for a civilian job, military service, or job in a police or fire department due to their previous medical history. Among those ≥20 years of age, the frequency of marriage or cohabitation did not differ between AML survivors and siblings (39% vs. 37%) (Table III).

Tobacco use. Ever smokers were defined as ever having smoked at least 100 cigarettes. Current smokers reported smoking on a regular basis. No significant difference was observed between respondents and siblings concerning the proportion of ever smokers (41% vs. 28%, $P = 0.3$), current smokers (23% vs. 24%), age when starting smoking (15.3 vs. 15.1 years), or number of cigarettes smoked per day (10.1 vs. 10.5) (Table III). Four AML survivors were regularly using snuff tobacco, and another four survivors occasionally used chewing tobacco, smoked the pipe or cigars. Two siblings regularly used snuff tobacco.

TABLE V. AML Survivors' Anxiety Because of Previous AML and Treatment. Age ≥10 Years

	n = 86	%
No anxiety	59	69
Small/medium amount of anxiety	24	28
A lot of anxiety	1	1
Very much/extreme anxiety	2	2

Characteristics of the Non-respondents

Among 36 non-respondents, 22 refused to participate, eight did not respond, five had moved abroad, and one was lost to follow-up. The 36 non-respondents had a follow-up visit within the last 0.1–19.3 (median 3.1) years. The vital status was known from civil registries for 30 of these former AML patients. For the remaining six (five

TABLE VI. AML Survivors' and Their Parents' Concern About Future Health, Fertility, or Relapse/Developing a New Cancer

	Very concerned		Concerned		Not very concerned		Not at all concerned		Data missing	
	n	%	n	%	n	%	n	%	n	%
AML survivors' concerns about[a] (n = 86)										
Future health	1	1	6	7	23	27	55	64	1	1
Fertility	5	6	11	13	14	16	56	65	0	0
Relapse/developing a new cancer	1	1	8	9	31	36	45	53	1	1
Parents' concerns about[b] (n = 46)										
Future health	3	7	5	11	25	54	8	17	5	11
Fertility	3	6	9	20	21	46	8	17	5	11
Relapse/developing a new cancer	3	6	11	24	21	46	6	13	5	11

[a]Survivors ≥10 years. Time since diagnosis; median 11.7 (range 4.4–25.0) years; [b]Parents of survivors <15 years. Time since diagnosis; median 8.6 (range 5.0–14.2) years.

emigrated, one lost to follow-up), status was unknown, but they had been seen at the treating department 1.8–12.7 years previously. The registration form was completed by the local pediatrician for 33 (94%) of the 36 non-respondents.

Two of the 33 non-respondents had a pre-existing disease at the time of AML diagnosis. One had a congenital heart disease and insulin-dependent diabetes mellitus; this was the only non-responding survivor who received medication at the time of diagnosis. One non-respondent had myelomeningocele with severe neurological complications.

Thirty (91%) of 33 non-respondents had been seen in the follow-up clinic of the treating department 1 year after end of AML treatment. Twenty-five (76%) were still seen 5 years after termination of treatment; at 10 years, this percentage had decreased to 59%.

Three (9%) non-respondents were reported to have late effects after AML. One had typhlitis at diagnosis resulting in right hemicolectomy and ileostomy. One had cardiomyopathy, NYHA class I/II, and a shortening fraction of 28%. The third non-respondent diagnosed at the age of 2 months suffered from pneumocystis jirovecii pneumonia during consolidation leading to thoracotomy causing breast asymmetry. She later received a breast implant at the age of 24.

Deaths From Late Effects

A previous study of all deaths in 525 patients included in the NOPHO-AML-84, -88, and -93 protocols identified five children in CR1 who died more than 3 months after end of treatment [16]. Three died from initial AML manifestations or late side effects 7–12 years after termination of treatment with chemotherapy only. One patient died due to anthracycline-induced cardiomyopathy. A 17-year-old male had candidiasis in the liver and spleen during induction. Later, liver cirrhosis with esophageal varices developed. He died from multiorgan failure following a month with symptoms of pulmonary infection. The third patient presented with a cerebral bleeding at diagnosis and died 12 years later as a consequence of the severe brain damage.

Two children died from secondary malignancy. One patient with AML FAB M1, 46,XX,t(2;5)(q35;q31) was treated for a Ewing sarcoma in the left frontal lobe and later developed a second AML-M1 with t(2;3)(p23;q26). The other patient was diagnosed with a pre-B acute lymphoblastic leukemia (ALL) with t(4;11)(q21;q23).

DISCUSSION

The Nordic AML Late Effect Study was initiated to assess the late morbidity and social outcomes in Nordic childhood AML survivors diagnosed between 1984 and 2003 and treated with chemotherapy only. The results of the present study are reassuring. The health condition of AML survivors did not differ from that of their siblings in terms of frequency of hospitalization, including surgical procedures, and only few survivors had been admitted to hospital due to a possible late effect of their previous AML treatment. Survivors reported using prescription drugs more frequently than controls, especially for asthma. None of the chemotherapeutic agents used in the NOPHO-AML protocols are known to involve major pulmonary toxicity [19].

A significant fraction of young adult survivors of childhood cancer experience symptoms of posttraumatic stress disorders related to residual anxiety about their cancer experience [20]. In our study, only few survivors reported serious anxiety regarding their previous AML or its treatment. Possible explanations may be that they had few or no health problems and rated their overall health as good. The majority of survivors experienced no problems during education or when applying for a job despite their previous disease. The free access to health care service in the Nordic countries may also reduce worries that could otherwise lead to anxiety.

Smoking increases the risk of serious morbidity and mortality in the general population and may increase the risk of adverse late effects among childhood cancer survivors. In our study, smoking did not differ significantly between AML survivors and sibling controls, but the prevalence of current smoking was higher than among most studies of childhood cancer survivors in the United States and United Kingdom [15,21–23]. Contrary to most other studies, the percentage of current smokers among our AML survivors was not lower than in the general population in the Nordic countries, where 16% (Sweden) to 26% (Norway) of the adult population report to be current smokers (Tobacco Control Database from WHO, 2010. http://data.euro.who.int/tobacco). The high frequency of tobacco smoking in our cohort of long-term AML survivors is worrying, and more attention should be given to improve their lifestyle behavior at long-term follow-up visits.

The proportion of AML survivors needing special educational services in elementary school was not different from that of their siblings, and the number undertaking or having completed vocational training or academic education was high and similar in the two groups. This may be due to the educational support available for

children with cancer in the Nordic countries or to the avoidance of cranial irradiation in the NOPHO-AML protocols. However, studies focusing on the cognitive functions of AML survivors are needed to elucidate this. The role of chemotherapy alone in causing cognitive impairment has been studied in survivors of AML and ALL but its significance remains controversial [24–26]. Few previous studies have evaluated the school performance of AML survivors only, and results have varied. In the CCSS, where 30% of AML survivors had been treated with cranial irradiation, the rate of high school completion among AML survivors was like in sibling controls, whereas their college graduation rate was lower [6]. In a Nordic study including AML survivors among whom more than 60% had undergone HSCT, the proportion of survivors with an academic education ($\geq$4 years) was similar to the general population [12].

The good educational level and achievement of AML survivors in our study probably contributed to their favorable employment status. The proportion of individuals who were turned down when applying for a job due to previous medical history did not differ between survivors and sibling controls. One explanation may be that all citizens in the Nordic countries receive a public health insurance coverage and the employer will thus not have to cover health costs. No difference was seen in the proportion retired or being unable to work due to illness or disability. This is in line with the study by Mulrooney et al. [6]. However, fewer survivors were employed and more received social benefits in the Nordic study by Jóhannsdóttir et al. in which the majority of the subjects were HSCT survivors [12].

Only five deaths from late effects of treatment, initial AML manifestations or secondary malignancy have occurred in the NOPHO-AML-84/88/93 protocols. In a report from the CCSS, the risk of deaths among AML survivors was increased compared with the general population, and they had a statistically significant excess mortality rate due to subsequent malignancies (standardized mortality rate (SMR) = 11.1) as well as cardiac (SMR = 5.0), pulmonary (SMR = 24.9) and other diseases (SMR = 3.2) [27]. Other studies have also reported an increased incidence of second malignancies in survivors of childhood AML or childhood leukemia in general, but the results are difficult to compare because treatment regimes varied extensively, and the use of radiotherapy varied considerably between the studies [28,29]. The NOPHO-AML protocols did not include cranial irradiation, which may explain why we only identified two patients with a second malignancy. The frequency of cardiac mortality was low in our population, but additional follow-up is needed to determine if the number of cardiovascular events, including deaths, accumulates as survivors reach ages at which the frequency of cardiac disease increases in the general population.

Although our study included all childhood AML survivors from the five Nordic countries over a 20-year period, the participants were rather few and young, with only 35% being $\geq$20 years of age. The follow-up period may have been too short to demonstrate specific late sequelae like, a negative impact on social status. Incomplete participation might influence the study results, but we found no significant differences between respondents and non-respondents. Furthermore, some results were based upon self-reporting, which might lead to under- or over-reporting. Finally, siblings may not constitute an ideal control group as their psychosocial outcomes may be affected by the previous illness in the family.

Our study has several strengths: treatment was uniform, participation rate was high, and we were able to collect basic background and clinical data on most non-respondents from the NOPHO-AML database and the treating physicians.

In conclusion, children treated on NOPHO-AML protocols without HSCT had no increased rate of hospitalization compared with sibling controls, but more often received prescription drugs for minor illnesses. Most AML survivors seemed to have coped well with their transition into adulthood, and their reported educational achievement, employment and marital status were comparable to those of their sibling controls.

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