Received: 14 April 2021 | Revised: 4 June 2021 | Accepted: 18 June 2021

DOI: 10.1002/ijc.33741

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Skeletal adverse events in childhood cancer survivors: An Adult Life after Childhood Cancer in Scandinavia cohort study

Trausti Oskarsson[1,2] | Anne Katrine Duun-Henriksen[3] | Andrea Bautz[3] | Scott Montgomery[4,5,6] | Arja Harila-Saari[2,7] | Cecilia Petersen[1] | Riitta Niinimäki[8] | Laura Madanat-Harjuoja[9,10,11] | Laufey Tryggvadóttir[12,13] | Anna Sällfors Holmqvist[14,15] | Henrik Hasle[16] | Mats Heyman[1,2] | Jeanette Falck Winther[3,17] | ALiCCS study group

[1]Department of Paediatric Oncology, Astrid Lindgren Children's Hospital, Stockholm, Sweden

[2]Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[3]Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark

[4]Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden

[5]Clinical Epidemiology Division, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

[6]Department of Epidemiology and Public Health, University College London, London, UK

[7]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[8]Department of Children and Adolescents, Oulu University Hospital, Oulu, Finland

[9]Finnish Institute for Statistical and Epidemiological Cancer Research, Finnish Cancer Registry, Helsinki, Finland

[10]Dana-Farber Cancer Institute/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, Massachusetts, USA

[11]Department of Pediatrics, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[12]The Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland

[13]Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[14]Division of Paediatric Oncology and Haematology, Skåne University Hospital, Lund, Sweden

[15]Department of Clinical Sciences, Lund University, Lund, Sweden

[16]Department of Paediatrics, Aarhus University Hospital, Aarhus, Denmark

[17]Department of Clinical Medicine, Faculty of Health, Aarhus University and University Hospital, Aarhus, Denmark

Correspondence
Trausti Oskarsson, Department of Paediatric Oncology, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Solna, 17176 Stockholm, Sweden.
Email: trausti.oskarsson@ki.se

Funding information
Swedish Childhood Cancer Foundation, Grant/Award Number: PR2011-0047

Abstract

The dynamic growth of the skeleton during childhood and adolescence renders it vulnerable to adverse effects of cancer treatment. The lifetime risk and patterns of skeletal morbidity have not been described in a population-based cohort of childhood cancer survivors. A cohort of 26 334 1-year cancer survivors diagnosed before 20 years of age was identified from the national cancer registries of Denmark,

Abbreviations: AER, absolute excess risks; ALiCCS, Adult Life after Childhood Cancer in Scandinavia; ALL, acute lymphoblastic leukemia; BMD, bone mineral density; CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ICCC, International Classification of Childhood Cancer; ICD, International Classification of Diseases; NOPHO, Nordic Society of Paediatric Haematology and Oncology; NPR, National patient registry; PWP, Prentice-Williams-Peterson; RR, rate ratio.

Mats Heyman and Jeanette Falck Winther contributed equally as last coauthors.

Finland, Iceland and Sweden as well as a cohort of 127 531 age- and sex-matched comparison subjects randomly selected from the national population registries in each country. The two cohorts were linked with data from the national hospital registries and the observed numbers of first-time hospital admissions for adverse skeletal outcomes among childhood cancer survivors were compared to the expected numbers derived from the comparison cohort. In total, 1987 childhood cancer survivors had at least one hospital admission with a skeletal adverse event as discharge diagnosis, yielding a rate ratio (RR) of 1.35 (95% confidence interval, 1.29-1.42). Among the survivors, we observed an increased risk for osteonecrosis with a RR of 25.9 (15.0-44.5), osteoporosis, RR 4.53 (3.28-6.27), fractures, RR 1.27 (1.20-1.34), osteochondropathies, RR 1.57 (1.28-1.92) and osteoarthrosis, RR 1.48 (1.28-1.72). The hospitalization risk for any skeletal adverse event was higher among survivors up to the age of 60 years, but the lifetime pattern was different for each type of skeletal adverse event. Understanding the different lifetime patterns and identification of high-risk groups is crucial for developing strategies to optimize skeletal health in childhood cancer survivors.

KEYWORDS
ALiCCS, childhood cancer, late effects, skeletal adverse events, survivorship

What's new?

The dynamic growth of the skeleton during childhood renders it vulnerable to adverse effects of cancer treatment. In this comprehensive, large-scale population-based retrospective cohort study, childhood cancer survivors were more likely to be hospitalised for skeletal adverse events than matched population comparison subjects. Although the risk of adverse events was highest in the period close to the cancer treatment, the excess risk continued for decades. Osteonecrosis, osteoporosis, fractures, osteochondropathies, and osteoarthrosis all showed different lifetime patterns. Understanding the lifetime patterns of skeletal adverse events and identifying high-risk groups could help develop strategies to optimise skeletal health in childhood cancer survivors.

1 | BACKGROUND

The improved childhood cancer survival rates over recent decades have resulted in a growing number of survivors reaching adulthood.[1,2] Simultaneously, the knowledge on treatment-related long-term adverse health conditions is constantly increasing. It is estimated that more than two-thirds of childhood cancer survivors suffer from at least one chronic health condition.[3,4] Thus, health-related problems in childhood cancer survivors are a growing concern from a public health perspective.[5] In order to decrease long-term morbidity, it is important to identify patients at risk for specific toxicities and find ways to modify the treatment without jeopardizing the positive trends in overall survival.

Skeletal morbidity has been described at diagnosis, during treatment and in long-time survivors of childhood cancer.[6] Besides discomfort, skeletal morbidity may cause permanent disability and reduced quality of life and may require major surgical interventions. The most severe treatment-associated skeletal morbidity is osteonecrosis defined as one of the 14 most serious acute toxicities of childhood acute lymphoblastic leukemia (ALL) treatment.[7] However, osteonecrosis has also been reported in other types of childhood cancer, mainly in survivors of lymphomas and as a complication after allogeneic hematopoietic stem cell transplantation (HSCT) but less is known regarding the frequency of osteonecrosis among patients with solid tumors and tumors of the central nervous system (CNS).[8-10]

The majority of people attain their peak bone mass by late adolescence.[11] Any disturbance in the bone mineralization may have long-term effects on the density and the quality of the bone. Previous studies have shown an increased risk of low bone mineral density (BMD) during and early after cessation of childhood cancer treatment but results are more conflicting on the long-term effect and the risk of fractures.[12,13] Data on the risk of osteochondropathies and osteoarthritis in childhood cancer survivors, however, are sparse.

In the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), there is a long-standing tradition of operating national population and health registries. The population-based coverage of a

variety of registries with high data quality and validity, and the long follow-up time provide an ideal setting for studying rare health outcomes in rare diseases like childhood cancer.[14,15]

Our study is the first comprehensive, yet detailed, large-scale population-based study of the lifetime risk for medically verified skeletal morbidity in a cohort of childhood cancer survivors and a randomly selected and matched population comparison group estimating the incidence and risk of hospitalization for osteonecrosis, osteoporosis, fractures, osteochondropathies and osteoarthrosis. Furthermore, we aim to identify high-risk groups of survivors as this is essential for the development of treatment modifications and appropriate follow-up recommendations to decrease the burden of skeletal morbidity in childhood cancer survivors.

2 | MATERIAL AND METHODS

2.1 | Survivor and comparison cohorts

This retrospectively defined register-based cohort study originates from the study "Adult Life after Childhood Cancer in Scandinavia" (ALiCCS; www.aliccs.org); a research program initiated in 2010 in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) with the overall purpose to investigate late complications of treatment in childhood cancer survivors.[16]

The childhood cancer cohort in the present study is a subcohort of ALiCCS, comprising 33 576 patients diagnosed with cancer before 20 years of age in Denmark (1943-2008), Finland (1971-2008), Iceland (1955-2008) and Sweden (1958-2008) as reported by the national cancer registries (Table 1). As full access to complete hospitalization histories needed for our study was not available for Norway, our study only includes data from four Nordic countries. From the nationwide Nordic cancer registries, we obtained the patient's personal identification number, date of diagnosis and type of cancer, and patients were assigned to 1 of 12 main diagnostic groups in the third edition of the International Classification of Childhood Cancer (ICCC-3).[17] The unique personal identification number available for every citizen in the Nordic countries allowed accurate linkage of data across registries.

To measure rates of skeletal morbidity in the general population, we randomly selected five comparison subjects for each childhood cancer patient from the national population registries that did not have a childhood cancer diagnosis before the age of 20 years and were alive at the time of cancer diagnosis of the corresponding patient. Subjects in the comparison cohort were matched by age, sex and country (Denmark, Iceland) or county/municipality of residence (Finland, Sweden). Fewer than five comparison subjects were available for a minority of childhood cancer survivors (n = 168), where the matching criteria could not be met, leaving 167 712 comparison subjects for study.

Before linkage of study subjects to the national patient registries (NPRs), we excluded individuals in both cohorts with constitutional chromosomal abnormalities (International Classification of Diseases—ICD codes: ICD-8: 759.3-759.5, ICD-9: 758 and ICD-10: Q90-Q99) as the main or supplemental discharge diagnosis in the hospital registries to avoid potential confounding by genetic predisposition. The final study cohort included 26 334 1-year survivors and 127 531 comparison subjects (Figure 1).

2.2 | Hospitalizations for skeletal adverse events

Based on information in the NPRs, we obtained information on hospitalizations for skeletal diseases as markers for adverse events in the skeletal system and identified patients with the following skeletal diseases according to successive revisions of the ICD coding systems (ICD-7 to ICD-10): osteonecrosis, osteoporosis, fractures, osteochondropathies and osteoarthritis (Table S1). The coding of skeletal diseases was adapted to ICD-10 as far as possible. The group "osteochondropathies" was made up of several subdiagnoses that all

TABLE 1 Final study population of childhood cancer survivors and population comparison subjects and recruitment period in Nordic cancer and hospital registries

Country	Childhood cancer survivors (n)	Population comparison subjects (n)	Cancer registries[a]	Hospital registries
			Recruitment period	Recruitment period
Denmark	7265	34.391	1943-2008	1977-2010
Finland	6369	31.020	1971-2008	1975-2012
Iceland	402	1.983	1955-2008	1999-2008
Sweden	12.298	60.137	1958-2008	1964[b]-2009
Total	26.334	127.531	1943-2008	1964-2012

[a]Over time, cancers have been notified according to the International Classification of Diseases, 7th-10th revisions (ICD-7-10), or the ICD for Oncology, 1st-3rd editions (ICD-O1-O3).

[b]Established in 1964, reaching complete nationwide coverage in 1987. To be included in the cohort, patients had to be alive or born after the start of complete centralized registration of residents, when all citizens were assigned a unique personal identification number that permits linkage among registers (Iceland 1955; Denmark and Sweden 1968; Finland 1971). Information on vital status and emigration during the follow-up period was obtained for both patients and comparison subjects from the central population registries, which started in 1952 in Iceland, 1967 in Sweden, 1968 in Denmark and 1969 in Finland.

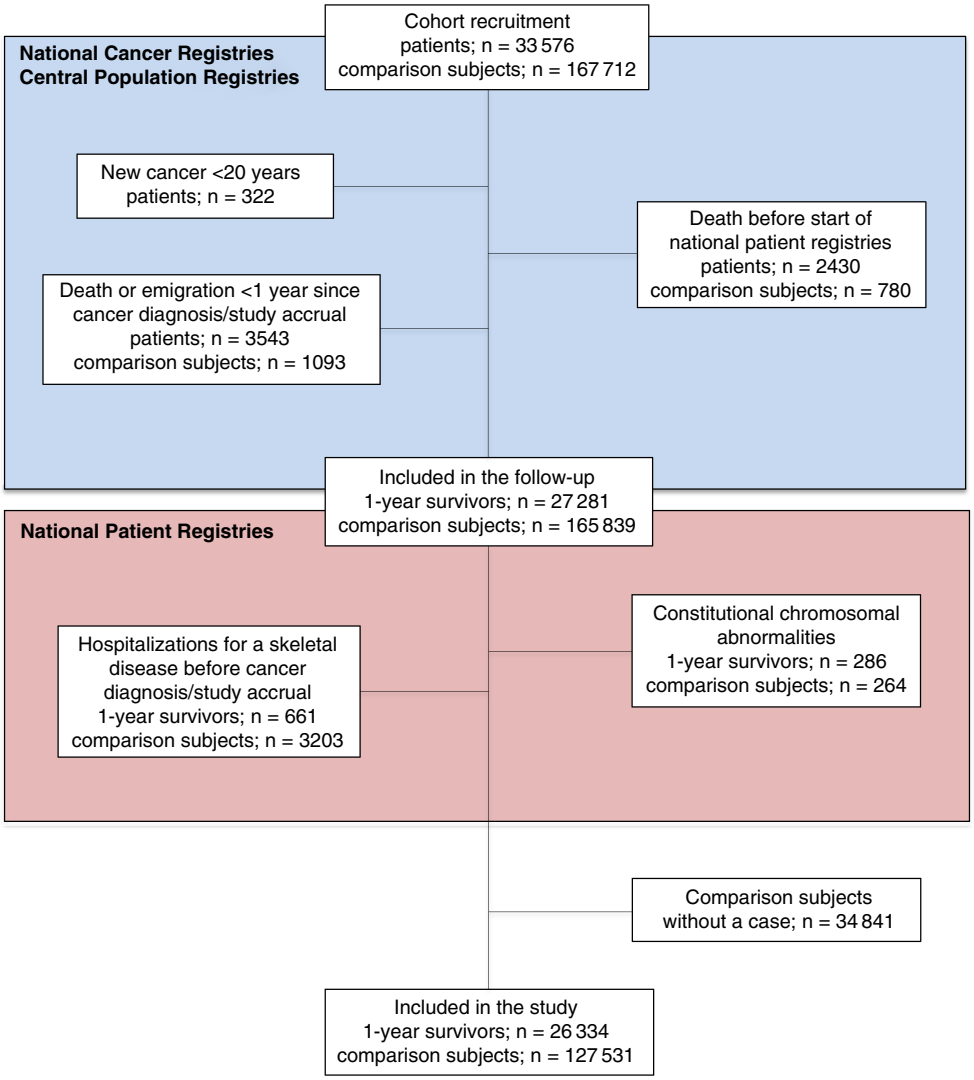

FIGURE 1 Flow chart with study inclusions and exclusions

identify cartilage disorders (Table S1). We did not include bone or joint diseases with infectious (osteomyelitis, septic arthritis) or rheumatic (inflammatory arthritis) etiologies. The first record of hospitalization for each diagnosis was used, regardless of whether it was the main or a supplemental diagnosis. In the event that patients or comparison subjects were hospitalized for multiple skeletal diseases either simultaneously or separately, the first hospitalization for each skeletal disease was accounted for as an event when investigating skeletal diseases separately.

In Denmark (from 1995) and Sweden (from 2001), the NPRs hold information about the diagnostic codes used also in hospital-based outpatient clinics. We decided primarily to use diagnostic codes from inpatient discharge records to avoid discrepancies between the participating countries and time periods but conducted a separate sensitivity analysis including outpatient data only.

To take into account potential effect modification by other adverse events, we looked at endocrine disorders (adapted ICD-10 codes: E01-E35, E89) and neurological disorders (adapted ICD-10- codes: H53.0-H54.9, G40.0-G41.9, G50-G59.8, G80.0-G83.9) specifically, since both groups could theoretically modify the risk of being hospitalized for skeletal adverse events and contained sufficient numbers of cases to enable subanalyses.

2.3 | Statistical analysis

The follow-up period started 1 year after the date of cancer diagnosis or when national inpatient registration started, whichever occurred later. For the main analyses, the follow-up ended at the time of first hospitalization for a skeletal disease, the time of diagnosis of a new primary cancer, at the time of death or emigration or at the end of the study (Finland: December 31, 2012; Denmark: October 31, 2010; Sweden: December 31, 2009; Iceland: December 31, 2008), whichever occurred first.

We used hospitalization rates per 100 000 person-years as the main measure of frequency and standardized hospitalization rate ratios (RRs) were used as the main relative risk estimate. This relative risk estimate represents the relative risk for skeletal adverse events among childhood cancer survivors by comparing the observed number of first hospitalizations to the expected number of hospitalizations in

the comparison cohort with similar age, sex and calendar period distribution. To estimate the absolute additional risk of hospitalization for a skeletal disease, we calculated the absolute excess risks (AER) as the difference between the observed and expected first hospitalization rates for the respective skeletal diseases per 100 000 person-years. The 95% confidence intervals (CIs) were computed from Fieller's theorem based on the assumption that the observed numbers of hospital admissions follow a Poisson distribution.[18] RRs with 95% CIs not including 1.0 were considered statistically significantly increased and are referred to as "significantly increased" in the text. Risk estimates were calculated for each type of skeletal adverse event and then stratified by age at cancer diagnosis, sex, cancer type and attained age. To illustrate how hospitalizations among survivors advanced over time, we calculated the cumulative excess hazards for each type of skeletal adverse event.

We used Prentice-Williams-Peterson (PWP) models to estimate the hazard ratio of recurrent fractures (only first recurrence counted) and applied the same adjustment methods as in the above-mentioned models. The PWP models were performed on a restricted risk set that only included subjects with previous hospitalizations for fractures. We calculated the cause-specific hazard ratios for all types of skeletal events combined with and without hospitalizations for endocrine and neurological disorders.

To validate our study design, we calculated the RR for each type of skeletal adverse event by including different subsets of study participants in sensitivity analyses: (a) the impact of bone tumors on the overall risk estimates, by exclusion of patients with malignant bone tumors (ICD-10, C40-41, C76.0-76.8); (b) outcome differences between 1- and 5-year survivors to study the impact of late treatment failures due to the cancer, by only including 5-year survivors and their comparison subjects; (c) the influence of left truncation, since the study did not capture events that occurred prior to the start of NPR in each country, by only including survivors diagnosed maximum 1 year prior to the start of the NPR and their comparison subjects; (d) the effect of coding discrepancies over time, by only including hospitalizations coded by the ICD-9 and ICD-10 coding systems; (e) discrepancies in the outcome registration between the inpatient and outpatient hospital registries in Denmark and Sweden by including only outpatient visits.

All statistical calculations and models were performed with SAS software version 9.4 and R version 3.5.1, with the following packages: Epi,[19] etm,[20] ggplot2,[21] mets,[22,23] survival.[24,25]

3 | RESULTS

Among the 26 334 1-year childhood cancer survivors, 1987 were diagnosed with at least one skeletal adverse event, compared to 8986 subjects with events among the 127 531 population comparison subjects. The follow-up time for the survivor cohort was 383 551 person-years (median 13.6 years, range 0-42 years) and 3 091 712 person-years (median 18.4 years, range 0-42 years) for the comparison cohort. This yielded a RR of 1.35 (95% CI, 1.29-1.42) and an AER of 135 (110-159) per 100 000 person-years for any skeletal adverse event in the survivor cohort (Table 2). Descriptions of the cohort characteristics and RR by clinical characteristics are available in Table S2. The RR was highest for the first 5 years from diagnosis; RR 1.6 (1.5-1.8), then dropped to 1.3 (1.2-1.4), 1.2 (1.1-1.3) and 1.4 (1.2-1.5) 5-9, 10-19 and ≥20 years from diagnosis, respectively (not shown).

The RR was significantly increased for all five groups of skeletal adverse events (Table 2) but osteonecrosis generated the highest RR, 25.9 (15.0-44.5). Hospitalizations for skeletal adverse events were significantly increased among childhood cancer survivors with the following cancer diagnoses: leukemia RR 1.6 (1.4-1.7), lymphoma 1.2 (1.0-1.3), CNS tumors 1.5 (1.4-1.7), sympathetic nervous system tumors 1.7 (1.4-2.1) and malignant bone tumors 2.6 (2.2-3.1) (Table 3).

Hospitalizations for skeletal adverse events occurred between 1.6 and 83.6 years of age in the survivor cohort and between 1.7 and 84.5 years in the comparison cohort. Figure 2 (hospitalization rates) and Figure S1 (cumulative excess hazards) illustrate the patterns of hospitalizations, overall and for each skeletal adverse event over time. Since fractures accounted for 1637 (82%) of all hospitalizations among the survivors, the hospitalization pattern for all events combined was mostly influenced by the pattern for fractures. For all skeletal adverse events combined, the hospitalization rates, RR and AER were significantly higher among survivors up to the age of 60 years (Table 4) but the lifetime hospitalization patterns differed between the types of events, as shown in Figure 2. Of all first hospitalizations for skeletal adverse events in the survivor cohort, 856 (43%) occurred before 20 years of age but only 166 (8%) among survivors 50 years and older. Thus, risk estimates for the oldest survivors were based on a very limited number of individuals.

Overall, hospitalizations for skeletal adverse events were more common among males than females. In the survivor cohort, 8.6% of males were hospitalized for skeletal adverse events compared to 6.3% of the females. In both cohorts, there was a marked increase in the hospitalizations after 60 years of age, especially among females (Figure S2). As expected, the incidence rates for osteoporosis and osteoarthrosis increased in both cohorts after 60 years of age. The increased risk for skeletal adverse events was more pronounced for female survivors, RR 1.6 (1.5-1.8) compared to 1.2 (1.1-1.3) for male survivors. This was true for all skeletal adverse events except osteoporosis (Table 2).

3.1 | Osteonecrosis

Among all skeletal outcomes, the RR was highest for osteonecrosis, RR 25.9 (15.0-44.5) (Table 2), especially among survivors of leukemia 133.7 (70.9-252.4) (Table 3). Among the 69 survivors hospitalized for osteonecrosis, 55 were diagnosed with cancer in 1990 or later and 11 between 1975 and 1989 (not shown). The RR was significantly increased for survivors up to the age of 40 years but due to low numbers, RRs could not be estimated in the older population (Table 4). The relative risk estimates for osteonecrosis were

TABLE 2 Observed and expected hospitalizations, RR and AER for skeletal adverse events among 1-year childhood cancer survivors, by age and gender

Skeletal disorder	ICD-10[a] codes	Obs[b]	Exp[b]	RR (95% CI)	AER (95% CI)
All skeletal events		1987	1471.3	1.35 (1.29-1.42)	135 (110-159)
Male		1211	996.1	1.22 (1.14-1.29)	109 (72-146)
Female		776	475.2	1.63 (1.51-1.77)	162 (131-193)
Age 0-9 y		963	712.1	1.35 (1.27-1.45)	134 (101-168)
Age 10-19 y		1024	759.2	1.35 (1.26-1.44)	135 (102-168)
Osteonecrosis	M87, M90.5	69	2.7	25.85 (15.02-44.49)	16 (12-20)
Male		37	1.7	21.79 (10.97-43.31)	17 (11-22)
Female		32	1.0	32.95 (13.53-80.26)	16 (10-22)
Age 0-9 y		6	1.0	6.23 (2.33-16.63)	2.5 (0.1-5.0)
Age 10-19 y		63	1.7	36.94 (22.37-61.01)	30 (22-38)
Osteoporosis	M80-81, M82.1, M82.8	64	14.1	4.53 (3.28-6.27)	12 (8-16)
Male		31	5.5	5.63 (3.46-9.17)	12 (7-17)
Female		33	8.6	3.83 (2.47-5.94)	13 (7-19)
Age 0-9 y		25	3.7	6.77 (4.15-11.0)	11 (6-16)
Age 10-19 y		39	10.4	3.74 (2.61-5.36)	14 (8-20)
Fractures	S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, M90.6, M90.7, M48.4, M48.5	1637	1288.5	1.27 (1.20-1.34)	90 (68-112)
Male		1038	895.0	1.16 (1.09-1.24)	72 (38-106)
Female		599	393.5	1.52 (1.39-1.67)	110 (83-137)
Age 0-9 y		844	655.2	1.29 (1.20-1.38)	100 (69-131)
Age 10-19 y		793	633.3	1.25 (1.16-1.35)	81 (52-109)
Osteochondropathies	M23.4, M24.0, M24.1, M42, M89.5, M91-94	118	75.1	1.57 (1.28-1.92)	11 (5-16)
Male		71	51.3	1.38 (1.07-1.79)	9 (1-18)
Female		47	23.8	1.97 (1.42-2.75)	12 (5-19)
Age 0-9 y		69	37.2	1.85 (1.44-2.38)	16 (7-25)
Age 10-19 y		49	37.8	1.30 (0.97-1.74)	5 (−1 to 12)
Osteoarthrosis	M15-19	213	143.6	1.48 (1.28-1.72)	17 (10-25)
Male		98	73.0	1.34 (1.08-167)	12 (2-22)
Female		115	70.6	1.63 (1.32-2.00)	23 (12-35)
Age 0-9 y		53	32.6	1.63 (1.22-2.17)	10 (3-18)
Age 10-19 y		160	111.0	1.44 (1.22-1.70)	24 (12-36)

Abbreviations: AER, absolute excess risk; RR, standardized hospitalization rate ratio.
[a]ICD 7-9 codes were adapted to the ICD-10 version.
[b]Observed (obs) and expected (exp) number of hospitalizations.

particularly high for patients diagnosed with cancer in the age group of 10-19 years (63 observed cases), RR 36.9 (22.4-61.1) compared to those diagnosed under 10 years of age (6), RR 6.2 (2.3-16.6) (Table 2). Among the 46 leukemia survivors hospitalized for osteonecrosis, 36 had ALL, 4 acute myeloid leukemia and 6 other types of leukemia (not shown).

We also observed a few cases of osteonecrosis among survivors with nonhematological cancers; that is, CNS tumors (4 observed cases), sympathetic nervous system tumors (1), renal tumors (1) and malignant bone tumors (3). Seven of these nine patients were older than 25 years at the time of hospitalization and seven were hospitalized for osteonecrosis in 2004 or later.

3.2 | Osteoporosis

The overall RR for osteoporosis was 4.5 (3.3-6.3) (Table 2), but the overall excess risk was only significant for survivors hospitalized before 30 years of age (Table 4). Of the 64 hospitalizations for osteoporosis, 38 occurred before 20 years of age. As expected, the hospitalization rates for osteoporosis increased among survivors as well as in the general population after 50 years of age but there were only eleven hospitalizations for osteoporosis among the survivors in the age group 60 years or older, RR 1.8 (0.9-3.5) (Table 4). For survivors 0-9 years of age at cancer diagnosis, the RR for osteoporosis was 6.7 (4.1-11.0) compared to a RR of 3.7 (2.6-5.4) for those diagnosed at 10-19 years of age (Table 2).

TABLE 3 Observed and expected hospitalizations and RR for skeletal adverse events among 1-year childhood cancer survivors, by cancer type

Diagnostic groups by ICCC-3	Obs[a]	Exp	RR (95% CI)	Diagnostic groups by ICCC-3	Obs	Exp	RR (95% CI)
I. Leukemias (n = 5803)	389	249.4	1.6 (1.4-1.7)	**V. Retinoblastoma (n = 618)**	57	53.0	1.1 (0.8-1.4)
Osteonecrosis	46	0.3	133.7 (70.9-252.4)	Osteonecrosis	0	0.1	NA
Osteoporosis	25	0.9	28.2 (16.7-47.8)	Osteoporosis	1	0.4	2.8 (0.4-20.1)
Fractures	287	232.7	1.2 (1.1-1.4)	Fractures	48	48.0	1.0 (0.8-1.3)
Osteochondropathies	29	13.4	2.2 (1.5-3.1)	Osteochondropathies	6	2.8	2.2 (1.0-4.8)
Osteoarthrosis	34	8.4	4.0 (2.8-5.8)	Osteoarthrosis	3	3.8	0.8 (0.3-2.5)
II. Lymphomas (n = 3635)	253	216.2	1.2 (1.0-1.3)	**VI. Renal tumors (n = 1128)**	81	72.6	1.1 (0.9-1.4)
Osteonecrosis	14	0.5	31.2 (15.7-62.1)	Osteonecrosis	1	0.1	11.3 (1.5-87.9)
Osteoporosis	3	1.5	2.0 (0.6-6.4)	Osteoporosis	3	0.3	9.6 (3.0-31.3)
Fractures	202	189.0	1.1 (0.9-1.2)	Fractures	72	66.7	1.1 (0.9-1.4)
Osteochondropathies	13	11.6	1.1 (0.7-1.9)	Osteochondropathies	9	3.9	2.3 (1.2-4.5)
Osteoarthrosis	36	20.7	1.7 (1.2-2.4)	Osteoarthrosis	2	3.3	0.6 (0.2-2.4)
III. CNS tumors (n = 5990)	523	343.1	1.5 (1.4-1.7)	**VII. Hepatic tumors (n = 163)**	11	7.4	1.5 (0.8-2.7)
Osteonecrosis	4	0.6	6.6 (2.2-19.8)	Osteonecrosis	0	0.0	NA
Osteoporosis	13	3.3	4.0 (2.2-7.2)	Osteoporosis	3	0.0	153.7 (46.1-505.3)
Fractures	467	301.2	1.6 (1.4-1.7)	Fractures	8	6.9	1.2 (0.6-2.3)
Osteochondropathies	18	17.7	1.0 (0.6-1.6)	Osteochondropathies	0	0.4	NA
Osteoarthrosis	47	33.0	1.4 (1.1-1.9)	Osteoarthrosis	0	0.2	NA
IV. Sympathetic nervous system tumors (n = 1125)	89	51.7	1.7 (1.4-2.1)	**VIII. Malignant bone tumors (n = 1240)**	154	58.7	2.6 (2.2-3.1)
Osteonecrosis	1	0.1	12.5 (1.6-95.5)	Osteonecrosis	3	0.1	25.4 (7.5-86.0)
Osteoporosis	2	0.2	10.5 (2.5-43.9)	Osteoporosis	2	0.7	2.7 (0.7-11.0)
Fractures	76	48.0	1.6 (1.3-2.0)	Fractures	133	49.9	2.7 (2.2-3.2)
Osteochondropathies	12	2.7	2.6 (4.5-2.5)	Osteochondropathies	6	3.1	1.9 (0.9-4.3)
Osteoarthrosis	3	2.0	1.5 (0.5-4.6)	Osteoarthrosis	17	8.0	2.1 (1.3-3.4)
IX. Soft tissue sarcomas (n = 1746)	120	109.4	1.1 (0.9-1.3)	**XI. Carcinoma and other malignant epithelial neoplasms (n = 2818)**	183	181.4	1.0 (0.9-1.2)
Osteonecrosis	0	0.2	NA	Osteonecrosis	0	0.4	NA
Osteoporosis	2	2.0	1.0 (0.3-4.1)	Osteoporosis	4	3.8	1.1 (0.4-2.8)
Fractures	90	92.2	1.0 (0.8-1.2)	Fractures	144	143.3	1.0 (0.9-1.2)
Osteochondropathies	10	5.2	1.9 (1.0-3.6)	Osteochondropathies	5	8.2	0.6 (0.3-1.5)
Osteoarthrosis	25	15.4	1.6 (1.1-2.4)	Osteoarthrosis	37	34.3	1.1 (0.8-1.5)
X. Germ cell tumors (n = 1701)	106	110.6	1.0 (0.8-1.2)	**XII. Other and unspecified malignant neoplasms (n = 347)**	21	17.8	1.2 (0.8-1.8)
Osteonecrosis	0	0.2	NA	Osteonecrosis	0	0.0	NA
Osteoporosis	3	0.9	3.3 (1.0-10.4)	Osteoporosis	3	0.2	17.1 (5.4-54.0)
Fractures	93	95.1	1.0 (0.8-1.2)	Fractures	17	15.6	1.1 (0.7-1.8)
Osteochondropathies	7	5.2	1.4 (0.6-2.9)	Osteochondropathies	3	0.9	3.6 (1.1-11.0)
Osteoarthrosis	8	12.6	0.6 (0.3-1.3)	Osteoarthrosis	1	1.8	0.6 (0.1-3.9)

Abbreviations: CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, version 3; NA, not applicable; RR, standardized hospitalization rate ratio.

[a]Observed (obs) and expected (exp) number of hospitalizations. The total number accounts for the first hospitalization for each skeletal adverse event. Individual numbers account for the first hospitalizations for osteonecrosis, osteoporosis and osteoarthrosis and the first hospitalization for each new fracture and different types of osteochondropathies.

A strong association was found between osteoporosis and leukemias, with a RR of 28.2 (16.7-47.8), whereas among lymphoma survivors, only three hospitalizations occurred (Table 3). Furthermore, a significant excess risk was observed among survivors of CNS tumors, RR 4.0 (2.2-7.2).

3.3 | Fractures

The RR for fractures was 1.3 (1.2-1.3) (Table 2). The relative risk was higher for serious fractures such as hip fractures (104 observed cases), RR 2.9 (2.3-3.7) and femur fractures (23), RR 2.00 (1.6-2.5)

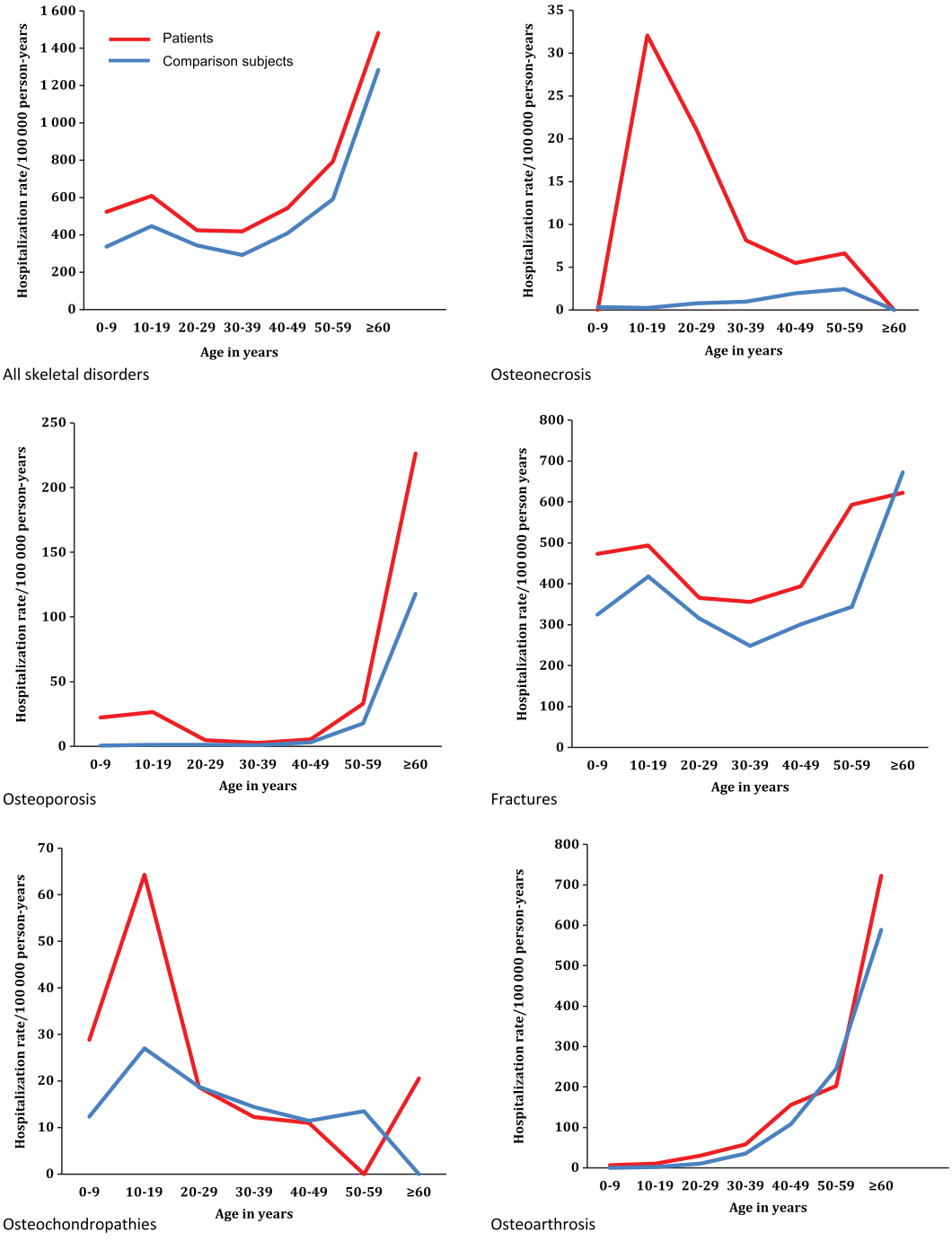

FIGURE 2 Observed and expected hospitalization rates per 100 000 person-years for any and for specific skeletal adverse event in 26 334 1-year survivors of childhood cancer in four Nordic countries, by age at first hospitalization for a skeletal adverse event

(not shown). Looking specifically at osteoporotic fractures (fractures of proximal humerus, distal radius, hip, distal femur, proximal tibia, pelvis and vertebrae; 382 observed cases) a higher risk was observed among survivors, RR 1.4 (1.3-1.6) but the risk patterns (sex, age, cancer type) were very similar to fractures in the general population (not shown). Compared to the general population, childhood cancer survivors were more likely to have recurrent fractures as well; the adjusted cause-specific hazard ratio for a second fracture was 1.28 (1.14-1.45).

Significant associations between cancer types and fractures were found for patients with leukemia (287 observed cases), CNS tumors (467), sympathetic nervous system tumors (76) and malignant bone tumors (133) (Table 3).

The excess fracture risk persisted until the age of 60 years (Table 4). As Figure 2 illustrates, the patterns of hospitalizations for fractures were very similar among survivors and comparison subjects, but the expected age-dependent rise in the hospitalization rate happened earlier among survivors.

TABLE 4 Hospitalization frequencies, hospitalization rates per 100 000 person-years, standardized hospitalization rate ratios and absolute excess risks per 100 000 person-years by skeletal adverse events and attained age

		Frequencies		Hospitalization rates per 100 000 person-years (95% CI)			
	Attained age (y)	Obs	Exp	Survivors	Comparison subjects	Rate ratios (95% CI)	Absolute excess risk[a] (95% CI)
All skeletal events	0-9	233	146.7	525 (461-596)	330 (281-338)	1.59 (1.37-1.84)	194 (123-265)
	10-19	623	456.3	610 (564-660)	447 (408-490)	1.37 (1.25-1.49)	163 (113-214)
	20-29	496	401.8	423 (388-462)	343 (311-378)	1.23 (1.12-1.36)	80 (41-120)
	30-39	288	198.5	419 (373-470)	289 (251-332)	1.45 (1.28-1.65)	130 (79-181)
	40-49	181	137.5	544 (470-629)	410 (347-485)	1.33 (1.13-1.56)	134 (50-217)
	50-59	106	79.1	786 (649-950)	586 (470-731)	1.34 (1.09-1.65)	200 (41-358)
	≥60	60	52.4	1484 (1152-1911)	1298 (990-1701)	1.14 (0.87-1.51)	186 (−216 to 588)
Osteonecrosis	0-9	0	0.2	0.0	0.4 (0.0-37.4)	NA	0
	10-19	34	0.0	32.1 (22.9-44.9)	0.0	NA	32 (21-43)
	20-29	26	0.9	21.1 (14.4-31.0)	0.7 (0.1-5.8)	30.5 (11.8-78.7)	20 (12-29)
	30-39	6	0.6	8.1 (3.7-18.1)	0.8 (0.1-10.2)	10.0 (2.8-36.2)	7 (1-14)
	40-49	2	0.6	5.5 (1.4-21.9)	1.7 (0.1-20.4)	3.2 (0.6-17.3)	3.8 (−4 to 12)
	50-59	1	0.4	6.6 (0.9-46.8)	2.6 (0.1-58.7)	2.5 (0.2-25.9)	4.0 (−10 to 17)
	≥60	0	0.0	0.0	0.0	NA	0
Osteoporosis	0-9	10	0.3	22.2 (12.0-41.3)	0.7 (0.0-22.4)	30.6 (6.3-148.9)	22 (8-35)
	10-19	28	1.6	26.4 (18.3-38.3)	1.5 (0.3-7.1)	17.7 (8.4-37.4)	25 (15-35)
	20-29	6	1.3	4.9 (2.2-10.8)	1.1 (0.2-5.9)	4.6 (1.6-13.4)	4 (0-8)
	30-39	2	0.9	2.7 (0.7-10.8)	1.3 (1.6-9.6)	2.2 (0.4-10.8)	2 (−2 to 5)
	40-49	2	1.0	5.5 (1.4–21.9)	2.7 (0.4-19.5)	2.1 (0.4-10.1)	3 (−5 to 11)
	50-59	5	2.8	33.0 (13.7-79.3)	18.5 (5.7-59.6)	1.8 (0.7-4.9)	15 (−16 to 45)
	≥60	11	6.2	226 (126-410)	128 (58.5-282)	1.8 (0.9-3.5)	98 (−43 to 239)
Fractures	0-9	211	140.9	474 (414-543)	317 (268-374)	1.5 (1.3-1.7)	158 (90-225)
	10-19	507	429.1	494 (453-539)	418 (380-460)	1.2 (1.1-1.3)	76 (30-122)
	20-29	431	372.2	365 (332-401)	315 (285-349)	1.2 (1.0-1.3)	50 (13-87)
	30-39	247	170.2	356 (314-403)	245 (211-285)	1.5 (1.3-1.7)	111 (64-157)
	40-49	133	99.7	394 (332-467)	295 (243-359)	1.3 (1.1-1.6)	99 (28-169)
	50-59	81	46.5	586 (471-729)	337 (252-449)	1.7 (1.4-2.2)	158 (90-225)
	≥60	27	29.9	623 (428-909)	691 (483-988)	0.9 (0.6-1.4)	−67 (−324 to 189)
Osteochondropathies	0-9	13	5.7	28.9 (16.8-49.7)	12.6 (5.5-28.7)	2.3 (1.2-4.4)	16 (0-33)
	10-19	68	28.7	64.4 (50.8-81.7)	27.2 (18.8-39.2)	2.4 (1.8-3.1)	37 (21-53)
	20-29	23	23.8	18.7 (12.4-28.2)	19.4 (13.0-28.9)	1.0 (0.6-1.5)	−1 (−9 to 8)
	30-39	9	10.3	12.3 (6.4-23.6)	14.0 (7.6-25.8)	0.9 (0.4-1.8)	−2 (−11 to 7)
	40-49	4	4.5	11.0 (4.1-29.4)	12.3 (4.9-31.1)	0.9 (0.3-2.5)	−1 (−13 to 10)
	50-59	0	2.2	0.0	14.5 (3.8-54.5)	NA	0
	≥60	1	0.0	20.6 (2.9-146)	0.0	NA	21 (−20 to 61)
Osteoarthrosis	0-9	3	0.0	6.7 (2.2-20.7)	0.0	NA	7 (−1 to 14)
	10-19	11	2.6	10.4 (5.8-18.7)	2.5 (0.7-8.3)	4.2 (1.9-9.1)	8 (2-14)
	20-29	37	12.6	30.0 (21.8-41.4)	10.2 (5.9-17.7)	2.9 (2.0-4.4)	20 (10-30)
	30-39	43	26.1	58.5 (43.4-78.8)	35.5 (24.2-52.1)	1.6 (1.2-2.3)	23 (5-41)
	40-49	56	39.7	155 (120-202)	110 (80.6-150)	1.4 (1.1-1.9)	45 (2-88)
	50-59	30	36.9	203 (142-290)	249 (180-344)	0.8 (0.6-1.2)	−46 (126 to 34)
	≥60	33	25.9	724 (514-1018)	567 (386-834)	1.3 (0.9-1.9)	157 (−107 to 420)

Abbreviations: Exp, expected; NA, not applicable due to no cases in either group; Obs, observed.

[a]Absolute excess risk per 100 000 person-years.

3.4 | Osteochondropathies and osteoarthrosis

The overall RR for osteochondropathies was 1.6 (1.3-1.9) and 1.5 (1.3-1.7) for osteoarthrosis (Table 2). A significant excess risk for osteochondropathies was only observed among survivors younger than 20 years and for osteoarthrosis among survivors younger than 50 years (Table 4). In both cohorts, the majority of hospitalizations for osteochondropathies occurred before 30 years of age, 103 of the 118 (87.3%) among survivors and 58 of 75 (77.3%) among the comparison subjects. Among all cancer diagnoses, leukemias (29 observed cases) sympathetic nervous system tumors (12), retinoblastomas, (6), renal tumors (9) and soft tissue sarcomas (10) were significantly associated with an increased risk of hospitalization for osteochondropathies (Table 3). A different pattern was observed for osteoarthrosis. Significant excess hospitalization risks for osteoarthrosis were found in survivors with leukemia (34 observed cases), lymphoma (36), CNS tumors (47), malignant bone tumors (17) and soft tissue sarcoma (25).

3.5 | Stratification by endocrine and neurological disorders

For childhood cancer survivors as compared to directly matched comparison subjects, the hazard ratio for hospitalizations for any of the skeletal adverse events was 1.34 (1.09-1.64) if a hospitalization for endocrine disorders occurred prior to the skeletal adverse event but 1.32 (1.26-1.39) if it did not occur. For patients that were also hospitalized for neurological disorders, the hazard ratio for a skeletal adverse event was 1.40 (1.22-1.61) compared to 1.28 (1.22-1.35) if a hospitalization for a neurological disorder did not occur. We looked specifically at each group of skeletal adverse events but for some of the subgroups the risk estimates were underpowered due to low number of events (Table S3).

3.6 | Sensitivity analyses

Sensitivity analyses conducted to address several issues regarding the study design and interpretations are presented in Table S4. In summary, when we (a) *excluded* cases with malignant bone tumors or (b) *included only*: 5-year survivors, cases diagnosed with cancer less than 1 year prior to the start of NPR or events coded by ICD-9 and ICD-10, it resulted in fewer events but without a major effect on the risk estimates. When we analyzed separately events recorded as outpatient visits (Denmark and Sweden), it yielded lower risk estimates but overall, they were still significantly higher compared to the matched comparison group, RR 1.2 (1.2-1.3).

4 | DISCUSSION

In this large population-based retrospective cohort study, we observed an excess risk of hospitalization for skeletal adverse events among 26 334 1-year survivors of childhood cancer compared to 127 531 age- and sex-matched population comparison subjects. To our knowledge, this is the first study describing the long-term risk and patterns of skeletal adverse events in survivors across the spectrum of childhood cancer.

The long follow-up time and the population-based design allowed us to capture events occurring both during treatment and over a long period after completion of therapy. In general, the hospitalization risk was higher in the survivor cohort up to the age of 60 years. However, we found a distinct age pattern between the different types of skeletal adverse events. For osteochondropathies the risk was significantly higher among survivors <20 years of age, for osteoporosis <30 years of age, for osteonecrosis <40 years of age, for osteoarthrosis <50 years of age and for fractures among survivors <60 years of age. Apart from the increased prevalence of skeletal morbidity in the aging comparison cohort, the shorter lifespan of the survivor cohort could be one of the explanations for the lack of differences between the older age groups. Survivorship bias is another possible contributing factor, since there might be a selection of the healthiest individuals among the oldest survivors.[26] Finally, for many cancer types, especially the ones where survival was very poor before the 1970s such as leukemia, the number of survivors older than 40 years was low. This made the estimation of the long-term risk more difficult for some of the subgroups. Since the overall survival in childhood cancer has improved markedly, especially for hematological malignancies, the number of aging survivors is rising. Therefore, with a longer follow-up time, we could have seen a different pattern in the older population and repeated follow-up investigations are warranted.

In the general population, osteonecrosis, osteoporosis and osteoarthrosis are very uncommon conditions in children and young adults. For that reason, only a few events among childhood cancer survivors may result in high and statistically significant risk estimates. This needs to be taken into account when interpreting the results of our study.

4.1 | Osteonecrosis

Although osteonecrosis is not life-threatening, it is a serious complication that may have a large impact on the quality of life.[10] In cases where osteonecrosis causes a collapse of the joint surface, joint-replacement surgery may be indicated to alleviate pain and restore joint function.[27] Multiple studies have shown an increased risk of osteonecrosis among children and adolescents with hematological malignancies, particularly if ≥10 years of age at cancer diagnosis.[27-30] In the Childhood Cancer Survivor Study (CCSS), the estimated RR for osteonecrosis was 6.2 (95% CI 2.3-17.2) among 5-year childhood cancer survivors diagnosed between 1970 and 1986 compared to a random sample of siblings.[10] In our study the RR was 14.8 (7.9-27.6) for 5-year survivors and 25.9 (15.0-44.5) for 1-year survivors. More intensive therapy in later years (>80% of all hospitalizations for osteonecrosis in our study occurred among patients diagnosed >1990), improved detection techniques and differences in study design may all contribute to the difference between these studies.

Both in our study and the CCSS study, the risk of osteonecrosis was highest among survivors of hematological malignancies and survivors ≥10 years at diagnosis but although the risk was highest the first years after diagnosis, the excess risk continued until the age of 40 in our study. Interestingly, we also found an excess risk among patients with nonhematological malignancies. This is a very rare finding and poorly described in the literature. The pathogenic mechanisms for nonhematologic malignancies are likely more heterogeneous (radiation therapy, fractures etc.) than for hematological malignancies.

The main iatrogenic risk factor for osteonecrosis among patients with hematological malignancies is high glucocorticoid exposure.[31] Attempts to reduce the frequency of osteonecrosis among patients with ALL without compromising survival outcomes have been successful but future studies should focus on developing treatment strategies that minimize the duration and the total dose of glucocorticoids, especially for the most vulnerable risk groups.[32]

An excess risk of osteonecrosis has been reported among female patients with ALL, especially if ≥10 years at cancer diagnosis but this association has not been consistent in all studies.[29,31,33,34] In our study, the RR for osteonecrosis was highest for the age group 10-19 years at cancer diagnosis but the risk was similar between male and female survivors, both overall and for survivors of hematological malignancies specifically.

Osteonecrosis was not available as a diagnostic code in the ICD-7 or ICD-8 classification systems (1955-1986) therefore it can be argued that our study design underestimated the incidence of osteonecrosis. Furthermore, it is possible that some of the osteonecrosis events were coded as osteochondropathies before ICD-9 and ICD-10. In ICD-10, a more detailed coding with regard to the localization of osteonecrosis was introduced. This will facilitate future studies on osteonecrosis using register data.

4.2 | Osteoporosis and fractures

In children and adolescents, the mineralization of the growing skeleton is very active and negative effects on this process may lead to BMD deficits and subsequent fractures. Osteopenia and osteoporosis have been described in patients with lymphoid malignancies, CNS tumors, Wilms' tumors, sarcomas and neuroblastoma.[35-42] In our study, the risk of osteoporosis was particularly high among survivors of leukemia but the excess risk extended to other groups of cancer as well, both CNS and solid tumors but not for lymphomas.

Low BMD is generally associated with an increased risk of fractures; therefore, early detection of low BMD and preventive measures are of importance to lower the fracture risk and fracture-associated complications. We observed a significantly increased risk of hospitalization for osteoporosis in the survivor cohort up to the age of 30 years. Since recovery from bone loss during cancer treatment may take several years, it is not surprising that the risk of osteoporosis was highest among the younger survivors. Van Atteveld et al developed a prediction model for low (*Z*-score below −1.0) and very low (*Z*-score below −2.0) BMD in adult survivors of childhood cancer.[43] As in our study, the risk was highest among the younger survivors but decreased with attained age. However, the model was not designed to predict the risk after the age of 40 years.

In contrast to the other skeletal adverse events, the RR for osteoporosis among male survivors was higher than among female survivors. The association between male sex and the risk of BMD deficits has been described in survivors of childhood ALL and could be explained by different biological responses to the cancer treatment and the fact that osteoporosis is very rare among younger males in the general population.[37,44] In the prediction model developed by Van Atteveld et al, male sex was a predictor for both low and very low BMD.[43]

The lifetime pattern we observed for fractures reflects the pattern in the general population, where fractures are more common among males than females during childhood and early adulthood but become more common among females at older ages.[45] However, survivors were more likely to be hospitalized prior to the expected age-related rise in incidence of fractures. In our study, the RR for fractures was higher in female survivors but the RR for the age groups 0-9 years and 10-19 years at cancer diagnosis were very similar. In the Childhood Cancer Survivor Study, an increased risk of fractures was only observed in females >50 years, whereas male survivors were at lower risk compared to their siblings.[13]

In concordance with previous reports, survivors of leukemia were at a significantly higher risk for both osteoporosis and fractures. Direct effects of leukemic cells on the bone tissue and the high exposure to glucocorticoids are likely the most important risk factors. However, subgroups of leukemia survivors have additional risk factors such as allogeneic HSCT and/or craniospinal irradiation that render them particularly susceptible to skeletal adverse events. Since we did not have data on HSCT or radiotherapy, we were unable to take into account the impact of these therapeutic interventions.

We found both a significantly increased risk for osteoporosis and fractures among survivors of CNS tumors. Survivors of brain tumors commonly have hormone deficiencies (growth hormone deficiency, hypogonadism), especially if exposed to cranial irradiation, which may lead to secondary osteoporosis and fractures. However, we did not find a significant modifying effect of hospitalizations for endocrinological and neurological disorders on the risk of skeletal adverse events in general, nor for osteoporosis or fractures. The effect of these factors may be mitigated by hormone substitution that most childhood cancer survivors with endocrinopathies need. Due to lack of statistical power, we could not perform stratified analyses by specific endocrinopathies such as in patients with gonadal insufficiencies. For survivors of CNS tumors, factors other than bone fragility could contribute to the fracture risk, such as increased risk of falls due to neurological deficits, visual impairment and seizures.

4.3 | Osteochondropathies and osteoarthrosis

Osteochondropathies and osteoarthrosis have not been described previously in childhood cancer survivors. Interestingly, we found an increased hospitalization risk for both of these conditions in the

survivor cohort. The age pattern of hospitalizations for osteochondropathies shows that the risk is highest during the age period when the activity is highest in the growth plates (10-19 years). Hospitalizations for osteoarthrosis were more common among survivors younger than 50 years of age. This could be caused by premature aging of the articular cartilage.

4.4 | Study strengths and limitations

The population demographics, health care resources and childhood cancer epidemiology are very similar in the Nordic countries. Along with the unique personal identification number, this enables researchers to create large homogeneous cohorts and track patients through different population and quality registries over the lifetime of the patient.[14] Previous studies using data from the ALiCCS cohort have shown that childhood cancer survivors are at higher risk for numerous adverse events that need continuous medical attention.[46-50] These studies have also proved that using hospital registries as the source of study endpoints is comparable to other sources such as questionnaires and single-center registries/cohorts.[47] It is possible that some of the study outcomes would have been better captured using other methods as we only included skeletal adverse events resulting in hospital admissions, possibly underestimating the number of events. However, less serious events will have been underrecorded equally in both cohorts, so differential bias is unlikely to be an issue. Compared to the CCSS, our study design is less affected by information bias since our endpoints are medically verified and the registration is mandatory.[16] To address the issue of possible surveillance/hospitalization bias, we conducted a sensitivity analysis only analyzing data from the outpatient registries in Denmark and Sweden. The risk estimates were lower for all types of skeletal diseases suggesting that surveillance/hospitalization bias might have influenced the results in the main analysis.

A major limitation of our study was the lack of treatment data. Although a specific cancer diagnosis and the associated treatment protocols may to some degree serve as an indirect indicator of the treatment given, the lack of data on specific therapeutic interventions, cancer staging and remission status limited our ability to conduct risk-group analyses and draw conclusions on causal inferences. More detailed patient information is available in various quality registries such as the Nordic Society of Paediatric Haematology and Oncology (NOPHO) registry and could be accessible by data linkage methods.

One might ask whether the interpretations of our results are applicable to the current clinical practice since our estimations are based on a treatment era extending over several decades and thus may not reflect the modern landscape of pediatric oncology. However, over recent decades only relatively minimal changes have been made in the backbone treatment for the majority of childhood cancer subtypes, whereas in some cases the treatment has intensified. Attempts to improve survival by increasing treatment intensity have often failed and caused more toxicity. These efforts have added further to the burden of expected late morbidity among subgroups of patients.[51,52] Some hope is placed on newer, more targeted therapy, but the development of such novel therapies will also introduce a new spectrum of toxicities and we have sparse knowledge at this point how these will affect the future health of childhood cancer survivors.[53]

5 | CONCLUSIONS

In our study, childhood cancer survivors were more likely to be hospitalized for skeletal adverse events than matched population comparison subjects. Although the risk of adverse events was highest in the time period close to the cancer treatment, the excess risk continued for decades. Therefore, assessment of skeletal health is important both during treatment and in the long-term follow-up. Future studies should focus on treatment modifications and preventive strategies in high-risk groups and the development of evidence-based follow-up guidelines.

ACKNOWLEDGEMENTS

This project was supported by a grant from the Swedish Childhood Cancer Foundation, Barncancerfonden (PR2011-0047). The funding sources had no involvement in the content or preparation of the article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The ALiCCS study group welcomes collaboration with other researchers in using our registry data. Study protocols can be planned in collaboration with us, and the study material can be analyzed accordingly at the Danish Cancer Society Research Center in Copenhagen, Denmark. Further information about the present study or regarding collaborative ALiCCS projects are available from Professor Jeanette Falck Winther, MD, DMSc (jeanette@cancer.dk).

ETHICS STATEMENT

This retrospective, register-based cohort study is part of the collaborative study Adult Life after Childhood Cancer in Scandinavia (ALiCCS) (www.aliccs.org). No consent was required for our study. Our study was approved by the national ethical review authorities, national departments for health and welfare, or data protection authorities in the respective countries.

ORCID

Trausti Oskarsson https://orcid.org/0000-0002-2494-5514
Anna Sällfors Holmqvist https://orcid.org/0000-0002-3756-8148

REFERENCES

1. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5 – a population-based study. *Lancet Oncol*. 2014;15(1):35-47.

2. Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. *J Natl Cancer Inst*. 2017;109(9):djx030.
3. Phillips SM, Padgett LS, Leisenring WM, et al. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. *Cancer Epidemiol Biomarkers Prev*. 2015;24(4):653-663.
4. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. 2013;309(22):2371-2381.
5. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet*. 2017;390(10112):2569-2582.
6. Hogler W, Wehl G, van Staa T, Meister B, Klein-Franke A, Kropshofer G. Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: comparison of fracture risk with the General Practice Research Database. *Pediatr Blood Cancer*. 2007;48(1):21-27.
7. Schmiegelow K, Attarbaschi A, Barzilai S, et al. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. *Lancet Oncol*. 2016;17(6):e231-e239.
8. Niinimaki RA, Harila-Saari AH, Jartti AE, et al. Osteonecrosis in children treated for lymphoma or solid tumors. *J Pediatr Hematol Oncol*. 2008;30(11):798-802.
9. Niinimaki TT, Ohtonen P, Harila-Saari AH, Niinimaki RA. Young patients with hematologic and lymphatic malignancies have an increased risk of hip and knee arthroplasty. *Acta Oncol*. 2016;55(5):567-571.
10. Kadan-Lottick NS, Dinu I, Wasilewski-Masker K, et al. Osteonecrosis in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2008;26(18):3038-3045.
11. Henry YM, Fatayerji D, Eastell R. Attainment of peak bone mass at the lumbar spine, femoral neck and radius in men and women: relative contributions of bone size and volumetric bone mineral density. *Osteoporos Int*. 2004;15(4):263-273.
12. Cummings EA, Ma J, Fernandez CV, et al. Incident vertebral fractures in children with leukemia during the four years following diagnosis. *J Clin Endocrinol Metab*. 2015;100(9):3408-3417.
13. Wilson CL, Dilley K, Ness KK, et al. Fractures among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2012;118(23):5920-5928.
14. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: possibilities and pitfalls when combining Nordic registry data. *Scand J Public Health*. 2017;45(17_suppl):14-19.
15. Pukkala E, Engholm G, Højsgaard Schmidt LK, et al. Nordic cancer registries – an overview of their procedures and data comparability. *Acta Oncol*. 2018;57(4):440-455.
16. Asdahl PH, Winther JF, Bonnesen TG, et al. The Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: design and characteristics. *Pediatr Blood Cancer*. 2015;62(12):2204-2210.
17. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103(7):1457-1467.
18. Fieller EC. Some problems in interval estimation. *J R Stat Soc Series B Stat Methodol*. 1954;16(2):175-185.
19. Carstensen B, Plummer M, Laara E, Hills MD. Epi: a package for statistical analysis in epidemiology. 2020, R package version 2.43.
20. Arthur A, Martin S, Jan B. Empirical transition matrix of multi-state models: the etm package. *J Stat Softw*. 2011;38(4):1-15.
21. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. 1st ed. New York: Springer-Verlag; 2016.
22. Holst KK, Scheike TH, Hjelmborg JB. The liability threshold model for censored twin data. *Comput Stat Data Anal*. 2016;93:324-335.
23. Scheike TH, Holst KK, Hjelmborg JB. Estimating heritability for cause specific mortality based on twin studies. *Lifetime Data Anal*. 2014;20(2):210-233.
24. Therneau TM. A package for survival analysis in R. 2000, R package version 3.1-12.
25. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. 1st ed. New York: Springer; 2000.
26. Asdahl PH, Ojha RP, Winther JF, et al. Measuring childhood cancer late effects: evidence of a healthy survivor effect. *Eur J Epidemiol*. 2017;32(12):1089-1096.
27. Niinimaki R, Hansen LM, Niinimaki T, et al. Incidence of severe osteonecrosis requiring total joint arthroplasty in children and young adults treated for leukemia or lymphoma: a nationwide, register-based study in Finland and Denmark. *J Adolesc Young Adult Oncol*. 2013;2(4):138-144.
28. te Winkel ML, Pieters R, Hop WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. *J Clin Oncol*. 2011;29(31):4143-4150.
29. Burger B, Beier R, Zimmermann M, Beck JD, Reiter A, Schrappe M. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)—experiences from trial ALL-BFM 95. *Pediatr Blood Cancer*. 2005;44(3):220-225.
30. Kuhlen M, Bader P, Sauer M, et al. Low incidence of symptomatic osteonecrosis after allogeneic HSCT in children with high-risk or relapsed ALL – results of the ALL-SCT 2003 trial. *Br J Haematol*. 2018;183(1):104-109.
31. Mattano LA, Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *J Clin Oncol*. 2000;18(18):3262-3272.
32. Mattano LA, Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. *Lancet Oncol*. 2012;13(9):906-915.
33. Mogensen SS, Harila-Saari A, Mäkitie O, et al. Comparing osteonecrosis clinical phenotype, timing, and risk factors in children and young adults treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2018;65(10):e27300.
34. Amin NL, Kinsey S, Feltbower R, et al. Analysis of long-term outcomes, management and prevalence of osteonecrosis in UKALL 2003: 3.5% of adolescents and young Aadults over 10 years of age with acute lymphoblastic leukaemia required hip replacement. *Blood*. 2015;126(23):2083.
35. Sala A, Talsma D, Webber C, Posgate S, Atkinson S, Barr R. Bone mineral status after treatment of malignant lymphoma in childhood and adolescence. *Eur J Cancer Care*. 2007;16(4):373-379.
36. Arikoski P, Komulainen J, Voutilainen R, et al. Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 1998;20(3):234-240.
37. Kaste S, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. *Leukemia*. 2001;15(5):728-734.
38. Barr RD, Simpson T, Webber CE, et al. Osteopenia in children surviving brain tumours. *Eur J Cancer*. 1998;34(6):873-877.
39. Othman F, Guo CY, Webber C, Atkinson SA, Barr RD. Osteopenia in survivors of Wilms tumor. *Int J Oncol*. 2002;20(4):827-833.
40. Pirker-Fruhauf UM, Friesenbichler J, Urban EC, Obermayer-Pietsch B, Leithner A. Osteoporosis in children and young adults: a late effect after chemotherapy for bone sarcoma. *Clin Orthop Relat Res*. 2012;470(10):2874-2885.

41. Kaste SC, Ahn H, Liu T, et al. Bone mineral density deficits in pediatric patients treated for sarcoma. *Pediatr Blood Cancer*. 2008;50(5):1032-1038.
42. Al-Tonbary YA, El-Ziny MA, Elsharkawy AA, El-Hawary AK, El-Ashry R, Fouda AE. Bone mineral density in newly diagnosed children with neuroblastoma. *Pediatr Blood Cancer*. 2011;56(2):202-205.
43. van Atteveld JE, Pluijm SMF, Ness KK, et al. Prediction of low and very low bone mineral density among adult survivors of childhood cancer. *J Clin Oncol*. 2019;37(25):2217-2225.
44. Tillmann V, Darlington ASE, Eiser C, Bishop NJ, Davies HA. Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. *J Bone Miner Res*. 2002;17(6):1073-1080.
45. Singer B, McLauchlan G, Robinson C, Christie J. Epidemiology of fractures in 15 000 adults: the influence of age and gender. *J Bone Joint Surg*. 1998;80:243-248.
46. de Fine LS, Winther JF, Gudmundsdottir T, et al. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. *Lancet*. 2014;383 (9933):1981-1989.
47. Gudmundsdottir T, Winther JF, de Fine LS, et al. Cardiovascular disease in Adult Life after Childhood Cancer in Scandinavia: a population-based cohort study of 32,308 one-year survivors. *Int J Cancer*. 2015;137(5):1176-1186.
48. Kenborg L, Winther JF, Linnet KM, et al. Neurologic disorders in 4,858 survivors of central nervous system tumors in childhood – an Adult Life after Cancer in Scandinavia (ALiCCS) study. *Neuro Oncol*. 2018;21(1):125-136.
49. Bonnesen TG, Winther JF, Asdahl PH, et al. Long-term risk of renal and urinary tract diseases in childhood cancer survivors: a population-based cohort study. *Eur J Cancer*. 2016;64:52-61.
50. Asdahl PH, Winther JF, Bonnesen TG, et al. Gastrointestinal and liver disease in Adult Life After Childhood Cancer in Scandinavia: a population-based cohort study. *Int J Cancer*. 2016;139(7):1501-1511.
51. Bisogno G, Jenney M, Bergeron C, et al. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet Oncol*. 2018;19(8):1061-1071.
52. Albertsen BK, Grell K, Abrahamsson J, et al. Intermittent versus continuous PEG-asparaginase to reduce asparaginase-associated toxicities: a NOPHO ALL2008 randomized study. *J Clin Oncol*. 2019;37 (19):1638-1646.
53. Filippini DM, Gatti M, Di Martino V, et al. Bone fracture as a novel immune-related adverse event with immune checkpoint inhibitors: case series and large-scale pharmacovigilance analysis. *Int J Cancer*. 2021;149:675-683. https://doi.org/10.1002/ijc.33592

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Oskarsson T, Duun-Henriksen AK, Bautz A, et al. Skeletal adverse events in childhood cancer survivors: An Adult Life after Childhood Cancer in Scandinavia cohort study. *Int. J. Cancer*. 2021;149(11):1863-1876. https://doi.org/10.1002/ijc.33741