Late-onset epilepsy in survivors of childhood cancer outside the central nervous system: a study within the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study

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Abstract

Although epilepsy has been reported in survivors of childhood cancer outside the central nervous system (CNS), little evidence exists on risk factors for this late complication. Our study aimed to identify risk factors of late-onset epilepsy.

A case-cohort study was conducted within 5-year survivors of non-CNS childhood cancer from the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study, including 81 survivors diagnosed with late-onset epilepsy and a sub-cohort of 231 randomly selected survivors. Detailed treatment information was obtained from medical records. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were calculated to assess the association between treatment-related factors and epilepsy.

Survivors of acute lymphoblastic leukemia (ALL) and other types of leukemia exhibited significantly higher IRRs for epilepsy compared to survivors of solid tumors (ALL: 4.4, 95% CI 2.2–8.5; other leukemia: 14.1, 95% CI 3.4–57.9). Relapse was associated with an increased IRR of epilepsy (3.5, 95% CI 1.5–8.6). Specifically, survivors of relapsed leukemia demonstrated a high IRR for epilepsy (11.4, 95% CI 3.5 – 37.3) compared to non-relapsed survivors. No association was found between epilepsy and bone marrow transplantation, radiotherapy, total body irradiation, or treatment with specific chemotherapeutic agents. Finally, survivors diagnosed after 1990 had a decreased IRR of epilepsy (0.4, 95% CI 0.2 – 0.8) compared to survivors diagnosed in 1970 – 1979.

Conclusion: Relapsed leukemia survivors were at increased risk for late-onset epilepsy.

Introduction

With the introduction of more effective treatment protocols for childhood cancer, the survival rates have increased and prompted focus on long-term consequences of cancer treatment [1]. These encompass a wide range of adverse late effects, ranging from transient to severe, chronic, and fatal [2,3,4,5].

In previous Adult Life after Childhood Cancer in Childhood (ALiCCS) study examining neurological late complications among 5-year survivors of non-CNS tumors in childhood, epilepsy was identified as the most common complication leading to hospitalization in survivors. We observed a significantly increased relative hospitalization rate ratio (HRR) of 2.9 (95% confidence interval (CI) 2.5–3.4) for epilepsy among the survivors, and the risk was increased for survivors in eight out of twelve types of childhood cancer [6]. An increased risk for epilepsy among survivors has also recently been showed in the French Childhood Cancer Survivor Study (FCCSS), with a HRR of 5.1 (95% CI 4.4–5.7) for all survivors, except leukemia, which were not included in the cohort [7]. Other studies have shown that seizures are relatively common during acute lymphoblastic leukemia (ALL) treatment [8], but seizure or epilepsy may also develop as a late complication years after treatment cessation [9].

Brain tumors and brain metastases are known risk factors for epilepsy [10]; however, the association between specific treatment-related factors for childhood cancer and the development of late-onset epilepsy is poorly understood. Chemotherapy, particularly methotrexate, has been associated with seizures during treatment [11], but radiation-induced brain injury and comorbid conditions, such as cerebrovascular disease, may also increase the risk of epilepsy later in life [12]. Given the significant impact of epilepsy on quality of life—including seizures, psychiatric comorbidities, cognitive impairments, and medication-related adverse effects [13] — it is crucial to identify childhood cancer survivors at risk for late-onset epilepsy. Therefore, we conducted a case-cohort study within the ALiCCS study to examine the association between treatment exposures and the risk of late-onset epilepsy in 5-year survivors of a non-CNS cancer in childhood.

Materials and methods

Cases with epilepsy and sub-cohort

The study population was identified within the ALiCCS cohort, which includes all childhood cancer patients diagnosed according to the International Classification of Childhood Cancer, before the age of 20 years, since the start of the cancer registries until 2008, in Denmark, Finland, Iceland, Norway, and Sweden [14]. For this case-cohort study, we used the study population from our previous study on neurological disorders in non-CNS childhood cancer survivors to identify cases with epilepsy [6]. Due to differences in tumor location and risk of epilepsy, we chose to only include survivors of non-CNS tumors in this study [6, 15].

The inclusion criteria encompassed 5-year survivors diagnosed between 1970 and 2008 (see flow chart in Fig. 1). Due to the lack of epilepsy data for survivors in Norway and the absence of diagnosed cases in Iceland, only survivors from Denmark, Finland, and Sweden were eligible for inclusion in our case group of survivors with epilepsy (n = 13,943). A sub-cohort of 5-year survivors was randomly selected from the ALiCCS cohort to be used in several case cohort studies (n = 600) [16]. The selection was based on number of contributing person-years in each country, ensuring that the sub-cohort represented the entire ALiCCS cohort with respect to cancer type and treatment.

Among the 13,943 five-year survivors, we identified 174 survivors (Denmark, n = 51; Finland, n = 56; Sweden, n = 67), who at least 5 years after their childhood cancer diagnosis had been discharged with a primary or supplementary diagnosis of epilepsy (ICD-7 353; ICD-8 345; ICD-9 345; ICD-10 G40 and G41), limited to those diagnosed during inpatient admissions. Medical records were collected to abstract information on cancer predisposition syndrome, radiotherapy (including total body irradiation (TBI), which for Nordic patients include a fractioned dose of 12 Gy), surgery, chemotherapy, bone marrow transplantation (BMT), and relapse for both cases with epilepsy and sub-cohort members. A standardized abstraction form was developed by medical doctors and epidemiologists in the ALiCCS team to ensure consistent data collection and uniformity in the description of information across all countries. The information was abstracted by trained medical students and doctors and subsequently entered into a centralized database.

Exclusion of survivors

We excluded 30 survivors from Iceland and Norway in the sub-cohort. We also had to exclude Swedish survivors from other counties than Skåne (cases 54; sub-cohort 225) as we were not able to collect their medical records. Additionally, we excluded 25 cases and 30 sub-cohort survivors with inaccessible medical records, as well as 78 sub-cohort survivors diagnosed with a CNS tumor. We also excluded three cases and six survivors in sub-cohort who just turned 20 years at diagnosis or had a cancer predisposition syndrome. Finally, we excluded 11 cases who had epilepsy before reaching 5-year survival or after end of study (Fig. 1). The final case group comprised of 81 survivors diagnosed with epilepsy at least 5 years after their childhood cancer diagnosis, while the sub-cohort included 231 survivors. As the survivors of the sub-cohort were selected randomly from the large ALiCCS cohort of all survivors, the sub-cohort included < 3 survivors who also developed epilepsy [17].

Information on cancer treatment

Data on chemotherapy, including doses, were abstracted from medical records. For this study, we included information on antimetabolites, alkylating and antimitotic agents, including the following specific chemotherapeutic agents and doses: methotrexate (MTX, administered intravenously (IV) or intrathecally (IT), high-dose MTX (≥ 5 g/m2; ≥ 10 g/m2)); cytarabine (IV, IT), vincristine (IV), and cyclophosphamide (IV). The specific chemotherapeutic agents were primarily considered binary outcomes. When possible, cumulative doses were calculated, in milligram/m2 (mg/m2) or unit/m2. Cumulative doses were divided into an upper and a lower group separated by the median dose specific to the agent. Finally, we also included information on radiotherapy (including TBI), bone marrow transplantation, and relapse.

Statistical analyses

Time at risk started 5 years after cancer diagnosis and ended on date of hospitalization for epilepsy, death, emigration, secondary primary cancer, or end of follow-up (Sweden, 31 December 2009; Denmark, 10 November 2010; Finland, 31 December 2012), whichever came first.

All analyses were conducted according to the principles for case-cohort studies described by Prentice [18] and Barlow et al. [19]. As cases are overrepresented compared to the original cohort from which the sub-cohort and cases are drawn, we used a weighted Cox proportional hazards model to ensure unbiased effect estimates [20]. The modified Cox proportional hazards model used age in years as the underlying time scale to evaluate the association between different patient- and treatment related characteristics and late-onset epilepsy. The results were expressed as incidence rate ratios (IRRs), which represent the relative rate of epilepsy occurrence in childhood cancer survivors exposed to specific treatment-related risk factors compared to those unexposed. The following variables were considered binary variables: sex (female, male), relapse (0, ≥ 1), radiotherapy (no, yes), BMT (no, yes), TBI (no, yes), and chemotherapy (no, yes). We further examined various treatment combinations (surgery only; chemotherapy only; radiotherapy only, and chemotherapy + radiotherapy) as well as combinations of relapse and cancer type (no relapse, relapse following other cancer type than leukemia, and relapse following leukemia). Finally, the associations between late-onset epilepsy and specific chemotherapeutic groups (antimetabolites, alkylating agents, and antimitotic drugs) and agents (MTX (IT), cytarabine (IT), cyclophosphamide (IV), vincristine, high-dose MTX (IV), and high-dose cytarabine (IV)) were evaluated.

The analyses were adjusted for (1) country (Denmark, Finland, Sweden) and (2) country, sex, year of diagnosis (1970–1989, 1990–2008), and type of cancer (leukemia, other). We also conducted a sub-analysis including only survivors of leukemia. All analyses were based on the Wald's test of the Cox regression parameter, and two-sided 95% confidence intervals (CIs) were calculated for incidence rate ratios (IRRs). Due to varying selection probabilities across countries, influenced by differences in population sizes and data availability periods, we applied sampling weights inversely proportional to these probabilities [21]. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc.).

Results

Table 1 displays demographic and clinical characteristics of survivors of non-CNS childhood cancer with late-onset epilepsy and sub-cohort members. The median time from study entry 5 years after cancer diagnosis to the first epilepsy diagnosis was 10.6 years (IQR 7.5–16.3). Most survivors with late-onset epilepsy had a history of leukemia (n = 49, 60%), with the predominant diagnosis being ALL, whereas survivors with leukemia accounted for 30% in the sub-cohort. More survivors with epilepsy were diagnosed before 1990 (n = 52, 64%) vs. 80 survivors (35%) in the sub-cohort. Finally, compared to survivors in the sub-cohort, a larger proportion of survivors with epilepsy had been treated with radiotherapy (48% vs. 38%), chemotherapy (82% vs. 68%), and had experienced at least one relapse (17% vs. 8%).

The IRR of epilepsy was decreased for survivors diagnosed after 1990 (0.4, 95% CI 0.2 – 0.8) compared to survivors diagnosed in 1970 – 1979. An increased IRR of epilepsy was observed among survivors of ALL and acute myeloid leukemia (AML)/other leukemia (ALL: 4.4, 95% CI 2.2–8.5; AML/other leukemia: 14.1, 95% CI 3.4–57.9) compared to survivors of non-CNS solid tumors (Table 2). Survivors of lymphomas did not have an increased IRR of epilepsy (1.4, 95% CI 0.5–4.0). In addition, survivors who experienced a relapse had an elevated rate of epilepsy (IRR 3.5, 95% CI 1.5–8.6). When examining relapse in combination with cancer type, survivors who experienced a relapse of leukemia exhibited an increased IRR for epilepsy (11.4, 95% CI 3.5 – 37.3) in comparison to survivors who did not experience a relapse. Survivors, who experienced a relapse of other cancer types, did not demonstrate an elevated rate of epilepsy (IRR 1.1, 95% CI 0.3–4.2).

Neither BMT (IRR 2.3, 95% CI 0.7–7.0) nor TBI (IRR 1.5, 95% CI 0.5–6.5) were significantly associated with an increased rate of epilepsy. Any treatment with chemotherapy was associated with epilepsy (IRR 2.4, 95% CI 1.3–4.7), but the IRR decreased to 1.1 (95% CI 0.5–2.5) after further adjustment for cancer type. Both treatment with MTX IT (IRR 2.7, 95% CI 1.6 – 4.7) and doses ≥ 155 mg/m2 (IRR 6.4, 95% CI 3.1–13.3) and treatment with vincristine and doses > 19.0 mg/m2 were associated with epilepsy before adjustment for cancer type but showed no association with epilepsy after adjustment. None of the other chemotherapeutic agents increased the rate of epilepsy.

In the sub-analysis of leukemia survivors, we only observed an increased rate of epilepsy in survivors with a relapse (IRR 4.7, 95% CI 1.9 – 31.2) compared to non-relapsed leukemia survivors (Table 3). Finally, leukemia survivors diagnosed in 1990 or later had a decreased IRR of epilepsy (0.4, 95% CI 0.2 – 0.9) compared to those diagnosed before 1990.

Discussion

To the best of our knowledge, this is the first study to assess the association between clinical and treatment-related risk factors and the risk of developing late-onset epilepsy in survivors of non-CNS childhood cancer. We found that leukemia survivors who experienced a relapse had an increased rate of epilepsy but did not identify any individual treatment-related factors associated with epilepsy after adjustment for cancer type. These findings align with the Childhood Cancer Survivor Study (CCSS), which reported a higher risk of late seizure disorders in ALL survivors (RR, 4.6; P < 0.001) compared to their siblings. When they evaluated treatment-related risk factors, only patients who experienced a relapse had an elevated risk (RR, 2.6; P = 0.002). Cranial irradiation, high-dose IV MTX (defined as ≥ 5000 mg/m2), or BMT did not show any association with late-onset seizures [9], although treating a relapse of ALL necessitates highly intensive therapy. In many instances, patients with relapsed ALL undergo BMT, typically preceded by conditioning treatment comprising chemotherapy combined with TBI. Especially busulfan-containing regimens are associated with neurotoxicity and risk of acute seizures [22], but neither the CCSS nor our study found any association between BMT and epilepsy. MTX-related central neurotoxicity, including seizures, is recognized as a common acute complication during treatment [23]. However, it has also been proposed that MTX may increase the risk of developing epilepsy as a late complication. Despite this, our findings did not support MTX as a risk factor for epilepsy, consistent with the results from the CCSS. The burden of CNS disease at initial diagnosis of ALL has shown to increase the risk of relapse, including isolated CNS relapse [24], which could explain the higher risk for epilepsy seen in relapsed leukemia survivors. However, CNS status at diagnosis was not available in our study and was also not assessed as a separate risk factor in the CCSS study.

A few studies have assessed the risk of epilepsy among survivors of cancer located outside the CNS. In our previous large register-based cohort study, we found the highest increased risk of epilepsy among leukemia survivors (RR 5.5, 95% CI 4.4–6.8). Additionally, elevated risks were observed among survivors of hepatic tumors, germ cell neoplasms, neuroblastoma, non-Hodgkin lymphoma, soft tissue sarcomas, carcinomas, and other cancers, with HRRs ranging from 1.7 to 4.4 [6]. These estimates are comparable to the epilepsy risk observed among survivors of neuroblastoma, sarcomas, and other cancer types in the FCCSS, where HRRs ranged from 1.8 to 2.8 [7]. The findings underscore that epilepsy is a significant late complication among the survivors, potentially having a profound impact on their quality of life. In a separate study from the CCSS examining the risk of adverse medical conditions in survivors of rhabdomyosarcoma, an increased risk of seizures was reported among 5-year survivors (RR 2.3, 95% CI 1.2–4.4) compared to siblings. However, only cranial radiotherapy was examined as a risk factor, which was not associated with repeated seizures (RR 1.0, 95% CI 0.2–4.6) when compared with survivors with no cranial irradiation [25]. Also, in a large study from St Jude, Mulrooney et al. reported that seizures accounted for a significant portion of the neurological burden reported in ALL survivors in early treatment protocols (1962–1979). Further, Mulrooney et al. concluded that seizures were likely to be a complication of cranial and/or cranial-spinal radiotherapy as the burden was reduced in survivors treated on later protocols in which use of cranial radiotherapy was markedly reduced [26]. We found that survivors treated after 1990 had a decreased risk of epilepsy compared to survivors treated in the period 1970 to 1979. However, we were not able to assess whether this decrease in risk was due to less frequent use of cranial or cranial-spinal radiotherapy as this information was not available for the survivors. Additionally, we

cannot rule out the possibility that the difference in risk is related to the shorter follow-up period for more recently diagnosed survivors.

The strengths of the study include the population-based design with the identification of survivors from national cancer registries in which the data are of high quality. Moreover, the incorporation of individual treatment details from medical records represents a strength, given that most previous studies relied on self-reported data, which is susceptible to recall bias. The Nordic countries have similar health and welfare systems, which enables combining their data to increase the size of the study population. Despite the inclusion of survivors from Denmark, Finland, and parts of Sweden, the size of the study population constrained the scope of detailed statistical analyses that could be performed. The size also limited the ability to categorize cancer types in the analyses and restricted the number of potential confounders that could be adjusted for. Additionally, residual confounding cannot be ruled out due to potential unknown confounders, such as pre-existing diseases, which may be associated with both childhood cancer and epilepsy. We assessed the risk of a first epilepsy discharge diagnosis after 5 years of survival. As a result, the exclusion of survivors of early-onset epilepsy and the lack of inclusion of milder cases managed in outpatient setting may have led to underestimation of the risk. We also included a sub-cohort that was randomly selected to be used as a comparison group in several case cohort studies. However, we had to exclude survivors with a tumor in CNS and Swedish survivors from regions outside Skåne, which reduced the size of the sub-cohort and the statistical power. Finally, it can be challenging to separate the effects of the cancer itself, relapse events, acute complications, and various treatment types on late complications as these factors are often interrelated. Even though we adjusted for cancer type and conducted sub-analyses only including leukemia survivors, our results regarding treatment-related risk factors remain inconclusive.

Conclusion

Epileptic seizures are a well-recognized symptom and/or complication of CNS cancers in childhood, primarily attributed to the tumors' location [15]. However, survivors of cancer outside the CNS in childhood are at increased risk for developing epilepsy as a late complication. Our study found that especially patients treated for leukemia and those experiencing a relapse of leukemia were at increased risk for epilepsy. The risk was particularly pronounced among leukemia survivors who were diagnosed before 1990. We were unable to identify any treatment-related factors contributing to an increased rate of late-onset epilepsy. This finding may be attributed to the study's limited patient cohort, suggesting that further research involving larger populations should explore this issue in greater detail.

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Data availability

The data that support the findings of this study were collected from Denmark, Sweden and Finland with the purpose of setting up different case cohort studies to assess specific late complications after childhood cancer. Danish, Finish and Swedish laws and regulations do not allow sharing of personal sensitive data, which can only be made available for researchers who fulfill the legal requirements for access to such data. Please contact Line Kenborg (kenborg@cancer.dk) with inquiries regarding data access.

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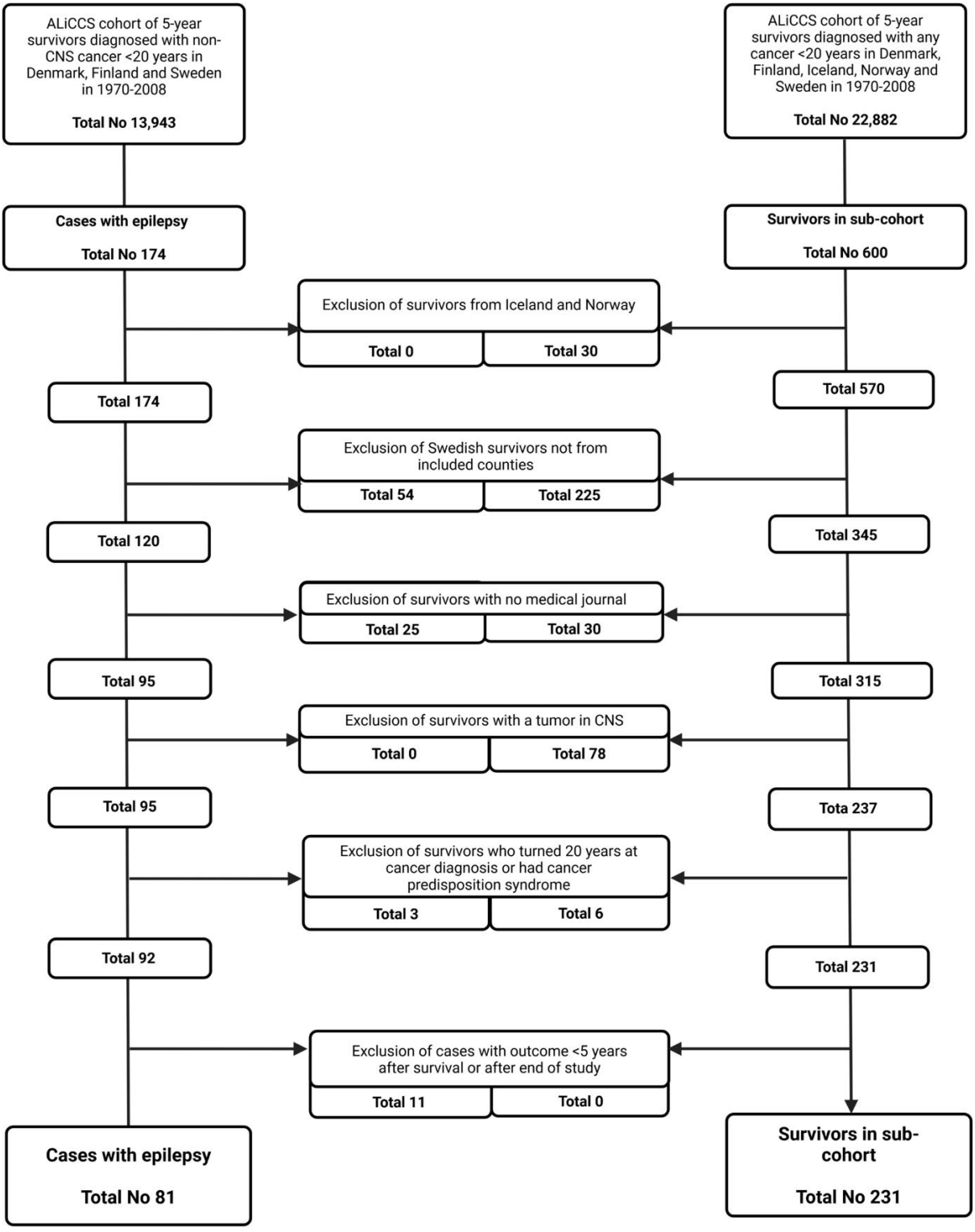
Figure 1. Flowchart of the study



ALiCCS = Adult Life after Childhood Cancer in Scandinavia; CNS = central nervous system

Table 1 Characteristics of 81 survivors of non-CNS cancer in childhood with late-onset epilepsy and 231 survivors in sub-cohort

	Survivors with epilepsy (*n* = 81)	Survivors in sub-cohort (*n* = 231)
Sex (%)		
Female	36 (44)	105 (45)
Male	45 (56)	126 (55)
Country (%)		
Denmark	35 (43)	105 (45)
Finland	40 (49)	103 (45)
Sweden	6 (7)	23 (10)
Year of cancer diagnosis (%)		
1970–1979	27 (33)	36 (16)
1980–1989	25 (31)	44 (19)
1990–1999	24 (30)	108 (47)
2000–2008	5 (6)	43 (19)
Childhood cancer type[a] (%)		
Leukemia	49 (60)	70 (30)
ALL	43	63
Lymphoma	8 (10)	36 (16)
Neuroblastoma	5 (6)	7 (3)
Soft tissue sarcomas	≤ 5	11 (5)
Carcinomas and other malignant epithelial neoplasms	≤ 5	40 (17)
Other	10 (12)	67 (29)
Age at cancer diagnosis (%)		
0–4	34 (42)	72 (31)
5–9	23 (28)	34 (15)
10–14	13 (16)	46 (20)
15–19	11 (14)	79 (34)
Median age at diagnosis of epilepsy/end of follow-up, years (IQR)	18.1 (13.0–26.5)	27.3 (21.0–36.3)

	Survivors with epilepsy (*n* = 81)	Survivors in sub-cohort (*n* = 231)
Median time from entry to exit, years (IQR)	10.6 (7.5–16.3)	16.8 (10.8–23.0)
Radiotherapy (%)		
No	42 (52)	144 (62)
Yes	39 (48)	87 (38)
Bone marrow transplantation		
No	73 (90)	212 (92)
Yes	8 (10)	19 (8)
Chemotherapy (%)		
No	15 (19)	74 (32)
Yes	66 (81)	157 (68)
Relapse (%)		
0	67 (83)	213 (92)
≥ 1	14 (17)	18 (8)

IQR, interquartile range

[a]According to the International Classification of Childhood Cancer (Birch and Marsden 1987)

Table 2 Incidence rate ratios (IRRs) for late-onset epilepsy and 95% confidence intervals (CIs) for different patient characteristics, treatment modalities, and chemotherapeutic drugs

	Survivors with epilepsy/sub-cohort	IRR (95% CI)[a]	IRR (95% CI)[b]
Sex			
Female	36/105	Ref	Ref
Male	45/126	1.2 (0.7–2.0)	1.3 (0.7–2.4)
Year of cancer diagnosis (%)			
1970–1979	27/36	Ref	Ref
1980–1989	25/44	0.9 (0.4–1.8)	0.6 (0.2–1.4)
1990–2008	29/151	0.3 (0.3–1.1)	0.4 (0.2–0.8)
Cancer type			
Solid tumors	24/125	Ref	Ref
Lymphomas	8/36	1.4 (0.5–3.5)	1.4 (0.5–4.0)
ALL	43/63	4.0 (2.1–7.5)	4.4 (2.2–8.5)
AML and other leukemia	6/7	8.6 (2.4–30.7)	14.1 (3.4–57.9)
Relapse			
0	67/213	Ref	Ref
≥ 1	14/18	3.2 (1.4–7.5)	3.5 (1.5–8.6)
Relapse and type of cancer			
No relapse	67/213	Ref	Ref
Relapse of leukemia	10/7	7.9 (1.2–24.5)	11.4 (3.5–37.3)
Relapse of other cancer than leukemia	4/11	1.2 (0.4–4.5)	1.1 (0.3–4.2)
Radiotherapy			
No	42/144	Ref	Ref
Yes	39/87	1.5 (0.8–2.5)	1.5 (0.8–2.8)
Bone marrow transplantation			
No	73/212	Ref	Ref
Yes	8/19	2.2 (0.9–5.7)	2.3 (0.7–7.0)
TBI			

	Survivors with epilepsy/sub-cohort	IRR (95% CI)[a]	IRR (95% CI)[b]
No	75/220	Ref	Ref
Yes	6/11	2.7 (0.9–8.0)	1.8 (0.5–6.5)
Treatment combination			
Surgery only	8/51	Ref	Ref
Chemotherapy only	34/93	2.9 (1.2–7.3)	1.2 (0.4–3.8)
Radiotherapy only	7/23	2.0 (0.6–6.7)	2.0 (0.6–6.9)
Chemotherapy and radiotherapy	32/64	3.5 (1.2–7.3)	1.7 (0.6–4.9)
Chemotherapy			
No	15/74	Ref	Ref
Any	66/157	2.4 (1.3–4.7)	1.1 (0.5–2.5)
Antimetabolites			
No	31/148	Ref	Ref
Any	50/83	3.4 (1.9–5.9)	1.2 (0.3–5.0)
Methotrexate IT			
No	37/153	Ref	Ref
Yes	44/78	2.7 (1.6 – 4.7)	0.4 (0.1 – 2.0)
Methotrexate IT (mg/m^2)[c]			
0	37/153	Ref	Ref
> 0 – < 155	14/47	1.2 (0.6–2.6)	0.1 (0.0–1.1)
≥ 155	29/30	6.4 (3.1–13.3)	1.5 (0.2–13.3)
Methotrexate IV			
No	51/161	Ref	Ref
Yes	30/70	1.6 (0.9–2.9)	0.4 (0.2–1.1)
High-dose methotrexate ≥ 10 g/m^2 *IV*			
No	70/192	Ref	Ref
Yes	11/39	1.1 (0.5–2.5)	0.6 (0.2–1.7)
High-dose methotrexate ≥ 5 g/m^2 *IV*[c]			
No	68/184	Ref	Ref
Yes	13/47	1.0 (0.5–2.1)	0.4 (0.2–1.0)

	Survivors with epilepsy/sub-cohort	IRR (95% CI)[a]	IRR (95% CI)[b]
Cytarabine IT			
No	73/216	Ref	Ref
Yes	8/15	2.2 (0.8–5.7)	1.5 (0.5–4.7)
High-dose cytarabine IV[d]			
No	67/176	Ref	Ref
Yes	14/55	0.9 (0.4–1.7)	0.3 (0.1–0.6)
Alkylating agents			
No	52/131	Ref	Ref
Yes	29/100	0.9 (0.5–1.5)	0.4 (0.2–0.9)
Cyclophosphamide IV			
No	61/158	Ref	Ref
Yes	20/73	0.8 (0.4–1.5)	0.4 (0.2–0.9)
Cyclophosphamide IV (mg/m^2)[c]			
0	61/158	Ref	Ref
> 0 – < 3059	8/38	0.6 (0.3–1.5)	0.3 (0.1–0.8)
≥ 3059	11/34	0.9 (0.4–2.1)	0.5 (0.2–1.3)
Antimitotic drugs			
Vincristine			
No	25/119	Ref	Ref
Yes	56/112	2.7 (1.5–4.8)	1.3 (0.5–3.1)
Vincristine (mg/m^2)[c]			
0	25/119	Ref	Ref
> 0 – 19.0	17/64	1.4 (0.7–3.0)	0.8 (0.3–2.1)
> 19.0	35/46	4.1 (2.1–8.2)	1.7 (0.6–5.3)

IRRs, incidence rate ratios; *CI*, confidence interval; *ALL*, acute lymphoblastic leukemia, *AML*, acute myeloid leukemia, *TBI*, total body irradiation; *IV*, intravenous; *IT*, intrathecal

[a]Analyses adjusted for country, [b]Analyses adjusted for sex (except analyses of sex), cancer type (except analyses of cancer type), year of diagnosis (except analyses of year of diagnosis), and country, [c]Survivors with missing dose were included in a separate group in analyses, [d]High-dose cytarabine IV is defined as cumulative dose of more than 1 g/m^2

Table 3 Incidence rate ratios (IRRs) for late-onset epilepsy and 95% confidence intervals (CIs) for different patient characteristics, treatment modalities, and chemotherapeutic drugs in leukemia survivors

	Leukemia survivors with epilepsy/sub-cohort	IRR (95% CI)[a]
Sex		
Female	25/37	Ref
Male	24/33	1.1 (0.5–2.8)
Year of diagnosis		
1970 – 1989	32/20	Ref
1990 – 2008	17/50	0.4 (0.2 – 0.9)
Relapse		
0	39/63	Ref
≥ 1	10/7	4.7 (1.9–31.2)
Radiotherapy		
None	24/42	Ref
Any	25/28	1.8 (0.7–4.6)
TBI		
No	44/59	Ref
Yes	5/11	1.7 (0.4–7.4)
Antimetabolites		
Methotrexate IT (mg/m^2)[c]		
0	8/4	Ref
> 0 – < 155	14/36	0.1 (0.0–0.8)
≥ 155	26/29	1.4 (0.1–16.1)
High-dose methotrexate ≥ 10 g/m^2 *IV*		
No	38/38	Ref
Yes	11/32	1.2 (0.5–2.6)
High-dose methotrexate ≥ 5 g/m^2 *IV*[c]		
No	36/31	Ref
Yes	13/39	0.5 (0.2–1.2)

	Leukemia survivors with epilepsy/sub-cohort	IRR (95% CI)[a]
High-dose cytarabine IV[d]		
No	36/22	Ref
Yes	13/48	0.3 (0.1–0.6)
Alkylating agents		
Cyclophosphamide IV (mg/m^2)		
0	34/27	Ref
> 0 – < 3059	6/26	0.2 (0.1–0.6)
≥ 3059	9/17	0.5 (0.2–1.5)
Antimitotic drugs		
Vincristine (mg/m^2)[c]		
0	7/8	Ref
> 0 – 19.0	13/29	0.3 (0.1–1.6)
> 19.0	27/32	0.6 (0.1–2.9)

[a]Analyses adjusted for country, [b]Analyses adjusted for sex (except analyses of sex), year of diagnosis (except analyses of year of diagnosis), and country, [c]Survivors with missing dose were included in a separate group in analyses, [d]High-dose cytarabine IV is defined as cumulative dose of more than 1 g/m^2