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ORIGINAL ARTICLE

Neurologic disorders in long-term survivors of neuroblastoma – a population-based cohort study within the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) research program

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ABSTRACT

Background: Neuroblastoma is the commonest extracranial solid tumor of childhood, yet rare, and with poor survival before 1990, especially for high-risk disease; thus, information on late effects is sparse. With great advances in cancer treatment, survival has reached 80% in the Nordic countries. The aim of the study was to investigate the risk of developing neurologic disorders after neuroblastoma.

Material and methods: Through population-based cancer registries of four Nordic countries we identified 654 5-year survivors of neuroblastoma (diagnosed 1959–2008) and 133,668 matched population comparisons. We grouped neurologic diagnoses from national hospital registries into 11 main diagnostic categories and 56 disease-specific sub-categories and calculated relative risks (RRs), absolute excess risks (AERs), cumulative incidence and mean cumulative count (MCC). Information on cancer treatment was available for 49% of survivors.

Results: A hospital contact for a neurologic disorder was observed in 181 survivors 5 years or more from cancer diagnosis with 59 expected, yielding a RR of 3.1 (95% CI 2.7–3.6) and an AER of 16 per 1,000 person-years (95% CI 12–19). The most frequent disorders included epilepsy, paralytic syndromes, diseases of the eyes and ears and hearing loss. The cumulative incidence of any neurologic disorder was 31% in survivors 20 years after cancer diagnosis with a MCC of 0.5 unique diagnoses. All risks were highest in survivors of high-risk neuroblastoma.

Conclusion: Neuroblastoma survivors represent a population with a high risk of developing neurologic disorders. Our results should contribute to improving health care planning and underscores the need for systematic follow-up care of this vulnerable group of survivors.

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Introduction

Neuroblastoma is the commonest extracranial solid malignant tumor in childhood accounting for 8–10% of all childhood cancers [1]. The disease is characterized by its clinical heterogeneity and survival varies widely according to stage of disease, with 5-year survival ranging from 95% for low-risk to less than 50% for high-risk disease [2–4]. Nonetheless, in the Nordic countries the overall 5-year survival for neuroblastoma reached 80% in 2005–2007 [5]. The rarity of neuroblastoma combined with poor survival prior to 1990, especially for patients with high-risk disease, explains the very sparse information on late effects in survivors of this tumor [6,7].

In a recent study, providing a comprehensive overview of somatic late effects in neuroblastoma survivors, we found a highly increased risk of developing a broad variety of diseases compared with the general population [8], and in particular, a high risk of neurologic disorders. The risk was overall more than 3-fold increased and neurologic disorders constituted about 20% of all excess hospital contacts in neuroblastoma survivors [8]. However, since the study was an overview of all somatic diseases in neuroblastoma

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Supplemental data for this article can be accessed here.

survivors, we were not able to show details on the neurologic disorders that these patients encounter.

Similar overall findings were reported within the North American Childhood Cancer Survivor Study (CCSS), which showed that 5-year survivors of neuroblastoma had an eight times increased risk of reporting neurologic and sensory complications compared with siblings [9]. Few studies have also reported overall neurologic and sensory disorders in smaller populations of survivors of advanced stage neuroblastoma [7,10,11].

In this study, we provide detailed data on the burden of neurologic complications, including sensory organ disorders, following neuroblastoma and its treatment in a population-based cohort of 654 five-year neuroblastoma survivors from four Nordic countries.

Material and methods

The neuroblastoma cohort is a sub-cohort of the Nordic Adult Life after Childhood Cancer in Scandinavia research program (www.aliccs.org) including 33,576 individuals in Denmark, Finland, Iceland, and Sweden in whom cancer was diagnosed before the age of 20 years between the start of the cancer registries in the 1940s and 1950s and December 31, 2008 (Finland, 1971–2008) [12]. Of the 33,576 cancer patients, 1,443 had neuroblastoma.

Five comparison subjects without cancer before the age of 20, who were alive in the year of cancer diagnosis in the corresponding survivor and of the same sex, age, and country of residence, were randomly selected from the national population registries [12]. Main exclusion criteria were: more than one primary cancer before age 20 years, death or emigration before the start of the hospital registries, a diagnosis of chromosome abnormalities, less than 5 years of follow-up after the date of cancer diagnosis or without complete follow-up in the national hospital registries (footnote c, Table 1). After exclusions, 654 5-year neuroblastoma survivors and 133,668 comparisons were available for analysis (Figure 1).

Information on cancer treatment from clinical registries based on medical charts covering the period 1980–2008 was available for 321 (49%) of the 654 survivors of whom 71 were treated with high-dose chemotherapy followed by autologous stem-cell transplant (ASCT) (high-risk), 149 with chemotherapy ± irradiation ± surgery (intermediate-risk) and 101 by surgery only (low-risk) (Figure 1; Table 1, footnote) [4,13–15].

We identified all hospital admissions and outpatient visits (referred to as "hospital contacts") with a primary or supplementary diagnosis for a neurologic disorder in the nationwide hospital registries (Table 1, footnote) [12]. These registries contain information on all non-psychiatric hospital admissions (since 1964 in Sweden, 1975 in Finland, 1977 in Denmark, and 1999 in Iceland) [16,17]. Registration is mandatory and is recorded by the treating physician. Out-patient visits have been included in Denmark since 1995 and in Sweden since 2001. We grouped neurologic disorders into 11 main diagnostic groups of diseases within the nervous system and sensory organs and 56 disease-specific subcategories according to the International Classification of Diseases, revisions 7–10 with diagnoses adapted to those of ICD-10 (Supplementary Table S1).

Statistical analysis

Follow-up for neurologic disorders started 5 years after the date of neuroblastoma diagnosis (corresponding date for comparison subjects) and ended on the date of death, emigration, or end of the study (Iceland: December 31, 2008; Sweden: December 31, 2009; Denmark: October 31, 2010; Finland: December 31, 2012). If a person had more than one hospital contact within a disease category, only the first record was retained (except in the analysis of mean cumulative count (MCC) in which we included readmissions).

Standardized rate ratios (RRs) were calculated as the observed number of first hospital contacts among neuroblastoma survivors, overall and in the 11 main diagnostic groups and 56 sub-categories, divided by the expected number derived from the appropriate country, sex-, age-, and calendar period-specific hospital contact rates of the comparison cohort. The 95% confidence intervals (CIs) of the RRs were estimated with Fieller's theorem, assuming that the observed number of first hospital contacts followed a Poisson distribution. The absolute excess risks (AERs) were calculated as the difference between the observed and expected hospital contact rates for a particular disease category per 1,000 person-years of follow-up. Note, that the 133,668 study subjects in the comparison cohort were not used as comparisons *as such*, but to generate a Nordic population-based dataset on sex-, age-, and calendar period-specific hospitalization rates.

We estimated the cumulative incidence of first hospital contacts for any neurologic disorder, taking the competing event of death into account and with time since neuroblastoma diagnosis as the underlying time scale. To investigate the burden of neurologic disorders in survivors, we used the method of MCC, which allows a summarization of all events that occur in a population by a given time [18]. The cumulative incidence and MCC of hospital contacts for any neurologic or sensory organ disorder was estimated in the 654 5-year survivors, in the clinical sub-cohort divided by treatment group, and for the 3,192 comparisons directly matched to the cohort of neuroblastoma survivors by country, sex, age and calendar period with time since neuroblastoma diagnosis as the underlying time scale. The MCC was calculated for all first-time neurologic disorders in the 56 sub-categories and also including readmissions.

To examine whether the mean number of hospital contacts in the three treatment groups were statistically significantly different, we performed regression models of the mean expected number of hospital contacts with the reference group being those treated with surgery only.

We investigated the effect of cancer treatment on the hazard of having a first-time hospital contact for a neurologic disorder using a Cox proportional hazards model with surgery only as reference group and with time to first diagnosis as the underlying time scale.

To evaluate the influence of missing treatment information on the results, we performed a sensitivity analysis using

Table 1. Standardized rate ratios (RRs) and absolute excess risks (AERs) for first-time hospital contacts for neurologic disorders per 1,000 person-years of follow-up starting 5 years after the date of cancer diagnosis[a], among the full cohort of 654 five-year survivors diagnosed from 1959–2008 and in the clinical sub-cohort of 321 survivors with treatment information available[b] diagnosed from 1980–2008, respectively.

Main diagnostic group of neurologic disorders Disease category	No. of first-time hospital contacts[c,d] Observed	 Expected	 RR (95% CI)	AER per 1,000 person-years (95% CI)
Full cohort of 654 five-year survivors RRs and AERs for all first-time hospital contacts, and in each of the main disease categories and sub-categories with at least 3 observations in each (leaving 5 main categories and 14 sub-categories)				
Total no. of persons with a first-time hospitalization for a neurologic disorder	181	58.7	3.1 (2.7–3.6)	16.0 (12.4–19.2)
Episodic and paroxysmal disorders	49	14.6	3.4 (2.5–4.5)	3.9 (2.3–5.4)
Epilepsy	27	5.7	4.7 (3.2–6.9)	2.4 (1.2–3.5)
Migraine and headache	19	7.7	2.5 (1.6–3.9)	1.2 (0.3–2.2)
Sleep disturbances, incl narcolepsy and cataplexi	6	1.9	3.3 (1.5–7.3)	0.4 (−0.1–1.0)
Nerve, nerve root and plexus disorders	15	4.5	3.3 (2.0–5.5)	1.2 (0.3–2.0)
Mononeuropathies	8	3.1	2.6 (1.3–5.1)	0.5 (−0.1 – 1.1)
Paralytic syndromes	31	0.8	40.1 (27.5–58.7)	3.4 (2.2–4.6)
Hemiplegia	6	0.2	26.2 (11.3–60.9)	0.6 (0.1–1.1)
Paraplegia and tetraplegia	20	0.4	52.7 (32.5–85.3)	2.2 (1.2–3.1)
Monoplegia	5	0.1	51.0 (19.5–134)	0.5 (0.1–1.0)
Hydrocephalus, Horner's syndrome and other disorders of the nervous system	28	1.6	18.1 (12.3–26.6)	2.9 (1.8–4.1)
Hydrocephalus	6	0.4	16.3 (7.1–37.3)	0.6 (0.1–1.1)
Horner's syndrome	4	0	555 (94.0–3272)	0.4 (0–0.9)
Cord bladder NOS, myelopathy (drug– or radiation induced) and other specified diseases of spinal cord	5	0	304 (81.6–1129)	0.5 (0.1–1.0)
Diseases within sensory organs	117	45.7	2.6 (2.1–3.1)	8.5 (6.0–11.0)
Inflammatory and other diseases of the eye	59	26.0	2.3 (1.8–2.9)	3.7 (2.0–5.4)
Inflammatory diseases of the ear	44	17.9	2.5 (1.8–3.3)	2.9 (1.5–4.4)
Méniere's disease and otosclerosis	3	1.7	1.8 (0.6–5.6)	0.1 (−0.2 – 0.5)
Hearing loss, deafness and other diseases of the ear	40	6.8	5.9 (4.3–8.1)	3.7 (2.3–5.0)
Clinical sub-cohort of 321 five-year survivors RRs and AERs for all first-time hospital contacts, by treatment group[e]				
Low-risk neuroblastoma (surgery only; n = 101)	26	13	2.0 (1.4–2.9)	14 (3.1–24)
Intermediate risk neuroblastoma (chemotherapy ± irradiation ± surgery; n = 149)	44	14	3.1 (2.3–4.1)	21 (12–30)
High-risk neuroblastoma (high-dose chemotherapy followed by autologous stem cell transplant; n = 71)	27	2.9	9.4 (6.4–14)	68 (39–97)

[a]Follow-up ended on the date of death, emigration, or end of the study (Iceland: December 31, 2008; Sweden: December 31, 2009; Denmark: October 31, 2010; Finland: December 31, 2012).
[b]Periods with treatment information available from clinical registries for a sub-cohort of survivors diagnosed from 1980–2008: Denmark: Danish Neuroblastoma Registry (1981–2004), Danish Childhood Cancer Registry (2005–2008); Finland: Helsinki Pediatric Cancer Registry (1990–2008); Iceland: Icelandic Cancer Registry (1980–2008); Sweden: Swedish Childhood Cancer Registry (1980–2008). The clinical registries are population-based, except the Finnish registry that covers 1/3 of the national total.
[c]Periods with information on hospital discharge diagnoses for neurologic disorders available from hospital registries and classified according to the International Classification of Diseases; Denmark 1977–2010 (ICD-8 in 1977–1993, ICD-10 since 1994); Finland 1983–2009 (ICD-8 in 1983–1986, ICD-9 in 1987–1995 and ICD-10 since 1996); Iceland 1999–2008 (ICD-10); Sweden 1964–2009 with stepwise inclusion of counties from 1964 to 1987, and national coverage since 1987 (ICD-7 in 1964–1968, ICD-8 in 1969–1986, ICD-9 in 1987–1996 and ICD-10 since 1997). We only included 5-year survivors with complete coverage in the national hospital registries leaving out 67 survivors diagnosed more than 5 years before the patient registries in the respective countries started.
[d]If participants had more than one hospital contact for a disorder within a particular disease category, only the first record for each patient in the 56 sub-categories of neurologic disorders was retained.
[e]Not including 9 survivors who received no treatment awaiting spontaneous regression of the tumor. None of the survivors in our cohort received immunotherapy since immunotherapy was only introduced as part of the treatment for neuroblastoma more recently.

multiple imputation. This analysis was based on the survivors diagnosed with neuroblastoma from 1980 and onwards ($n = 543$). We included the 226 (41%) survivors who lacked treatment information by using 100 imputed datasets.

We used SAS software version 9.4 to determine RRs and AERs. To estimate cumulative incidence and MCC, we used R software version 3.3.2 and the packages mets with the 95% CIs calculated by using the Lin and Ghosh standard errors [19]. To conduct multiple imputation we used the smcfcs function in stata [20].

Results

The overall cohort comprised 654 five-year survivors of neuroblastoma (81% neuroblastoma, 19% ganglioneuroblastoma) with 60% diagnosed after 1990. Survivors were followed in the hospital registries for a median of 9.3 years (range, 0–42), yielding 7,731 person-years of follow-up. In all, 181 survivors had at least one hospital contact for a neurologic disorder while 59 was expected, yielding a RR of 3.1 (95% CI 2.7–3.6) and an overall AER of 16 per 1,000 person-years (95% CI 12–19) (Table 1). The RR and the AER decreased markedly with increasing time since diagnosis with a RR of 4.8 (95% CI 4.0–5.8) in the period 5–9 years after to 1.1 (95% CI 0.7–1.7) after more than 20 years, and the AERs decreasing from 36 (95% CI 28–44) to 1 (95% CI −3 – 5) per 1,000 person-years of follow-up (numbers not shown). Risks were much elevated in high-risk survivors (RR = 9.4; 95% CI 6.4–13.7; AER = 68; 95% CI 39–97) compared with those of intermediate- or low-risk survivors, and displayed a

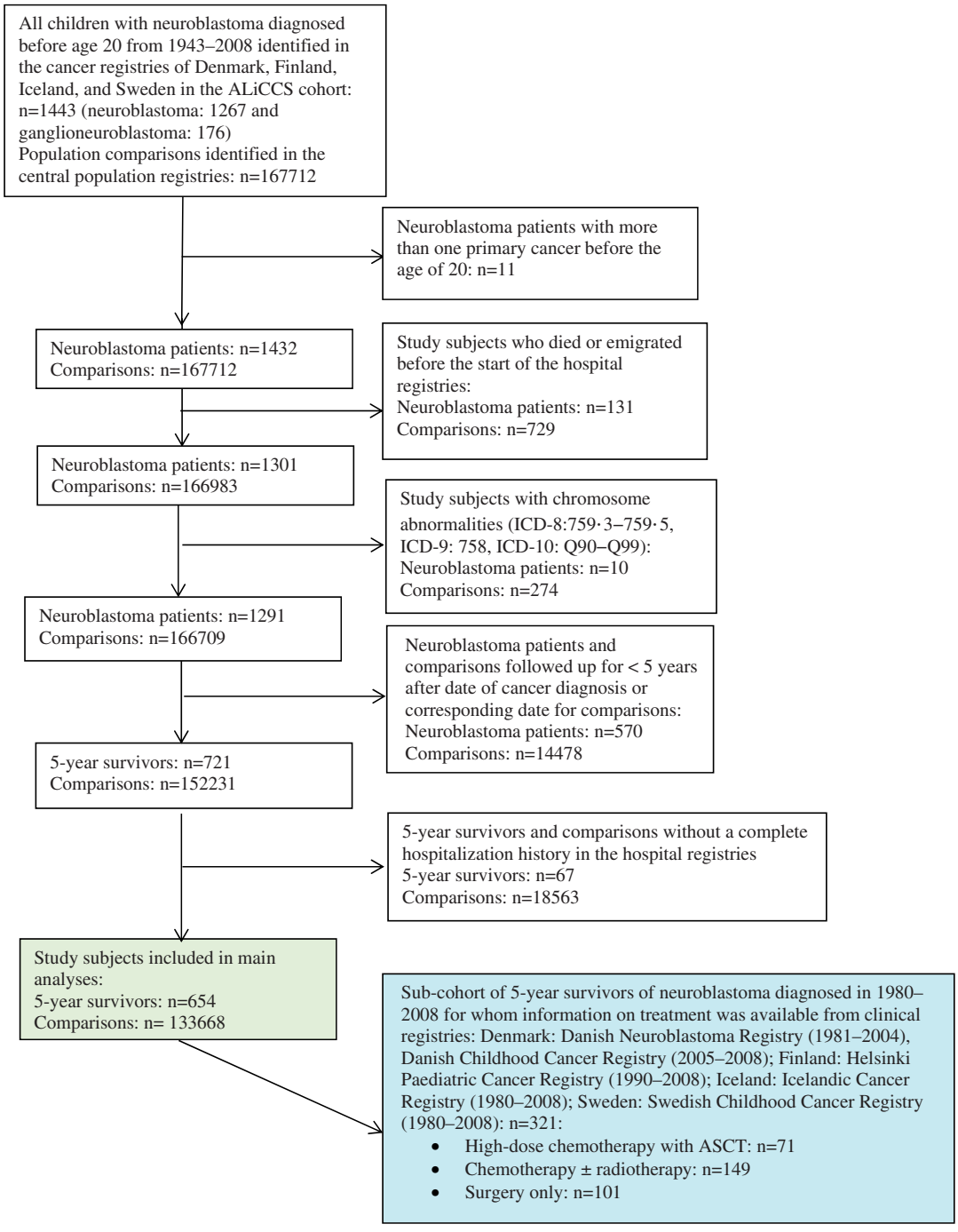

Figure 1. Flow chart with reasons for exclusion of study subjects and size of final study cohorts of survivors of neuroblastoma and population comparisons.

dose-response pattern according to intensity of cancer treatment (Table 1).

Considering both relative and absolute numbers, highest risks were within the main groups of episodic and paroxysmal disorders (RR: 3.4 95% CI 2.5–4.5; AER: 3.9); nerve, nerve root and plexus disorders (RR: 3.3 95% CI 2.0–5.5; AER: 1.2); paralytic syndromes (RR: 40.1 95% CI 27.5–58.7; AER: 3.4); hydrocephalus, Horner's syndrome and other disorders of the nervous system (RR: 18.1 95% CI 12.3–26.6; AER: 2.9); and diseases within the sensory organs (RR: 2.6 95% CI 2.1–3.1; AER: 8.5) (Table 1); all together, constituting 96% of all excess hospital contacts for neurologic disorders in survivors.

Figure 2 shows that 31% (95% CI 26–35) of all 5-year survivors had at least one first hospital contact for a neurologic disorder within 20 years after the date of cancer diagnosis. The highest cumulative risk was for survivors of high-risk neuroblastoma of whom 37% (95% CI 25–49) had at least one first hospital contact within 10 years after diagnosis compared with 22% (95% CI 15–29) in intermediate risk survivors and 14% (95% CI 7–21) in low-risk survivors (Figure 2B).

At any given time, neuroblastoma survivors had a higher mean number of first-time hospital contacts for neurologic disorders than comparisons (Figure 2C). Further, high-risk survivors had a higher mean number of first-time hospital contacts (0.6; 95% CI 0.4–0.8) 10 years after diagnosis compared

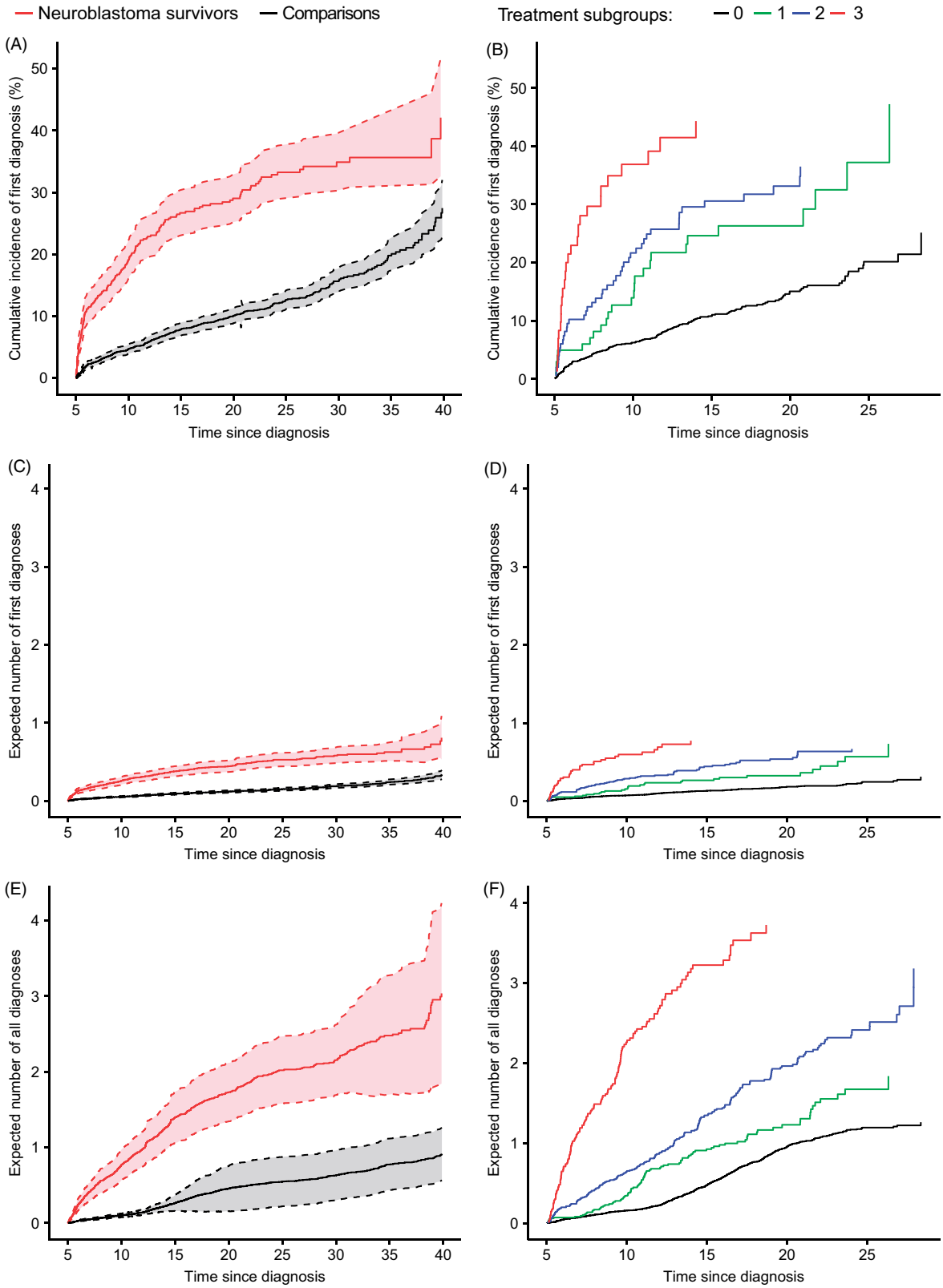

Figure 2. Cumulative incidence (A and B) and mean cumulative count (C–F) for all first-time hospital contacts and for all hospital contacts, including readmissions, respectively, for all 654 survivors and for the clinical sub-cohort of 321 survivors with treatment information available with follow-up starting 5 years after the date of neuroblastoma diagnosis and with time since the neuroblastoma diagnosis as the underlying time scale and the corresponding date for 3,192 directly matched comparisons (figure B,D,F: 0 = comparisons, 1 = low-risk neuroblastoma, 2 = intermediate risk neuroblastoma, 3 = high-risk neuroblastoma).

with intermediate- (0.3; 95% CI 0.2–0.4) or low-risk survivors (0.2; 95% CI 0.1–0.2) (Figure 2D), with the difference being statistically significant; i.e., at any given time high-risk survivors had a 2.6 (95% CI 1.6–4.2) times higher expected number of hospital contacts for different neurologic diagnoses than survivors of low-risk disease. When including

readmissions (Figure 2E and F), we found more pronounced patterns and at any given time high-risk survivors had a 3.7 (95% CI 2.5–5.3) times higher expected number of hospital contacts than survivors of low-risk disease.

The within cohort analysis estimating the hazard of a first-time hospital contact for a neurologic disorder also displayed a statistically significant effect of intensity of cancer treatment, i.e., survivors of high-risk neuroblastoma at any given time had a 4 times higher risk (HR: 4.0; 95% CI 2.1–7.7) than low-risk survivors. The sensitivity analysis using multiple imputation, performed to test the influence of the missing treatment information, showed results very similar to those based on the observations with complete treatment information only (HR: 3.8; 95% CI 2.0–7.4).

Discussion

This population-based study of 654 5-year neuroblastoma survivors in the Nordic countries evaluates the risk and illustrates the frequency of neurologic late effects serious enough to require a hospital visit. Survivors had a hospital contact for a new neurologic disorder more than 3 times as often as the general population and an AER of 16 per 1,000 survivors followed for a year. The risks decreased with increasing time since diagnosis and displayed a dose-response pattern according to intensity of cancer treatment. Disorders with the highest both relative and absolute excess risks were epilepsy, para- and tetraplegia, inflammatory and other diseases of the eyes and ears, and hearing loss and deafness. Further, survivors' disorders generally required more readmissions.

We found a highly increased risk of epilepsy in survivors. Bone metastases of the skull and orbits might cause brain irritation/compression which could also be associated with the development of epilepsy and headaches/migraine [21]. Total body irradiation (TBI) increases the risk of developing meningioma's, which may cause seizures. However, only 12 survivors in our cohort were treated with TBI (only used in Finland) of whom only one survivor had a diagnosis of epilepsy.

The increased risk of paralytic syndromes is most likely a result of tumors arising close to the spine and with an intraspinal tumor component, so-called dumbbell tumors, with following medullary compression causing irreversible neurologic damage [22,23]. Medullary compression can be the presenting symptom of neuroblastoma and cause nerve, nerve root and plexus disorders, such as mononeuropathies, and paralytic syndromes, which are thereby not treatment-induced, but a direct cause of the tumor or the subsequent surgery.

Another common late effect after treatment of high-risk neuroblastoma is hearing loss with the greatest risk factors being use of cisplatin and carboplatin during induction treatment. This was supported in our study where survivors had a 6 times increased risk of hearing loss, even if hearing problems will rarely lead to hospitalization and are therefore not fully covered in this study.

We found that the number of expected hospital contacts was much higher than the expected number of different diagnoses, indicating that most of survivors have few different diagnoses, but more readmissions than comparisons. This suggests that not only do survivors suffer from a greater number of different neurologic disorders than the general population, but are also more heavily burdened with each disorder.

Using the exceptional opportunities to carry out population-based research in the Nordic countries, we were able to include up to 42 years of follow-up in the national hospital registers with virtually no loss to follow-up, which is important since many treatment-related complications may be clinically silent for many years after cancer therapy [8]. Diagnoses for both neuroblastoma and neurologic disorders were based on medically verified diagnoses covering the whole population of four countries contributing with register-based data to this study. Further, we were able to include detailed treatment information from clinical registries based on medical charts for half of the long-term survivors. This unique combination of data sources enabled us to provide a detailed overview of neurologic complications in an understudied group of former childhood cancer patients using, to our knowledge, the largest population-based cohort of neuroblastoma survivors to date. In addition, we were able to include population-based comparisons representing the level of neurologic disorders in the general population.

The use of hospital-based diagnoses as markers of neurologic disorders makes the diagnostic information highly valid but implies that less severe disorders treated in the primary health care system are not included. Moreover, information on outpatient visits was available only in Denmark and Sweden and only recently, therefore the overall burden of neurologic problems experienced by neuroblastoma survivors might be underestimated. However, for serious diseases, such as epilepsy and paralytic syndromes, that require going to hospital we consider the data to be practically complete [24]. Further, childhood cancer survivors are likely to be followed more intensively in the health care system, leading to earlier detection of health care problems than in the general population, which might explain the relatively large number of survivors diagnosed with disorders such as inflammatory diseases of the eyes and ears. Still, the overall relative risk for neurologic disorders remained significantly increased up to 20 years after cancer diagnosis and the cumulative risk remained increased even 40 years after. There is a potential risk that some of these disorders represent a late relapse, and unfortunately, the cancer registries do not hold information on relapse. However, the risk of late relapse is limited to around 4% of 5-year survivors [25].

In conclusion, we found that neuroblastoma survivors represent a population with a high risk of developing a wide range of neurologic disorders, some caused by treatment and some by the tumor. The increased risk displayed a dose-response pattern according to intensity of cancer treatment, with high-risk survivors carrying the greatest risk. Survivors had more different neurologic disorders and more readmissions than the general population. Since some symptoms

may be clinically silent for years after cancer treatment and since some disorders can be detected early to minimize their consequences, we recommend that this vulnerable group of former childhood cancer patients are followed throughout life, especially survivors of high-risk disease, with more frequent visits up to 10 years post cancer diagnosis.

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Disclosure statement

None declared.

Approvals

The design of the ALiCCS study was approved by national bioethics committees, data protection authorities, or the national institutes for health and welfare in each country (Denmark: 2010-41-4334, Finland: THL/520/5.05.00/2016, Iceland: VSN 10-041 & VSN 12-084-V1 and Sweden: Ö 10-2010, 2011/19).

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