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Somatic late effects in 5-year survivors of neuroblastoma: a population-based cohort study within the Adult Life after Childhood Cancer in Scandinavia study

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Because of the rarity of neuroblastoma and poor survival until the 1990s, information on late effects in neuroblastoma survivors is sparse. We comprehensively reviewed the long-term risk for somatic disease in neuroblastoma survivors. We identified 721 5-year survivors of neuroblastoma in Nordic population-based cancer registries and identified late effects in national hospital registries covering the period 1977–2012. Detailed treatment information was available for 46% of the survivors. The disease-specific rates of hospitalization of survivors and of 152,231 randomly selected population comparisons were used to calculate standardized hospitalization rate ratios (SHRRs) and absolute excess risks (AERs). During 5,500 person-years of follow-up, 501 5-year survivors had a first hospital contact yielding a SHRR of 2.3 (95% CI 2.1–2.6) and a corresponding AER of 52 (95% CI 44–60) per 1,000 person-years. The highest relative risks were for diseases of blood and blood-forming organs (SHRR 3.8; 95% CI 2.7–5.4), endocrine diseases (3.6 [3.1–4.2]), circulatory system diseases (3.1 [2.5–3.8]), and diseases of the nervous system (3.0 [2.6–3.3]). Approximately 60% of the excess new hospitalizations of survivors were for diseases of the nervous system, urinary system, endocrine system, and bone and soft tissue. The relative risks and AERs were highest for the survivors most intensively treated. Survivors of neuroblastoma have a highly increased long-term risk for somatic late effects in all the main disease groups as compared to background levels. Our results are useful for counseling survivors and should contribute to improving health care planning in post-therapy clinics.

Introduction

Neuroblastoma is the commonest extracranial solid cancer in childhood and the commonest cancer in infancy, accounting for 8–10% of childhood cancers.[1] In the Nordic countries, the 5-year survival after neuroblastoma increased from 61% in 1999–2001 to 80% in 2005–2007,[2] although wide variations were seen by both age and stage of disease at diagnosis.[2,3] To attain the current survival rates, a high proportion of the survivors were exposed to intensive radiation and highly toxic chemotherapeutic compounds;[4,5] there is thus mounting

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What's new?

Recent decades have seen great gains in neuroblastoma survival, but as people live longer after treatment, more long-term complications emerge. Here, the authors investigated how often late effects afflicted 5-year neuroblastoma survivors. They found that in the years after treatment, neuroblastoma survivors went to the hospital 2.5 times as often as the general population. They saw the highest increases among patients who had high-dose chemotherapy with autologous stem cell transplant. In addition, the cumulative incidence of somatic disease did not appear to plateau over time. Life-long follow up will ensure timely diagnosis and treatment of these late effects.

concern about late effects, most of which become clinically evident years after the children have been cured of their cancer.[6–10] Neuroblastoma is a relatively rare disease, with poor survival before 1990,[11] especially for high risk patients, and long follow-up is required to detect possible late effects.[6] Information about late effects in survivors of this tumor is therefore sparse.

In the largest study on late effects in neuroblastoma survivors to date,[12] conducted within the North American Childhood Cancer Survivor Study, the relative risk for selected chronic health conditions in neuroblastoma survivors diagnosed between 1970 and 1986 was eight times higher than in their siblings, and the 20-year cumulative incidence of overall chronic health conditions was 41%. The most prevalent conditions involved the neurological, sensory, endocrine, and musculoskeletal systems. Survivors who received multimodality therapy were more than twice as likely to have a chronic health condition than those treated by surgery only.[12] These findings were, however, based on self-reports, and treatment protocols have further lengthened survival since 1986.[13] Clinical trials have improved and sustained cure rates with less exposures in low and intermediate risk patients, and improved cure rates for high risk patients using multimodality therapy, including high-dose chemotherapy, targeted radiotherapy and immunotherapy.

To fully understand the health risks associated with the disease and its treatment, we studied 5-year neuroblastoma survivors in four Nordic countries identified from nationwide, population-based cancer registries dating back to the 1940s and 1950s; late effects were identified as medically verified discharge diagnoses in national hospital registries. Using population comparisons as the reference, we assessed the risks for somatic disease in all organ systems from information on hospital visits. We had information on treatment from clinical registries for 46% of the survivors.

Methods

The neuroblastoma cohort is a subcohort of the Nordic Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study (www.aliccs.org), which comprises 33,576 individuals in Denmark, Finland, Iceland, and Sweden in whom cancer was diagnosed before they were aged 20 between the start of the cancer registries in the 1940s and 1950s and December 31, 2008 (Finland, 1971–2008).[14,15] Of the 33,576 cancer patients, 1,562 had neuroblastoma (Figure S1).

As previously described in greater detail,[10] five comparison subjects with no cancer diagnosed before the age of 20, who were alive in the year of diagnosis of cancer in the corresponding survivor and of the same sex, age, and country (Denmark, Finland and Iceland) or county (Sweden) of residence, were randomly selected from the national population registries, for a total of 167,712 individuals. All had to be alive at or born after the start of centralized registration of residents in each country (Iceland, 1955; Denmark and Sweden, 1968; Finland, 1971). Information on vital status and emigration during follow-up was also retrieved from these registries. Main exclusion criteria were: a diagnosis of ganglioneuroma, being diagnosed with more than one primary cancer before the age of 20, having died or emigrated before the start of the hospital registries, a diagnosis of chromosome abnormalities, or less than 5 years of follow-up. After exclusions, there were 721 5-year neuroblastoma survivors and 152,231 comparisons for analysis (further details in Figure S1).

Information on treatment from clinical registries based on medical charts (Figure S1) was available for a subcohort of 332 (46%) of the 721 survivors,[3,16–18] of whom 71 were treated with high-dose chemotherapy with autologous stem-cell transplant (ASCT), 149 with chemotherapy ±irradiation ±surgery, 103 by surgery only, and 9 received no treatment (Table 1, footnote).

For all study subjects, we identified all hospital admissions and outpatient visits (referred to as "first hospital contacts") with a primary or supplementary diagnosis in the nationwide hospital registries. These registries contain information on all hospital admissions for somatic disease (since 1964 in Sweden, 1975 in Finland, 1977 in Denmark, and 1999 in Iceland), including outpatient visits since 1995 in Denmark and 2001 in Sweden (Table 2, footnote).[15] We grouped the diagnoses into ten main diagnostic groups (Table 3, footnote) and 104 disease-specific subcategories according to the International Classification of Diseases (ICD) (Table 3), with ICD-7, ICD-9, and ICD-10 codes adapted to ICD-8 codes to the extent possible (Table S1).

Statistical analysis

We used the Kaplan–Meier estimator to estimate the survival probability of all 1,443 neuroblastoma patients according to period of diagnosis, with time since diagnosis as the underlying timescale. The end of follow-up was January 1, 2010, for Denmark, Sweden, and Finland and January 1, 2009, for Iceland.

Table 1. Characteristics of the cohort of all 1,443 neuroblastoma patients, 721 five-year neuroblastoma survivors, a subcohort of 323 5-year survivors for whom information on treatment was available and the population-based comparison cohort in four Nordic countries

	Basic cohort	5-Year survivors				Population comparisons
			Clinical subcohort for whom information on treatment was available[a]			
	All neuroblastoma patients	All 5-year survivors	High-dose chemotherapy with ASCT[b]	Chemotherapy ±radiation[c]	Surgery only[d]	
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
All	1,443 (100.0)	721 (100.0)	71 (100.0)	149 (100.0)	103 (100.0)	152,231 (100.0)
Sex	786 (54.4)	372 (51.5)	33 (46.·4)	72 (48.3)	55 (53.3)	82,990 (54.5)
Male						
Female	657 (45.5)	349 (48.4)	38 (53.5)	77 (51.6)	48 (46.6)	69,241 (45.4)
Age at cancer diagnosis (months)						
< 2	154 (10.6)	113 (15.6)	4 (5.6)	22 (14.7)	26 (25.2)	
2–11	313 (21.6)	231 (32.0)	8 (11.2)	69 (46.3)	30 (29.1)	
12–17	135 (9.3)	66 (9.1)	11 (15.4)	11 (7.3)	8 (7.7)	
18–23	109 (7.5)	39 (5.4)	5 (7.0)	9 (6.0)	4 (3.8)	
24–59	414 (28.6)	143 (19.8)	35 (49.2)	26 (17.4)	21 (20.3)	
≥ 60	318 (22.0)	129 (17.8)	8 (11.2)	12 (8.0)	14 (13.5)	
Calendar period at cancer diagnosis[e]						
1943–1959	16 (1.1)	15 (2.0)				
1960–1969	81 (5.6)	51 (7.0)				
1970–1979	305 (21.1)	110 (15.2)				
1980–1989	304 (21.0)	157 (21.7)		46 (30.8)	30 (29.1)	
1990–1999	410 (28.4)	237 (32.8)	31 (43.6)	73 (48.9)	50 (48.5)	
2000–2008	327 (22.6)	151 (20.9)	40 (56.3)	30 (20.1)	23 (22.3)	
Age at end of follow-up (years)	48 (3.3)					
<1						
1–9	641 (44.4)	82 (11.3)	17 (23.9)	24 (16.1)	19 (18.4)	2,942 (1.9)
10–19	322 (22.3)	224 (31.0)	40 (56.3)	63 (42.2)	43 (41.7)	20,914 (13.7)
20–39	348 (24.1)	332 (46.0)	14 (19.7)	62 (41.6)	41 (39.8)	75,797 (49.7)
40–59	81 (5.6)	80 (11.0)				46,470 (30.5)
≥60	3 (0.2)	3 (0.4)				6,108 (4.0)
Vital status at end of follow-up						

(Continues)

Table 1. Continued

	Basic cohort	5-Year survivors				Population comparisons
			Clinical subcohort for whom information on treatment was available[a]			
	All neuroblastoma patients	All 5-year survivors	High-dose chemotherapy with ASCT[b]	Chemotherapy ±radiation[c]	Surgery only[d]	
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Alive	734 (50.8)	655 (90.8)	65 (91.5)	142 (95.3)	102 (99.0)	144,838 (95.1)
Emigrated	28 (1.9)	19 (2.6)		1 (0.6)		4,096 (2.6)
Dead	681 (47.1)	47 (6.5)	6 (8.4)	6 (4.0)	1 (0.9)	3,297 (2.1)
Country of origin	401 (27.7)	165 (22.8)	25 (35.2)	59 (39.5)	8 (7.7)	43,461 (28.5)
Denmark						
Finland	355 (24.6)	187 (25.9)	20 (28.1)	9 (6.0)	4 (3.8)	37,909 (24.9)
Iceland	20 (1.3)	8 (1.1)		3 (2.0)	3 (2.9)	3,004 (1.9)
Sweden	667 (46.2)	361 (50.0)	26 (36.6)	78 (52.3)	88 (85.4)	67,857 (44.5)
Type of neuroblastoma						
Neuroblastoma	1,267 (87.8)	584 (80.9)	70 (98.5)	128 (85.9)	71 (68.9)	
Ganglioneuroblastoma	176 (12.1)	137 (19.0)	1 (1.4)	21 (14.0)	32 (31.0)	

[a]Of the 332 5-year survivors for whom information on treatment was available, 9 received no treatment (awaiting spontaneous regression of the tumor) and are therefore not included in the analyses, leaving 323 in the three treatment groups. None of the survivors in our cohort received immunotherapy.
[b]High-dose chemotherapy with ASCT ± irradiation ± surgery (26 of the 72 survivors in this group also received radiotherapy out of which 12 received total body irradiation)
[c]Chemotherapy ± irradiation ± surgery, but not ASCT
[d]Treated with surgery only
[e]The earliest diagnosis of neuroblastoma in the cancer registries was in 1943 and in 1951 for the 5-year survivors.

Table 2. Observed and expected numbers of first hospital contacts for a disease in any of the 10 main diagnostic groups among 721 5-year survivors of neuroblastoma in the Nordic countries by attained age

				Hospitalization rate per 1,000 person-years		
	Observed	Expected	SHRR (95% CI)	Observed	Expected	AER (95% CI)
Total no. of people ever hospitalized	501	214.9	2.3 (2.1–2.6)	91	39	52 (44–60)
Total no. of first hospitalizations[a,b]	1,789	730.7	2.5 (2.3–2.6)	160	65	94 (87–102)
Attained age (years)						
<10	391	103.4	3.8 (3.4–4.2)	209	55	154 (133–175)
10–19	652	225.3	2.9 (2.7–3.1)	150	52	98 (87–110)
20–29	398	201.1	2.0 (1.8–2.2)	134	67	66 (53–79)
30–39	230	124.8	1.8 (1.6–2.1)	159	86	73 (52–94)
40–49	81	56.0	1.5 (1.2–1.8)	175	121	54 (16–92)
50–59	36	18.7	1.9 (1.4–2.7)	358	186	172 (55–289)
60–69	1	1.35	0.7 (0.1–5.3)	185	250	−64 (−427–298)

[a]Hospital discharge diagnoses 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) and Sweden 1964–2009 with stepwise inclusion of counties between 1964 and 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). Information on outpatient visits available in Denmark since 1995 and in Sweden since 2001. [b]For participants with more than one hospital contact for a particular disease category, only the first record in the 104 disease categories was retained. The relative risk was estimated for each of the 104 disease categories and for the ten main diagnostic groups by adding the numbers of first hospital contacts within each disease category. Thus, for each person, the total number of hospital contacts equalled the sum of hospital contacts for one of the 104 disease subcategories.

Abbreviations: SHRR, standardized hospitalization rate ratio; CI, confidence interval; AER, absolute excess risk per 1,000 person-years.

Follow-up for hospital contacts started 5 years after the date of diagnosis (corresponding date for comparison subjects) or the start of the hospital registers, whichever occurred later. Follow-up ended on 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), whichever occurred first. Both primary and supplementary diagnoses were included. If a person had more than one hospital contact for a disease subcategory, only the first record was retained. The risk for a first hospital contact was estimated for each of the 104 disease subcategories and for the ten main diagnostic groups; for each person, the total number of hospital contacts equalled the sum of first hospital contacts for the 104 disease subcategories. Standardized hospitalization rate ratios (SHRR) were calculated as the observed number of first hospital contacts among neuroblastoma survivors in a given disease category divided by the expected number derived from the appropriate country, sex-, age-, and calendar period-specific hospitalization rates of the comparison cohort. The 95% confidence intervals (CIs) of the SHRRs were estimated with Fieller's theorem, on the assumption that the observed number of first hospital contacts followed a Poisson distribution. The absolute excess risks (AERs) of survivors for a first hospital contact were calculated as the difference between the observed and expected hospitalization rates for a particular disease category per 1,000 person-years of follow-up.

To test the robustness of the overall results, we conducted a sensitivity analysis restricted to neuroblastoma survivors diagnosed 5 years before the start of the national patient registries until the end of the study period.

We used the Aalen-Johansen estimator to estimate the cumulative incidence of first hospital contacts for each of the ten main diagnostic groups and for all groups combined, taking the competing risk for death into account and time since diagnosis as the underlying timescale.[19] For this analysis, we used the comparisons directly matched to the cohort of neuroblastoma survivors by country, sex, age and calendar period (n = 3,511).

To estimate the effects of sex, age at diagnosis, and treatment on the hazard for a first hospital contact, we conducted a multivariable analysis with these covariates within the clinical subcohort of 5-year survivors for whom information on treatment was available. A Cox proportional hazards model was used to estimate the cause-specific hazard ratios (HRs) of a first hospital contact with follow-up starting 5 years after neuroblastoma diagnosis and with time since diagnosis as the underlying time scale and censoring for the competing event, death.[20] The reference groups were male patients for sex and patients treated by surgery only for treatment.

We used SAS software versions 9.3 and 9.4 to determine the relative (SHRR) and absolute (AER) risks. To estimate the probability of survival, the cumulative incidence of hospitalizations and for the within-cohort analysis, we used the statistical software R version 3.3.2 and the packages survival, etm and timereg.

The design of the ALiCCS study was approved by the national bioethics committees, the data protection authorities, or the national institutes for health and welfare in the respective countries (Denmark: 2010–41-4334, Finland: THL/520/5.05.00/2016,

Table 3. Standardized hospitalization rate ratios (SHRRs) and absolute excess risks (AERs) of 721 5-year survivors of neuroblastoma in each of the 104 specific somatic disease categories for which there were at least five* observations (leaving 77 disease categories) including diagnoses for both inpatient and outpatient visits**

Main diagnostic group	No. of first hospital contacts			
Disease category	Observed	Expected	SHRR (95% CI)	AER per 1,000 person-years (95% CI)
Infectious and parasitic diseases				
Intestinal infectious diseases	27	13·7	2·0 (1·6–2·9)	1·2 (0·3–2·1)
Sepsis	12	1·5	8·3 (4·6–14·7)	1·0 (0·3–1·6)
Erysipelas	9	2·3	3·9 (2·0–7·6)	0·6 (0·1–1·1)
Other bacterial diseases	9	2·3	3·9 (2·0–7·5)	0·6 (0·1–1·1)
Other viral diseases with exanthem	7	4·9	1·4 (0·7–3·0)	0·2 (–0·3–0·7)
Infectious hepatitis, HIV infections (only in ICD-9 and -10), and other viral diseases	44	14·1	3·1 (2·3–4·2)	2·8 (1·6–4·0)
Syphilis and other venereal diseases	9	10·7	0·8 (0·4–1·6)	– 0·2 (–0·7–0·4)
Mycoses	9	5·0	1·8 0·9–3·4)	0·4 (–0·2–0·9)
Other infectious and parasitic diseases	6	4·1	1·5 (0·7–3·3)	0·2 (–0·3–0·6)
Endocrine diseases, nutritional deficiencies, and other metabolic diseases				
Diseases of the thyroid gland	33	5·0	6·6 (4·7–9·4)	2·5 (1·5–3·6)
Diabetes mellitus	10	7·5	1·3 (0·7–2·5)	0.2 (–0.3–0.8)
Pituitary hypofunction	21	0·6	35·7 (22·6–56·5)	1·8 (1·0–2·6)
Ovarian dysfunction	10	1·7	6·1 (3·2–11·3)	0·7 (0·2–1·3)
Testicular dysfunction	6	0·1	67·5 (27·4–166·4)	0·5 (0·1–1·0)
Disorders of other endocrine organs	25	4·1	6·1 (4·1–9·0)	1·9 (1·0–2·8)
Other metabolic disorders	31	2·6	11·9 (8·3–17·0)	2·6 (1·6–3·5)
Male sterility	11	2·2	5·1 (2·8–9·2)	0·8 (0·2–1·4)
Abnormal menstruation	19	11·1	1·7 (1·1–2·7)	0·7 (–0·1–1·5)
Female infertility	11	6·7	1·7 (0·9–3·0)	0·4 (–0·2–1·0)
Other disorders of the female reproductive system	14	9·6	1·5 (0·9–2·5)	0·4 (–0·3–1·1)
Diseases of the blood and blood-forming organs				
Anemias	19	3·3	5·9 (3·7–9·2)	1·4 (0·6–2·2)
Coagulation defects, purpura, and other hemorrhagic conditions	10	2·8	3·6 (1·9–6·8)	0·7 (0·1–1·2)
Diseases of the nervous system and sense organs				
Epilepsy	30	6·58	4·6 (3·2–6·5)	2·1 (1·2–3·1)
Migraine and other diseases of the brain and spinal cord	30	10·71	2·8 (2·0–4·0)	1·8 (0·8–2·7)
Diseases of the nerves and peripheral ganglia	34	9·25	3·7 (2·6–5·2)	2·3 (1·2–3·3)
Inflammatory and other diseases of the eye	62	30·5	2·0 (1·6–2·6)	2·9 (1·5–4·4)
Inflammatory diseases of the ear	45	19·4	2·3 (1·7–3·1)	2·4 (1·2–3·6)
Other diseases of the ear and deafness	40	8·4	4·8 (3·5–6·5)	2·9 (1·7–4·0)
Paralytic syndromes	34	0·9	36·6 (25·6–52·4)	3·0 (2·0–4·1)
Diseases of the circulatory system				
Hypertensive disease	16	4·0	4·0 (2·5–6·6)	1·1 (0·4–1·8)
Pericardial, myocardial, and endocardial disease	6	1·35	4·4 (2·0–10·0)	0·4 (0–0·8)

(Continues)

Table 3. Continued

Main diagnostic group	No. of first hospital contacts			
Disease category	Observed	Expected	SHRR (95% CI)	AER per 1,000 person-years (95% CI)
Valvular disease (non-rheumatic)	6	0·6	9·5 (4·2–21·4)	0·5 (0·1–0·9)
Heart failure	10	0·8	12·7 (6·7–23·9)	0·8 (0·3–1·4)
Conduction disorders	9	4·6	2·0 (1·0–3·8)	0·4 (–0·1–0·9)
Cerebrovascular disease	10	2·1	4·7 (2·5–8·9)	0·7 (0·2–1·3)
Diseases of the arteries, arterioles, and capillaries	7	1·6	4·5 (2·1–9·5)	0·5 (0–1·0)
Venous and lymphatic disease	16	11·0	1·5 (0·9–2·4)	0·5 (–0·3–1·2)
Diseases of the respiratory system				
Acute upper respiratory infections	52	31·7	1·6 (1·3–2·2)	1·9 (0·6–3·2)
Other disorders of the upper respiratory tract	74	53·8	1·4 (1·1–1·7)	2·0 (0·3–3·6)
Pneumonia	32	10·3	3·1 (2·2–4·4)	2·0 (1·0–3·0)
Abscess of lung and pyothorax	6	0·87	6·9 (3·1–15·5)	0·5 (0–0·9)
Bronchitis and emphysema	11	4·19	2·6 (1·5–4·8)	0·6 (0–1·2)
Asthma	21	20·97	1·0 (0·7–1·5)	0 (–0·8–0·8)
Respiratory failure	13	0·60	21·8 (12·4–38·5)	1·1 (0·5–1·8)
Other diseases of the respiratory system	5	0·64	7·8 (3·2–19·1)	0·4 (0–0·8)
Diseases of the digestive organs				
Diseases of the teeth and supporting structures	34	10·70	3·2 (2·3–4·5)	2·1 (1·1–3·2)
Other diseases of the oral cavity and salivary glands	6	3·42	1·8 (0·8–3·9)	0·2 (–0·2–0·7)
Diseases of the esophagus	10	4·23	2·4 (1·3–4·4)	0·5 (0–1·1)
Diseases of stomach and duodenum	24	8·23	2·9 (2·0–4·4)	1·4 (0·6–2·3)
Appendicitis	19	21·48	0·9 (0·6–1·4)	– 0·2 (–0·1–0·6)
Hernia of the abdomal cavity	14	10·89	1·3 (0·8–2·2)	0·3 (–0·4–0·9)
Non-infective enteritis and colitis	8	7·48	1·1 (0·5–2·1)	0·0 (–0·5–0·5)
Paralytic ileus and intestinal obstruction	20	1·14	17·5 (11·1–27·6)	1·7 (0·9–2·5)
Diseases of the anal and rectal regions	6	5·21	1·2 (0·5–2·6)	0·1 (–0·4–0·5)
Diseases of the peritoneum	8	0·83	9·7 (4·8–19·6)	0·6 (0·1–1·1)
Other diseases of the digestive system	38	14·27	2·7 (1·9–3·7)	2·2 (1·1–3·3)
Diseases of the liver	9	1·43	6·3 (3·2–12·2)	0·7 (0·2–1·2)
Diseases of the gallbladder and biliary ducts	10	7·79	1·3 (0·7–2·4)	0·2 (–0·4–0·8)
Diseases of the urinary system and genital organs				
Glomerular diseases	7	1·4	4·9 (2·3–10·3)	0·5 (0–1·0)
Chronic kidney disease	18	1·6	11·2 (7·0–17·9)	1·5 (0·7–2·2)
Urolithiasis	8	3·4	2·4 (1·2–4·7)	0·4 (–0·1–0·9)
Obstructive uropathy	11	1·5	7·4 (4·0–13·4)	0·9 (0·3–1·4)
Infections of the urinary system	40	14·1	2·8 (2·1–3·9)	2·4 (1·2–3·5)
Other and unspecified disorders of the urinary system	50	4·3	11·8 (8·9–15·6)	4·3 (3·0–5·6)
Hydrocele and spermatocele	5	1·5	3·3 (1·4–8·1)	0.3 (–0·1–0·7)
Other diseases of the male genital organs	17	11·3	1·5 (0·9–2·4)	0·5 (–0·2–1·3)
Chronic cystic disease and other diseases of the breast	19	7·7	2·5 (1·6–3·9)	1·0 (0·2–1·8)

(Continues)

Table 3. Continued

Main diagnostic group	No. of first hospital contacts			
Disease category	Observed	Expected	SHRR (95% CI)	AER per 1,000 person-years (95% CI)
Inflammatory diseases of the female pelvic organs	26	15·3	1·7 (1·2–2·5)	1·0 (0·1–1·9)
Endometriosis	5	3·1	1·6 (0·7–3·8)	0·2 (–0·2–0·6)
Non-inflammatory disorders of the female genital tract	26	16·1	1·6 (1·1–2·4)	0·9 (0–1·8)
Diseases of the skin and subcutaneous tissue				
Infections of the skin and subcutaneous tissue	27	12·3	2·2 (1·5–3·2)	1·3 (0·4–2·3)
Other inflammatory conditions of the skin and subcutaneous tissue	33	24·4	1·4 (1·0–1·9)	0·8 (–0·3–1·8)
Disorders of skin appendages (hair, nails, sweat glands)	18	12·1	1·5 (0·9–2·4)	0·5 (–0·2–1·3)
Other disorders of the skin and subcutaneous tissue	55	7·7	7·2 (5·5–9·4)	4·4 (3·0–5·7)
Diseases of the bone, joints, and soft tissue				
Arthritis and rheumatism	21	14·3	1·5 (1·0–2·3)	0·6 (–0·2–1·4)
Osteomyelitis and other diseases of the bone and joints	138	49·4	2·8 (2·4–3·3)	8·7 (6·4–11·0)
Other diseases of the musculoskeletal system	86	32·1	2·7 (2·2–3·3)	5·4 (3·6–7·2)

*To provide a complete and comprehensive overview of all diseases with an observed number 5. Note that some CI's are very wide and thus should be interpreted with caution.
**Including outpatient visits since 1995 in Denmark and 2001 in Sweden.
We did not include the following ICD sections: second malignant neoplasms, as we excluded all subjects with more than one cancer before age 20 from the survivor group and all subjects with a primary cancer before age 20 from the comparisons; mental disorders, as these are reported in a separate registry; symptoms and ill-defined diseases, as these were regarded not specific enough for solid conclusions; and injuries and violence, as these conditions are of external origin. We did not include the sections on deliveries and reproductive difficulties, as these require special consideration and will be dealt with in a separate publication.

Iceland: VSN 10–041 & VSN 12–084-V1 and Sweden: Ö 10–2010, 2011/19).

Results

Table 1 shows the main characteristics of all children with neuroblastoma, 5-year survivors, and population comparisons. The basic cohort comprised 1,443 individuals, of whom 721 survived for 5 years or more. Information on treatment was available for 332 (46%) of all 5-year survivors.

Figure 1 shows the 5-year survival of children with neuroblastoma by period of diagnosis from before 1980 and up until 2004. Survival increased significantly and steadily over time: the 5-year survival of children with neuroblastoma diagnosed in 1980–1989 was 53% (95% CI 47–59), and that of cases diagnosed in 2000–2004 was 68% (95% CI 63–74).

The 5-year survivors were followed in the national hospital registries for a median of 13.4 years (range, 0.08–42), yielding 5,500 person-years of observation. A total of 501 survivors had a first hospital contact, while 215 would have been expected, giving a significantly increased relative risk of 2.3 (95% CI 2.1–2.6) (Table 2), with no apparent difference between males (SHRR 2.3 95% CI 2.0–2.6) and females (SHRR 2.4 95% CI 2.1–2.7). The AER of survivors was 52 per 1,000 person-years (95% CI 44–60). Thus, for each additional year of follow-up, approximately five of every 100 5-year survivors had a first hospital contact for a new disease beyond background levels.

The relative risk for a first hospital contact for a disease in any of the ten main diagnostic groups was increased at all ages, even for survivors approaching 60 years. However, the risk decreased with increasing age, from 3.8 (95% CI 3.4–4.2) for survivors below 10 years to 1.9 in survivors aged 50–59 years (Table 2), as did the AER, except for patients aged 50–59 years, who had an AER of 172 for a first hospital contact per 1,000 person-years (95% CI 55–289).

The relative risks for a first hospital contact for diseases in all ten main diagnostic groups as well as for any disease were statistically significantly increased among survivors (SHRR 2.5; CI 95% 2.3–2.6) (Figure 2(a)). The risks of survivors for diseases in nine of the ten main diagnostic groups were more than double those of comparisons. The highest relative risks were seen for diseases of blood and blood-forming organs (SHRR 3.8; 95% CI 2.7–5.4), endocrine organs (SHRR 3.6; 95% CI 3.1–4.2), the circulatory system (SHRR 3.1; 95% CI 2.5–3.8), and the nervous system (SHRR 3.0; 95% CI 2.6–3.3). The increases were even higher for the group of survivors treated with high-dose chemotherapy with ASCT (Figure 2b).

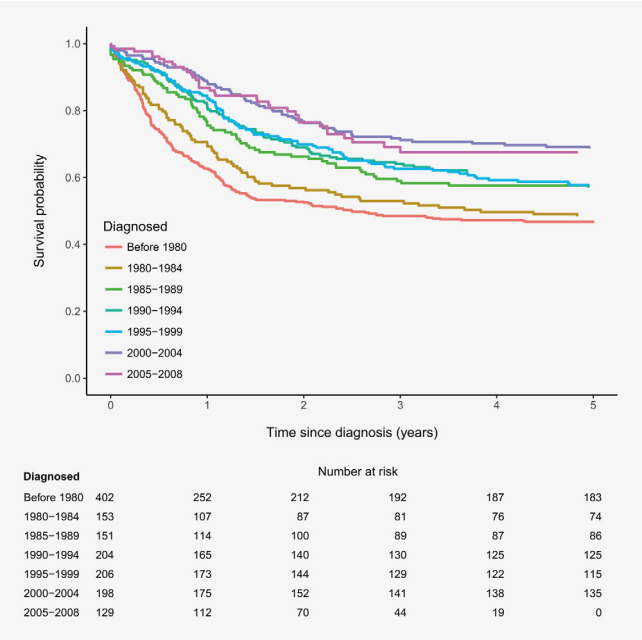

Figure 1. Survival curves for the basic cohort of 1,143 children with neuroblastoma, by period of diagnosis. [Color figure can be viewed at wileyonlinelibrary.com]

The analysis limited to 654 survivors with a full hospital history did not show any notable difference for the total number of first hospital contacts for any disease (RR 2.6; CI 95% 2.5–2.7).

Diseases of the nervous system and sense organs (AER 17 per 1,000 person-years; 95% CI 14–20), the urinary system and genital organs (AER 13; 95% CI 10–15), endocrine diseases and nutritional deficiencies (AER 13; 95% CI 10–15), and diseases of bone and soft tissue (AER 12; 95% CI 10–15) were the reasons for almost 60% of all excess new hospital contacts (Figure 2a; Table 3). The disease pattern was similar for the 71 survivors treated with high-dose chemotherapy with ASCT and for the 149 survivors treated with chemotherapy ±irradiation, with slight variations. For those treated by surgery only, diseases of the nervous system, infections, diseases of the skin, and diseases of bone and soft tissue were the reasons for 65% of all excess new hospital contacts, whereas the AER for hospitalization for endocrine diseases was not significantly increased (AER 1; 95% CI –4–6) (Figure 2b).

Figure 3 shows that 69% (95% CI 65.0–72.6) of all 5-year survivors and 45% (95% CI 43.0–47.0) of the population comparisons had had at least one first hospital contact 20 years after diagnosis; after 40 years, the proportions were 89% (95% CI 86.1–92.7) and 79% (95% CI 77.1–81.7), respectively.

For the subcohort of survivors for whom information on treatment was available, the cumulative incidence of a first hospital contact was significantly higher than that for comparisons 15 years after diagnosis. The highest cumulative risk was seen for survivors treated with high-dose chemotherapy with ASCT, of whom 79% had had a first hospital contact, as compared with 41% of comparisons. The cumulative risks for diseases in the other main diagnostic groups are presented in Figure S2.

The within-cohort analysis of 5-year survivors for whom information on treatment was available showed no significant effect of sex (HR 1.00; 95% CI 0.76–1.31) or age at diagnosis (HR 1.04; 95% CI 0.99–1.08). The cause-specific hazard of patients treated with chemotherapy ±irradiation (HR 1.00; 95% CI 0.73–1.37) was not significantly different from that of patients treated by surgery only (reference group). The hazard for a first hospitalization of patients treated with high-dose chemotherapy with ASCT was significantly higher than that of patients treated by surgery only (HR 1.54; 95% CI 1.06–2.26).

Discussion

This population-based study of 721 5-year neuroblastoma survivors in the Nordic countries illustrates the pattern of somatic late effects serious enough to require a hospital contact. The survivors had a hospital contact for a new somatic disease 2.5 times as often as the general population, and the increased risk was higher for the subgroup of survivors who received the most intensive treatment (RR 5.8; 95% CI 5.0–6.8). Both the cancer and its treatment may adversely affect virtually any organ or body system; however, survivors who had been treated with high-dose chemotherapy with ASCT had the highest relative and absolute excess risks for somatic diseases in all ten main diagnostic groups.

Before the mid-1990s, almost no children in the Nordic countries with disseminated neuroblastoma (stage IV) survived. Those who survived had either been diagnosed as infants (<12 months of age) or had localized disease. Their treatment included surgery and/or radiotherapy. In few cases, i.e., in very young children or infants, no treatment was given awaiting spontaneous tumor regression. In the late 1980s, the Nordic countries (except from Finland) joined the European Neuroblastoma Study Group (ENSG) and participated in ENSG protocols investigating the role of cis-retinoic acid (ENSG4) and that of intensified induction chemotherapy (COJEC *vs.* OPEC/OJEC, ENSG5, [21]). Nevertheless, survival of disseminated neuroblastoma first improved after the introduction of high dose chemotherapy (melphalan +/− busulfan or carboplatin) followed by autologous stem cell rescue in the mid-1990s. Irradiation of the primary tumor bed was only performed in case of inoperable tumor or macroscopic tumor rest. Inoperable localized tumors received preoperative chemotherapy (OPEC/OJEC[22]) prior to tumor resection and/or radiotherapy. Finland used its own protocols, which included total body irradiation (TBI) since 1987 and high dose chemotherapy with stem cell rescue since 1982.[23] TBI has not been used in Denmark, Iceland and Sweden.

The Nordic countries are now part of the SIOPEN–NB group (except Finland). Thus, since the early 2000s high-risk neuroblastoma patients have been treated according to the SIOPEN-NB protocols. Today, the treatment of disseminated/

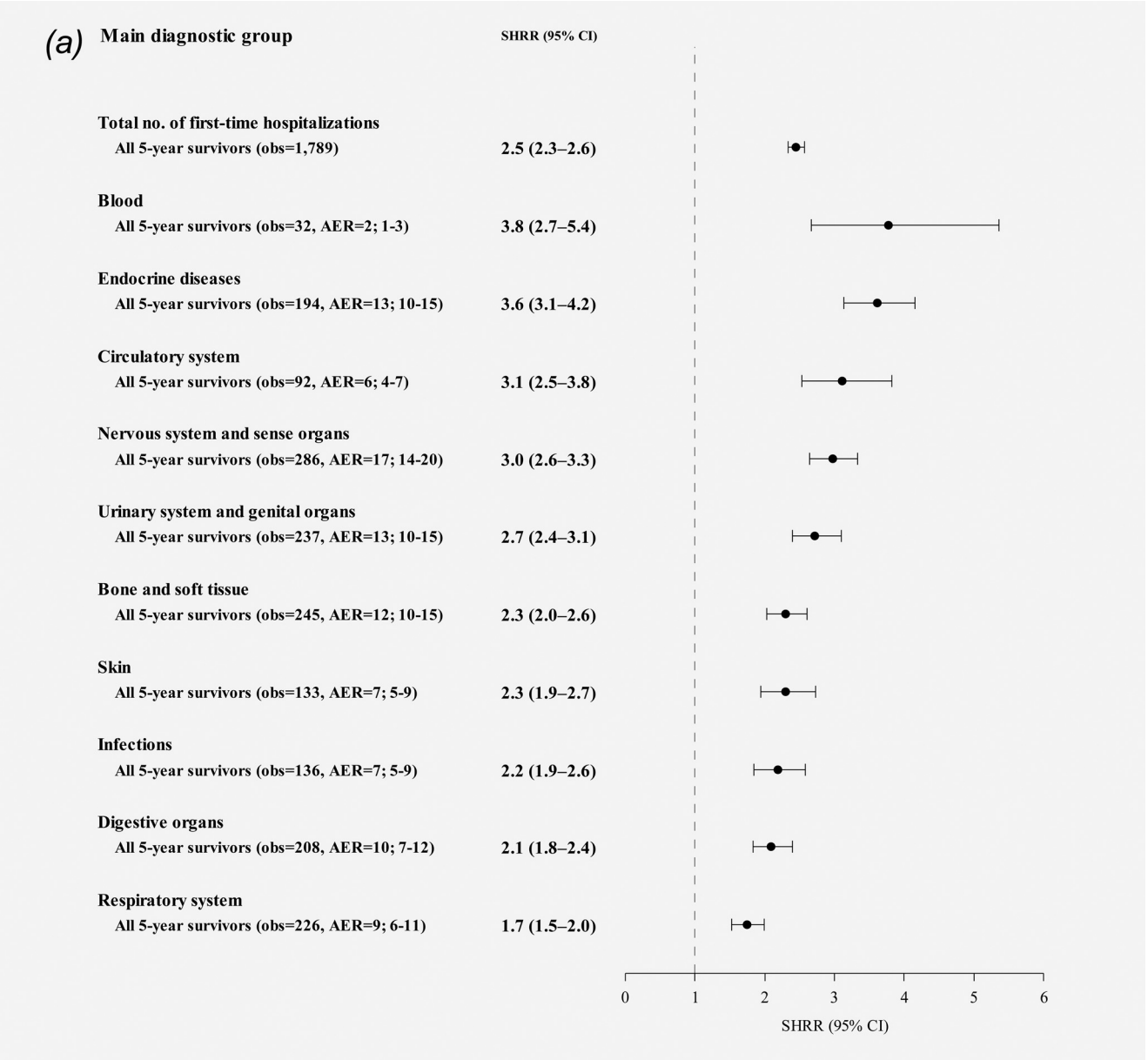

Figure 2. (*a* and *b*) Standardized hospitalization rate ratios (SHRRs) and absolute excess risks (AERs) per 1,000 person-years of follow-up for first hospital contacts for any disease and diseases in ten main diagnostic groups among 5-year survivors of neuroblastoma diagnosed from 1951–2008 and of the subcohort of survivors diagnosed from 1980–2008 for whom information on treatment was available, by treatment group.

high risk neuroblastoma consists of intensive induction treatment, surgery of the primary tumor, high dose chemotherapy with autologous stem cell rescue, radiotherapy to the field of the primary, cis-retinoic acid and in more recent time also anti-GD2 antibody.

Localized or metastatic disease with favorable tumor characteristics in young children under the age of 1–1½ year has the ability of spontaneous regression, whereas older children with localized disease are treated with surgery only and/or with chemotherapy. Children with disseminated disease or unfavorable tumor characteristics require very intensive multimodal treatment including high-dose chemotherapy, targeted radiotherapy and immunotherapy. Contemporary regimens, which incorporate chemotherapeutic agents and treatment modalities used for many decades, have evolved to improve relapse-free survival (as shown in Figure 1) and reduce long-term toxicity. Despite that, more than 50% of patients need intensive treatment that may cause unavoidable long-term toxicity.

The cumulative incidence of adverse health conditions in survivors increased with time and did not appear to plateau during the follow-up period. The cumulative incidence of somatic diseases was much higher in survivors than comparisons at an

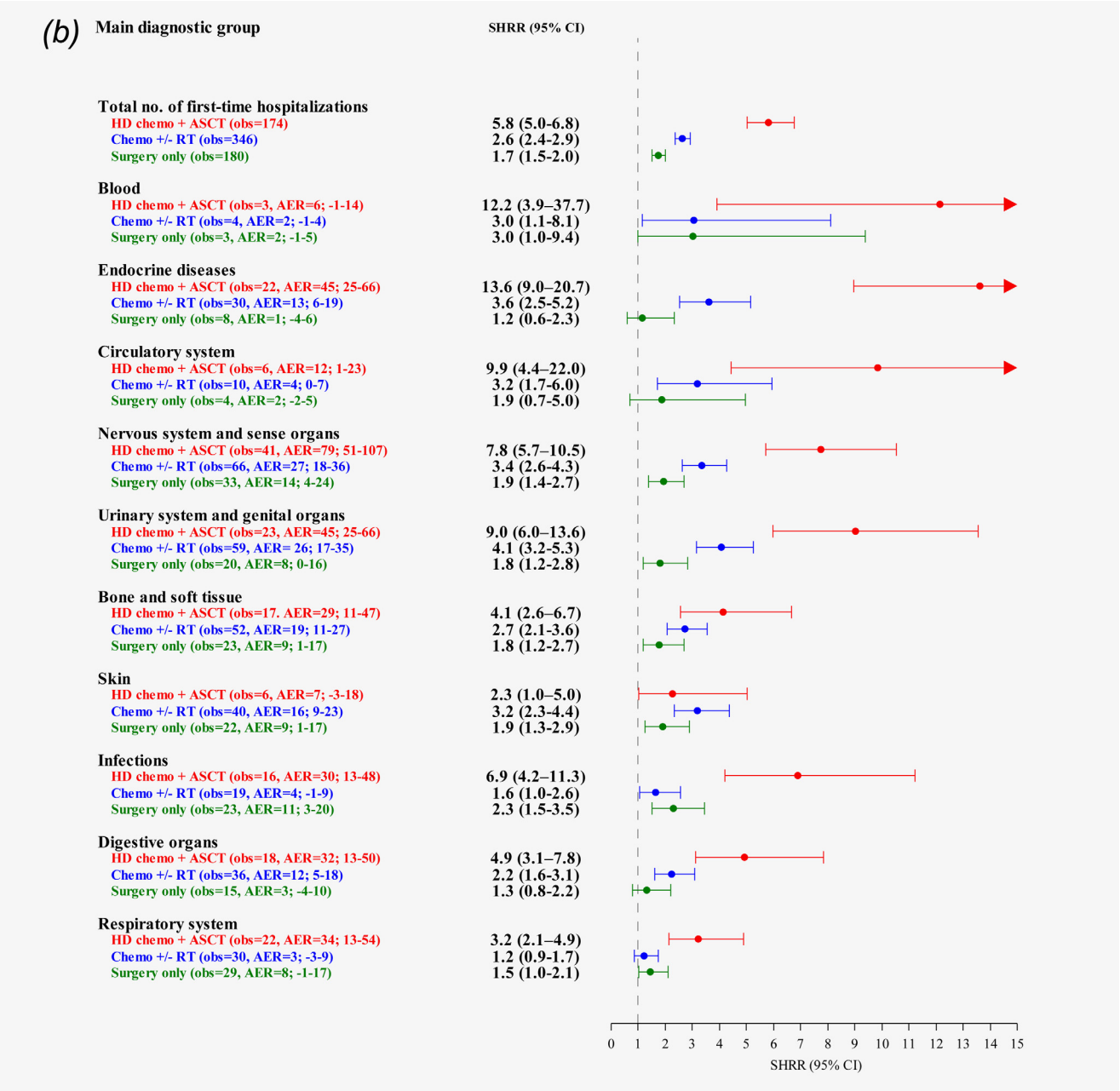

Figure 2. Continued [Color figure can be viewed at wileyonlinelibrary.com]

earlier stage of life, both for overall somatic diseases as well as for specific main diagnostic groups, implying premature aging or frailty in survivors[24] (Figure 3). The increases in relative and absolute excess risks for a hospital contact were higher in the youngest group of survivors (<10 years) and decreased with time since diagnosis. Although variations were seen by age and treatment, the findings imply that the majority of neuroblastoma survivors are at substantial risk for somatic late effects and that the risk remains increased throughout life. For survivors treated by surgery only, the overall risk was moderate.

Although little has been known about treatment-induced late effects in neuroblastoma survivors until today, it was evident that this group of survivors had an excess risk for long-term morbidity[25–30] Oeffinger et al. showed that 416 5-year neuroblastoma survivors included in the Childhood Cancer Survivor Study had twice the risk of reporting at least one adverse chronic health condition than siblings and an almost five times greater risk for a severe or life-threatening condition.[9] Laverdiére et al. found that the risk of neuroblastoma survivors for a chronic health condition primarily involving the neurological,

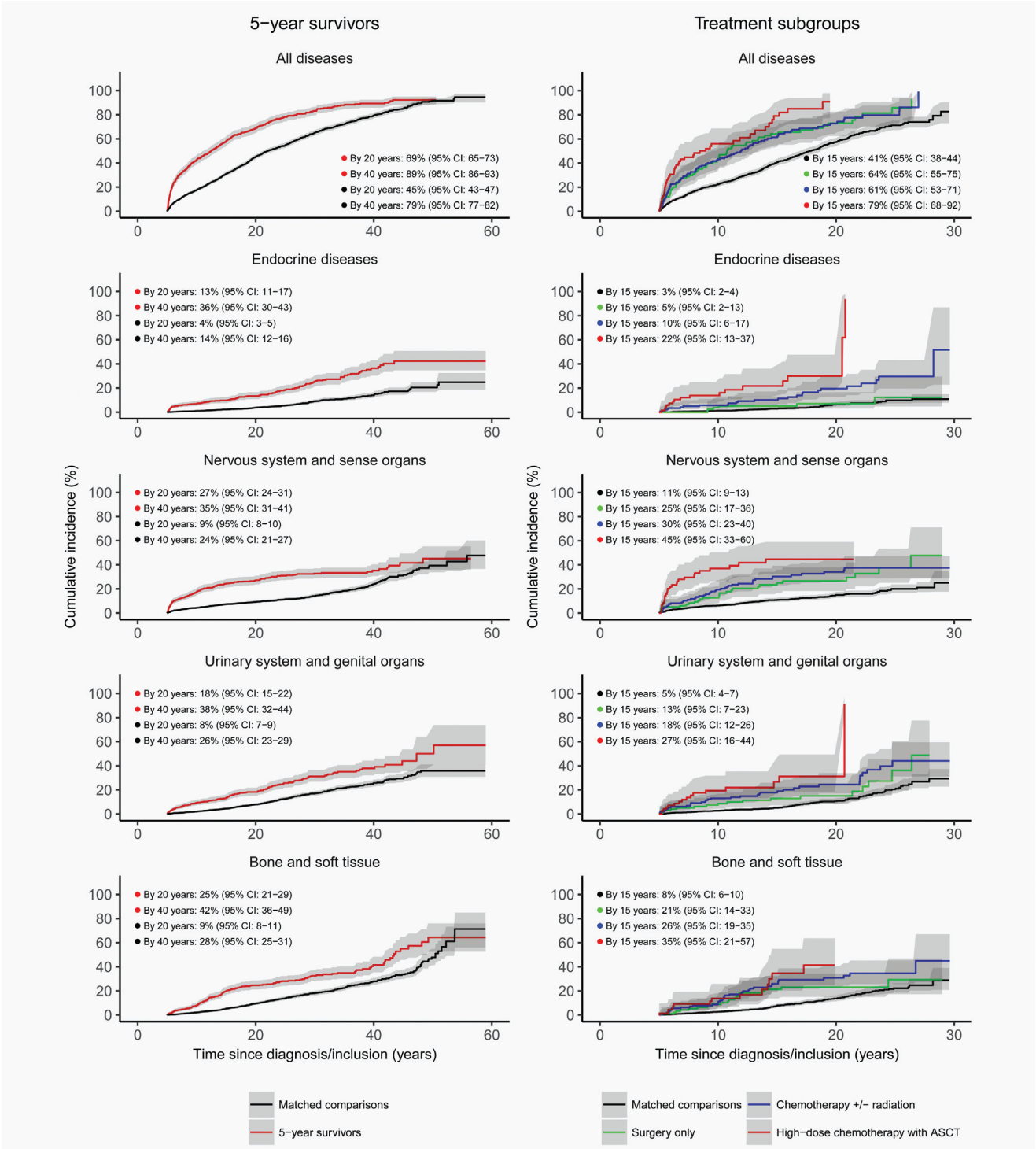

Figure 3. Cumulative incidence of first hospital contacts for any disease and for four main diagnostic groups among 5-year survivors and for the subcohort for whom information on treatment was available, by time since cancer diagnosis and the corresponding date for comparisons. Note, that beyond 40–50 years from time of diagnosis for all 5-year survivors there are few cases, and correspondingly beyond 20 years from time of diagnosis in the treatment subgroups. [Color figure can be viewed at wileyonlinelibrary.com]

sensory, endocrine, and musculoskeletal systems was almost eight times higher than that of siblings.[12] Kurt et al. found a relative risk for self-reported hospitalization of 1.7 for neuroblastoma survivors as compared with the population rates derived from a United States National Hospital Discharge Survey covering the period 1992–2005.[31] This finding is fairly

consistent with ours, despite differences in the source of hospitalizations and the period of diagnosis (1970–1986 in the Childhood Cancer Survivor Study; 1951–2008 in ALiCCS).

Studying late effects in long-term neuroblastoma survivors, the majority of the study subjects will be survivors of low-stage tumors. According to Fox et al.[4] 50–60% of all children with neuroblastoma included in the Childhood Cancer Survivor Study and diagnosed in the 1970s had metastatic disease (stage IV) at presentation, but less than 15% of these patients survived for 5 years. Thus, 75% of the survivor cohort were presumably survivors of stage I or II disease,[4] which would result in underestimation of the risk for late effects of patients with intermediate and high-risk neuroblastoma. The Nordic survivors who were treated with high-dose chemotherapy with ASCT and all diagnosed between 1990 and 2008 had a relative risk for somatic disease of 5.8 as compared with 2.6 in the subgroup treated with chemotherapy ±irradiation. This high relative risk implies that intensive treatment of high-risk patients since the 1990s has improved survival but results in more late effects.

Disorders of the nervous system accounted for 18% of the absolute excess risk for any disorder in 5-year survivors and for 21–25% in the subgroups for whom information on treatment was available, with AERs ranging from 14 per 1,000 survivors (95% CI 4–24) for those treated by surgery only to 79 (95% CI 51–107) for those treated with high-dose chemotherapy with ASCT. The increased risk for late effects of patients treated by surgery only is probably due to the fact that the tumor can arise close to the spine and grow into the spinal canal, causing medullary compression (dumbbell tumor), resulting in permanent neurological deficits.

We used hospital-based diagnoses as markers of somatic diseases. This increased the validity of the diagnostic information but may have overlooked less severe late effects treated in the primary health care system or in outpatient clinics. As information on outpatient visits was available only in Denmark and Sweden and only recently, the overall burden of somatic disease experienced by neuroblastoma survivors is probably underestimated. As such underregistration can be assumed to affect survivors and comparisons equally, thus, it is not expected to affect the risk estimates. However, some diagnoses, such as cisplatin-induced hearing impairment, may not be systematically registered by the treating physician since hearing loss is commonly seen after treatment with cisplatin. Another possible limitation is that survivors of childhood cancer are likely to be followed more intensively in the health care system than the average population, so that any health problems may be detected at an earlier stage than in comparisons.

Our study was population-based, and we had randomly selected comparisons, data from high-quality health registries, and information on treatment for a large sample of long-term survivors. Thus, we consider that our results are applicable to children treated for neuroblastoma in other countries with similar health care systems. A more thorough evaluation of this group of survivors would include medical record abstraction to obtain detailed information on drugs and doses, radiotherapy and radiation fields, surgical procedures, as well as clinical examinations.

In conclusion, we found that neuroblastoma survivors had a much higher long-term risk for late somatic effects in all main diagnostic groups than a background population of similar age and matched on sex. The increased relative risk was seen for all treatment groups but was most pronounced for the survivors who had been treated most intensively.

Clinicians in primary and secondary health care should be aware that survivors of neuroblastoma are hospitalized more than twice as often as the general population for a wide range of serious somatic conditions. The excess risk could be translated into nine new excess hospital contacts for every 100 survivors followed for a year. Life-long follow-up in late effect clinics is highly recommended to ensure timely diagnosis and management of emerging and established late effects in this vulnerable group of patients.

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