Childhood cancer survivors: Evidence and care

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Chapter 4

High hospitalization rates in survivors of childhood cancer: a follow-up study using medical record linkage

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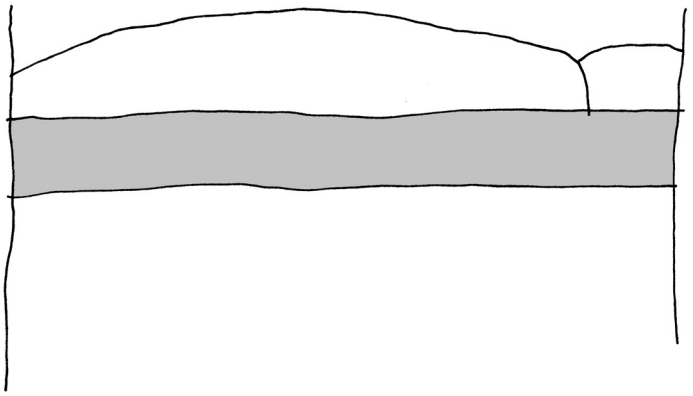

Abstract

Background

Childhood cancer survivors (CCS) have an increased risk of unfavorable health conditions related to previous cancer treatment. Hospitalization rates over time of CCS compared to the general population are unknown and provide insight into the burden and timing of these health conditions.

Objective

To define trends in hospitalization rate of CCS in comparison with the general population.

Methods

We identified hospitalizations in a complete cohort of ≥5 years survivors of childhood cancer (treated in a single center between 1966 and 1999) by performing medical record linkage with the Dutch Hospital Discharge Register from 1995 until 2005. We compared CCS hospitalization rates with rates from a random sample from the general Dutch population, matched on age, gender and calendar year. We quantified hospitalization rates of CCS and reference persons for the complete observation period and over time by fitting multivariable Poisson models. We analyzed risk factors for hospitalization within the CCS cohort.

Results

Of 1564 eligible CCS, we retrieved hospitalization information of 1382 CCS (88%, median follow-up time since cancer diagnosis 18.6 years, median attained age 25.7 years). Hospitalization rates in CCS were increased compared to reference persons up to at least 30 years after primary diagnosis, with highest rates 5-10 and 20-30 years after primary cancer. The relative hospitalization rate (RHR) in CCS was 2.2 (95% confidence interval (CI): 1.9-2.5). RHRs were highest for the hospitalization diagnosis groups neoplasms (10.7; 95% CI: 7.1-16.3) and endocrine/nutritional/metabolic disorders (7.3; 95% CI: 4.6-11.7). Female gender (P<0.001), radiotherapy to head and/or neck (P<0.001) or thorax and/or abdomen (P=0.03) and surgery (P=0.01) were associated with higher hospitalization rates within CCS.

Conclusion

CCS have increased hospitalization rates compared to the general population, up to at least 30 years after primary cancer treatment. These findings imply a high and long-term burden of health conditions after childhood cancer.

Introduction

More than 75% of children with cancer are cured of their cancer and become a long-term survivor.[1, 2] Unfortunately, childhood cancer survivors (CCS) do not always have similar perspectives of a healthy life compared to their peers. CCS are at increased risk of unfavorable health conditions that are often associated with their previous cancer treatment.[3-6] More than 60% of CCS has at least one health problem and around one third a severe or life-threatening health problem two decades after the cancer diagnosis.[7, 8] It is likely that with steadily growing numbers of CCS the impact of these so-called late effects of cancer treatment is increasing for societies and their health care systems.[9]

Hospital admissions influence a patient's daily life and quality of life, affect the health care system and generate societal costs.[10-13] Hospitalization rates over time can provide insight into the burden of health conditions on individuals and on health care resources.[14] For both perspectives it is essential that hospital admissions of the growing group of CCS are prevented if feasible. Thus far, few studies focused on hospital admissions and only determined average hospitalization rates in CCS.[15-17] No study has analyzed hospitalization rates over time in CCS, even though such trends are likely to be a better measure for the burden of health conditions than the average hospitalization rate.[14] Insight into trends and risk factors for hospitalizations can also help to further focus and prioritize long-term follow-up care for CCS at highest risk to have health conditions requiring hospitalizations.

The objective of the current study was to define the burden of unfavorable health conditions in CCS as measured by trends in hospitalization rates. We determined hospitalization rates of CCS in comparison with a random reference sample from the general population, using medical record linkage between a cohort of CCS and Dutch administrative registers. Our secondary aim was to examine which subgroups within CCS are at highest risk for hospitalization.

Methods

Study population

The Emma Children's Hospital/Academic Medical Center (EKZ/AMC) childhood cancer survivor cohort is a single-center cohort study of CCS with near-complete information on patient, cancer, treatment characteristics and clinical follow-up.[7] For the current study, we included all individuals who were diagnosed with childhood cancer before the age of 18 years, primarily treated in the EKZ/AMC between January 1, 1966 and January 1, 1999 and survived at least five years since primary cancer diagnosis. The national administrative registers had electronic data available from 1995 onwards. As a result, CCS in this study were eligible for medical record linkage if they were alive at January 1, 1995.

From our EKZ/AMC cohort study database, we retrieved information on patient characteristics, cancer diagnosis, all cancer treatment before the date of five-year survival, recurrences and subsequent cancers. Informed consent for registration in our study registry was obtained from all patients. The Medical Ethics Committee of our hospital exempted us to ask for additional informed consent for the current study.

We used the Municipal Personal Records Database (Dutch acronym: GBA) to obtain a random reference population from the Dutch general population. For every CCS that was retrieved from GBA, we sampled 20 persons at maximum from GBA with corresponding year of birth and gender. We assigned the date of primary cancer diagnosis of the corresponding CCS to reference persons in order to analyze data per survival year and to adjust for age and calendar period. See appendix for more detailed information.

Linkage procedure

We retrieved longitudinal hospitalization data from 1995 until 2005 using medical record linkage. Because an individual identification number is lacking in the Hospital Discharge Register (Dutch acronym: LMR), we used a two-step medical record linkage approach.[18] We linked a dataset of 1564 eligible five-year CCS to GBA, which registers individual postal code history of all citizens in the Netherlands, and subsequently to LMR. The LMR contains electronic information on all hospitalizations (day case admissions and clinical hospitalizations) of almost every hospital in the Netherlands from 1995 onwards (coverage >99% until 2004 and 96.7% in 2005).[19] Uncomplicated (day case) hospitalizations for delivery are not included in the registry. See appendix for more detailed information.

For all CCS retrieved in GBA and for all sampled reference persons, we defined during which time periods individuals were unique based on gender, date of birth and postal code (i.e. no other individuals registered in GBA with exactly the same combination of values for these variables). We extracted hospitalization data from LMR when an individual was unique at the date of hospital discharge.

Accrual of time at risk for hospitalization began at the first date a person was unique since the date of five-year survival (i.e. five years after the date of primary childhood cancer diagnosis) or January 1, 1995, whatever came later. Accrual of time at risk ended at the date a person was not unique anymore or January 1, 2006, whatever came earlier. Time at risk was not counted during hospitalizations. When multiple unique periods were available, we summed up the time of the unique periods to define the total time at risk for hospitalization.

We hypothesized that CCS having a primary cancer recurrence or ongoing primary cancer recurrence therapy beyond the date of five-year survivorship would have increased exposure to cancer treatment and would simultaneously inflate the hospitalization rate. Because our interest was in hospitalizations beyond primary cancer survival, we therefore censored these individuals. Censoring (i.e. end of time at risk) was applied at the date of

five-year survival in case of ongoing cancer therapy for a primary cancer recurrence at that moment or at the incidence date of first primary cancer recurrence after the date of five-year survival.

Hospitalization characteristics and comparison of hospitalization rates of CCS with the reference population

We assessed the total number of hospitalizations and the total time at risk in CCS and reference persons during the study period. Two hospitalizations of which the second had a date of admission equal to the date of discharge of the first hospitalization were counted as one hospitalization.

We determined characteristics of hospitalizations in CCS and matched reference persons. Available hospitalization characteristics included the principal hospital discharge diagnosis (coded according to International Classification of Disease version 9 – clinical modification (ICD9-CM), [20] urgency of admission (acute vs. non-acute), type of admission (day care vs. clinical hospitalization) and type of hospital (general vs. university hospital).

In all analyses we used a Poisson regression model in which we corrected for recurrent hospitalizations via generalized estimating equations (GEE). An exchangeable correlation structure was assumed.

In a first comparison of hospitalization rates, we determined average hospitalization rates during the complete study period of CCS compared to matched reference persons. We calculated relative hospitalization rates (RHR) and absolute excess risks (AER) of hospitalization per 1000 person years at risk using the Poisson model.

We subsequently calculated average RHRs and AERs for CCS categories (gender, cancer diagnosis categories, four possible treatment categories based on chemotherapy and radiotherapy, and recurrence status before five-year survival) compared to matched reference persons. We also defined average RHR and AER for specific ICD9-CM hospitalization diagnosis groups in CCS and reference persons.

In a second comparison of hospitalization rates, we analyzed hospitalization rates over time in both groups, by including follow-up time since primary cancer diagnosis or attained age as covariate in the regression model. We modeled both covariates via natural splines with 7 knots to allow for non-linear changes over time. Parameter estimates of the individual spline components are hard to interpret. Therefore, we used graphs to describe trends. We also estimated hospitalization trends over follow-up time for CCS categories.

Risk factor analysis for hospitalization within CCS

In our final analyses, we examined risk factors associated with higher hospitalization rates *within* the cohort of CCS. In addition to follow-up time since primary cancer diagnosis, we included gender, calendar year of primary cancer diagnosis, age at primary cancer diagnosis and cancer treatment (cancer surgery; anthracyclines; alkylating agents; other

chemotherapy; radiotherapy to the head and/or neck; radiotherapy to the thorax and/or abdomen; radiotherapy to extremities) in the model. We took all cancer treatment that was given before the date of five-year survival into account.

We first fitted a model allowing for effect modification between all included variables and follow-up time, between main cancer treatment modalities (i.e. surgery, chemotherapy, radiotherapy) and gender, calendar year of primary cancer diagnosis and age at primary cancer diagnosis, and between the main cancer treatments themselves. We explored effect modification and included it in the final model when statistically significant at the 0.05 level. We modeled the effects of follow-up time, (corresponding) age at primary cancer diagnosis and (corresponding) calendar year of primary cancer diagnosis via natural splines with 4 or 5 knots to allow for a non-linear relationship with the hospitalization rate. Besides providing P-values for the overall effects of the variables, we also present results graphically.

We performed analyses using statistical software R version 2.15.0. P values <0.05 were considered statistically significant.

Results

Study population and results of linkage procedure

After the complete medical record linkage procedure, the study population consisted of 1382 (88%) of 1564 eligible CCS and of 26, 583 reference persons. For more information about the linkage procedure, see appendix.

Table 1 shows characteristics of CCS and reference persons contributing to unique follow-up time. There were no differences in distribution of gender, year of birth, (corresponding) age at primary cancer diagnosis and (corresponding) calendar year of primary cancer diagnosis induced by the two-step linkage process. The sampled reference persons and consequently the reference persons contributing to unique follow-up time had a higher proportion of non-native individuals, primarily due to a larger number of first generation non-native individuals. CCS accrued slightly more years of time at risk compared to the reference population (median of 8.8 and 8.1 years respectively). At the end of follow-up CCS and reference persons had a median attained age of 25.7 and 25.9 years respectively. The median duration of follow-up since (corresponding) date of primary cancer diagnosis was 18.6 years in both groups. Censoring at the date of five-year survival in case of ongoing cancer therapy for a primary cancer recurrence at that moment applied to 39 CCS. Censoring at the incidence date of first primary cancer recurrence after the date of five-year survival applied to 86 CCS.

Table 1 Characteristics of CCS and reference persons contributing to unique follow-up time

	CCS (n=1382)		**Reference persons (n=26583)**	
	n	%	*n*	%
Gender				
Male	738	53.4	14347	54.0
Female	644	46.6	12236	46.0
Year of birth				
1954 – 1969	205	14.8	4066	15.3
1970 – 1985	819	59.3	15462	58.2
1986 – 1999	358	25.9	7055	26.5
Type of inhabitant				
Native inhabitant	1148	83.1	19461	73.2
Non-native inhabitants	234	16.9	7122	26.8
First generation	44	3.2	4137	15.6
Second generation	190	13.7	2984	11.2
Calendar year of primary cancer diagnosis[1]				
1966-1974	117	8.5	2309	8.7
1975-1984	464	33.6	8932	33.6
1985-1994	529	38.3	10037	37.8
1995-1999	272	19.7	5305	20.0
Age at primary cancer diagnosis[1]				
Median (range), y	6.1	0 - 17.8	6.0	0 - 18.4
0-4 y	607	43.9	11518	43.3
5-9 y	364	26.3	7197	27.1
10-14 y	318	23.0	6118	23.0
15-18 y	93	6.7	1750	6.6
Primary cancer diagnosis				
Leukemia/lymphoma	624	45.2		
CNS tumor	98	7.1		
Sarcoma	269	19.5		
Other solid tumors	356	25.8		
Other and unspecified tumors	35	2.5		
Recurrences of primary cancer				
None	1161	84.0		
Any recurrence	221	16.0		
Second tumors				
None	1310	94.8		
Any second tumor	74	0.9		
Cancer treatment groups[2,3]				
No chemotherapy/radiotherapy (± surgery)	112	8.1		
Chemotherapy (± surgery)	726	52.5		
Radiotherapy (± surgery)	83	6.0		

Table 1 Characteristics of CCS and reference persons contributing to unique follow-up time (*continued*)

	CCS (n=1382)		**Reference persons (n=26583)**	
	n	%	*n*	%
Chemotherapy and radiotherapy (± surgery)	460	33.3		
Specific cancer treatments before five-year survival[3]				
Anthracyclines	586	42.4		
Alkylating agents	700	50.7		
Other chemotherapy	364	26.3		
Radiotherapy to head and/or neck region	374	27.1		
Radiotherapy to thoracic and/or abdominal region	302	21.9		
Radiotherapy to extremities[4]	92	6.7		
Vital status at the end of follow-up according to GBA				
Living	1334	96.5	26491	99.7
Deceased	48	3.5	92	0.3
Attained age at the end of follow-up, y				
Median	25.7		25.9	
Range	5.9 - 51.3		6.1 - 52.0	
Follow-up time since (corresponding[1]) date of primary cancer diagnosis, y				
Median	18.6		18.6	
Range	5.0 - 39.8		5.7 - 39.8	
Years at risk for hospitalization (1995 – 2005)				
Sum	10,645		194,208	
Median	8.8		8.1	
Range	0.1 – 11.0		0.0 – 11.0	

[1] Corresponding date of primary cancer diagnosis of a CCS was assigned to matching reference persons in order to analyze data per survival year (starting at the 5th) and to adjust for calendar period and age.
[2] Cancer treatment groups were mutually exclusive, i.e. persons could contribute to one cell only. Treatment categories were irrespective of surgical treatment.
[3] We took all cancer treatment that was given before the date of five-year survival into account.
[4] Including 8 CCS with radiotherapy localization defined as "other"
Abbreviations: CCS: childhood cancer survivors; n: number; y:years; GBA: Dutch acronym for Municipal Personal Records Database.

Hospitalization characteristics and comparison of hospitalization rates of CCS with the reference population

Without censoring, 45% of 1382 CCS were hospitalized 2293 times in 10, 622 years at risk (average hospitalization rate 216 per 1000 person years). Of 26, 583 reference persons, 28% were hospitalized 15, 169 times in 194, 094 years at risk (hospitalization rate 78 per 1000 person years). When applying the censoring, 43% of 1292 CCS were hospitalized

during our study, with an average rate of 172 hospitalizations per 1000 person years. Hospitalization rate in matched reference persons was 79 per 1000 person years.

The average age at hospitalization was 22.9 years in CCS and 25.7 years in the reference persons. The average length of stay in the hospital was 4.9 days in CCS and 3.8 days in reference persons. Hospitalizations of CCS were more often in a university hospital (49% versus 15%), slightly more often in a non-acute setting (74% versus 70%) and slightly more often day care hospitalization (42% versus 39%) compared to hospitalizations in matched reference persons.

Table 2 shows average RHR, 95% confidence intervals (CI) and AER of the CCS cohort as well as for categories of CCS compared to matched reference persons. The overall RHR and AER were 2.2 (95% CI: 1.9-2.5) and 93.3 per 1000 person years at risk respectively for CCS compared to reference persons. RHR was 2.4 in males (95% CI: 2.0-3.0, AER 76.4) and 2.0 in females (95% CI: 1.7-2.4, AER: 112.8). RHRs and AERs were increased in all CCS cancer diagnosis and treatment categories compared to reference persons, with highest RHRs for CCS originally diagnosed with primary central nervous system tumors (3.4; 95% CI: 2.7-4.4, AER: 187.1), other solid tumors (2.6; 95% CI: 2.0-3.5, AER: 130.8) and other and unspecified cancers (3.4; 95% CI: 2.0-5.5, AER: 231.8). CCS who experienced a recurrence before five-year survival had an increased RHR (3.3; 95% CI: 2.5-4.5, AER: 194.3), but in CCS without any recurrence RHR was still 2.0 (95% CI: 1.7-2.3, AER: 81.2) compared to reference persons. Radiotherapy (with or without surgery, without chemotherapy) was associated with highest treatment-related RHRs (3.4; 95% CI: 2.2-5.0, AER: 242.7) compared to reference persons.

Table 3 shows that CCS had significantly higher hospitalization rates in comparison to the reference population for 11 of 20 diagnosis groups, especially for neoplasms (RHR: 10.7; 95% CI: 7.1-16.3, AER: 24.2), endocrine/nutritional/metabolic disorders (RHR: 7.3; 95% CI: 4.6-11.7, AER: 6.3), diseases of the eye (RHR: 4.4; 95% CI: 2.7-7.3, AER: 2.9), diseases of the circulatory system (RHR: 3.5; 95% CI: 2.4-5.1, AER: 4.3) and for the two diagnosis groups "symptoms, signs and abnormal findings not elsewhere specified" (RHR: 3.8; 95% CI: 2.4-5.9, AER: 12.6) and "factors influencing health status and contact with health services" (RHR: 3.1; 95% CI: 2.5-3.9, AER: 14.3).

Figure 1 shows the hospitalization rates over follow-up time since (corresponding) date of primary cancer diagnosis (1a) and attained age (1b) for CCS and reference persons. Hospitalization rates in CCS were highest between 5-10 and 20-30 years since primary cancer diagnosis and before the attained age of 10 and between the attained age of 15 and 40 years. We found generally similar trends in most other CCS categories, such as in males and females, in groups based on recurrence status and in the various treatment groups (Supplementary Figures 2a-2m in the Appendix).

Table 2 Average hospitalization rates, relative hospitalization rates and absolute excess rates in CCS and matched reference persons

	CCS[1]		**Matched reference persons**				
	Hospitalizations	*Hospitalization rate per 1000 py at risk*	*Hospitalizations*	*Hospitalization rate per 1000 py at risk*	*RHR*	*95%CI*	*AER per 1000 py at risk*
All individuals	1736	*172.4*	13765	*79.1*	2.2	1.9 - 2.5	93.3
Gender							
Male	693	*129.5*	4876	*53.1*	2.4	2.0 - 3.0	76.4
Female	1043	*221.0*	8889	*108.2*	2.0	1.7 - 2.4	112.8
Primary cancer diagnosis							
Leukemia/lymphoma	530	*120.0*	5536	*72.8*	1.6	1.4 - 2.0	46.7
CNS	184	*264.3*	939	*77.2*	3.4	2.7 - 4.4	187.1
Sarcomas	369	*185.9*	3224	*90.8*	2.0	1.5 - 2.8	95.1
Other solid tumors	563	*210.1*	3631	*79.3*	2.6	2.0 - 3.5	130.8
Other and unspecified cancers	90	*329.8*	435	*98.0*	3.4	2.0 - 5.5	231.8
Recurrences of primary cancer before five-year survival							
None	1436	*159.8*	11995	*78.6*	2.0	1.8 - 2.4	81.2
Any	300	*277.2*	1770	*82.9*	3.3	2.5 - 4.5	194.3
Cancer treatment[2,3]							
No chemotherapy or radiotherapy	180	219.5	1255	88.6	2.5	1.5 - 4.1	130.9
Chemotherapy	614	119.0	6020	67.8	1.8	1.4 - 2.2	51.2
Radiotherapy	240	344.6	1188	102.0	3.4	2.2 - 5.0	242.7
Chemotherapy and radiotherapy	701	206.9	5298	89.4	2.3	2.0 - 2.7	117.6

[1] Time at risk in CCS was censored at the date of five-year survival in case of ongoing primary cancer recurrence treatment or at the incidence date of first primary cancer recurrence after the date of five-year survival.

[2] Cancer treatment groups were mutually exclusive, i.e. persons could contribute to one cell only. Treatment categories were irrespective of surgical treatment.

[3] We took all cancer treatment that was given before the date of five-year survival into account.

Abbreviations: CCS: childhood cancer survivors; py: person years; RHR: relative hospitalization rate; CI: confidence interval; AER: absolute excess rate.

Table 3 Average hospitalization rates, relative hospitalization rates and absolute excess rates for ICD9-CM hospitalization diagnosis groups in CCS and matched reference persons

	CCS[1]		**Matched reference persons**				
	Hospitalizations	*Hospitalization rate per 1000 py at risk*	*Hospitalizations*	*Hospitalization rate per 1000 py at risk*	*RHR*	*95%CI*	*AER per 1000 py at risk*
ICD group							
Infectious and parasitic diseases	14	*1.4*	101	*0.6*	2.4	1.1 - 5.1	0.8
Neoplasms	269	*26.7*	433	*2.5*	10.7	7.1 - 16.3	24.2
Diseases of blood, blood forming organs and disorders involving immune mechanism	17	*1.7*	135	*0.8*	2.2	0.7 - 6.5	0.9
Endocrine, nutritional and metabolic diseases	74	*7.4*	174	*1.0*	7.3	4.6 - 11.7	6.3
Mental and behavioral disorders	14	*1.4*	161	*0.9*	1.5	0.8 - 2.8	0.5
Diseases of the nervous system	39	*3.9*	428	*2.5*	1.6	0.7 - 3.3	1.4
Diseases of the eye and adnexa	38	*3.8*	149	*0.9*	4.4	2.7 - 7.3	2.9
Diseases of the ear and mastoid process	28	*2.8*	332	*1.9*	1.5	0.7 - 2.9	0.9
Diseases of the circulatory system	61	*6.1*	300	*1.7*	3.5	2.4 - 5.1	4.3
Diseases of the respiratory system	89	*8.8*	1055	*6.1*	1.5	0.9 - 2.3	2.8
Diseases of the digestive system	125	*12.4*	1112	*6.4*	1.9	1.3 - 3.0	6.0
Diseases of the skin and subcutaneous tissue	35	*3.5*	335	*1.9*	1.8	0.9 - 3.7	1.6
Diseases of the musculoskeletal system and connective tissue	95	*9.4*	1680	*9.7*	1.0	0.7 - 1.3	-0.2
Diseases of the genitourinary system	143	*14.2*	911	*5.2*	2.7	1.7 - 4.2	9.0
Pregnancy, childbirth and the puerperium	188	*18.7*	3231	*18.6*	1.0	0.8 - 1.3	0.1

Table 3 Average hospitalization rates, relative hospitalization rates and absolute excess rates for ICD9-CM hospitalization diagnosis groups in CCS and matched reference persons (*continued*)

	CCS[1]		**Matched reference persons**				
	Hospitalizations	*Hospitalization rate per 1000 py at risk*	*Hospitalizations*	*Hospitalization rate per 1000 py at risk*	*RHR*	*95%CI*	*AER per 1000 py at risk*
Conditions originating in the perinatal period	0	*0.0*	4	*0.0*	-	-	-
Congenital malformations, deformations and chromosomal abnormalities	34	*3.4*	222	*1.3*	2.6	1.7 - 4.2	2.1
Symptoms, signs and abnormal clinical findings not elsewhere specified	173	*17.2*	789	*4.5*	3.8	2.4 – 5.9	12.6
Injury, poisoning and other consequences of external causes	88	*8.7*	1046	*6.0*	1.5	1.1 – 1.9	2.7
Factors influencing health status and contact with health services	212	*21.1*	1167	*6.7*	3.1	2.5 – 3.9	14.3

[1] Time at risk in CCS was censored at the date of five-year survival in case of ongoing primary cancer recurrence treatment or at the incidence date of first primary cancer recurrence after the date of five-year survival.

Abbreviations: CCS: childhood cancer survivors; py: person years; RHR: relative hospitalization rate; CI: confidence interval; AER: absolute excess rate.

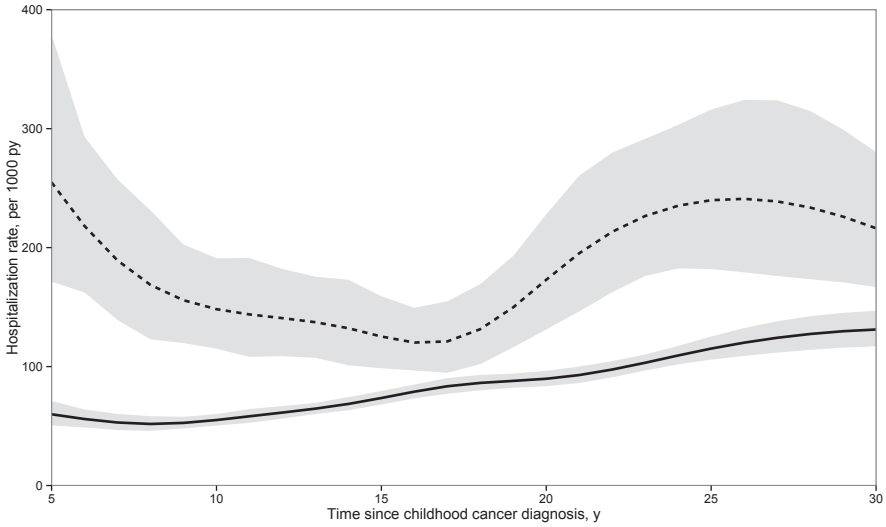

Figure 1a Hospitalization rate of CCS and matched reference persons over follow-up time since (corresponding) date of primary childhood cancer diagnosis
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years

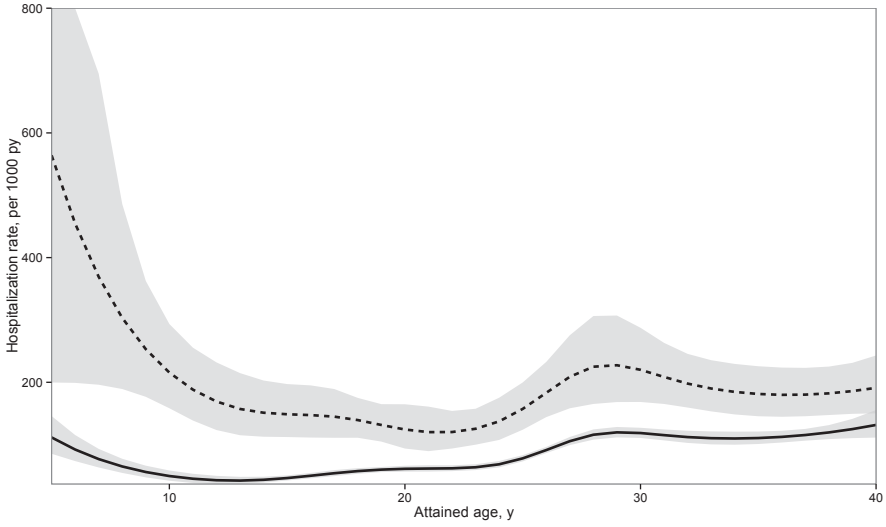

Figure 1b Hospitalization rate of CCS and matched reference persons over attained age
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over attained age. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations. Abbreviations: CCS: childhood cancer survivors; py: person years; y: years

Table 4 Multivariable model of risk factors for hospitalizations within CCS[1]

	RHR (95% CI)	P-value	Figure of RHR
Characteristic			
Follow-up time since primary cancer diagnosis		<0.001	
Gender (female versus male)	Increased risk, non-monotone trend over follow-up time.	<0.001	Figure 2a
Surgery	Increased risk, non-monotone trend over follow-up time (non-significant)	0.01	Figure 2b
Calendar year of primary cancer diagnosis		0.08	
Radiotherapy to thorax and/or abdomen[2]	1.2 (0.9 – 1.6)	0.04	
Radiotherapy to head and/or neck[2]	1.7 (1.2 – 2.4)	<0.001	
Radiotherapy to extremities[2,3]	1.2 (0.8 – 1.7)	0.08	
Age at primary cancer diagnosis		0.17	
Anthracyclines	0.9 (0.7 – 1.3)	0.72	
Alkylating agents	0.8 (0.6 – 1.1)	0.12	
Other chemotherapy	0.9 (0.6 – 1.3)	0.52	

[1] Model includes the following effect modification: gender*follow-up time (P=0.04), gender*radiotherapy (P=0.02), calendar year of primary cancer incidence date*radiotherapy (P=0.04), surgery*follow-up time (P=0.06)
[2] RHR of radiotherapy groups given for the reference calendar year of primary cancer diagnosis (1986) because calendar year is an effect modifier for radiotherapy in the model. No figure provided because the overall effect of calendar year of primary cancer diagnosis was not significant. P-values are the overall p-values of the specific RT groups, which include calendar year.
[3] Including 8 CCS with radiotherapy localization defined as "other"
Abbreviations: CCS: childhood cancer survivors; RHR: relative hospitalization rate.

Risk factor analysis within CCS

We identified risk factors for hospitalization within CCS, based on our final multivariate model including several effect-modifying factors that were significant in the first step of the model (Table 4). Overall, hospitalization rate was not constant over follow-up time since primary cancer diagnosis (P<0.001). Hospitalization rates over follow-up time were higher in females (P<0.001), after treatment with surgery (P=0.01), after treatment with radiotherapy to the head and/or neck (P<0.001) and after treatment with radiotherapy to thorax and/or abdomen (P=0.04). We included the following effect modifiers in the final model: follow-up time for gender (P=0.04, Figure 2a), radiotherapy for gender (P=0.02, Figure 2a), follow-up time for surgery (P=0.06, Figure 2b), and calendar year of primary cancer diagnosis for radiotherapy (P=0.04, no figure provided because the overall effect of calendar year of primary cancer diagnosis was not significant).

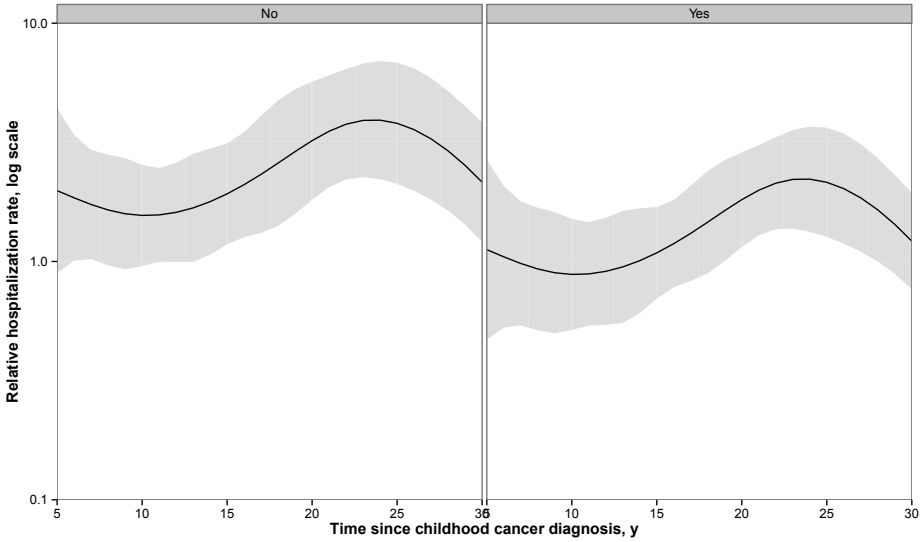

Figure 2a RHR of female CCS versus male CCS treated with (Yes) or without (No) radiotherapy over follow-up time

Estimates were made with a Poisson regression model corrected for recurrent hospitalizations. The model includes the following interactions: gender and follow-up time, gender and radiotherapy, calendar year of primary cancer diagnosis and radiotherapy and surgery and follow-up time. Other variables included are radiotherapy to thorax and/or abdomen; radiotherapy to head and/or neck; radiotherapy to extremities (including 8 CCS with radiotherapy localization defined as "other"); anthracyclines; alkylating agents; other chemotherapy. Grey areas represent 95% confidence intervals. Abbreviations: RHR: relative hospitalization rate; CCS: childhood cancer survivors; py: person years; y: years

Discussion

Survivors of childhood cancer have increased hospitalization rates compared to the general population up to at least 30 years after primary cancer diagnosis. The average hospitalization rate in our CCS cohort was increased 2.2-fold compared to the general population after censoring in case of primary cancer recurrence treatment during or after five year-survival. In absolute terms: during ten years of follow-up of 100 CCS and 100 individuals from the general population, there are 93 more hospitalizations in the CCS than in the general population. Compared to the general population CCS have highest RHR for neoplasms and endocrine/nutritional/metabolic disorders, but the risk of several other hospitalization diagnoses is also increased. These trends imply a high and long-term burden of unfavorable health conditions after childhood cancer compared to the general population. Since health conditions that do not lead to hospitalizations are not included, it could well be that the burden of health conditions in CCS is even higher.

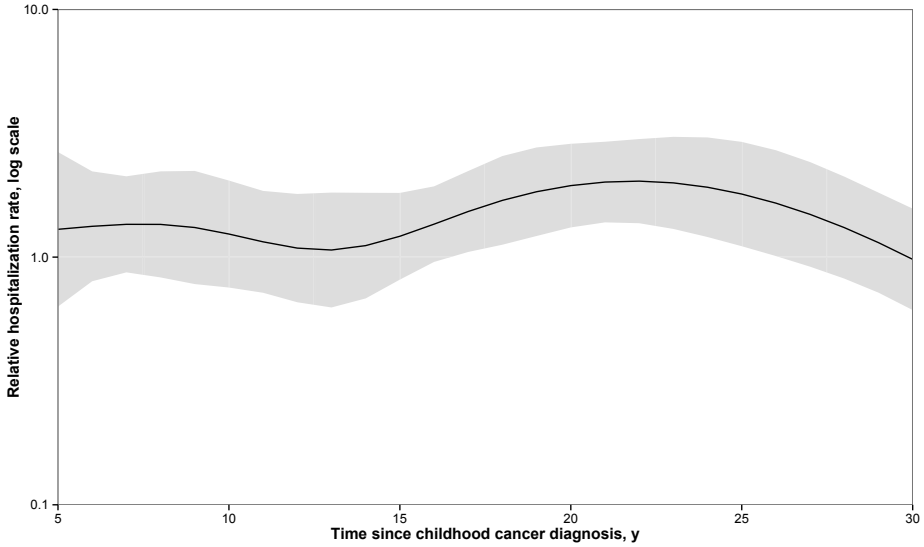

Figure 2b RHR of CCS treated with versus without surgery over follow-up time
Estimates were made with a Poisson regression model corrected for recurrent hospitalizations. The model includes the following interactions: gender and follow-up time, gender and radiotherapy, calendar year of primary cancer diagnosis and radiotherapy and surgery and follow-up time. Other variables included are radiotherapy to thorax and/or abdomen; radiotherapy to head and/or neck; radiotherapy to extremities (including 8 CCS with radiotherapy localization defined as "other"); anthracyclines; alkylating agents; other chemotherapy. Grey areas represent 95% confidence intervals. After 30 years of follow-up numbers were too small to give appropriate estimates.
Abbreviations: RHR: relative hospitalization rate; CCS: childhood cancer survivors; py: person years; y: years

It is concerning to see that after an initial decline in hospitalization rate between the 10th and 15th follow-up year since primary cancer diagnosis, the hospitalization rate of CCS increases steeply between 20th and 30th follow-up year compared to the general population.

Possible explanations for this late enhanced increase in hospitalization could be deterioration of existing health conditions in CCS due to aging as well as new, late onset health conditions. With regard to treatment, this second increase in hospitalizations seemed at least partly related to the combination of radiotherapy and chemotherapy.

As far as we are aware, no study has examined trends in hospitalization of CCS over time. Three study groups have addressed average hospitalization rates or hospitalization characteristics in CCS.[15-17] Two of these studies compared hospitalizations retrieved from questionnaires compared to available reference rates obtained from another questionnaire.[16, 17] Both studies assessed average risk of hospitalization over 2 and 13 years of follow-up respectively, which was increased in both studies (odds ratio 1.9 and relative rate 1.6 respectively). The third study retrieved hospitalization data from administrative health registers, but defined the risk of any hospitalization during 12 years of follow-up in CCS compared to a reference population (odds ratio 4.4).[15] Our study thus confirms increased

average hospitalization rates in CCS, but adds new and more detailed information about the long-term trends of hospitalization.

In our CCS cohort, there was an increased hospitalization rate for several hospitalization diagnosis groups compared to the general population, especially for neoplasms, endocrine/metabolic/nutritional diseases, diseases of the eye, diseases of the circulatory system and for the two diagnosis groups "symptoms, signs and abnormal findings not elsewhere specified" and "factors influencing health status and contact with health services". The increased risk of hospitalization for neoplasms will be due for a considerable part to secondary neoplasms, either malignant or benign, since we applied censoring at a recurrence or recurrence treatment beyond five-year survival. The increased risk of secondary neoplasms in CCS is well known and primarily related to radiotherapy.[21, 22] The high risk of endocrine and circulatory diseases has also been described commonly as adverse event of childhood cancer treatment, related to local radiotherapy as well as several chemotherapeutic agents.[23-29] Our study shows that the previously described risks in CCS of neoplasms, endocrine disease and circulatory disease translate into an increased risk of hospitalization. The risk of diseases of the eye is known, but less often described in CCS. Likely explanations for the increased hospitalization rate are diseases such as cataract after radiotherapy and other problems after orbital tumors, retinoblastoma and glucocorticoids, in combination with a low background risk of eye disease in the general population.[30, 31] Finally, it is difficult to speculate why the risk in CCS of hospitalization for "factors influencing health status and contact with health services" and "symptoms, signs and abnormal findings not elsewhere specified" compared to the general population were increased. Clinical signs and symptoms in CCS unusual for the age range and low-threshold clinical evaluations because of anxiety for cancer recurrence could explain the increased rates. Future studies should explore the underlying diagnoses of the hospitalization diagnosis groups.

We found that female survivors are at increased risk of hospitalization compared to male survivors. Female gender has been previously defined as a risk factor for unfavorable health conditions in CCS.[32] However, we showed that the increased hospitalization rate of females within the survivor population might be partly due to increased risks (of hospitalization) in females in general in this age range. When comparing hospitalizations of CCS to the general population for both sexes, males had a higher relative risk, but a lower excess risk of hospitalization than females (Table 2). The main treatment-related risk factors for hospitalization within CCS were surgery and radiotherapy, specifically head and/or neck irradiation. These findings confirm many late effects studies finding that irradiated survivors are the most vulnerable CCS risk group.[33] It should be noted that we did not judge if a hospitalization was related to previous cancer treatment or not. However, due to the representative reference population with which we compared all rates (and which could suffer as well from chronic health conditions), we conclude that the excess hospitalizations in CCS are likely related to being a survivor of childhood cancer.

The most important strength of our study is that we determined hospitalization rates over follow-up time. In all three other studies that provided average risks of hospitalization the risk estimates will likely change with longer follow-up of the cohorts. In addition, hospitalizations in our study were prospectively registered in a national administrative register in the same way for CCS and reference persons. We therefore had an appropriate reference group, no risk of selection bias due to (non-)response and low risk of differential misclassification of the outcome. The reference population had a higher proportion of (first-generation) non-native inhabitants, but in a separate analysis this did not influence the study outcomes (data not shown). Our statistical analyses robustly accounted for the longitudinal design with left-truncation and recurrent hospitalizations, as well as for the confounding influences of age, gender, calendar period and late recurrences of primary cancer. Without applying the censoring at late primary cancer recurrences in our analyses, the average RHR would have increased substantially to 2.8, primarily due to hospitalizations in the first 5 to 10 years since cancer diagnosis (data not shown).

A limitation of our study is that the national administrative registers did not have data electronically available before 1995. In addition, the linkage possibilities in the Netherlands enforced us to exclude time at risk of individuals who were (temporarily) not unique based on the combination of gender, date of birth and postal code. We cannot be completely sure whether these missing data had the same distributions as data from 1995 onwards and during unique periods, even though we used appropriate statistical models to adjust for these missing data and for calendar year. Also, numbers of CCS with follow-up beyond 30 years since primary cancer diagnosis were very small, so it was not possible to analyze data beyond that follow-up time. A disadvantage of using administrative registers is that you have to rely on coding of diagnoses by others. Although this was similar for CCS and reference persons and has been found acceptable, [34] coding of diagnoses could be performed differently in individuals with a history of cancer compared to others.

Our findings show a high burden of unfavorable health conditions in CCS up to many years after reaching adulthood. This underscores the need for awareness and knowledge among all health care professionals, including general practitioners and other (adult) physicians, about this patient group and their main risk factors. Our study also leads to many more research questions about the trends in specific health conditions underlying the increased hospitalization rates, related risk factors and trends beyond 30 years of follow-up. For these studies larger cohorts of CCS should be assessed. In addition, future studies should define if (multidisciplinary) follow-up care, screening or medical treatments can prevent hospitalizations in CCS, taking into account benefits as well as risks of such interventions. Finally, details about the impact of high hospitalization rates on the health care system should be defined, including economic consequences and the health care professionals/departments confronted most with CCS over time.

Acknowledgement

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References

1. Gatta G, Zigon G, Capocaccia R et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer 2009;45(6):992-1005.
2. Steliarova-Foucher E, Stiller C, Kaatsch P et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. Lancet 2004;364(9451):2097-2105.
3. Wallace WH, Green D (eds). Late effects of childhood cancer. London: Arnold; 2004.
4. Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, eds. Survivors of childhood and adolescent cancer: a multidisciplinary approach. Berlin: Springer; 2005.
5. Mulrooney DA, Neglia JP, Hudson MM. Caring for adult survivors of childhood cancer. Curr Treat Options Oncol 2008;9(1):51-66.
6. Oeffinger KC, Nathan PC, Kremer LC. Challenges after curative treatment for childhood cancer and long-term follow up of survivors. Hematol Oncol Clin North Am 2010;24(1):129-149.
7. Geenen MM, Cardous-Ubbink MC, Kremer LC et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 2007;297(24):2705-2715.
8. Oeffinger KC, Mertens AC, Sklar CA et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355(15):1572-1582.
9. Curry HL, Parkes SE, Powell JE, Mann JR. Caring for survivors of childhood cancers: the size of the problem. Eur J Cancer 2006;42(4):501-508.
10. Kilian R, Matschinger H, Angermeyer MC. The impact of chronic illness on subjective quality of life: A comparison between general population and hospital inpatients with somatic and psychiatric diseases. Clin Psychol and Psychother 2001;8:206-213.
11. Reynolds MR, Morais E, Zimetbaum P. Impact of hospitalization on health-related quality of life in atrial fibrillation patients in Canada and the United States: results from an observational registry. Am Heart J 2010;160(4):752-758.
12. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. Eur J Heart Fail 2002;4(3):361-371.
13. Cohen JW, Krauss NA. Spending and service use among people with the fifteen most costly medical conditions, 1997. Health Aff (Millwood) 2003;22(2):129-138.
14. Metcalfe C, Thompson SG, Cowie MR, Sharples LD. The use of hospital admission data as a measure of outcome in clinical studies of heart failure. Eur Heart J 2003;24(1):105-112.
15. Bradley NM, Lorenzi MF, Abanto Z et al. Hospitalisations 1998-2000 in a British Columbia population-based cohort of young cancer survivors: report of the Childhood/Adolescent/Young Adult Cancer Survivors (CAYACS) Research Program. Eur J Cancer 2010;46(13):2441-2448.
16. Kurt BA, Nolan VG, Ness KK et al. Hospitalization rates among survivors of childhood cancer in the Childhood Cancer Survivor Study cohort. Pediatr Blood Cancer 2012;59(1):126-132.
17. Rebholz CE, Reulen RC, Toogood AA et al. Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol 2011;29(31):4181-4188.
18. Reitsma JB, Kardaun JW, Gevers E, de BA, van der Wal J, Bonsel GJ. [Possibilities for anonymous follow-up studies of patients in Dutch national medical registrations using the Municipal Population Register: a pilot study]. Ned Tijdschr Geneeskd 2003;147(46):2286-2290.
19. de Bruin A, Kardaun J.W.P.F., Gast A, de Bruin EI, van Sijl M, Verweij GCG. Record linkage of hospital discharge register with population register: experiences at Statistics Netherlands. Statistical Journal of the United Nations Economic Commission for Europe 2004;21(1):23-32.

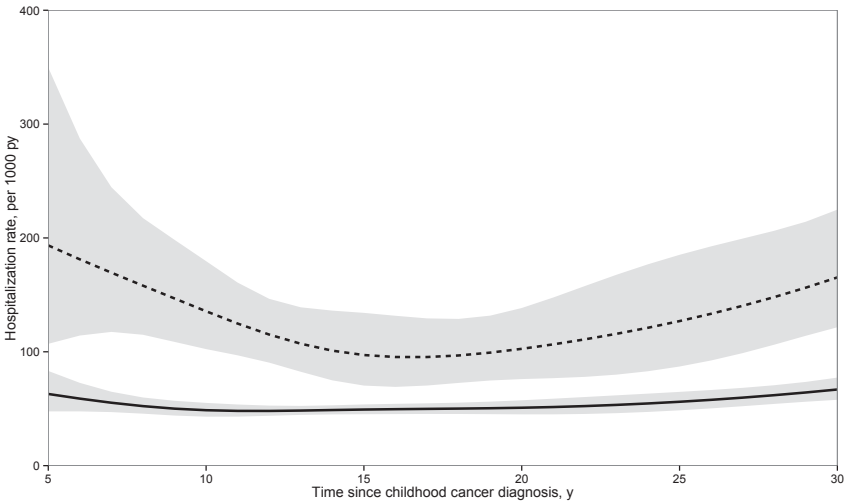
20. Stichting Medische Registratie. Classification of Diseases 1980, based on the International Classification of Disease 9th revision, Clinical Modification (ICD9-CM) [article in Dutch]. 1980
21. Meadows AT, Friedman DL, Neglia JP et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27(14):2356-2362.
22. Reulen RC, Frobisher C, Winter DL et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 2011;305(22):2311-2319.
23. Gurney JG, Kadan-Lottick NS, Packer RJ et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 2003; 97(3):663-673.
24. Gurney JG, Ness KK, Sibley SD et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. Cancer 2006;107(6):1303-1312.
25. Mulder RL, Kremer LC, van Santen HM et al. Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review. Cancer Treat Rev 2009;35(7):616-632.
26. Mulrooney DA, Yeazel MW, Kawashima T et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009;339:b4606.
27. Poutanen T, Tikanoja T, Riikonen P, Silvast A, Perkkio M. Long-term prospective follow-up study of cardiac function after cardiotoxic therapy for malignancy in children. J Clin Oncol 2003; 21(12):2349-2356.
28. van Dalen EC, van der Pal HJ, Kok WE, Caron HN, Kremer LC. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer 2006;42(18): 3191-3198.
29. van der Pal HJ, van Dalen EC, Hauptmann M et al. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. Arch Intern Med 2010;170(14):1247-1255.
30. Whelan KF, Stratton K, Kawashima T et al. Ocular late effects in childhood and adolescent cancer survivors: a report from the childhood cancer survivor study. Pediatr Blood Cancer 2010; 54(1):103-109.
31. Punyko JA, Mertens AC, Gurney JG et al. Long-term medical effects of childhood and adolescent rhabdomyosarcoma: a report from the childhood cancer survivor study. Pediatr Blood Cancer 2005;44(7):643-653.
32. Armstrong GT, Sklar CA, Hudson MM, Robison LL. Long-term health status among survivors of childhood cancer: does sex matter? J Clin Oncol 2007;25(28):4477-4489.
33. Armstrong GT, Stovall M, Robison LL. Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the childhood cancer survivor study. Radiat Res 2010;174(6):840-850.
34. Paas GR, Veenhuizen KC. Research on the validity of the LMR. Utrecht: Prismant; 2002.

Appendix

Supplementary figures

Hospitalization rate of CCS and matched reference persons based on CCS categories.

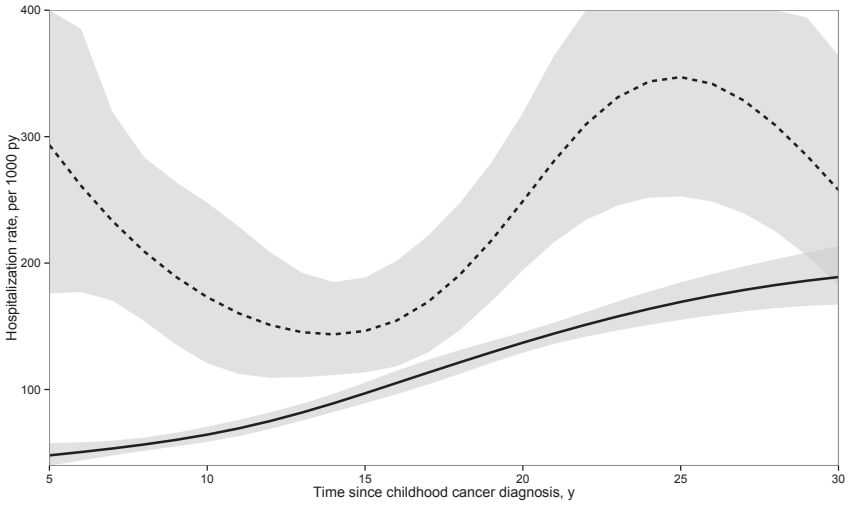
Please note that numbers of hospitalizations differed between categories and that we adjusted the y-axes accordingly in the figures.



Supplementary Figure 1a Hospitalization rate of male CCS and matched reference persons over follow-up time

Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.

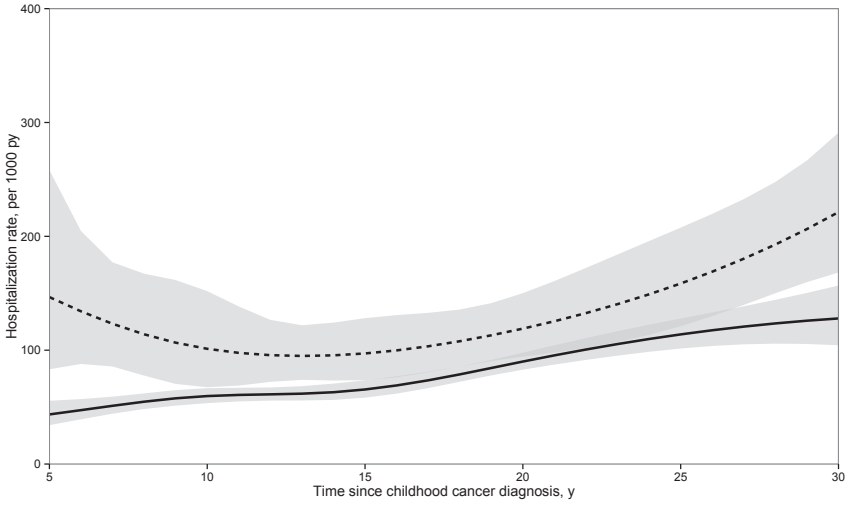
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



Supplementary Figure 1b Hospitalization rate of female CCS and matched reference persons over follow-up time

Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.

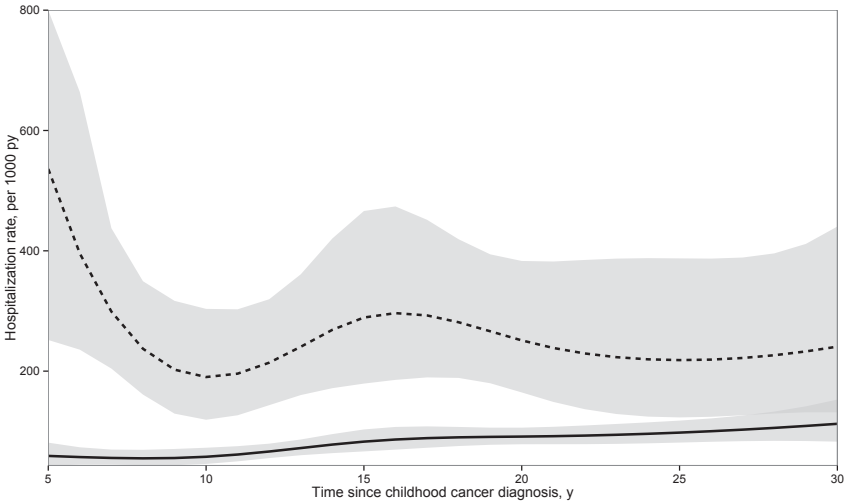
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



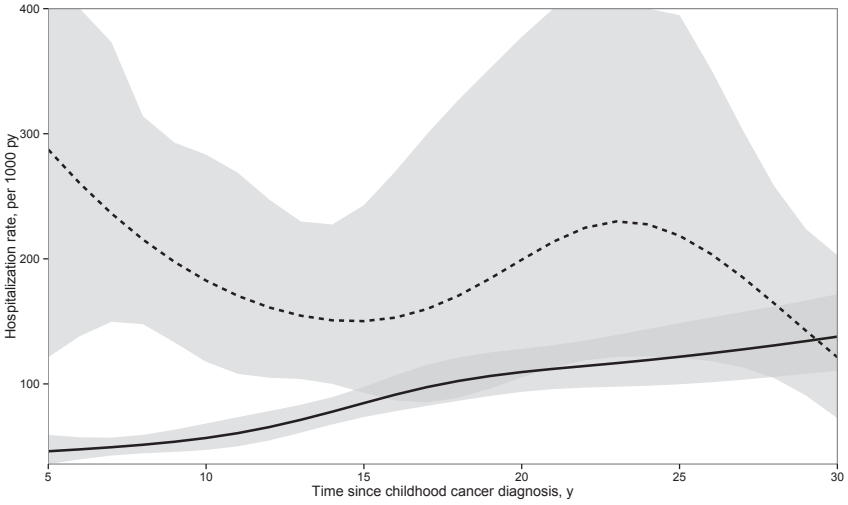
Supplementary Figure 1c Hospitalization rate of CCS previously diagnosed with leukemia or lymphoma and matched reference persons over follow-up time

Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.

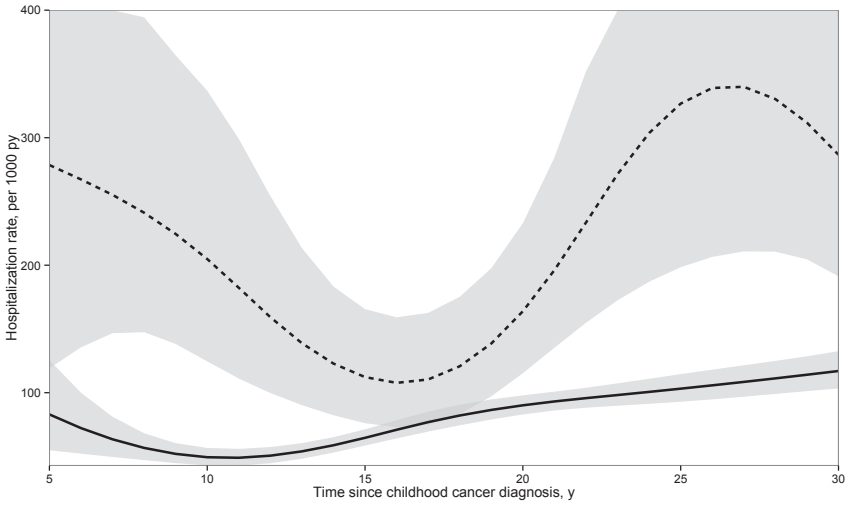
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



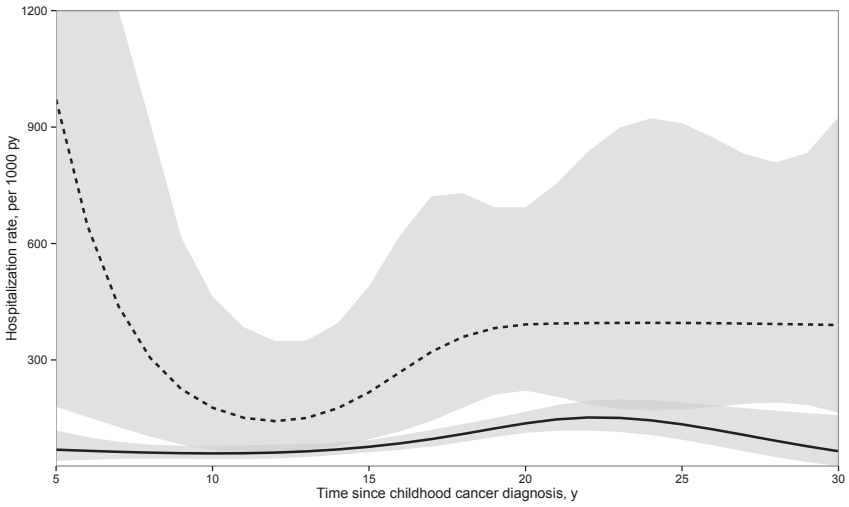
Supplementary Figure 1d Hospitalization rate of CCS previously diagnosed with a central nervous system tumor and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



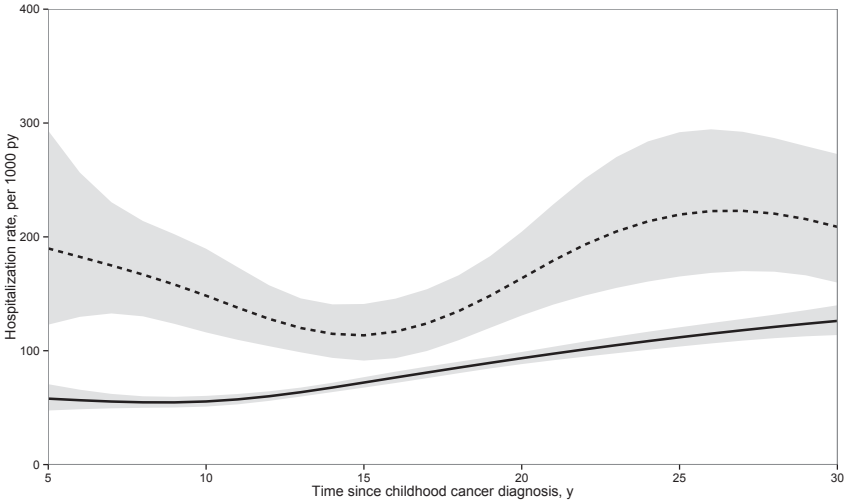
Supplementary Figure 1e Hospitalization rate of CCS previously diagnosed with a sarcoma and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



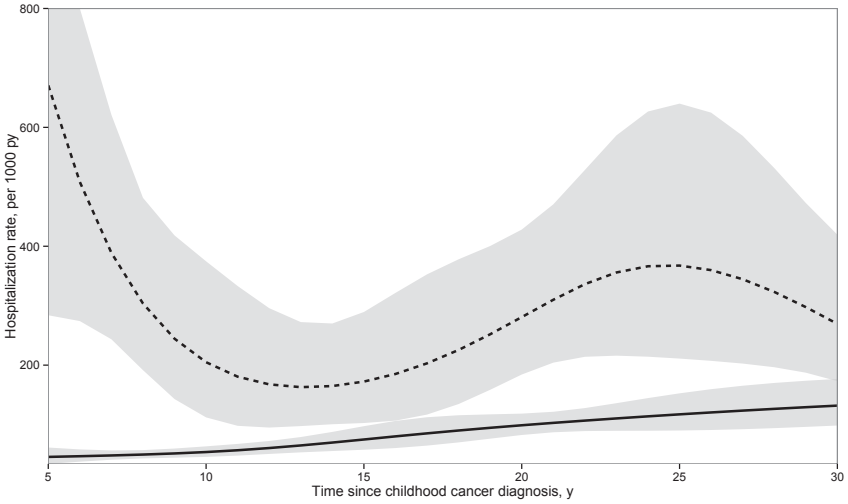
Supplementary Figure 1f Hospitalization rate of CCS previously diagnosed with other solid tumors and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



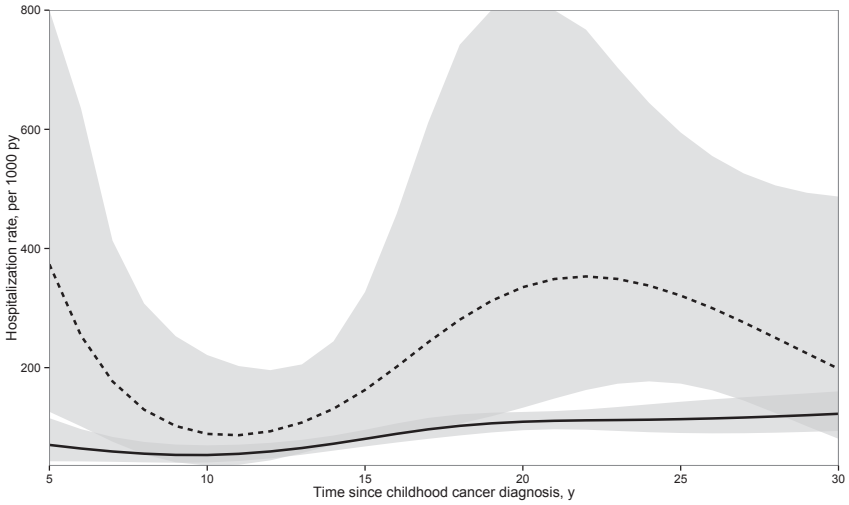
Supplementary Figure 1g Hospitalization rate of CCS previously diagnosed with other and unspecified cancers and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



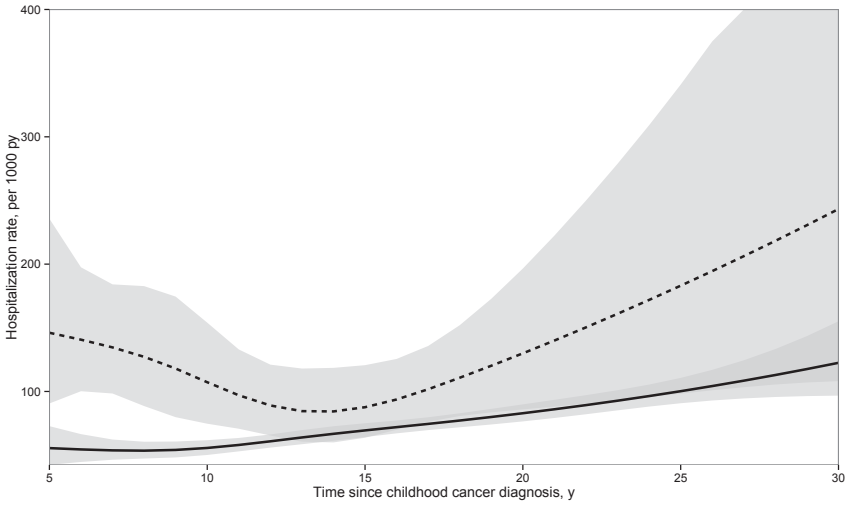
Supplementary Figure 1h Hospitalization rate of CCS without a recurrence before five-year survival and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



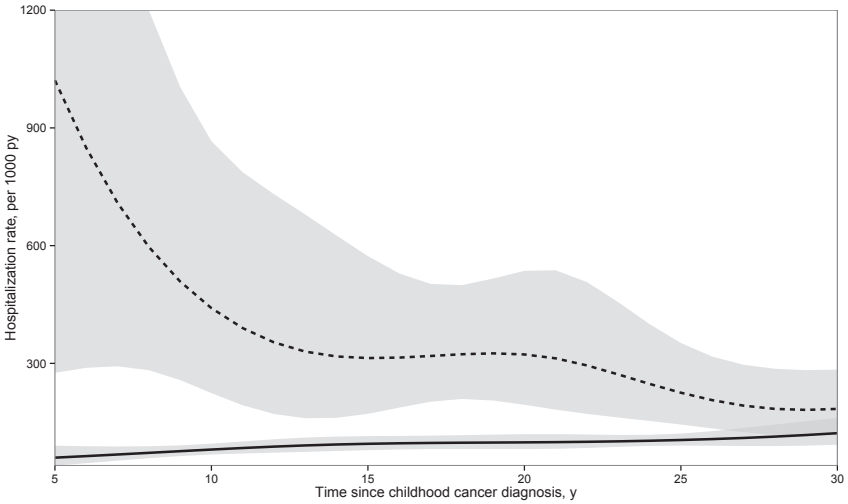
Supplementary Figure 1i Hospitalization rate of CCS with a recurrence before five-year survival and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



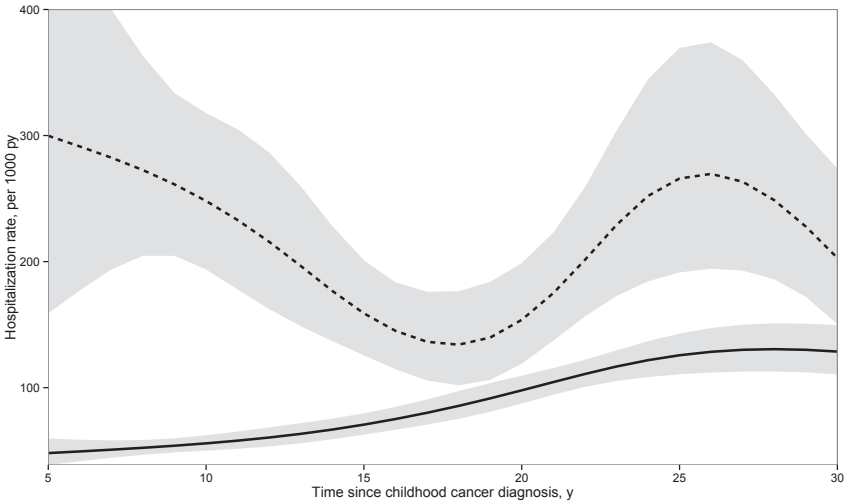
Supplementary Figure 1j Hospitalization rate of CCS treated without chemotherapy and radiotherapy (with or without surgery) and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



Supplementary Figure 1k Hospitalization rate of CCS treated with chemotherapy and without radiotherapy (with or without surgery) and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



Supplementary Figure 1l Hospitalization rate of CCS treated with radiotherapy and without chemotherapy (with or without surgery) and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years



Supplementary Figure 1m Hospitalization rate of CCS treated with chemotherapy and radiotherapy (with or without surgery) and matched reference persons over follow-up time
Hospitalization rates per 1000 person years of CCS (dotted line) and matched reference persons (continuous line) over follow-up time since (corresponding) date of primary childhood cancer diagnosis. Grey areas represent 95% confidence intervals. Estimates were made with a Poisson regression model corrected for recurrent hospitalizations.
Abbreviations: CCS: childhood cancer survivors; py: person years; y: years