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The cumulative burden of self-reported, clinically relevant outcomes in long-term childhood cancer survivors and implications for survivorship care: A DCCSS LATER study

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Abstract

Background: The aim of this study is to evaluate how cumulative burden of clinically relevant, self-reported outcomes in childhood cancer survivors (CCSs) compares to a sibling control group and to explore how the burden corresponds to levels of care proposed by existing risk stratifications.

Methods: The authors invited 5925 5-year survivors from the Dutch Childhood Cancer Survivor Study (DCCSS LATER) cohort and their 1066 siblings to complete a questionnaire on health outcomes. Health outcomes were validated by selfreported medication use or medical record review. Missing data on clinically relevant outcomes in CCSs for whom no questionnaire data were available were imputed with predictive mean matching. We calculated the mean cumulative count (MCC) for clinically relevant outcomes. Furthermore, we calculated 30-year MCC for groups of CCSs based on primary cancer diagnosis and treatment, ranked 30-year MCC, and compared the ranking to levels of care according to existing risk stratifications.

Results: At median 18.5 years after 5-year survival, 46% of CCSs had at least one clinically relevant outcome. CCSs experienced 2.8 times more health conditions than siblings (30-year MCC = 0.79; 95% confidence interval [CI], 0.74–0.85 vs. 30-year MCC = 0.29; 95% CI, 0.25–0.34). CCSs' burden of clinically relevant outcomes consisted mainly of endocrine and vascular conditions and varied by primary cancer type. The ranking of the 30-year MCC often did not correspond with levels of care in existing risk stratifications.

Conclusions: CCSs experience a high cumulative burden of clinically relevant outcomes that was not completely reflected by current risk stratifications. Choices for survivorship care should extend beyond primary tumor and treatment parameters, and should consider also including CCSs' current morbidity.

Introduction

Survival following the diagnosis of childhood cancer has significantly improved over the past decades.[1] This progress has resulted in increasing numbers of long-term childhood cancer survivors (CCSs). However, even decades after initial treatment, CCSs are at risk of developing long-term morbidity related to their primary cancer and its treatment, such as organ dysfunction and second

neoplasms.[2–5] This high risk of long-term morbidity emphasizes the need for survivorship care. Several efforts have been undertaken to develop risk stratified survivorship care to support choices for the location, services, and the frequency of survivorship care. In 2001, Wallace et al.[6] proposed a risk stratification incorporating three levels of care for CCSs based on treatment parameters. Subsequently, other groups developed new risk stratification strategies that incorporated primary cancer diagnosis and more detailed treatment parameters.[7–9] Based on these risk stratifications, levels of care are assigned to a survivor that designate telephone followup, follow-up led by a nurse, or survivorship care in a (multidisciplinary) late effects clinic.

Insight in the cumulative burden of clinically relevant outcomes, such as outcomes with symptoms or need for medical intervention, is needed to investigate if these risk stratifications reflect the burden of the survivors and needed survivorship care. Recently, St. Jude Lifetime Cohort Study (SJLIFE) investigators described clinically assessed long-term cumulative burden using the mean cumulative count method, which includes multiple events during follow-up.[10] The study included symptomatic and asymptomatic events graded for severity by an adapted version of the Common Terminology Criteria for Adverse Events (CTCAE).[10]

We evaluated the cumulative burden of clinically relevant health outcomes in CCSs compared to siblings, and we explored how this cumulative burden corresponds to levels of care proposed by existing risk stratifications guiding survivorship care in the Dutch Childhood Cancer Survivor Study (DCCSS) LATER questionnaire study.

Materials and methods

Study population

In this multicenter retrospective cohort study, we included CCSs from the DCCSS LATER cohort. This cohort consists of 6165 5-year CCSs, diagnosed with a malignancy between January 1, 1963 and December 31, 2001 before the age of 18 in one of the seven pediatric oncology centers in The Netherlands. Methods of patient identification and data collection have been previously described.[11]

DCCSS LATER questionnaire

A questionnaire on general health and lifestyle (Table S1) was sent to all CCSs in the DCCSS LATER cohort that were alive and living in The Netherlands (n = 5327 of 6165) in 2013–2014, of whom 3369 CCSs were willing to participate (63%, Figure S1). The same questionnaire was sent to living siblings without a history of malignancy during childhood for whom CCSs provided contact details (n = 1662). Of all approached siblings, 1080 agreed to participate (65%, Figure S1).

This study was declared exempt from review of medical intervention research by the Medical Ethics Committee and by the boards of all participating centers. All questionnaire participants gave written informed consent.

In total, 3152 CCSs and 1066 siblings completed the questionnaire sections concerning health condition(s). CCSs were asked to report specific health condition(s) throughout their life with corresponding year or age of diagnosis (Figure S1). CCSs without information on health condition(s) from the questionnaire (n = 3013) included survivors who were ineligible for participation (n = 838, of which n = 611 deceased), survivors who did not respond to the questionnaire (n = 1958), and survivors who participated in the questionnaire, but did not (completely) answer the section on health condition(s) (n = 217). For those survivors, clinical outcome data were imputed using multiple imputation with predictive mean- matching based on data of the 3152 CCSs of whom validated

questionnaire data was available (see Supporting Methods including Figure S2A,B) for details). We could only perform multiple imputation in CCSs of whom complete treatment data were available (n = 2773). As a result, 5925 CCSs were included in the analysis.

Outcome definition

Outcome of interest was the incidence of self-reported clinically relevant outcomes defined as health conditions that were symptomatic and/or for which medical intervention was required or recommended at time of the questionnaire (Figure S3). Health conditions were not included if they did not require medical treatment (e.g., detected during routine screening and no treatment needed). Following a survivor-centered approach, we established criteria for 75 clinically relevant outcomes (Table S2).[12] Data on cardiac outcomes were used as previously validated by Feijen et al.[13] and data on malignant neoplasms were used as previously ascertained by Teepen et al.[11]

Data validation

CCSs and siblings information on reported health conditions was combined with information on reported medication use and surgical treatment from the questionnaires, to determine whether reported health conditions met criteria for inclusion. For survivors and siblings for whom the reported medication use and surgical treatment information was not sufficient to determine whether the reported health condition met criteria for inclusion (e.g., obstructive pulmonary disease reported, but no medication was listed in the questionnaire) or for which the incidence date was unknown, medical record abstraction was performed. For CCSs (n = 714), medical record data were obtained from the late effects outpatient clinics; for siblings (n = 115), the primary care physician was contacted if the sibling consented and provided contact information (Figure S4).

Follow-up

Time at risk started 5 years after childhood cancer diagnosis and ended at the date of the questionnaire completion. Siblings were assigned the date of diagnosis of the corresponding CCS. Health conditions occurring within 5 years of the (assigned) date of childhood cancer diagnosis were included if they were clinically relevant at time of questionnaire completion. The incidence date of those health conditions was set at the date of 5-year survival (start of follow-up). If a reported condition was included after validation, but the incidence year was missing, it was included with the median age at diagnosis of participants with the same condition, for CCSs and siblings separately (Table S3).

Statistical analysis

Differences in prevalence of clinically relevant outcomes between CCS questionnaire responders and siblings were tested using Mann-Whitney U tests when variables were continuous and Pearson χ^2tests (if $n \geq 5$) or Fisher exact tests (if $n < 5$) when variables were categorical.

The cumulative burden of morbidity was calculated using the MCC method that estimates the total number of events over a certain time period.[14] The MCC can be interpreted as the average number of new clinically relevant outcomes per CCS or sibling in our cohort up to a specific time point.14 Death was considered as a competing risk. For each specific outcome as mentioned in Table S2, the first occurrence was counted, except for malignant neoplasms, for which each new occurrence of a different type was counted. We used multiple imputation methods to create 10 imputed data sets. The mean MCC for these 10 data sets was calculated separately for CCSs and

siblings and 95% confidence intervals (CI) were calculated using the bootstrap percentile method, with 1000 bootstrap samples.[15] MCCs were also calculated per type of outcome and by childhood cancer type.

STATA/IC (version 13.1) was used for the imputation and SPSS (version 24) and R (version 3.4.3) were used for statistical analyses. All p values of less than .05 were regarded as statistically significant.

Cumulative burden of morbidity and risk stratification for survivorship care

To compare levels of care for three published risk stratifications, we stratified our CCS cohort into 27 combinations of primary cancer diagnosis and previous treatment. We then assigned levels of care as proposed by Wallace et al.,[6] the NHS Improvement,[7] and Frobisher et al.[9] to each combination of primary cancer diagnosis and previous treatment (Table S5). We calculated the MCC at 30 years post primary cancer diagnosis for each combination of primary cancer diagnosis and treatment and ranked the 30-year MCC for these combinations. We explored how the MCC corresponds to the levels of care described in previously published risk stratifications.

Results

Study population

Characteristics of the CCS study population and siblings are described in Table 1. The median follow-up because 5-year survival was 18.5 years for CCS questionnaire participants (interquartile range [IQR], 13.2–25.1 years) and 18.6 years for siblings (IQR, 12.8–26.9 years). Characteristics of the participating and nonparticipating CCS cohort members are described in Table S4. We did not observe important differences between those groups by childhood cancer diagnosis and treatment characteristics.

[Table 1], [Figure 1]

Clinically relevant outcomes

At the time of questionnaire, 1444 CCSs (46.4% of the 3152 CCSs questionnaire participants) and 243 siblings (23.8%) had developed at least one outcome (Table 1). CCSs more often had two or more outcomes than siblings (39.9% and 21.0%, respectively). All types of conditions, except for hepatic and pulmonary conditions, were more prevalent in CCSs than in siblings (Table 1). Endocrine conditions were the most prevalent type of condition in both groups and were more prevalent in CCSs (n = 834, 26.7% and n = 158, 14.8% respectively, Table 1). Obesity (body mass index >30) was the most prevalent endocrine condition in both CCSs and siblings (Table S6).

Cumulative burden of clinically relevant outcomes

At 30 years post diagnosis, the cumulative burden of morbidity was 2.7-fold higher in the total imputed CCS cohort (MCC = 0.79; 95% CI, 0.74–0.85) than in siblings (MCC = 0.29; 95% CI, 0.25–0.34) (Figure 1). The contribution of different types of outcomes to the cumulative burden for CCSs and siblings is illustrated in Figure 2. Among CCSs, endocrine conditions were the main contributors to the cumulative burden, followed by gastrointestinal, vascular, neurological, and musculoskeletal conditions (Figure 2A). In siblings, endocrine conditions were also the main contributor, followed by

vascular and pulmonary conditions (Figure 2B). In an analysis excluding obesity, endocrine conditions remained the main contributor to the cumulative burden in both groups (Figure S5).

By tumor type, the cumulative burden varied in both magnitude and type of outcomes (Figure 3). Central nervous system (CNS) tumor survivors had the highest cumulative burden, which mainly consisted of endocrine, neurologic and ophthalmologic conditions. Hodgkin lymphoma survivors had a high burden of cardiac and vascular morbidity, whereas bone tumor survivors had a high burden of musculoskeletal morbidity, often due to major amputations.

Cumulative burden of clinically relevant outcomes and risk stratification for survivorship care

Table 2 presents the groups of primary cancer diagnosis and treatment combinations, with the assigned levels of care according to the three published risk stratifications for survivorship care.

[Figure 2]

The calculations and ranking of theMCCat 30 years post diagnosis for the 27 combinations of primary cancer diagnoses and treatment showed that the highest MCC at 30 years post diagnosis was found in CNS tumor survivors treated with chemotherapy and radiotherapy (30-year MCC = 1.29), followed by neuroblastoma survivors treated with radiotherapy without chemotherapy (30-year MCC = 1.14) and bone tumor survivors treated with chemotherapy without radiotherapy (MCC = 1.12), The lowest MCC was found in renal tumor survivors treated with surgery only (30-year MCC = 0.31, 1.1 times as high as the 30-year MCC in siblings: 30-year MCC = 0.29).

For the two groups of survivors with highest MCC (CNS tumors þ chemotherapy and radiotherapy), all risk stratifications recommended a high level of care. For the group with the lowest MCC (renal tumors þ surgery only), all existing risk stratifications methods advised level 1 care. However, when all groups of survivors were considered, the ranking of the 30-year MCC did not correspond with high, moderate, and low levels of care in existing risk stratification models.

Discussion

We highlighted that the risk and spectrum of clinically relevant selfreported long-term outcomes observed in CCSs varies substantially by primary cancer diagnosis and treatment modalities. We explored how the cumulative burden corresponded to levels of survivorship care proposed in published risk stratifications.[6–9] Our study findings indicate that the level of cumulative burden of clinically relevant outcomes was not completely reflected by current risk stratifications.

In our study, CCSs experienced a 2.8 times higher cumulative burden than siblings, which mainly consisted of endocrine, vascular, and gastrointestinal conditions, followed by neurological and musculoskeletal conditions. CCSs' excess risk for long-term morbidity, including asymptomatic and symptomatic events, is well established.[2,3,10] Even when we only focused on clinically relevant outcomes, the cumulative burden was higher for CCSs than for the sibling control group. Our study shows that nearly 50% of CCSs had developed at least one clinically relevant outcome after a median follow-up time of 18.5 years after 5-year survival. To present results that are generalizable, we presented data on clinically relevant outcomes for the total CCS cohort, including imputed data for questionnaire nonparticipants based on demographics and childhood cancer and treatment details. Our results concur with those from the SJLIFE study that identified cardiovascular conditions and

endocrine conditions as the main contributors to cumulative burden when both symptomatic and asymptomatic health events are considered.[10]

Because this study provides unique data on the cumulative burden of clinically relevant long-term morbidity in CCSs divided in different tumor and treatment groups, we are able to explore how the cumulative risk at 30 years post diagnosis corresponds to levels of care in existing risk stratifications. Previous risk stratifications were developed to define which type of care survivors need. For one risk stratification, the association between the cumulative incidences of serious adverse health conditions was investigated for different levels of care.9 However, by using all events during follow-up, our results show that CCSs assigned to a low level of care by three existing risk stratifications could show a medium high cumulative burden (e.g., CNS tumors treated with surgery only) and vice versa (e.g., renal tumor survivors treated with radiotherapy only). However, it is important to realize that we calculated the MCC at 30 years post diagnosis and it is known that the excess risks of most specific morbidities increase substantially with attained age and duration of follow-up.[16,17] The presented survivorship care risk stratifications were all from the United Kingdom. Decisions on how to organize follow-up care may vary between countries, also based on available resources. Because the cumulative burden of clinically relevant outcomes was not completely reflected by levels of care in these current risk stratifications, we recommend that choices for frequencies and services of all survivorship care stratifications should extend beyond the expected risks based on diagnosis and treatment, and might also consider current morbidity.

[Figure 3], [Table 2]

A strength of this study is that we focused on clinically relevant outcomes, and we did not investigate the occurrence pre-clinical outcomes detected by routine screening, such as untreated hypertension. Validation of outcomes was possible because many CCSs regularly visit the late effects outpatient clinics in The Netherlands.[8] A limitation is that outcomes that were clinically relevant at a certain point in time, but not anymore during questionnaire study, were not captured as outcomes in the study, and we did not have information on recurrent events. Although the vast majority of included outcomes are chronic and require long-term treatment, we may have underestimated the occurrence of some events that can be cured (e.g., diabetes and obesity after lifestyle changes or infections that have resolved) and events that can recur (e.g., cardiac ischemia and stroke). We may have underestimated the MCC in deceased CCSs, because this group of individuals might have experienced more health problems than were imputed based on the information of CCS questionnaire participants. A limitation of the current study design is that psychosocial factors that might impact survivorship needs were not included in the analyses.

In conclusion, we evaluated the cumulative burden of clinically relevant outcomes in CCSs, which was not completely reflected by existing risk stratifications based on primary cancer diagnosis and previous treatment. Therefore, our data reinforce that risk stratification for survivorship care planning should extend beyond diagnosis and treatment and should consider incorporating current morbidity. The development of such a person-centered care model is highly needed for this group of vulnerable individuals.

Author contributions

Nina Streefkerk: Conceptualization, data curation, formal analysis, methodology, project administration, supervision, writing–original draft, and writing–review and editing. **Jop C. Teepen**: Conceptualization, data curation, formal analysis, methodology, writing–original draft preparation,

and writing–review and editing. **Elizabeth A. M. Feijen**: Data curation, formal analysis, methodology, supervision, and writing–review and editing. **Katarzyna Jóźwiak**: Formal analysis and writing–review and editing. **Helena J. H. van der Pal**: Conceptualization, methodology, resources, and writing–review and editing. **Cecile M. Ronckers**: Conceptualization, methodology, and writing–review and editing. **Andrica C. H. De Vries**: Conceptualization and writing–review and editing. **Margriet Van der Heiden-van der Loo:** Data curation, resources, and writing–review and editing. **Nynke Hollema**: Data curation, resources, and writing–review and editing. **Marleen van den Berg**: Conceptualization, resources, and writing–review and editing. **Jacqueline Loonen**: Conceptualization, methodology, resources, and writing–review and editing. **Martha A. Grootenhuis**: Conceptualization and writing–review and editing. **Dorine Bresters**: Conceptualization, resources, and writing–review and editing. A. **Birgitta Versluys**: Conceptualization, resources, and writing–review and editing. **Eline van Dulmen-den Broeder:** Conceptualization, resources, and writing–review and editing. **Marry M. van den Heuvel-Eibrink**: Conceptualization, resources, and writing–review and editing. **Flora E. van Leeuwen**: Conceptualization and writing–review and editing. **Sebastian J. C. M. M. Neggers**: Conceptualization and writing–review and editing. **Hanneke M. Van Santen**: Conceptualization and writing–review and editing. **Mike Hawkins**: Conceptualization and writing–review and editing. **Michael Hauptmann**: Methodology and writing–review and editing. **Daisuke Yoneoka**: Formal analysis and writing–review and editing. **Joke C. Korevaar**: Conceptualization, funding acquisition, methodology, supervision, and writing–review and editing. **Wim J. E. Tissing**: Conceptualization, funding acquisition, methodology, resources, supervision, and writing–review and editing. **Leontien C. M. Kremer**: Conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, supervision, writing–original draft preparation, and writing–review and editing.

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Conflict of interest statement

Dorine Bresters reports fees for Professional Activities from Princess Maxima Center. Cecile M. Ronckers reports grant and/or contract funding from the Dutch Cancer Society. Sebastian J. C. M. M. Neggers reports consulting fees from Erasmus Medisch Centrum. Nina Streefkerk reports grant and/or contract funding from KWF Kankerbestrijding. The other authors declare no conflicts of interest.

Data availably statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Tables and figures

Table 1 Characteristics of childhood cancer survivors and siblings and prevalence of clinically relevant outcomes.

	CCSs included in the MCC analyses (*n* = 5925)	CCS questionnaire participants (*n* = 3152)	Siblings (*n* = 1066)
Sex, No. (%)			
Male	3313 (55.9)	1637 (51.9)	452 (42.4)
Female	2,612 (44.1)	1515 (48.1)	614 (57.6)
Age at diagnosis (median, in years, IQR)	5.6 (2.8–10.6)	5.3 (2.7–10.3)	–
Diagnosis, No. (%)			
Leukemia	2002 (33.8)	1081 (34.3)	–
Hodgkin lymphoma	389 (6.6)	201 (6.4)	–
Non-Hodgkin lymphoma	558 (9.4)	308 (9.8)	–
CNS tumors	790 (13.3)	390 (12.4)	–
Neuroblastoma	319 (5.4)	174 (5.5)	
Bone tumors	358 (6.0)	177 (5.6)	–
Soft tissue sarcomas	436 (7.4)	222 (7.0)	–
Renal tumors	582 (9.8)	345 (10.9)	–
Other	491 (8.3)	254 (8.1)	–
Treatment modality, No. (%)			
Surgery only	579 (9.8)	285 (9.0)	–
Chemotherapy ± surgery	2907 (49.1)	1636 (51.9)	–
Radiotherapy ± surgery	464 (7.8)	226 (7.2)	–
Chemotherapy + radiotherapy ± surgery	1936 (32.7)	989 (31.4)	–
Missing data	39 (0.7)	16 (0.5)	
Follow-up			
Age at questionnaire (median, in years, IQR)	–	29.7 (22.5–37.5)	31.9 (24.5–39.4)
Time 5-year survival to questionnaire (median, in years, IQR)	–	18.5 (13.2–25.1)	18.6 (12.8–26.9)

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Table 1 (Continued)

Questionnaire data, No. (%)			
≥1 Clinically relevant validated outcome[a]	—	1444 (46.4)	243 (23.8)
1 Clinically relevant validated outcome	—	868 (60.1)	192 (79.0)
2–4 Clinically relevant validated outcomes	—	549 (38.0)	51 (21.0)
≥5 Clinically relevant validated outcomes	—	27 (1.9)	0
≥1 Specific type of a condition			
Malignant neoplasm[b]	—	96 (3.0)	19 (1.8)
Cardiac	—	101 (3.2)	5 (0.5)
Vascular	—	146 (4.7)	29 (2.7)
Gastrointestinal	—	137 (4.3)	13 (1.2)
Pulmonary	—	76 (2.4)	17 (1.6)
Renal/urinary tract	—	69 (2.2)	2 (0.2)
Hepatic	—	38 (1.2)	8 (0.8)
Musculoskeletal	—	182 (5.9)	9 (0.9)
Endocrine	—	834 (26.7)	158 (14.8)
Neurological	—	176 (5.6)	11 (1.0)
Eye	—	123 (3.9)	4 (0.4)
Ear (*n*, %)	—	91 (2.9)	6 (0.6)
Other (*n*, %)	—	28 (0.9)	9 (0.8)

Note: *p* values calculate the difference in proportions or distributions between CCSs and siblings.
Abbreviations: CCSs, childhood cancer survivors; IQR, interquartile range; —, not applicable.
[a]In 38 CCS questionnaire participants, it was unknown whether they had a clinically relevant outcome.
[b]Excluding basal cell carcinoma of the skin.

Figure 1 Cumulative burden of new clinically symptomatic outcomes in childhood cancer survivors and in a sibling control group. The dotted lines represent 95% confidence intervals. A indicates the mean number of childhood cancer survivors at risk for all 10 imputed data sets.

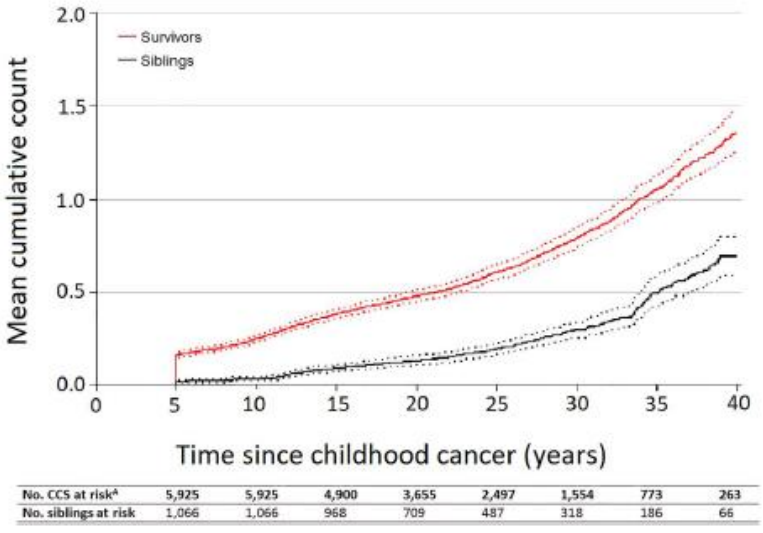

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Figure 2 Cumulative burden of new clinically symptomatic patient-reported outcomes stacked by type of outcome for all childhood cancer survivors (A) and for siblings (B). A indicates the mean number of childhood cancer survivors at risk for all 10 imputed data sets.

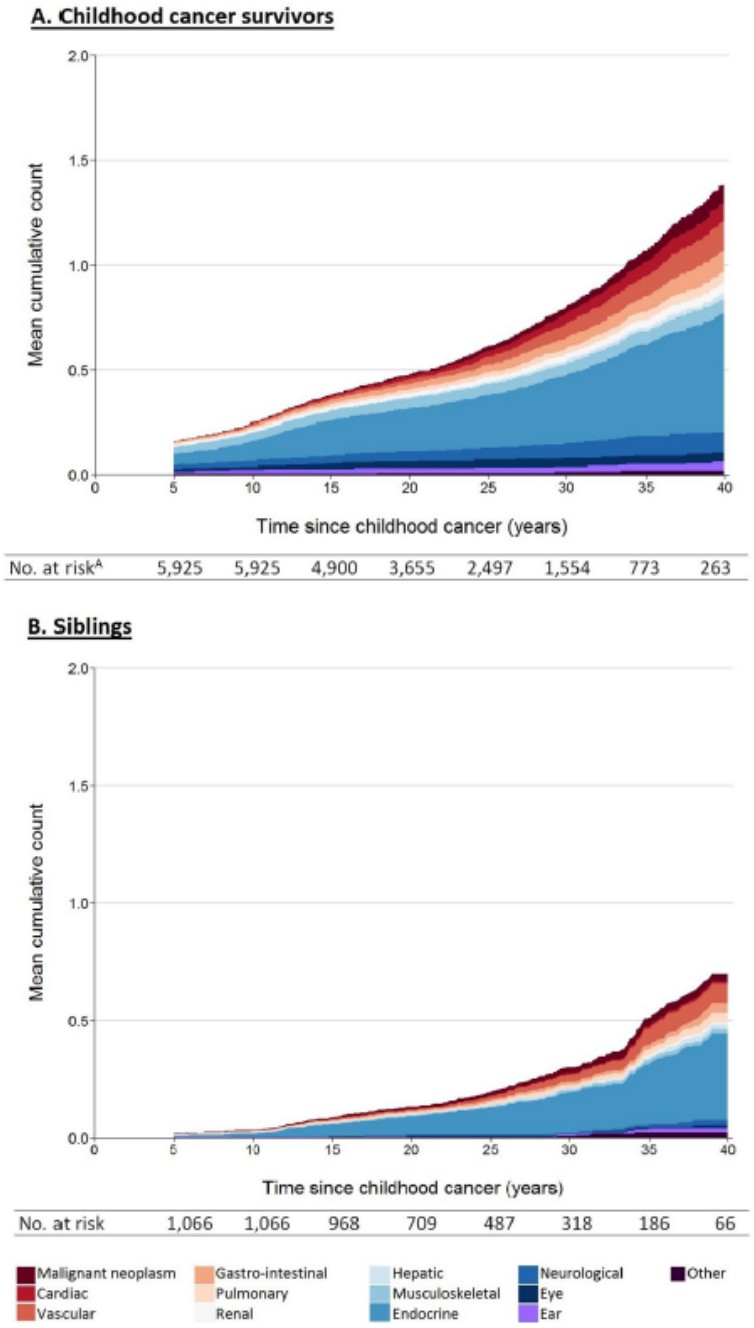

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Figure 3 Cumulative burden of new clinically symptomatic outcomes in childhood cancer survivors stacked by type of outcome stratified by primary cancer diagnosis. A indicates the mean number of childhood cancer survivors at risk for all 10 imputed data sets.

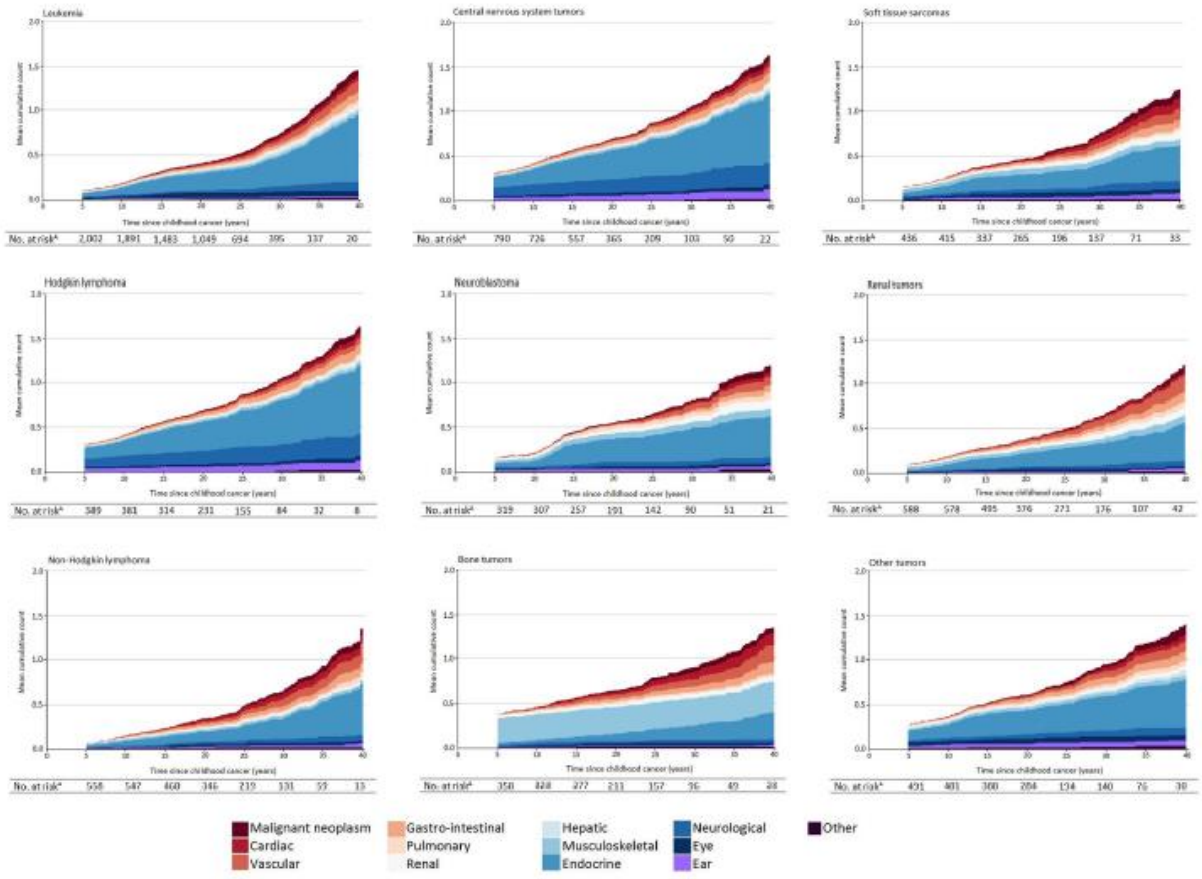

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Table 2 The mean cumulative count of long-term morbidity in childhood cancer survivors for groups of survivors based on combinations of primary cancer diagnosis and treatment, combined with levels of care according to three previously published risk stratification classifications.

Rank	Combination of primary cancer diagnosis and treatment	30-year MCC[a]	Wallace et al.[b]	NHS Improvement[b]	Frobisher et al.[b]
1	Central nervous system tumors + chemotherapy and radiotherapy	1.29	3	3	3
2	Neuroblastoma + radiotherapy only	1.14	3	2	2
3	Bone tumors + chemotherapy only	1.12	2	2	2
4	Central nervous system tumors + radiotherapy only	1.11	3	3	3
5	Hodgkin lymphoma + chemotherapy and radiotherapy	1.00	3	3	3
6	Soft tissue sarcoma + chemotherapy and radiotherapy	0.95	3	3	3
7	Neuroblastoma + chemotherapy and radiotherapy	0.91	3	3	3
8	Hodgkin lymphoma + radiotherapy only	0.90	3	2	3
9	Bone tumors + radiotherapy only	0.87	3	2	2
10	Non-Hodgkin lymphoma + chemotherapy and radiotherapy	0.86	3	3	2
11	Neuroblastoma + chemotherapy only	0.84	2	2	2
12	Renal tumors + chemotherapy and radiotherapy	0.81	3	3	3
13	Soft tissue sarcoma + radiotherapy only	0.79	3	2	2
14	Hodgkin lymphoma + chemotherapy only	0.78	2	2	2
15	Bone tumors + surgery only	0.76	1	1	1
16	Bone tumors + chemotherapy and radiotherapy	0.74	3	3	3
17	Central nervous system tumors + surgery only	0.74	1	1	2
18	Leukemia + chemotherapy and radiotherapy	0.74	3	3	3
19	Neuroblastoma + surgery only	0.73	1	1	1
20	Soft tissue sarcoma + chemotherapy only	0.71	2	2	2
21	Leukemia + chemotherapy only	0.71	2	1	1
22	Central nervous system tumors + chemotherapy only	0.61	2	2	2
23	Non-Hodgkin lymphoma + chemotherapy only	0.60	2	2	2
24	Soft tissue sarcoma + surgery only	0.59	1	1	1
25	Renal tumors + chemotherapy only	0.56	2	2	2
26	Renal tumors + radiotherapy only	0.49	3	2	2
27	Renal tumors + surgery only	0.31	1	1	1
	Siblings	0.29			

Abbreviations: MMC, mean cumulative count; NCSI, National Cancer Survivorship Initiative; NHS, National Health Service; 30-year MCC, MMC at 30 years post diagnosis.

[a]For each combination of primary cancer diagnoses and treatment, the MCC for clinically relevant outcomes was calculated at 30 years post diagnosis. We subsequently ranked all combinations of primary cancer diagnosis and treatment in descending order by mean cumulative count values. For five combinations of primary cancer diagnosis and treatment we did not calculate the MCC due to them not being relevant for clinical practice, and therefore had a very low number of cases: leukemia + surgery only, Hodgkin lymphoma + surgery only, non-Hodgkin lymphoma + surgery only, leukemia + radiotherapy only and non-Hodgkin lymphoma + radiotherapy only. Moreover, the group of "Other tumors" was not included in this table because it comprises a very heterogeneous group of tumors with respect to histology and treatment intensity.

[b]The colors and numbers in the columns represent the levels of care, based on the risk stratification classifications previously developed. Level 1 care (green) implicates: post or telephone follow-up every 1–2 years for Wallace et al.[6] and for the NHS Improvement,[7] self-care with support and open access for Frobisher et al.[9] Level 2 care (orange) implicates: follow-up led by nurse or primary care physician every 1–2 years for Wallace et al.[6] and for the NHS Improvement,[7] shared care for Frobisher et al.[9] Level 3 care (red) implicates: follow-up by medically supervised late effects clinic every year for Wallace et al.[6] and for the NHS Improvement,[7] complex case management through multidisciplinary team for Frobisher et al.[9] The risk stratification classifications are displayed in Table S5.