The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE)

Nickhill Bhakta, Qi Liu, Kirsten K Ness, Malek Baassiri, Hesham Eissa, Frederick Yeo, Wassim Chemaitilly, Matthew J Ehrhardt, Johnnie Bass, Michael W Bishop, Kyla Shelton, Lu Lu, Sujuan Huang, Zhenghong Li, Eric Caron, Jennifer Lanctot, Carrie Howell, Timothy Folse, Vijaya Joshi, Daniel M Green, Daniel A Mulrooney, Gregory T Armstrong, Kevin R Krull, Tara M Brinkman, Raja B Khan, Deo K Srivastava, Melissa M Hudson, Yutaka Yasui, Leslie L Robison**

Summary

Background Survivors of childhood cancer develop early and severe chronic health conditions (CHCs). A quantitative landscape of morbidity of survivors, however, has not been described. We aimed to describe the cumulative burden of curative cancer therapy in a clinically assessed ageing population of long-term survivors of childhood cancer.

Methods The St Jude Lifetime Cohort Study (SJLIFE) retrospectively collected data on CHCs in all patients treated for childhood cancer at the St Jude Children's Research Hospital who survived 10 years or longer from initial diagnosis and were 18 years or older as of June 30, 2015. Age-matched and sex-frequency-matched community controls were used for comparison. 21 treatment exposure variables were included in the analysis, with data abstracted from medical records. 168 CHCs for all participants were graded for severity using a modified Common Terminology Criteria of Adverse Events. Multiple imputation with predictive mean matching was used for missing occurrences and grades of CHCs in the survivors who were not clinically evaluable. Mean cumulative count was used for descriptive cumulative burden analysis and marked-point-process regression was used for inferential cumulative burden analysis.

Findings Of 5522 patients treated for childhood cancer at St Jude Children's Research Hospital who had complete records, survived 10 years or longer, and were 18 years or older at time of study, 3010 (54·5%) were alive, had enrolled, and had had prospective clinical assessment. 2512 (45·5%) of the 5522 patients were not clinically evaluable. The cumulative incidence of CHCs at age 50 years was 99·9% (95% CI 99·9–99·9) for grade 1–5 CHCs and 96·0% (95% CI 95·3–96·8%) for grade 3–5 CHCs. By age 50 years, a survivor had experienced, on average, 17·1 (95% CI 16·2–18·1) CHCs of any grade, of which 4·7 (4·6–4·9) were CHCs of grade 3–5. The cumulative burden in matched community controls of grade 1–5 CHCs was 9·2 (95% CI 7·9–10·6; p<0·0001 *vs* total study population) and of grade 3–5 CHCs was 2·3 (1·9–2·7, p<0·0001 *vs* total study population). Second neoplasms, spinal disorders, and pulmonary disease were major contributors to the excess total cumulative burden. Notable heterogeneity in the distribution of CHC burden in survivors with differing primary cancer diagnoses was observed. The cumulative burden of grade 1–5 CHCs at age 50 years was highest in survivors of CNS malignancies (24·2 [95% CI 20·9–27·5]) and lowest in survivors of germ cell tumours (14·0 [11·5–16·6]). Multivariable analyses showed that older age at diagnosis, treatment era, and higher doses of brain and chest radiation are significantly associated with a greater cumulative burden and severity of CHCs.

Interpretation The burden of CHCs in survivors of childhood cancer is substantial and highly variable. Our assessment of total cumulative burden in survivors of paediatric cancer, with detailed characterisation of long-term CHCs, provide data to better inform future clinical guidelines, research investigations, and health services planning for this vulnerable, medically complex population.

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Introduction

With 10-year survival for paediatric cancer now more than 80%, and late mortality decreasing in long-term survivors, the population of survivors of paediatric cancer is ever increasing.[1–4] Incidence and prevalence data, mostly generated by cohort studies, have documented that survivors have a lifelong increased risk of morbidity associated with their curative therapies.[5–10] However, the true price of cure is reflected by the cumulative burden of disease, or total disease morbidity, after taking into account the occurrences and severities of multiple medical conditions and recurrent events.

Comprehensive characterisation of the excess cumulative burden of morbidity associated with childhood cancer survivorship is a missing but necessary piece of evidence for addressing clinical and health policy interventions in this population. Previous research has focused on reporting relative risk, cumulative incidence (ie, time to first occurrence), or prevalence of chronic health conditions (CHCs). Furthermore, other cohort studies have often used

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*Joint senior authors

Department of Global Pediatric Medicine (N Bhakta MD), **Department of Epidemiology and Cancer Control** (N Bhakta, K K Ness PhD, W Chemaitilly MD, M J Ehrhardt MD, K Shelton MPH, L Lu MS, S Huang MSPH, Z Li MS, E Caron MSN, J Lanctot PhD, C Howell PhD, T Folse MD, D M Green MD, D A Mulrooney MD, G T Armstrong MD, K R Krull PhD, T M Brinkman PhD, M M Hudson MD, Y Yasui PhD, L L Robison PhD), **Department of Oncology** (N Bhakta, M Baassiri MD, H Eissa MD, F Yeo, M J Ehrhardt, M W Bishop MD, T Folse, D A Mulrooney, G T Armstrong, M M Hudson), **Rehabilitation Services** (J Bass AuD), **Department of Pediatric Medicine** (W Chemaitilly, R B Khan MD), **Department of Psychology** (K R Krull, T M Brinkman), **and Department of Biostatistics** (D K Srivastava PhD), **St Jude Children's Research Hospital, Memphis, TN, USA; School of Public Health, University of Alberta, Edmonton, AB, Canada** (Q Liu MS)**; and Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA** (W Chemaitilly, V Joshi MD)

Correspondence to: Dr Nickhill Bhakta, Department of Global Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN 38105, USA
nickhill.bhakta@stjude.org

Research in context

Evidence before this study

Because of their curative treatment-related exposures, survivors of childhood cancer are at increased risk for a broad range of chronic health conditions. We searched PubMed from database inception to Oct 13, 2016, using the terms "childhood cancer survivor" and "childhood or adolescent" and "burden or chronic health conditions or morbidity or long-term outcome" for English language publications describing the burden of chronic health conditions in the population of survivors of childhood cancer. Previous efforts to describe disease burden in childhood cancer survivors have all used traditional statistics such as relative risk and cumulative incidence, largely relied on either patient-reported data without concurrent medical validation of chronic health conditions, did not have a control cohort, or were missing the detailed radiation and chemotherapy exposure data we have abstracted in our cohort.

Added value of the study

To our knowledge, this is the first study to provide a comprehensive medical account of the disease burden landscape for a clinically assessed cohort of childhood cancer survivors, with comparison of survivor morbidity to a community control population. Earlier studies have examined few aspects of this narrative, generally within selected subsets of the survivor population and relying upon self-reported outcomes. None have explored, in a clinically assessed cohort, how a large and diverse series of chronic health conditions in all major organ systems relate to one another to form unique patterns of illness between survivor subgroups that, when combined, result in a cumulative burden of disease that is substantially larger than and distinct from that observed in the general population.

Implications of all the available evidence

By the addition of a new statistical method, which provides greater resolution of disease burden than ever before, and addressing long-standing cohort limitations in survivorship research, we present and visualise a detailed condition-by-condition assessment of morbidity in the growing high-risk population of childhood cancer survivors. Previous work has shown, in less comprehensively assessed and characterised populations than that used in our study, that survivors of childhood cancer have more chronic health conditions than do the general population. Our data go much further and provide a comprehensive landscape of morbidity while presenting context on the interrelationships between the various components of disease burden. In clinical and research settings, general health practitioners and clinical investigators can use the information we provide to address risks as part of patient care, assess trade-offs between exposures and different chronic health conditions to aid the design of future clinical trials, and inform the development of follow-up guidelines. Furthermore, from a policy perspective, our data offer the most extensive documentation to date that survivors of childhood cancer are not a monolithic population but are instead heterogeneous subgroups with complex medical needs and a substantially higher overall disease burden. Although adjunctive survivorship care clinics and close adherence to survivorship guidelines in primary health-care settings are the current global standard, the numerous morbidity profiles that we describe suggest that survivors might benefit from specialised health-care delivery, similar to that being advocated for other high-risk populations.

patient-reported morbidities without medical validation, not had a control population, or not obtained detailed treatment exposure data. By addressing each of these limitations and using new analytical methods, the St Jude Lifetime Cohort Study (SJLIFE) provides an opportunity to describe and visualise, for the first time, the overall and excess cumulative burdens of curative cancer therapy in a clinically assessed ageing population of long-term survivors.

Methods

Study design and participants

All data were obtained from two ongoing cohort studies approved by the St Jude Children's Research Hospital (SJCRH; Memphis, TN, USA) institutional review board (IRB): the SJLIFE and the St Jude Long-term Follow-up Study (SJLTFU).[11,12] The SJLIFE is a retrospective cohort study initiated in April, 2007, with prospective follow-up and ongoing data accrual (appendix p 5). All patients treated at SJCRH for an oncological disease, who are 18 years or older at June 30, 2015, and were diagnosed with their malignancy at least 10 years ago are eligible for the cohort. The first survivor in our analysis was diagnosed on Oct 15, 1961, and met eligibility on Oct 15, 1971, and the final survivor was diagnosed on July 2, 2004.[11] SJLIFE community control participants matched on 5-year age blocks in each sex were included for comparison. Exclusion criteria for community controls were being a first-degree relative of an SJLIFE participant, having a history of childhood cancer, or being pregnant (appendix p 5).

See Online for appendix

Written informed consent was obtained from all SJLIFE participants. Demographic, mortality, and therapy-related exposure data for the cancer survivors who died before recruitment into SJLIFE, refused participation, or had not completed an SJLIFE clinical assessment visit were obtained from medical records using an IRB-approved waiver from the SJLTFU, an administrative system-based study initiated in the year 2000 that collects data on treatment, outcome, and late toxicity for all patients ever treated at SJCRH for childhood cancer. Because these individuals did not return to campus for prospective medical follow-up, they could not be clinically assessed, and their chronic

health condition outcomes were not directly assessed and graded.

Procedures

21 treatment exposure variables were included in the analysis, with selection and categorisation of specific treatment-related exposures on the basis of long-term follow-up guidelines.[13] Cumulative doses of chemotherapeutic agents were abstracted by trained research staff from medical records using a structured protocol.[11] Radiation dosimetry was done or estimated from primary radiation prescription records.

168 CHCs were classified using the SJCRH-modified version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03: mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4), or death (grade 5).[14] To better accommodate the grading of CHCs in long-term survivors, modifications were made to the CTCAE for the following reasons: (1) to define how clinical data (eg, medical or surgical interventions) were used in severity grading; (2) to define more conservative diagnostic ranges with the objective of avoiding overdiagnosis of specific conditions; and (3) to conform to diagnostic practice at SJCRH. To describe components of total disease burden, the 168 CHCs were grouped into 48 condition-specific categories (appendix p 7).

All clinically evaluable SJLIFE participants (campus-visit) and community control participants completed at least one comprehensive clinical assessment at SJCRH including medical outcome surveys, a complete medical history and physical examination, a standardised battery of laboratory tests, a formal analysis of neuromuscular function and additional risk-directed diagnostic imaging, and additional risk-directed diagnostic imaging and testing as previously described.[11] CHCs identified from clinical assessments after completion of therapy were identified by retrospective medical record review. Survivor-reported clinical events were validated by diagnostic reports obtained from community health-care providers (appendix p 6). Medical conditions were clinically assessed in the same way for SJLIFE survivors and community controls[11] with the exception of five conditions: hearing loss, glaucoma, cataracts, and retinopathy were self-reported by community controls and decreased bone mineral density was analysed only in survivors using dual-energy x-ray absorptiometry. Decreased bone mineral density was not directly assessed for community controls but incorporated into analyses by multiple imputation using robust population-based normative data from the National Health and Nutrition Examination Survey (NHANES), which used the same device used at SJCRH.[15,16]

Fatal health-related events (grade 5) were ascertained using a combination of data from (1) a national death index (NDI) search done on June 30, 2013, of participants in the SJLTFU who survived up to Dec 31, 2011, and (2) continuous annual follow-up from the SJCRH Cancer Registry. Cause of death was identified using International Classification of Diseases (ICD)-9 and ICD-10 codes from the NDI or direct assessment of death certificates, medical records, or next-of-kin interviews conducted by SJLIFE staff or the SJCRH Cancer Registry.

Statistical analysis

Survivors entered the cohort at age 18 years or 10 years from their primary cancer diagnosis, whichever occurred later. At-risk status ended on June 30, 2015 (censoring), or on the date of death. Community control participants entered the analysis cohort at age 18 years and were censored 1 day after the completion of clinical assessment. Demographic and treatment differences between campus-visit and non-campus-visit SJLIFE-eligible survivors were compared using χ^2 and t tests. Occurrences and CTCAE grades of CHCs for SJLIFE-eligible survivors who were not clinically assessed (non-campus-visit survivors) were handled by the predictive-mean-matching method of multiple imputation to minimise potential bias by the missing CHC data.[16,17] This approach assumes the data are missing-at-random, which is a weaker, more tenable assumption than assuming complete randomness of non-campus visits in the whole cohort. Specifically, missing-at-random assumes that, after considering the demographic and treatment-exposure variables, non-campus visits occur at random within each subgroup of survivors formed by these variables, but with potentially different rates across the subgroups. In the first step of predictive-mean-matching, a piecewise exponential model for each of the 48 grouped CHC outcomes was built using the demographic and 21 treatment variables that are available for all survivors regardless of clinical assessment status (appendix pp 12–13). Then, for each non-campus-visit survivor, 50 closest matched campus-visit survivors were identified on the basis of the sum of the squared distances of standardised predicted rates of the 48 grouped CHC outcomes, of whom one campus-visit survivor was eventually selected using applied Bayesian bootstrap to donate their CHC data to the non-campus-visit survivor.[16] This multivariate imputation of CHC data was repeated ten times to generate ten complete datasets of observed plus imputed CHC data for all survivors in our cohort, reflecting the uncertainty for missing CHCs of each non-campus-visit survivor with ten possible sets of CHCs. Complete imputation methods are described with greater technical details in the appendix pp 2–4.

CHC data were processed using previously described cumulative burden subtypes based on clinical definitions of chronicity and recurrence.[12,14] Three event subtypes were clinically assigned to each of the 168 graded CHCs: (1) single, recurrent events that can occur multiple times at any grade; (2) chronic, non-recurrent events that were counted only once at the time of onset; and (3) chronic,

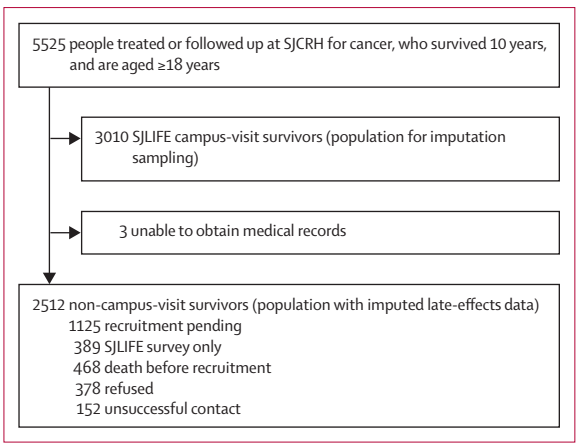


Figure 1: **Flow diagram of survivors treated or followed up at SJCRH**
SJCRH=St Jude Children's Research Hospital. SJLIFE=St Jude Lifetime Cohort Study.

recurrent events, which represent a hybrid of the first two subtypes. Full classification of conditions and their assigned subtype are presented in the appendix pp 7–11. Cumulative burden was calculated using the method of mean cumulative count, which estimates the mean number of recurrent or multiple health events that a cohort member has by a given timepoint in the presence of competing risk events.[18] The cumulative burden for each of the 168 CHCs was individually calculated and then summed to generate the grouped condition and organ system categories. The bootstrap percentile method was used to estimate 95% CIs for individual and organ system categories. Since survivors entered the cohort at different ages, our calculation of cumulative burden by age accounted for left truncation.[19] All curves and analyses were continued until age 50 years, because beyond this timepoint our overall and primary-diagnosis-specific cumulative burden estimates were less stable because of low numbers of survivors older than 50 years.

Marked-point-process regression was done to assess associations of treatment exposures with cumulative burden (appendix pp 2–4).[12,20] This method separates the associations into two stages while assessing and adjusting for demographic and treatment variables for the following: (1) the overall rate of developing any of the 168 grade 1–5 CHCs (associations with the variables expressed as rate ratios) and (2) the propensity for a CHC to be a worse grade given that a condition has developed (associations with the variables expressed as odds ratios for a condition to be grade 2 or 3–5, compared with grade 1). Variables were selected in each model on the basis of backward selection, removing a variable by likelihood-ratio-test-based p values, stopping at p=0·05. Complete marked-point-process regression methods with greater technical detail are further described in the appendix p 4. All statistical analyses were done for each of the ten complete datasets and then ten sets of the results are summarised by the standard multiple imputation methods.[15,16] SAS (version 9.4), R (version 3.2.3), and STATA (version 14.1) were used for statistical analyses.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 5525 eligible survivors who had survived for 10 years and were 18 years or older, 5522 had complete records and were included in the analysis (figure 1). As of the cut-off date for this analysis (June 30, 2015), 5054 (91·5%) of the 5522 patients were still alive, 3399 (61·6%) had actively enrolled in SJLIFE, and 3010 (54·5%) had completed their initial clinical assessment. The remaining 2512 (45·5%) of the 5522 eligible survivors were not clinically evaluable because they died before recruitment, refused to participate, or did not complete the clinical assessment. Demographic characteristics of the two SJLIFE-eligible groups (clinically evaluable and non-clinically evaluable) and community controls (n=272) are presented in table 1. Radiation and chemotherapy differences between the campus-visit and non-campus-visit SJLIFE-eligible survivors are further detailed in the appendix pp 12–13. Using NHANES data, age-standardised, sex-standardised, and race-standardised prevalence rates for CHCs obtained in an analogous manner to SJLIFE showed that the prevalence in SJLIFE community controls (n=272) is similar that in the general US population (appendix p 14).

The cumulative incidence and cumulative burden of all grade 1–5 (figure 2) and grade 3–5 (figure 3) events for the total study population, clinically evaluable survivors, community controls, and each of the primary cancer-specific diagnoses from the total study population were calculated (appendix pp 15–27). For the total study population, the cumulative burden was slightly lower than in the clinically evaluable survivors alone starting after age 35 years. At age 50 years, the cumulative incidence of grade 1–5 CHCs was 99·9% (95% CI 99·9–99·9) and grade 3–5 CHCs was 96·0% (95·3–96·8) in the total study population (appendix pp 16–17). The cumulative burden in the total study population at age 50 years was 17·1 (95% CI 16·2–18·1) grade 1–5 conditions per individual, including 4·7 (4·6–4·9) grade 3–5 conditions (figure 2, 3). By contrast, in the community controls, the cumulative incidence of grade 1–5 CHCs was 96·0% (93·6–98·5; p<0·0001 *vs* total study population) and grade 3–5 CHCs was 84·9% (77·1–90·0; p<0·0001 *vs* total study population). The cumulative burden in the community controls was 9·2 (7·9–10·6; p<0·0001 *vs* total study population) grade 1–5 events and 2·3 (1·9–2·7, p<0·0001 *vs* total study population) grade 3–5 events. The grade 1–5

	Total study population (n=5522)	Comparison of survivor groups			Community controls* (n=272)
		Clinically evaluable (n=3010)	Non-clinically evaluable (n=2512)	p value	
Sex				<0·0001	
Female	2456 (44·5%)	1442 (47·9%)	1014 (40·4%)	..	142 (52·2%)
Male	3066 (55·5%)	1568 (52·1%)	1498 (59·6%)	..	130 (47·8%)
Age at diagnosis, years				0·0684	
Mean (SD)	8·4 (5·6)	8·3 (5·6)	8·6 (5·6)	..	NA
Median (IQR)	7·6 (3·4–13·2)	7·3 (3·3–13·1)	7·9 (3·6–13·3)	..	NA
Range	0·0–28·6	0·0–24·8	0·0–28·6	..	NA
Age at censor, years				<0·0001	
Mean (SD)	34·8 (9·5)	36·1 (9·1)	33·3 (9·8)	..	35·1
Median (IQR)	33·8 (27·4–41·3)	35·1 (29·2–42·3)	32·3 (25·0–40·1)	..	34·7 (28·0–42·3)
Range	18·1–70·4	18·9–68·3	18·1–70·4	..	18·3–70·2
Race				0·0047	
White	4550 (82·4%)	2520 (83·7%)	2030 (80·8%)	..	238 (87·5%)
Other	972 (17·6%)	490 (16·3%)	482 (19·2%)	..	34 (12·5%)
Treatment era				<0·0001	
Pre-1980	1200 (21·7%)	649 (21·6%)	551 (21·9%)	..	NA
1980–94	2775 (50·3%)	1632 (54·2%)	1143 (45·5%)	..	NA
1995 or later	1547 (28·0%)	729 (24·2%)	818 (32·6%)	..	NA
Any death (any grade 5 event), per 10 000 person-years	70·3	17·7	148·2	<0·0001	NA
Competing death†, per 10 000 person-years	22·6	6·6	46·2	<0·0001	NA
Primary cancer diagnosis				<0·0001	
Acute lymphoblastic leukaemia	1685 (30·5%)	1007 (33·5%)	678 (27·0%)	..	NA
Acute myeloid leukaemia	214 (3·9%)	104 (3·5%)	110 (4·4%)	..	NA
Hodgkin's lymphoma	667 (12·1%)	368 (12·2%)	299 (11·9%)	..	NA
Non-Hodgkin lymphoma	440 (8·0%)	223 (7·4%)	217 (8·6%)	..	NA
CNS tumour	673 (12·2%)	312 (10·4%)	361 (14·4%)	..	NA
Bone sarcoma‡	375 (6·8%)	208 (6·9%)	167 (6·6%)	..	NA
Soft tissue sarcoma	354 (6·4%)	188 (6·2%)	166 (6·6%)	..	NA
Wilms' tumour	358 (6·5%)	200 (6·6%)	158 (6·3%)	..	NA
Neuroblastoma	239 (4·3%)	137 (4·6%)	102 (4·1%)	..	NA
Retinoblastoma	153 (2·8%)	90 (3·0%)	63 (2·5%)	..	NA
Germ cell tumour	141 (2·6%)	69 (2·3%)	72 (2·9%)	..	NA
Other§	223 (4·0%)	104 (3·5%)	119 (4·7%)	..	NA
Treatments¶				0·0101	
Chemotherapy only	713 (12·9%)	392 (13·0%)	321 (12·8%)	..	NA
Radiation only	28 (0·5%)	16 (0·5%)	12 (0·5%)	..	NA
Surgery only	463 (8·4%)	217 (7·2%)	246 (9·8%)	..	NA
Chemotherapy and radiation	866 (15·7%)	491 (16·3%)	375 (14·9%)	..	NA
Chemotherapy and surgery	1151 (20·8%)	638 (21·2%)	513 (20·4%)	..	NA
Radiation and surgery	397 (7·2%)	204 (6·8%)	193 (7·7%)	..	NA
Chemotherapy, radiation, and surgery	1884 (34·1%)	1045 (34·7%)	839 (33·4%)	..	NA

Data are n (%) unless otherwise stated. NA=not applicable. *p values comparing the total study population and our community controls are: sex p=0·012, age at censor p=0·632, and race p=0·0301. †Competing deaths are any grade 5 events that were not categorised as one of the 168 graded conditions (ie, accidents or suicide). ‡Bone sarcoma: osteosarcoma and Ewing's sarcoma. §Other includes chronic myeloid leukaemia (n=46), biphenotypic leukaemia (n=5), colon carcinoma (n=15), nasopharyngeal carcinoma (n=38), carcinoma not otherwise specified (n=38), liver malignancies (n=46), and melanomas (n=35). ¶Full treatment characteristics are in the appendix (pp 10–11).

Table 1: **Characteristics of the St Jude Lifetime Cohort Study eligible survivors and community controls**

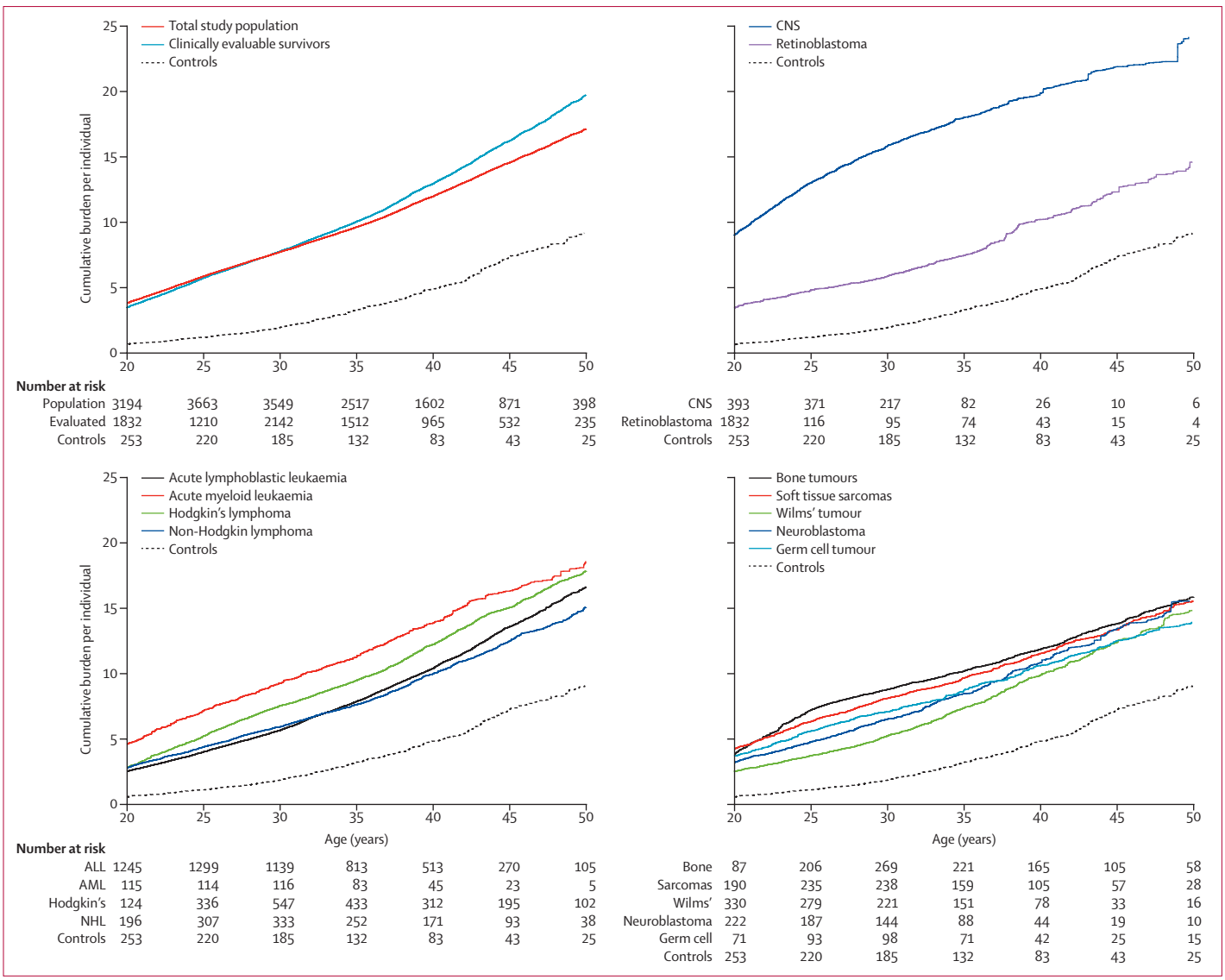


Figure 2: **Cumulative burden of all (grade 1–5) chronic health conditions in St Jude Lifetime Cohort Study survivors of childhood cancer and in community controls**
ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. Bone tumour=osteosarcoma and Ewing sarcoma. CNS=CNS malignancies. Hodgkin's=Hodgkin's lymphoma. NHL=non-Hodgkin lymphoma.

cumulative incidences and cumulative burdens at age 50 years in the total study population were highest for the cardiovascular (incidence 93·2% [95% CI 92·4–94·0]; burden 4·0 [3·9–4·2]), endocrine (incidence 91·6% [90·6–92·5]; burden 2·6 [2·0–3·2]), and musculoskeletal (incidence 83·6% [82·3–85·0]; burden 1·7 [1·5–2·0]) systems. The cumulative incidence of second neoplasms was 37·3% (95% CI 34·4–40·2) by age 50 years with corresponding cumulative burden of 0·9 (0·8–1·1), highlighting that multiple second neoplasms are an important late effect in the survivor cohort.

The cumulative burden at age 30 years and rate of cumulative burden growth were variable across cancer subtypes and organ systems. For Hodgkin's lymphoma survivors, the mean number of grade 1–5 cardiovascular CHCs per survivor nearly quadrupled from 1·2 (0·9–1·5) at age 30 years to 4·4 (4·0–4·8) by age 50 years, whereas the mean number of grade 1–5 second neoplasms increased nearly six times from 0·2 (0·1–0·3) at age 30 years to 1·0 (0·8–1·2) by 50 years (appendix pp 18, 21). By contrast, the CHC burden for other organ systems started high and only slowly increased with age. For example, the mean number of CNS tumour survivors that had grade 1–5 hearing loss at age 30 years was 67 per 100 (95% CI 0·6–0·7), increasing to 83 per 100 (0·7–1·0) at age 50 years. Neurological outcomes were similar, increasing slowly from high baseline of 3·7 (3·4–4·0) at age 30 years to 4·7 (4·2–5·2) by age 50 years (appendix pp 18–22).

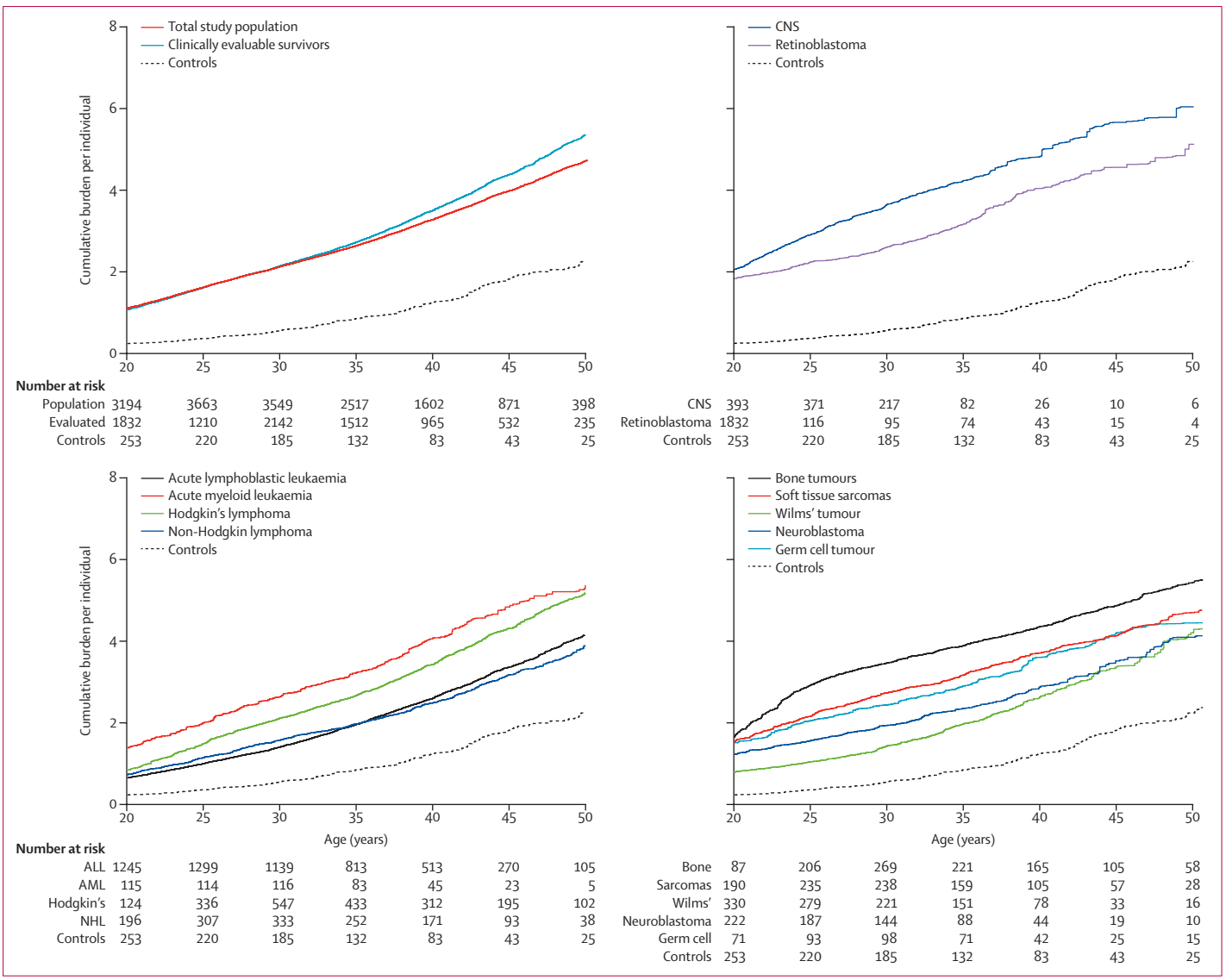


Figure 3: **Cumulative burden of severe (grade 3–5) chronic health conditions in St Jude Lifetime Cohort Study survivors of childhood cancer and in community controls**
ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. Bone tumour=osteosarcoma and Ewing sarcoma. CNS=CNS malignancies. Hodgkin's=Hodgkin's lymphoma. NHL=non-Hodgkin lymphoma.

The cumulative burden of grade 1–5 CHCs at age 50 years was highest in survivors of CNS malignancies (24·2 [95% CI 20·9–27·5]) and lowest in survivors of germ cell tumours (14·0 [11·5–16·6]; figure 4A). The cumulative burden of grade 3–5 CHCs ranged from 3·9 (95% CI 3·3–4·5) for survivors of non-Hodgkin lymphoma to 6·0 (4·7–7·3) for survivors of CNS malignancies (figure 4B). We also analysed the proportional contributions of outcome-specific categories by age in participants and community controls (figure 5). A pairwise analysis of proportional differences in grade 1–5 cumulative burden in the community controls and cancer diagnosis subgroups showed that two pairs of primary cancers, germ cell tumours and soft-tissue sarcomas and germ cell tumours and bone tumours, had a similar paired pattern of outcome-specific morbidity, with distributions of morbidity being significantly different across all other paired groups (appendix p 34).

The ranked and absolute cumulative burden of CHCs at age 50 years was analysed by outcome and all cohort subgroups (figure 6). Conditions contributing to metabolic syndrome (essential hypertension, dyslipidaemia, abnormal glucose metabolism, and obesity) were highly ranked in both survivors and community controls, with each group having similar absolute cumulative burdens. Of the grade 1–5 outcome-specific categories, arrhythmias and structural heart defects ranked highly in both community controls and survivors, whereas secondary and recurrent neoplasms, spinal disorders, and pulmonary function deficits were ranked highly in

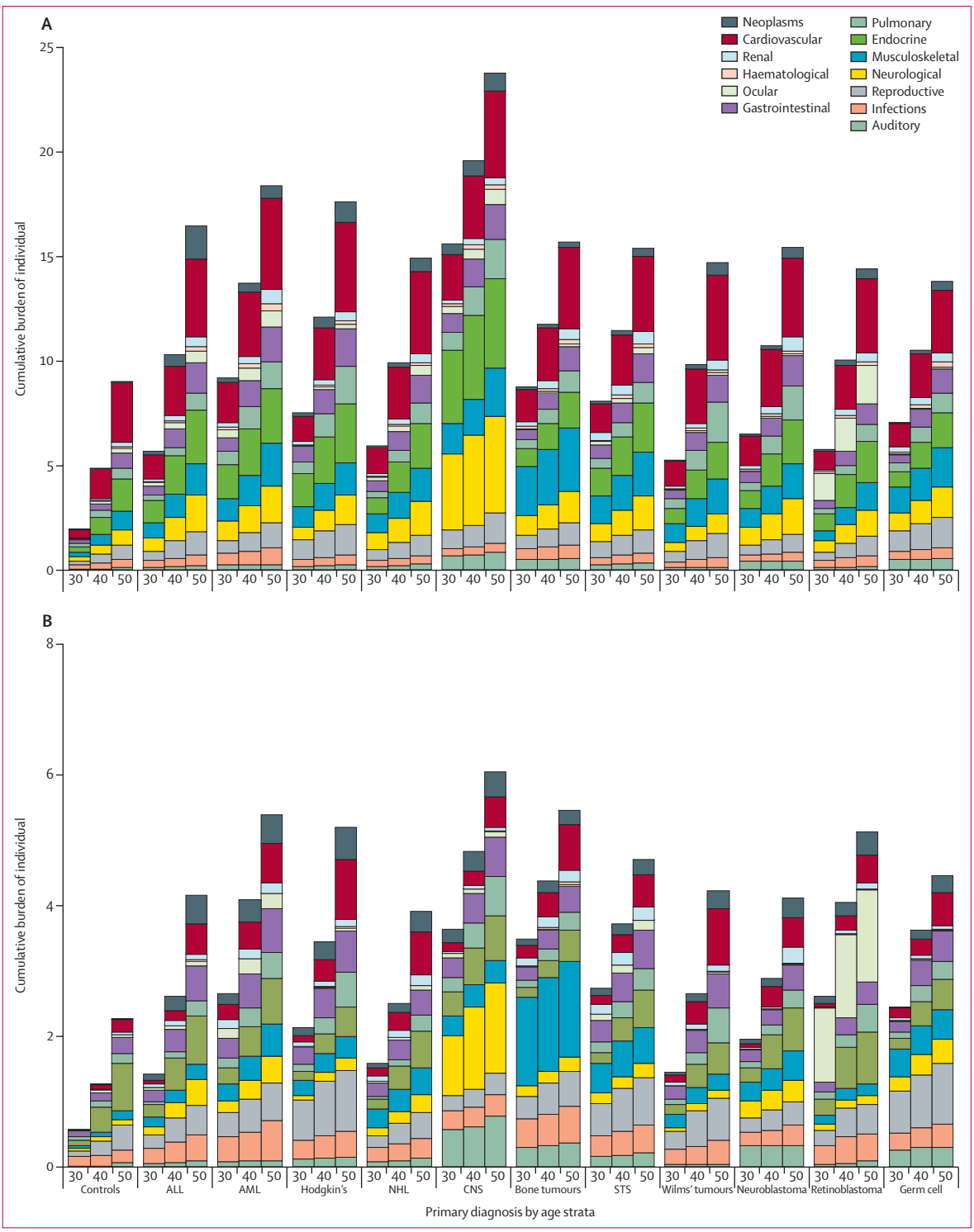


Figure 4: **Distribution of cumulative burden in St Jude Lifetime Cohort Study childhood cancer survivors and community controls by diagnosis group and age**
(A) Grades 1–5. (B) Grades 3–5. Numbers on the x-axis show age in years. All data, with 95% CIs, are provided in the appendix pp 14–23. ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. Hodgkin's=Hodgkin's lmphoma. NHL=non-Hodgkin lymphoma. CNS=CNS malignancies. Bone tumour=osteosarcoma and Ewing sarcoma. STS=soft tissue sarcomas.

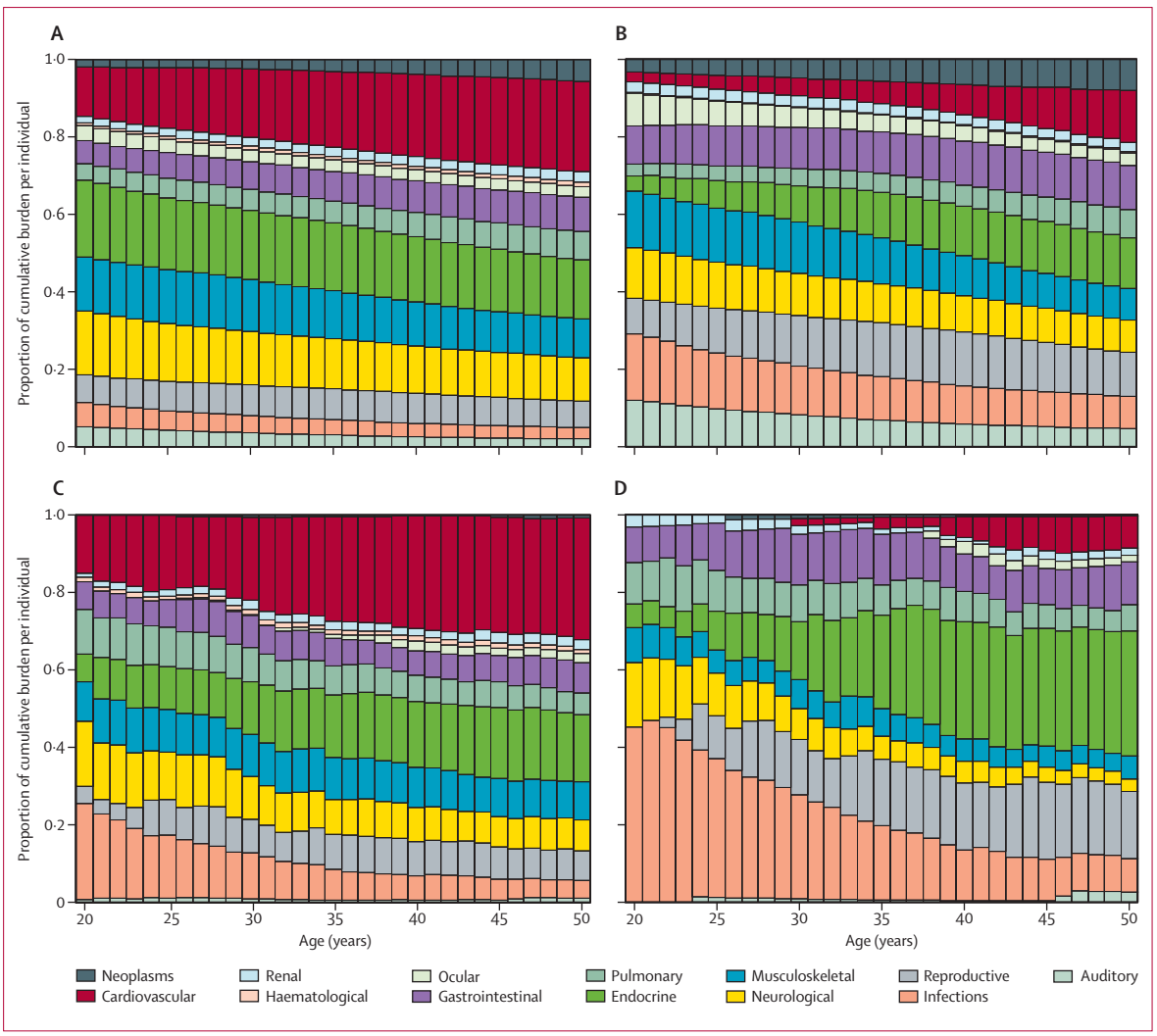


Figure 5: **Stacked bar-plots representing the proportional contribution of organ system cumulative burden to the total cumulative burden in controls and each of the primary cancer subgroups**

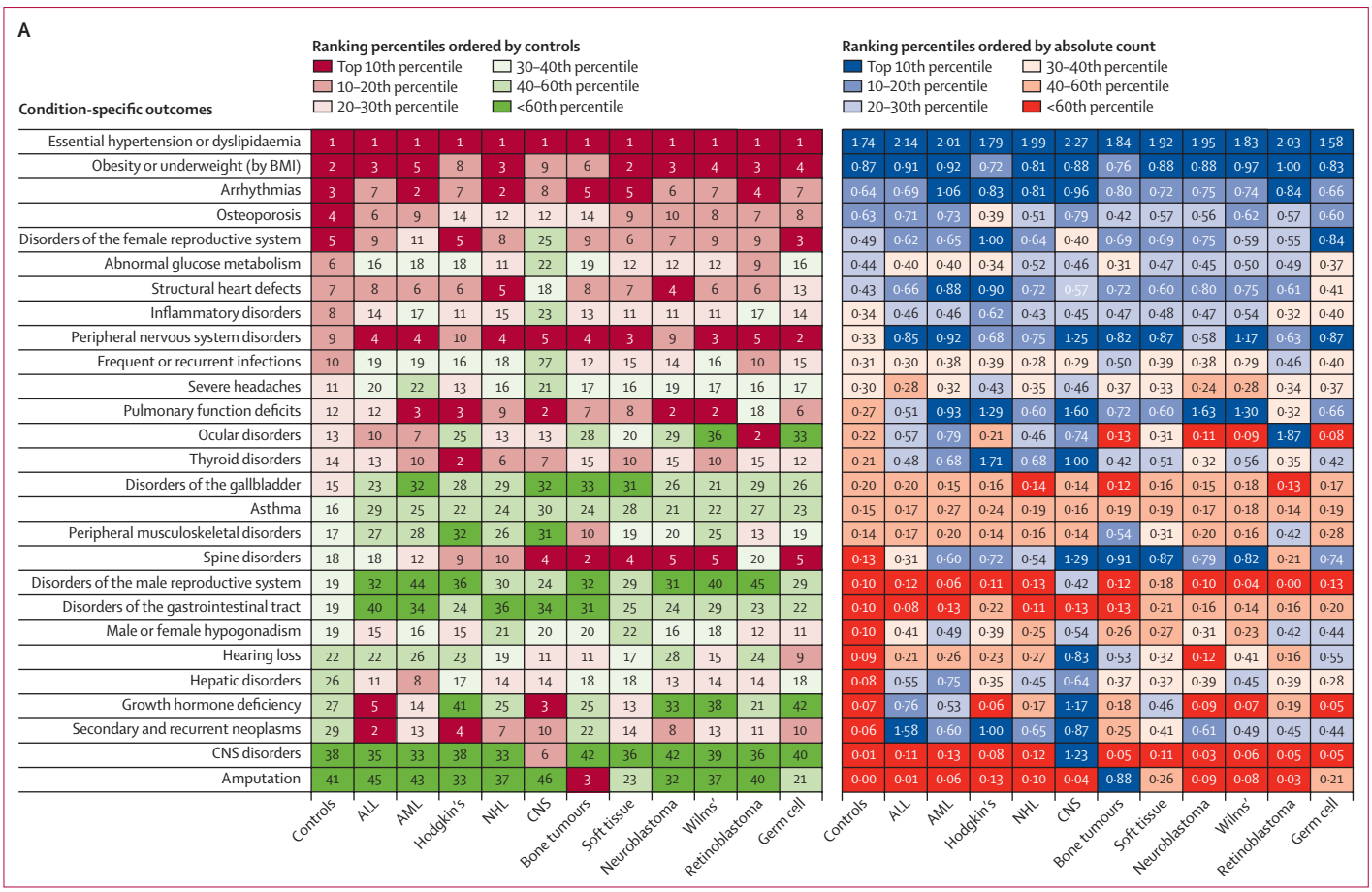
(A) All survivors, grades 1–5. (B) All survivors, grades 3–5. (C) Community controls, grades 1–5. (D) Community controls, grades 3–5.

survivors only. For the grade 3–5 categories, secondary and recurrent neoplasms and pulmonary function deficits were ranked below the top ten for community controls but were ranked in the top five for two or more primary diagnosis subgroups.

Table 2 shows results of multivariable regression analyses. Two models are provided that separate associations into an overall rate of developing a condition (model 1) and, if a condition had developed, the propensity for it being a more severe grade (model 2). After adjusting for all significant demographics and treatment exposures, age at diagnosis, treatment era, and higher brain and chest radiation doses were associated with increased cumulative burden and more severe CHCs. Plant alkaloid and methotrexate exposure were associated with decreased cumulative burden (table 2).

Discussion

Using the SJLIFE cohort, we present, to our knowledge, the most extensive assessment and comprehensive characterisation to date of the long-term health-related morbidity of survivors of childhood cancer. Our current analysis goes beyond previously published results in two important ways. First, many cohort studies are limited by either relying solely upon self-reported outcomes without concurrent medical validation of CHCs,[9] absence of an appropriate control population, or scarce detailed treatment exposure data. The SJLIFE cohort used prospective clinical assessment and retrospective medical record validation of 168 graded CHCs, recruitment of a similarly assessed community control population, and abstraction of medical records with detailed survivor-specific demographic and treatment exposure data.[7,11,12,18] Second, the traditional methods used to characterise



(Figure 6 continues on next page)

long-term morbidity in survivor populations, such as cumulative incidence and prevalence of health conditions,[6–8,21] only describe the first occurrence of an outcome and do not adequately show the many different morbidities that occur in the survivorship population. By analysing the cumulative burden (a method of disease burden measurement that incorporates multiple health conditions and recurrent events into a single metric) in the SJLIFE cohort, we define the landscape of disease burden by providing a clinically informative description of the long-term pattern of morbidity in survivors of childhood cancer.[12,22] Using cumulative prevalence, we previously reported that by age 45 years, 95·2% of survivors in the SJLIFE cohort had at least one CHC and 80% had at least one serious, disabling, or life-threatening CHC.[5] Now, within the same cohort, we report more specifically that survivors have twice the burden of disease compared with the general population at age 45 years, shown by an excess of seven more CHCs per individual than in the general population, two of which will be serious or disabling, life threatening, or fatal.

Our findings have wide-ranging implications for health-care delivery, clinical research, and health policy. For clinicians, the complex patterns of CHCs contributing to cumulative burden in different subgroups of survivors highlights the health-care needs of this population, which surpass those commonly provided for in routine practice. Based on changes in cumulative burden over time (appendix pp 15–27), survivors appear to have two classes of morbidities: late-occurring morbidities, increasing as the cohort ages and at a faster rate than in community controls; and early-onset conditions associated with the acute effects of cancer therapy. For example, in survivors of haematological malignancies, the contribution of cardiovascular disease and secondary and recurrent neoplasms to overall cumulative burden increases at a faster relative rate over time than other contributors to overall burden, contributing a greater proportion as survivors age. Alternatively, the cumulative burden of neurological and auditory outcomes in survivors of CNS malignancies remained mostly static over our period of follow-up and are primarily irreversible early toxicities such as hearing loss and neuropathies. At any timepoint, these static conditions might be either controlled or inadequately managed, adding another complex, time-consuming task for health-care practitioners who must

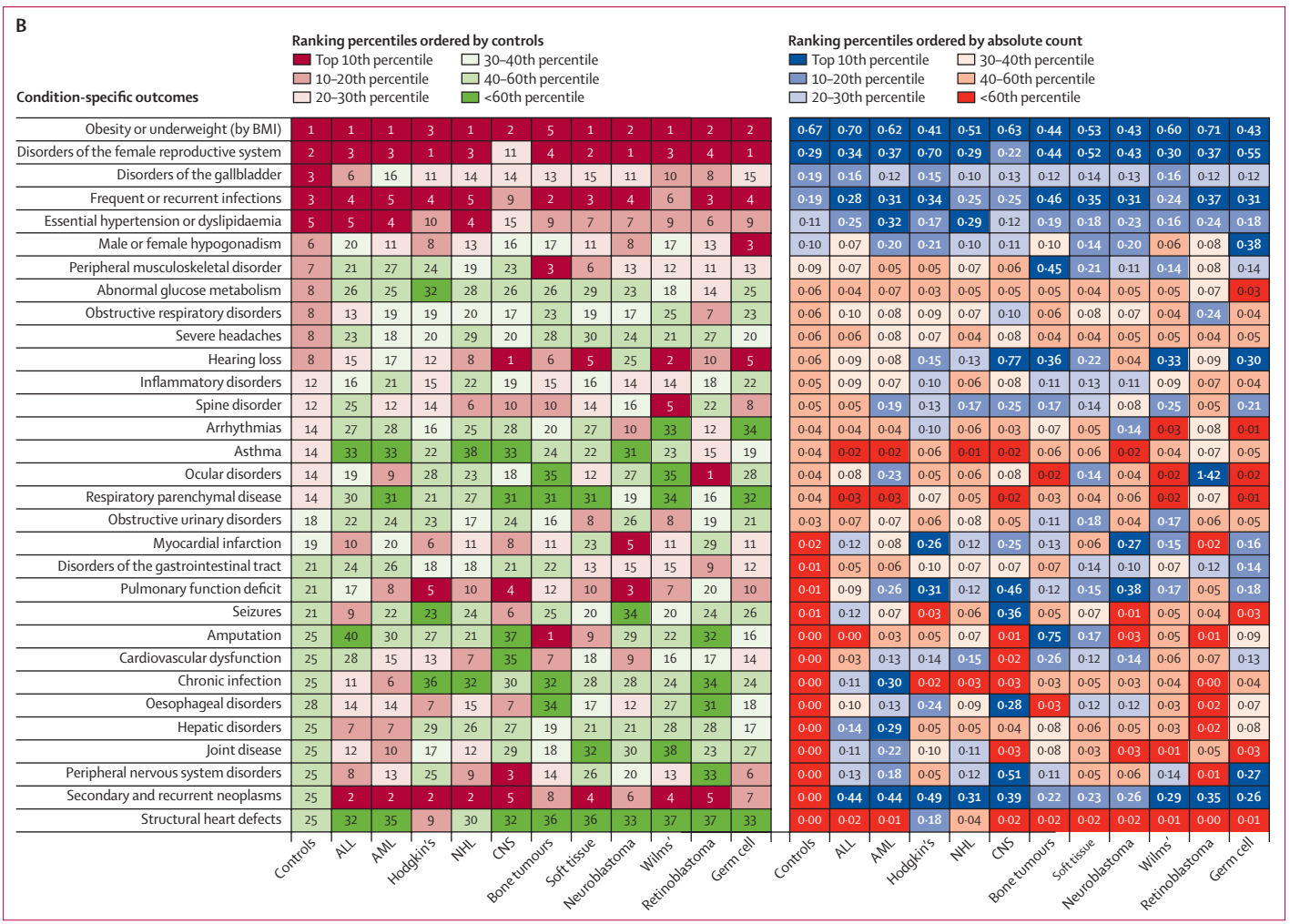


Figure 6: **Rank and contribution to cumulative burden of condition-specific outcomes in St Jude Lifetime Cohort Study survivors of childhood cancer and community controls by diagnosis group at age 50 years**

(A) Grade 1–5 outcomes. (B) Grade 3–5 outcomes. Condition-specific outcomes (detailed composition in the appendix pp 5–9) are rank ordered in the red and green boxes according to the top 20 community control cumulative burden. All condition-specific outcomes ranked below the top 20 in community controls but within the top ten in any primary cancer subgroup were also included. In the blue boxes, each box corresponds to absolute cumulative burden count per person for each condition-specific outcome and cohort subgroup. For example, ocular disorders rank 14th in terms of absolute grade 3–5 cumulative burden per individual in controls with, on average, one occurrence of a severe or life-threatening ocular condition per 25 people (0·04 cumulative burden per individual). In survivors of AML, ocular disorders rank as the ninth largest absolute cumulative burden with, on average, one occurrence of a grade 3–5 condition for every four survivors (0·23 cumulative burden per survivor). Colours represent overall percentiles (defined in the key). ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. Bone tumours=osteosarcoma and Ewing sarcoma.

not only tailor and implement survivorship management guidelines to their patients but also consistently monitor potentially numerous previously diagnosed conditions with vigilance.

By ranking and quantifying condition-specific outcomes, we provide a more comprehensive knowledge base that clinical investigators can use when designing cancer therapy trials for newly diagnosed patients or intervention approaches for early detection, prevention, or amelioration of treatment-related late effects in long-term survivors of childhood cancer. An increasing number of clinical trials are being designed to minimise risk of selected treatment-related morbidities. Design of these therapeutic trials is largely based on the results of previous trials or disease-risk measures (eg, incidence or prevalence), or both.[23] The additional information provided by the cumulative burden metric allows investigators to look beyond associations with individual late effects, and characterise subpopulations of survivors with multiple comorbidities who might benefit from more precise therapeutic interventions.

From a health policy perspective, the heterogeneity of CHCs that comprise the cumulative burden between survivor subgroups emphasises that this population is not homogeneous. Our data show the complexity of their medical needs, which vary on the basis of primary cancer diagnosis, treatment, and era of exposure. These results, when combined with the early onset and increased

	Model 1: overall rate		Model 2: propensity for a higher grade condition			
	Rate ratio (95% CI)	p value	Grade 2 *vs* grade 1		Grades 3–5 *vs* grade 1	
			OR (95% CI)	p value	OR (95% CI)	p value
Sex						
Male	..	..	Ref	Ref	Ref	Ref
Female	..	..	1·26 (1·18–1·35)	<0·0001	1·31 (1·22–1·41)	<0·0001
Race						
White	..	..	Ref	Ref	Ref	Ref
Other	..	..	1·00 (0·92–1·09)	0·93	1·15 (1·05–1·27)	0·0030
Age at diagnosis, years						
0–4	Ref	Ref	Ref	Ref	Ref	Ref
5–9	0·71 (0·66–0·76)	<0·0001	1·04 (0·95–1·13)	0·39	1·12 (1·01–1·24)	0·029
10–14	0·46 (0·43–0·50)	<0·0001	1·06 (0·93–1·19)	0·38	1·26 (1·10–1·44)	0·0005
15 or older	0·33 (0·30–0·35)	<0·0001	1·06 (0·90–1·26)	0·47	1·51 (1·28–1·78)	<0·0001
Year of diagnosis						
Pre-1980	0·48 (0·44–0·51)	<0·0001	1·21 (1·08–1·35)	0·0012	1·57 (1·36–1·80)	<0·0001
1980–94	Ref	Ref	Ref	Ref	Ref	Ref
1995 or later	2·54 (2·37–2·72)	<0·0001	0·94 (0·82–1·07)	0·34	0·59 (0·51–0·68)	<0·0001
Anthracycline dose, mg/m²						
None	Ref	Ref	Ref	Ref	Ref	Ref
1–249	1·18 (1·10–1·27)	<0·0001	0·89 (0·81–0·98)	0·015	0·78 (0·71–0·85)	<0·0001
250 or more	1·22 (1·12–1·33)	<0·0001	0·94 (0·84–1·05)	0·28	0·95 (0·85–1·07)	0·40
Methotrexate						
No	Ref	Ref	..	..	..	..
Yes	0·83 (0·75–0·91)	<0·0001	..	..	..	..
CED dose*, mg/m²						
None	..	..	Ref	Ref	Ref	Ref
1–6300	..	..	1·04 (0·94–1·14)	0·48	1·04 (0·94–1·16)	0·42
6301–10 892	..	..	0·98 (0·89–1·08)	0·62	0·99 (0·90–1·09)	0·86
≥10 893	..	..	1·10 (0·99–1·21)	0·061	1·12 (1·01–1·25)	0·023
Bleomycin						
No	..	..	Ref	Ref	Ref	Ref
Yes	..	..	1·20 (1·04–1·38)	0·010	1·25 (1·06–1·47)	0·0062
Cytarabine						
No	Ref	Ref	..	..	..	..
Yes	1·23 (1·13–1·34)	<0·0001	..	..	..	..
Plant alkaloids						
No	Ref	Ref	..	..	..	..
Yes	0·88 (0·82–0·96)	0·0014	..	..	..	..
Platinum agents						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1·29 (1·16–1·43)	<0·0001	1·12 (0·98–1·29)	0·089	1·07 (0·92–1·23)	0·38
Steroids						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1·13 (1·02–1·26)	0·016	0·97 (0·87–1·07)	0·50	0·92 (0·84–1·01)	0·078
Brain radiation dose†, Gy						
None	Ref	Ref	Ref	Ref	Ref	Ref

(Table 2 continues on next page)

severity of medical conditions relative to the general population, show that specialised health delivery services could benefit survivors of childhood cancer. Previously, others have argued that a community-based shared-care model provided through specialised clinics would be valuable.[24] In the USA, these efforts have been complicated because survivors have historically had poor access to health services and insurance because of increased disability and unemployment compared with the general population. Additionally, recent work from SJLIFE found that protocol-based screening and clinical assessment identified undiagnosed conditions, in part because of the unfamiliarity that general practitioners have with recommended screening guidelines.[7,25] These findings align with studies done in Europe where access to primary care services is not dependent on insurance but childhood cancer survivors are still more likely to be admitted to hospital and have poorer health outcomes than the general population.[21,26,27] This combination of poor access to health services combined with the severe excess morbidity we present in our analysis confirm the vulnerability of this population and question whether consultant long-term follow-up in which primary responsibility remains with community physicians is sufficient. An alternative option being broadly tested in the USA in other vulnerable populations such as HIV-infected individuals,[28] is the patient-centred medical home model, which addresses unique medical and psychosocial needs through coordinated multidisciplinary services.[29] Despite rapid changes occurring in insurance coverage and reimbursement because of ongoing debate surrounding the US Patient Protection and Affordable Care Act, US cancer centres that already provide survivorship services have a unique opportunity to provide global leadership in survivorship health-care delivery. They can benefit both themselves and the population they serve by accepting increased liability and piloting the feasibility of multidisciplinary survivorship patient-centred medical homes as a model for comprehensive and consolidated services (ie, primary care, cardiology, pulmonary, and endocrine care).

Although our application of the cumulative burden metric has quantified morbidity in a new way that complements other approaches or metrics for measuring disease occurrence, we consider several limitations and biases as important when interpreting our results.[12,22] First, some of the treatments used to treat childhood cancer do not reflect modern standards of care, because older cohort members might have received greater radiation or chemotherapy doses or delayed access to screening for late-effect conditions than younger cohort members.[23] Second, screening guidelines have evolved over time, so numbers of low-grade conditions (CTCAE grades 1–2) in our cohort might have been underestimated in earlier cases because they would not be identified without active screening.[7] To address both of these concerns, treatment era was incorporated as a variable in

our regression models. Furthermore, although we recognise that the observed descriptive data are not easily generalised across treatment eras, they are still clinically relevant for older survivors who will still benefit from improved characterisation of their health deficits. Third, although we report the cumulative burden of 168 CTCAE conditions, we restricted these outcomes to non-psychiatric diagnoses. Inclusion of other medical outcomes such as neurocognitive or psychiatric disorders could have resulted in different estimates and explained the protective effects seen with methotrexate.[30] In exploring potential trade-offs between treatment exposures affecting cumulative burden, careful and transparent consideration of measured outcomes included in multivariable analyses will be important. Fourth, as previously described,[12] the cumulative burden itself does not incorporate the effect of clinically relevant factors such as social function and health-related quality of life. Although we ranked our results in figure 6 on the basis of the quantity of burden, the clinical discretion of patient perspectives when making decisions on the basis of these data is still important because survivors would probably estimate their burden not on the basis of quantity but quality.

	Model 1: overall rate		Model 2: propensity for a higher grade condition			
	Rate ratio (95% CI)	p value	Grade 2 *vs* grade 1		Grades 3–5 *vs* grade 1	
			OR (95% CI)	p value	OR (95% CI)	p value
(Continued from previous page)						
<18	1·08 (0·97–1·20)	0·17	1·12 (0·95–1·31)	0·16	1·07 (0·92–1·24)	0·37
18 to <30	1·04 (0·97–1·12)	0·28	1·11 (1·00–1·24)	0·053	1·14 (1·03–1·28)	0·014
30 to <40	1·19 (0·93–1·52)	0·15	1·09 (0·76–1·56)	0·63	1·10 (0·78–1·55)	0·56
≥40	1·57 (1·43–1·72)	<0·0001	1·27 (1·09–1·46)	0·0013	1·24 (1·09–1·42)	0·0014
Chest radiation dose†, Gy						
None	Ref	Ref	Ref	Ref	Ref	Ref
<10	0·95 (0·87–1·05)	0·33	1·20 (1·03–1·40)	0·016	1·08 (0·92–1·28)	0·34
≥10	1·41 (1·32–1·50)	<0·0001	1·31 (1·18–1·46)	<0·0001	1·14 (1·01–1·28)	0·030
Pelvic radiation						
No	..	..	Ref	Ref	Ref	Ref
Yes	..	..	1·12 (1·01–1·24)	0·029	1·05 (0·94–1·18)	0·35

For both models, backward selection was done from a set of exposure variables. OR=odds ratio. CED=cyclophosphamide equivalent dose. *CED dose with category cutoffs based on tertiles. †Assigned dose is the maximum dose received within the region.

Table 2: **Results of regression analysis of cumulative burden by demographic and treatment exposures**

To report results that represent a complete cohort and are broadly generalisable, we used imputation methods and assumed that the missing data in the non-clinically evaluable survivors were missing at random after considering demographic characteristics and treatment exposures. Although we incorporated all available data, potentially important characteristics such as lifestyle factors and socioeconomic status were not known for our non-clinically evaluable survivors and could potentially bias our imputation process and results. Yet, without knowing the true CHC status of the non-clinically evaluable SJLIFE eligible survivors, we cannot know whether the combined estimate that we report or the higher estimate from the clinically assessed survivors only is closer to the truth. However, to provide generalisable data for a clearly defined cohort of survivors, which we have previously shown[7,11] is representative of childhood cancer survivors in the USA, we elected to include all long-term survivors eligible for SJLIFE, while acknowledging that our estimates are probably a conservative lower bound of disease burden in this population. To further examine the generalisability of our results with respect to potential bias due to differences in diagnosis mix between SJLIFE and the general population, we also estimated the cumulative burden of CHCs at age 50 years in the 10-year survivors of childhood cancer in the population of the Surveillance, Epidemiology, and End Results (SEER) programme, a population-based cancer registry of the USA covering approximately 10% of the US population. This cumulative burden was estimated by taking a weighted average of diagnosis-specific cumulative burden values from SJLIFE survivors at age 50 years, with weights being the diagnosis-specific numbers of SEER childhood cancer survivors who were age 50 years or older and alive on Dec 31, 2016. The estimated cumulative burden of CHCs at age 50 years in the SEER population, compared with the overall SJLIFE cohort, was not different (grades 1–5, SEER 17·4 [95% CI 15·5–19·3] *vs* SJLIFE 17·1 [16·2–18·1]; and grades 3–5, SEER 4·9 [4·0–5·8] *vs* SJLIFE 4·7 [4·5–4·8]).

Finally, several potential biases should be considered when interpreting our results. First, race and sex differences exist between our total study population and our community controls. Furthermore, our community control population is quite small, thus, although we show significant differences between survivor and control groups, high precision is not achieved. Although we do adjust for demographic variation in our marked-point-process regression models and have shown that the CHCs in our community controls are representative of the general population of the USA, these are two important limitations of this initial report and we anticipate that the continued recruitment and matching of our community controls will reduce potential bias and improve precision in subsequent analyses. Second, for five of the CHCs, measurement methods differed between survivors and community controls. Although the controls did not have formal audiology or ophthalmological assessments, all controls had a complete history and physical examination that would have identified severe grade 2–4 conditions. For grade 1 (asymptomatic or mild) hearing loss or vision CHCs, community controls might have been under-diagnosed since low-grade conditions are unlikely to be identified by physical examination alone. As a final point, we acknowledge that a potential surveillance bias exists

between our survivor population and community controls, especially for grade 1 conditions. Because of more frequent recommended screenings, survivors were probably more closely assessed over time. Thus, the onset date for CHCs in survivors is probably closer to the physiological date of onset than that in the community controls, especially for asymptomatic conditions that are unlikely to be identified without active screening.

In summary, survivors of childhood cancer have an excess burden of disease associated with their curative therapies. Within this vulnerable population, this study is the first to comprehensively measure and report the landscape of absolute and excess morbidity. Our findings reinforce the importance and complexity of successfully providing active clinical management for these high-risk patients.

Contributors

NB, MMH, YY, and LLR designed and supervised the study. NB, KKN, MB, HE, FY, WC, MJE, JB, MWB, KS, LL, SH, ZL, and CH prepared the data. NB, QL, YY analysed the data and prepared the manuscript. NB, QL, KKN, MB, HE, FY, WC, MJE, JB, MWB, EC, JL, TF, VJ, DMG, DAM, GTA, KRK, TMB, RBK, DKS, MMH, YY, and LLR discussed and revised the manuscript. NB, QL, KKN, MMH, YY, and LLR had access to the raw data.

Declaration of interests

We declare no competing interests.

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