Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study

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Summary

Background Treatment outcomes among survivors of cancer diagnosed during adolescence and early young adulthood have not been characterised independently of survivors of cancers diagnosed during childhood. We aimed to describe chronic health conditions and all-cause and cause-specific mortality among survivors of early-adolescent and young adult cancer.

Methods The Childhood Cancer Survivor Study (CCSS) is a retrospective cohort study with longitudinal follow-up of 5-year survivors diagnosed with cancer before the age of 21 years at 27 academic institutions in the USA and Canada between 1970 and 1999. We evaluated outcomes among survivors of early-adolescent and young adult cancer (aged 15–20 years at diagnosis) and survivors diagnosed at age younger than 15 years (matched on primary cancer diagnosis, including leukaemia, lymphoma, CNS tumours, neuroblastoma, Wilms tumour, soft-tissue sarcomas, and bone cancer) by comparing both groups to siblings of the same age. Mortality was ascertained with the National Death Index. Chronic health conditions were classified with the Common Terminology Criteria for Adverse Events. Standardised mortality ratios (SMRs) were estimated with age-specific, sex-specific, and calendar year-specific US rates. Cox proportional hazard models estimated hazard ratios (HRs) for chronic health conditions and 95% CIs.

Findings Among 5804 early-adolescent and young adult survivors (median age 42 years, IQR 34–50) the SMR compared to the general population for all-cause mortality was 5·9 (95% CI 5·5–6·2) and among 5804 childhood cancer survivors (median age 34 years; 27–42), it was 6·2 (5·8–6·6). Early-adolescent and young adult survivors had lower SMRs for death from health-related causes (ie, conditions that exclude recurrence or progression of the primary cancer and external causes, but include the late effects of cancer therapy) than did childhood cancer survivors (SMR 4·8 [95% CI 4·4–5·1] *vs* 6·8 [6·2–7·4]), which was primarily evident more than 20 years after cancer diagnosis. Early-adolescent and young adult cancer survivors and childhood cancer survivors were both at greater risk of developing severe and disabling, life-threatening, or fatal (grade 3–5) health conditions than siblings of the same age (HR 4·2 [95% CI 3·7–4·8] for early adolescent and young adult cancer survivors and 5·6 [4·9–6·3] for childhood cancer survivors), and at increased risk of developing grade 3–5 cardiac (4·3 [3·5–5·4] and 5·6 [4·5–7·1]), endocrine (3·9 [2·9–5·1] and 6·4 [5·1–8·0]), and musculoskeletal conditions (6·5 [3·9–11·1] and 8·0 [4·6–14·0]) when compared with siblings of the same age, although all these risks were lower for early-adolescent and young adult survivors than for childhood cancer survivors.

Interpretation Early-adolescent and young adult cancer survivors had higher risks of mortality and severe and life threatening chronic health conditions than the general population. However, early-adolescent and young adult cancer survivors had lower non-recurrent, health-related SMRs and relative risks of developing grade 3–5 chronic health conditions than childhood cancer survivors, by comparison with siblings of the same age, which were most notable more than 20 years after their original cancer. These results highlight the need for long-term screening of both childhood and early-adolescent and young adult cancer survivors.

Funding National Cancer Institute and American Lebanese-Syrian Associated Charities.

Lancet Oncol 2020; 21: 421–35

Published **Online** February 14, 2020 https://doi.org/10.1016/S1470-2045(19)30800-9

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Introduction

Nearly 70 000 adolescents and young adults aged 15–39 years are diagnosed with cancer annually in the USA.[1] Almost 80% of these adolescents and young adults will survive more than 5 years after their cancer diagnosis.[2] As such, survivors of adolescent and young adult cancer represent a population with a substantial number of potential life-years saved who remain at risk of developing long-term morbidity or dying prematurely because of their previous cancer treatments.

In 2006, the Adolescent and Young Adult Oncology Progress Review Group (PRG), supported by the National

Research in context

Evidence before this study

Long-term outcomes in survivors of cancer diagnosed during adolescence or young adulthood are not well understood. We searched PubMed from database inception to May 18, 2019, using the terms "adolescent and young adult or AYA cancer survivors" and "health conditions or morbidity" and "death or mortality" for English language publications describing the health consequences of cancer treatment in this population. Many studies have described the important psychosocial consequences of being treated for cancer as an adolescent or young adult, including decrements in health-related quality of life. Several studies have examined the morbidity and mortality of adolescents and young adults based on large cancer registries (eg, registries in Denmark and in England and Wales); however, detailed treatment exposure data or severity of illness were not considered in these studies.

Added value of the study

To our knowledge, this retrospective cohort study is the first to provide a comprehensive assessment of long-term health outcomes in early-adolescent and young adult cancer survivors. We used detailed outcome and treatment data to summarise the long-term outcomes of early-adolescent and young adult survivors in comparison with survivors of childhood cancer (aged <15 years at diagnosis), a cohort of siblings, and the general population. In general, the patterns of chronic health conditions in early-adolescent and young adult survivors reflect those of childhood cancer survivors, although we identified differences in risk for non-recurrent, health-related causes of death and chronic cardiac, endocrine, and musculoskeletal conditions between survivors of childhood cancer and early-adolescent and young adult cancer (despite similar treatment exposures).

Implications of all the available evidence

Our previous understanding of the long-term consequences of cancer treatment on adolescents and young adults was largely extrapolated from data describing survivors of childhood cancer. This analysis confirms the substantial burden of long-term health complications in the youngest subset of adolescents and young adults, can be used to inform current therapies for this population, and underscores the need for targeted interventions to ensure life-long, risk-based follow-up care for this population.

Cancer Institute (NCI) and the LIVESTRONG Foundation, identified research priorities to improve outcomes for adolescent and young adult cancer survivors.[3] One priority called for research to understand the long-term health outcomes associated with adolescent and young adult cancer and its treatment—an essential step towards providing appropriate risk-based care. Yet, a decade after the PRG report, a paucity of data exists about long-term morbidity and late mortality in this population. Although studies have examined the morbidity and premature mortality of survivors of both paediatric and adult cancers,[4–7] few have focused on those treated for their cancer as adolescents and early young adults (aged 15–20 years). Thus, the aim of the current analysis was to describe chronic health conditions and all-cause and cause-specific late mortality among survivors of cancer diagnosed during adolescence and early young adulthood within the Childhood Cancer Survivor Study (CCSS), compared with survivors diagnosed as children with the same primary cancers and compared with non-cancer populations.

For **additional details of the CCSS** see https://ccss.stjude.org

Methods

Study design and participants

The CCSS is a retrospective cohort with longitudinal follow-up of 24 363 5-year survivors diagnosed with cancer aged younger than 21 years at 27 academic institutions in the USA and Canada between 1970 and 1999 (appendix p 26). Details of the CCSS have been reported previously.[8] Briefly, eligible survivors were identified and initially recruited through their original cancer treatment institutions. Survivors who died after their 5-year anniversary of cancer diagnosis were eligible and a proxy (parent, sibling, or spouse) was asked to answer a baseline survey on their behalf. A sibling control group of 5059 individuals was enrolled by randomly selecting 30% of the participating survivors, determining whether they had a full sibling and inviting that sibling to participate through their survivor sibling. The study was approved by the institutional review board at each institution and informed consent was obtained. Continued contact with participating survivors and siblings is done through the coordinating centre at St Jude Children's Research Hospital (Memphis, TN, USA).

In this analysis, CCSS participants diagnosed with cancer aged 15 years or older up to 21 years were defined as early-adolescents and young adults. Early-adolescent and young adult cancer diagnoses included leukaemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumour, neuroblastoma, soft-tissue sarcoma, and bone cancer. Since the youngest survivor of an early-adolescent and young adult cancer would be at least 20 years of age at cohort entry, only siblings aged 20 years at the time of baseline completion were included in comparisons with early-adolescents and young adults. Additionally, to eliminate potential sources of bias, a cohort of survivors diagnosed with cancer during childhood (aged <15 years) was randomly selected from frequency-matched (1:1) strata based on primary cancer diagnosis, with siblings aged 5 years or older as a comparison group for survivors of childhood cancers.

Procedures

Primary cancer characteristics and detailed treatment information were extracted from medical records.[8] Cumulative alkylating agent dose was reported as

cyclophosphamide-equivalent dose (CED),[9] whereas cumulative anthracycline dose was reported as doxorubicin-equivalent.[10] Radiation records were used to estimate region and organ-based dosimetry.[11]

Cause of death was ascertained among all participants eligible for the CCSS through a search of the US National Death Index (NDI) through to 2013. The NDI identified the underlying and multiple causes of death for deceased patients by use of the International Classification of Diseases (ICD), 9th and 10th revision. For deaths that predated the NDI, death certificates were requested from states where deaths occurred. Deaths were reviewed by two or more clinicians and grouped into three mutually exclusive categories with ICD-9 and ICD-10 coding: first, for recurrence or progression of the primary cancer; second, for external causes (accidents, suicides, and homicide); and third, for non-recurrent, health-related causes including subsequent malignant neoplasms, cardiovascular causes, pulmonary causes, and all other medical causes. Canadian participants were excluded from mortality analyses since the NDI does not ascertain deaths of individuals outside the USA.

Chronic health conditions were reported by participating survivors and siblings on one baseline survey and up to three follow-up surveys administered at 2–4-year intervals. The severity of each health condition was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, developed by the NCI. Conditions were coded as mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4), or fatal (grade 5), as previously described,[12] on the basis of questions about age at onset of specific chronic health conditions (appendix pp 1–3).[4] The self-reported health conditions were reviewed and CTCAE grading was adjudicated by an expert panel (appendix pp 4–6). If the available information was insufficient to assign between two grades, the lower severity grade was assigned. Grade 5 conditions were obtained from the cause of death information ascertained from the NDI. Questionnaires were completed by a proxy if the survivor was deceased, younger than 18 years of age, or unable to complete the questionnaire themselves. Self-reporting of a subsequent malignant neoplasm was validated by review of a pathology report, medical record, or death certificate.

The objective of the study was to describe the chronic health conditions and late mortality of survivors diagnosed with cancer as early-adolescents and young adults, compared with a matched population of survivors diagnosed as children and a population with no history of cancer.

Statistical analysis

Among the eligible US-based survivors for the CCSS, Kaplan–Meier estimates of overall survival probabilities were computed, first as a function of time since cancer diagnosis and second, with age as the time scale, by use of left-truncation to account for staggered age of entry to the cohort.[13] The Greenwood formula was used to calculate 95% CIs. To compare data with the US population, expected survival was computed on the basis of the expected number of deaths each year since diagnosis using sex-specific, age-specific, and calendar year-specific US mortality rates from the National Center for Health Statistics[14] and plotted as comparative survival curves. Cumulative mortality was conditional on survival at 5 years since diagnosis. Cumulative incidence was also estimated for each cause-specific mortality, treating other causes of death as competing risks.

Standardised mortality ratios (SMRs) were estimated as the number of observed deaths divided by the expected number of deaths based on the same US mortality rates used for the Kaplan–Meier curves. Cause-specific SMRs were generated for deaths attributable to subsequent malignant neoplasms, cardiac causes, pulmonary causes, external (accidents, suicide, or homicide), and all other medical causes, stratified by both attained age and time since diagnosis. 95% CIs and p values for SMRs were calculated on the basis of Poisson probability models for deaths, splitting each person's data record into person-year intervals with unique combinations of age, calendar year, and sex, with relevant covariate and death data for each and using the number of expected events in the USA in that time interval as the offset term. Since recurrence or progression of the primary cancer could not be specifically examined by SMRs (no recurrences in the general population) and since recurrence or progression is more dependent on time since diagnosis than on attained age, the risk of death due to recurrence or progression of the primary cancer was examined via Cox models, with time since diagnosis as the time scale.

See Online for appendix

Cumulative incidence was estimated for grade 1–5 and grade 3–5 conditions, overall and by organ system, based on time from diagnosis to the first condition after cohort entry and also calculated with age as the timescale.[13] Death from chronic conditions was treated as an event, but death from other causes was treated as a competing risk. Age-matched groups of siblings were used to calculate comparative incidence estimates. To evaluate potential follow-up bias, among early-adolescent and young adult survivors diagnosed between 1970 and 1986 (since they had multiple follow-up surveys) who were eligible (alive) for at least one follow-up survey, we fit logistic regression models to evaluate the association between prior maximum chronic condition grade and likelihood of participating at the last survey for which they were eligible.

To evaluate risks of chronic health conditions in comparison with non-cancer survivors of the same age, Cox proportional hazards models evaluated hazard ratios (HRs) comparing grade 1–5 and grade 3–5 chronic health conditions for early-adolescent and young adult cancer survivors relative to siblings of the same age, and

	Chronic health condition analyses			Late mortality analyses	
	Early-adolescent and young adult survivors (n=4082)	Childhood survivors (n=4082)	Siblings (n=3806)	Early-adolescent and young adult survivors (n=5804)	Childhood survivors (n=5804)
Vital status					
Alive	..	..	..	4452 (76·7%)	4867 (83·9%)
Dead	..	..	..	1352 (23·3%)	937 (16·1%)
Sex					
Female	1909 (46·8%)	1847 (45·2%)	2043 (53·7%)	2556 (44·0%)	2413 (41·6%)
Male	2173 (53·2%)	2235 (54·8%)	1763 (46·3%)	3248 (56·0%)	3391 (58·4%)
Race or ethnicity*					
Non-Hispanic white	3501 (86·0%)	3311 (81·5%)	3340 (90·7%)	3356 (85·8%)	3080 (80·1%)
Non-Hispanic black	196 (4·8%)	286 (7·0%)	101 (2·7%)	192 (4·9%)	277 (7·2%)
Hispanic	253 (6·2%)	324 (8·0%)	152 (4·1%)	249 (6·4%)	349 (9·1%)
Non-Hispanic other	120 (2·9%)	143 (3·5%)	90 (2·4%)	114 (2·9%)	140 (3·6%)
Missing	12	18	123	1893	1958
Treatment period					
1970–79	1230 (30·1%)	1222 (29·9%)	NA	1751 (30·2%)	1718 (29·6%)
1980–89	1561 (38·2%)	1514 (37·1%)	NA	2158 (37·2%)	2060 (35·5%)
1990–99	1291 (31·6%)	1346 (33·0%)	NA	1895 (32·6%)	2026 (34·9%)
Diagnosis					
Acute lymphoblastic leukaemia	440 (10·8%)	440 (10·8%)	NA	588 (10·1%)	588 (10·1%)
Acute myeloid leukaemia	142 (3·5%)	142 (3·5%)	NA	193 (3·3%)	193 (3·3%)
Other leukaemia	61 (1·5%)	61 (1·5%)	NA	91 (1·6%)	91 (6·1%)
Astrocytomas	293 (7·2%)	293 (7·2%)	NA	434 (7·5%)	434 (7·5%)
Medulloblastoma or primitive neuroectodermal tumour	58 (1·4%)	58 (1·4%)	NA	81 (1·4%)	81 (1·4%)
Other CNS tumours	110 (2·7%)	110 (2·7%)	NA	156 (2·7%)	156 (2·7%)
Hodgkin lymphoma	1438 (35·2%)	1438 (35·2%)	NA	2023 (34·9%)	2023 (34·9%)
Non-Hodgkin lymphoma	409 (10·0%)	409 (10·0%)	NA	577 (9·9%)	577 (9·9%)
Kidney tumours	23 (0·6%)	23 (0·6%)	NA	24 (0·4%)	24 (0·4%)
Neuroblastoma	18 (0·4%)	18 (0·4%)	NA	31 (0·5%)	31 (0·5%)
Non-rhabdomyosarcoma, soft-tissue sarcoma	201 (4·9%)	201 (4·9%)	NA	372 (6·4%)	372 (6·4%)
Rhabdomysarcoma	126 (3·1%)	126 (3·1%)	NA	130 (2·2%)	130 (2·2%)
Ewings sarcoma	209 (5·1%)	209 (5·1%)	NA	289 (5·0%)	289 (5·0%)
Osteosarcoma	513 (12·6%)	513 (12·6%)	NA	742 (12·8%)	742 (12·8%)
Other bone tumours	41 (1·0%)	41 (1·0%)	NA	73 (1·3%)	73 (1·3%)
Treatment					
No chemotherapy or radiotherapy	312 (8·3%)	259 (7·0%)	NA	305 (7·9%)	210 (5·6%)
Missing	34	19	NA	37	20
Any chemotherapy	2817 (75·5%)	3017 (82·1%)	NA	2939 (76·4%)	3230 (84·8%)
Missing	47	31	NA	52	28
Alkylating agent	2245 (60·4%)	2427 (66·1%)	NA	2342 (61·2%)	2598 (68·8%)
Missing	63	34	NA	69	31
Platinum based	389 (10·4%)	365 (12·6%)	NA	420 (10·9%)	521 (13·6%)
Missing	33	18	NA	37	19
Anti-metabolites	1463 (39·0%)	1558 (42·2%)	NA	1529 (39·3%)	1625 (42·5%)
Missing	26	17	NA	27	14
Anthracyclines	2014 (53·9%)	2117 (57·5%)	NA	2121 (55·1%)	2263 (59·0%)
Missing	42	24	NA	45	27
Plant alkaloids	2390 (63·7%)	2593 (70·3%)	NA	2489 (64·9%)	2789 (72·9%)
Missing	26	17	NA	27	14
Bleomycin	655 (17·5%)	653 (17·7%)	NA	707 (18·3%)	709 (18·6%)

(Table 1 continues on next page)

	Chronic health condition analyses			Late mortality analyses	
	Early-adolescent and young adult survivors (n=4082)	Childhood survivors (n=4082)	Siblings (n=3806)	Early-adolescent and young adult survivors (n=5804)	Childhood survivors (n=5804)
(Continued from previous page)					
Missing	36	24	NA	38	22
Any irradiation	2383 (63·3%)	2172 (58·4%)	NA	2452 (63·1%)	2250 (58·5%)
Missing	50	25	NA	54	26
Brain irradiation	572 (15·6%)	582 (16·1%)	NA	574 (15·9%)	647 (17·1%)
Missing	159	133	NA	173	135
Chest irradiation	1436 (39·3%)	1182 (32·7%)	NA	1487 (39·6%)	1179 (31·1%)
Missing	158	132	NA	172	135
Spine irradiation	109 (3·0%)	103 (2·9%)	NA	114 (3·0%)	121 (3·2%)
Missing	161	133	NA	175	136
Abdominal irradiation	952 (26·0%)	726 (20·1%)	NA	980 (26·0%)	731 (19·6%)
Missing	158	134	NA	172	137
Pelvic irradiation	733 (20·0%)	555 (15·4%)	NA	758 (20·1%)	588 (15·7%)
Missing	158	133	NA	172	136
Total body irradiation	104 (2·8%)	67 (1·9%)	NA	109 (2·9%)	81 (2·2%)
Missing	161	133	NA	175	136
Any surgery	3258 (87·2%)	3181 (86·5%)	NA	3346 (86·8%)	3279 (86·5%)
Missing	42	27	NA	43	28
Follow-up time† (years)					
≤10 years	1035 (25·4%)	903 (22·1%)	869 (22·8%)	852 (14·7%)	616 (10·6%)
11–20 years	1831 (44·9%)	1993 (48·8%)	1634 (42·9%)	1952 (33·6%)	2070 (35·7%)
21–30 years	1089 (26·7%)	1023 (25·1%)	1047 (27·5%)	2002 (34·5%)	1981 (34·1%)
>30 years	127 (3·1%)	163 (4·0%)	256 (6·7%)	998 (17·2%)	1137 (19·6%)
All: median (IQR)	16·0 (9·9–21·2)	16·0 (10·6–21·1)	16·6 (10·6–22·6)	20·6 (12·5–27·8)	21·1 (13·5–28·4)
Alive: median (IQR)	16·9 (11·5–22·1)	16·7 (11·6–21·7)	16·6 (10·6–22·6)	22·9 (15·2–28·8)	22·4 (15·1–29·1)
Dead: median (IQR)	4·2 (1·7–8·0)	4·8 (1·6–9·6)	16·8 (12·8–20·8)	10·2 (3·3–20·8)	11·9 (4·3–22·4)
Age at cancer diagnosis (years)					
Median (IQR)	17 (15–18)	10 (5–13)	NA	17 (15–18)	10 (5–12)
Age at last follow-up† (years)					
All: median (IQR)	38 (32–43)	30 (24–36)	36 (30–42)	42 (34–50)	34 (27–42)
Alive: median (IQR)	39 (33–44)	30 (25–37)	36 (30–42)	45 (37–51)	36 (29–43)
Dead: median (IQR)	26 (24–31)	20 (16–25)	36 (32–40)	33 (26–43·5)	26 (19–37)

Data are n (%) or median (IQR). Percentages shown among those with known values. Treatment data are shown among those with medical record abstraction: (chronic health conditions: n=3779 early-adolescent and young adult cancers, n=3706 childhood cancers; mortality: n=3897 early-adolescent and young adult cancers, n=3838 childhood cancers). NA=not applicable. *Race known for those who completed the baseline questionnaire. †Age at last follow-up represents date of last questionnaire or death for morbidity; date of death or Dec 31, 2013, for mortality. Follow-up time represents years since study entry.

Table 1: **Demographic and treatment characteristics of early-adolescent and young adult cancer survivors, childhood cancer survivors matched on primary diagnosis, and siblings**

childhood cancer survivors compared to siblings of the same age, adjusted for sex, race (or ethnicity), and censored at the earliest age of death or last follow-up. Age was used as the scale to adjust for the increasing risk of severe health conditions with age, with siblings of similar ages used as the reference group. Rather than modelling the time to first condition, the models used a counting process approach to account for all reported unique conditions until death or last follow-up.[15] Sandwich standard-error estimates adjusted for intraparticipant correlations and survivor–sibling pairs.[16] Among early-adolescent and young adult cancer survivors, treatment-related risk factors for grade 3–5 conditions in specific organ systems were assessed in additional multivariable Cox models, adjusted for sex and race (or ethnicity). Survivors with missing treatment data were excluded from these models. The initial choice of treatment covariates was based on previous CCSS publications, and final models retained factors significant at the 0·05 level in addition to a priori selected factors of interest.[17] Models included any surgery, any bleomycin, any platinum, any methotrexate, CED dose (none, <4000, 4000 to <8000, and ≥8000), anthracycline dose (none, <300, and ≥300), and radiation location in hierarchy: total

	Early-adolescent and young adult cancer survivors				Childhood cancer survivors				p value
	Observed number of deaths	Expected number of deaths	Rate per 1000 person-years	SMR (95% CI)	Observed number of deaths	Expected number of deaths	Rate per 1000 person-years	SMR (95% CI)	
All causes									
Among all patients	1357	231·9	11·5	5·9 (5·5–6·2)	963	155·7	7·5	6·2 (5·8–6·6)	0·22
Primary diagnosis									
Leukaemia	166	30·4	9·9	5·5 (4·6–6·5)	128	19·6	5·5	6·5 (5·2–8·2)	0·23
CNS	170	21·8	14·1	7·8 (6·6–9·2)	113	12·2	9·0	9·3 (7·6–11·3)	0·18
Hodgkin lymphoma	561	82·6	13·4	6·8 (6·2–7·4)	395	65·2	8·8	6·1 (5·5–6·7)	0·083
Non-Hodgkin lymphoma	91	24·0	7·7	3·8 (3·1–4·7)	52	16·0	4·3	3·3 (2·5–4·3)	0·38
Soft-tissue sarcoma	109	25·7	9·2	4·2 (3·5–5·2)	77	12·2	7·0	6·3 (4·9–8·0)	0·014
Bone cancer	240	45·8	10·7	5·2 (4·6–6·0)	195	29·6	8·6	6·6 (5·7–7·7)	0·027
Non-recurrent, health-related cause									
Among all patients	711	149·0	6·0	4·8 (4·4–5·1)	506	74·4	4·0	6·8 (6·2–7·4)	<0·0001
Primary diagnosis									
Leukaemia	57	17·8	3·4	3·2 (2·5–4·2)	41	8·0	1·8	5·1 (3·5–7·4)	0·056
CNS	75	13·4	6·2	5·6 (4·4–7·1)	49	5·2	3·9	9·4 (7·0–12·7)	0·0066
Hodgkin lymphoma	359	55·2	8·6	6·5 (5·9–7·2)	271	32·7	6·0	8·3 (7·4–9·3)	0·0026
Non-Hodgkin lymphoma	66	14·7	5·6	4·5 (3·5–5·8)	32	7·0	2·6	4·6 (3·2–6·5)	0·92
Soft-tissue sarcoma	49	17·6	4·2	2·8 (2·1–3·7)	37	5·8	3·4	6·4 (4·6–9·0)	0·0002
Bone cancer	101	29·2	4·5	3·5 (2·8–4·2)	75	15·4	3·3	4·9 (3·9–6·1)	0·029
Subsequent malignant neoplasm									
Among all patients	323	41·5	2·7	7·8 (7·0–8·7)	221	18·6	1·7	11·9 (10·4–13·6)	<0·0001
Primary diagnosis									
Leukaemia	20	4·6	1·2	4·4 (2·8–6·9)	17	2·0	0·7	8·8 (5·3–14·5)	0·042
CNS	26	3·7	2·2	7·1 (4·8–10·6)	17	1·2	1·4	13·6 (8·4–22·1)	0·043
Hodgkin lymphoma	172	16·1	4·1	10·7 (9·2–12·4)	120	8·2	2·7	14·7 (12·3–17·6)	0·0072
Non-Hodgkin lymphoma	28	3·8	2·4	7·4 (5·0–10·8)	8	1·6	0·7	5·0 (2·5–10·0)	0·34
Soft-tissue sarcoma	27	5·1	2·3	5·3 (3·6–7·8)	23	1·5	2·1	15·6 (10·2–23·8)	0·0002
Bone cancer	48	7·9	2·1	6·1 (4·6–8·1)	36	4·1	1·6	8·8 (6·3–12·3)	0·097
Cardiac causes									
Among all patients	141	32·3	1·2	4·4 (3·7–5·2)	101	14·8	0·8	6·8 (5·6–8·3)	0·0007
Primary diagnosis									
Leukaemia	11	3·9	0·7	2·9 (1·6–5·2)	2	1·4	0·1	1·4 (0·4–5·6)	0·36
CNS	3	2·9	0·2	1·0 (0·3–3·3)	5	1·0	0·4	5·1 (2·1–12·4)	0·031
Hodgkin lymphoma	95	11·7	2·3	8·1 (6·6–9·9)	70	6·7	1·6	10·4 (8·2–13·2)	0·11
Non-Hodgkin lymphoma	11	3·3	0·9	3·3 (1·8–6·0)	7	1·5	0·6	4·8 (2·3–10·1)	0·44
Soft-tissue sarcoma	3	3·8	0·3	0·8 (0·3–2·4)	3	1·1	0·3	2·6 (0·8–8·2)	0·14
Bone cancer	18	6·4	0·8	2·8 (1·8–4·4)	13	3·0	0·6	4·3 (2·5–7·4)	0·24
Pulmonary causes									
Among all patients	58	7·9	0·5	7·4 (5·7–9·5)	42	4·1	0·3	10·3 (7·6–14·0)	0·095
Primary diagnosis									
Leukaemia	7	0·9	0·4	8·1 (3·8–17·0)	2	0·5	0·1	4·2 (1·0–16·7)	0·41
CNS	11	0·7	0·9	15·4 (8·5–28·0)	4	0·3	0·3	13·4 (5·0–35·8)	0·81
Hodgkin lymphoma	26	3·0	0·6	8·6 (5·9–12·7)	23	1·7	0·5	13·4 (8·9–20·1)	0·13
Non-Hodgkin lymphoma	6	0·8	0·5	8·0 (3·6–17·7)	5	0·4	0·4	13·5 (5·6–32·3)	0·39
Soft-tissue sarcoma	2	1·0	0·2	2·1 (0·5–8·4)	3	0·3	0·3	9·2 (3·0–28·8)	0·11
Bone cancer	6	1·5	0·3	3·9 (1·8–8·8)	5	0·8	0·2	5·9 (2·5–14·2)	0·50

(Table 2 continues on next page)

body irradiation, chest or neck, abdomen or pelvis, brain, other, or none. Organ-specific treatments used for organ-specific models are listed in the appendix (pp 17–18). Smoking status was also included in pulmonary, cardiovascular, and musculoskeletal models. Proportional hazards were assessed by examining plots of Schoenfeld

	Early-adolescent and young adult cancer survivors				Childhood cancer survivors				p value
	Observed number of deaths	Expected number of deaths	Rate per 1000 person-years	SMR (95% CI)	Observed number of deaths	Expected number of deaths	Rate per 1000 person-years	SMR (95% CI)	
(Continued from previous page)									
Other medical causes*									
Among all patients	188	67·2	1·6	2·8 (2·4–3·2)	141	36·9	1·1	3·8 (3·2–4·6)	0·0073
Primary diagnosis									
Leukaemia	18	8·4	1·1	2·2 (1·4–3·5)	19	4·1	0·8	4·7 (2·5–8·8)	0·060
CNS	35	6·2	2·9	5·7 (4·1–7·9)	23	2·7	1·8	8·6 (5·7–13·1)	0·12
Hodgkin lymphoma	66	24·3	1·6	2·7 (2·1–3·5)	58	16·1	1·3	3·6 (2·8–4·7)	0·11
Non-Hodgkin lymphoma	21	6·8	1·8	3·1 (2·0–4·7)	12	3·5	1·0	3·4 (1·9–6·0)	0·79
Soft-tissue sarcoma	17	7·7	1·4	2·2 (1·4–3·6)	8	2·9	0·7	2·8 (1·4–5·6)	0·58
Bone cancer	29	13·4	1·3	2·2 (1·5–3·1)	21	7·5	0·9	2·8 (1·8–4·3)	0·37
External causes									
Among all patients	91	82·9	0·8	1·1 (0·9–1·3)	95	81·3	0·7	1·2 (0·9–1·5)	0·65
Primary diagnosis									
Leukaemia	10	12·6	0·6	0·8 (0·4–1·5)	17	11·6	0·7	1·5 (0·8–3·0)	0·17
CNS	14	8·4	1·2	1·7 (1·0–2·8)	9	7·0	0·7	1·3 (0·7–2·5)	0·54
Hodgkin lymphoma	27	27·4	0·6	1·0 (0·7–1·4)	37	32·6	0·8	1·1 (0·8–1·6)	0·57
Non-Hodgkin lymphoma	10	9·3	0·8	1·1 (0·6–2·0)	12	9·0	1·0	1·3 (0·8–2·3)	0·62
Soft-tissue sarcoma	8	8·1	0·7	1·0 (0·5–2·0)	3	6·4	0·3	0·5 (0·1–1·4)	0·27
Bone cancer	22	16·6	1·0	1·3 (0·9–2·0)	16	14·1	0·7	1·1 (0·7–1·9)	0·63
Recurrence or progression of primary cancer									
Among all patients	492	NA	NA	NA	325	NA	NA	NA	NA
Primary diagnosis									
Bone cancer	109	NA	NA	NA	100	NA	NA	NA	NA
CNS	72	NA	NA	NA	51	NA	NA	NA	NA
Hodgkin lymphoma	152	NA	NA	NA	67	NA	NA	NA	NA
Leukaemia	86	NA	NA	NA	64	NA	NA	NA	NA
Non-Hodgkin lymphoma	11	NA	NA	NA	7	NA	NA	NA	NA
Soft-tissue sarcoma	46	NA	NA	NA	35	NA	NA	NA	NA

Data are n or SMR (95% CI), unless otherwise indicated. SMR=standardised mortality ratio. NA=not applicable. Numbers, percentages, and all estimates are weighted to account for undersampling of acute lymphocytic leukaemia survivors. Some variation in totals is due to rounding. Kidney tumours and neuroblastoma not examined separately. *Other medical causes: non-recurrent, health-related causes of death other than subsequent malignant neoplasms, cardiac causes, or pulmonary causes.

Table 2: **Standardised mortality ratios and frequency of death among survivors of early-adolescent and young adult cancer and matched childhood cancer, overall and by diagnosis**

residuals for each covariate and via additional models that added an interaction of time with the covariate. No evidence of non-proportionality was found.

Standardised incidence ratios (SIRs) were calculated for subsequent malignant neoplasms, with the number observed divided by the number expected on the basis of sex-specific, age-specific, and calendar year-specific US incidence rates from the Surveillance, Epidemiology, and End Results programme,[1] stratified by time since diagnosis and attained age. 95% CI and p values for SIRs were calculated with similar Poisson probability models as described for SMRs. Comparisons of SIRs and SMRs between groups were based on tests of coefficients for group membership in these Poisson models. For all analyses, sampling weights were applied to account for under-sampling of survivors of acute lymphoblastic leukaemia diagnosed from 1987 to 1999 (weight=3·61 for age 1–10 years at diagnosis and 1·21 for other ages). Data were analysed with SAS (version 9.4), and Stata/SE (version 14.1).

Role of the funding source

The funders had no role in study design, data collection, data interpretation, or 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

5979 survivors were diagnosed with cancer as early-adolescents and young adults in the CCSS (table 1). The mortality analysis excluded 175 Canadian participants or those not in the NDI (appendix p 7), resulting in 5804 survivors of early-adolescent and young adult cancer followed up for a median of 20·6 years (IQR 12·5–27·8), and 5804 childhood cancer survivors

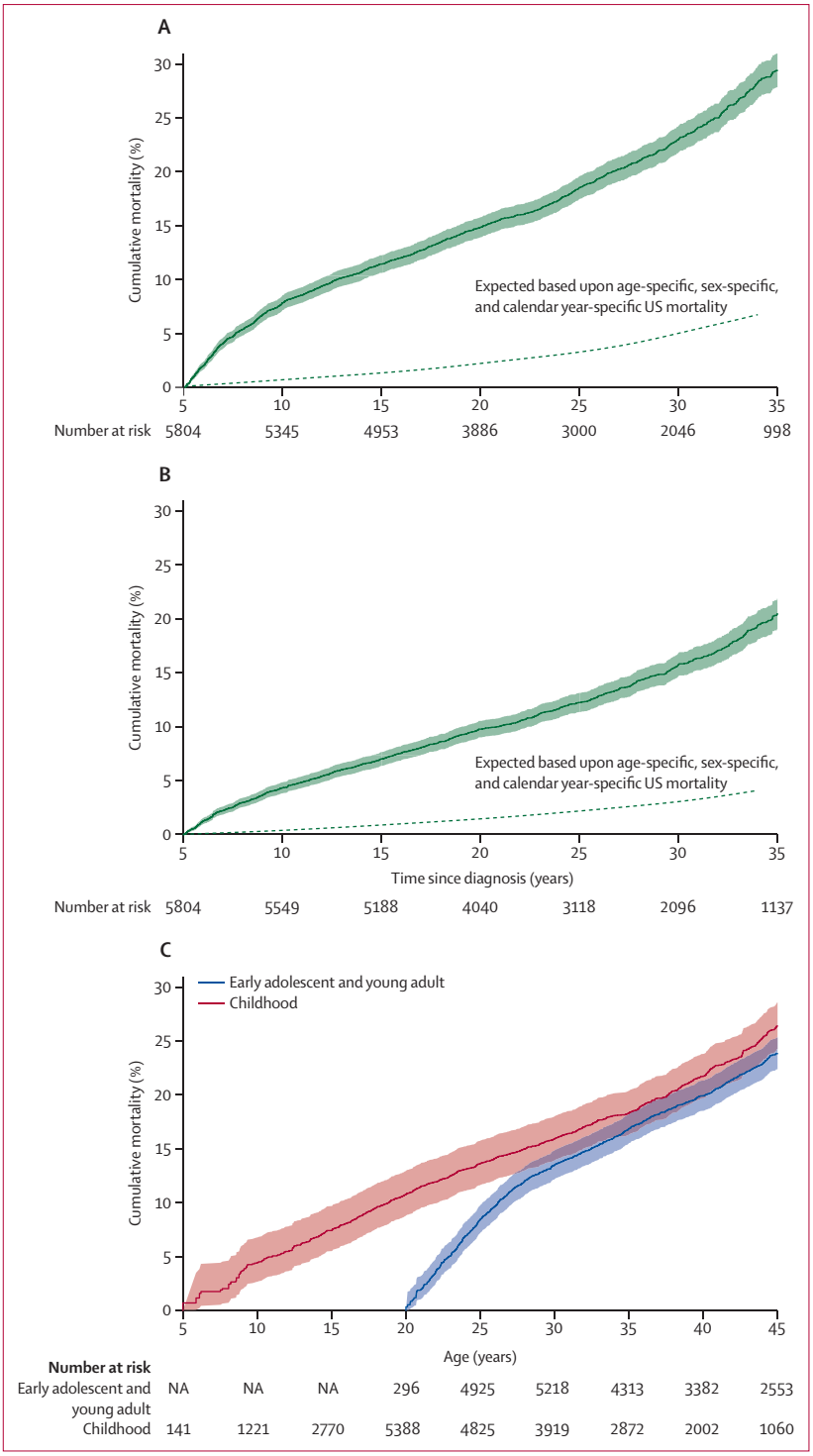


Figure 1: **All-cause cumulative mortality more than 5 years from cancer diagnosis for cancer survivors**
(A) Survivors of early-adolescent and young adult cancers compared to US population by time since diagnosis. (B) Survivors of childhood cancers compared to US population by time since diagnosis. (C) Survivors of early-adolescent and young adult cancers and childhood cancers by attained age. The solid line represents cumulative mortality. The shaded area represents 95% CI. The dashed line represents expected mortality rates in the USA. Numbers at risk are unweighted.

followed up for a median of 21·1 years (13·5–28·4), up to death or the date of the NDI search. The chronic health condition analysis comprised 4082 early-adolescent and young adult cancer survivors with a median age at last follow-up of 38 years (IQR 32–43), 36 years (30–42) for 3806 siblings, and 30 years (24–36) for 4082 childhood cancer survivors. Among living participants, the median time of follow-up since cohort entry was 16·9 years (IQR 11·5–22·1) for early-adolescent and young adult cancer survivors, 16·6 years (10·6–22·6) for siblings, and 16·7 years (11·6–21·7) for childhood cancer survivors. At their most recent survey, 3504 (86%) of 4082 early-adolescent and young adult cancer survivors and 3304 (81%) of 4082 childhood cancer survivors completed their own survey, as opposed to a proxy responder. There was some evidence that early-adolescent and young adult survivors who had at least one severe chronic health condition were more likely to respond to a subsequent survey than those who did not have a severe condition (odds ratio 1·6 [95% CI 1·3–2·1]; appendix p 27). The majority of early-adolescents and young adults were diagnosed with lymphoma: 1438 (35·2%) of 4082 with Hodgkin lymphoma and 409 (10·0%) of 4082 with non-Hodgkin lymphoma.

Among 5804 early-adolescent and young adult 5-year survivors, 1352 (23·3%) deaths were reported (table 1). Health-related causes of late mortality (other than recurrence or progression of the primary cancer or external causes) including subsequent malignant neoplasm, cardiovascular disease, pulmonary disease, and other medical causes accounted for 711 (52·4%) of 1357 (weighted) deaths among early-adolescent and young adult cancer survivors, followed by recurrence or progression of the primary cancer (492 [36·3%] of 1357) and external causes (91 [6·7%] of 1357; table 2).

Cumulative mortality is summarised in figure 1 by time since diagnosis and attained age. At 30 years after diagnosis, cumulative mortality was 23·0% (95% CI 21·8–24·2) for early-adolescent and young adult survivors, at which time they were aged 45–50 years. This estimate corresponds to a cumulative mortality of 24·0% (95% CI 22·4–25·4) at 45 years of age (figure 1). Cumulative mortality at 30 years after diagnosis for childhood cancer survivors was 15·6% (95% CI 14·6–16·7), when survivors ranged from 30–44 years of age. This also corresponds to a cumulative mortality of 16·0% (95% CI 14·0–18·1) at age 30 years and 26·5% (24·4–28·7) at age 45 years (figure 1, appendix p 8).

Compared to expected rates at the same ages in the general population, the SMR for all-cause mortality among early-adolescent and young adult survivors was 5·9 (95% CI 5·5–6·2; table 2). The highest SMRs were for diagnoses of Hodgkin lymphoma and CNS malignancies. Compared with the general population, early-adolescent and young adult survivors had a significantly higher risk of death from any non-recurrent, health-related cause, subsequent malignant neoplasm,

cardiovascular event, pulmonary disease, or from another medical cause. The risk of death from external causes was similar to the general population.

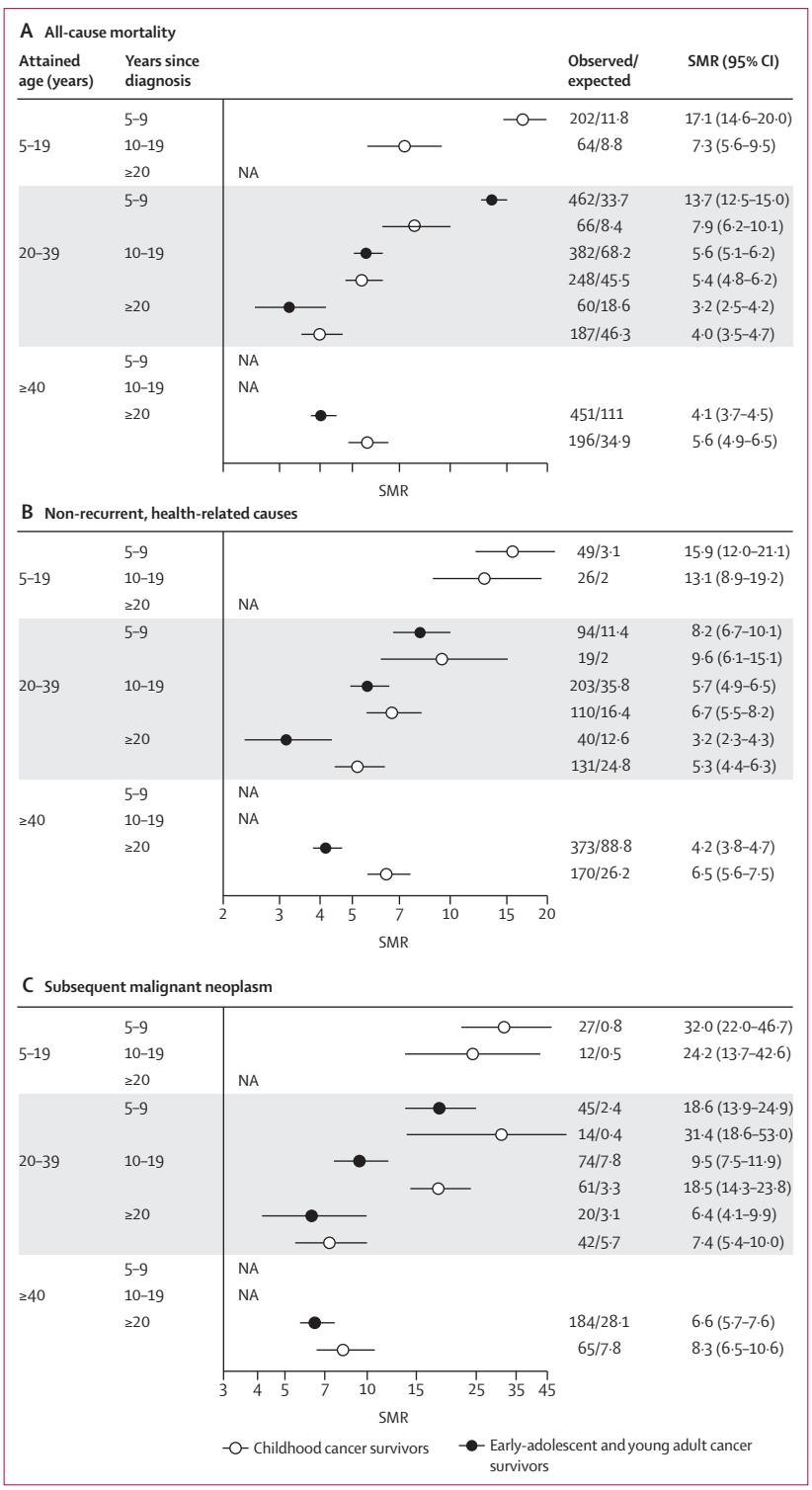
The SMR for all-cause mortality among childhood cancer survivors was 6·2 (95% CI 5·8–6·6) compared with the deaths expected in the general population of the same age (table 2). Children diagnosed with bone cancers and CNS malignancies had the highest risk of death compared with other diagnoses. All SMRs, except for those for pulmonary deaths, were significantly higher than SMRs for the same causes among early-adolescent and young adult survivors (table 2). Childhood cancer survivors had a similar SMR to the general population for death from external causes.

Evaluation of SMRs for non-recurrent, health-related causes of death showed decreasing SMRs with increasing number of years from diagnosis for both childhood and early-adolescent and young adult cancer survivors (figure 2; appendix pp 9–15). However, starting at 20 years after diagnosis, the SMR for non-recurrent health-related deaths was greater for childhood cancer survivors than for early-adolescent and young adult survivors. Similarly, childhood cancer survivors had greater SMRs than early-adolescent and young adult survivors for cardiac deaths also beginning 20 years after diagnosis (figure 2). This late cardiac mortality risk was seen at attained ages of both 20–39 years and 40 years and older. SMRs for deaths from subsequent malignant neoplasms showed a decreasing risk with increasing age; however, childhood cancer survivors had greater SMRs than early-adolescent and young adult survivors, starting 5 years after diagnosis and peaking 10–19 years after diagnosis (figure 2).

Early-adolescent and young adult survivors had a higher risk of death due to recurrence or progression of the primary cancer than did childhood cancer survivors, at similar times since diagnosis, adjusted for sex (HR 1·6 [95% CI 1·4–1·9]; appendix p 16).

By the age of 45 years, the cumulative incidence of a grade 3–5 health condition was 39·4% (95% CI 36·9–42·0) among early-adolescents and young adults, 56·3% (52·0–60·3) among childhood cancer survivors, and 12·1% (10·5–13·8) among siblings. At 30 years after diagnosis, the cumulative incidence of a grade 3–5 health condition was 45·6% (95% CI 42·8–48·5) among early-adolescent and young adult survivors and 39·6% (36·6–42·5) among childhood cancer survivors (table 3). Compared with siblings of the same age, early-adolescent and young adult survivors were more likely to develop any chronic health condition (HR 2·2 [95% CI, 2·0–2·3]; table 3) and any grade 3–5 health condition (4·2 [3·7–4·8]).

Childhood cancer survivors had higher HRs in comparison with siblings of a similar age than did early-adolescent and young adult survivors for developing any chronic health condition and any grade 3–5 health condition (table 3). HRs were also higher for childhood cancer survivors than for early-adolescents and young adults for the development of grade 3–5 cardiac, endocrine, and musculoskeletal conditions, with siblings of the same age as the reference group for both. HRs of grade 3–5 pulmonary or neurological conditions were



(Figure 2 continues on next page)

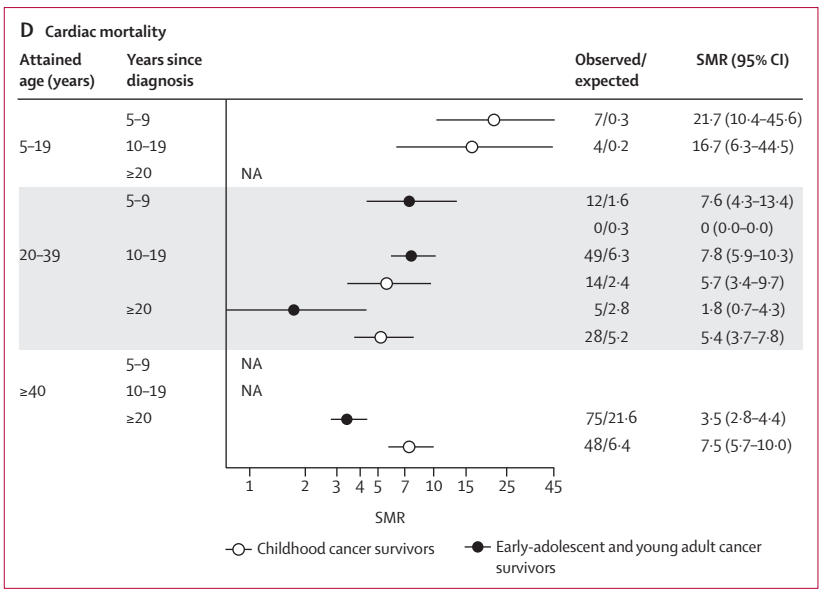


Figure 2: **SMRs for all-cause mortality (A), non-recurrent, health-related causes (B), subsequent malignant neoplasm (C), and cardiac mortality (D) among early-adolescent and young adult cancer survivors and matched childhood cancer survivors stratified by attained age and time since diagnosis**
NA=not possible based on age at diagnosis and follow-up. SMR=standardised mortality ratio. No cardiac deaths at 5–9 years after diagnosis among childhood cancer survivors aged 20–39 years.

similar for childhood and early-adolescent and young adult cancer survivors, with siblings of the same age as the reference group for both.

Multivariable analyses describing the risk factors associated with grade 3–5 chronic health conditions are described in the appendix (pp 17–18). The risk of developing a grade 3–5 chronic health condition according to tumour type shows high hazard ratios compared to siblings for all diagnosis groups (appendix p 19).

SIRs for subsequent malignant neoplasms were evaluated for early-adolescent and young adult cancer survivors and childhood cancer survivors, providing risks relative to age-matched, calendar-year-matched, and sex-matched members of the general population. Although SIRs were elevated across all timepoints relative to diagnosis for both groups, childhood cancer survivors had a significantly higher SIR for subsequent malignant neoplasms than did early-adolescent and young adult cancer survivors (6·9 [95% CI 6·0–7·8] *vs* 4·7 [4·2–5·3], p<0·0001; appendix pp 20–25). A higher SIR for subsequent malignant neoplasms was evident among childhood cancer survivors between 10–19 years from diagnosis at 20–39 years of age compared with early-adolescent and young adult survivors (figure 3). Specifically, higher SIRs for thyroid cancer and soft-tissue sarcomas were observed among childhood cancer survivors compared with early-adolescent and young adult survivors during this time period (figure 3). Although SIRs for breast cancer were high for both groups, SIRs did not differ significantly between childhood cancer survivors and early-adolescent and young adult cancer survivors (figure 3, appendix pp 22–23).

Discussion

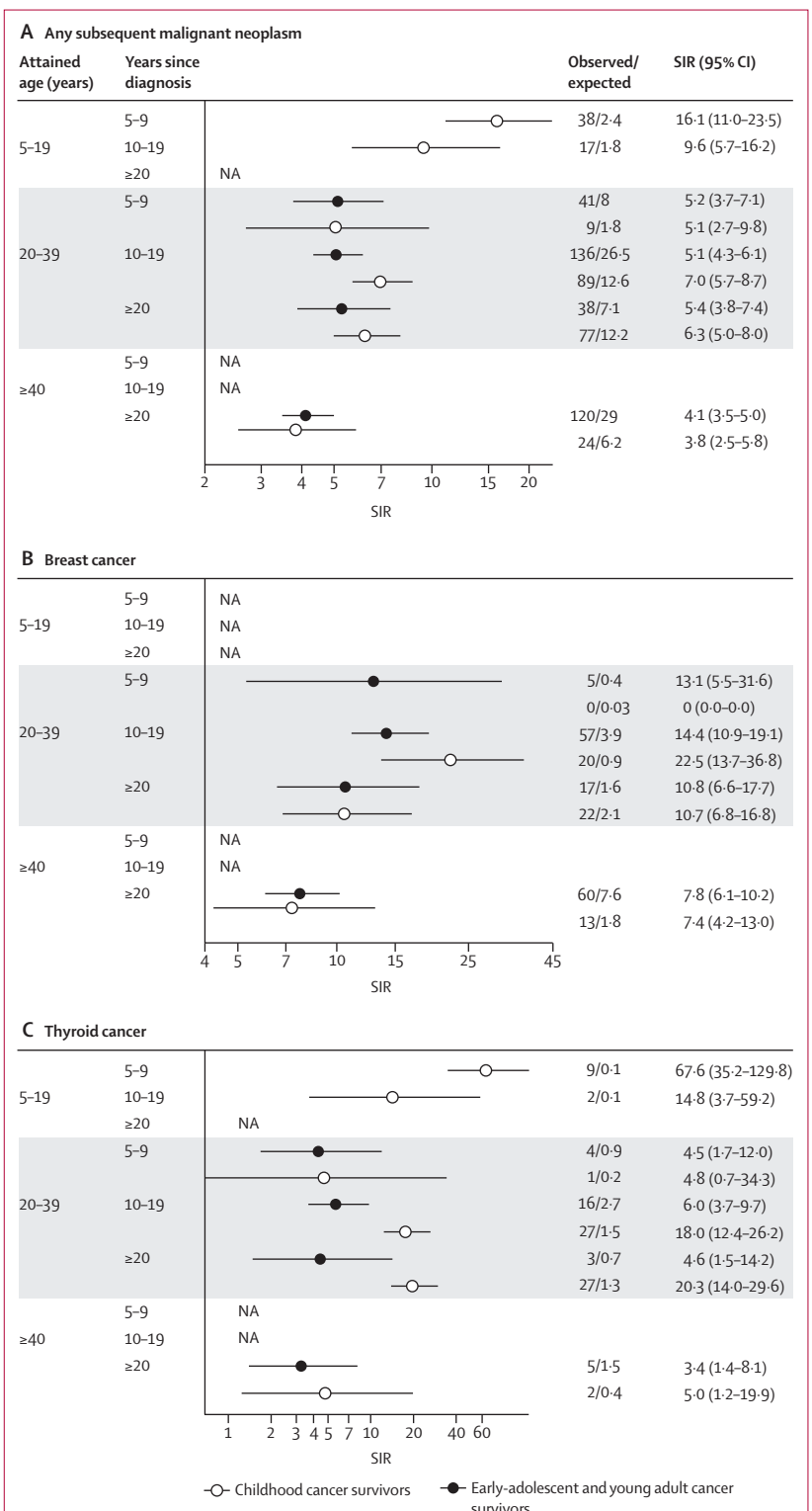
To our knowledge, this retrospective cohort study is the first to comprehensively characterise long-term health outcomes in a large cohort of cancer survivors diagnosed and treated in adolescence and early adulthood (≥15 to <21 years of age) and to describe their outcomes relative to survivors of similar cancers diagnosed in childhood (<15 years of age) as well as the general population. Our cohort of more than 4000 survivors of early-adolescent and young adult cancer was at greater risk of developing chronic health conditions and late mortality than the general population. Early-adolescent and young adult cancer survivors and childhood cancer survivors both had significantly higher risks of developing chronic health conditions than their siblings. However, early-adolescent and young adult survivors had a lower magnitude of risk than childhood cancer survivors. Moreover, the SMRs for non-recurrent, health-related deaths were lower among early-adolescent and young adult cancer survivors than among childhood cancer survivors—a difference most evident two decades after cancer diagnosis.

When considering the composite effect of attained age and follow-up time, all-cause cumulative mortality appears to be consistent between childhood cancer survivors and early-adolescent and young adult cancer survivors. Similarly, we observed no difference in the risk of all-cause death compared with the general population between early-adolescent and young adult cancer survivors and childhood cancer survivors. Our study showed that early-adolescent and young adult survivors were more than 1·5 times more likely to die from a recurrence or progression of the primary cancer than childhood cancer survivors. When examining these differences by primary cancer diagnosis, this finding extends to leukaemia and Hodgkin lymphoma survivors. Inferior outcomes for patients diagnosed with Hodgkin lymphoma when aged 17–21 years compared with patients diagnosed before the age of 17 years or aged older than 21 years have been described in analyses of clinical trials done in North America.[18] The greater risk of death due to late recurrence or progression of the primary cancer observed in our study might also be a reflection of known factors that contribute to poorer outcomes for adolescents and young adults with their primary cancer; these factors include delays in diagnosis, lack of health insurance, inferior compliance with treatment, follow-up and transition to long-term follow-up care, and suboptimal primary care provider familiarity with adolescent and young adult cancer and cancer survivorship recommendations.[19] This finding might be further explained by differences in disease biology. In acute lymphoblastic leukaemia, patients aged older than 10 years are considered high-risk on paediatric trials and

	Early-adolescent and young adult survivors (n=4082)	Childhood survivors (n=4082)	Siblings (n=3806)	HR for early-adolescent and young adult survivors*	HR for childhood survivors*
Any grade 1–5 conditions					
Number of patients (%)	2637 (64·6%)	2419 (59·3%)	1562 (41·0%)	..	..
Cumulative incidence by age 45 years (95% CI)	73·0% (70·1–75·6)	87·1% (84·0–90·0)	56·7% (53·6–59·6)	..	..
Cumulative incidence by 30 years after diagnosis (95% CI)	80·8% (77·8–83·9)	74·5% (71·2–77·8)	NA	..	..
HR (95% CI)	..	..	..	2·2 (2·0–2·3)	2·7 (2·5–2·9)
Any grade 3–5 conditions					
Number of patients (%)	1254 (30·7%)	1044 (25·6%)	320 (8·4%)	..	..
Cumulative incidence by age 45 years (95% CI)	39·4% (36·9–42·0)	56·3% (52·0–60·3)	12·1% (10·5–13·8)	..	..
Cumulative incidence by 30 years after diagnosis (95% CI)	45·6% (42·8–48·5)	39·6% (36·6–42·5)	NA	..	..
HR (95% CI)	..	..	..	4·2 (3·7–4·8)	5·6 (4·9–6·3)
Grade 3–5 cardiac conditions					
Number of patients (%)	464 (11·4%)	334 (8·2%)	107 (2·8%)	..	..
Cumulative incidence by age 45 years (95% CI)	15·4% (13·8–17·0)	19·9% (17·3–22·7)	4·1% (3·2–5·1)	..	..
Cumulative incidence by 30 years after diagnosis (95% CI)	19·7% (17·6-21·7)	13·6% (11·7-15·4)	NA	..	..
HR (95% CI)	..	..	..	4·3 (3·5–5·4)	5·6 (4·5–7·1)
Grade 3–5 endocrine conditions					
Number of patients (%)	244 (6·0%)	324 (7·9%)	65 (1·7%)	..	..
Cumulative incidence by age 45 years (95% CI)	8·1% (7·0–9·3)	15·3% (13·3–17·4)	2·9% (2·1–3·8)	..	..
Cumulative incidence by 30 years after diagnosis (95% CI)	8·8% (7·6–10·1)	11·4% (9·9–12·9)	NA	..	..
HR (95% CI)	..	..	..	3·9 (2·9–5·1)	6·4 (5·1–8·0)
Grade 3–5 pulmonary conditions					
Number of patients (%)	66 (1·6%)	44 (1·1%)	11 (0·3%)	..	..
Cumulative incidence by age 45 years (95% CI)	2·0% (1·5–2·6)	2·8% (1·8–4·0)	0·5% (0·3–0·9)	..	..
Cumulative incidence by 30 years after diagnosis (95% CI)	2·5% (1·7–3·2)	1·7% (1·0–2·3)	NA	..	..
HR (95% CI)	..	..	..	6·3 (3·2–12·7)	7·3 (3·6–14·9)
Grade 3–5 musculoskeletal conditions					
Number of patients (%)	110 (2·7%)	80 (2·0%)	17 (0·4%)	..	..
Cumulative incidence by age 45 years (95% CI)	3·4% (2·7–4·3)	3·7% (2·6–5·0)	0·5% (0·3–1·0)	..	..
Cumulative incidence by 30 years after diagnosis (95% CI)	3·6 % (2·7– 4·5)	2·7% (2·0–3·4)	NA	..	..
HR (95% CI)	..	..	..	6·5 (3·9–11·1)	8·0 (4·6–14·0)
Grade 3–5 neurological conditions					
Number of patients (%)	83 (2·0%)	77 (1·9%)	33 (0·9%)	..	..
Cumulative incidence by age 45 years (95% CI)	2·4% (1·8–3·0)	3·7% (2·5–5·3)	1·4% (0·9–2·0)	..	..
Cumulative incidence by 30 years after diagnosis (95% CI)	2·7% (2·0–3·4)	2·4% (1·7–3·1)	NA	..	..
HR (95% CI)	..	..	..	2·2 (1·4–3·3)	3·2 (2·1–5·0)

CTCAE=Common Terminology Criteria for Adverse Events. HR=hazard ratio. HRs adjusted for sex and race (or ethnicity). Comparisons between survivors and siblings used age as the time scale and late entry, with survivor entering at an age equivalent to 5 years after diagnosis and siblings aged 5 years or older. *Siblings as reference group.

***Table 3*: Chronic health conditions among early-adolescent and young adult cancer survivors, childhood cancer survivors, and siblings, according to CTCAE severity grade**



(Figure 3 continues on next page)

young adults have been shown to have poorer outcomes than paediatric patients, which appears to be in part due to biology in addition to other factors related to diagnosis delays and barriers with compliance described above.[20]

The rate of development of subsequent malignant neoplasms compared with the general population was lower among early-adolescent and young adult survivors than among childhood cancer survivors 10–19 years after diagnosis and at 20–39 years of attained age. Childhood cancer survivors had higher SIRs for both thyroid cancer and soft-tissue sarcomas during this time and age interval. The higher SIRs for soft-tissue sarcomas might reflect a higher prevalence of familial or genetic cancer predisposition. Indeed, when examining subsequent malignant neoplasms by primary cancer diagnosis, childhood soft-tissue sarcoma survivors had a 7·6 times higher risk, whereas early-adolescent and young adult soft-tissue sarcoma survivors had a 2·2 times higher risk. Future studies examining the genome of survivors with subsequent malignant neoplasms in the CCSS might provide greater clarity on these differences. Reflective of these subsequent malignant neoplasms, the SMRs for death due to a subsequent malignant neoplasm were higher in childhood cancer survivors than in early-adolescent and young adult survivors, although deaths due to subsequent malignant neoplasms were significantly elevated in both groups when compared with the general population. When stratified by years from diagnosis and current age, only childhood survivors with a current age of 20–39 years, 10–19 years after diagnosis, had a significantly higher associated risk of death from a subsequent malignant neoplasm compared with early-adolescent and young adult survivors, although similar relationships were noted for other time-by-age intervals. Importantly, the risk of development of subsequent breast cancer was higher than in the general population in both early-adolescent and young adult cancer survivors and childhood cancer survivors. Taken together, these findings support focused efforts towards maximising surveillance efforts for subsequent malignant neoplasms in both early-adolescent and young adult cancer survivors and childhood cancer survivors to reduce mortality from subsequent malignant neoplasms (particularly breast cancer and colorectal cancer, since early surveillance results in reduced morbidity in both cases).

Our analyses confirm the findings of previous studies suggesting that younger children might be more vulnerable to the effects of cancer treatment, such as the impact of radiation and anthracycline exposure on the development of cardiovascular conditions.[17] When compared with siblings of the same age, survivors of early-adolescent and young adult cancers had lower relative risks than childhood cancer survivors for development of any grade 3–5 chronic condition, as well as grade 3–5 endocrine and musculoskeletal conditions. Consistent with these morbidities, early-adolescent and young adult cancer survivors had a lower standardised

risk of mortality from cardiac causes and non-recurrent, health-related causes. Younger age at cancer treatment has been previously shown to be associated with an increased risk of certain endocrinopathies, including obesity[21] and diabetes mellitus.[22] For other endocrine outcomes, older age at exposure is associated with greater risk. Female patients treated in early adolescence, when the number of primordial follicles is reduced in comparison with before puberty, have an increased risk of primary ovarian insufficiency.[23] Likewise, Sklar and colleagues reported an increased risk of radiotherapy-induced hypothyroidism with older age.[24] In contrast to previous studies, we observed a lower risk of musculoskeletal morbidity in early-adolescent and young adult cancer survivors than in childhood cancer survivors. In a previous CCSS analysis of osteonecrosis in survivors, older age increased the risk of this outcome, consistent with studies of avascular necrosis in patients with acute lymphoblastic leukaemia.[25] However, musculoskeletal morbidity due to cancer treatment includes various other conditions, such as osteoporosis, scoliosis, joint dysfunction, and so on.[26] Examination of the individual contributions of these outcomes were outside the scope of this analysis.

Several limitations should be considered when interpreting our findings. This report did not include the full spectrum of malignant diagnoses seen in early-adolescents and young adults. Notably, survivors of gonadal tumours, melanomas, and thyroid cancer, which account for almost 40% of cancers diagnosed between the ages of 15 and 20 years,[1] were not enrolled in the CCSS cohort. Furthermore, the early-adolescents and young adults within the CCSS might not be representative of all early-adolescents and young adults treated for cancer in the USA, as many early-adolescents and young adults in the USA are treated by community providers outside of tertiary academic centres or paediatric hospitals.[27] Additionally, since age at diagnosis defines the groups we compared, and with equal follow-up there are therefore different attained ages for groups (and vice versa), we cannot easily make direct comparisons between these groups. We have therefore presented results for each cohort in comparison with age-matched general population groups, and have attempted to illustrate the impact of advancing age and time since diagnosis, but these factors must be carefully considered in interpretation of these findings since it is not possible to perfectly account for the intrinsic differences between the groups. The response rates across CCSS follow-up surveys ranged from 64% (6603 of 10 375) to 84% (1170 of 2116), declining over time, but with only moderate differences between the slightly higher responses for early-adolescent and young adult cancer survivors than those of childhood cancer survivors. There is some evidence that early-adolescent and young adult survivors who have had at least one severe chronic health condition are more likely to respond to a subsequent survey than those who did not have a severe condition, (appendix p 27), which could bias our survey-based results towards worse outcomes. Chronic health conditions are ascertained by self-reporting in our study and thus there might be some misclassification with regard to these outcomes, although subsequent malignant neoplasms are validated and mortality is ascertained via NDI. Furthermore, although we utilise reported causes of death for grade 5 morbidities, these data were derived from death certificates, which might have missing information. Additionally, cancer treatments have evolved over time and thus the results of this study might not be generalisable to patients treated today. However, similar chemotherapy and radiotherapy treatments still remain in use for many cancers affecting early-adolescents and young adults. Lastly, we recognise that risky health behaviours, such as smoking, are associated with adverse health outcomes such as early cardiovascular disease. Our data are restricted to ever smokers, which might influence our ability to detect a significant effect. Assessment of the number of pack-years smoked would provide a better evaluation of the potential contribution of smoking.

As highlighted by the Adolescent and Young Adult Oncology PRG,[3] data that are specific to the adolescent and young adult age group must be collected in order to develop and support recommendations and policy for health care for adolescent and young adult cancer survivors. Our results suggest that guidelines for risk-based long-term follow-up care, such as the Children's Oncology Group Long-Term Follow-Up (COG LTFU) Guidelines and National Comprehensive Cancer Network Guidelines, are appropriate for survivors of

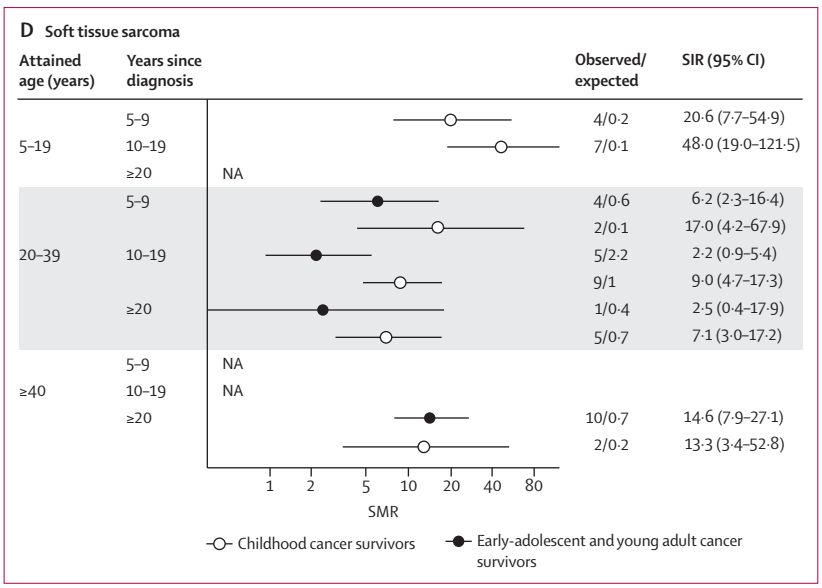


Figure 3: **SIRs and frequency of subsequent malignant neoplasms in survivors of early-adolescent and young adult and matched childhood cancer survivors by attained age and time since diagnosis**
(A) Any subsequent malignant neoplasm. (B) Breast cancer. (C) Thyroid cancer. (D) Soft-tissue sarcoma. NA=not possible based on age at diagnosis and follow-up or number expected too low to reasonably estimate SIR. SIR=standardised incidence ratio. No breast cancers for childhood cancer survivors at an attained age of 20–39 years, 5–9 years since diagnosis.

early-adolescent and young adult cancer. Although some of the risks of morbidities (eg, cardiac and musculoskeletal outcomes) seem to be lower in early-adolescent and young adult cancer survivors than in childhood cancer survivors, early adolescents and young adults still have substantially elevated risks compared with siblings of the same age. In fact, our findings suggest that the recent changes to cardiac surveillance in version 5.0 of the COG LTFU Guidelines, which no longer stratify patients by age of exposure to chest radiotherapy or anthracyclines, or both, are appropriate. Whether these guidelines are also applicable to young adults treated after the age of 21 years will require study in other cohorts. Our data underscore that focused efforts are needed to ensure early-adolescent and young adult cancer survivors are receiving recommended risk-based care, with a focus on high-risk cancer screening, to reduce morbidity and premature mortality. Studies to date indicate that adherence to such high-risk screening is poor.[28] More than 85% of long-term survivors of adolescent and young adult cancer receive their care in the community from a primary care provider.[28] These providers, although willing to care for cancer survivors, are often unfamiliar with available guidelines and would prefer to care for patients in communication with providers at the cancer centre.[29] New models for delivering risk-based survivorship care that incorporate both cancer specialists and primary care providers should be studied, such as the Patient Centered Medical Home,[30] and the classic chronic disease models of care used for management of diabetes mellitus and cardiovascular diseases.[31] Electronic medical records and treatment summaries should be accessible to cancer survivors and their health-care providers, and primary care providers should be able to communicate readily with cancer specialists. Lastly, information and recommendations about adolescent and young adult cancer survivors should be widely disseminated and accessible, beyond academic journals. A primary care provider's search engine investigation should easily take them to the appropriate information source. In summary, these data highlight the need for multifaceted efforts to improve health outcomes of this vulnerable population.

Contributors

ES, KLS, WML, PCN, DRF, GTA, JPN, KCO, and TOH designed the study. GTA and LLR provided financial support. All authors were involved in acquisition of the data. ES, KLS, WML, PCN, KRK, CAS, GTA, KCO, and TOH were involved in analysis of the data. ES, KLS, WML, and TOH drafted the manuscript. All authors were involved in revising the work for intellectual content. All authors interpreted the data, contributed to the report, and approved the final version of the paper for publication.

Declaration of interests

KRK and CAS declare funding from the NCI. KLS and WML declare funding from the US National Institutes of Health. CAS declares funding from Novo Nordisk, outside the submitted work. All other authors declare no competing interests.

Acknowledgments

This work was supported by a grant (U24 CA-55727) to GTA from the US National Institute of Health, Bethesda, MD, USA; Cancer Center Support (CORE) Grant (CA-21765) to St Jude Children's Research Hospital, Memphis, TN, USA; and the American Lebanese Syrian Associated Charities, Memphis, TN, USA. The CCSS is a publicly available data resource. Investigators can apply for specific analyses through a proposal process available on the website. The dataset specific to these analyses is not publicly available.

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