CHILDHOOD CANER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

Project Title: Comparison of risks of mortality (all-cause, cause-specific) and invasive second or subsequent cancers: a Childhood Cancer Survivor Study and British Childhood Cancer Survivor Study collaboration

Working Group & Investigators: Chronic Diseases Working Group
Second Malignancy Working Group (secondary oversight)

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Background & Rationale:
Survivorship from childhood cancer has increased since the 1970s due to improved treatment therapies. Currently, approximately 80% of children diagnosed with malignancy will become 5-year survivors (1, 2). Although the 5-year survival rate is encouraging, these individuals continue to have significant long-term adverse outcomes compared to the general population (3, 4). Due to the fact that the number of survivors of childhood cancer is expected to continue to increase with time, it has become ever more important to investigate these adverse outcomes, particularly as more survivors are reaching middle age – a period in which the general population begins to face morbidity as well.

Previous studies have shown that childhood cancer survivors have an increased risk for premature mortality (5-10), subsequent malignant neoplasms (11, 12), chronic health conditions (13, 14), poor overall health (15-17), and many other adverse outcomes, compared to the reference population, far beyond 5-year survivorship. However, the majority of these adverse outcomes are estimated using individual childhood cancer survivor cohorts, which has led to concerns on the generalizability of results across countries and regions where cohort type, follow-up time, and treatment may differ. Thus, the purpose of this proposal is to use the Childhood Cancer Survivor Study (CCSS) and British Childhood Cancer Survivor Study (BCCSS), two of the largest childhood cancer survivor studies in the world, to compare and offer validation for the two most prominent adverse outcomes following 5-year survivorship of childhood cancer: premature mortality (all-cause and cause-specific) and subsequent malignant neoplasms (overall and type-specific). In doing so, this collaborative analysis will provide better evidence on the overall burden of mortality and morbidity in childhood cancer survivors. Additionally, these findings could have important implications for policy and practice in the United States, United Kingdom, and potentially other developed countries.

This collaboration will serve three purposes. Firstly, the comparison will serve as a method of validation of previously reported results for mortality and subsequent malignant neoplasms when the cohorts are restricted in terms of the eligibility criteria (i.e.: diagnosis period, first primary neoplasm diagnoses, and age at diagnosis). Regardless of whether the findings are similar or different, something new will be established. If results are comparable, which is hypothesized, this study will provide increased reliability in the findings and in the risk-factors associated with each outcome as well. If results differ, then explanations may be different treatment exposures and/or loss to follow-up, the latter of which can then be assessed with available information. If differences still remain then different treatment exposures becomes a likely explanation, although other

possibilities can be hypothesized. Secondly, by completing a pooled analysis, this study will analyze the largest cohort to date of 5-year childhood cancer survivors. This pooled analysis will have increased statistical power compared to all previously reported studies, which will ultimately provide more accurate estimates of the mortality and subsequent malignant neoplasm burden in 5-year childhood cancer survivors. Internal analyses will also strengthen our knowledge on risk-factors for each outcome. Finally, this study will overcome previous limitations in literature in regards to outcomes with a low number of events, which to date still need further exploration. By achieving all three objectives, this study will provide the most accurate risk estimates to date to justify recommendations for changes in policy and practice. Additionally, the findings may provide further insight into research areas that warrant further exploration.

As international, collaborative projects are increasingly becoming important to reduce the frequency, severity, and impact of late side effects of childhood cancer, the findings of this project are important not only for validation, but also for increasing assurance in the generalizability of results and the feasibility of pooling results between countries. Findings from this study will update existing mortality and subsequent malignant neoplasm data with potentially increased statistical power and will potentially provide more accurate estimates for outcomes that were previously reported as rare in individual cohorts. With these findings, this study may have important research, practice, and policy implications, which may lead to further exploration of interventions, programs, and services needed in order to prevent or reduce adverse outcomes in childhood cancer survivors.

Proposed Specific Aims:
This proposed analysis will look at mortality and subsequent malignant neoplasm (SMN) information to determine the differences and similarities, after adjustment, between the Childhoood Cancer Survivor Study (CCSS) and British Childhood Cancer Survivor Study (BCCSS). We propose the following objectives:

- **Objective 1:** To compare risks of all-cause and cause-specific mortality among 5-year survivors in the CCSS and BCCSS
- **Objective 2:** To compare risks of overall and type-specific SMNs among 5-year survivors in the CCSS and BCCSS

If not comparable:

- **Objective 3:** To determine potential explanations for why there are differences in mortality and SMNs between the CCSS and BCCSS cohorts

If comparable:

- **Objective 3:** To estimate and describe the burden of all-cause and cause-specific mortality among 5-year survivors of childhood cancer in a pooled analysis of both the CCSS and BCCSS
- **Objective 4:** To estimate and describe the burden of overall and type-specific SMNs among 5-year survivors of childhood cancer in a pooled analysis of both the CCSS and BCCSS

Hypotheses:

- When the cohorts are restricted to comparable ages at diagnosis, diagnosis period, and cancer types, risks of death and SMNs will be comparable between the CCSS and BCCSS cohorts
- When the cohorts are combined:
    - Overall, risk of death will remain increased in survivors compared to that expected (with attained age, the multiplicative risk will decline and additive risk will increase)
    - As attained age increases, the percentage of excess deaths due to recurrence will decrease
    - As attained age increases, the percentage of excess deaths attributable to chronic health conditions (SMNs, circulatory, and respiratory causes) will increase

- Overall, risk of SMNs will remain increased in survivors compared to that expected (with attained age, the multiplicative risk will decline and additive risk will increase)
- As attained age increases, the percentage of excess bone tumors and gliomas will decrease
- As attained age increases, the percentage of excess digestive and genitourinary subsequent neoplasms will increase

Methods:

Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional cohort study comprised of 36,049 5-year survivors of cancer diagnosed under the age of 21 from 1970-1999 in the United States or Canada (18). Participants were identified by each institution with the objective to achieve complete ascertainment for survivors meeting the eligibility criteria (18). The CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. Written informed consent was received from all participating subjects 18 years of age or older and from a parent or guardian for subjects under the age of 18.

British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study (BCCSS) is a population-based cohort study comprised of 34,489 5-year survivors of childhood cancer diagnosed from 1940-2006 under the age of 15 in Britain (19). The cohort was identified using the National Registry of Childhood Tumors, which has a high estimated level of ascertainment (~99%) (20). Ethical approval for the study was obtained from a Multi-Center Research Ethics Committee and every Local Research Ethics Committee in Britain.

Study Population

As the CCSS and BCCSS cohorts differ in their inclusion criteria, only survivors who fulfilled the following eligibility criteria will be included as the aim of the study was to perform comparative analyses: (a) diagnosis of leukemia (acute lymphoblastic leukemia, acute myeloid leukemia, other leukemias), central nervous system (CNS) tumor (excludes meningioma and craniopharyngioma), Hodgkin lymphoma, non-Hodgkin lymphoma, kidney cancer, neuroblastoma, soft tissue sarcoma, and bone tumors (osteosarcoma, Ewing sarcoma, other bone tumors); (b) age less than 15 years at diagnosis. For the mortality analysis, a diagnosis period of January 1, 1970 to December 31, 1999 will be used, which is the full diagnosis period that the CCSS and BCCSS overlap. For the SMN analysis, a diagnosis period of January 1, 1970 to December 31, 1991 will be used as the BCCSS only has complete validation for second malignancies for this period (original cohort).

Statistical Analyses

- Descriptive analysis

A descriptive analysis summarizing and comparing the characteristics of the CCSS and BCCSS cohorts in detail will be performed looking at the following measures: primary cancer diagnosis, age at diagnosis, year of diagnosis (6-year bands), binary treatment information (yes/no), vital status, attained age, gender, follow-up time since five year survival.

- Mortality

All individuals included in the CCSS who were reported to have died or had an uncertain vital status were included in a National Death Index (NDI) search in order to accurately ascertain the vital status of each survivor. Similarly, the BCCSS cohort was able to ascertain each survivor's vital and embarkation status by linking with the National Health Service Central Registries, which is a national population-based death registration system. The death certificate and primary underlying cause-of-death, as coded using the relevant *International Classification of Diseases,* were obtained for all survivors who died. If a cause-of-death was unable to be identified, the individuals will be excluded from the cause-specific mortality analysis.

Time at risk will start at five years post-diagnosis and continue until individuals exited from risk at the first occurrence of emigration (for the BCCSS), death, or mortality exit date. The mortality exit date will be defined as the date of the most recent NDI search for the CCSS and date of most recent vital status update from the National Health Service Central Registries for the BCCSS. The standardized mortality ratio (SMR) will be defined as the ratio of the observed over expected number of deaths. The absolute excess risk (AER) will be defined as the observed minus the expected number of deaths divided by person-years at risk multiplied by 10,000. To determine the expected number of deaths used in the calculation of the SMR and AER, person-years for each sex-specific, age-specific, and calendar year-specific stratum will be multiplied by the corresponding mortality rate for the general population of the United States (CCSS) or England and Wales (BCCSS). Derivation of SMRs for deaths due to recurrence would not be appropriate because the corresponding mortality rate in the general population would be 0. However, to describe excess mortality from recurrences, the AER will be used as it corresponds to the crude mortality rate for recurrence. Similar calculations will be carried out for overall mortality and cause-specific mortality.

Cumulative overall and cause-specific mortality, as a function of follow-up or attained age, will be estimated by using the stcompet command in Stata (StataCorp, College Station, Texas). Causes-of-death other than the one under study will be treated as competing risks.

- Subsequent Malignant Neoplasms

Preliminary notifications of SMNs were initially screened for in both the CCSS and BCCSS. SMNs that were deemed likely or possible were confirmed by writing to the relevant clinician(s) to obtain diagnostic reports to confirm site, type, and date of diagnosis. Premalignant or dysplastic conditions will not be included in the analysis. Furthermore, nonmelanoma skin cancers, meningiomas, and other nonmalignant CNS tumors will be excluded from the analysis.

Time at risk for a SMN will begin at five years post-diagnosis and individuals will exit from risk at the first occurrence of an SMN, emigration (for the BCCSS), death, or SMN exit date. The SMN exit date will be the date of last contact with the survivor for the CCSS and the date of most recent SMN validation exercise for the BCCSS. Standardized incidence ratios (SIRs) will be calculated as the ratio of observed to expected number of malignant neoplasms. AERs will be calculated as described previously for the mortality analyses. To determine the expected number of neoplasms used in the calculation for the SIR and AER, person-years for each sex-specific, age-specific, and calendar year-specific stratum will be multiplied by the corresponding neoplasm rates from SEER (CCSS) or the general population of England and Wales (BCCSS). Similar calculations will be carried out for overall SMN and SMN-specific analyses.

Cumulative incidence for all SMNs and specific SMNs, as a function of follow-up or attained age, will be estimated by using the stcompet command in Stata (StataCorp, College Station, Texas). Death and SMNs other than the one of interest will be treated as competing risks.

- Analyses comparing the CCSS and BCCSS

To compare risks of death and SMNs between cohorts, multivariable Poisson models will be used where both the CCSS and BCCSS will be analyzed at one time. By using a cohort indicator (e.g. 1 = CCSS, 2 =BCCSS), we will test for heterogeneity between the cohorts, after adjusting for the following risk factors: sex, age at diagnosis, year of diagnosis, time since diagnosis/attained age, and first primary neoplasm type. Heterogeneity between the cohorts will also be tested in a separate model that will take into account the effect of treatment exposures whilst adjusting for sex, age at diagnosis, year of diagnosis, radiotherapy exposure, chemotherapy exposure, and time since diagnosis/attained age.

If results are not comparable, multivariable Poisson models with interactions between risk factors and the cohort indicator will be assessed to determine differences between the cohorts.

- Pooled Analyses

If results are comparable, pooled analyses will be completed where mortality and SMNs will be assessed irrespective of the cohort indicator. Univariable Poisson models will be used to evaluate potential explanatory factors for cause-specific deaths or SMNs. Multivariable Poisson models will be used to evaluate the simultaneous effect of the following demographic- and cancer-related factors: sex, age at diagnosis, year of diagnosis, time since diagnosis/attained age, and first primary neoplasm type. If the results from the univariable and multivariable models are similar, then the univariable findings will be reported due to increased robustness. If the results from the models differ, then the multivariable results will be reported in terms of relative risks for the SMRs/SIRs and relative excess risks for the AERs.

In order to test for heterogeneity or trend, likelihood-ratio tests will be used. All analyses will be completed using Stata statistical software (StataCorp, College Station, Texas) where the criteria for statistical significance will be a 2-sided $P<0.05$.

Results:

Table 1**:** Descriptive characteristics of study population by cohort

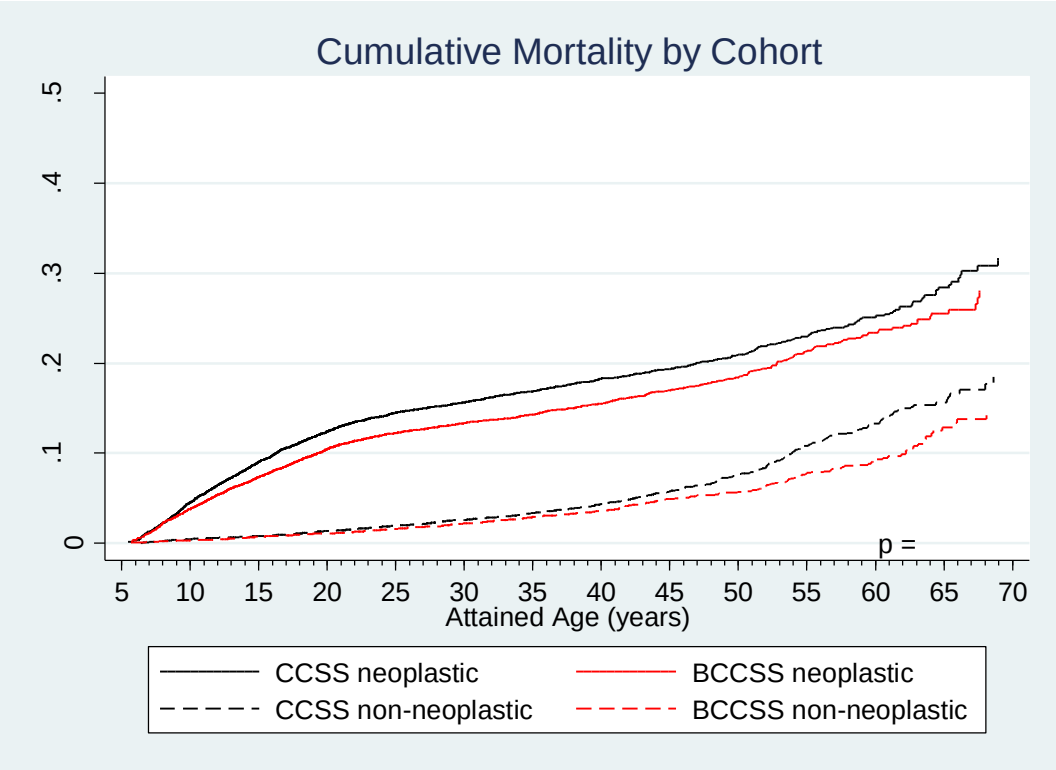
Characteristic	Childhood Cancer Survivor Study (N=)	British Childhood Cancer Survivor Study (N=)
All Patients		
Sex		
Male		
Female		
Diagnosis		
Leukemia		
CNS tumor		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Wilms		
Neuroblastoma		
Soft tissue sarcoma		
Bone sarcoma		
Age at Diagnosis		
Mean (range)		
0-4 years		
5-9 years		
10-14 years		
Year of Diagnosis		
1970-1974		
1975-1979		
1980-1984		
1985-1989		
1990-1994		
1995-1999		
Time since Diagnosis		
Mean (range)		
5-24 years		
25-34 years		
35-44 years		
45+ years		
Attained Age at Exit		
Mean (range)		
5-24 years		
25-34 years		
35-44 years		
45+ years		
Radiotherapy		
No		
Yes		
Chemotherapy		
No		
Yes		
Surgery		
No		
Yes		
Vital Status		
Alive		
Dead		

Table 2: Comparison of SMRs/AERs for all-cause and cause-specific mortality between cohorts, adjusting for all potential confounders available

	Childhood Cancer Survivor Study				British Childhood Cancer Survivor Study				P value
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**Person-Years**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	
All Causes									
Neoplastic									
Non-Neoplastic									
Circulatory									
Cardiac									
Stroke									
Respiratory									
Nervous									
Infection									
Digestive									
Perinatal									
Endocrine									
Genitourinary									
Musculoskeletal									
Mental									
Blood									
External									
Other									

*Note: Cause-of-death groups currently defined as the chapters within the 'International Classification of Diseases.' These groups may be further subdivided or excluded pending numbers/statistical power and clinical importance in the manuscript

Figure 1: Comparison of neoplastic and non-neoplastic cumulative mortality between cohorts



*Note: This is only an example, but a similar figure will be used

Table 3: Multivariable relative risks for all-cause and cause-specific SMRs by risk factors, stratified by cohort

	All Causes			Recurrence Deaths			SMN Deaths			Circulatory Deaths		
Characteristic	**CCSS**	**BCCSS**	**Interaction P value**	**CCSS**	**BCCSS**	**Interaction P value**	**CCSS**	**BCCSS**	**Interaction P value**	**CCSS**	**BCCSS**	**Interaction P value**
Sex												
Male	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Female												
Diagnosis												
Leukemia	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
CNS tumor												
Hodgkin lymphoma												
Non-Hodgkin lymphoma												
Wilms												
Neuroblastoma												
Soft tissue sarcoma												
Bone sarcoma												
Age at Diagnosis												
0-4 years	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
5-9 years												
10-14 years												
Year of Diagnosis												
1970-1975	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
1976-1981												
1981-1986												
1987-1991												
Time since Diagnosis												
5-24 years	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
25-34 years												
35-44 years												
45+ years												
Attained Age at Exit												
5-24 years	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
25-34 years												
35-44 years												
45+ years												
Radiotherapy												
No	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Yes												
Chemotherapy												
No	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Yes												
Surgery												
No	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Yes												

*Note: To be completed if mortality results are not comparable between the CCSS and BCCSS

Table 4: Pooled SMRs/AERs for all-cause and cause-specific mortality

	All Survivors (CCSS & BCCSS)			
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
All Causes				
Neoplastic				
Non-Neoplastic				
Circulatory				
Cardiac				
Stroke				
Respiratory				
Nervous				
Infection				
Digestive				
Perinatal				
Endocrine				
Genitourinary				
Musculoskeletal				
Mental				
Blood				
External				
Other				

*Note: Cause-of-death groups currently defined as the chapters within the 'International Classification of Diseases.' These groups may be further subdivided or excluded pending numbers/statistical power and clinical importance in the manuscript

*Note: To be completed if mortality results are comparable between the CCSS and BCCSS

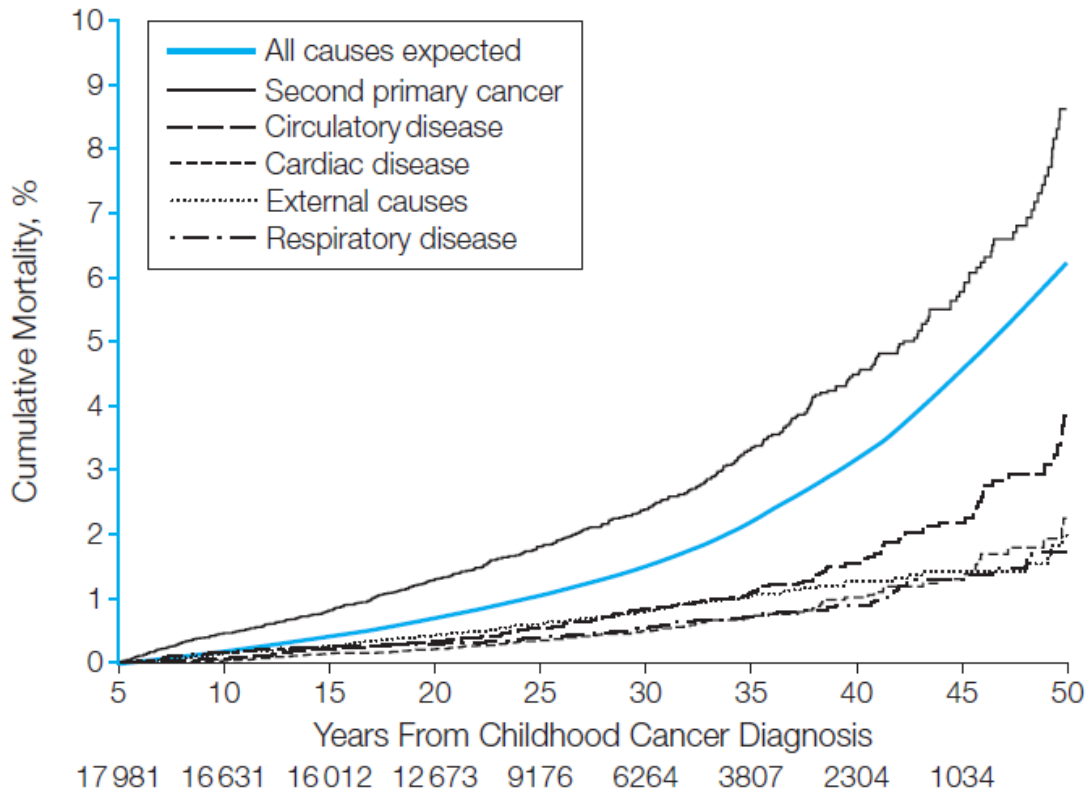
Table 5: Pooled SMRs/AERs for all-cause and cause-specific mortality, by risk factors

	All Causes				Recurrence Deaths		Second Primary Cancer Deaths		
	Person-Years	Obs/Exp	SMR (95% CI)	AER (95% CI)[a]	Obs	Crude Rate (95% CI)[a,b]	Obs/Exp	SMR (95% CI)	AER (95% CI)[a]
Years from cancer diagnosis, y									
5-14	166 059	1970/69.1	28.5 (27.3-29.8)	114.5 (109.4-119.8)	1604	96.6 (92.0-101.4)	145/9.3	15.5 (13.2-18.3)	8.2 (6.9-9.7)
15-24	120 182	535/78.4	6.8 (6.3-7.4)	38.0 (34.4-42.0)	227	18.9 (16.6-21.5)	136/12.1	11.3 (9.5-13.3)	10.3 (8.6-12.4)
25-34	57 900	304/61.8	4.9 (4.4-5.5)	41.8 (36.3-48.2)	64	11.1 (8.7-14.1)	99/16.0	6.2 (5.1-7.5)	14.3 (11.3-18.1
35-44	21 028	159/49.8	3.2 (2.7-3.7)	51.9 (41.4-65.1)	19	9.0 (5.8-14.2)	64/18.1	3.5 (2.8-4.5)	21.8 (15.5-30.7
≥45	4855	81/25.8	3.1 (2.5-3.9)	113.7 (82.6-156.5)	4	8.2 (3.1-22.0)	39/10.8	3.6 (2.6-4.9)	58.0 (37.5-89.6
P_{trend}			<.001	<.001		<.001		<.001	<.001
Attained age, y									
0-19	139 996	1629/49.5	32.9 (31.3-34.5)	112.8 (107.3-118.6)	1343	95.9 (90.9-101.2)	124/6.9	18.1 (15.1-21.5)	8.4 (6.9-10.1)
20-29	125 988	744/78.5	9.5 (8.8-10.2)	52.8 (48.7-57.2)	422	33.5 (30.4-36.8)	126/9.8	12.8 (10.8-15.3)	9.2 (7.6-11.1)
30-39	69 696	374/62.4	6.0 (5.4-6.6)	44.7 (39.6-50.5)	119	17.1 (14.3-20.4)	117/14.1	8.3 (6.9-10.0)	14.8 (12.0-18.1
40-49	26 171	184/51.2	3.6 (3.1-4.2)	50.7 (41.5-62.0)	28	10.7 (7.4-15.5)	66/17.2	3.8 (3.0-4.9)	18.6 (13.4-25.8
≥50	8173	118/43.2	2.7 (2.3-3.3)	91.6 (68.9-121.7)	6	7.3 (3.3-16.3)	50/18.4	2.7 (2.1-3.6)	38.6 (24.9-59.9
P_{trend}			<.001	<.001		<.001		<.001	<.001

Abbreviations: AER, absolute excess risk; AML, acute myeloid leukemia; CI, confidence interval; CNS, central nervous system; Exp, expected; NH, nonheritable; NHL, non-Hodgki lymphoma; Obs, observed; PNET, primitive neuroectodermal tumor; SMR, standardized mortality ratio.
[a] Per 10 000 person-years.
[b] May be interpreted as an AER.

*Note: This is only an example, but a similar table will be used (6)
*Note: To be completed if mortality results are comparable between the CCSS and BCCSS

Figure 2: Pooled all-cause and cause-specific cumulative mortality



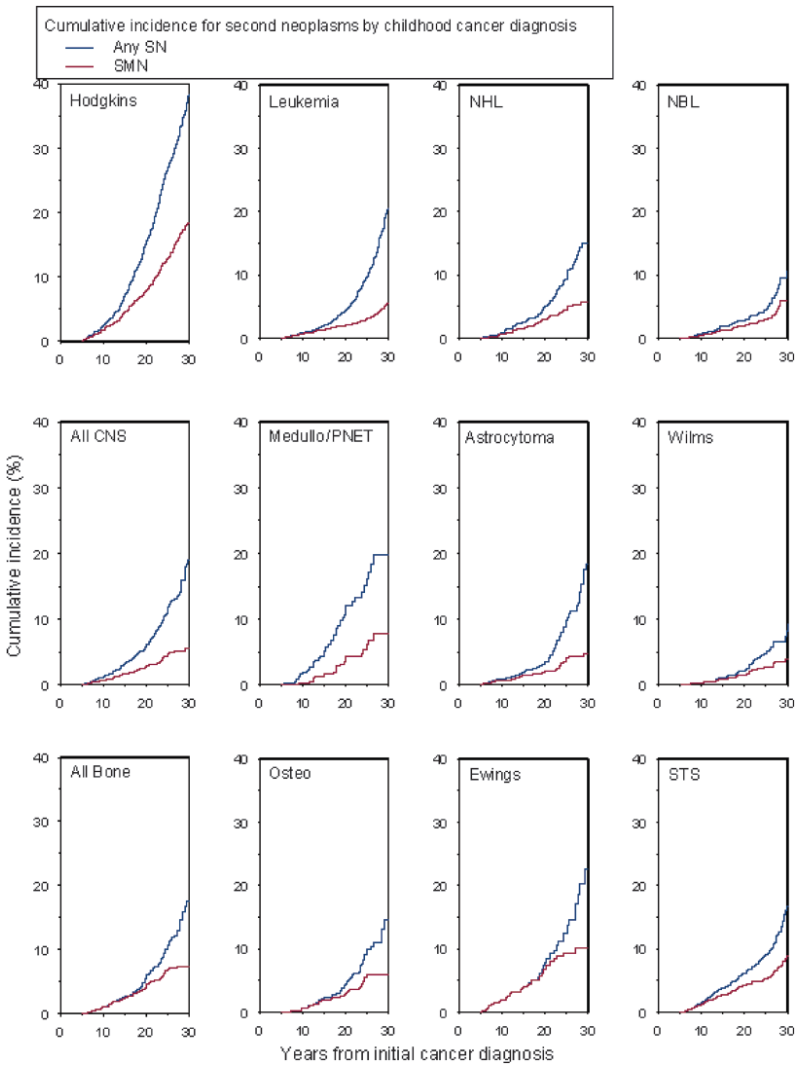
*Note: This is only an example, but a similar figure will be used (6)
*Note: To be completed if mortality results are comparable between the CCSS and BCCSS

Table 6: Comparison of SIRs/AERs for overall and type-specific SMNs, adjusting for all potential confounders available

	Childhood Cancer Survivor Study				British Childhood Cancer Survivor Study				P value
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**Person-Years**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	
All SMNs									
Digestive									
Genitourinary									
Glioma									
Breast									
Bone									
Leukemia									
Hodgkin lymphoma									
Non-Hodgkin lymphoma									
CNS									
Soft tissue sarcoma									
Thyroid									
Other solid tumors									
Melanoma									

*Note: SMN groups are currently listed in a similar format used in previous papers. These groups may be further subdivided or excluded pending numbers/statistical power and clinical importance in the manuscript

Figure 3: Comparison of overall and type-specific cumulative incidence of SMNs between cohorts, by first primary neoplasm diagnosis



*Note: This is only an example, but a similar figure will be used as so (11): 1 line CCSS, 1 line BCCSS, analysis only on first SMN

Table 7: Multivariable relative risks for overall and type-specific SIRs by risk factors, stratified by cohort

	All SPNs			Bone SMNs			Breast SMNs			Digestive SMNs			Genitourinary SMNs		
Characteristic	**CCSS**	**BCCSS**	**Interaction P value**	**CCSS**	**BCCSS**	**Interaction P value**	**CCSS**	**BCCSS**	**Interaction P value**	**CCSS**	**BCCSS**	**Interaction P value**	**CCSS**	**BCCSS**	**Interaction P value**
Sex															
Male	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Female															
Diagnosis															
Leukemia	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
CNS tumor															
Hodgkin lymphoma															
Non-Hodgkin lymphoma															
Wilms															
Neuroblastoma															
Soft tissue sarcoma															
Bone sarcoma															
Age at Diagnosis															
0-4 years	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
5-9 years															
10-14 years															
Year of Diagnosis															
1970-1975	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
1976-1981															
1981-1986															
1987-1991															
Time since Diagnosis															
5-24 years	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
25-34 years															
35-44 years															
45+ years															
Attained Age at Exit															
5-24 years	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
25-34 years															
35-44 years															
45+ years															
Radiotherapy															
No	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Yes															
Chemotherapy															
No	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Yes															
Surgery															
No	1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)		1 (ref)	1 (ref)	
Yes															

*Note: To be completed if SMN results are not comparable between the CCSS and BCCSS

Table 8: Pooled SIRs/AERs for overall and type-specific SMNs

	All Survivors (CCSS & BCCSS)			
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
All SMNs				
Digestive				
Genitourinary				
Glioma				
Breast				
Bone				
Leukemia				
Hodgkin lymphoma				
Non-Hodgkin lymphoma				
CNS				
Soft tissue sarcoma				
Thyroid				
Other solid tumors				
Melanoma				

*Note: SMN groups are currently listed in a similar format used in previous papers. These groups may be further subdivided or excluded pending numbers/statistical power and clinical importance in the manuscript
*Note: To be completed if SMN results are comparable between the CCSS and BCCSS

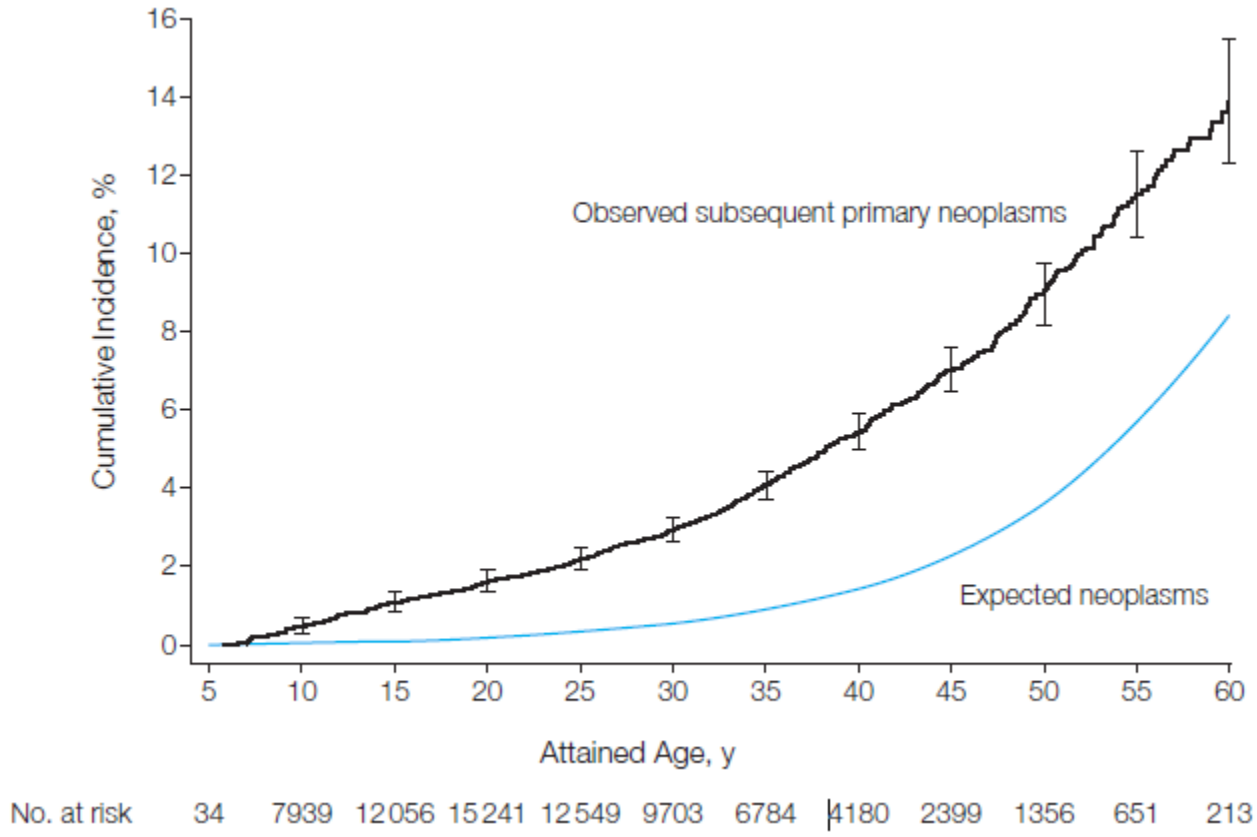
Table 9: Pooled SIRs/AERs for overall and type-specific SMNs, by risk factors

	Subsequent Primary Neoplasms									
	All				Digestive			Genitourinary		
	Person-Years	No. Obs/Exp	SIR (95% CI)[a]	AER (95% CI)[b]	No. Obs/Exp	SIR (95% CI)[a]	AER (95% CI)[b]	No. Obs/Exp	SIR (95% CI)[a]	AER (95% CI)[b]
Overall	369 909.9	837/215.5	3.9 (3.6 to 4.2)	16.8 (15.3 to 18.3)	105/22.7	4.6 (3.8 to 5.6)	2.2 (1.7 to 2.8)	100/51.3	1.9 (1.6 to 2.4)	1.3 (0.8 to 1.8)
Sex										
Male	200 390.0	429/95.6	4.5 (4.1 to 4.9)	16.6 (14.6 to 18.7)	75/14.0	5.4 (4.3 to 6.7)	3.0 (2.2 to 3.9)	42/26.2	1.6 (1.2 to 2.2)	0.8 (0.2 to 1.4)
Female	169 519.9	408/119.9	3.4 (3.1 to 3.8)	17.0 (14.7 to 19.3)	30/8.7	3.5 (2.4 to 4.9)	1.3 (0.6 to 1.9)	58/25.1	2.3 (1.8 to 3.0)	1.9 (1.1 to 2.8)
$P_{heterogeneity}$			<.001	.82		.04	.001		.07	.03
Childhood cancer type[c]										
Central nervous system	86 150.9	165/60.1	2.7 (2.4 to 3.2)	12.2 (9.3 to 15.1)	25/6.9	3.6 (2.5 to 5.4)	2.1 (1.0 to 3.2)	23/14.3	1.6 (1.1 to 2.4)	1.0 (–0.1 to 2.1)
Leukemia	80 028.1	115/26.7	4.3 (3.6 to 5.2)	11.0 (8.4 to 13.7)	5/1.5	3.2 (1.3 to 7.8)	0.4 (–0.1 to 1.0)	10/6.5	1.5 (0.8 to 2.9)	0.4 (–0.3 to 1.2)
Hodgkin lymphoma	27 231.5	104/18.6	5.6 (4.6 to 6.8)	31.3 (24.0 to 38.7)	13/2.4	5.5 (3.2 to 9.4)	3.9 (1.3 to 6.5)	5/4.8	1.1 (0.4 to 2.5)	0.1 (–1.5 to 1.7)
Non-Hodgkin lymphoma	18 522.5	48/12.8	3.8 (2.8 to 5.0)	19.0 (11.7 to 26.3)	9/1.7	5.4 (2.8 to 10.4)	4.0 (0.8 to 7.1)	10/3.2	3.1 (1.7 to 5.8)	3.7 (0.3 to 7.0)
Neuroblastoma	16 970.4	20/7.2	2.8 (1.8 to 4.3)	7.5 (2.4 to 12.7)	3/0.7	4.5 (1.5 to 14.0)	1.4 (–0.6 to 3.4)	3/1.6	1.8 (0.6 to 5.7)	0.8 (–1.2 to 2.8)
Heritable retinoblastoma[d]	15 158.3	113/8.4	13.4 (11.1 to 16.1)	69.0 (55.2 to 82.7)	11/0.9	12.5 (6.9 to 22.6)	6.7 (2.4 to 11.0)	15/1.9	7.9 (4.8 to 13.1)	8.6 (3.6 to 13.7)
Nonheritable retinoblastoma	18 369.9	19/11.2	1.7 (1.1 to 2.7)	4.2 (–0.4 to 8.9)	1/1.2	0.8 (0.1 to 5.7)	–0.1 (–1.2 to 0.9)	2/2.6	0.8 (0.2 to 3.1)	–0.3 (–1.8 to 1.2)
Wilms tumor	34 287.6	72/15.2	4.7 (3.8 to 6.0)	16.6 (11.7 to 21.4)	17/1.3	13.0 (8.1 to 20.8)	4.6 (2.2 to 6.9)	9/3.5	2.6 (1.3 to 4.9)	1.6 (–0.1 to 3.3)
Bone tumor	12 913.4	49/11.2	4.4 (3.3 to 5.8)	29.3 (18.7 to 39.9)	3/1.3	2.3 (0.7 to 7.0)	1.3 (–1.3 to 3.9)	4/2.7	1.5 (0.6 to 4.0)	1.0 (–2.0 to 4.0)
Soft tissue sarcoma	26 667.1	57/17.9	3.2 (2.5 to 4.1)	14.7 (9.1 to 20.2)	7/2.1	3.3 (1.6 to 6.9)	1.8 (–0.1 to 3.8)	12/4.3	2.8 (1.6 to 5.0)	2.9 (0.4 to 5.4)
Other	33 610.1	75/26.1	2.9 (2.3 to 3.6)	14.5 (9.5 to 19.6)	11/2.7	4.1 (2.3 to 7.5)	2.5 (0.5 to 4.4)	7/6.0	1.2 (0.6 to 2.5)	0.3 (–1.2 to 1.9)
$P_{heterogeneity}$			<.001	<.001		<.001	<.001		<.001	<.001
Attained age, y										
5-19	140 017.6	189/18.2	10.4 (9.0 to 12.0)	12.2 (10.3 to 14.1)	14/0.5	28.3 (16.7 to 47.7)	1.0 (0.4 to 1.5)	5/1.8	2.7 (1.1 to 6.6)	0.2 (–0.1 to 0.5)
20-29	125 942.9	207/42.5	4.9 (4.3 to 5.6)	13.1 (10.8 to 15.3)	20/1.9	10.4 (6.7 to 16.2)	1.4 (0.7 to 2.1)	22/13.1	1.7 (1.1 to 2.5)	0.7 (–0.0 to 1.4)
30-39	69 626.9	231/56.9	4.1 (3.6 to 4.6)	25.0 (20.7 to 29.3)	35/4.5	7.8 (5.6 to 10.9)	4.4 (2.7 to 6.0)	32/15.9	2.0 (1.4 to 2.8)	2.3 (0.7 to 3.9)
40-49	26 157.7	133/52.4	2.5 (2.1 to 3.0)	30.8 (22.2 to 39.5)	23/7.1	3.2 (2.1 to 4.8)	6.1 (2.5 to 9.7)	20/9.8	2.0 (1.3 to 3.2)	3.9 (0.5 to 7.2)
≥50	8164.7	77/45.5	1.7 (1.4 to 2.1)	38.6 (17.5 to 59.7)	13/8.7	1.5 (0.9 to 2.6)	5.3 (–3.3 to 14.0)	21/10.6	2.0 (1.3 to 3.0)	12.7 (1.7 to 23.7)
P_{trend}			<.001	<.001		<.001	<.001		.96	<.001

Abbreviations: AER, absolute excess risk; CI, confidence interval; Exp, expected; Obs, observed; SIR, standardized incidence ratio.
[a] CIs should be interpreted cautiously if based on fewer than 5 observed events.
[b] AER is shown per 10 000 person-years; CIs should be interpreted cautiously if based on fewer than 5 observed events.
[c] Based on *International Classification of Childhood Cancer*.
[d] Heritable retinoblastoma defined as bilateral retinoblastoma or family history of retinoblastoma.

*Note: This is only an example, but a similar table will be used (12)
*Note: To be completed if SMN results are comparable between the CCSS and BCCSS

Figure 4: Pooled overall and type-specific cumulative incidence of SMNs



*Note: This is only an example, but a similar figure will be used (12)
*Note: To be completed if SMN results are comparable between the CCSS and BCCSS

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