

SUPPLEMENTARY MATERIALS

Table of Contents

	Page
1. Section 1. Derivation and validation of treatment scores	2
2. Section 2. Multiple imputation of missing treatment information	9
3. Figure S1. Cumulative all-cause, recurrence/progression and health-related cause late mortality among five-year survivors of childhood cancer by decade for specific childhood cancer diagnoses.	13
4. Figure S2. Among five-year survivors, (A) percentage receiving radiotherapy and (B) mean cumulative dose of anthracycline chemotherapy by decade and by primary cancer diagnosis.	17
5. Figure S3. Among five-year survivors, box plots providing median cumulative anthracycline dose along with 25 th and 75 th percentiles by decade and by primary cancer diagnosis.	18
6. Table S1. Demographic and treatment characteristics by treatment era and life status of five-year survivors of childhood cancer	20
7. Table S2. Distribution of treatment exposure for acute lymphoblastic leukemia, Hodgkin lymphoma, Wilms tumor and astrocytoma across three decades	22
8. Table S3. Cumulative incidence of all-cause, recurrence/progression, and health-related cause late mortality at 15 years from primary cancer diagnosis	24
9. Table S4. Frequencies of underlying cause of death in five-year survivors of childhood cancer	26
10. Table S5. Relative rates for mortality among five-year survivors of childhood cancer	45
11. Table S6. All-cause and cause-specific standard mortality ratios in five-year survivors of childhood cancer followed for 15 years	46
12. Table S7. Relative rates of Other Health-Related Cause Mortality Based on Treatment Era Among Five-Year Survivors of Specific Childhood Cancers and the Impact of Specific Treatment Exposures Upon Treatment Era	47
13. Table S8. Cumulative incidence of all cause and cause-specific mortality at 10 years from primary cancer diagnosis among five-year survivors	48

Section 1: Derivation and validation of treatment scores

A. The motivation for and concept of treatment scores

Treatment scores were derived as a way of quantifying treatment-associated propensity for late mortality (from health-related causes other than recurrence/progression of the initial cancer) based on the therapeutic exposures that CCSS survivors received for their childhood cancer. Our intention was to augment the formal regression-based inference with a descriptive visualization of data. That is, this summary score permits a graphical evaluation of data with respect to whether, and how much, treatment-associated propensity for late mortality has declined over time (box plots in Figure 2 within the manuscript), potentially paralleling the temporal reduction in late mortality (exemplified by the red dots in Figure 2).

For example, for certain primary cancer diagnoses, we hypothesized that historical changes (reductions) in treatment exposure over the three decades would result in appreciable reductions in the treatment-related propensity for late mortality (box plots), parallel to the reductions of actual late mortality rates (red dots). Graphing these quantities comparatively allowed visualization of evidence that the treatment changes over time are associated with reduced risk of late mortality. On the other hand, in some childhood cancer types, there may be little change in the treatment-related propensity for late mortality, possibly because no major treatment changes have taken place and/or treatment changes have not resulted in the reduction of propensity for late mortality. Among survivors of such childhood cancer diagnoses, a decline in rates of late mortality over time would suggest that something other than their childhood cancer treatment has contributed to the established reduction in late mortality (e.g., effective follow-up screening or care of severe chronic conditions).

The methodologies used for deriving, validating, and applying the summary treatment score are described in detail below.

B. The derivation of treatment scores

A set of treatment variables that were considered to potentially contribute to the treatment-associated propensity for late mortality were a priori selected for each of the four childhood cancer types where statistically significant reduction in late mortality (from health-related causes) was identified (i.e., Acute Lymphoblastic Leukemia, Astrocytoma, Hodgkin Lymphoma, and Wilms Tumor). Treatment variables were categorized based on clinical relevance by the investigator team. They included:

- Acute Lymphoblastic Leukemia

Cranial radiation (Gy)	None, (>0, 19), 20 or greater
Anthracyclines (mg/m ²)	None, (>0, 149), (150, 299), (300, 449), (450, 599), 600 or greater
Epipodophyllotoxin	None, Any
Steroid	None, Prednisone, Dexamethasone, Both

- Astrocytoma

Cranial radiation	None, Any
Chemotherapy	None, Any
- Hodgkin Lymphoma

Chest radiation (Gy)	None, (>0, 19), (20, 29), 30 or greater
Anthracyclines (mg/m ²)	None, (>0, 149), (150, 299), (300, 449), (450, 599), 600 or greater
Alkylating agents* (mg/m ²)	None, (>0, 3999), (4000, 7999), (8000, 11999), (12000, 15999), (16000, 19999), 20000 or greater
Splenectomy	No, Yes
- Wilms Tumor

Abdomen radiation (Gy)	None, (>0, 19), (20, 29), 30 or greater
Anthracyclines (mg/m ²)	None, (>0, 149), (150, 299), (300, 449), (450, 599), 600 or greater

*Cyclophosphamide Equivalent Dose¹

The treatment score model was developed using multivariable piecewise exponential models with late mortality (from health-related causes other than recurrence/progression of the initial cancer) as the outcome. For each childhood cancer diagnosis group, we fitted the model with logarithm of person years at risk as an offset (the person years at risk were terminated at death or censoring). The model was of the form:

$$\log (E[Y_{ij}]) = \log (PY_{ij}) + Z_{ij}\alpha + X_i\beta$$

where, for the i^{th} survivor in the j^{th} year of attained age, Y_{ij} is the Poisson random variable indicating alive/death status, PY_{ij} is the person years at risk observed (during the j^{th} year of attained age), Z_{ij} is the vector of adjustment variables (age at diagnosis, sex, and attained age in j^{th} year), X_i is the vector of the diagnosis-specific fixed set of treatment variables described above that the survivor received, and α and β are model parameters. The baseline log mortality rate was modeled by a natural cubic spline function of the attained age in $Z_{ij}\alpha$ with five knots placed at 10, 20, 30, 40, 45 years old.

The treatment score for a given survivor refers to the estimated partial linear predictor $X_i\hat{\beta}$ of health-related late mortality from the treatment portion of the model, i.e., estimated log rate of death, corresponding to the specific set of treatments the survivor has received (X_i), adjusted for age at diagnosis, sex, and attained age.

C. The validation of treatment scores

To validate the treatment score as a summary scale that measures the propensity for late mortality, we performed an internal validation by splitting the contributing CCSS treatment institutions into two groups by stratified random sampling, and used one group of CCSS institutions for developing the treatment score and the other group for validating it. Specifically, the CCSS institutions were stratified based on their membership to the Pediatric Oncology Group or Children’s Cancer Group (the primary legacy treatment consortia to the Children’s Oncology Group for the eras in which this analysis takes place) and their patient volumes (approximated by the numbers of CCSS survivors contributed to the cohort). Within each stratum, the institutions were randomly split into the two groups. St. Jude Children’s Research Hospital, the largest CCSS institution, was the only exception where the survivors were randomly split into the two groups within the institution.

Note that the treatment score was not developed for the purpose of predicting individual survivors’ deaths. Thus, our validation was not concerned with the score’s predictive power for individual survivors’ deaths. Rather, we are interested in determining the degree to which stratum defined by treatment scores correlate with mortality risks. We therefore focused our validation of the treatment score’s utility on calibration of the treatment-associated propensity for late mortality. Our approach was similar to the methods used for validation of risk calibration for the most widely-used breast cancer risk prediction model developed by Gail et al²⁻⁴ and for other risk scores of clinical utility.^{5,6}

Specifically, using one of the two groups of CCSS institutions as the “training dataset”, we fitted a treatment score model as described in the previous section. Note that we employed the multiple imputation methodology for missing treatment information, which created 10 complete training datasets. Thus, we fitted the same treatment score model to each of the 10 training datasets and averaged the resulting β parameter estimates to obtain a single trained treatment score model. Using this trained model, the treatment score $X_i\hat{\beta}$ was calculated for each survivor of the training institutions based on his/her treatment exposures X_i . We defined treatment score groups by dividing the training institutions’ survivors of each childhood cancer type into three groups for Acute Lymphoblastic Leukemia and Hodgkin Lymphoma, where the counts of late mortality from health-related causes were sufficiently large, and two groups for Astrocytoma and Wilms Tumor. The highest treatment score group was defined by a cutoff that approximately placed survivors with the top 20% of treatment scores within each childhood cancer diagnosis group. For Acute Lymphoblastic Leukemia and Hodgkin Lymphoma, the remaining survivors were approximately equally split into two groups by a cutoff of the treatment score (each 40% of the diagnosis

specific training set). For Astrocytoma, due to having only two binary treatment factors in the model, the cutoff placed approximately half of the survivors in the higher score group.

Using the fixed β parameter estimates from the training model, the treatment scores $X_i\hat{\beta}$'s were also calculated for survivors from the other group of CCSS institutions: these institutions and survivors served as the "validation dataset". Then, they were also grouped into the two or three treatment score groups using the same cutoff values as the training dataset/institutions.

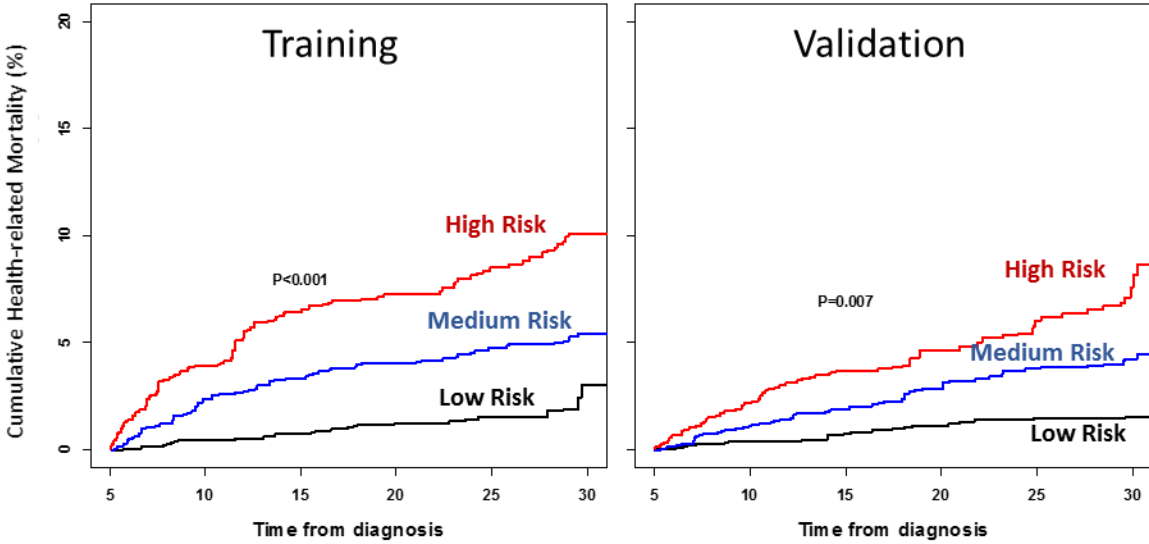
The table below shows the validation results of the treatment score with respect to the calibration.²⁻⁶ Rates of each treatment score group agree well between the survivors of the training institutions and those of the independent validation institutions. This validates the calibration capacity of the treatment score. In addition, we calculated cumulative incidence of late mortality from health-related causes by the training/validation status for each childhood cancer diagnosis group. While cumulative incidence of cause-specific mortality has competing risks and even a perfect calibration would not make it equal between the training and validation institutions, the figure below shows reasonably good agreement, further supporting the utility of the treatment score.

Observed rates of late mortality from health-related causes per 10,000 person years in training and validation institutions by treatment score group and childhood cancer type.

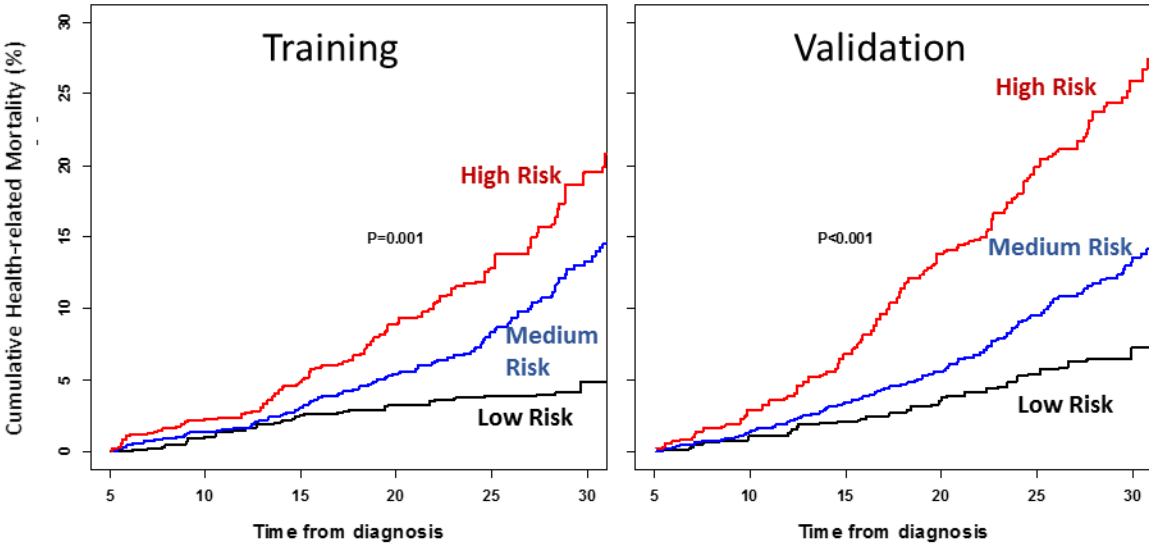
Childhood Cancer Type	Group	Treatment Score Groups (rates per 10,000 person-years)		
		Low risk	Medium risk	High risk
Acute Lymphoblastic Leukemia	Training	8.3	22.6	48.1
	Validation	8.1	20.1	44.2
Hodgkin Lymphoma	Training	21.5	56.4	89.7
	Validation	27.1	58.1	125.3
		Low risk	High risk	
Wilms Tumor	Training	7.3		37.3
	Validation	11.5		43.3
Astrocytoma	Training	16.9		55.3
	Validation	17.3		53.1

Cumulative incidence of late mortality from health-related causes by the training/validation status for each childhood cancer diagnosis group: (A) Acute Lymphoblastic Leukemia; (B) Hodgkin Lymphoma; (C) Wilms Tumor; and (D) Astrocytoma. Black, blue, and red lines are the low-, medium-, and high-risk groups, respectively.

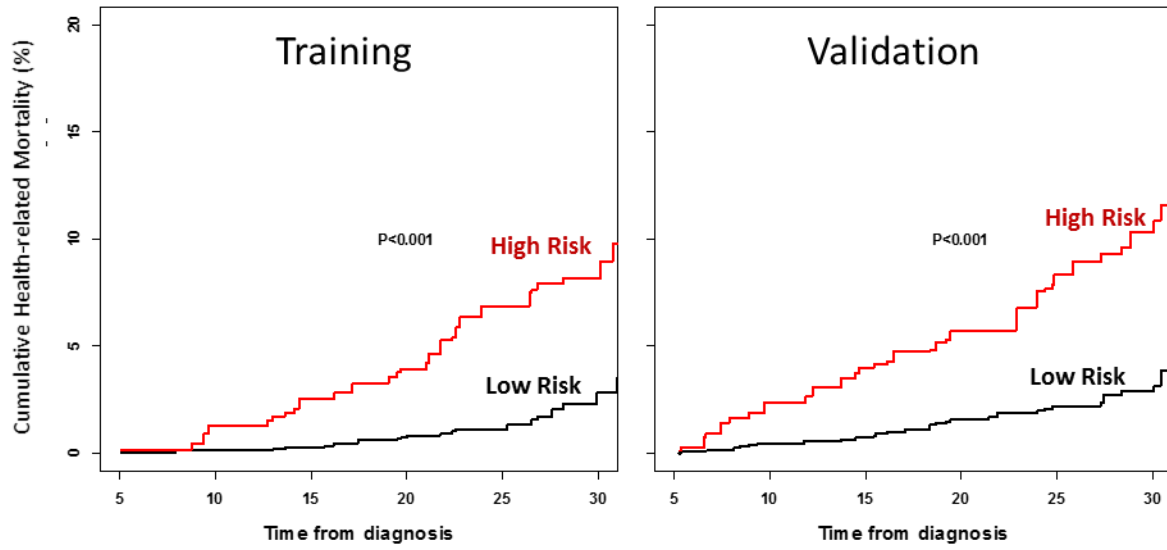
[A] Acute lymphoblastic leukemia



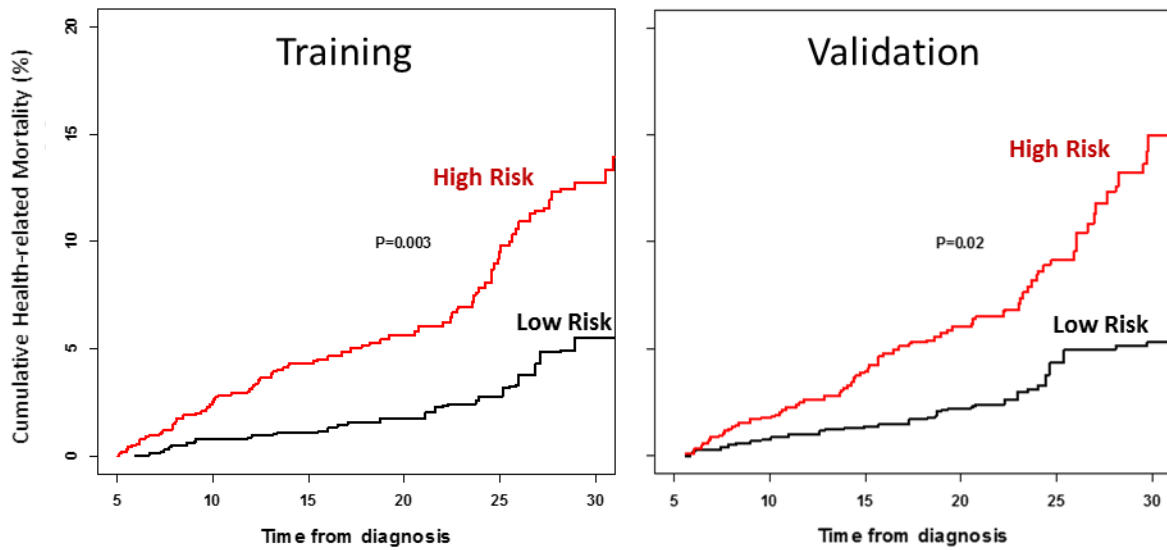
[B] Hodgkin lymphoma



[C] Wilms tumor



[D] Astrocytoma



These results validate the derived treatment score as a measure that summarizes treatment-associated propensity for late mortality.

D. The application of treatment scores

The validated treatment scores were standardized within each childhood cancer diagnosis group in order to enhance their interpretability with respect to changes over time. Specifically, we standardized the treatment scores such that those from 1970-1979 had a mean of 0.0 and standard deviation of 1.0 within each childhood cancer diagnosis group. If another time period of survivors (e.g., those from 1980-1989) had a tendency to have negative/similar/positive values of the standardized treatment score, then that would indicate a decrease/no change/increase in treatment-related propensity for late mortality as compared to 1970-1979.

E. References for Section 1

- 1. Green DM, Nolan VG, Goodman PJ, Whitton JA, Srivastava D, Leisenring WM, Neglia JP, Sklar CA, Kaste SC, Hudson MM, Diller LR, Stovall M, Donaldson SS, Robison LL. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer*. 2014 Jan;61(1):53-67.*
- 2. Costantino JP, Gail MH, Pee D, Anderson S, Redmond CK, Benichou J, Wieand HS. Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst*. 1999 Sep 15;91(18):1541-8.*
- 3. Bondy ML, Lustbader ED, Halabi S, Ross E, Vogel VG. Validation of a breast cancer risk assessment model in women with a positive family history. *J Natl Cancer Inst*. 1994 Apr 20;86(8):620-5.*
- 4. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. *J Natl Cancer Inst*. 1994 Apr 20;86(8):600-7.*
- 5. Rassi A Jr, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, Rassi GG, Hasslocher-Moreno A, Sousa AS, Scanavacca MI. Development and validation of a risk score for predicting death in Chagas' heart disease. *N Engl J Med*. 2006 Aug 24;355(8):799-808.*
- 6. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015 Feb 17;162(4):266-75.*

Section 2: Multiple imputation of missing treatment information

This section describes the issue of missing treatment information in our analysis of late mortality and our multiple imputation approach.¹

A. The issue of missing treatment information

Treatment information is not complete for a subset of study-eligible survivors in CCSS. This is due to a variety of reasons including: not being able to contact survivors for study recruitment (unsuccessful tracing); passive and active refusal of study participation; participation in the study without consenting to release medical record information; and incomplete treatment records at the treating institutions (primarily partial missing information on some treatment variables).

The table below shows the extent of incomplete/missing treatment information in all study-eligible survivors of each diagnosis group for which multiple imputation was used. The percentages of study-eligible survivors with complete treatment information varied from 74% in Astrocytoma to 56% in Hodgkin Lymphoma. Approximately one quarter of survivors in each diagnosis group had treatment information completely missing due to either unsuccessful tracing for study recruitment, passive/active refusal of study participation, or study participation without consenting to release medical record information. The remaining study-eligible survivors had partially missing treatment information with the majority consisting of only one missing treatment variable.

<i>Incompleteness of treatment data by diagnosis group</i>				
<i>Completeness of treatment data</i>	<i>Acute Lymphoblastic Leukemia (N=8,500)</i>	<i>Astrocytoma (N=3,904)</i>	<i>Hodgkin Lymphoma (N=4,332)</i>	<i>Wilms Tumor (N=3,055)</i>
<i>Complete</i>	5,637 (66.3%)	2,883 (73.8%)	2,421 (55.9%)	2,090 (68.4%)
<i>Missing</i>	2,185 (25.7%)	909 (23.3%)	1,079 (24.9%)	705 (23.1%)
<i>Partial missing [1 variable missing]</i>	678 (8.0%) [583 (6.9%)]	112 (2.9%) [112 (2.9%)]	832 (19.2%) [642 (14.8%)]	260 (8.5%) [260 (8.5%)]

For our late mortality analyses, the outcome (late mortality) data are available for all study-eligible survivors (except Canadian survivors) through the National Death Index, regardless of whether survivors participated in CCSS or not. This complete ascertainment of the outcome variable provides an exceptional opportunity for analyses free of any participation bias. Thus, some of the analyses in this paper that did not use treatment information (e.g., Tables 1 and 2, Figure 1 within the manuscript) were based on the entire study-eligible cohort and free of any participation bias. For the other analyses that utilized treatment information (e.g., Table 3 and Figure 2 within the manuscript), we still used all study-eligible survivors by addressing missing treatment information by a multiple imputation approach, motivated by a special context that applies to pediatric cancer treatment described below.

B. The special context of childhood cancer treatment

The CCSS cohort is hospital-based, consisting of institutions with a long-standing history of specializing in the diagnosis and treatment of children/adolescents with cancer. During the period covered by the CCSS cohort (1970-1999), the great majority of childhood cancer patients seen at CCSS institutions were treated on clinical trial protocols. While some deviations from protocols can take place and some patients may be treated off protocols, treatments a patient receives are largely determined by the protocol the patient is on, or a prior/similar protocol that applies to the patient. Protocols are specific to given childhood cancer diagnoses and, for some diagnoses, they are also specific to patients of certain ages. Given the rare nature of pediatric malignancies, the National Cancer Institute established cooperative clinical trials groups. Pediatric oncologists and other subspecialists involved in the treatment of childhood cancers, have since the 1960s collaborated at a national level to design and conduct protocol-driven clinical trials, while only a select few large pediatric oncology institutions (e.g., St. Jude Children's Research Hospital, Memorial Sloan Kettering Cancer Center, Dana Farber Cancer Center) develop/use their own institution-specific protocols for selected cancer diagnoses. Protocols are modified in successive trials aiming for improvement over current protocols, and therefore evolve over time.

Because of this special context of childhood cancer treatment, the combination of the following 4 variables is strongly indicative of what protocol a survivor might have been treated on and provides an excellent proxy metric for the survivor's treatment exposures: (a) childhood cancer type; (b) institution the survivor was treated at (informing the institution's membership to a specific cooperative oncology consortium; i.e., Children's Oncology Group and its legacy groups consisting of the Pediatric Oncology Group, Children's Cancer Group, National Wilms Tumor Study Group, Intergroup Rhabdomyosarcoma Study Group, Intergroup Ewings Sarcoma Group; or whether it is an institution that develops its own protocols); (c) age at diagnosis; and (d) year of diagnosis. This special context of pediatric oncology, together with the availability of both the outcome and these four variables on the full study-eligible cohort, provides us with an effective analytic approach for addressing missing treatment information through multiple imputation.

C. The multiple imputation approach

We make an assumption of "missing at random",^{1,2} i.e., conditioned on observed data, whether treatment data of a survivor are missing/incomplete or not does not depend on true (missing/incomplete) treatment itself the survivor had received. This assumption implies that, stratified by the observed data of survivors, the conditional distribution of treatment data within each stratum is equal between survivors with complete treatment information and those without.^{1,2} While we cannot assess whether the missing at random assumption holds or not directly using the observed data alone, our previous analysis³ with an additional aggregate set of data is consistent with, and supports, this assumption. Specifically, we had collected treatment data of study-eligible non-participants of CCSS in an aggregate form for group comparisons without allowing linkages to individual survivors. We compared participants and study-eligible non-participants of the CCSS study with respect to survivors' demographic and clinical characteristics including treatment modality. This comparison revealed no statistically significant difference between the two groups, in spite of their large sample sizes, in any characteristics including treatment modality, with an exception of vital status. Thus, we felt reasonably

assured to make the missing at random assumption in our analyses, that is, within each stratum formed by the key characteristics (the vital status and the four key variables (a)-(d) above that inform on treatment protocols), all of which are available on the full study-eligible cohort, we assume that missing/incomplete treatment data are due to chance alone.

Under the missing at random assumption, the following multiple imputation approach we employed provides valid statistical inference. For a given survivor with incomplete treatment information, we borrow sets of actual treatments from 10 survivors randomly selected from a pool of survivors with complete treatment information who match with the survivor in question on the key characteristics above. The 10 sets of treatments reflect the range and uncertainty of plausible sets of treatments the survivor in question had received based on the key characteristics. This is a hot-deck imputation method⁴ and we applied Approximate Bayesian Bootstrap to make it properly reflect the entire uncertainty associated with missing data.^{2,5} Specifically, for each survivor in question, we first bootstrapped the pool of the matched survivors with complete treatment information and then applied the hot-deck imputation above to draw 10 samples by simple random sampling with replacement from the bootstrapped matched pool. This approach is “proper” in the sense of reflect the entire uncertainty^{1,2} and preserves the combination structures of various treatments that are actually used in clinical practice, i.e., imputation is multivariate. This results in 10 complete datasets are then analyzed one by one with an identical statistical method (e.g., piecewise exponential regression) whose results are expected to differ to some degree depending on the range and uncertainty captured across the 10 imputations. A specific standard statistical method^{1,2} is used to summarize and provide a single set of results from the 10 sets of results accounting for the uncertainty of each quantity of interest (e.g., a parameter) within each of, and between, the 10 analyses.

The key characteristics on which a pool of survivors with complete treatment information were matched with a survivor with incomplete treatment information depended on the degree of the incompleteness. If a survivor was missing all treatment information, the key characteristics to match were the 4 variables (a)-(d) and the vital status. If a survivor was missing partial treatment information, we additionally matched on all available treatment variables.

D. Sensitivity analysis assessing impact of the imputation

We employed the multiple imputation to reduce potential bias and more properly reflect the level of uncertainties associated with the incomplete treatment data. We conducted a sensitivity analysis using only survivors with complete treatment information, with a caveat that this complete-data-only analysis is potentially biased.^{1,2}

The table below shows results from Table 3 in the manuscript with and without imputation. While individual parameter estimates of relative rates associated with treatment era are slightly different, their overall direction and magnitude of change when therapy is included in the model remained unchanged in each diagnosis group in the complete-data-only analysis. Thus, our main result of Table 3 (described at the end of Results section of the manuscript) is robust with respect to our use of the multiple imputation.

Relative rates of health-related cause mortality based on treatment era among five-year survivors of specific childhood cancers and the impact of specific treatment exposures on treatment era, based on survivors with complete treatment information using the complete-data-only analysis.*

	Acute Lymphoblastic Leukemia		Hodgkin Lymphoma		Wilms Tumor		Astrocytoma	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Model Without Therapy								
Treatment era	0.94	0.86 – 1.02	0.81	0.74 - 0.90	0.72	0.58 - 0.89	0.85	0.76 - 0.96
[Table 3 with imputation]	[0.88]	[0.81 – 0.95]	[0.79]	[0.72 – 0.87]	[0.68]	[0.56 – 0.84]	[0.81]	[0.73 – 0.91]
Model With Therapy								
Treatment era	1.10 ¹	0.94 - 1.28	0.79 ²	0.68 - 0.91	0.97 ³	0.66 - 1.40	0.85 ⁴	0.72 – 1.00
[Table 3 with imputation]	[1.02]	[0.83 – 1.24]	[0.79]	[0.70 – 0.89]	[0.80]	[0.59 – 1.08]	[0.82]	[0.72 – 0.94]

*all models adjusted for sex, age at diagnosis and attained age, ¹Adjusted for cranial RT dose, anthracycline dose, epipodophyllotoxin and steroid exposure, ²adjusted for chest-directed radiotherapy dose, anthracycline dose, cyclophosphamide equivalent dose and splenectomy, ³adjusted for abdominal RT dose and anthracycline dose, ⁴adjusted for cranial RT dose and any chemotherapy (yes/no).

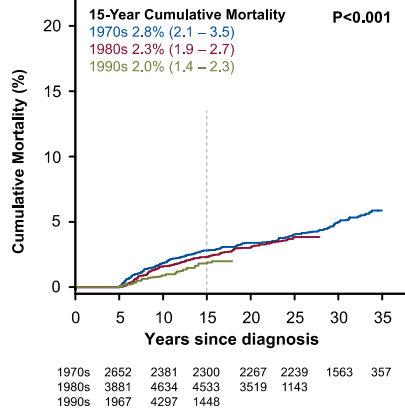
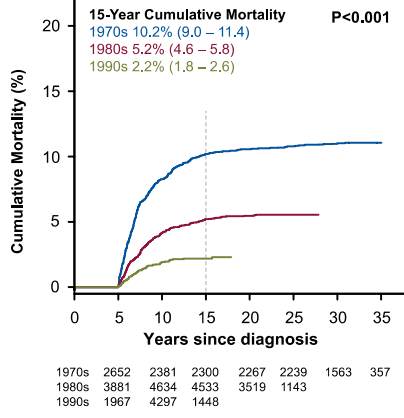
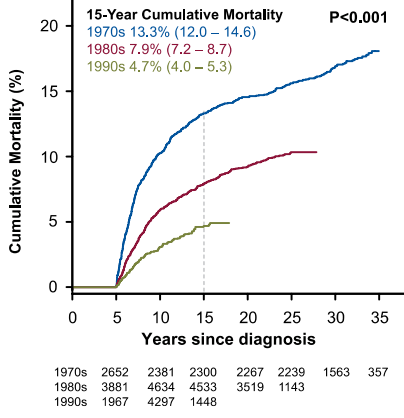
E. References for Section 2

1. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*, 2nd Edition. 2002. New York, John Wiley & Sons.
2. Molenberghs G., Fitzmaurice G., Kenward M.G., Tsiatis A., and Verbeke G. *Handbook of missing data methodology*. 2015. New-York: Chapman and Hall/CRC.
3. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit ME, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y, Zeltzer LK. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol*. 2002 Apr;38(4):229-39.
4. Andridge RR, Little RJA. A Review of Hot Deck Imputation for Survey Non-response. *International statistical review*. 2010;78(1):40-64.
5. Rubin DB, Schenker N. Multiple imputation for interval estimation from simple random samples with ignorable non-response. *J Amer Stat Assoc*. 1986;81:366–374.

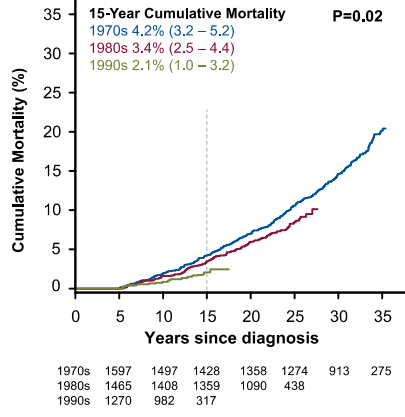
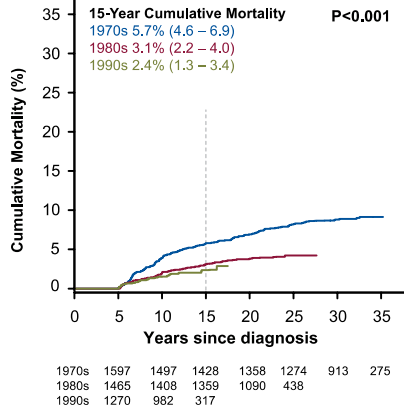
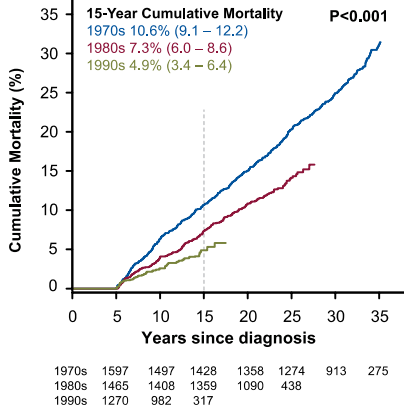
Figure 1. Cumulative all-cause, recurrence/progression and health-related cause late mortality among five-year survivors of childhood cancer by decade for specific childhood cancers

All Cause Recurrence/Progression Health-Related Cause

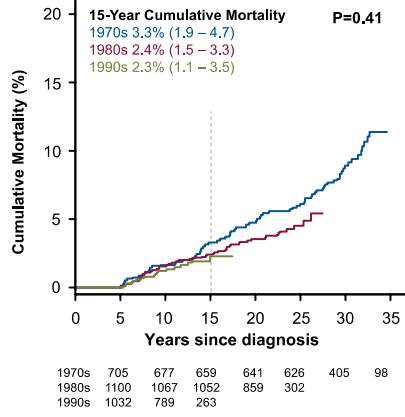
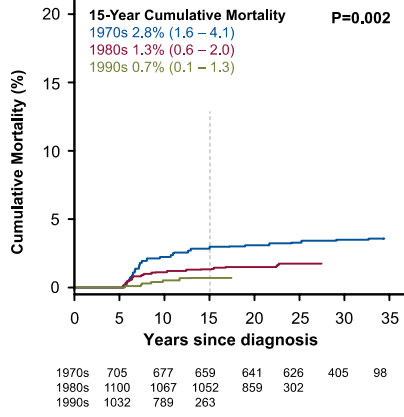
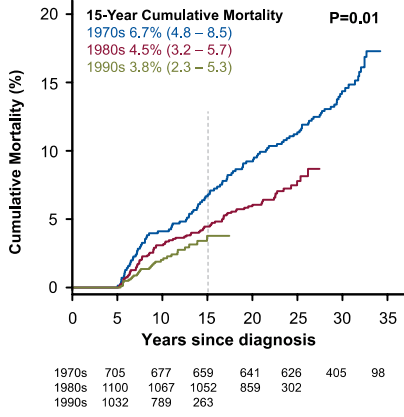
Acute lymphoblastic leukemia (n=8,500)



Hodgkin lymphoma (n=4,332)

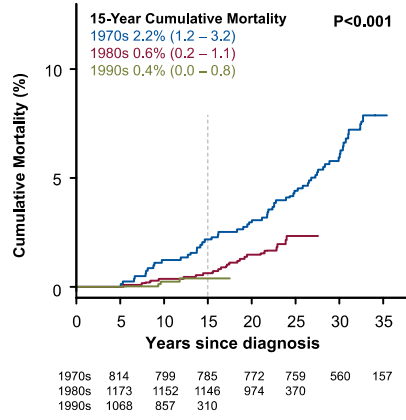
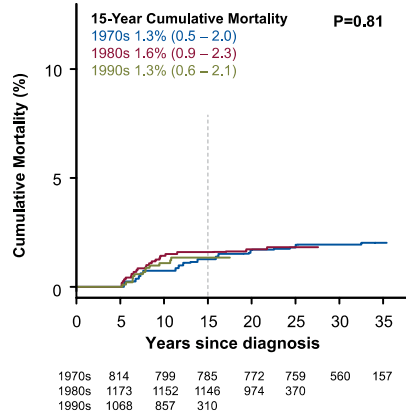
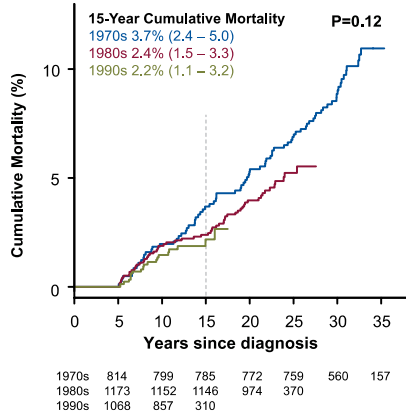


Non-Hodgkin lymphoma (n=2,837)

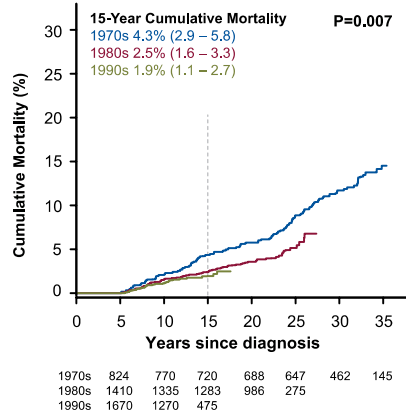
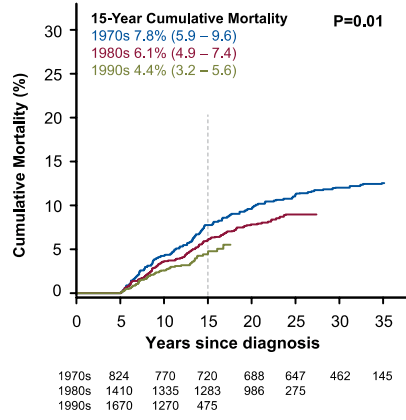
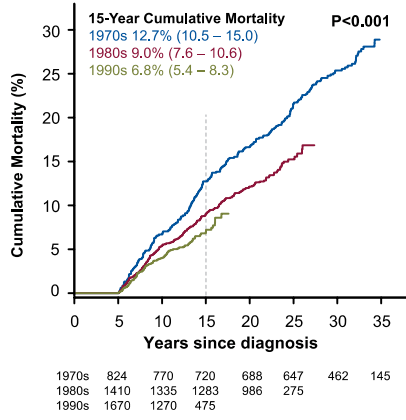


All Cause Recurrence/Progression Health-Related Cause

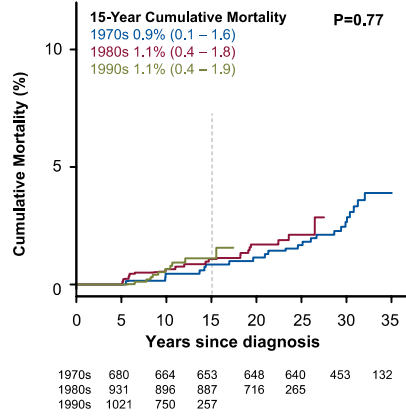
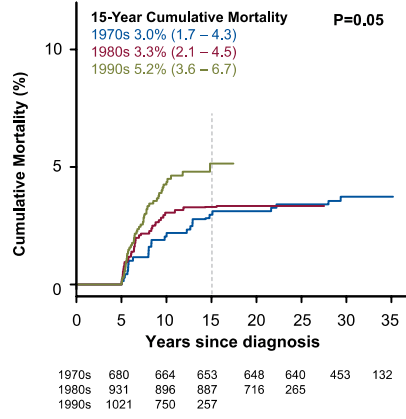
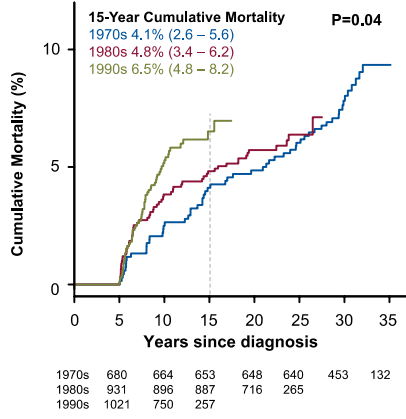
Wilms tumors (n=3,055)



Astrocytomas (n=3,904)

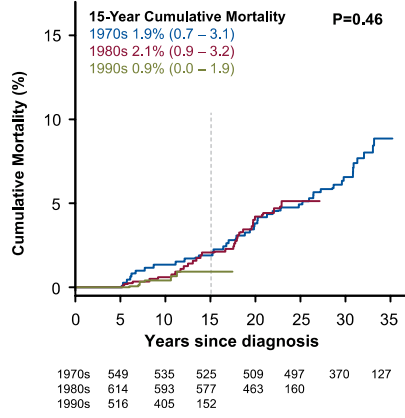
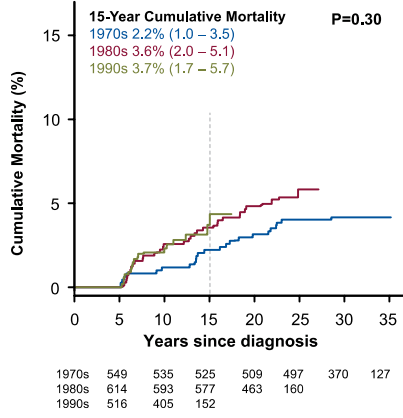
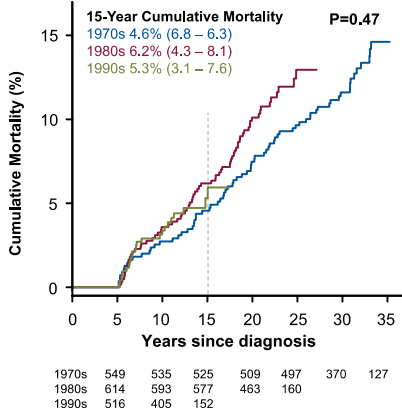


Neuroblastoma (n=2,632)



All Cause Recurrence/Progression Health-Related Cause

Rhabdomyosarcoma (n=1,679)



All Bone tumors (n=2,930)

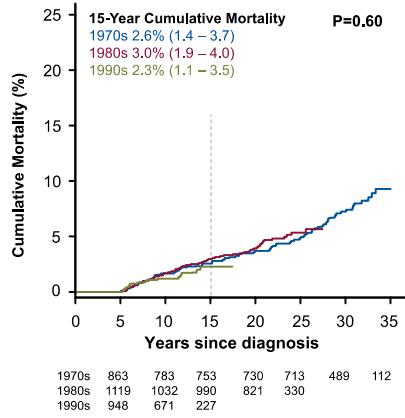
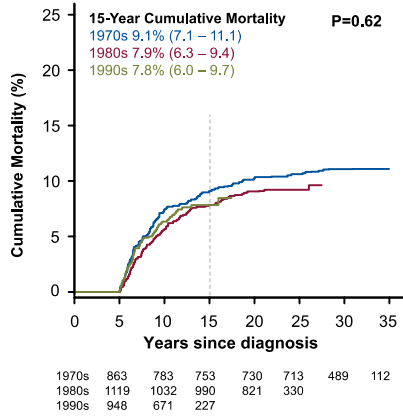
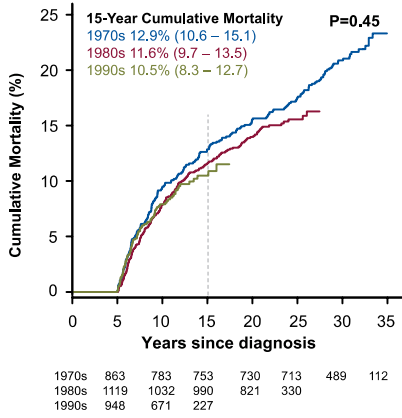


Figure S2. Among five-year survivors, (A) percentage receiving radiotherapy and (B) mean cumulative dose of anthracycline chemotherapy by decade and by primary cancer diagnosis.

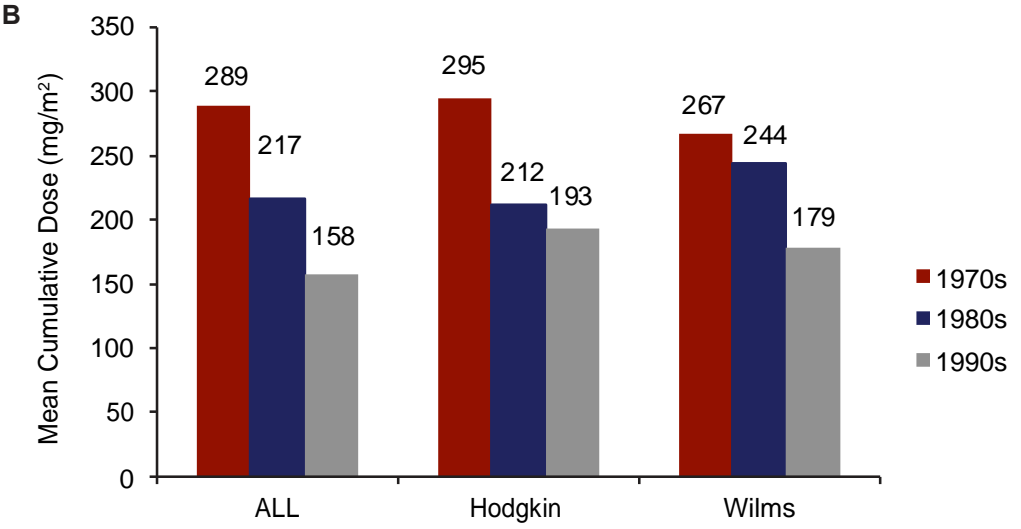
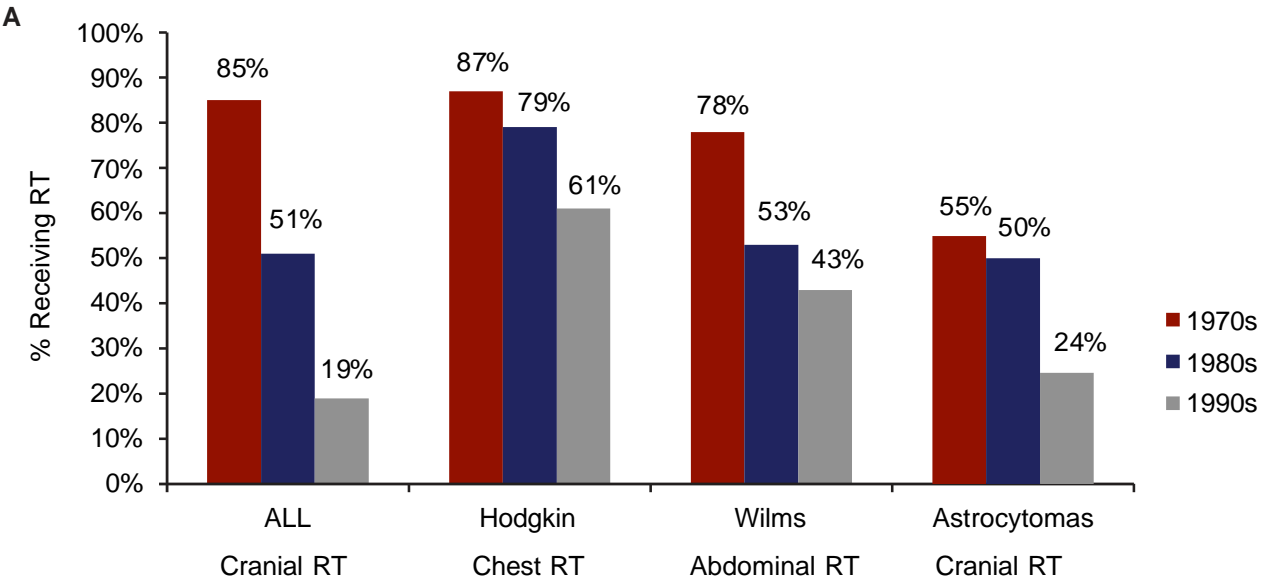


Figure S3. Among five-year survivors, box plots providing median cumulative anthracycline dose along with 25th and 75th percentiles by decade and by primary cancer diagnosis.

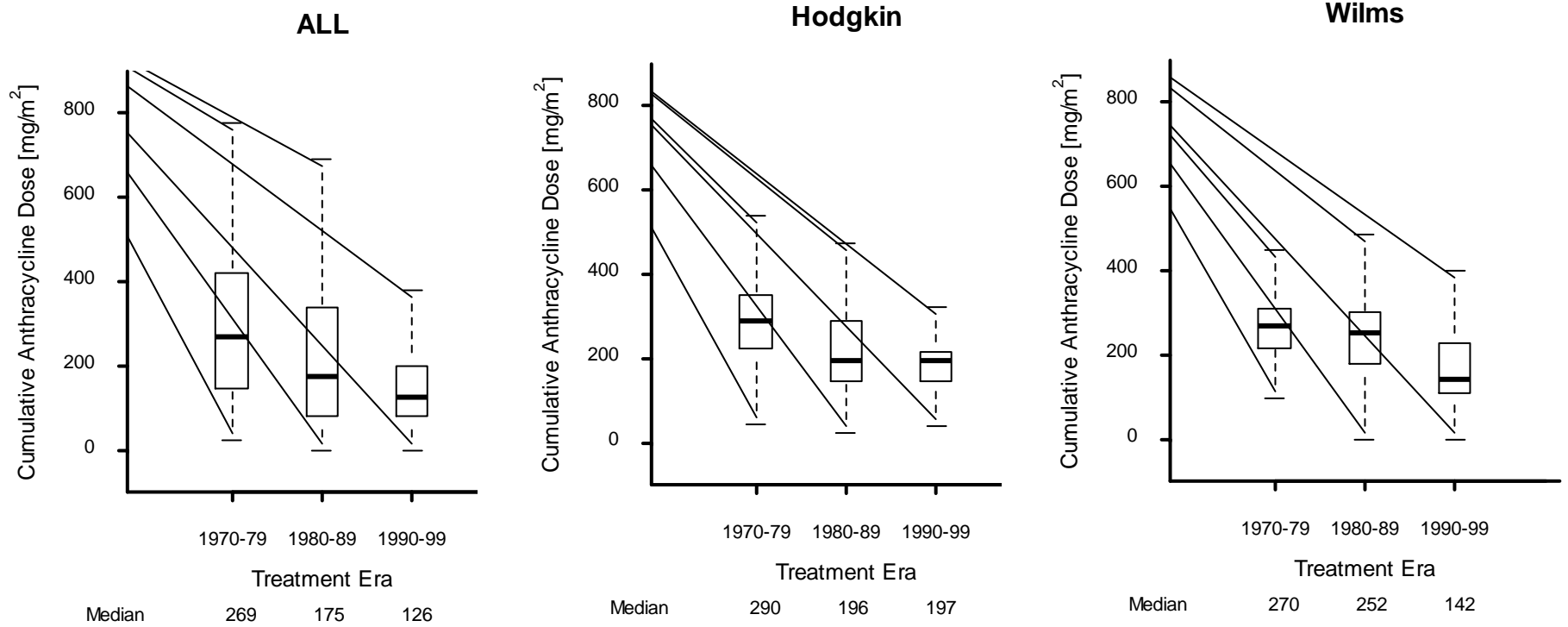


Table S1. Demographic and treatment characteristics by treatment era and life status of five-year survivors of childhood cancer

	Total	1970-1979	1980-1989	1990-1999	Alive	Dead
All Survivors*	34033	9416	13181	11436	30075	3958
Sex						
Male	18983 (55.8%)	5198 (55.2%)	7354 (55.8%)	6431 (56.2%)	16628 (55.3%)	2355 (59.5%)
Female	15050 (44.2%)	4218 (44.8%)	5827 (44.2%)	5005 (43.8%)	13447 (44.7%)	1603 (40.5%)
Race/Ethnicity						
Non-Hispanic white	21781 (64.0%)	5628 (59.8%)	8332 (63.2%)	7821 (68.4%)	19575 (65.1%)	2206 (55.7%)
Non-Hispanic black	2022 (5.9%)	242 (2.6%)	658 (5.0%)	1122 (9.8%)	1817 (6.0%)	205 (5.2%)
Hispanic	2287 (6.7%)	296 (3.1%)	688 (5.2%)	1303 (11.4%)	2094 (7.0%)	193 (4.9%)
Others	2057 (6.0%)	161 (1.7%)	706 (5.4%)	1190 (10.4%)	1849 (6.1%)	208 (5.3%)
Unknown	5886 (17.3%)	3089 (32.8%)	2797 (21.2%)	0 (0.0%)	4740 (15.8%)	1146 (28.9%)
Age at Diagnosis (years)						
0-4	13463 (39.6%)	3660 (38.9%)	5468 (41.5%)	4335 (37.9%)	12319 (41.0%)	1144 (28.9%)
5-9	7826 (23.0%)	2204 (23.4%)	2993 (22.7%)	2629 (23.0%)	6950 (23.1%)	876 (22.1%)
10-14	7144 (21.0%)	1903 (20.2%)	2670 (20.3%)	2571 (22.5%)	6185 (20.6%)	959 (24.2%)
15-20	5600 (16.5%)	1649 (17.5%)	2050 (15.6%)	1901 (16.6%)	4621 (15.4%)	979 (24.8%)
Survival after diagnosis (years)						
5-9	4210 (12.4%)	695 (7.4%)	716 (5.4%)	2799 (24.5%)	2349 (7.8%)	1861 (47.0%)
10-14	6298 (18.5%)	316 (3.4%)	323 (2.5%)	5659 (49.5%)	5523 (18.4%)	775 (19.6%)
15-19	5285 (15.5%)	224 (2.4%)	2083 (15.8%)	2978 (26.0%)	4758 (15.8%)	527 (13.3%)
20-24	6721 (19.8%)	240 (2.5%)	6481 (49.2%)	0 (0.0%)	6343 (21.1%)	378 (9.5%)
25-29	5964 (17.5%)	2386 (25.3%)	3578 (27.1%)	0 (0.0%)	5692 (18.9%)	272 (6.9%)
30-34	4051 (11.9%)	4051 (43.0%)	0 (0.0%)	0 (0.0%)	3924 (13.0%)	127 (3.2%)
≥35	1504 (4.4%)	1504 (16.0%)	0 (0.0%)	0 (0.0%)	1486 (4.9%)	18 (0.5%)
Diagnosis						
Leukemia	10199 (30.0%)	2982 (31.7%)	4485 (34.0%)	2732 (23.9%)	9019 (30.0%)	1180 (29.8%)
Acute lymphoblastic leukemia	8500 (25.0%)	2652 (28.2%)	3881 (29.4%)	1967 (17.2%)	7557 (25.1%)	943 (23.8%)
Acute myeloid leukemia	1222 (3.6%)	196 (2.1%)	438 (3.3%)	588 (5.1%)	1101 (3.7%)	121 (3.1%)
Other leukemia	477 (1.4%)	134 (1.4%)	166 (1.3%)	177 (1.5%)	361 (1.2%)	116 (3.0%)
Hodgkin lymphoma	4332 (12.7%)	1597 (17.0%)	1465 (11.1%)	1270 (11.1%)	3647 (12.1%)	685 (17.3%)
Non-Hodgkin lymphoma	2837 (8.3%)	705 (7.5%)	1100 (8.3%)	1032 (9.0%)	2621 (8.7%)	216 (5.5%)
CNS tumors	6369 (18.7%)	1225 (13.0%)	2294 (17.4%)	2850 (24.9%)	5443 (18.1%)	926 (23.4%)
Astrocytoma	3904 (11.5%)	824 (8.8%)	1410 (10.7%)	1670 (14.6%)	3383 (11.2%)	521 (13.2%)
Medulloblastoma, PNET	1380 (4.1%)	227 (2.4%)	493 (3.7%)	660 (5.8%)	1133 (3.8%)	247 (6.2%)
Other CNS	1085 (3.2%)	174 (1.8%)	391 (3.0%)	520 (4.5%)	927 (3.1%)	158 (4.0%)
Wilms tumor	3055 (9.0%)	814 (8.6%)	1173 (8.9%)	1068 (9.3%)	2898 (9.6%)	157 (4.0%)
Neuroblastoma	2632 (7.7%)	680 (7.2%)	931 (7.1%)	1021 (8.9%)	2457 (8.2%)	175 (4.4%)
Rhabdomyosarcoma	1679 (4.9%)	549 (5.8%)	614 (4.7%)	516 (4.5%)	1510 (5.0%)	169 (4.3%)
Bone tumors	2930 (8.6%)	864 (9.2%)	1119 (8.5%)	947 (8.3%)	2480 (8.2%)	450 (11.4%)
Ewing sarcoma	997 (2.9%)	279 (3.0%)	381 (2.9%)	337 (2.9%)	813 (2.7%)	184 (4.6%)
Osteosarcoma	1771 (5.2%)	539 (5.7%)	683 (5.2%)	549 (4.8%)	1518 (5.0%)	253 (6.4%)
Other bone tumors	162 (0.5%)	46 (0.5%)	55 (0.4%)	61 (0.5%)	149 (0.5%)	13 (0.3%)
Treatment exposure						
Any radiation						
Yes	19455 (57.2%)	7213 (76.6%)	7587 (57.6%)	4656 (40.7%)	16366 (54.4%)	3089 (78.0%)
No	14578 (42.8%)	2203 (23.4%)	5594 (42.4%)	6780 (59.3%)	13708 (45.6%)	870 (22.0%)
Chest radiation						
Yes	8299 (24.4%)	3073 (32.6%)	3062 (23.2%)	2163 (18.9%)	6715 (22.3%)	1584 (40.0%)
No	25734 (75.6%)	6343 (67.4%)	10119 (76.8%)	9273 (81.1%)	23360 (77.7%)	2375 (60.0%)
Chest radiation dose						
None	25734 (75.6%)	6343 (67.4%)	10119 (76.8%)	9273 (81.1%)	23360 (77.7%)	2375 (60.0%)
≥1-<20Gy	2230 (6.6%)	518 (5.5%)	965 (7.3%)	748 (6.5%)	1888 (6.3%)	342 (8.6%)
≥20-<30Gy	2189 (6.4%)	765 (8.1%)	679 (5.2%)	745 (6.5%)	1899 (6.3%)	290 (7.3%)
≥30Gy	3879 (11.4%)	1790 (19.0%)	1419 (10.8%)	671 (5.9%)	2928 (9.7%)	951 (24.0%)
Central nervous system radiation						
Yes	10185 (29.9%)	3655 (38.8%)	4344 (33.0%)	2186 (19.1%)	8457 (28.1%)	1728 (43.7%)
No	23848 (70.1%)	5761 (61.2%)	8837 (67.0%)	9250 (80.9%)	21618 (71.9%)	2230 (56.3%)
Central nervous system radiation dose						

None	23848 (70.1%)	5761 (61.2%)	8837 (67.0%)	9250 (80.9%)	21618 (71.9%)	2230 (56.3%)
≥1-<20Gy	3158 (9.3%)	570 (6.1%)	1864 (14.1%)	724 (6.3%)	2857 (9.5%)	302 (7.6%)
≥20-<30Gy	2654 (7.8%)	1823 (19.4%)	680 (5.2%)	151 (1.3%)	2276 (7.6%)	379 (9.6%)
≥30-<40Gy	347 (1.0%)	144 (1.5%)	136 (1.0%)	67 (0.6%)	256 (0.9%)	91 (2.3%)
≥40-<50Gy	726 (2.1%)	345 (3.7%)	298 (2.3%)	84 (0.7%)	484 (1.6%)	243 (6.1%)
≥50Gy	3300 (9.7%)	772 (8.2%)	1367 (10.4%)	1161 (10.2%)	2585 (8.6%)	715 (18.1%)
Craniospinal radiation						
Yes	2464 (7.3%)	789 (8.4%)	928 (7.0%)	747 (6.5%)	1902 (6.3%)	562 (14.2%)
No	31569 (92.8%)	8627 (91.6%)	12252 (93.0%)	10689 (93.5%)	28173 (93.7%)	3396 (85.8%)
Craniospinal radiation dose						
None	31569 (92.8%)	8627 (91.6%)	12252 (93.0%)	10689 (93.5%)	28173 (93.7%)	3396 (85.8%)
<30Gy	1447 (4.3%)	581 (6.2%)	488 (3.7%)	378 (3.3%)	1106 (3.7%)	341 (8.6%)
≥30Gy	1017 (3.0%)	208 (2.2%)	440 (3.3%)	369 (3.2%)	796 (2.6%)	221 (5.6%)
Abdominal radiation						
Yes	7912 (23.2%)	3081 (32.7%)	2839 (21.5%)	1991 (17.4%)	6466 (21.5%)	1446 (36.5%)
No	26121 (76.8%)	6335 (67.3%)	10342 (78.5%)	9445 (82.6%)	23609 (78.5%)	2513 (63.5%)
Abdominal radiation dose						
None	26121 (76.8%)	6335 (67.3%)	10342 (78.5%)	9445 (82.6%)	23609 (78.5%)	2513 (63.5%)
≥1-<20Gy	2440 (7.2%)	499 (5.3%)	959 (7.3%)	983 (8.6%)	2126 (7.1%)	314 (7.9%)
≥20-<30Gy	2097 (6.2%)	863 (9.2%)	786 (6.0%)	447 (3.9%)	1814 (6.0%)	283 (7.2%)
≥30Gy	3375 (9.9%)	1719 (18.3%)	1094 (8.3%)	562 (4.9%)	2526 (8.4%)	849 (21.5%)
Pelvic radiation						
Yes	6427 (18.9%)	2465 (26.2%)	2341 (17.8%)	1621 (14.2%)	5131 (17.1%)	1297 (32.8%)
No	27606 (81.1%)	6951 (73.8%)	10840 (82.2%)	9815 (85.8%)	24944 (82.9%)	2662 (67.3%)
Anthracycline (mg/m ²)						
None	18590 (54.6%)	6856 (72.8%)	6895 (52.3%)	4840 (42.3%)	16252 (54.0%)	2338 (59.1%)
0-<150	4202 (12.3%)	353 (3.7%)	1427 (10.8%)	2422 (21.2%)	3903 (13.0%)	299 (7.6%)
≥150-<300	5647 (16.6%)	764 (8.1%)	2198 (16.7%)	2685 (23.5%)	5109 (17.0%)	538 (13.6%)
≥300-<450	4198 (12.3%)	897 (9.5%)	2047 (15.5%)	1254 (11.0%)	3723 (12.4%)	475 (12.0%)
≥450-<600	1192 (3.5%)	475 (5.0%)	516 (3.9%)	200 (1.7%)	927 (3.1%)	264 (6.7%)
≥600	205 (0.6%)	71 (0.8%)	98 (0.7%)	35 (0.3%)	161 (0.5%)	44 (1.1%)
Cyclophosphamide Equivalent Dose (mg/m ²)						
None	16283 (47.8%)	5332 (56.6%)	5961 (45.2%)	4991 (43.6%)	14552 (48.4%)	1731 (43.7%)
0 - <4,000	4323 (12.7%)	665 (7.1%)	1973 (15.0%)	1684 (14.7%)	3880 (12.9%)	443 (11.2%)
≥4000-<8000	4502 (13.2%)	822 (8.7%)	1789 (13.6%)	1891 (16.5%)	4097 (13.6%)	405 (10.2%)
≥8000-<12,000	3527 (10.4%)	827 (8.8%)	1514 (11.5%)	1186 (10.4%)	3129 (10.4%)	398 (10.1%)
≥12,000-<16,000	2190 (6.4%)	668 (7.1%)	980 (7.4%)	542 (4.7%)	1810 (6.0%)	380 (9.6%)
≥16,000-<20,000	1267 (3.7%)	435 (4.6%)	499 (3.8%)	333 (2.9%)	1043 (3.5%)	223 (5.6%)
≥20,000	1941 (5.7%)	666 (7.1%)	466 (3.5%)	808 (7.1%)	1563 (5.2%)	378 (9.6%)
Epipodophyllotoxin (mg/m ²)						
Yes	5712 (16.8%)	206 (2.2%)	1798 (13.6%)	3708 (32.4%)	5048 (16.8%)	664 (16.8%)
No	28321 (83.2%)	9210 (97.8%)	11383 (86.4%)	7728 (67.6%)	25026 (83.2%)	3295 (83.2%)
Bleomycin						
Yes	2358 (6.9%)	271 (2.9%)	1153 (8.7%)	935 (8.2%)	2059 (6.8%)	299 (7.6%)
No	31675 (93.1%)	9145 (97.1%)	12028 (91.3%)	10501 (91.8%)	28015 (93.2%)	3659 (92.4%)
Platinum						
Yes	3757 (11.0%)	116 (1.2%)	1345 (10.2%)	2296 (20.1%)	3205 (10.7%)	552 (13.9%)
No	30277 (89.0%)	9301 (98.8%)	11836 (89.8%)	9140 (79.9%)	26870 (89.3%)	3407 (86.1%)
Methotrexate IV (mg/m ²)						
None	26963 (79.2%)	8052 (85.5%)	10187 (77.3%)	8724 (76.3%)	23744 (78.9%)	3219 (81.3%)
>0-<5000	3753 (11.0%)	923 (9.8%)	1661 (12.6%)	1169 (10.2%)	3322 (11.0%)	430 (10.9%)
≥5000	3318 (9.7%)	442 (4.7%)	1332 (10.1%)	1544 (13.5%)	3008 (10.0%)	309 (7.8%)
Methotrexate IT						
Yes	11036 (32.4%)	3090 (32.8%)	4993 (37.9%)	2954 (25.8%)	9834 (32.7%)	1203 (30.4%)
No	22997 (67.6%)	6326 (67.2%)	8189 (62.1%)	8482 (74.2%)	20241 (67.3%)	2756 (69.6%)

Table S2. Distribution of treatment exposure for acute lymphoblastic leukemia, Hodgkin lymphoma, Wilms tumor and astrocytoma across three decades

		1970-1979		1980-1989		1990-1999	
		N	%	N	%	N	%
Acute lymphoblastic leukemia		2652		4922		5472	
Anthracycline (mg/m ²)	None	1870	70.5	2042	41.5	856	15.6
	1-<150	211	7.9	1265	25.7	2758	50.4
	≥150-<300	227	8.6	810	16.4	1477	27.0
	≥300-<450	215	8.1	563	11.4	332	6.1
	≥450-<600	108	4.1	191	3.9	32	0.6
	≥600	21	0.8	51	1.0	17	0.3
Steroid	Prednisone	1659	62.6	3470	70.5	2164	39.5
	Dexamethasone	33	1.2	39	0.8	384	7.0
	Both	56	2.1	789	16.0	2461	45.0
		904	34.1	624	12.7	463	8.5
Epipodophyllotoxin	Yes	96	3.6	1134	23.0	1971	36.0
	No	2556	96.4	3787	77.0	3501	64.0
Cranial RT	None	384	14.5	2409	49.0	4409	80.6
	1-19.9 Gy	480	18.1	1813	36.8	820	15.0
	≥ 20 Gy	1788	67.4	699	14.2	243	4.4
Hodgkin Lymphoma		1597		1465		1270	
Chest RT dose	None	209	13.1	309	21.1	500	39.3
	≥1-<20Gy	23	1.5	48	3.2	36	2.9
	≥20-<30Gy	136	8.5	332	22.6	518	40.8
	≥30Gy	1228	76.9	777	53.1	216	17.0
Splenectomy	Yes	1186	74.3	819	55.9	103	8.1
	No	411	25.7	647	44.1	1167	91.9
Cyclophosphamide Equivalent Dose (mg/m ²)	None	308	45.2	443	47.6	414	40.5
	0-<4000	45	6.7	76	8.2	144	14.1
	≥4000-<8000	63	9.3	180	19.4	225	22.0
	≥8000-<12000	62	9.1	107	11.5	55	5.4
	≥12000-<16000	54	8.0	51	5.5	62	6.0
	≥16000-<20000	55	8.1	31	3.4	55	5.4
	≥20000	93	13.7	42	4.5	67	6.6
Anthracycline (mg/m ²)	None	581	85.4	595	63.9	472	46.2
	1-<150	13	1.9	112	12.1	296	29.0
	≥150-<300	24	3.6	166	17.9	219	21.5
	≥300-<450	41	6.0	46	5.0	25	2.4
	≥450-<600	20	2.9	10	1.1	3	0.3
	≥600	1	0.2	1	0.1	6	0.6
Wilms tumor		814		1173		1068	
Anthracycline (mg/m ²)	None	611	75.0	566	48.3	493	46.2
	1-<150	16	2.0	68	5.8	309	28.9
	≥150-<300	118	14.5	358	30.6	207	19.3
	≥300-<450	62	7.6	167	14.3	56	5.2
	≥450-<600	5	0.6	6	0.5	2	0.2
	≥600	3	0.3	7	0.6	2	0.2
Abdomen RT dose	None	180	22.1	552	47.1	604	56.5
	≥1-<20Gy	80	9.9	264	22.5	411	38.5

	≥ 20 - < 30 Gy	256	31.5	309	26.3	35	3.2
	≥ 30 Gy	297	36.5	48	4.1	19	1.8
Astrocytoma		824		1410		1670	
Cranial RT	Yes	454	55.0	704	49.9	407	24.4
	No	371	45.0	706	50.1	1263	75.6
Any Chemotherapy	Yes	136	16.5	329	23.3	540	32.4
	No	688	83.5	1081	76.7	1130	67.6

Table S3. Cumulative incidence of all-cause, recurrence/progression, and health-related cause late mortality at 15 years from primary cancer diagnosis

	1970-1979			1980-1989			1990-1999			P value
	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	
All cause										
All diagnoses	8406	10.74	10.1 - 11.4	13105	7.86	7.4 - 8.3	3924	5.80	5.4 - 6.3	<.001
All Leukemias	2559	14.22	13.0 - 15.5	5064	8.37	7.6 - 9.1	1657	4.74	4.1 - 5.4	<.001
Acute lymphoblastic leukemia	2300	13.31	12.0 - 14.6	4533	7.92	7.2 - 8.7	1448	4.67	4.0 - 5.3	<.001
Acute myeloid leukemia	169	14.29	9.4 - 19.2	404	7.99	5.5 - 10.5	161	3.55	1.9 - 5.2	<.001
Other leukemia	92	32.09	24.2 - 40.0	129	22.89	16.5 - 29.3	50	10.66	5.1 - 16.2	<.001
All CNS tumors	1051	14.36	12.4 - 16.3	2037	11.26	10.0 - 12.6	746	8.97	7.7 - 10.2	<.001
Astrocytoma	720	12.74	10.5 - 15.0	1283	9.06	7.6 - 10.6	475	6.82	5.4 - 8.3	<.001
Medulloblastoma	179	21.93	16.6 - 27.3	420	15.09	11.9 - 18.3	153	14.06	10.8 - 17.4	0.006
Other CNS tumors	154	12.07	7.2 - 16.9	336	14.32	10.9 - 17.8	121	9.70	6.4 - 13.0	0.03
Hodgkin lymphoma	1428	10.64	9.1 - 12.2	1359	7.30	6.0 - 8.6	317	4.89	3.4 - 6.4	<.001
Non-Hodgkin lymphoma	659	6.67	4.8 - 8.5	1052	4.45	3.2 - 5.7	263	3.78	2.3 - 5.3	0.01
Wilms tumor	785	3.69	2.4 - 5.0	1146	2.39	1.5 - 3.3	310	2.17	1.1 - 3.2	0.12
Neuroblastoma	653	4.12	2.6 - 5.6	887	4.82	3.4 - 6.2	257	6.52	4.8 - 8.2	0.04
Rhabdomyosarcoma	525	4.55	2.8 - 6.3	577	6.19	4.3 - 8.1	152	5.31	3.1 - 7.6	0.47
All Bone tumors	753	12.86	10.6 - 15.1	990	11.58	9.7 - 13.5	227	10.50	8.3 - 12.7	0.46
Ewing sarcoma	224	19.78	15.1 - 24.5	326	14.70	11.1 - 18.3	72	9.48	6.1 - 12.9	0.004
Osteosarcoma	487	9.83	7.3 - 12.3	613	10.34	8.0 - 12.6	141	11.94	8.9 - 15.0	0.34
Other bone tumors	44	6.52	0.0 - 13.7	53	5.45	0.0 - 11.5	16	2.86	0.0 - 8.4	0.55
Recurrence/Progression										
All diagnoses	8406	7.12	6.6 - 7.6	13105	4.89	4.5 - 5.3	3924	3.42	3.1 - 3.8	<.001
All Leukemias	2559	10.98	9.8 - 12.1	5064	5.49	4.9 - 6.1	1657	2.31	1.9 - 2.7	<.001
Acute lymphoblastic leukemia	2300	10.25	9.1 - 11.4	4533	5.23	4.6 - 5.9	1448	2.19	1.8 - 2.6	<.001
Acute myeloid leukemia	169	11.22	6.6 - 15.8	404	4.04	2.1 - 5.9	161	2.07	0.8 - 3.3	<.001
Other leukemia	92	25.00	17.5 - 32.5	129	17.11	11.2 - 23.0	50	6.83	2.1 - 11.6	<.001
All CNS tumors	1051	8.98	7.3 - 10.6	2037	7.49	6.4 - 8.6	746	5.91	4.9 - 6.9	0.003
Astrocytoma	720	7.72	5.8 - 9.6	1283	6.13	4.9 - 7.4	475	4.41	3.2 - 5.6	0.02
Medulloblastoma, PNET	179	16.14	11.3 - 21.0	420	11.08	8.2 - 13.9	153	10.11	7.5 - 12.7	0.05
Other CNS tumors	154	5.57	2.1 - 9.0	336	7.90	5.1 - 10.7	121	5.37	2.9 - 7.8	0.23
Hodgkin lymphoma	1428	5.74	4.6 - 6.9	1359	3.11	2.2 - 4.0	317	2.45	1.4 - 3.5	<.001
Non-Hodgkin lymphoma	659	2.75	1.5 - 4.0	1052	1.34	0.6 - 2.0	263	0.76	0.1 - 1.4	0.003
Wilms tumor	785	1.27	0.5 - 2.0	1146	1.59	0.9 - 2.3	310	1.34	0.6 - 2.1	0.81
Neuroblastoma	653	2.93	1.7 - 4.2	887	3.33	2.2 - 4.5	257	5.22	3.7 - 6.8	0.04
Rhabdomyosarcoma	525	2.22	1.0 - 3.5	577	3.62	2.1 - 5.2	152	3.83	1.8 - 5.8	0.29
All Bone tumors	753	9.15	7.2 - 11.1	990	7.91	6.3 - 9.5	227	7.80	6.0 - 9.6	0.59
Ewing sarcoma	224	14.53	10.3 - 18.7	326	10.89	7.7 - 14.0	72	6.98	4.1 - 9.9	0.02
Osteosarcoma	487	6.66	4.5 - 8.8	613	6.73	4.8 - 8.6	141	9.16	6.6 - 11.8	0.14
Other bone tumors	44	5.87	0.0 - 13.0	53	1.82	0.0 - 5.3	16	0.00	0.0 - 0.0	0.19
Health-related Cause										
All diagnoses	8406	3.11	2.7 - 3.5	13105	2.43	2.2 - 2.7	3924	1.90	1.6 - 2.2	<.001
All Leukemias	2559	2.92	2.3 - 3.6	5064	2.44	2.0 - 2.9	1657	1.88	1.4 - 2.3	<.001
Acute lymphoblastic leukemia	2300	2.76	2.1 - 3.4	4533	2.28	1.8 - 2.7	1448	1.87	1.4 - 2.3	<.001
Acute myeloid leukemia	169	2.35	0.0 - 4.9	404	3.17	1.5 - 4.9	161	1.31	0.3 - 2.3	0.21
Other leukemia	92	7.01	2.4 - 11.6	129	5.18	1.6 - 8.8	50	3.83	0.8 - 6.9	0.56
All CNS tumors	1051	4.80	3.5 - 6.1	2037	3.10	2.4 - 3.8	746	2.69	1.9 - 3.5	0.002
Astrocytoma	720	4.41	2.9 - 5.9	1283	2.44	1.6 - 3.3	475	1.91	1.1 - 2.7	0.01
Medulloblastoma, PNET	179	5.35	2.4 - 8.3	420	3.61	1.9 - 5.3	153	3.77	1.7 - 5.9	0.25
Other CNS tumors	154	5.92	2.4 - 9.5	336	4.86	2.6 - 7.1	121	4.11	1.6 - 6.6	0.34
Hodgkin lymphoma	1428	4.22	3.2 - 5.2	1359	3.43	2.5 - 4.4	317	2.01	0.9 - 3.1	0.02
Non-Hodgkin lymphoma	659	3.38	2.0 - 4.7	1052	2.44	1.5 - 3.4	263	2.24	1.1 - 3.4	0.34
Wilms tumor	785	2.17	1.2 - 3.2	1146	0.62	0.2 - 1.1	310	0.41	0.0 - 0.9	<.001
Neuroblastoma	653	0.87	0.1 - 1.6	887	1.10	0.4 - 1.8	257	1.14	0.4 - 1.9	0.75

Rhabdomyosarcoma	525	1.91	0.7 - 3.1	577	1.99	0.8 - 3.2	152	0.81	0.0 - 1.7	0.35
All Bone tumors	753	2.51	1.4 - 3.6	990	2.97	2.0 - 4.0	227	2.35	1.1 - 3.6	0.61
Ewing sarcoma	224	4.42	1.9 - 6.9	326	3.41	1.6 - 5.3	72	1.89	0.2 - 3.6	0.28
Osteosarcoma	487	1.74	0.5 - 3.0	613	2.66	1.4 - 3.9	141	2.53	0.8 - 4.2	0.63
Other bone tumors	44	0.00	0.0 - 0.0	53	3.64	0.0 - 8.6	16	2.86	0.0 - 8.4	0.43

Table S4. Frequencies of underlying cause of death in five-year survivors of childhood cancer			
Category of Death	Underlying Cause of Death	ICD-9/ICD-10 Code	Number of Deaths
Recurrence	Acute Leukemia	2040	392
	Brain, unspecified- Malignant neoplasms	1919	162
	Hodgkin's disease, unspecified- Malignant neoplasms	2019	154
	Bone and articular cartilage, site unspecified- Malignant neoplasms	1709	142
	Brain, unspecified - Malignant neoplasms	C719	80
	Cerebellum NOS- Malignant neoplasms	1916	79
	Bone and articular cartilage, unspecified – Malignant neoplasms	C419	60
	Unspecified leukemia- Malignant neoplasms	2089	58
	Acute leukemia, unspecified- Malignant neoplasms	2080	46
	Adrenal gland- Malignant neoplasms	1940	45
	Connective and other soft tissue, site unspecified- Malignant neoplasms	1719	41
	Acute lymphoblastic leukemia - Malignant neoplasms	C910	36
	Kidney, except pelvis- Malignant neoplasms	1890	36
	Other lymphomas- Malignant neoplasms	2028	36
	Adrenal gland, unspecified - Malignant neoplasms	C749	32
	Chronic leukemia- Malignant neoplasms	2051	30
	Cerebellum - Malignant neoplasms	C716	27
	Hodgkin's disease, unspecified - Malignant neoplasms	C819	27
	Acute Myeloid leukemia- Malignant neoplasms	2050	24
	Brain stem- Malignant neoplasms	1917	19
	Cerebrum, except lobes and ventricles	1910	19
	Malignant neoplasm without specification of site	1991	19
	Bronchus and lung, unspecified- Malignant neoplasms	1629	12
	Unspecified lymphoid leukemia- Malignant neoplasms	2049	12
	Leukemia, unspecified - Malignant neoplasms	C959	11
	Brain stem - Malignant neoplasms	C717	10
	Cranial nerves- Malignant neoplasms	1920	10
	Malignant neoplasm of kidney, except renal pelvis	C64	9
	Connective and soft tissue, unspecified – Malignant neoplasms	C499	8
	Long bones of lower limb- Malignant neoplasms	1707	8
	Chronic myeloid leukemia - Malignant neoplasms	C921	7
	Malignant neoplasm without specification of site	C80	7
	Acute myeloid leukemia - Malignant neoplasms	C920	6
	Malignant neoplasm of lymphatic and hematopoietic tissue	208	6
	Non-Hodgkin's lymphoma, unspecified type – Malignant neoplasms	C859	6
	Malignant neoplasms of independent (primary) multiple sites	C97	5

Nodular sclerosis- Malignant neoplasms	2015	5
Pelvis- Malignant neoplasms	1716	5
Pineal gland- Malignant neoplasms	1944	5
Cerebral meninges- Malignant neoplasms	1921	4
Cerebrum, except lobes and ventricles – Malignant neoplasms	C710	4
Nasopharynx, unspecified- Malignant neoplasms	1479	4
Peripheral nerves and autonomic nervous system, unspecified-Malignant neoplasms	C479	4
Vertebral column, excluding sacrum and coccyx- Malignant neoplasms	1702	4
Acute leukemia of unspecified cell type – Malignant neoplasms	C950	3
Frontal lobe- Malignant neoplasms	1911	3
Long bones of lower limb - Malignant neoplasms	C402	3
Malignant neoplasm of other and unspecified sites	199	3
Spinal cord- Malignant neoplasms	1922	3
Testis, unspecified - Malignant neoplasms	C629	3
Bladder, part unspecified- Malignant neoplasms	1889	2
Bones of skull and face, except mandible- Malignant neoplasms	1700	2
Malignant neoplasm of uterus, part unspecified	179	2
Mediastinum, part unspecified- Malignant neoplasms	1649	2
Nervous system, part unspecified- Malignant neoplasms	1929	2
Orbit- Malignant neoplasms	1901	2
Parietal lobe- Malignant neoplasms	1913	2
Pelvic bones, sacrum and coccyx - Malignant neoplasms	C414	2
Pelvic bones, sacrum, and coccyx- Malignant neoplasms	1706	2
Pituitary gland and craniopharyngeal duct- Malignant neoplasms	1943	2
Spinal cord - Malignant neoplasms	C720	2
Temporal lobe- Malignant neoplasms	1912	2
Ventricles- Malignant neoplasms	1915	2
Bladder, unspecified - Malignant neoplasms	C679	1
Brain, unspecified - Uncertain neoplasms	D432	1
Breast (female), unspecified	1749	1
Bronchus or lung, unspecified - Malignant neoplasms	C349	1
Cardia- Malignant neoplasms	1510	1
Central nervous system, unspecified - Malignant neoplasms	C729	1
Cerebral meninges - Malignant neoplasms	C700	1
Cervix uteri, unspecified- Malignant neoplasms	1809	1
Chronic Lymphoid leukemia - Malignant neoplasms	2041	1
Chronic Leukemia of unspecified cell type - Malignant neoplasms	2081	1
Chronic leukemia of unspecified cell type - Malignant	C951	1

	Colon, unspecified- Malignant neoplasms	1539	1
	Connective and soft tissue of lower limb,	C492	1
	Connective and soft tissue of thorax - Malignant	C493	1
	Frontal lobe - Malignant neoplasms	C711	1
	Head, face, and neck- Malignant neoplasms	1710	1
	Lymphocytic predominance - Malignant neoplasms	C810	1
	Megakaryocytic leukemia- Malignant neoplasms	2072	1
	Mixed cellularity- Malignant neoplasms	2016	1
	Mouth, unspecified- Malignant neoplasm	1459	1
	Nodular lymphoma- Malignant neoplasm	2020	1
	Other and unspecified T-cell lymphomas – Malignant neoplasm	C845	1
	Other and unspecified malignant neoplasm	2029	1
	Overlapping lesion of brain - Malignant neoplasms	C718	1
	Pharynx, unspecified- Malignant neoplasms	1490	1
	Rectum- Malignant neoplasms	1541	1
	Retina- Malignant neoplasms	1905	1
	Retroperitoneum- Malignant neoplasms	1580	1
	Retroperitoneum - Malignant neoplasms	C480	1
	Short bones of lower limb - Malignant neoplasms	C403	1
	Stomach, unspecified- Malignant neoplasms	1519	1
	Thorax- Malignant neoplasms	1951	1
	Unknown	Unknown	210
Subsequent neoplasm	Brain-Neoplasms of unspecified nature	2396	62
	Brain, unspecified- Malignant neoplasms	1919	49
	Acute Myeloid leukemia	2050	35
	Brain, unspecified - Malignant neoplasms	C719	35
	Breast (female), unspecified- Malignant neoplasms	1749	35
	Connective and other soft tissue, site unspecified- Malignant neoplasms	1719	33
	Bone and articular cartilage, site unspecified- Malignant neoplasms	1709	26
	Bronchus and lung, unspecified- Malignant neoplasms	1629	19
	Malignant neoplasms of independent (primary) multiple sites	C97	15
	Breast, unspecified - Malignant neoplasms	C509	13
	Hodgkin's disease, unspecified- Malignant neoplasms	2019	13
	Bone and articular cartilage, unspecified – Malignant neoplasms	C419	12
	Bronchus or lung, unspecified - Malignant neoplasms	C349	12
	Other lymphomas- Malignant neoplasms	2028	12
	Acute myeloid leukemia - Malignant neoplasms	C920	10
	Connective and soft tissue, unspecified – Malignant neoplasms	C499	10
	Malignant neoplasm without specification of site	1991	10

	Stomach, unspecified- Malignant neoplasms	1519	10
	Colon, unspecified- Malignant neoplasms	1539	9
	Malignant neoplasm without specification of site	C80	9
	Acute Lymphoid leukemia - Malignant neoplasms	2040	7
	Brain and spinal cord neoplasms of uncertain behavior	2375	7
	Unspecified leukemia- Malignant neoplasms	2089	7
	Colon, unspecified - Malignant neoplasms	C189	6
	Lymphosarcoma- Malignant neoplasms	2001	6
	Melanoma of skin, site unspecified- Malignant neoplasms	1729	6
	Neurofibromatosis	2377	5
	Acute Leukemia of unspecified cell type	2080	4
	Cerebellum nos- Malignant neoplasms	1916	4
	Cerebral meninges-benign neoplasm	2252	4
	Hodgkin's disease, unspecified - Malignant neoplasm	C819	4
	Kidney, except pelvis- Malignant neoplasms	1890	4
	Liver, not specified as primary or secondary	1552	4
	Malignant neoplasm of kidney, except renal pelvis	C64	4
	Malignant neoplasm of other and unspecified sites	199	4
	Mesothelioma, unspecified - Malignant neoplasms	C459	4
	Non-Hodgkin's lymphoma, unspecified type – Malignant neoplasms	C859	4
	Reticulosarcoma- Malignant neoplasms	2000	4
	Acute lymphoblastic leukemia - Malignant neoplasm	C910	3
	Adrenal gland, unspecified - Malignant neoplasms	C749	3
	Bladder, part unspecified- Malignant neoplasms	1889	3
	Cerebellum - Malignant neoplasms	C716	3
	Endocrine glands and other parts of nervous system	2397	3
	Leukemia, unspecified - Malignant neoplasms	C959	3
	Malignant melanoma of skin, unspecified - Malignant neoplasms	C439	3
	Other and unspecified testis- Malignant neoplasms	1869	3
	Pancreas, part unspecified- Malignant neoplasms	1579	3
	Adrenal gland- Malignant neoplasms	1940	2
	Bones of skull and face, except mandible- Malignant neoplasms	1700	2
	Brain stem - Malignant neoplasms	C717	2
	Cerebral meninges - Benign neoplasms	D320	2
	Cerebrum, except lobes and ventricles- Malignant neoplasms	1910	2
	Esophagus, unspecified- Malignant neoplasms	1509	2
	Head, face and neck - Malignant neoplasms	C760	2
	Liver cell carcinoma - Malignant neoplasms	C220	2

	Malignant neoplasm of digestive organs and peritoneum	155	2
	Malignant neoplasm of ovary	C56	2
	Malignant neoplasm of thyroid gland	C73	2
	Esophagus, unspecified - Malignant neoplasms	C159	2
	Ovary- Malignant neoplasms	1830	2
	Pancreas, unspecified - Malignant neoplasms	C259	2
	Pelvic bones, sacrum, and coccyx- Malignant neoplasms	1706	2
	Site unspecified benign neoplasm	2299	2
	Spinal cord- Malignant neoplasms	1922	2
	Spinal cord - Malignant neoplasms	C720	2
	Tongue, unspecified- Malignant neoplasms	1419	2
	Unspecified myeloid leukemia- Malignant neoplasms	2059	2
	Abdomen- Malignant neoplasms	1715	1
	Accessory sinus, unspecified- Malignant neoplasms	1609	1
	Accessory sinus, unspecified - Malignant neoplasms	C319	1
	Acute Monocytic Leukemia- Malignant neoplasms	2060	1
	Acute leukemia of unspecified cell type - Malignant neoplasms	C950	1
	Acute promyelocytic leukemia - Malignant neoplasms	C924	1
	Auditory tube, middle ear, and mastoid air cells- Malignant neoplasms	1601	1
	Base of tongue- Malignant neoplasms	1410	1
	Biliary tract, part unspecified- Malignant neoplasms	1569	1
	Bone, soft tissue, and skin-neoplasms of unspecified nature	2392	1
	Brain stem- Malignant neoplasms	1917	1
	Burkitt's tumor or lymphoma- Malignant neoplasms	2002	1
	Central nervous system, unspecified - Malignant neoplasms	C729	1
	Cerebral meninges- Malignant neoplasms	1921	1
	Cerebrum, except lobes and ventricles - Malignant neoplasms	C710	1
	Chronic myeloid leukemia	2051	1
	Chronic myeloid leukaemia - Malignant neoplasms	C921	1
	Colon, unspecified - Benign neoplasms	D126	1
	Connective and soft tissue of head, face and neck - Malignant neoplasms	C490	1
	Connective and soft tissue of pelvis - Malignant neoplasms	C495	1
	Corpus uteri, except isthmus- Malignant neoplasms	1820	1
	Cranial nerves benign neoplasms	2251	1
	Digestive system neoplasm of unspecified nature	2390	1
	Duodenum - Malignant neoplasms	C170	1
	Heart benign neoplasm	2127	1
	Ill-defined sites within the digestive system - Malignant neoplasms	C269	1
	Intrahepatic bile duct carcinoma - Malignant neoplasms	C221	1

	Liver, primary- Malignant neoplasms	1550	1
	Lymphoblastic (diffuse) - Malignant neoplasms	C835	1
	Malignant neoplasm of gallbladder	C23	1
	Malignant neoplasm of male breast	175	1
	Malignant neoplasm of other and unspecified sites	191	1
	Malignant neoplasm of other and unspecified sites	195	1
	Malignant neoplasm of other and unspecified sites	1985	1
	Malignant neoplasm of rectosigmoid junction	C19	1
	Malignant neoplasm of rectum	C20	1
	Malignant neoplasm of renal pelvis	C65	1
	Malignant neoplasm of respiratory and intrathoracic organs	164	1
	Malignant neoplasm of uterus, part unspecified	C55	1
	Mediastinum benign neoplasm	2125	1
	Megakaryocytic leukemia- Malignant neoplasms	2072	1
	Meninges, unspecified - Benign neoplasms	D329	1
	Meninges, unspecified - Malignant neoplasms	C709	1
	Mesothelioma of other sites - Malignant neoplasms	C457	1
	Mesothelioma of pericardium - Malignant neoplasms	C452	1
	Mouth, unspecified- Malignant neoplasms	1459	1
	Myeloid leukemia, unspecified - Malignant neoplasms	C929	1
	Nasopharynx, unspecified- Malignant neoplasms	1479	1
	Occipital lobe - Malignant neoplasms	C714	1
	Oropharynx, unspecified - Malignant neoplasms	C109	1
	Other and unspecified T-cell lymphomas - Malignant neoplasms	C845	1
	Other lymphatic and hematopoietic tissues	2387	1
	Other named variants- Malignant neoplasms	2008	1
	Other specified sites- Malignant neoplasms	1958	1
	Other specified sites neoplasms of unspecified nature	2398	1
	Parotid gland- Malignant neoplasms	1420	1
	Pelvis- Malignant neoplasms	1716	1
	Peripheral nerves and autonomic nervous system - Benign neoplasms	D361	1
	Peripheral nerves and autonomic nervous system, unspecified - Malignant neoplasms	C479	1
	Pineal gland neoplasms of uncertain behavior	2371	1
	Pleura, unspecified- Malignant neoplasms	1639	1
	Ribs, sternum, and clavicle- Malignant neoplasms	1703	1
	Secondary malignant neoplasm of bone and bone marrow - Malignant neoplasms	C795	1
	Secondary malignant neoplasm of brain and cerebral meninges - Malignant neoplasms	C793	1
	Secondary malignant neoplasm of other specified sites - Malignant neoplasms	C798	1

	Skin of lower limb, including hip- Malignant neoplasms	1737	1
	Skin of scalp and neck - Malignant neoplasms	C444	1
	Small intestine, unspecified- Malignant neoplasms	1529	1
	Small intestine, unspecified - Malignant neoplasms	C179	1
	Specified parts of peritoneum- Malignant neoplasms	1588	1
	Stomach, unspecified - Malignant neoplasms	C169	1
	Temporal lobe- Malignant neoplasms	1912	1
	Tonsil, unspecified - Malignant neoplasms	C099	1
	Unspecified lymphoid leukemia- Malignant neoplasms	2049	1
	Upper limb, including shoulder- Malignant neoplasms	1712	1
	Unknown	Unknown	87
Cardiac causes	Other primary cardiomyopathies	4254	30
	Acute myocardial infarction	410	24
	Coronary atherosclerosis	4140	11
	Atherosclerotic heart disease	I251	10
	Cardiac arrest	4275	10
	Secondary cardiomyopathy, unspecified	4259	10
	Congestive heart failure	4280	8
	Cardiomyopathy, unspecified	I429	7
	Acute myocardial infarction, unspecified	I219	6
	Chronic ischemic heart disease, unspecified	4149	6
	Dilated cardiomyopathy	I420	5
	Heart disease, unspecified	4299	5
	Cardiovascular disease, unspecified	4292	4
	Endocarditis, valve unspecified	4249	4
	Other forms of heart disease	425	4
	Aortic valve disorders	4241	3
	Atherosclerotic cardiovascular disease, so described	I250	3
	Congestive heart failure	I500	3
	Heart disease, unspecified	I519	3
	Myocarditis, unspecified	4290	3
	Other restrictive cardiomyopathy	I425	3
	Primary pulmonary hypertension	4160	3
	Pulmonary embolism and infarction	4151	3
	Pulmonary embolism without mention of acute cor pulmonale	I269	3
	Aortic valve disorder, unspecified	I359	2
	Cardiac arrest, unspecified	I469	2
	Cardiac arrhythmia, unspecified	I499	2
	Cardiac dysrhythmia, unspecified	4279	2

	Cardiomegaly	I517	2
	Cardiomyopathy due to drugs and other external agents	I427	2
	Endocarditis, valve unspecified	I38	2
	Mitral (valve) insufficiency	I340	2
	Myocarditis, unspecified	I514	2
	Other acute and subacute forms of ischemic heart disease	411	2
	Other and unspecified rheumatic aortic diseases	3959	2
	Other secondary pulmonary hypertension	I272	2
	Acute and subacute infective endocarditis	I330	1
	Constrictive pericarditis	4232	1
	Disorders of both mitral and aortic valves	I080	1
	Heart failure, unspecified	I509	1
	Hypertrophic obstructive cardiomyopathy	4251	1
	Ischemic heart disease	414	1
	Kyphoscoliotic heart disease	4161	1
	Mitral (valve) prolapse	I341	1
	Mitral stenosis	3940	1
	Mitral valve disease, unspecified	I059	1
	Mitral valve disorders	4240	1
	Other and unspecified rheumatic heart diseases	3989	1
	Other hypertrophic cardiomyopathy	I422	1
	Other specified forms of chronic ischemic heart disease	4148	1
	Primary pulmonary hypertension	I270	1
	Supraventricular tachycardia	I471	1
	Unspecified hypertensive heart disease	4029	1
	Unspecified disease of pericardium	4239	1
	Acute and subacute bacterial endocarditis	4210	1
	Unknown	Unknown	27
Pulmonary causes	Pneumonia, organism unspecified	486	18
	Postinflammatory pulmonary fibrosis	515	12
	Pneumonia, unspecified	J189	10
	Other specified alveolar and parietoalveolar pneumonopathies	5168	8
	Due to inhalation of food or vomitus	5070	5
	Other interstitial pulmonary diseases with fibrosis	J841	5
	Pulmonary insufficiency following trauma and surgery	5185	5
	Chronic and other pulmonary manifestations due to radiation	5081	4
	Other diseases of lung	5188	4
	Adult respiratory distress syndrome	J80	3
	Bronchopneumonia, organism unspecified	485	3

	Chronic airway obstruction, not elsewhere classified	496	3
	Chronic obstructive pulmonary disease, unspecified	J449	3
	Other disorders of lung	J984	3
	Pneumonitis due to food and vomit	J690	3
	Interstitial pulmonary disease, unspecified	J849	2
	Other chronic bronchitis	4918	2
	Pneumococcal pneumonia [streptococcus pneumoniae pneumonia]	481	2
	Pneumonia due to Streptococcus pneumoniae	J13	2
	Pneumonia due to pseudomonas	4821	2
	Pneumonia due to streptococcus	4823	2
	Viral pneumonia, unspecified	4809	2
	Hypertrophy of tonsils	J351	1
	Idiopathic fibrosing alveolitis	5163	1
	Influenza with other respiratory manifestations, virus not identified	J111	1
	Lobar pneumonia, unspecified	J181	1
	Other acute sinusitis	4618	1
	Other chronic sinusitis	4738	1
	Other diseases of mediastinum, not elsewhere classified	5193	1
	Other diseases of respiratory system	516	1
	Other diseases of vocal cords	J383	1
	Other specified chronic obstructive pulmonary disease	J448	1
	Other specified forms of effusion, except tuberculous	5118	1
	Pleural effusion, not elsewhere classified	J90	1
	Pulmonary alveolar proteinosis	5160	1
	Pulmonary congestion and hypostasis	514	1
	Respiratory failure, unspecified	J969	1
	Unspecified pleural effusion	5119	1
	Without mention of fistula	5109	1
	Unknown	Unknown	17
Other causes	Brain, unspecified - Uncertain neoplasms	D432	26
	Unspecified septicemia	389	9
	Intracerebral hemorrhage	431	8
	Septicemia, unspecified	A419	8
	Acquired immunodeficiency syndrome with or without other conditions	429	7
	Other specified viral hepatitis without mention of hepatic coma	705	7
	Diabetes mellitus without mention of complication	2500	6
	Other ill-defined and unspecified causes of mortality	R99	6
	Other unknown and unspecified cause	7999	6
	Pneumocystosis	1363	6

	Cirrhosis of liver without mention of alcohol	5715	5
	Diseases of arteries, arterioles, and capillaries	440	5
	Obstructive hydrocephalus	3314	5
	Other ill-defined conditions	7998	5
	Other specified diseases of blood and blood-forming organs	2898	5
	Acute pancreatitis	5770	4
	Cytomegaloviral disease	785	4
	HTLV-III/LAV infection causing other specified infections	421	4
	Kyphoscoliosis and scoliosis	7373	4
	Myelodysplastic syndrome, unspecified - Uncertain neoplasms	D469	4
	Neurofibromatosis (nonmalignant)	Q850	4
	Renal failure, unspecified	586	4
	Sequelae of viral hepatitis	B942	4
	Stroke, not specified as hemorrhage or infarction	I64	4
	Unspecified renal failure	N19	4
	Alcoholic cirrhosis of liver	5712	3
	Brain, infratentorial - Uncertain neoplasms	D431	3
	Cerebral artery occlusion, unspecified	4349	3
	Chickenpox	52	3
	Chronic viral hepatitis C	B182	3
	End-stage renal disease	N180	3
	Hemorrhage of gastrointestinal tract, unspecified	5789	3
	Hypopituitarism	E230	3
	Intracerebral hemorrhage, unspecified	I619	3
	Other and unspecified convulsions	R568	3
	Other and unspecified mycoses	1179	3
	Other specified disorders of liver	5738	3
	Tetraplegia, unspecified	G825	3
	Acute renal failure, unspecified	N179	2
	Acute, but ill-defined, cerebrovascular disease	436	2
	Agranulocytosis	2880	2
	Alcohol dependence syndrome	303	2
	Aspergillosis	1173	2
	Brain, supratentorial - Uncertain neoplasms	D430	2
	Diabetes with ketoacidosis	2501	2
	Disease of gallbladder, unspecified	K829	2
	Disseminated	1125	2
	Down's syndrome, unspecified	Q909	2
	Dyspnea and respiratory abnormalities	7860	2

	Encephalopathy, unspecified	3483	2
	Generalized and unspecified atherosclerosis	I709	2
	HTLV-III/LAV infection with specified malignant neoplasms	422	2
	Human immunodeficiency virus infection	449	2
	Infantile cerebral palsy, unspecified	G809	2
	Intestinal infectious diseases	79	2
	Meningitis due to unspecified bacterium	3209	2
	Other and unspecified cirrhosis of liver	K746	2
	Portal hypertension	5723	2
	Scoliosis, unspecified	M419	2
	Septicemia due to Streptococcus pneumoniae	A403	2
	Septicemia due to other Gram-negative organisms	A415	2
	Septicemia due to other gram-negative organisms	384	2
	Status epilepticus, unspecified	G419	2
	Streptococcal septicemia	380	2
	Subarachnoid hemorrhage, unspecified	I609	2
	Subarachnoid hemorrhage	430	2
	Systemic sclerosis	7101	2
	Thrombocytopenia, unspecified	2875	2
	Tuberous sclerosis	7595	2
	Unspecified	4019	2
	Unspecified anomaly of heart	7469	2
	Unspecified disorder of kidney and ureter	5939	2
	Unspecified site	5559	2
	Urinary tract infection, site not specified	5990	2
	Acute hepatitis B without delta-agent and without hepatic coma	B169	1
	Acute hepatitis C	B171	1
	Acute pancreatitis	K85	1
	Acute renal failure, unspecified	5849	1
	Adenovirus	790	1
	Agranulocytosis	D70	1
	Alcohol abuse	3050	1
	Alcohol withdrawal delirium	2910	1
	Alcoholic cirrhosis of liver	K703	1
	Alcoholic hepatic failure	K704	1
	Anomalies of spleen	7590	1
	Anoxic brain damage, not elsewhere classified	G931	1
	Aortic aneurysm of unspecified site, ruptured	I718	1
	Aplastic anemia, unspecified	2849	1

	Appendicitis, unqualified	541	1
	Arteritis, unspecified	I776	1
	Autoimmune disease, not elsewhere classified	2794	1
	Bipolar affective disorder, unspecified	F319	1
	Budd-chiari syndrome	4530	1
	Calculus of gallbladder without cholecystitis	K802	1
	Candidal septicemia	B377	1
	Carotid artery	4331	1
	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	I632	1
	Cerebral infarction, unspecified	I639	1
	Chromosomal abnormality, unspecified	Q999	1
	Chronic or unspecified with perforation	5325	1
	Chronic renal failure	585	1
	Chronic renal failure, unspecified	N189	1
	Cocaine abuse	3056	1
	Congenital factor viii disorder	2860	1
	Congenital insufficiency of aortic valve	7464	1
	Congenital malformations of spleen	Q890	1
	Connective and other soft tissue - Uncertain neoplasms	D481	1
	Constitutional aplastic anemia	2840	1
	Cord compression, unspecified	G952	1
	Creutzfeldt-Jakob disease - CJD	461	1
	Crohn's disease, unspecified	K509	1
	Cutaneous abscess, furuncle and carbuncle of buttock	L023	1
	Cystic fibrosis with pulmonary manifestations	E840	1
	Cystic fibrosis, unspecified	E849	1
	Cystitis, unspecified	N309	1
	Defibrination syndrome	2866	1
	Deficiency of cell-mediated immunity	2791	1
	Degenerative disease of nervous system, unspecified	G319	1
	Diabetes with neurological manifestations	2506	1
	Disease of blood and blood-forming organs, unspecified	D759	1
	Disease of spleen, unspecified	D739	1
	Disorder of kidney and ureter, unspecified	N289	1
	Disorder of vein, unspecified	I879	1
	Disorders of thyroid gland	240	1
	Disorders of urea cycle metabolism	E722	1
	Down's syndrome	7580	1

	Eating disorder, unspecified	F509	1
	Encephalopathy, unspecified	G934	1
	Eosinophilia	2883	1
	Epilepsy, unspecified	3459	1
	Esophageal varices with bleeding	4560	1
	Essential (primary) hypertension	I10	1
	Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforation	K259	1
	Gastroenteritis and colitis due to radiation	K520	1
	Gastrointestinal hemorrhage, unspecified	K922	1
	HIV disease resulting in multiple infections	B207	1
	HIV disease resulting in other infectious and parasitic diseases	B208	1
	Hemorrhage, unspecified	4590	1
	Hepatic coma	5722	1
	Hepatitis, unspecified	5733	1
	Hepatorenal syndrome	5724	1
	Hereditary progressive muscular dystrophy	3591	1
	Herpes simplex without mention of complication	549	1
	Hydrocephalus, unspecified	G919	1
	Hyperosmolality and/or hypernatremia	2760	1
	Hyperpotassemia	2767	1
	Hypertensive disease	403	1
	Hypertensive renal disease with renal failure	I120	1
	Hypoplasia and dysplasia of lung	Q336	1
	Hypotension, unspecified	4589	1
	Ileus, unspecified	K567	1
	Ill-defined and unknown causes of morbidity and mortality	799	1
	Immunodeficiency following hereditary defective response to	D823	1
	Infantile cerebral palsy, unspecified	3439	1
	Infectious mononucleosis	75	1
	Insulin-dependent diabetes mellitus, without complications	E109	1
	Intracranial and intraspinal phlebitis and thrombophlebitis	G08	1
	Intracranial hemorrhage (nontraumatic), unspecified	I629	1
	Ischaemic infarction of muscle	M622	1
	Late effects of cerebrovascular disease	438	1
	Meninges, unspecified - Uncertain neoplasms	D429	1
	Meningitis, unspecified	3229	1
	Meningococcal meningitis	360	1
	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances, harmful use	F191	1

	Mental and behavioural disorders due to use of alcohol, dependence syndrome	F102	1
	Motor neuron disease	3352	1
	Multiple sclerosis	340	1
	Myoclonus	3332	1
	Myotonic disorders	3592	1
	Necrotizing fasciitis	M726	1
	Neoplasm of uncertain or unknown behaviour of lymphoid, haematopoietic and related tissue, unspecified - Uncertain neoplasms	D479	1
	Neuronal ceroid lipofuscinosis	E754	1
	Obesity	2780	1
	Obesity, unspecified	E669	1
	Obstructive and reflux uropathy, unspecified	N139	1
	Esophageal varices with bleeding	I850	1
	Of deep vessels of lower extremities	4511	1
	Of unspecified site	1129	1
	Of vena cava	4532	1
	Opioid type dependence	3040	1
	Other and unspecified complications of the puerperium, not elsewhere classified	674	1
	Other and unspecified intestinal obstruction	K566	1
	Other and unspecified special symptoms or syndromes, not elsewhere classified	3079	1
	Other anomalies of aorta	7472	1
	Other anomalies of ribs and sternum	7563	1
	Other autoimmune haemolytic anaemias	D591	1
	Other conditions of brain	3488	1
	Other diseases of spleen	2895	1
	Other forms of systemic sclerosis	M348	1
	Other histiocytosis syndromes	D763	1
	Other pulmonary aspergillosis	B441	1
	Other sequelae of chronic liver disease	5728	1
	Other specified anomalies of muscle, tendon, fascia, and connective tissue	7568	1
	Other specified anomalies of spinal cord	7425	1
	Other specified congenital malformations	Q898	1
	Other specified diseases and conditions complicating pregnancy, childbirth and the puerperium	O998	1
	Other specified diseases of oesophagus	K228	1
	Other specified disorders of biliary tract	5768	1
	Other specified disorders of brain	G938	1
	Other specified disorders of intestine	5698	1
	Other specified disorders of metabolism	2778	1

	Other specified disorders of stomach and duodenum	5378	1
	Other specified general symptoms and signs	R688	1
	Other specified infectious and parasitic diseases	1368	1
	Other specified intestinal obstruction	5608	1
	Other specified sites - Uncertain neoplasms	D487	1
	Other spinocerebellar diseases	3348	1
	Other suppurative peritonitis	5672	1
	Other symptoms involving nervous and musculoskeletal systems	7819	1
	Pectus excavatum	Q676	1
	Pneumococcal septicemia [streptococcus pneumoniae septicemia]	382	1
	Polymyositis	7104	1
	Postmeasles pneumonia	551	1
	Quadriplegia and quadriplegia	3440	1
	Secondary thrombocytopenia	2874	1
	Septicemia due to Staphylococcus aureus	A410	1
	Sickle-cell anemia	2826	1
	Sleep apnea	G473	1
	Spinal muscular atrophy	3351	1
	Staphylococcus	411	1
	Streptococcal infection, unspecified	A491	1
	Subarachnoid hemorrhage	4301	1
	Subdural hemorrhage	4321	1
	Systemic lupus erythematosus, unspecified	M329	1
	Thoracic aneurysm, ruptured	4411	1
	Thrombotic microangiopathy	4466	1
	Unspecified	4379	1
	Unspecified cause of encephalitis	3239	1
	Unspecified diabetes mellitus, with ketoacidosis	E141	1
	Unspecified diseases due to mycobacteria	319	1
	Unspecified diseases of blood and blood-forming organs	2899	1
	Unspecified hemorrhagic conditions	2879	1
	Unspecified human immunodeficiency virus [HIV] disease	B24	1
	Unspecified immunity deficiency	2793	1
	Unspecified intestinal obstruction	5609	1
	Unspecified intracranial hemorrhage	4329	1
	Unspecified mental retardation	F79	1
	Unspecified mycosis	B49	1
	Unspecified peritonitis	5679	1
	Unspecified senile psychotic condition	2909	1

	Unspecified viral and chlamydial infections	799	1
	Unspecified viral encephalitis	A86	1
	Vascular disorder of intestine, unspecified	K559	1
	Viral encephalitis transmitted by other and unspecified arthropods	64	1
	Waterhouse-Friderichsen syndrome	A391	1
	With lesion of tubular necrosis	5845	1
	Unknown	Unknown	57
External causes	Person injured in unspecified motor-vehicle accident, traffic	V892	13
	Driver of motor vehicle other than motor	E8160	9
	Other and unspecified firearm	E9554	9
	Unspecified drugs	E8589	9
	Driver of motor vehicle other than motorcycle	E8120	8
	Motor vehicle traffic accidents	E812	8
	Handgun	E9550	7
	Motor vehicle traffic accidents	E819	7
	Other and unspecified firearm	E9654	7
	Pedestrian	E8147	7
	Unspecified person of motor vehicle traffic accident of unspecified nature	E8199	7
	Assault by other and unspecified firearm discharge	X95	6
	Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent	Y14	6
	Shotgun	E9551	6
	Driver of motor vehicle other than motorcycle	E8150	5
	Other specified procedures	E8798	5
	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	X42	4
	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances	X44	4
	Exposure to unspecified factor	X59	4
	Intentional self-harm by other and unspecified firearm discharge	X74	4
	Other medical procedures	Y848	4
	Passenger in motor vehicle other than motorcycle	E8121	4
	Unspecified person	E8159	4
	Car occupant injured in collision with car, pick-up truck or van, passenger injured in traffic accident	V436	3
	Motor vehicle traffic accidents	E818	3
	Other and unspecified fall	E888	3
	Passenger in motor vehicle other than mo	E8161	3
	Person injured in collision between other specified motor vehicles (traffic)	V877	3
	Striking by blunt or thrown object	E9682	3
	Suicide and self-inflicted injury	E955	3
	Unspecified suicide and self-inflicted injury	E9559	3

	Unspecified fall	W19	3
	Unspecified firearm missile	E9229	3
	Unspecified person of other motor vehicle traffic accident involving collision with motor vehicle	E8129	3
	Unspecified person of other noncollision motor vehicle traffic accident	E8189	3
	Accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics	X40	2
	Burning caused by conflagration	E8903	2
	Car occupant injured in collision with car, pick-up truck or van, driver injured in traffic accident	V435	2
	Car occupant injured in noncollision transport accident, driver injured in traffic accident	V485	2
	Drowning and submersion while in bath-tub	W65	2
	In bathtub	E9104	2
	Inhalation and ingestion of food causing obstruction of respiratory tract or suffocation	E911	2
	Intentional self-harm by hanging, strangulation and suffocation	X70	2
	Intentional self-harm by rifle, shotgun and larger firearm discharge	X73	2
	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified	X61	2
	Motor vehicle exhaust gas	E9520	2
	Motorcyclist	E8122	2
	Occupant of pick-up truck or van injured in noncollision transport accident, driver injured in traffic accident	V585	2
	Opiates and related narcotics	E8500	2
	Passenger in motor vehicle other than motorcycle	E8151	2
	Psychodysleptics (hallucinogens)	E8541	2
	Unspecified accidental poisoning by analgesics, antipyretics, and antirheumatics	E8509	2
	Unspecified drowning and submersion	W74	2
	Accidental poisoning by and exposure to alcohol	X45	1
	Accidental poisoning by and exposure to other gases and vapours	X47	1
	Accidental poisoning by drugs, medicinal substances, and biologicals	E850	1
	Accidental poisoning by other solid and liquid substances, gases, and vapors	E869	1
	Accidents caused by submersion, suffocation, and foreign bodies	E910	1
	Assault by cutting and piercing instrument	E966	1
	Assault by drugs, medicaments and biological substances	X85	1
	Assault by hanging and strangulation	E963	1
	Assault by sharp object	X99	1
	Burns, fire	E9581	1
	By nuclear weapons	E9963	1
	Car occupant [any] injured in unspecified traffic accident	V499	1
	Car occupant injured in collision with fixed or stationary object, driver injured in traffic accident	V475	1
	Car occupant injured in collision with fixed or stationary object, passenger injured in traffic accident	V476	1

	Car occupant injured in noncollision transport accident, unspecified car occupant injured in traffic accident	V489	1
	Contact with other specified venomous arthropods	X25	1
	Contaminated substance transfused or infused	E8750	1
	Domestic wiring and appliances	E9250	1
	Driver of motor vehicle other than motorcycle	E8190	1
	Driver of motor vehicle other than motorcycle	E8250	1
	Drowning and submersion while in natural water	W69	1
	Exposure to uncontrolled fire in building or structure	X00	1
	Fall from chair or bed	E8842	1
	Fall from cliff	W15	1
	Fall on and from stairs and steps	W10	1
	Fire	E9680	1
	Handgun	E9650	1
	Handgun	E9850	1
	Hanging	E9530	1
	Hunting rifle	E9552	1
	Hunting rifle	E9652	1
	Inhalation and ingestion of other object causing obstruction of respiratory tract or suffocation	E912	1
	Inhalation and ingestion of other objects causing obstruction of respiratory tract	W80	1
	Intentional self-harm by handgun discharge	X72	1
	Intentional self-poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified	X62	1
	Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances	X64	1
	Late effects of injury purposely inflicted by other person	E969	1
	Late effects of self-inflicted injury	E9598	1
	Local anesthetics	E8552	1
	Mixed sedatives, not elsewhere classified	E8525	1
	Motor vehicle nontraffic accidents	8E21	1
	Motorcycle rider injured in collision with fixed or stationary object, driver injured in traffic accident	V274	1
	Motorcycle rider injured in noncollision transport accident, driver injured in traffic accident	V284	1
	Motorcyclist	E8152	1
	Occupant of pick-up truck or van injured in collision with car, pick-up truck or van, driver injured in traffic accident	V535	1
	Occupant of pick-up truck or van injured in collision with car, pick-up truck or van, passenger injured in traffic accident	V536	1
	Other accidental drowning or submersion	E9108	1
	Other accidents	E928	1
	Other and unspecified	E8869	1
	Other carbon monoxide	E9521	1
	Other man-made structures	E9571	1

	Other road vehicle accidents	E826	1
	Other specified drugs	E8588	1
	Other specified drugs and medicinal substances	E9504	1
	Passenger in motor vehicle other than motorcycle	E8191	1
	Pedal cyclist	E8136	1
	Pedestrian injured in collision with car, pick-up truck or van, traffic accident	V031	1
	Person injured in unspecified vehicle accident	V899	1
	Radiological procedure and radiotherapy	E8792	1
	Radiological procedure and radiotherapy	Y842	1
	Sequelae of other accidents	Y86	1
	Submersion (drowning), undetermined whether accidentally or purposely inflicted	E984	1
	Suicide and self-inflicted injury	E952	1
	Suicide and self-inflicted injury	E953	1
	Suicide and self-inflicted injury by cutting and piercing instrument	E956	1
	Surgical and medical procedures as the cause of abnormal reaction of patient or later complication	E878	1
	Surgical operation with formation of external stoma	E8783	1
	Surgical operation with transplant of whole organ	Y830	1
	Tranquilizers and other psychotropic agents	E9503	1
	Unspecified drug or medicinal substance	E9805	1
	Unspecified means , undetermined whether accidentally or purposely inflicted	E9889	1
	Unspecified person of motor vehicle traffic accident due to loss of control, without collision on the highway	E8169	1
	Unspecified person of other accidental submersion or drowning in water transport accident	E8329	1
	Unspecified person of other and unspecified water transport accident	E8389	1
	Unspecified site, falling from high place, undetermined whether accidentally or purposely inflicted	E9879	1
	While engaged in other sport or recreational activity without diving equipment	E9102	1
	Unknown	Unknown	44

Table S5. Relative rates for mortality among five-year survivors of childhood cancer

	All cause		Health-related Cause		Subsequent Neoplasm		Cardiac Cause		Pulmonary Cause		Other Health-related Causes	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Treatment Era												
Per five years	0.83	0.81 - 0.85	0.86	0.82 - 0.89	0.83	0.78 - 0.88	0.77	0.68 - 0.86	0.77	0.66 - 0.89	0.97	0.90 - 1.05
Sex												
Male	1.0		1.0		1.0		1.0		1.0		1.0	
Female	0.85	0.80 - 0.90	0.99	0.90 - 1.09	1.12	0.96 - 1.30	0.80	0.61 - 1.05	0.99	0.70 - 1.39	0.90	0.75 - 1.09
Diagnosis												
Acute lymphoblastic leukemia	1.0		1.0		1.0		1.0		1.0		1.0	
Acute myeloid leukemia	1.10	0.91 - 1.32	1.44	1.06 - 1.94	0.68	0.38 - 1.23	2.00	0.85 - 4.73	3.23	1.43 - 7.30	2.13	1.34 - 3.41
Other leukemia	2.58	2.13 - 3.12	2.20	1.54 - 3.16	1.11	0.55 - 2.25	3.59	1.37 - 9.42	7.31	3.17 - 16.82	2.33	1.15 - 4.72
Astrocytoma	1.35	1.21 - 1.50	1.56	1.31 - 1.86	1.23	0.94 - 1.62	1.33	0.73 - 2.43	2.47	1.38 - 4.42	1.97	1.44 - 2.70
Medulloblastoma	2.19	1.90 - 2.51	2.01	1.55 - 2.60	2.61	1.89 - 3.61	0.65	0.16 - 2.71	1.10	0.33 - 3.66	1.66	1.01 - 2.75
Other CNS tumors	1.58	1.34 - 1.87	1.92	1.46 - 2.53	1.92	1.30 - 2.82	0.69	0.17 - 2.82	1.23	0.37 - 4.16	2.52	1.60 - 3.96
Hodgkin lymphoma	1.02	0.91 - 1.13	1.67	1.41 - 1.98	1.64	1.27 - 2.12	3.12	1.95 - 5.00	1.58	0.85 - 2.93	1.22	0.88 - 1.70
Non-Hodgkin lymphoma	0.63	0.54 - 0.73	1.16	0.94 - 1.43	1.09	0.79 - 1.50	1.89	1.07 - 3.33	1.03	0.48 - 2.23	1.08	0.74 - 1.58
Wilms tumor	0.52	0.44 - 0.62	0.80	0.62 - 1.02	0.56	0.38 - 0.82	1.82	0.97 - 3.40	0.73	0.26 - 2.04	0.95	0.62 - 1.46
Neuroblastoma	0.67	0.57 - 0.79	0.60	0.44 - 0.81	0.37	0.22 - 0.60	0.56	0.19 - 1.61	1.92	0.87 - 4.24	0.80	0.47 - 1.33
Soft tissue sarcoma	0.83	0.70 - 0.97	1.09	0.85 - 1.41	1.14	0.80 - 1.62	0.96	0.42 - 2.22	0.38	0.09 - 1.61	1.26	0.81 - 1.95
Ewing sarcoma	1.56	1.33 - 1.83	1.40	1.04 - 1.88	1.20	0.75 - 1.90	3.56	1.84 - 6.89	0.30	0.04 - 2.24	1.26	0.72 - 2.21
Osteosarcoma	0.98	0.84 - 1.13	0.92	0.71 - 1.19	0.83	0.56 - 1.23	1.18	0.58 - 2.37	0.83	0.33 - 2.08	1.03	0.64 - 1.66
Other bone tumors	0.53	0.31 - 0.92	0.44	0.16 - 1.17	0.67	0.21 - 2.12	0.00	0.00 - .	0.00	0.00 - .	0.37	0.05 - 2.69
Age at diagnosis												
0-4	1.0		1.0		1.0		1.0		1.0		1.0	
5-9	1.70	1.55 - 1.88	1.19	1.02 - 1.39	1.00	0.79 - 1.25	1.06	0.66 - 1.71	1.82	1.03 - 3.21	1.44	1.08 - 1.91
10-14	2.93	2.61 - 3.28	1.41	1.17 - 1.69	1.40	1.08 - 1.82	1.37	0.82 - 2.31	2.04	1.09 - 3.82	1.31	0.93 - 1.86
15-20	4.73	4.16 - 5.39	1.69	1.39 - 2.07	1.76	1.28 - 2.40	1.65	0.94 - 2.90	2.39	1.17 - 4.87	1.49	1.02 - 2.17

Table S6. All-cause and cause-specific standard mortality ratios in five-year survivors of childhood cancer followed for 15 years

	All cause			Health-related Cause			Subsequent Neoplasm			Cardiac Causes			Pulmonary Causes			Other Health-related Causes		
	No. of death	SMR	95%CI	No. of death	SMR	95%CI	No. of death	SMR	95%CI	No. of death	SMR	95%CI	No. of death	SMR	95%CI	No. of death	SMR	95%CI
All survivors	2960	12.8	12.3 - 13.3	906	12.8	11.9 - 13.7	455	25.0	22.6 - 27.7	97	11.7	9.4 - 14.4	77	17.7	13.8 - 22.6	276	6.9	6.1 - 7.8
Treatment Era																		
1970-1979	1059	14.0	13.2 - 14.9	314	13.7	12.2 - 15.4	160	26.3	22.2 - 31.3	44	16.7	12.0 - 23.2	30	21.4	14.4 - 32.0	80	6.2	4.9 - 7.9
1980-1989	1179	12.1	11.4 - 12.8	376	12.2	11.0 - 13.5	203	26.3	22.8 - 30.4	41	11.2	8.2 - 15.3	33	17.5	12.2 - 25.0	100	5.6	4.6 - 6.9
1990-1999	722	12.3	11.5 - 13.3	216	12.5	10.9 - 14.4	92	20.9	16.9 - 25.9	13	6.2	3.5 - 10.9	14	12.9	7.4 - 22.5	97	10.	8.2 - 12.2
Sex																		
Male	1755	10.0	9.6 - 10.5	507	10.9	9.9 - 11.9	250	22.8	19.8 - 26.2	58	9.8	7.4 - 13.1	42	15.9	11.4 - 22.2	157	5.8	4.9 - 6.8
Female	1205	21.2	20.1 - 22.5	399	16.4	14.8 - 18.1	206	28.4	24.7 - 32.6	39	16.1	11.6 - 22.2	35	20.4	14.3 - 29.1	119	9.2	7.6 - 11.1
Diagnosis																		
Acute lymphoblastic leukemia	979	15.2	14.3 - 16.2	276	14.9	13.1 - 16.9	153	31.0	25.8 - 37.2	17	8.5	5.1 - 14.4	18	14.6	8.9 - 24.2	87	8.4	6.8 - 10.6
Acute myeloid leukemia	86	13.3	10.8 - 16.5	27	12.7	8.5 - 19.2	5	8.8	3.2 - 24.3	4	15.7	5.3 - 46.5	5	41.2	16.9 - 100.2	13	10.6	5.8 - 19.5
Other leukemia	97	35.1	28.8 - 42.8	23	27.5	18.1 - 41.8	8	35.6	16.9 - 74.7	3	24.9	6.2 - 99.5	7	139.2	63.6 - 305.1	6	12.0	5.1 - 28.6
Astrocytoma	344	14.8	13.3 - 16.5	105	15.3	12.5 - 18.7	46	26.2	19.4 - 35.4	7	9.0	4.3 - 18.8	13	29.1	15.7 - 54.1	39	10.0	7.2 - 14.0
Medulloblastoma, PNET	200	27.1	23.6 - 31.1	45	22.4	16.7 - 30.1	31	60.4	42.4 - 86.0	2	9.5	2.4 - 37.8	2	15.4	3.9 - 61.6	10	8.4	4.3 - 16.5
Other CNS tumors	119	18.4	15.4 - 22.0	43	22.1	16.1 - 30.2	23	47.0	31.0 - 71.1	1	5.2	0.8 - 36.1	2	17.8	4.4 - 71.2	17	15.2	9.1 - 25.2
Hodgkin disease	352	8.6	7.7 - 9.5	155	11.2	9.5 - 13.2	77	22.5	17.9 - 28.1	30	16.5	11.4 - 23.9	16	21.0	12.4 - 35.5	32	4.1	2.9 - 5.9
Non-Hodgkin lymphoma	133	5.5	4.7 - 6.5	71	10.3	8.1 - 13.1	36	21.9	15.6 - 30.8	8	9.1	4.4 - 18.5	3	8.4	2.7 - 25.8	24	6.0	3.9 - 9.1
Wilms tumor	83	7.0	5.6 - 8.7	30	8.2	5.7 - 11.8	13	12.2	6.9 - 21.7	7	21.0	10.0 - 44.1	0	0.0	0.0 - 13.5	10	4.9	2.6 - 9.4
Neuroblastoma	136	17.2	14.6 - 20.4	27	9.5	6.3 - 14.2	11	12.6	6.8 - 23.6	2	8.4	2.1 - 33.7	4	20.3	7.4 - 56.1	10	6.3	3.2 - 12.5
Soft tissue sarcoma	92	8.6	7.0 - 10.5	30	9.3	6.4 - 13.5	18	22.5	14.0 - 36.0	3	8.5	2.7 - 26.4	0	0.0	0.0 - 18.5	8	4.4	2.1 - 9.3
Ewings sarcoma	145	18.6	15.8 - 21.9	34	13.9	9.8 - 19.7	17	29.2	18.0 - 47.6	8	26.2	12.1 - 56.6	0	0.0	0.0 - 27.0	8	6.0	2.9 - 12.4
Osteosarcoma	185	11.5	9.9 - 13.2	39	7.1	5.2 - 9.8	16	12.5	7.3 - 21.4	4	6.2	2.4 - 16.4	6	22.1	9.8 - 49.4	12	3.8	2.0 - 7.1
Other bone tumors	9	6.1	3.2 - 11.8	3	5.6	1.8 - 17.5	2	15.7	3.9 - 62.7	0	0.0	0.0 - 51.8	0	0.0	0.0 - 134.6	1	3.3	0.5 - 23.1
Year since original diagnosis																		
5-9	2019	20.8	19.9 - 21.7	514	17.6	16.0 - 19.4	269	33.7	29.5 - 38.5	46	15.0	10.7 - 21.1	39	19.9	14.2 - 27.8	159	9.9	8.3 - 11.7
10-14	819	7.3	6.9 - 7.9	335	9.8	8.8 - 10.9	161	19.2	16.3 - 22.5	42	9.8	7.1 - 13.4	31	15.7	10.9 - 22.7	101	5.1	4.2 - 6.3
15*	121	5.3	4.4 - 6.3	57	7.6	5.8 - 9.9	25	13.8	9.2 - 20.7	10	9.5	5.0 - 18.1	7	16.4	7.4 - 36.3	16	3.6	2.2 - 6.0

Table S7. Relative rates of Other Health-Related Cause Mortality Based on Treatment Era Among Five-Year Survivors of Specific Childhood Cancers and the Impact of Specific Treatment Exposures Upon Treatment Era*								
	Acute Lymphoblastic Leukemia		Hodgkin Lymphoma		Wilms Tumor		Astrocytoma	
	RR	95%CI	RR	95%CI	RR	95%CI		
Model Without Therapy								
Treatment era (per 5 years)	0.88	0.81 - 0.95	0.79	0.72 - 0.87	0.68	0.56 - 0.84	0.81	0.73 - 0.91
Model With Therapy								
Treatment era (per 5 years)	1.02	0.83 - 1.24	0.79	0.70 - 0.89	0.80	0.59 - 1.08	0.82	0.72 - 0.94
Cranial RT								
None	1.0		-	-	-	-		
1-19.9 Gy	1.02	0.63 - 1.66	-	-	-	-		
≥ 20 Gy	2.26	1.44 - 3.54	-	-	-	-		
Cranial RT								
No							1.0	
Yes							2.39	1.27 - 4.48
Any Chemotherapy								
No							1.0	
Yes							1.73	1.11 - 2.67
Epiodophyllotoxin								
No	1.0		-	-	-	-		
Yes	1.83	1.20 - 2.79	-	-	-	-		
Steroid								
None	1.0		-	-	-	-		
Prednisone	0.39	0.26 - 0.60	-	-	-	-		
Dexamethasone	0.33	0.15 - 0.75	-	-	-	-		
Both	0.21	0.13 - 0.35	-	-	-	-		
Anthracycline(mg/m ²)								
None	1.0		1.0		1.0			
1-<150	1.36	0.65 - 2.84	1.64	0.66 - 4.05	0.12	0.00 - 6.29		
≥150-<300	2.07	0.97 - 4.39	3.26	2.03 - 5.25	1.34	0.54 - 3.31		
≥300-<450	1.23	0.73 - 2.08	2.53	1.23 - 5.18	2.05	0.79 - 5.28		
≥450-<600	1.92	0.71 - 5.18	3.11	0.74 - 13.08	24.87	5.90 - 104.8		
≥600	3.09	1.16 - 8.23	9.56	1.29 - 70.93	-	-		
Cyclophosphamide Equivalent Dose (mg/m ²)								
None	-	-	1.0		-	-		
0-<4000	-	-	0.83	0.34 - 2.01	-	-		
≥4000-<8000	-	-	0.74	0.27 - 2.00	-	-		
≥8000-<12000	-	-	0.97	0.53 - 1.79	-	-		
≥12000-<16000	-	-	1.38	0.86 - 2.22	-	-		
≥16000-<20000	-	-	2.27	0.94 - 5.49	-	-		
≥20000	-	-	1.60	0.84 - 3.07	-	-		
Chest RT								
None	-	-			-	-		
1-19.9 Gy	-	-	1.00	0.22 - 4.43	-	-		
20-29.9 Gy	-	-	1.23	0.65 - 2.32	-	-		
≥30 Gy	-	-	2.60	1.63 - 4.15	-	-		
Splenuectomy								
No	-	-	1.0		-	-		
Yes	-	-	1.12	0.83 - 1.52	-	-		
Abdomen RT dose								
None	-	-	-	-	1.0			
1-19.9 Gy	-	-	-	-	0.67	0.06 - 6.84		
20-29.9 Gy	-	-	-	-	1.29	0.44 - 3.75		
≥ 30 Gy	-	-	-	-	2.60	0.88 - 7.70		

*adjusted for sex and age at diagnosis

Table S8. Cumulative incidence of all cause and cause-specific mortality at **10 years** from primary cancer diagnosis among five-year survivors

Year of Diagnosis	All Cause	Recurrence/Progression of Primary Disease	Health-related Cause
1970-1974	8.8%	6.3%	2.1%
1975-1979	6.5%	4.7%	1.6%
1980-1984	5.9%	4.1%	1.6%
1985-1989	5.0%	3.4%	1.4%
1990-1994	3.9%	2.7%	1.0%
1995-1999	3.6%	2.5%	0.9%