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A Model-Based Estimate of Cumulative Excess Mortality in Survivors of Childhood Cancer

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Abstract

Background—Although childhood cancer survival rates have dramatically increased, survivors continue to face elevated risks for life-threatening late-effects, including secondary cancers.

Objective—We sought to estimate the cumulative impact of disease- and treatment-related mortality risks on survivor life expectancy.

Design—State-transition model.

Setting—To simulate the lifetime clinical course of childhood cancer survivors, we estimated probabilities for the following competing risks from published studies: (1) risk of dying from original cancer diagnosis; (2) excess mortality from non-recurrence late-effects; and (3) background mortality.

Patients—Five-year childhood cancer survivors.

Measurements—Lifetime cause-specific mortality, life expectancy, cause-specific attributable proportion of overall mortality risk, conditional ten-year mortality probabilities.

Results—For a cohort of 15-year-old five-year survivors, diagnosed with cancer at age 10, the average lifetime probability of mortality was 0.10 for late-recurrence, 0.15 for treatment-related subsequent cancers, cardiac, pulmonary, and external causes, and 0.05 for other excess risk. Life expectancy for the cohort of 15-year-olds was 50.6 years, a loss of 10.4 years (17.1%) compared to the general population. Reduction in life expectancy varied by diagnosis, ranging from 4.0 years (6.0%) for kidney tumors to more than 17.8 years (>28.2%) for brain and bone tumor survivors, and was sensitive to late-recurrence mortality risk and duration of excess mortality risks.

Limitations—Estimates are based on data for survivors treated 20–40 years ago; patients treated more recently may have more favorable outcomes.

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REPRODUCIBLE RESEARCH STATEMENT

Study protocol: Available from Dr. Yeh (jyeh@hsph.harvard.edu).
Statistical code and data: Not available.

Conclusions—Despite surviving their initial cancer, childhood cancer survivors face considerable mortality during adulthood, with excess risks reducing life expectancy by as much as 28%. Our findings underscore the need to monitor the health of current survivors and carefully evaluate therapies with known late toxicities in newly diagnosed patients.

INTRODUCTION

Each year over 10,000 children and adolescents are diagnosed with cancer in the United States (1). Since the 1960s, advances in treatment have dramatically reduced mortality rates. Five-year survival rates now approximate 80% for children diagnosed with cancer. As the population of over 300,000 long-term survivors in the United States continues to grow, and the damaging effects of treatment become more widely recognized, there is a growing need to better understand the impact of late-effects on survivors' health (2).

Several long-term studies on the late-effects of disease and treatment have emerged in recent years (3–11). Providing natural history data, the most recent cohort study suggests that five-year childhood cancer survivors diagnosed prior to 1990 face an 8.4-fold increased risk of mortality compared to the general population (9). In particular, survivors face higher risks of dying from subsequent cancers, cardiac events and pulmonary complications. Survivors also experience a higher prevalence of chronic conditions, with as many as two-thirds of childhood cancer survivors reporting at least one chronic condition and one-fourth a severe, disabling or life-threatening condition (12). While these studies suggest the incidence of these conditions steadily increases with time, the full extent of disease and treatment-related late-effects has yet to be realized.

Although long-term studies provide estimates on the excess mortality risk survivors face in the decades immediately following their initial diagnosis, the cumulative lifelong impact of these risks on overall mortality in terms of life years lost is uncertain and has not been previously quantified. Using a model-based approach, we sought to estimate the overall impact of disease and treatment-related mortality risks on the life expectancy of childhood cancer survivors.

METHODS

Model Structure

We developed a state-transition model to simulate the lifetime clinical course of childhood cancer survivors (Figure 1) (13). At the start of simulation, a cohort of five-year survivors of childhood cancer enters the model. Each month, individuals face competing mortality risks which we categorized as 1) the risk of dying from the original cancer diagnosis (i.e., late recurrences), 2) excess mortality from non-recurrence late-effects (i.e., subsequent cancers, cardiac, pulmonary and other complications) and 3) background mortality (i.e., age-specific mortality rates for the general population). By following individuals throughout their lifetime and recording cause-specific mortality, the model estimates the following outcomes for cohorts of childhood cancer survivors: lifetime cause-specific mortality, life expectancy, cause-specific attributable proportion of overall mortality risk, and conditional ten-year mortality probabilities. Loss in life expectancy was calculated as the difference in life expectancy between a cohort of survivors and a cohort representative of the U.S. population (which face zero risk of cancer recurrence or treatment-related mortality). We conducted sensitivity analyses to assess how key parameters and assumptions might influence results, including a probabilistic sensitivity analysis using second-order Monte Carlo simulations to more fully account for uncertainty. The model was constructed using TreeAge Pro Suite 2006 (TreeAge Software, Inc., Williamstown, MA).

Model Inputs and Assumptions

Table 1 summarizes selected parameter estimates (4–8, 14). For our base case analysis, we simulated a cohort of 15-year old five-year childhood cancer survivors (mean diagnosis age of 10 years), representative of the Childhood Cancer Survivor Study (CCSS), the largest, multi-institutional, retrospective study of U.S. individuals who have survived for at least 5 years after childhood cancer treatment (see appendix for additional details) (15). The childhood cancer survivors were originally diagnosed before the age of 21 between 1970 and 1986. Parameter estimates for each of the following competing risks were based on a recent analysis of mortality from the CCSS, which included approximately 339,000 person-years of observation and 2820 deaths (9). Providing estimates by time since diagnosis for each late-effect-associated mortality risk (data previously unavailable in any published large population-or hospital-based cohort study), these data are the most comprehensive estimates available to date.

Mortality from late recurrence—Individuals faced a risk of dying from recurrence of their original cancer diagnosis. The risk varied by years since diagnosis, and was highest 5–9 years after diagnosis (0.0099 per year) before declining 30–34 years since diagnosis (0.0005 per year). For ≥35 years since diagnosis, we assumed that the risk remained at 30–34 years-since-diagnosis levels as follow-up data for the period are not yet available from the CCSS.

Non-recurrence excess mortality—Individuals faced excess risks of dying from disease- and treatment-related late effects. To reflect the additional mortality risk faced by childhood cancer survivors compared to the general population (16), we used published absolute excess risk (AER) estimates, which were based on cause-specific standard mortality ratios derived from multivariate Poisson regression (9). Based on death certificate data and the International Classification of Diseases, Ninth Revision (ICD-9) codes, AER estimates were categorized into four subtypes: secondary or subsequent cancers (ICD 140–239), cardiac (ICD 390–398, 402, 404, 410–429), pulmonary (ICD 460–519), external causes (accidents, suicide, poisoning, etc.; ICD 800–999), and other causes (all other ICD codes, such as infectious and parasitic diseases (ICD 001–139), diseases of the nervous system and sense organs (ICD 320–389), cerebrovascular diseases (ICD 430–438), and diseases of the digestive system (ICD 520–579)). Except for external causes of death, which only exceeded general population rates during 15–19 years since diagnosis, the excess risk for each competing risk increased with years since diagnosis (9).

As data for ≥25 years since diagnosis are unavailable, we assumed that non-recurrence excess mortality risks remained constant at published 20–24 years-since-diagnosis levels.

Background mortality—Individuals also faced age-specific general population mortality rates based on U.S. Life Tables from the National Center for Health Statistics for 1979–1998 (17).

Subgroup Analyses

For diagnosis age-, treatment era-, sex- and diagnosis-specific analyses, we incorporated subgroup-specific mean diagnosis age and risks for late recurrence mortality and non-recurrence excess mortality (Table 1). We used constant mortality risk estimates, as data by years since diagnosis were unavailable for subgroups. Data for the overall cohort suggest that for late-recurrence, the risk of mortality dramatically declines with time and for non-recurrence excess mortality, the risk increases as survivors age (9). For subgroup analyses, we therefore assumed that 1) the risk of late recurrence mortality was negligible after 35

years since diagnosis, and 2) the risks associated with non-recurrence late-effects were lifelong at constant rates.

Sensitivity Analysis

Univariate sensitivity analyses were performed to assess the stability of results to base case model estimates. We established a plausible range for each model variable using 95% confidence intervals (see appendix), and varied each one over its range while all other variables were held constant (9). We also used U.S. Life Tables for the years 1970 and 2004 to evaluate the impact of differential background mortality rates on results. To reflect the uncertainty in our estimates, we conducted a probabilistic sensitivity analysis using 1000 second-order Monte Carlo simulations in which all parameters values were simultaneous varied (except for background mortality) using normal distributions based on 95% confidence intervals, assuming a value of zero for any negative numbers that arose from sampling.

Role of the Funding Source

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RESULTS

Model Validation

To assess the external validity of the model, we compared modeled output with data not used to parameterize the model. At 15 years since diagnosis, the proportion of all deaths attributable to recurrence (69% model estimate vs. range = 69–74%), subsequent cancer (12% model estimate vs. 6–16%), and all other non-cancer causes (18% model estimate vs. range = 10–23%) approximated published estimates from large hospital- and population-base cohort studies in the Nordic countries (original cancer diagnosed between 1960 and 1989) (5), the Netherlands (1966–1996) (6), and Canada (1970–1995) (7) (see appendix).

Overall Cohort (Base Case)

Lifetime cause-specific mortality—For a cohort representative of the CCSS, we found that the average lifetime cause-specific mortality probability was 0.10 for late recurrence, 0.20 for non-recurrence excess mortality (subsequent treatment-related cancers=0.10; cardiac=0.03; pulmonary=0.02; external causes<0.001; other causes=0.05), and 0.70 for background mortality (Table 2). Combined, childhood cancer or its late-effects were responsible for a total of 30% of overall mortality probability (see appendix).

Life expectancy—For a cohort of five-year childhood cancer survivors diagnosed at age 10, the model projected a conditional life expectancy of 50.6 years. Compared to the model projection of 61.0 years for a cohort representative of the general population (0.6% discrepancy from the National Center for Health Statistics for 1989–1991) (18), our estimate represented a loss in life expectancy of 10.4 years, or 17.1% (see appendix), but differed depending on age at diagnosis, treatment era, and type of cancer (see subgroups).

Cause-specific attributable proportion of overall mortality risk—Figure 2 shows how the overall risk of dying each year attributed to each competing risk decreased over time. From 5 to 40 years after diagnosis, the risk of dying from cancer- or treatment-related causes exceeded background mortality in the general population. Beginning at 45 years after

diagnosis, however, the risk of dying from background causes exceeded the risk of all late-effects combined.

Conditional ten-year mortality probabilities—The model projected that for survivors who reach 40 years of age, the probability of dying before age 50 was 0.11, a 3.3 fold-higher risk than in the general population. For 60-year olds, the probability of dying before age 70 was 0.25, a 1.4 fold-higher risk relative to the general population. Compared to the general population, the relative likelihood of dying within 10 years decreased from 3.3-fold for 40-year olds to 1.4-fold for 60-year olds.

By Subgroup

The model predicted that individuals diagnosed at older ages or who received treatment in earlier eras had greater losses in life years (Table 2). The loss in life years was similar for men (9.0 years or 15.7%) and women (10.0 years or 15.6%). By diagnosis, the reduction in life expectancy ranged from 4.0 years (6.0%) for kidney tumors to more than 17.0 years (≥28.2%) for select brain tumors and Ewing sarcomas. For all subgroups, the relative likelihood of dying within 10 years also decreased with age (see appendix; 1.3–3.1 for 40-year olds to 1.1–1.2 for 60-year olds).

Sensitivity Analyses

We conducted a series of sensitivity analyses to evaluate the impact of alternative assumptions on the reduction in life expectancy for the base case cohort (see appendix). We found that results were sensitive to reductions in late recurrence mortality risk, which may result from more effective modern treatments, or lower magnitude or duration of risk for subsequent treatment-related late-effects, specifically for subsequent cancers and other causes, potentially resulting from safer or lower dose treatments. For example, if the excess risk for subsequent cancers was reduced by 50%, the loss in life expectancy declined from 10.4 to 9.0 years, a nearly 15% decline. If the risk for late recurrence mortality also fell by 50%, the loss in life years was 6.9 years, a combined decline of 33%.

We conducted several scenario analyses to provide insight on how late recurrence and non-recurrence excess mortality risks impacted overall reduction in life expectancy. If survivors were only at risk for mortality from late-recurrence (and negligible risk for all non-recurrence late-effects), the reduction in life expectancy was 4.8 years for the overall cohort (base case = 10.4 years), and ranged from 1.1 to 14.2 years for diagnosis-specific subgroups. If individuals did not relapse, but were at risk for non-relapse associated mortality, the loss was still 6.2 years. For diagnosis-specific subgroups, the reduction varied (ranging from 0.9 to 7.4 years), depending on the magnitude of late-recurrence mortality risk. For example, if survivors were at risk for only non-recurrence excess mortality, the reduction in life expectancy for medulloblastomas, which have significant late-recurrence mortality risk, fell from 17.3 years to 4.3 years. In contrast, for kidney tumors, which have relatively low risk of late-recurrence mortality, the reduction declined from only 4.0 to 2.9 years (see appendix for additional details).

Because follow-up data for more than 35 years since diagnosis are not yet available, we also conducted a scenario analysis in which the risk of recurrence and excess risk for non-recurrence late-effects were negligible upon reaching 45 years of age. For the overall cohort, the reduction in life expectancy was 8.2 years (base case = 10.4 years; see appendix for diagnosis-subgroup results which ranged between 3.0 and 16.4 years). The probability of dying from late recurrence remained largely unchanged (0.09 vs. 0.10 base case) for the overall cohort, although the risks of dying from excess subsequent cancers, cardiac, pulmonary or external causes (0.08 vs. 0.15 base case) and from other causes (0.02 vs. 0.05

base case) were considerably lower. These results suggest that recognition and treatment of illnesses associated with late effects in the first 35 years after childhood cancer therapy are likely to result in improved longevity.

Probabilistic sensitivity analysis suggested that the reduction in life expectancy for the overall cohort ranged between 8.9 to 12.2 years. Table 2 depicts uncertainty intervals for all subgroup analyses. Reflecting uncertainty, probabilistic sensitivity analysis suggested that the reduction in life expectancy increased with diagnosis age, likely associated with age-specific cancer subtypes. Between 1970 and 1981, serial reductions in the impact of late-effects on life expectancy were observed, although improvements appeared to level off during 1982–1986. Additional details are provided in the appendix.

DISCUSSION

Five-year survivors of childhood cancer face considerable excess mortality risks during their adult years. Using data from the Childhood Cancer Survivors Study (CCSS) based on 26 collaborating U.S. and Canadian institutions that treat children with cancer and thought to be largely representative of the population of U.S. cancer survivors, our findings provide valuable information on the prognosis for cancer survivors by translating mortality risks into losses in life expectancy and distinguishing between late cancer recurrence and other disease- and treatment-related late effects. We estimated that these childhood cancer survivors, depending on their original cancer diagnosis, will live 4 to 18 fewer years on average than like-aged general populations, a reduction in life expectancy of up to 28%. Approximately one in every four survivors is estimated to die from late recurrence or late-effects related to secondary cancer and cardiopulmonary conditions, and another one in twenty from other excess risk. These findings suggest that the combined impact of late-effects on life expectancy are substantial, vary by cancer diagnosis and even tumor type, and underscore the importance of monitoring the health of the growing population of childhood cancer survivors and evaluating therapies for newly diagnosed patients which might be associated with decreased late toxicity.

Several long-term cohort studies on childhood cancer survivors in the published literature (English language MEDLINE search to October 2008) describe the excess mortality risk associated with disease- and treatment late effects, but the most recent data from the CCSS provide the most comprehensive estimates to date on mortality, as well as morbidity. Oeffinger et al. found that survivors of childhood cancer report disabling or life-threatening conditions in over 6% of cases, and severe chronic conditions in an additional 20% (12). Geenen et al. similarly estimated nearly 25% of survivors had a high or severe burden of adverse events, comprising of at least 2 severe events or 1 or more life-threatening or disabling event (19). Although many of these conditions might be expected to be associated with cardiac, pulmonary or cancer deaths, survivors self-report higher than expected rates of other conditions such as renal failure, major joint replacement and neurologic and neurosensory dysfunction. In aggregate, these chronic illnesses will likely lead to other disabling conditions via multifactorial pathways, and are likely to adversely affect the progression of other health problems associated with aging. For example, a history of radiation therapy which includes the coronary arteries, as is used in treatment of many adolescent lymphomas, increases the risk for ischemic heart disease and its associated mortality. This ischemia may result, alternatively, in long-term chronic heart disease as a comorbid condition in an aging survivor with illnesses that may be unrelated to the childhood cancer. A recent analysis by Mulrooney et al. found that young adults who survive childhood cancer are clearly at risk for early cardiac morbidity and mortality not typically recognized in the age group, and that the cumulative incidence of adverse cardiac outcomes continues to increase up to 30 years after diagnosis (20). The excess risk related to

childhood cancer therapy may lead to additional excess mortality risks other than those already observed. For some survivors, the increased risk of developing multiple comorbidities at young ages from treatment-related late-effects may lead to even worse survival outcomes.

Our study has several limitations. First, our estimates of excess mortality risk rely on the accuracy of cause-of-death information obtained from the National Death Index (21, 22). An analysis of the Framingham Heart Study participants found that death certificate data correctly identified 78–97% of coronary heart disease and cancer deaths (23). Multiple large-scale survivor cohort studies have also reported very similar rates of absolute excess mortality risks, suggesting some reliability of estimates (5–7, 24). We also assumed that survivors undergo average patterns of care by using background mortality rates for the general population. Second, we used late-effects mortality risks only from the CCCS, and many variables are uncertain. While other cohort studies also provide mortality risks, the CCSS is the only study to date that provides estimates by time since diagnosis and by tumor type within cancer diagnoses and reflects the underlying variation in mortality risks. Using probabilistic sensitivity analysis, we were able to reflect the uncertainty surrounding model inputs and their impact on model estimates, and provide a range of likely outcomes. Third, given the limited sample size of the CCSS, our subgroup analyses by sex- and cancer diagnosis assumed constant annual excess mortality risks for the entire follow-up period. In the overall cohort of survivors, assuming a constant rate reduced the loss in life expectancy from 10.4 years (17.1%) in the base case to 9.6 years (15.7%), but raised the lifetime likelihood of dying from recurrence from 0.10 in the base case to 0.12 and reduced the likelihood of dying from non-recurrence late-effects from 0.20 to 0.12. As such, our subgroup estimates may underestimate the loss in life expectancy. Fourth, our estimates also do not reflect heterogeneity in mortality risks by treatment *within* a given diagnosis. As treatment-specific estimates become available, our model can be used to compare the relative outcomes among different regimens. For example, our model can provide insight into how life expectancy may vary between individuals with Hodgkin's disease or leukemia treated with and without radiation. Changes in therapies that limit exposure to high dose anthracyclines may also be modeled to determine if the expected reduction in overall mortality will be achieved. With subgroup-specific mortality estimates, we can explore whether disparities in long-term outcomes by race or ethnicity exist, as survival rates have been shown to differ by these factors in childhood leukemia (25).

Despite these limitations, our findings have several important implications for the growing population of childhood cancer survivors. First, our results suggest that the impact of late-effects is greatest in the decades immediately following initial diagnosis of childhood cancer. As such, multidisciplinary surveillance of survivors' health during these years may be most important in reducing mortality associated with late-effects. Clinicians providing ongoing care for these aging childhood cancer survivors should be familiar with late-effects surveillance guidelines, such as those compiled by the Children's Oncology Group (http://www.survivorshipguidelines.org/) (26). Dissemination of surveillance guidelines to patients and primary care providers will improve coordination of care and potentially improve the long-term health outcomes of survivors. Our findings suggest that for survivors who do not experience late recurrence of their original cancer, the major determinant of decreased life expectancy is the excess risk associated with subsequent cancers, accounting for approximately 50% of all non-recurrence excess mortality. Careful consideration of increased risk should be incorporated into clinical evaluation of symptoms, and screening should be tailored to take treatment-related risk factors into account. Currently, the majority of adult survivors of childhood cancer do not receive regular medical care focused on their long-term risks based upon exposures. For example, many young female survivors do not

undergo screening mammograms, recommended to start at age 25 if chest radiation was a component of childhood cancer treatment (27).

Research in health care communication that leads to better physician and patient education in this field will be required. In addition, policies are strongly needed to ensure that survivors have access to their needed medical care. Compared to their siblings, survivors have lower rates of insurance coverage and face more difficulty obtaining coverage (28). As the long-term health risks of childhood cancer survivors become more widely recognized, governments, insurers, employers and/or patients may face financial challenges in providing or obtaining coverage for survivor health care needs.

Changes in childhood cancer therapy have resulted in increasing cure rates over the past four decades. Consistent with serial improvements over time, we found life expectancy reductions were most pronounced in the group of survivors with the earliest dates of diagnosis (1970–1973), compared with children treated in more recent decades (1978 – 1986). This improvement in outcome over time can be attributed, in our model, to better maintenance of primary cancer control as well as to reductions in mortality from late effects. In subgroup analyses, however, we found that even if the risk for late recurrence is negligible, late-effects will reduce life expectancy by 12% or more in survivors of Hodgkin's disease, select brain tumors and Ewing sarcomas (see appendix). This finding is consistent with cancer treatment changes for these diseases during this time period; the aggressive combined-modality therapies utilized are associated with significant cardiopulmonary toxicities and second cancer risks. More recent treatments have been developed which are directed toward maintenance of cure, along with reduction of long-term late effects. Therapies which utilize specific cardio-protectant medications, reduced-dose radiation, and dose-limitation of organ-toxic agents may result in improved outcomes, and as such, further analyses of the impact of this strategy on long-term mortality risk is needed.

Our estimates are based on data from survivors treated 20 to 40 years ago. As treatment has changed since then, data on survivors treated more recently can provide insight on how advances in treatment since 1986 have impacted life expectancy. In 2007, the CCSS began recruiting a second set of participants who were treated for cancer as children between 1987 and 1999 (29); however data are not available yet. Other smaller cohort studies (with 1400 to 2400 patients) provide some data on the absolute excess risk for overall death for patients treated more recently. For example, in the Netherlands cohort, compared to patients diagnosed between 1966 and 1984, the absolute excess risk for death overall was 7% lower among patients diagnosed after 1984 until 1996 (6). In a Canadian cohort, between the treatment eras of 1980–1989 and 1990–1995, the absolute excess risk increased 5% (7). Excess mortality risks by late-recurrence and other specific causes were not reported in either study. As better data become available, our model can be used to estimate and compare how the cumulative impact of late-effects on life expectancy has changed for those treated more recently and inform clinical trials on pediatric cancer treatment which are increasingly informed by adverse outcomes experienced by survivors.

While our model predicts significant reductions in life expectancy in childhood cancer survivors treated in previous decades, often with now historical therapies, this work highlights the need to minimize the use of agents associated with late toxicities for newly diagnosed patients, and to follow survivors of these newer therapies to assess late toxicities. The considerable impact of these excess risks on life expectancy emphasizes the need for primary care physicians to attend not only to the risk of cancer recurrence, but risks for non-recurrence side effects. For the now adult group of childhood cancer survivors, increased awareness of the long-term effects of treatment and the need to adhere to guideline

recommendations by both patients and physicians can help to minimize their impacts on their long-term survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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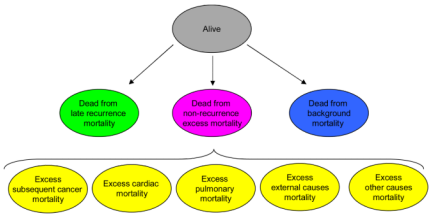

Figure 1. Model structure

At the start of the simulation, a cohort of five-year childhood cancer survivors enters the model. Each month, they face a risk of dying from late recurrence, non-recurrence excess mortality and background mortality. Non-recurrence excess mortality includes risks associated with subsequent cancers, cardiac, pulmonary, external causes and other causes. Individuals are followed throughout their lifetime.

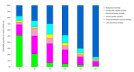

Figure 2. Cause-specific attributable proportion of overall mortality risk

The bar graph depicts the proportion of overall mortality risk attributed to each specific mortality cause at 10, 20, 30, 40, 50 and 60 years after diagnosis. As survivors age, the cumulative proportion of overall mortality attributable to background mortality increases relative to the proportion for all late-effects from cancer or cancer treatment combined.

Table 1

Model inputs: Select parameters

Cohort	Mean diagnosis age, years* (14)	Mortality Risks, yearly rate† (9)					
		Late recurrence mortality	Absolute Excess Mortality				
			Subsequent cancers	Cardiac	Pulmonary	External	Other
Overall (base case)‡	10	0.0005–0.0099	0.0011–0.0023	0.0002–0.0007	0.0001–0.0005	0.0000–0.0001	0.0004–0.0013
Sex§							
Men	10	0.0048	0.0012	0.0004	0.0002	0.0003	0.0000
Women	10	0.0038	0.0014	0.0003	0.0002	0.0005	0.0000
Age at diagnosis§							
0–4 years	2	0.0033	0.0009	0.0002	0.0001	0.0002	0.0000
5–9 years	7	0.0044	0.0010	0.0003	0.0001	0.0004	0.0000
10–14 years	12	0.0050	0.0014	0.0004	0.0003	0.0005	0.0001
15–20 years	17	0.0059	0.0025	0.0009	0.0003	0.0006	0.0000
Year of diagnosis§							
1970–1973	10	0.0048	0.0019	0.0004	0.0004	0.0005	0.0000
1974–1977	10	0.0043	0.0015	0.0006	0.0002	0.0004	0.0000
1978–1981	10	0.0040	0.0010	0.0004	0.0001	0.0003	0.0001
1982–1986	10	0.0044	0.0011	0.0002	0.0001	0.0004	0.0000
Diagnosis§							
Acute lymphoblastic leukemia	7	0.0053	0.0009	0.0001	0.0001	0.0002	0.0000
Acute myeloid leukemia	9	0.0055	0.0008	0.0002	0.0005	0.0005	0.0005
Other leukemia	8	0.0089	0.0014	0.0002	0.0006	0.0000	0.0000
Astrocytomas	8	0.0064	0.0010	0.0003	0.0004	0.0007	0.0006
Medulloblastoma, PNET	8	0.0114	0.0016	0.0000	0.0001	0.0002	0.0000
Other CNS tumors	8	0.0095	0.0010	0.0000	0.0003	0.0009	0.0007
Hodgkin disease	15	0.0034	0.0030	0.0012	0.0003	0.0006	0.0000
Non-Hodgkin lymphoma	12	0.0016	0.0013	0.0004	0.0002	0.0003	0.0000
Kidney tumors	5	0.0007	0.0008	0.0003	0.0001	0.0003	0.0000
Neuroblastoma	3	0.0018	0.0005	0.0001	0.0002	0.0001	0.0003

Cohort	Mean diagnosis age, years* (14)	Mortality Risks, yearly rate† (9)					
		Late recurrence mortality	Absolute Excess Mortality				
			Subsequent cancers	Cardiac	Pulmonary	External	Other
Soft tissue sarcoma	9	0.0038	0.0013	0.0002	0.0001	0.0005	0.0000
Ewing sarcoma	9	0.0095	0.0021	0.0009	0.0001	0.0009	0.0000
Osteosarcoma	13	0.0042	0.0010	0.0003	0.0001	0.0002	0.0009
Other bone tumors	13	0.0041	0.0004	0.0000	0.0000	0.0000	0.0000

CNS = central nervous system; PNET = primitive neuroectodermal tumor; ICD = International Classification of Diseases, Ninth Revision.

*Age at start of model simulation for a cohort of 5-year survivors = mean diagnosis age + 5 years.

†Mortality categories defined as follows: subsequent cancer (ICD-9 140–239), cardiac (ICD-9 390–398, 402, 404, 410–429), pulmonary (ICD-9 460–519), external causes (accidents, suicide, poisoning, etc; ICD-9 800–999), and other causes (all other ICD-9 codes).

‡Years since diagnosis-specific mortality rates.

§Constant mortality rates.

Table 2

Model results: Life expectancy and lifetime cause-specific mortality risk

Subgroup	Mean diagnosis age, years (14)	Conditional Life Expectancy*				Lifetime cause-specific mortality probabilities†		
		U.S. general population, years†	Five-year childhood cancer survivors, years†	Loss in life expectancy, years† (range‡)	Reduction in life expectancy, %†	Recurrence	Excess subsequent cancers, cardiac, pulmonary, external causes	Excess other causes
Overall (base case)§	10	61.0	50.6	10.4 (8.9–12.2)	17.1%	0.10	0.15	0.05
Sex§								
Men	10	57.7	49.2	9.0 (8.3–9.8)	15.7%	0.11	0.09	0.02
Women	10	64.2	54.8	10.0 (8.8–10.6)	15.6%	0.09	0.12	0.03
Age at diagnosis‖								
0–4 years	2	68.9	61.4	8.1 (7.3–9.4)	11.8%	0.08	0.08	0.01
5–9 years	7	63.9	54.7	9.9 (8.3–10.8)	15.5%	0.10	0.09	0.03
10–14 years	12	59.1	49.2	10.5 (8.9–11.8)	17.7%	0.12	0.11	0.02
15–20 years	17	54.4	43.5	11.4 (10.5–13.0)	21.0%	0.13	0.15	0.03
Year of diagnosis‖								
1970–1973	10	61.0	50.1	11.5 (10.0–12.8)	18.8%	0.11	0.14	0.02
1974–1977	10	61.0	51.9	9.7 (8.8–11.3)	15.8%	0.10	0.11	0.02
1978–1981	10	61.0	53.5	8.1 (7.2–9.6)	13.2%	0.09	0.08	0.01
1982–1986	10	61.0	52.6	9.0 (7.7–9.6)	14.8%	0.10	0.08	0.02
Diagnosis‖								
Acute lymphoblastic leukemia	7	63.9	54.7	10.1 (8.5–10.9)	15.7%	0.12	0.07	0.01
Acute myeloid leukemia	9	62.0	50.9	11.8 (6.4–16.4)	19.0%	0.13	0.12	0.03
Other leukemia	8	63.0	49.7	14.4 (10.5–19.5)	22.9%	0.20	0.10	0.00
Astrocytomas	8	63.0	50.0	13.7 (10.2–14.9)	21.8%	0.14	0.13	0.03
Medulloblastoma, PNET	8	63.0	47.0	17.3 (12.8–21.1)	27.5%	0.24	0.09	0.01
Other CNS tumors	8	63.0	46.3	17.8 (11.2–21.9)	28.2%	0.20	0.14	0.05
Hodgkin disease	15	56.2	46.2	10.4 (9.7–12.7)	18.5%	0.08	0.19	0.03
Non-Hodgkin lymphoma	12	59.1	53.4	5.9 (4.1–7.9)	10.0%	0.04	0.11	0.02
Kidney tumors	5	65.9	62.1	4.0 (2.7–6.0)	6.0%	0.02	0.07	0.02

Subgroup	Mean diagnosis age, years (14)	Conditional Life Expectancy*				Lifetime cause-specific mortality probabilities†		
		U.S. general population, years†	Five-year childhood cancer survivors, years†	Loss in life expectancy, years† (range‡)	Reduction in life expectancy, %†	Recurrence	Excess subsequent cancers, cardiac, pulmonary, external causes	Excess other causes
Neuroblastoma	3	67.9	62.7	5.5 (3.0–7.2)	8.1%	0.04	0.07	0.01
Soft tissue sarcoma	9	62.0	53.2	9.3 (7.1–10.7)	15.1%	0.09	0.10	0.03
Ewing sarcoma	9	62.0	45.7	17.4 (13.5–21.8)	28.0%	0.20	0.14	0.04
Osteosarcoma	13	58.1	50.0	8.7 (5.7–10.4)	14.9%	0.10	0.11	0.01
Other bone tumors	13	58.1	52.9	5.8 (1.0–14.9)	10.0%	0.10	0.03	0.00

CNS = central nervous system; PNET = primitive neuroectodermal tumors

*Conditional on surviving initial cancer diagnosis for 5 years after diagnosis, such that: overall life expectancy = diagnosis age + 5 years + conditional life expectancy.

†Based on deterministic results.

‡Based on probabilistic sensitivity analysis.

§Based on years since diagnosis-specific mortality rates.

||Based on constant non-background mortality rates