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

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Background: Although childhood cancer survival rates have dramatically increased, survivors face elevated risk for life-threatening late effects, including secondary cancer.

Objective: To estimate the cumulative effect of disease- and treatment-related mortality risks on survivor life expectancy.

Design: State-transition model to simulate the lifetime clinical course of childhood cancer survivors.

Setting: Childhood Cancer Survivor Study.

Patients: Five-year survivors of childhood cancer.

Measurements: Probabilities of risk for death from the original cancer diagnosis, excess mortality from subsequent cancer and cardiac, pulmonary, external, and other complications, and background mortality (age-specific mortality rates for the general population) were estimated over the lifetime of survivors of childhood cancer.

Results: For a cohort of 5-year survivors aged 15 years who received a diagnosis of cancer at age 10 years, the average lifetime probability was 0.10 for late-recurrence mortality; 0.15 for treatment-related subsequent cancer and death from cardiac, pulmonary, and external causes; and 0.05 for death from other excess risks. Life expectancy for the cohort of persons aged 15 years was 50.6 years, a loss of 10.4 years (17.1%) compared with the general population. Reduction in life expectancy varied by diagnosis, ranging from 4.0 years (6.0%) for kidney tumor survivors to more than 17.8 years (≥28.0%) for brain and bone tumor survivors, and was sensitive to late-recurrence mortality risk and duration of excess mortality risk.

Limitation: Estimates are based on data for survivors who received treatment 20 to 40 years ago; patients who received treatment more recently may have more favorable outcomes.

Conclusion: Childhood cancer survivors face considerable mortality during adulthood, with excess risks reducing life expectancy by as much as 28%. Monitoring the health of current survivors and carefully evaluating therapies with known late toxicities in patients with newly diagnosed cancer are needed.

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More than 10 000 children and adolescents receive a diagnosis of cancer in the United States each year (1). Since the 1960s, advances in treatment have dramatically reduced mortality rates. Five-year survival rates now approximate 80% for children who receive a diagnosis of cancer. As the population of more than 300 000 long-term survivors in the United States continues to grow and the damaging effects of treatment become more widely recognized, a better understanding of the impact of late effects on survivors' health is needed (2).

Several long-term studies on the late effects of disease and treatment have emerged in recent years (3–11). The most recent cohort study provides natural history data and suggests that 5-year survivors of childhood cancer who received a diagnosis before 1990 face an 8.4-fold increased risk for death compared with the general population (9). In particular, survivors face higher risks for death from subsequent cancer, cardiac events, and pulmonary complications. Survivors also have a higher prevalence of chronic conditions, with as many as two thirds reporting at least 1 chronic condition and one fourth reporting a severe disabling or life-threatening condition (12). Although these studies suggest that 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 estimate the excess mortality risk that survivors face in the decades immediately after initial diagnosis, the cumulative lifelong effect of these risks on overall mortality in life-years lost is uncertain and has not been previously quantified. By using a model-based approach, we estimated the overall effect of disease- and treatment-related mortality risks on the life expectancy of survivors of childhood cancer.

METHODS

Model Structure

We developed a state-transition model to simulate the lifetime clinical course of survivors of childhood cancer (**Figure 1**) (13). At the start of the simulation, a cohort of

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Context

Many people who received treatment for childhood cancer survive cancer and live into adulthood; therefore, it is important to understand the late health effects of childhood cancer treatments.

Contribution

The researchers developed a computer model to simulate outcomes for persons who survived at least 5 years after receiving treatment for childhood cancer. Survivors face health risks that shorten their life span by about 10 years on average.

Caution

Data used in the model reflected treatments that were used 20 to 40 years ago.

Implication

Survivors of childhood cancer face health risks from cancer recurrence, treatment-related cancer, and other treatment-related problems. Close follow-up and less toxic treatments may improve outcomes among childhood cancer survivors.

—The Editors

5-year survivors of childhood cancer enters the model. Each month, individuals face competing mortality risks, which we categorized as the risk for death from the original cancer diagnosis (late recurrence); excess mortality from nonrecurrence late effects (subsequent cancer and cardiac, pulmonary, external, and other complications); and background mortality (age-specific mortality rates for the general population). By following persons throughout their lifetime and recording cause-specific mortality, the model estimates the following outcomes for cohorts of survivors of childhood cancer: lifetime cause-specific mortality, life expectancy, cause-specific attributable proportion of overall mortality risk, and conditional 10-year mortality probabilities. We calculated loss in life expectancy as the difference in life expectancy between a cohort of survivors and a cohort representative of the U.S. population (which faces zero risk for recurrence or treatment-related mortality). We conducted sensitivity analyses to assess how key variables and assumptions might influence results, including a probabilistic sensitivity analysis using second-order Monte Carlo simulations to more fully account for uncertainty. We constructed the model by using TreeAge Pro Suite 2006 (TreeAge Software, Williamstown, Massachusetts).

Model Inputs and Assumptions

Table 1 summarizes selected variable estimates (9, 14). For our base-case analysis, we simulated a cohort of 5-year survivors of childhood cancer aged 15 years (mean age at diagnosis, 10 years), which represented that of the Childhood Cancer Survivor Study (CCSS)—the largest, multiinstitutional, retrospective study of U.S. persons who have survived at least 5 years after childhood cancer treatment (**Appendix**, available at www.annals.org) (15). The survivors originally received a diagnosis before age 21 years from 1970 to 1986. We based variable estimates for each of the competing risks on a recent analysis of mortality from the CCSS, which included approximately 339 000 person-years of observation and 2820 deaths (9). The data from this analysis are the most comprehensive estimates available to date and reflect time-since-diagnosis estimates for each late effect–associated mortality risk (data previously unavailable in any published large population- or hospital-based cohort study).

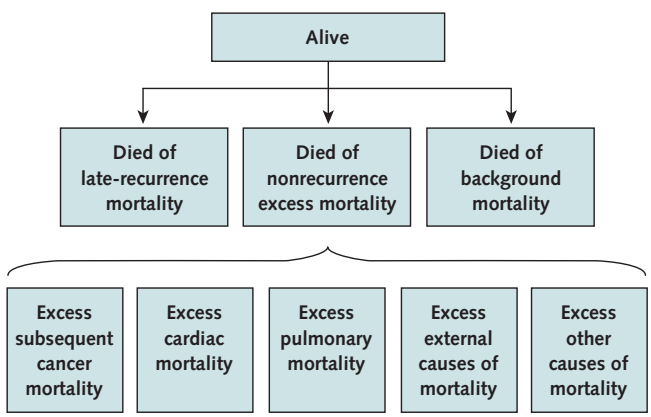
Mortality From Late Recurrence

Individuals faced risk for death from recurrence of the original cancer. The risk varied by years since diagnosis and was highest 5 to 9 years after diagnosis (0.0099 per year). Risk for death declined 30 to 34 years after diagnosis (0.0005 per year). For 35 years or more since diagnosis, we assumed that risk remained at the same level as that for 30 to 34 years since diagnosis, because follow-up data for the period were not yet available from the CCSS.

Nonrecurrence Excess Mortality

Persons faced excess risks for death from disease- and treatment-related late effects. We used published absolute excess risk (AER) estimates, which were based on cause-specific standard mortality ratios derived from multivariate Poisson regression (9), to show the additional mortality risk that survivors of childhood cancer faced compared with the general population (16). On the basis of death certificate data and International Classification of Diseases,

Figure 1. **Model structure.**



At the start of the simulation, a cohort of 5-year survivors of childhood cancer enters the model. Each month, they face a risk for late-recurrence mortality, nonrecurrence excess mortality, and background mortality. Nonrecurrence excess mortality includes risks associated with subsequent cancer; cardiac, pulmonary, and external causes; and other causes. Persons are followed throughout their lifetime.

Table 1. **Model Inputs: Selected Variable Estimates***

Cohort	Mean Age at Diagnosis, y†	Mortality Risks (Annual Rate)‡					
		Late-Recurrence Mortality	Absolute Excess Mortality				
			Subsequent Cancer	Cardiac	Pulmonary	External	Other Cause
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‖							
Male	10	0.0048	0.0012	0.0004	0.0002	0.0003	0.0000
Female	10	0.0038	0.0014	0.0003	0.0002	0.0005	0.0000
Age at diagnosis‖							
0–4 y	2	0.0033	0.0009	0.0002	0.0001	0.0002	0.0000
5–9 y	7	0.0044	0.0010	0.0003	0.0001	0.0004	0.0000
10–14 y	12	0.0050	0.0014	0.0004	0.0003	0.0005	0.0001
15–20 y	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
Astrocytoma	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
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-9 = International Classification of Diseases, 9th Revision.
* See references 9 and 14.
† Age at start of model simulation for a cohort of 5-y survivors = mean age at diagnosis + 5 y.
‡ Mortality categories were subsequent cancer (ICD-9 codes 140–239), cardiac (ICD-9 codes 390–398, 402, 404, 410–429), pulmonary (ICD-9 codes 460–519), external (accidents, suicide, poisoning [ICD-9 codes 800–999]), and other causes (all other ICD-9 codes).
§ Range reflects mortality rates specific to years since diagnosis.
‖ Estimates are constant mortality rates.

9th revision (ICD-9), codes, we categorized AER estimates into 5 subtypes: secondary or subsequent cancer (ICD-9 codes 140 to 239), cardiac causes (ICD-9 codes 390 to 398, 402, 404, or 410 to 429), pulmonary causes (ICD-9 codes 460 to 519), external causes (accidents, suicide, or poisoning [ICD-9 codes 800 to 999]), and other causes (all other ICD-9 codes, such as infectious and parasitic diseases [ICD-9 codes 001 to 139], diseases of the nervous system and sense organs [ICD-9 codes 320 to 389], cerebrovascular diseases [ICD-9 codes 430 to 438], and diseases of the digestive system [ICD-9 codes 520 to 579]). Except for external causes of death, which only exceeded general population rates during 15 to 19 years since diagnosis, the AER for each competing risk increased with years since diagnosis (9).

Because data were unavailable for 25 years or more since diagnosis, we assumed that nonrecurrence excess mortality risks remained constant at the levels of 20 to 24 years since diagnosis.

Background Mortality

Individuals also faced age- and sex-specific general population mortality rates on the basis of U.S. life tables from the National Center for Health Statistics from 1979 to 1998 (17).

Subgroup Analyses

For specific analyses related to diagnosis age, treatment era, sex, and cancer diagnosis, we incorporated subgroup-specific mean age at diagnosis and risks for late-recurrence mortality and nonrecurrence excess mortality (**Table 1**). We used constant mortality risk estimates because data by years since diagnosis were unavailable for subgroups. Data

for the overall cohort suggest that for late recurrence, the risk for mortality dramatically decreases with time; for nonrecurrence excess mortality, the risk increases as survivors age (9). Therefore, for subgroup analyses, we assumed that the risk for late-recurrence mortality was negligible after 35 years since diagnosis, and the risks associated with nonrecurrence late effects were lifelong at constant rates.

Sensitivity Analysis

We conducted univariate sensitivity analyses to assess the stability of results of base-case model estimates. We established a plausible range for each model variable by using 95% CIs (**Appendix**, available at www.annals.org) and varied each one over its range while we held other variables constant (9). We also used U.S. life tables from 1970 to 2004 to evaluate the effect of differential background mortality rates on results (17, 18). To show the uncertainty in our estimates, we conducted a probabilistic sensitivity analysis by using 1000 second-order Monte Carlo simulations in which all values were simultaneously varied (except for background mortality) by using normal distributions based on 95% CIs, assuming a value of 0 for any negative numbers that occurred from sampling.

Role of the Funding Source

This study was supported in part by the National Cancer Institute. The funding source had no involvement in the design of the study; collection, analysis, or interpretation of the data; preparation, review, or approval of the finished manuscript; or the decision to submit the manuscript for publication.

RESULTS

Model Validation

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

Overall Cohort (Base Case)

Lifetime Cause-Specific Mortality

For a cohort representative of the CCSS, we found that the average lifetime cause-specific probability was 0.10 for late-recurrence mortality, 0.20 for nonrecurrence excess mortality (subsequent treatment-related cancer, 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 30% of overall mortality probability (**Appendix**, available at www.annals.org).

Life Expectancy

For a cohort of 5-year survivors of childhood cancer that was diagnosed at age 10 years, the model projected a conditional life expectancy of 50.6 years. Compared with 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 from 1989 to 1991) (17), our estimate represented a loss in life expectancy of 10.4 years (17.1%) (**Appendix**, available at www.annals.org) but differed depending on age at diagnosis, treatment era, and type of cancer (see the Subgroups section below).

Cause-Specific Attributable Proportion of Overall Mortality Risk

Figure 2 shows how the overall risk for death each year attributed to each competing risk changed over time. From 5 to 40 years after diagnosis, the risk for death from cancer- or treatment-related causes exceeded background mortality in the general population. Beginning at 45 years after diagnosis, however, the risk for death from background causes exceeded the risk for all late effects combined.

Conditional 10-Year Mortality Probabilities

The model projected that for survivors who reached age 40 years, the probability of dying before age 50 years was 0.11. For survivors aged 60 years, the probability of dying before age 70 years was 0.25. As such, compared with the general population, the relative likelihood of dying within 10 years decreased from 3-fold among persons aged 40 years to 1.4-fold for those aged 60 years.

Subgroups

The model estimated that persons who received a diagnosis at an older age or received treatment in earlier eras had greater loss in life-years (**Table 2**). The loss in life-years was similar for men (9.0 years [15.7%]) and women (10.0 years [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 ($\geq$28.0%) for selected brain tumors and Ewing sarcoma. For all subgroups, the relative likelihood of dying within 10 years also decreased with age (1.3 to 3.1 for persons aged 40 years to 1.1 to 1.2 for persons aged 60 years) (**Appendix**, available at www.annals.org).

Sensitivity Analyses

We conducted a series of sensitivity analyses to evaluate the effect of alternative assumptions on the reduction in life expectancy for the base-case cohort (**Appendix**, available at www.annals.org). We found that results were sensitive to reductions in late-recurrence mortality risk; this may result from more effective modern treatments or safer or lower-dose treatments that reduce the magni-

Table 2. **Model Results: Life Expectancy and Lifetime Cause-Specific Mortality Risk**

Cohort	Mean Age at Diagnosis, y*	Conditional Life Expectancy†				Lifetime Cause-Specific Mortality Probabilities‡		
		U.S. General Population, y‡	Five-Year Survivors of Childhood Cancer, y‡	Loss in Life Expectancy‡ (Range§), y	Reduction in Life Expectancy, %‡	Late Recurrence	Excess Subsequent Cancer and Cardiac, Pulmonary, and 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‖								
Male	10	57.7	49.2	9.0 (8.3–9.8)	15.7	0.11	0.09	0.02
Female	10	64.2	54.8	10.0 (8.8–10.6)	15.6	0.09	0.12	0.03
Age at diagnosis¶								
0–4 y	2	68.9	61.4	8.1 (7.3–9.4)	11.8	0.08	0.08	0.01
5–9 y	7	63.9	54.7	9.9 (8.3–10.8)	15.5	0.10	0.09	0.03
10–14 y	12	59.1	49.2	10.5 (8.9–11.8)	17.7	0.12	0.11	0.02
15–20 y	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
Astrocytoma	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
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

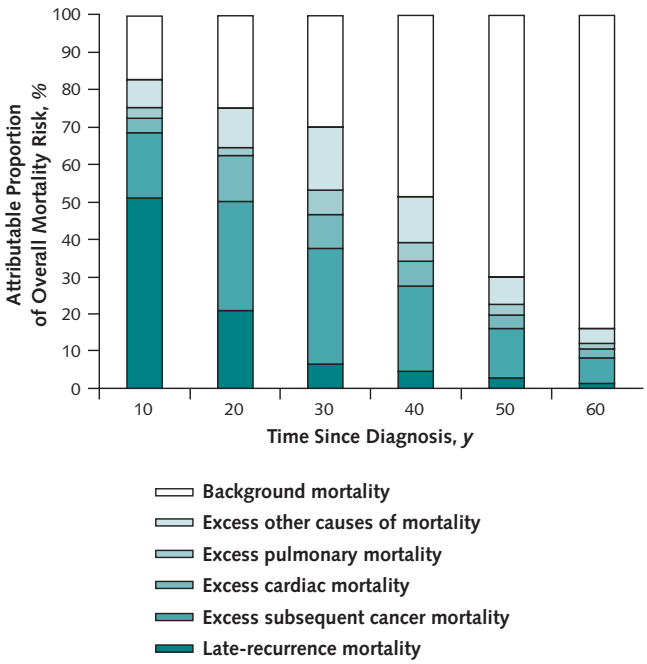
CNS = central nervous system; PNET = primitive neuroectodermal tumor.
* See reference 14.
† Conditional on surviving initial cancer diagnosis for 5 y after diagnosis, such that overall life expectancy = mean age at diagnosis + 5 y + conditional life expectancy. For example, overall life expectancy for the base case = 10 y + 5 y + 50.6 = 65.6 y.
‡ Based on deterministic results.
§ Based on probabilistic sensitivity analysis.
‖ Based on years since diagnosis-specific mortality rates.
¶ Based on constant nonbackground mortality rates.

tude or duration of risk for subsequent treatment-related late effects, specifically for subsequent cancer and other causes. For example, if the excess risk for subsequent cancer was reduced by 50%, the loss in life expectancy declined from 10.4 to 9.0 years, a decrease of nearly 15%. If the risk for late-recurrence mortality also decreased by 50%, the loss in life-years was 6.9 years, a combined decrease of 33%.

We analyzed several scenarios to provide insight on how late-recurrence and nonrecurrence excess mortality risks affected overall reduction in life expectancy. If survivors were only at risk for late-recurrence mortality (and negligible risk for all nonrecurrence 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 persons did not have relapse but were at risk for non–relapse-associated mortality, the loss was still 6.2 years. Reduction varied for diagnosis-specific subgroups (range, 0.9 to 7.4 years), depending on the magnitude of nonrecurrence mortality risk. For example, if survivors were at risk for only nonrecurrence excess mortality, the reduction in life expectancy for medulloblastomas, which have substantial late-recurrence mortality risk, decreased from 17.3 years to 4.3 years. In contrast, for kidney tumors, which have relatively low risk for late-recurrence mortality, the life expectancy reduction decreased from only 4.0 to 2.9 years (see **Appendix**, available at www.annals.org, for additional details).

Because follow-up data for more than 35 years since diagnosis are not yet available, we also conducted a sce-

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



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.

nario analysis in which the risk for recurrence and excess risk for nonrecurrence late effects were negligible for persons aged 45 years. For the overall cohort, the reduction in life expectancy was 8.2 years (base case, 10.4 years; diagnosis-specific results ranged from 3.0 to 16.4 years; see **Appendix**, available at www.annals.org). The probability of late-recurrence mortality remained largely unchanged (base case, 0.09 vs. 0.10) for the overall cohort, although the risks for death from excess subsequent cancer; cardiac, pulmonary, or external causes (base case, 0.08 vs. 0.15); and other causes (base case, 0.02 vs. 0.05) were considerably lower. These results suggest that recognition and treatment of illnesses associated with late effects in the first 35 years after therapy for childhood cancer will probably result in improved longevity.

Probabilistic sensitivity analysis, reflecting uncertainty, suggested that the reduction in life expectancy for the overall cohort ranged from 8.9 to 12.2 years. **Table 2** shows uncertainty intervals for all subgroup analyses. The reduction in life expectancy increased with age at diagnosis, which is probably associated with age-specific cancer subtypes. In addition, from 1970 to 1981, serial reductions in the impact of late effects on life expectancy were observed, although improvements seemed to level off between 1982 and 1986. The **Appendix** (available at www.annals.org) shows additional details.

Discussion

Five-year survivors of childhood cancer face considerable excess mortality risks during adulthood. By using data from the CCSS, which is based on 26 collaborating U.S. and Canadian institutions that treat children with cancer and is considered largely representative of the population of U.S. cancer survivors, we provided 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 survivors, depending on their original cancer diagnosis, will live 4 to 18 fewer years on average than similar-aged general populations—a reduction in life expectancy of up to 28%. Approximately 1 in 4 survivors is estimated to die of late recurrence or late effects related to secondary cancer and cardiopulmonary conditions, and 1 in 20 will die of other excess risk. These findings suggest that the combined impact of late effects on life expectancy is substantial and varies by cancer diagnosis and even tumor type; this underscores the importance of monitoring the health of the growing population of survivors of childhood cancer and evaluating newer therapies for patients with newly diagnosed cancer, which might be associated with decreased late toxicity.

Several long-term cohort studies on survivors of childhood cancer in the published literature (MEDLINE search of studies published in English to October 2008) describe the excess mortality risk associated with disease- and treatment-related late effects, but the most recent data from the CCSS provide the most comprehensive estimates to date on mortality as well as morbidity. Oeffinger and coworkers (12) found that more than 6% of survivors of childhood cancer report disabling or life-threatening conditions and an additional 20% report severe chronic conditions. Another group of investigators similarly estimated that nearly 25% of survivors had a high or severe burden of adverse events comprising at least 2 severe events or 1 or more life-threatening or disabling events (19). Survivors self-report not only higher-than-expected rates of cardiac, pulmonary, or oncologic conditions but also increased rates of renal disease, major joint replacement, and neurologic and neurosensory dysfunction.

In aggregate, these chronic illnesses will probably lead to other disabling conditions through multifactorial pathways and will probably adversely affect the progression of other health problems associated with aging. For example, a history of radiation therapy, which includes the coronary arteries and is used to treat many adolescent lymphomas, increases the risk for ischemic heart disease and its associated mortality. Alternatively, this ischemia may result 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 and colleagues (20) found that young adults who survive child-

hood cancer are clearly at risk for early cardiac morbidity and mortality not typically recognized in this age group and that the cumulative incidence of adverse cardiac outcomes continues to increase up to 30 years after diagnosis. The excess risk related to therapy for childhood cancer may lead to additional excess mortality risks other than those already observed. For some survivors, the increased risk for several comorbid conditions 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 participants in the Framingham Heart Study found that death certificate data correctly identified 78% to 97% of coronary heart disease and cancer deaths (23). Several large-scale survivor cohort studies have reported very similar rates of absolute excess mortality risks, however, suggesting some reliability of estimates (5–7, 24). By applying background mortality rates for the general population, we also assumed that survivors have average patterns of care.

Second, we used late-effects mortality risks from the CCSS only, and many variables are uncertain. Although other cohort studies also provide mortality risks, the CCSS is the only study to date that provides estimates by time since diagnosis and tumor type within cancer diagnoses and shows the underlying variation in mortality risks. By using probabilistic sensitivity analysis, we present the uncertainty surrounding model inputs and the effect 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. 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%); the lifetime likelihood of dying of recurrence increased from 0.10 in the base case to 0.12, and the likelihood of dying of nonrecurrence late effects decreased from 0.20 to 0.12. As such, our subgroup estimates may underestimate the loss in life expectancy.

Finally, 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 patients with Hodgkin disease or leukemia who received treatment with and without radiation. Changes in therapies that limit exposure to high-dose anthracyclines may also be modeled to determine whether the expected reduction in overall mortality is attainable. With subgroup-specific mortality estimates, we can explore whether disparities in long-term outcomes by race or ethnicity exist, because 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 after initial diagnosis of childhood cancer. As such, multidisciplinary surveillance of survivors' health during these years may be most important in reducing mortality. Clinicians providing ongoing care for these aging survivors should be familiar with surveillance guidelines on late effects, such as those compiled by the Children's Oncology Group (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 have late recurrence of their original cancer, the major determinant of decreased life expectancy is the excess risk associated with subsequent cancer, which accounts for approximately 50% of all nonrecurrence 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. Most adult survivors of childhood cancer do not receive regular medical care focused on their long-term risks based on exposures. For example, many young female survivors do not undergo screening mammography, which is recommended for those aged 25 years 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 is required. In addition, policies are strongly needed to ensure that survivors have access to their needed medical care. Compared with 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 patients may face financial challenges in providing or obtaining coverage for survivor health care needs.

Changes in childhood cancer therapy have increased cure rates over the past 4 decades. Consistent with serial improvements over time, we found that survivors with the earliest dates of diagnosis (1970 to 1973) had the most pronounced reductions in life expectancy compared with those who received treatment in more recent decades (1978 to 1986). In our model, this improvement in outcome over time can be attributed to better maintenance of primary cancer control and 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 disease, selected brain tumors, and Ewing sarcoma (**Appendix**, available at www.annals.org). This finding is consistent with changes in treatment for these diseases during this interval; the aggressive, combined-method therapies used are associated with substantial cardiopulmonary toxicities and risks for secondary cancer. More recent treatments have been developed that are directed toward

maintenance of cure, along with reduction of long-term late effects. Therapies that use specific cardioprotectant medications, reduced-dose radiation, and dose-limitation of organ-toxic agents may result in improved outcomes, and as such, further analyses of the effect of these strategies on long-term mortality risk are needed.

Our estimates are based on data from survivors treated 20 to 40 years ago. Because treatment has since changed, data on survivors treated more recently can provide insight on how advances in treatment since 1986 have affected life expectancy. In 2007, the CCSS began recruiting a second set of participants who received treatment for cancer as children from 1987 to 1999 (29); however, data are not available yet. Other, smaller cohort studies (with 1400 to 2400 patients) provide some data on the AER for overall death for patients treated more recently. For example, in the Netherlands cohort, compared with patients whose cancer was diagnosed from 1966 to 1984, the AER for death overall was 7% lower among patients in whom cancer was diagnosed after 1984 until 1996 (6). In a Canadian cohort, between the treatment eras of 1980 to 1989 and 1990 to 1995, the AER increased 5% (7). Neither study reported excess mortality risks by late recurrence and other specific causes. 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 patients treated more recently and inform clinical trials on pediatric cancer treatment, which are increasingly informed by adverse outcomes in survivors.

Although our model predicts substantial reductions in life expectancy in survivors of childhood cancer who received treatment in previous decades, often with now-historical therapies, it highlights the need to minimize the use of agents associated with late toxicities for patients with newly diagnosed cancer and to follow survivors of these newer therapies to assess late toxicities. The considerable effect of these excess risks on life expectancy emphasizes the need for primary care physicians to attend not only to the risk for cancer recurrence but also to the risks for nonrecurrence side effects. For the now-adult survivors of childhood cancer, 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 effects on their long-term survival.

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References

1. **National Cancer Institute.** A snapshot of pediatric cancers. Vol. 2008. Bethesda, MD: National Cancer Institute; 2007.
2. **Hewitt M, Weiner SL, Simone JV, eds.** Childhood cancer survivorship: improving care and quality of life. Washington DC: National Academies Pr; 2003.
3. **Simone JV.** Late mortality in childhood cancer: two excellent studies bring good news tempered by room for improvement [Editorial]. J Clin Oncol. 2001;19:3161-2. [PMID: 11432881]
4. **Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al.** Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol. 2001;19:3163-72. [PMID: 11432882]
5. **Möller TR, Garwicz S, Barlow L, Falck Winther J, Glattre E, Olafsdottir G, et al; Association of the Nordic Cancer Registries.** Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: a population-based study in the Nordic countries. J Clin Oncol. 2001;19:3173-81. [PMID: 11432883]
6. **Cardous-Ubbink MC, Heinen RC, Langeveld NE, Bakker PJ, Voûte PA, Caron HN, et al.** Long-term cause-specific mortality among five-year survivors of childhood cancer. Pediatr Blood Cancer. 2004;42:563-73. [PMID: 15127410]
7. **MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Abanto ZU, McBride ML.** Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. Pediatr Blood Cancer. 2007;48:460-7. [PMID: 16767717]
8. **Inskip PD, Curtis RE.** New malignancies following childhood cancer in the United States, 1973-2002. Int J Cancer. 2007;121:2233-40. [PMID: 17557301]
9. **Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, et al.** Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2008;100:1368-79. [PMID: 18812549]
10. **Green DM, Hyland A, Chung CS, Zevon MA, Hall BC.** Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. J Clin Oncol. 1999;17:3207-15. [PMID: 10506620]
11. **Lawless SC, Verma P, Green DM, Mahoney MC.** Mortality experiences among 15+ year survivors of childhood and adolescent cancers. Pediatr Blood Cancer. 2007;48:333-8. [PMID: 16453299]
12. **Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al; Childhood Cancer Survivor Study.** Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355:1572-82. [PMID: 17035650]
13. **Sonnenberg FA, Beck JR.** Markov models in medical decision making: a practical guide. Med Decis Making. 1993;13:322-38. [PMID: 8246705]
14. **U.S. Cancer Statistics Working Group.** U.S. Cancer Statistics: 1999–2004 Incidence and Mortality Web-based Report, vol. 2008. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2007.
15. **Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, et al.** Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol. 2002;38:229-39. [PMID: 11920786]
16. **Kuntz KM, Weinstein MC.** Life expectancy biases in clinical decision mod-

eling. Med Decis Making. 1995;15:158-69. [PMID: 7783577]
17. **Centers for Disease Control and Prevention, National Center for Health Statistics.** CDC WONDER On-line Database, compiled from Compressed Mortality File CMF 1968-1988, Series 20, No. 2A, 2000 and CMF 1989-1998, Series 20, No. 2E, 2003.; 2009.
18. **Arias E.** United States life tables, 2004. Natl Vital Stat Rep. 2007;56:1-39. [PMID: 18274319]
19. **Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, et al.** Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA. 2007;297:2705-15. [PMID: 17595271]
20. **Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, et al.** Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ. 2009;339:b4606. [PMID: 19996459]
21. **Kircher T, Anderson RE.** Cause of death. Proper completion of the death certificate. JAMA. 1987;258:349-52. [PMID: 3599328]
22. **Sirken MG, Rosenberg HM, Chevarley FM, Curtin LR.** The quality of cause-of-death statistics [Editorial]. Am J Public Health. 1987;77:137-9. [PMID: 3799853]
23. **Lloyd-Jones DM, Martin DO, Larson MG, Levy D.** Accuracy of death certificates for coding coronary heart disease as the cause of death. Ann Intern Med. 1998;129:1020-6. [PMID: 9867756]
24. **Ries LA, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, et al.** Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, MD: National Cancer Institute; 1999. NIH publication no. 99-4649.
25. **Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG.** Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. JAMA. 2003;290:2008-14. [PMID: 14559954]
26. **Children's Oncology Group**. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Bethesda, MD: Children's Oncology Group; 2006.
27. **Nathan PC, Greenberg ML, Ness KK, Hudson MM, Mertens AC, Mahoney MC, et al.** Medical care in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2008;26:4401-9. [PMID: 18802152]
28. **Park ER, Li FP, Liu Y, Emmons KM, Ablin A, Robison LL, et al; Childhood Cancer Survivor Study.** Health insurance coverage in survivors of childhood cancer: the Childhood Cancer Survivor Study. J Clin Oncol. 2005;23:9187-97. [PMID: 16361621]
29. **Twombly R.** Childhood cancer survivor study doubles to examine late effects of new treatments. J Natl Cancer Inst. 2007;99:1574-6. [PMID: 17971522]

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Appendix: The CCSS

The CCSS is the largest, multi-institutional, retrospective study of persons who have survived for at least 5 years after treatment of childhood cancer in the United States (15). Diagnoses include leukemia, central nervous system tumors, Hodgkin disease, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft-tissue sarcoma, and bone tumors. Germ-cell tumors, liver tumors, and retinoblastoma were excluded. With leukemia representing one third of all types of cancer, the composition of the CCSS cohort is reasonably representative of the distribution of childhood types of cancer reported in the U.S. Surveillance, Epidemiology, and End Results (SEER) cancer registry (24), except for underrepresentation of central nervous tumor (13% in CCSS vs. 22% in SEER) and overrepresentation of Wilms tumors (9% in CCSS vs. 5% in SEER).

Technical Details: State-Transition Markov Model

At the start of the model simulation, a cohort of 5-year survivors of childhood cancer enters the state-transition Markov model. Each month, they face a risk for death, characterized by:

$$pr(Die) = 1 - \exp(-muDie)$$

where

$$pr(Die) = \text{probability of dying}$$

$$muDie = \text{rate of dying}$$

As such, each month, they either die or remain alive. The cohort is followed throughout their lifetime. The rate of dying (*muDie*), defined as the sum of individual competing risks, is characterized by the following equation:

$$muDie = \sum_{i=1}^{7} mu_i(t)$$

where

$$i = \begin{cases} 1 = \text{late recurrence mortality} \\ 2 = \text{excess mortality from secondary or subsequent cancer} \\ 3 = \text{excess mortality from cardiac causes} \\ 4 = \text{excess mortality from pulmonary causes} \\ 5 = \text{excess mortality from external causes} \\ 6 = \text{excess mortality from other causes} \\ 7 = \text{background mortality} \end{cases}$$

and

$$t = \text{month since diagnosis}$$

The total rate of dying each month was then allocated according to the ratio of each individual competing risk divided by the total rate ($mu_i/muDie$).

For the base case, risks for late-recurrence mortality and nonrecurrence late effects mortality (that is, excess mortality from second or subsequent cancer, cardiac causes, pulmonary causes, external causes, or other causes) vary by years since diagnosis. For all analyses, background mortality risk was age- and sex-specific. Late-recurrence mortality risks were based on published estimates from the CCSS cohort (9). We assumed that rates for late-recurrence mortality risk at 35 years or more since diagnosis remained the same as those at 30 to 34 years since diagnosis (9); for all nonrecurrence late effects at 25 years or more since diagnosis, rates remained the same as those at 20 to 24 years since diagnosis; and because individuals can die of only 1 cause, mortality risks were mutually exclusive.

For the subgroup analyses, mortality risks by time since diagnosis were unavailable for all late effects. We therefore used constant mortality rates for the overall follow-up period and made the following additional assumptions. For late-recurrence mortality risk at 35 years or more since diagnosis, risk was negligible; this was based on specific time-since-diagnosis estimates for the overall cohort, which showed that the risk dramatically decreased with time from 0.99% at 5 to 9 years since diagnosis to 0.05% per year at 30 to 34 years since diagnosis (9). We also assumed that for nonrecurrence excess mortality (that is, subsequent cancer and cardiac, pulmonary, external, and other causes), risks were lifelong because overall cohort data showed that rates increased with time.

The model simulates the cohort throughout their lifetime and records cause-specific mortality, which allows the estimation of the following outcomes: lifetime cause-specific mortality probability, life expectancy, cause-specific attributable proportion of overall mortality risk by year since diagnosis, and conditional 10-year mortality probabilities.

Plausible Ranges Used for Sensitivity Analyses

Appendix Table 1 provides details on the 95% CIs used for univariate and probabilistic sensitivity analyses. For probabilistic sensitivity analysis, normal distributions based on 95% CIs were

used, assuming a value of 0 for any negative numbers that occurred from sampling.

Additional Results: Model Validation

Appendix Figure 1 shows that model estimates of the proportion of deaths attributable to late recurrence, subsequent cancer, and all other noncancer causes approximated published estimates from other large population- and hospital-based cohort studies of 5-year survivors of childhood cancer at 15 years since diagnosis.

Lifetime Cause-Specific Mortality

Appendix Figure 2 shows the lifetime cause-specific mortality probability for a cohort of 5-year survivors of childhood cancer and compares the overall lifetime mortality probability with that of the general U.S. population.

Conditional 10-Year Mortality Probabilities

For a cohort of 5-year survivors of childhood cancer, the probabilities of dying within 10 years upon reaching age 40, 50, and 60 years varied by subgroup. **Appendix Table 2** summarizes subgroup-specific results.

Additional Sensitivity Analyses: Univariate Sensitivity Analysis

Appendix Figure 3 summarizes univariate sensitivity analyses on select variables by using a tornado diagram.

Probabilistic Sensitivity Analysis for Selected Subgroups

Appendix Figure 4 shows probabilistic sensitivity analyses for selected subgroups. The impact of late effects on overall life expectancy seems to increase with earlier treatment eras and age at diagnosis.

Appendix Table 1. **Late-Effects Mortality Risks**

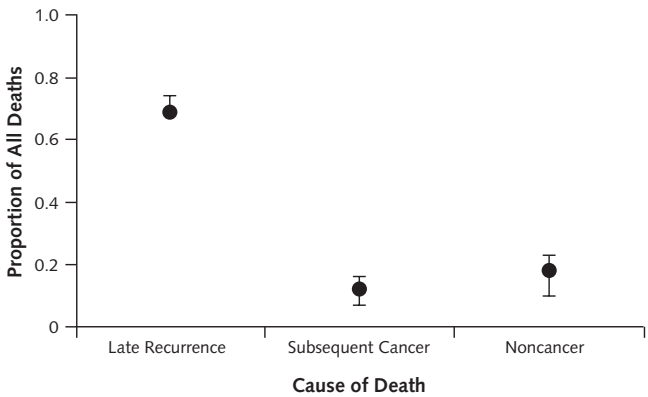
Cohort	Late-Recurrence Mortality (95% CI), %*	Mortality Risk From Nonrecurrence Late Effects (95% CI)†				
		Subsequent Cancer	Cardiac	Pulmonary	External Causes	Other Causes
Overall (base case) years since original diagnosis						
5–9 y	0.93–1.06	1.06–1.53	0.12–0.32	0.06–0.22	0.00–0.02	0.10–0.33
10–14 y	0.29–0.37	0.90–1.35	0.16–0.39	0.11–0.31	0.00–0.08	0.25–0.57
15–19 y	0.12–0.18	0.94–1.45	0.29–0.62	0.08–0.29	0.00–0.29	0.12–0.46
20–24 y	0.08–0.14	1.17–1.96	0.40–0.94	0.03–0.29	0.00–0.26	0.20–0.76
25–29 y‡	0.06–0.16	1.64–3.09	0.31–1.18	0.22–0.92	0.00–0.38	0.73–1.94
30–34 y	0.00–0.26	–	–	–	–	–
Age at diagnosis						
0–4 y	0.30–0.37	0.77–1.11	0.13–0.30	0.07–0.21	0.00–0.04	0.09–0.28
5–9 y	0.40–0.49	0.78–1.25	0.16–0.43	0.04–0.22	0.00–0.17	0.27–0.64
10–14 y	0.45–0.56	1.15–1.75	0.21–0.54	0.14–0.41	0.00–0.33	0.31–0.76
15–20 y	0.53–0.66	2.05–2.92	0.62–1.16	0.15–0.46	0.00–0.07	0.31–0.86
Year of diagnosis						
1970–1973	0.43–0.54	1.57–2.29	0.27–0.63	0.22–0.54	0.00–0.00	0.30–0.77
1974–1977	0.38–0.47	1.21–1.75	0.39–0.74	0.11–0.33	0.00–0.21	0.21–0.56
1978–1981	0.36–0.45	0.78–1.22	0.23–0.51	0.02–0.16	0.00–0.29	0.13–0.43
1982–1986	0.40–0.48	0.86–1.28	0.09–0.27	0.07–0.23	0.00–0.06	0.23–0.52
Sex						
Male	0.45–0.51	1.06–1.39	0.31–0.52	0.13–0.26	0.00–0.08	0.19–0.42
Female	0.35–0.42	1.21–1.61	0.22–0.41	0.10–0.24	0.00–0.06	0.33–0.59
Diagnosis						
Acute lymphoblastic leukemia	0.48–0.58	0.71–1.13	0.05–0.23	0.01–0.14	0.00–0.00	0.12–0.39
Acute myeloid leukemia	0.40–0.74	0.28–1.80	0.00–0.89	0.12–1.32	0.00–1.51	0.00–1.32
Other leukemia	0.69–1.13	0.64–2.51	0.00–0.90	0.19–1.51	0.00–0.36	0.00–0.54
Astrocytoma	0.54–0.73	0.65–1.45	0.11–0.58	0.22–0.75	0.00–0.43	0.35–1.07
Medulloblastoma, PNET	0.92–1.40	0.81–2.75	0.00–0.42	0.00–0.69	0.00–0.51	0.00–0.93
Other CNS tumors	0.73–1.21	0.32–2.05	0.00–0.48	0.01–1.05	0.00–1.90	0.27–2.09
Hodgkin disease	0.28–0.38	2.52–3.56	0.90–1.58	0.18–0.55	0.00–0.27	0.34–0.93
Non-Hodgkin lymphoma	0.10–0.20	0.91–1.88	0.19–0.79	0.06–0.48	0.00–0.38	0.04–0.68
Kidney tumors	0.05–0.11	0.53–1.24	0.15–0.62	0.00–0.22	0.00–0.18	0.08–0.56
Neuroblastoma	0.13–0.24	0.24–0.88	0.00–0.34	0.03–0.41	0.00–0.39	0.00–0.43
Soft-tissue sarcoma	0.31–0.45	0.95–1.82	0.06–0.47	0.00–0.25	0.00–0.20	0.20–0.83
Ewing sarcoma	0.76–1.18	1.22–3.33	0.32–1.75	0.00–0.62	0.00–0.68	0.26–1.84
Osteosarcoma	0.33–0.53	0.55–1.60	0.06–0.71	0.00–0.38	0.00–0.63	0.00–0.60
Other bone tumors	0.17–0.85	0.00–3.11	0.00–2.05	0.00–2.14	0.00–2.59	0.00–1.77

CNS = central nervous system; PNET = primitive neuroectodermal tumor.
* Annual mortality rate as reported by the Childhood Cancer Survivor Study. See reference 8.
† Absolute excess risk (per 1000 person-years) as estimated by the Childhood Cancer Survivor Study (Personal communication).
‡ For nonrecurrence late effects, the value is for ≥25 y since diagnosis.

Scenario Analysis for Subgroups

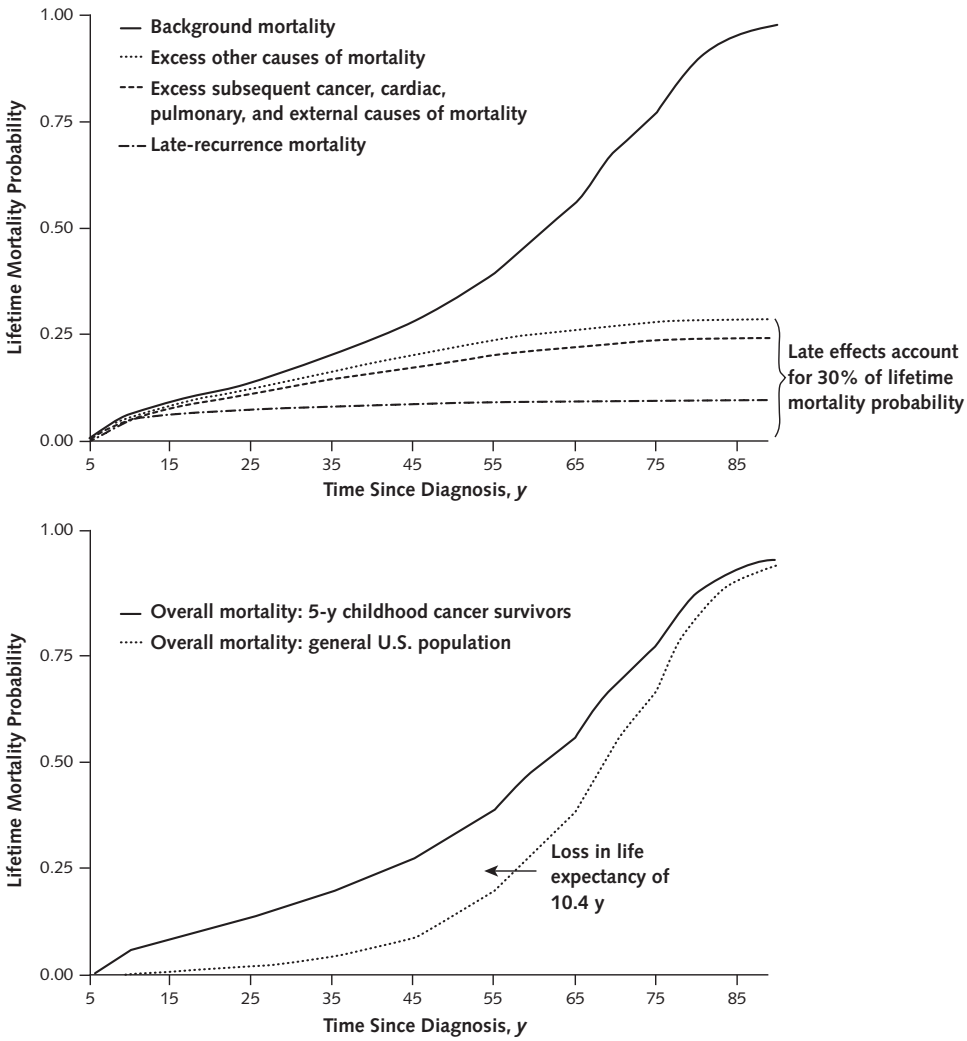
Appendix Table 3 shows additional results for scenario analyses. In addition to background mortality, survivors were at risk for only late-recurrence mortality; only nonrecurrence excess mortality (that is, subsequent cancer and cardiac, pulmonary, external, and other causes); and late effects for only 34 years since diagnosis (that is, after 35 years or more since diagnosis, risks for late-recurrence mortality or nonrecurrence excess mortality were negligible).

Appendix Figure 1. **Model validation on proportion of all deaths attributable to specific causes at 15 years since diagnosis.**



The proportion of deaths attributable to late recurrence, subsequent cancer, and all other noncancer causes approximates published estimates from other large population- and hospital-based cohort studies of 5-year childhood cancer survivors. Solid circles indicate model estimates, and bars indicate the range among published estimates (5–7).

Appendix Figure 2. **Lifetime cause-specific mortality probability.**



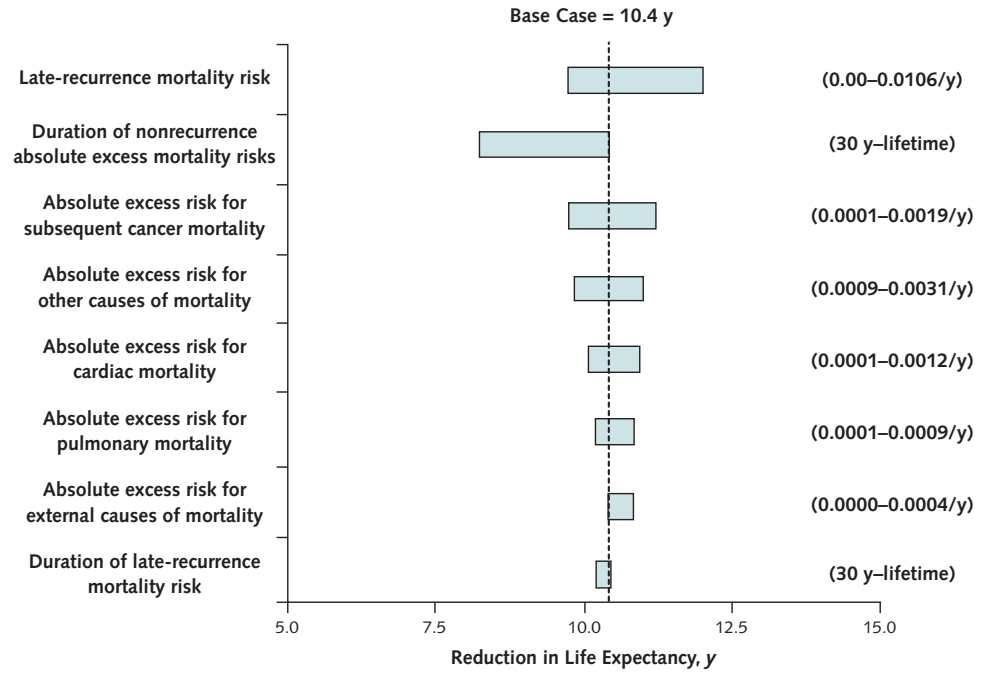
Top. Incremental lifetime cause-specific mortality probability for late recurrence; excess risk for subsequent cancer and cardiac, pulmonary, and external causes; excess risk for other causes; and background mortality. **Bottom.** Overall lifetime mortality probability for a cohort of 5-year childhood cancer survivors and the general U.S. population. The area between the curves represents a loss in life expectancy of 10.4 years.

Appendix Table 2. **Subgroup-Specific Probabilities of Death Within 10 y of Age 40, 50, and 60 y for a Cohort of 5-y Survivors of Childhood Cancer**

Cohort	Mean Age at Diagnosis, *y**	Conditional 10-y Cumulative Mortality Probability (Relative Risk)†		
		Age 40 y	Age 50 y	Age 60 y
Overall (base case)	10	0.11 (3.3)	0.16 (1.9)	0.25 (1.4)
Sex				
Male	10	0.09 (1.9)	0.13 (1.2)	0.25 (1.1)
Female	10	0.07 (2.7)	0.08 (1.4)	0.16 (1.2)
Age at diagnosis				
0–4 y	2	0.06 (1.8)	0.09 (1.1)	0.19 (1.1)
5–9 y	7	0.08 (2.1)	0.10 (1.2)	0.20 (1.1)
10–14 y	12	0.09 (2.4)	0.11 (1.3)	0.20 (1.1)
15–20 y	17	0.10 (2.8)	0.12 (1.4)	0.21 (1.2)
Year of diagnosis				
1970–1973	10	0.09 (2.5)	0.11 (1.4)	0.21 (1.1)
1974–1977	10	0.08 (2.2)	0.10 (1.3)	0.20 (1.1)
1978–1981	10	0.07 (2.0)	0.10 (1.2)	0.19 (1.1)
1982–1986	10	0.07 (2.1)	0.10 (1.2)	0.20 (1.1)
Diagnosis				
Acute lymphoblastic leukemia	7	0.06 (1.7)	0.10 (1.2)	0.19 (1.1)
Acute myeloid leukemia	9	0.08 (2.3)	0.11 (1.3)	0.20 (1.1)
Other leukemia	8	0.08 (2.2)	0.10 (1.2)	0.20 (1.1)
Astrocytoma	8	0.08 (2.4)	0.11 (1.4)	0.21 (1.1)
Medulloblastoma, PNET	8	0.09 (2.5)	0.10 (1.2)	0.20 (1.1)
Other CNS tumors	8	0.10 (2.8)	0.12 (1.4)	0.21 (1.2)
Hodgkin disease	15	0.11 (3.1)	0.12 (1.5)	0.22 (1.2)
Non-Hodgkin lymphoma	12	0.07 (1.9)	0.10 (1.3)	0.20 (1.1)
Kidney tumors	5	0.05 (1.4)	0.09 (1.1)	0.19 (1.1)
Neuroblastoma	3	0.05 (1.3)	0.09 (1.1)	0.19 (1.1)
Soft-tissue sarcoma	9	0.07 (2.1)	0.10 (1.3)	0.20 (1.1)
Ewing sarcoma	9	0.11 (3.0)	0.12 (1.4)	0.21 (1.2)
Osteosarcoma	13	0.09 (2.5)	0.10 (1.3)	0.20 (1.1)
Other bone tumors	13	0.07 (2.0)	0.09 (1.1)	0.18 (1.0)

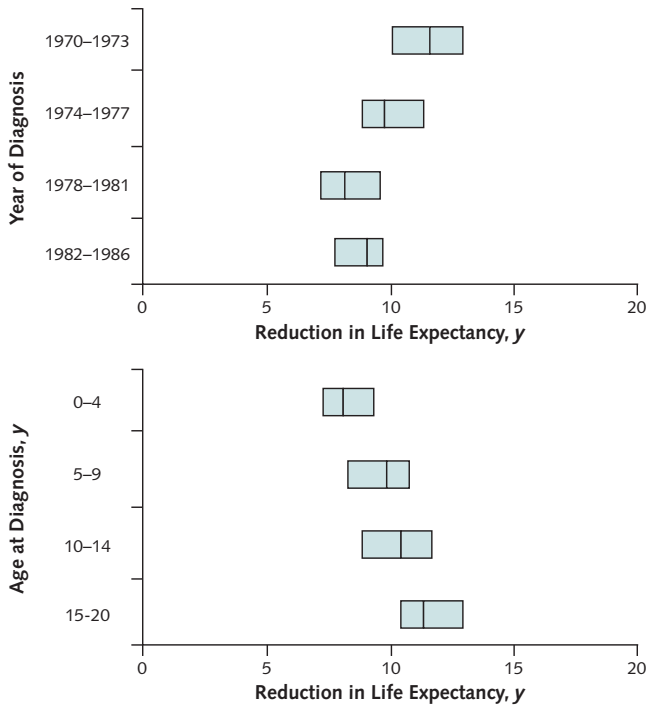
CNS = central nervous system; PNET = primitive neuroectodermal tumor.
* See reference 14.
† Conditional on surviving the initial cancer diagnosis for 5 y after diagnosis and reaching 40, 50, or 60 years of age, as specified. Comparison is with the conditional 10-y cumulative mortality probability for the general population of the same age.

Appendix Figure 3. **Tornado diagram of sensitivity analysis on selected model variables.**



Variables are ranked to show their relative influence on the base-case results. The effect of changes in selected variables on the loss in life-years for the base-case estimate is shown. Information in parentheses is the upper and lower bounds used in the sensitivity analysis. The shaded bars indicate the variation in the loss of life-years caused by changes in the value of the specified variable while all other variables were held constant; longer bars indicate greater sensitivity. The vertical dashed line indicates the base-case estimate of loss in life-years.

Appendix Figure 4. **Probabilistic sensitivity analysis for selected subgroups.**



Lines within the bars indicate the mean reduction in life expectancy. **Top.** Uncertainty intervals for treatment-era subgroups, using 1000 second-order Monte Carlo simulations. **Bottom.** Uncertainty intervals estimated for diagnosis age subgroups.

Appendix Table 3. Additional Sensitivity Analyses: Selected Scenarios Analysis

Cohort	Life Expectancy, by Scenario, *y (%)*					
	Survivors at Risk for Late-Recurrence Mortality Only*		Survivors at Risk for Nonrecurrence Excess Mortality Only†		Survivors at Risk for Late Effects for 34 y Since Diagnosis Only‡	
	Conditional§	Reduction	Conditional§	Reduction	Conditional§	Reduction
Overall (base case)	56.2	4.8 (7.8)	54.8	6.2 (10.2)	52.8	8.2 (13.5)
Sex						
Male	51.9	5.8 (10.1)	54.0	3.7 (6.4)	49.5	8.2 (14.2)
Female	58.8	5.4 (8.4)	59.1	5.2 (8.0)	55.6	8.6 (13.5)
Age at diagnosis						
0–4 y	63.7	5.2 (7.5)	65.7	3.2 (4.6)	61.7	7.1 (10.3)
5–9 y	57.8	6.2 (9.6)	59.7	4.2 (6.6)	55.2	8.8 (13.7)
10–14 y	52.8	6.3 (10.6)	54.2	4.8 (8.2)	49.7	9.4 (15.8)
15–20 y	47.9	6.5 (11.9)	48.6	5.8 (10.7)	44.1	10.3 (18.9)
Year of diagnosis						
1970–1973	54.8	6.2 (10.2)	55.0	6.0 (9.8)	51.0	10.0 (16.4)
1974–1977	55.3	5.6 (9.3)	56.5	4.5 (7.4)	52.5	8.5 (14.0)
1978–1981	55.8	5.2 (8.5)	57.8	3.2 (5.3)	53.7	7.2 (11.9)
1982–1986	55.2	5.8 (9.5)	57.4	3.6 (6.0)	52.9	8.1 (13.3)
Diagnosis						
Acute lymphoblastic leukemia	56.7	7.2 (11.3)	60.7	3.3 (5.1)	54.7	9.2 (14.4)
Acute myeloid leukemia	54.7	7.3 (11.7)	56.7	5.3 (8.5)	51.5	10.5 (16.9)
Other leukemia	51.6	11.4 (18.1)	59.1	3.9 (6.1)	49.4	13.5 (21.5)
Astrocytoma	54.5	8.4 (13.4)	56.6	6.3 (10.1)	50.7	12.2 (19.4)
Medulloblastoma, PNET	48.8	14.2 (22.5)	58.6	4.3 (6.9)	46.6	16.4 (26.1)
Other CNS tumors	50.9	12.1 (19.2)	55.6	7.4 (11.8)	46.8	16.2 (25.7)
Hodgkin disease	52.2	4.0 (7.1)	49.2	7.0 (12.5)	47.4	8.9 (15.8)
Non-Hodgkin lymphoma	57.1	2.0 (3.4)	55.1	4.0 (6.8)	54.2	4.8 (8.2)
Kidney tumors	64.8	1.1 (1.7)	63.0	2.9 (4.5)	62.9	3.0 (4.6)
Neuroblastoma	65.1	2.8 (4.1)	65.0	2.8 (4.2)	63.3	4.6 (6.7)
Soft-tissue sarcoma	56.8	5.2 (8.3)	57.3	4.6 (7.5)	53.9	8.1 (13.1)
Ewing sarcoma	50.1	11.8 (19.1)	54.8	7.2 (11.6)	46.1	15.8 (25.6)
Osteosarcoma	53.0	5.2 (8.9)	54.2	3.9 (6.7)	50.4	7.7 (13.3)
Other bone tumors	53.1	5.0 (8.6)	57.3	0.9 (1.5)	52.6	5.6 (9.6)

CNS = central nervous system; PNET = primitive neuroectodermal tumor.
* Negligible nonrecurrence excess mortality.
† Negligible late-recurrence mortality.
‡ Negligible risk ≥35 y since diagnosis.
§ Conditional on surviving the initial cancer diagnosis for 5 y after diagnosis, such that overall life expectancy = mean age at diagnosis + 5 y + conditional life expectancy.