ORIGINAL ARTICLE

Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer

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ABSTRACT

BACKGROUND

Among patients in whom childhood cancer was diagnosed in the 1970s and 1980s, 18% of those who survived for 5 years died within the subsequent 25 years. In recent decades, cancer treatments have been modified with the goal of reducing life-threatening late effects.

METHODS

We evaluated late mortality among 34,033 patients in the Childhood Cancer Survivor Study cohort who survived at least 5 years after childhood cancer (i.e., cancer diagnosed before the age of 21 years) for which treatment was initiated during the period from 1970 through 1999. The median follow-up was 21 years (range, 5 to 38). We evaluated demographic and disease factors that were associated with death from health-related causes (i.e., conditions that exclude recurrence or progression of the original cancer and external causes but include the late effects of cancer therapy) using cumulative incidence and piecewise exponential models to estimate relative rates and 95% confidence intervals.

RESULTS

Of the 3958 deaths that occurred during the study period, 1618 (41%) were attributable to health-related causes, including 746 deaths from subsequent neoplasms, 241 from cardiac causes, 137 from pulmonary causes, and 494 from other causes. A reduction in 15-year mortality was observed for death from any cause (from 12.4% in the early 1970s to 6.0% in the 1990s, P<0.001 for trend) and from health-related causes (from 3.5% to 2.1%, P<0.001 for trend). These reductions were attributable to decreases in the rates of death from subsequent neoplasm (P<0.001), cardiac causes (P<0.001), and pulmonary causes (P=0.04). Changes in therapy according to decade included reduced rates of cranial radiotherapy for acute lymphoblastic leukemia (85% in the 1970s, 51% in the 1980s, and 19% in the 1990s), of abdominal radiotherapy for Wilms' tumor (78%, 53%, and 43%, respectively), of chest radiotherapy for Hodgkin's lymphoma (87%, 79%, and 61%, respectively), and of anthracycline exposure. Reduction in treatment exposure was associated with reduced late mortality among survivors of acute lymphoblastic leukemia and Wilms' tumor.

CONCLUSIONS

The strategy of lowering therapeutic exposure has contributed to an observed decline in late mortality among 5-year survivors of childhood cancer. (Funded by the National Cancer Institute and the American Lebanese–Syrian Associated Charities.)

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In the 1960s, fewer than half the children in whom cancer was diagnosed were still alive 5 years later.[1] Now, more than 83% of patients with a childhood cancer in the United States become 5-year survivors of the disease.[2] As a result, in 2013 it was estimated that there were more than 420,000 survivors of childhood cancer in the United States and that by the year 2020 this number would surpass 500,000.[3] Increased success in the treatment of childhood cancers has been achieved through the systematic conduct of clinical trials to assess the efficacy of multimodal approaches involving combination chemotherapy, radiotherapy, and surgery, along with increased expertise in supportive care.[4,5] Five-year overall survival has been the primary benchmark of therapeutic success. However, as 5-year survival rates increased, it became clear that long-term survivors of childhood cancer were at increased risk for severe and life-threatening therapy-related late effects[6-8] and excess late mortality (i.e., death ≥5 years after diagnosis).[9-16] Previous results from the Childhood Cancer Survivor Study (CCSS) showed that by 30 years after the diagnosis of childhood cancer, 18% of 5-year survivors had died.[17]

In more recent decades, risk stratification of therapy has increasingly guided the design of treatment regimens for the majority of pediatric cancers. Recent expansion of the CCSS cohort, which now includes survivors in whom cancer was diagnosed from 1970 through 1999, provides an excellent opportunity to evaluate changes over time in therapy and the effect of these changes on overall and cause-specific late mortality.

Methods

Population

The CCSS is a multi-institutional, retrospective, hospital-based cohort study, with longitudinal follow-up of survivors of childhood cancer that was diagnosed and treated at 31 institutions in the United States and Canada (https://ccss.stjude.org). The 34,033 eligible patients in our study included those who had received a diagnosis of cancer before the age of 21 years, with initial treatment performed between January 1, 1970, and December 31, 1999, and who were alive 5 years after the diagnosis. The survivors who were included in the evaluation — and who had received the diagnosis of leukemia, tumor of the central nervous system, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Wilms' tumor, neuroblastoma, soft-tissue sarcoma, and bone tumor — represented approximately 20% of childhood-cancer survivors in the United States during the study period. The study methods and design have been described in detail previously.[18] The CCSS was approved by the institutional review board at each of the 31 participating centers. All the participants provided informed consent either in writing or by completing a survey. For participants under the age of 18, consent was provided by a parent or guardian.

Ascertainment of Cause of Death

The patients who were eligible to participate were included in a search for matching death records in the National Death Index through 2007. The index provided underlying and multiple causes of death for deceased patients according to the criteria of the *International Classification of Diseases, 9th* and *10th Revisions* (ICD-9 and ICD-10). For the 139 deaths that predated the National Death Index (i.e., patients who died during the period of 1975 through 1978), we requested death certificates from states in which the deaths had occurred. We used ICD-9 and ICD-10 coding to group the deaths into three mutually exclusive categories: recurrence or progression of the primary cancer; external causes, including accidents, suicides, and poisonings (ICD-9 codes 800–999 and ICD-10 codes V00–V99, W00–W99, X00–X99, and Y00–Y89); and health-related causes, including subsequent neoplasms (ICD-9 codes 140–239 and ICD-10 codes C00–C97 and D10–D36), cardiac causes (ICD-9 codes 390–398, 402, 404, and 410–429 and ICD-10 codes I00–I02, I05–I09, I11, I13, I14, I20–I28, and I30–I52), pulmonary causes (ICD-9 codes 460–519 and ICD-10 codes J00–J99), and all other causes.

Data on Cancer Treatments

Using standardized CCSS protocols, we abstracted data regarding cancer diagnosis and treatment, including chemotherapy and radiotherapy exposures, from the medical records of 24,243 survivors who provided authorization.[19,20] For the 9790 survivors for whom treatment information was not available, we used multiple-imputation methods.

STATISTICAL ANALYSIS

Late mortality was evaluated from 5 years after diagnosis until either death or December 31, 2007, the last date of the National Death Index search. We estimated the cumulative incidence of cause-specific death, stratified according to treatment era as defined by 5-year or 10-year intervals and according to the primary cancer diagnosis. We calculated standardized mortality ratios to quantify the rate of death in the CCSS cohort as compared with rates in the U.S. population, according to age, calendar year, and sex.[21]

We used multivariable piecewise exponential models to assess relative rates, with 95% confidence intervals, of death from health-related causes in specific treatment eras, as compared with a reference treatment era from 1970 through 1979, after adjustment for sex, primary cancer diagnosis, age at diagnosis, and attained age (which was defined as single-year age segments of the piecewise exponential regression, modeled according to natural cubic splines with knots at 10, 20, 30, and 40 years). We hypothesized that if changes in treatment were responsible for changes in mortality, adjustment for treatment should attenuate the observed effects of treatment eras. Thus, within specific primary cancer groups, we evaluated changes in mortality by comparing the treatment-era effects with and without adjustment for the treatment variables in the model, after adjustment for sex, age at diagnosis, and attained age.

To augment the regression-based analysis with a visual description of changes in treatment according to era, we calculated treatment scores for individual survivors from the multivariable piecewise exponential model that included treatment variables, with adjustment for sex, age at diagnosis, and attained age but not with adjustment for treatment era. (Details regarding the derivation and use of the treatment score are provided in Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

For each survivor with missing treatment data, we used multiple-imputation methods.[22] (Details regarding the methods that were used and an associated sensitivity analysis are provided in Section 2 in the Supplementary Appendix.) For the 440 Canadian patients, for whom the specific cause of death was unknown, we used the predictive-mean-matching method to impute the cause of death, using the age at diagnosis, year of diagnosis, treatment institution, cancer-diagnosis group, and treatment variables as predictors of causes of death. For 27 patients with missing data regarding the time of death, we used the multiple-imputation method proposed by Taylor et al.[23] Because the specific cause of death was not available for Canadian patients, we performed a sensitivity analysis that was restricted to only U.S. survivors. Since no appreciable differences were found, we present the original analysis results. Because of the many comparisons made with these data, P values for differences in mortality among patients with specific cancer types or from specific causes should be regarded as exploratory.

RESULTS

STUDY PATIENTS

The cohort of 34,033 eligible survivors included more than 9000 survivors who received their initial diagnosis in the 1970s, more than 13,000 survivors from the 1980s, and more than 11,000 survivors from the 1990s (Table 1, and Table S1 in the Supplementary Appendix). These patients provided a total of 705,806 person-years of observation. Of the survivors, 30% were between the ages of 30 and 39 years and 15% were older than 40 years of age at the last follow-up (median age, 28.5 years; range, 5.5 to 58.5). Overall, 57% of the cohort received radiotherapy, including 77% of survivors from the 1970s, as compared with only 41% from the 1990s. In contrast, more survivors received chemotherapy (including anthracyclines and alkylating agents) in the 1990s than in the 1970s, but the average cumulative dose of chemotherapeutic agents was lower (Table S2 and Fig. S1 and S2 in the Supplementary Appendix).

RATES OF DEATH

A total of 3958 deaths occurred in the cohort, with 2002 attributable to recurrence or progression of the primary cancer, 338 to external causes, and 1618 to health-related causes, including 746 from subsequent neoplasms, 241 from cardiac causes, 137 from pulmonary causes, and 494 from other causes. At 15 years after diagnosis, the cumulative incidence of death from any

Table 1. Characteristics of 5-Year Survivors of Childhood Cancer.

Characteristic	All Patients	Living	Dead
	no.	*no. (%)*	
All patients	34,033	30,075 (88.4)	3958 (11.6)
Sex			
Male	18,983	16,628 (87.6)	2355 (12.4)
Female	15,050	13,447 (89.3)	1603 (10.7)
Race or ethnic group*			
Non-Hispanic white	21,781	19,575 (89.9)	2206 (10.1)
Non-Hispanic black	2,022	1,817 (89.9)	205 (10.1)
Hispanic	2,287	2,094 (91.6)	193 (8.4)
Other	2,057	1,849 (89.9)	208 (10.1)
Unknown	5,886	4,740 (80.5)	1146 (19.5)
Treatment era			
1970–1979	9,416	7,548 (80.2)	1868 (19.8)
1980–1989	13,181	11,699 (88.8)	1482 (11.2)
1990–1999	11,436	10,828 (94.7)	608 (5.3)
Age at diagnosis (yr)			
0–4	13,463	12,319 (91.5)	1144 (8.5)
5–9	7,826	6,950 (88.8)	876 (11.2)
10–14	7,144	6,185 (86.6)	959 (13.4)
15–20	5,600	4,621 (82.5)	979 (17.5)
Survival after diagnosis (yr)			
5–9	4,210	2,349 (55.8)	1861 (44.2)
10–14	6,298	5,523 (87.7)	775 (12.3)
15–19	5,285	4,758 (90.0)	527 (10.0)
20–24	6,721	6,343 (94.4)	378 (5.6)
25–29	5,964	5,692 (95.4)	272 (4.6)
30–34	4,051	3,924 (96.9)	127 (3.1)
≥35	1,504	1,486 (98.8)	18 (1.2)
Diagnosis			
Leukemia	10,199	9,019 (88.4)	1180 (11.6)
Acute lymphoblastic leukemia	8,500	7,557 (88.9)	943 (11.1)
Acute myeloid leukemia	1,222	1,101 (90.1)	121 (9.9)
Other leukemia	477	361 (75.7)	116 (24.3)
Hodgkin's lymphoma	4,332	3,647 (84.2)	685 (15.8)
Non-Hodgkin's lymphoma	2,837	2,621 (92.4)	216 (7.6)
Central nervous system tumor	6,369	5,443 (85.5)	926 (14.5)
Astrocytoma	3,904	3,383 (86.7)	521 (13.3)
Medulloblastoma or PNET†	1,380	1,133 (82.1)	247 (17.9)
Other	1,085	927 (85.4)	158 (14.6)
Wilms' tumor	3,055	2,898 (94.9)	157 (5.1)
Neuroblastoma	2,632	2,457 (93.4)	175 (6.6)
Rhabdomyosarcoma	1,679	1,510 (89.9)	169 (10.1)
Bone tumor	2,930	2,480 (84.6)	450 (15.4)
Ewing's sarcoma	997	813 (81.5)	184 (18.5)
Osteosarcoma	1,771	1,518 (85.7)	253 (14.3)
Other	162	149 (92.0)	13 (8.0)

* Race or ethnic group was self-reported.
† PNET denotes primitive neuroectodermal tumor.

cause among survivors was 10.7% among those whose disease was diagnosed in the 1970s, 7.9% among those whose disease was diagnosed in the 1980s, and 5.8% among those whose disease was diagnosed in the 1990s (P<0.001 for the comparison among the three decades) (Fig. 1, and Table S3 and Fig. S1 in the Supplementary Appendix). Across these decades, the cumulative incidence of death from recurrence or progression of a primary cancer decreased, from 7.1% in the 1970s to 4.9% in the 1980s and 3.4% in the 1990s (P<0.001). Death from health-related causes, which included deaths from late effects of cancer therapy, decreased from 3.1% to 2.4% and 1.9%, respectively (P<0.001) and reflected significant reductions across the three decades in the rate of death from subsequent malignant neoplasms and from cardiac- and pulmonary-related events (Table 2, and Table S4 in the Supplementary Appendix).

In a multivariable model adjusted for cancer diagnosis, age at diagnosis, sex, and attained age, more recent treatment eras were associated with a reduced rate of death. The adjusted relative rate per every 5 years differed significantly from 1.0 for any health-related cause (relative rate, 0.86; 95% confidence interval [CI], 0.82 to 0.89) and for cause-specific death related to subsequent malignant neoplasms (relative rate, 0.83; 95% CI, 0.78 to 0.88), cardiac causes (relative rate, 0.77; 95% CI, 0.68 to 0.86), and pulmonary causes (relative rate, 0.77; 95% CI, 0.66 to 0.89) (Table S5 in the Supplementary Appendix). Similar patterns were seen with respect to reductions in standardized mortality ratios (Table S6 in the Supplementary Appendix).

We observed significant reductions across treatment eras in the rate of death from any health-related cause among survivors of acute lymphoblastic leukemia (from 3.2% in the early 1970s to 2.1% in the 1990s, P<0.001), Hodgkin's lymphoma (from 5.3% to 2.6%, P=0.006), Wilms' tumor (from 2.6% to 0.4%, P=0.005), and astrocytoma (from 4.7% to 1.8%, P=0.02) (Table 2) but not among survivors of the other primary cancer groups. Cardiac mortality declined among patients with acute lymphoblastic leukemia (from 0.6% to 0.1%, P=0.003), Hodgkin's lymphoma (from 0.9% to 0.5%, P=0.06), Wilms' tumor (from 0.3% to 0%, P=0.04), and astrocytoma (from 0.9% to 0%, P=0.02), and the rate of death from subsequent neoplasms was significantly reduced among survivors of Wilms' tumor (from 1.9% to 0%, P<0.001).

EFFECTS OF CHANGES IN TREATMENT

Temporal reductions in exposure to radiotherapy and anthracyclines were observed among patients with acute lymphoblastic leukemia, Hodgkin's lymphoma, Wilms' tumor, and astrocytoma (Table S2 and Fig. S2 and S3 in the Supplementary Appendix). Changes in therapy according to decade included reduced rates of cranial radiotherapy for acute lymphoblastic leukemia (85% in the 1970s, 51% in the 1980s, and 19% in the 1990s), of abdominal radiotherapy for Wilms' tumor (78%, 53%, and 43%, respectively), and of chest radiotherapy for Hodgkin's lymphoma (87%, 79%, and 61%, respectively). For the diagnoses of acute lymphoblastic leukemia, Hodgkin's lymphoma, Wilms' tumor, and astrocytoma, temporal reductions in 15-year rates of death from health-related causes followed temporal reductions in therapeutic exposure (Fig. 2). The effect of the treatment era on the rate of death from a health-related cause was assessed in multivariable models with and without adjustment for therapy (Table 3, and Table S7 in the Supplementary Appendix). The effect of the treatment era on the relative rate of death from health-related causes was attenuated in models adjusted for therapy for acute lymphoblastic leukemia (unadjusted relative rate, 0.88; adjusted relative rate, 1.02) and Wilms' tumor (relative rate, 0.68 and 0.80, respectively) but not in models adjusted for therapy for Hodgkin's lymphoma (relative rate, 0.79 in the two models) and astrocytoma (relative rate, 0.81 and 0.82, respectively).

DISCUSSION

Approaches to the treatment of pediatric cancers have evolved during the past five decades with the global objective of achieving increasing rates of cure while minimizing the risk of short-term and long-term toxic effects.[4,5] In this study, we confirmed previously published data showing that patients who were treated in the 1990s had a significantly lower rate of death from recurrence or progression of their primary cancer than did patients who were treated in earlier decades.[10,24-26] We now also document the reduced rate of death from treatment-related late effects, such as subsequent cancers and cardio-

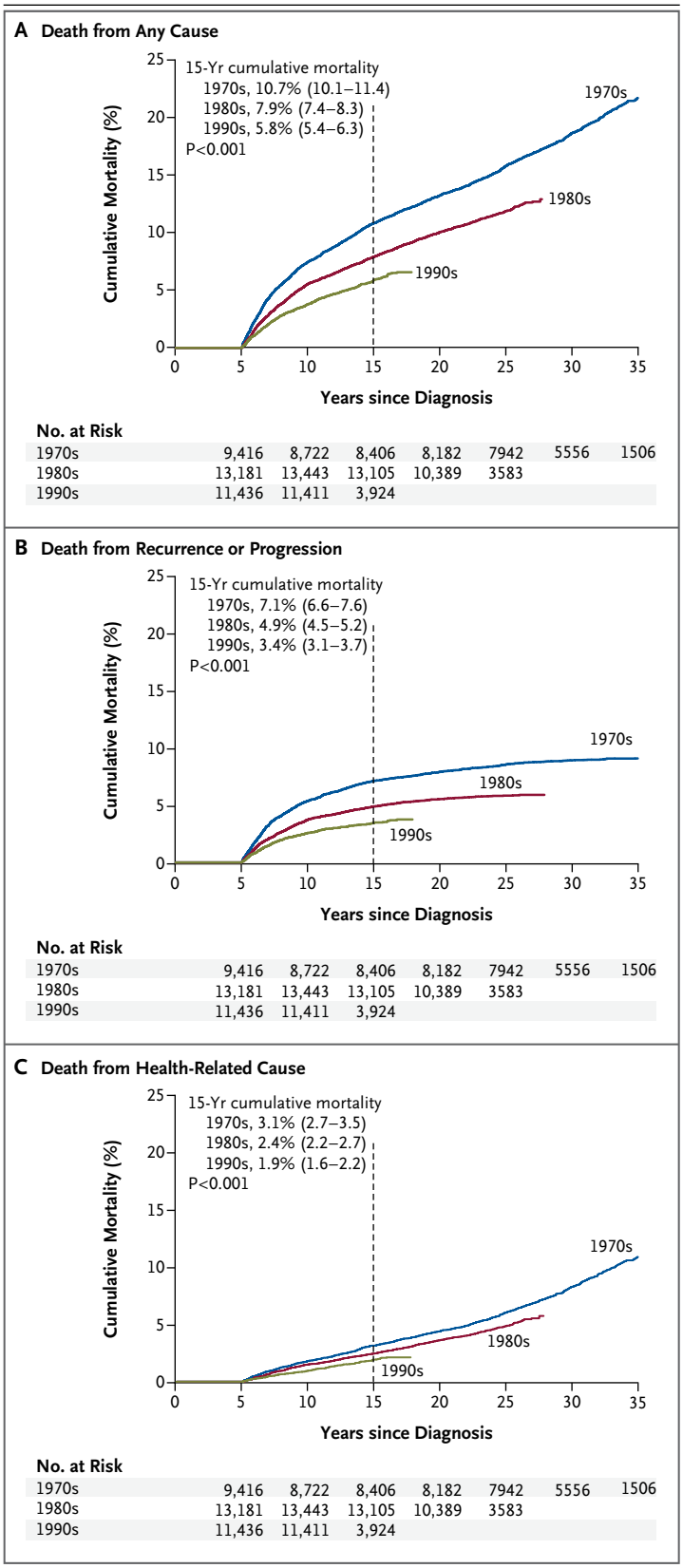

Figure 1. All-Cause and Cause-Specific Cumulative Mortality among 5-Year Survivors of Childhood Cancer, According to Decade.

Shown is the cumulative incidence of death from any cause (Panel A), from disease recurrence or progression (Panel B), and from any health-related cause (Panel C) among 34,033 patients who survived at least 5 years after childhood cancer for which treatment was initiated during the period from 1970 through 1999. The values in parentheses are 95% confidence intervals. The vertical dashed lines indicate 15-year mortality. P values are for the comparisons among the three decades.

pulmonary conditions. In addition, the results that were generated from the CCSS cohort provide evidence that the strategy of reducing treatment exposure in order to decrease the frequency of late effects is translating into a significant reduction in observed late mortality and an extension of the life span of children and adolescents who are successfully treated for cancer.

Appreciation of the risk of long-term adverse consequences of therapy[6-8] resulted in the design and testing of newer treatment regimens to reduce the potential for late effects. This was generally achieved by a reduction in therapeutic exposures in patients who were considered to be at low risk for recurrence of the primary cancer, while providing therapy that would maintain or improve long-term disease-free survival.[14,27-35] The availability of treatment-exposure data in the CCSS cohort, including cumulative doses of most chemotherapeutic regimens and organ-specific radiotherapy dosimetry, provided an excellent opportunity to evaluate whether the risk reduction that had been observed in more recent treatment eras was directly associated with a reduction in therapeutic exposure. We observed temporal reductions in health-related mortality concurrent with a reduction in therapeutic exposure among patients with acute lymphoblastic leukemia and Wilms' tumor. However, with respect to Hodgkin's lymphoma and astrocytoma, our findings suggest that factors other than reduced treatment exposures may have caused the observed reductions in late health-related mortality. Potential contributors to decreased late mortality include increased use and accuracy of screening methods.[36-38] Although data suggest that guideline-based screening and care have not been universally adopted,[39] it should be expected that these efforts would have a positive effect on

Table 2. Cumulative Incidence of Death at 15 Years after Primary Cancer Diagnosis among 5-Year Survivors.*

Diagnosis and Year	Death from Any Cause	Death from Recurrence or Progression	Death from Health-Related Cause				
			Any	Subsequent Neoplasm	Cardiac Cause	Pulmonary Cause	Other†
			percentage				
All diagnoses‡							
Year of diagnosis							
1970–1974	12.4	8.4	3.5	1.8	0.5	0.5	0.9
1975–1979	9.7	6.2	2.9	1.5	0.4	0.2	0.8
1980–1984	8.8	5.5	2.7	1.3	0.3	0.3	0.8
1985–1989	6.9	4.2	2.2	1.3	0.1	0.1	0.5
1990–1994	6.0	3.6	2.1	1.0	0.1	0.1	0.9
P value	<0.001	<0.001	<0.001	<0.001	0.001	0.04	0.13
Acute lymphoblastic leukemia							
Year of diagnosis							
1970–1974	16.6	13.0	3.2	0.9	0.6	0.4	1.2
1975–1979	11.4	8.5	2.6	1.2	0.4	0.1	0.9
1980–1984	9.1	6.6	2.0	1.1	0.1	0.1	0.7
1985–1989	6.9	4.0	2.6	1.9	0.1	0.2	0.5
1990–1994	4.6	2.0	2.1	1.4	0.1	0	0.6
P value	<0.001	<0.001	<0.001	0.14	0.003	0.05	<0.001
Hodgkin's lymphoma							
Year of diagnosis							
1970–1974	13.1	6.9	5.3	2.9	0.9	0.9	0.7
1975–1979	8.6	4.8	3.3	2.0	0.5	0.7	0.8
1980–1984	8.8	3.2	4.6	1.9	1.3	0.5	0.9
1985–1989	5.3	2.9	1.9	1.1	0.5	0	0.3
1990–1994	5.8	2.7	2.6	1.3	0.5	0.5	0.9
P value	<0.001	<0.001	0.006	0.19	0.06	0.05	0.69
Wilms' tumor							
Year of diagnosis							
1970–1974	4.2	1.6	2.6	1.9	0.3	0.9	0.4
1975–1979	3.3	1.1	1.9	0.4	0.8	0.7	0.6
1980–1984	2.5	1.3	0.8	0.5	0	0.5	0.3
1985–1989	2.3	1.9	0.4	0	0.2	0	0.2
1990–1994	2.3	1.6	0.4	0	0	0.5	0.4
P value	0.37	0.80	0.005	<0.001	0.04	0.05	0.83
Astrocytoma							
Year of diagnosis							
1970–1974	13.5	8.5	4.7	2.1	0.9	0.5	1.2
1975–1979	12.2	7.2	4.1	2.4	0.2	0.4	1.1
1980–1984	11.3	7.7	3.0	1.8	0.2	0.6	0.6
1985–1989	7.1	4.8	1.9	0.9	0.2	0.1	0.9
1990–1994	7.4	5.4	1.8	0.5	0	0.2	0.9
P value	<0.001	0.08	0.02	0.02	0.02	0.72	0.84

* All P values are for testing for a trend from 1970–1974 to 1990–1994.
† Other health-related causes are those not included in the listed categories.
‡ The total numbers of survivors were 3696 in 1970–1974, 5720 in 1975–1979, 7184 in 1980–1984, 5997 in 1985–1989, and 5442 in 1990–1994.

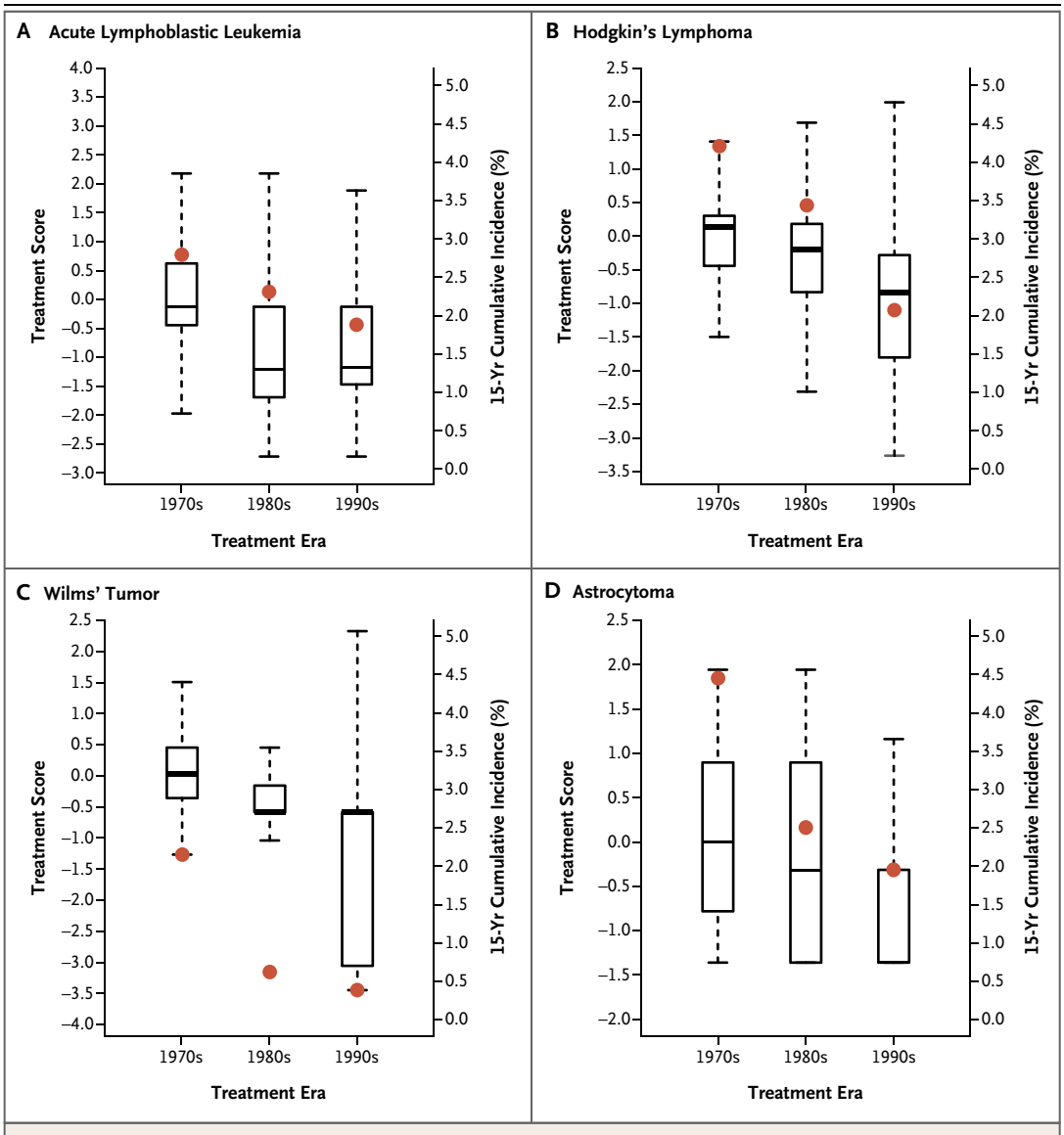

Figure 2. Treatment Score and 15-Year Cumulative Mortality, According to Type of Cancer and Decade.

Shown are box plots of treatment scores (left y axis) and 15-year cumulative mortality (red dot, right y axis) among 5-year survivors of childhood acute lymphoblastic leukemia (Panel A), Hodgkin's lymphoma (Panel B), Wilms' tumor (Panel C), and astrocytoma (Panel D), according to the decade during which treatment was received. Treatment scores quantify the treatment-associated propensity for late mortality from health-related causes. Scores are standardized so that those from the 1970s have a mean of 0 and a standard deviation of 1.0. The reductions in treatment scores that are shown over the decades indicate a reduced treatment-associated propensity for late death. The horizontal line in each box plot shows the median, and the bottom and top of the box are located at the 25th and 75th percentiles, respectively. The I bars represent values that are more than 1.5 times the interquartile range from the border of each box.

health-related mortality. In addition, during the past several decades, there have been improvements in medical care that may delay or prevent death from the late effects of therapy. However, our ability to directly measure these changes in the CCSS population is limited. It should also be

Table 3. Relative Rates of Death from Health-Related Causes and the Effect of Treatment Exposure among 5-Year Survivors of Specific Childhood Cancers per 5-Year Treatment Era, According to Multivariable Model.*

Treatment Era	Acute Lymphoblastic Leukemia	Hodgkin's Lymphoma	Wilms' Tumor	Astrocytoma
		relative rate (95% CI)		
No adjustment for therapy	0.88 (0.81– 0.95)	0.79 (0.72–0.87)	0.68 (0.56–0.84)	0.81 (0.73–0.91)
Adjustment for therapy	1.02 (0.83–1.24)†	0.79 (0.70–0.89)‡	0.80 (0.59–1.08)§	0.82 (0.72–0.94)¶

* All models were adjusted for sex, age at diagnosis, and attained age. CI denotes confidence interval.
† Data were adjusted for cranial radiotherapy dose, anthracycline dose, and exposure to epipodophyllotoxins and glucocorticoids.
‡ Data were adjusted for chest-directed radiotherapy dose, anthracycline dose, cyclophosphamide-equivalent dose, and splenectomy.
§ Data were adjusted for abdominal radiotherapy dose and anthracycline dose.
¶ Data were adjusted for cranial radiotherapy dose and exposure to chemotherapy.

noted that for certain cancers, primarily neuroblastoma, there has been an increase in late mortality in more recent decades, presumably attributable to increased therapeutic intensity that has resulted in improved 5-year survival but an increased risk of late effects and delayed recurrence or progression of the primary cancer.

The overall decrease in all-cause mortality is attributable primarily to a reduction in the rate of death from recurrence or progression of primary cancers, a finding that is consistent with that in previous studies,[12,25] and suggests that 5-year survivors in more recent eras have more durable remissions or a more favorable response to therapy for relapse or recurrence of their primary cancers. Combined improvements in the treatment of primary cancers and reductions in health-related mortality have resulted in a relative reduction of almost 50% in all-cause late mortality among survivors of childhood cancer (from 10.7% at 15 years after diagnosis among survivors from the 1970s to 5.8% among survivors from the 1990s).

Our previous study of registry data suggested that survivors in recent eras may be at a lower risk for death from late effects of cancer therapy than were survivors in earlier eras.[24] The large size of the CCSS cohort and its detailed treatment information provided compelling evidence of a reduction in rates of death from subsequent neoplasm, cardiac causes, and pulmonary causes over the course of three decades. However, any evaluation of our current findings needs to consider several limitations of our study. First, the outcome of health-related causes of death does not allow direct attribution of deaths to sequelae from the treatment of childhood cancer. Second, we could not quantify and directly consider temporal changes in medical care as part of our review. Third, there was a potential for bias resulting from shorter follow-up of survivors from the 1990s (although 10-year patterns appeared to be consistent with those for 15-year mortality [Table S8 in the Supplementary Appendix]). Fourth, we did not evaluate temporal trends in the incidence of specific treatment-related chronic health conditions that could increase the risk of death.

In conclusion, in our study of long-term survivors of pediatric cancer, we confirmed the effect of treatment regimens that have been designed to reduce the potential risk and severity of late effects. Quantitative evidence now shows that the modification of treatment regimens to reduce radiotherapy and chemotherapy exposures, along with increased promotion of strategies for early detection of late effects and improvements in medical care for late effects of therapy, has resulted in the extension of life spans for many survivors of childhood cancer.

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