Late Mortality Experience in Five-Year Survivors of Childhood and Adolescent Cancer: The Childhood Cancer Survivor Study

By Ann C. Mertens, Yutaka Yasui, Joseph P. Neglia, John D. Potter, Mark E. Nesbit Jr, Kathy Ruccione, W. Anthony Smithson, and Leslie L. Robison

Purpose: **Survivors of childhood and adolescent cancer are at risk for long-term effects of disease and treatment. The Childhood Cancer Survivor Study assessed overall and cause-specific mortality in a retrospective cohort of 20,227 5-year survivors.**

Patients and Methods: **Eligible subjects were individuals diagnosed with cancer (from 1970 to 1986) before the age of 21 who had survived 5 years from diagnosis. Underlying cause of death was obtained from death certificates and other sources and coded and categorized as recurrent disease, sequelae of cancer treatment, or non–cancer-related. Age and sex standardized mortality ratios (SMRs) were calculated using United States population mortality data.**

Results: **The cohort, including 208,947 person-years of follow-up, demonstrated a 10.8-fold excess in overall mortality (95% confidence interval, 10.3 to 11.3). Risk of death was statistically significantly higher in females (SMR = 18.2), individuals diagnosed with cancer before the age of 5 years (SMR = 14.0), and those with an initial diagnosis of leukemia (SMR = 15.5) or CNS tumor (SMR = 15.7). Recurrence of the original cancer was the leading cause of death among 5-year survivors, accounting for 67% of deaths. Statistically significant excess mortality rates were seen due to subsequent malignancies (SMR = 19.4), along with cardiac (SMR = 8.2), pulmonary (SMR = 9.2), and other causes (SMR = 3.3). Treatment-related associations were present for subsequent cancer mortality (radiation, alkylating agents, epipodophyllotoxins), cardiac mortality (chest irradiation, bleomycin), and other deaths (radiation, anthracyclines). No excess mortality was observed for external causes (SMR = 0.8).**

Conclusion: **While recurrent disease remains a major contributor to late mortality in 5-year survivors of childhood cancer, significant excesses in mortality risk associated with treatment-related complications exist up to 25 years after the initial cancer diagnosis.**

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APPROXIMATELY 12,400 children and adolescents younger than 20 years of age are diagnosed with cancer each year in the United States.[1] With the introduction of new therapeutic strategies during the past 30 years, survival for many diagnostic groups has increased dramatically. The Surveillance, Epidemiology and End Results Program estimates that the overall 5-year survival rate in 1998 was 80% for children and adolescents diagnosed before the age of 20. Nevertheless, cancer remains the leading medical cause of death among children between 1 and 19 in the United States.

Numerous reports and reviews of the late effects of chemotherapy and radiation[2-5] describe the occurrence of selected late complications. It is well recognized that both type and intensity of therapy as well as the patient's age at therapy are important factors in both overall survival and the frequency of late effects of therapy. Previous investigations with smaller cohorts have shown excessive mortality rates in 5-year survivors of childhood cancer.[6-11] Increased mortality rates are primarily due to recurrence of the primary disease, but there are suggestions that rates of other causes of death may also be increased. Childhood cancer survivors are known to be at risk for serious late effects that may result in death. Secondary and subsequent malignancies may result directly from therapy or may reflect host factors.[12-15] Congestive heart failure is a complication of both anthracycline therapy and mediastinal radiation[16,17]; recent studies have also shown evidence of delayed cardiac impairment associated with these therapies.[18,19] Pulmonary sequelae of chemotherapy and radiation can result in pulmonary fibrosis, acute pulmonary toxicity, and restrictive lung disease.[20-22] Radiation administered at a young age to patients with Wilms tumor progres-

From the Department of Pediatrics, University of Minnesota Medical School and Cancer Center, Minneapolis, and Department of Pediatrics, Mayo Clinic, Rochester, MN; Fred Hutchinson Cancer Research Center, Seattle, WA; and Division of Oncology, Children's Hospital of Los Angeles, Los Angeles, CA.

Other investigators and institutions participating in the Childhood Cancer Survivor Study are listed in the Appendix.

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Address reprint requests to Ann C. Mertens, PhD, Division of Epidemiology and Clinical Research, University of Minnesota, 420 Delaware St SE, MMC 715, Minneapolis, MN 55455; email: mertens@epi.umn.edu.

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sively reduces lung volume and dynamic compliance over time.[23] Late toxicities of chemotherapeutic agents and radiation also have been reported for hepatic, renal, and gastrointestinal systems.[24-26]

The Childhood Cancer Survivor Study (CCSS), a retrospective cohort study initiated in 1994, was designed to study late effects among long-term survivors of childhood cancer. Results are presented here for overall and cause-specific mortality and on risk factors for late mortality based on 208,947 person-years of follow-up of the CCSS cohort.

PATIENTS AND METHODS

Subject Selection and Contact

The Long-Term Follow-Up Study is a multi-institutional study (see Appendix) of individuals who have survived for 5 or more years after treatment for cancer, leukemia, tumors or similar illnesses diagnosed during childhood or adolescence. The present report from CCSS is restricted to those individuals who participated in the Long-Term Follow-Up Study and met the following eligibility criteria: (1) diagnosis of leukemia, CNS tumors (all histologies), Hodgkin's disease, non-Hodgkin's lymphoma, malignant kidney tumor (Wilms), neuroblastoma, soft tissue sarcoma, or bone tumor (list of eligible International Classification of Diseases [ICD]-O codes can be found at www.cancer.umn.edu/ccss); (2) diagnosis and initial treatment at one of the 25 collaborating CCSS institutions; (3) diagnosis date between January 1, 1970 and December 31, 1986; (4) age less than 21 years at diagnosis; and (5) survival 5 years from diagnosis.

The CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. Baseline data were collected for members of the study cohort using a 24-page questionnaire. The baseline questionnaire was designed to capture a wide range of information, including demographic characteristics, education, income, employment, insurance coverage, marital status, health habits (ie, smoking, alcohol consumption, physical activity, self-screening examinations), family history, access and utilization of medical care, medication use, frequency of diagnosed medical conditions (ie, hearing/vision/speech, urinary, hormonal, cardiovascular, respiratory, digestive, brain and CNS), surgical procedures, recurrent cancer, subsequent new neoplasms, and offspring/pregnancy history. If the patient had survived for 5 years but subsequently died, selected information was obtained from a family member, usually a parent, including the state in which the subject had died and whether the death was due to the original cancer.

Cancer Treatment Information

Information on the characteristics of the original cancer diagnosis was obtained on all eligible cases from the treating institution. For all CCSS participants who returned a signed medical release, information concerning primary cancer therapy was collected, including initial treatment, treatment for relapse, and preparatory regimens for bone marrow transplantation (if applicable) until the time of last contact. Qualitative information was abstracted from the medical record for 42 specific chemotherapeutic agents, for which quantitative information was abstracted on 22. Data were also obtained on tumor site, fields of radiation therapy, and surgeries performed from the time of diagnosis onward. Copies of the abstraction form used in data collection are available for review and downloading at www.cancer.umn.edu/ccss.

For analytic purposes, specific chemotherapeutic agents were grouped. Alkylating agent scores were calculated, summing the tertiles of each drug received, as previously described.[27] Anthracycline dose per meter squared was the sum of the doxorubicin, the daunorubicin, and three times the idarubicin dose.[28] The epipodophyllotoxin dose per meter squared was the sum of teniposide (VM-26) and etoposide (VP-16). Anthracycline doses were grouped as follows: less than 100, 100 to 400, and more than 400 mg/m^2. Epipodophyllotoxin doses were grouped into tertiles as less than 983, 983 to 4,108, and more than 4,108 mg/m^2. Bleomycin drug dose was grouped into tertiles as less than 60, 60 to 118, and more than 118 mg/m^2.

For radiation exposure (dichotomous yes/no variable), analysis of overall mortality and for causes due to a subsequent malignancy radiation exposure was defined as exposure to any site. For causes of death related to cardiac toxicity, radiation exposure to the chest or spine was considered cardiac exposure. For pulmonary complications, radiation exposure was considered for chest only.

Cause of Death Information

The vital status of each CCSS subject was ascertained as of December 31, 1996. Names of individuals who were reported to have died after entry into the cohort plus individuals who were lost to follow-up (no vital status available) were included in the search for deaths occurring between 1979 to 1996, using the National Death Index (NDI). Copies of the death certificates were requested from all states where a death was known to have occurred. For deaths before 1979, a copy of the death certificate was requested from the state identified as the state of death. Death certificate data were not available for 139 patients who were Canadian residents at the time of death. Death certificates were successfully obtained for 1,727 (91%) of United States patients.

A trained nosologist coded the causes of death using the ninth revision of the ICD.[29] In addition, the death certificate (or cause of death codes returned by NDI if a death certificate could not be obtained), information on original cancer diagnosis, and information from parent's interview were used to categorize the cause of death as (1) a direct consequence of the original cancer diagnosis, including deaths due to recurrent or progressive disease, or death due to acute toxicity while on therapy for the original disease; (2) cancer treatment sequelae, defined as a death where nonacute treatment effects were considered to be the major contributing factor to the death (eg, subsequent malignant neoplasm, cardiac toxicity); or (3) non–treatment-related causes, such as deaths due to other medical conditions or external causes (eg, suicide, car accident, and so on).

Data Analysis

Mortality rates and standardized mortality ratios (SMRs) were used to quantify the risk of death in this cohort. The mortality rate was calculated as the number of deaths before December 31, 1996, divided by the number of person-years at risk for death. Person-years at risk were computed, beginning on the date 5 years from date of original diagnosis, and included time to either the date of death or date of censoring for those still alive. Censoring dates differed by whether or not survivors returned their baseline surveys before our request to NDI for their vital status investigations. If a survivor had not returned the survey, his or her name was sent to NDI, and vital status was requested. Survivors confirmed alive as of December 31, 1996, were censored on that date. If the survey was returned before the NDI search was requested, the censoring date was December 31, 1996, or the date of baseline survey completion.

To compute the SMR, an expected number of deaths was calculated using age- and sex-specific United States mortality rates, reported by the National Center for Health Statistics.[30] Patients were grouped by age into 5-year intervals. All-cause SMRs were computed for all deaths. Only deaths with known causes not due to recurrence of the original cancer were included in cause-specific SMRs for secondary or subsequent cancer (ICD 140 to 239), cardiac causes (ICD 390 to 398, 402, 404, 410 to 429), pulmonary causes (ICD 460 to 519), external causes (accidents, suicides, poisonings, and so on; ICD 800 to 999), and other causes (all other ICD codes).

Survival functions were estimated by the product-limit method by age and by diagnosis. To compare survival curves for this cohort with the age-comparable United States population, an expected number of deaths for each year since diagnosis was calculated based on the United States age- and sex-specific mortality rates, yielding an expected survival function for each sex. Cumulative mortality rates were calculated for each cause of death.[31]

Multiple Poisson regression[30] was used to assess the simultaneous impact of multiple factors, especially the effects of treatment modalities, on the cause-specific mortality risks that were not due to recurrence. Adjustment factors included sex, age at diagnosis, and years since diagnosis. Using the logarithm of expected numbers of death as offsets, we assessed the influence of radiation exposure, dose levels of alkylating agents, anthracyclines, epipodophyllotoxins, and bleomycin, controlling for the adjustment variables above. The same model was fitted to each cause-specific SMR, namely, subsequent cancer mortality, cardiac-related mortality, respiratory-related mortality, external-cause mortality, and all-other-cause mortality. An exposure/nonexposure indicator (instead of dose) for each of the specific chemotherapy drugs was used for the respiratory-related SMR regression because of its small number of related deaths.

Absolute excess risk was calculated as an additional measure of the impact of treatment-related mortality within the cohort. Absolute excess risk was determined by subtracting the expected number of deaths, within cause-specific categories, from the observed number, dividing the difference by the person-years of follow-up, and multiplying by one thousand.

Missing data on survivors whose medical records were not abstracted due to refusal, loss to follow-up, or delay in submitting the medical record release form were handled by multiple imputation.[32] For each survivor with one or more missing values of medical-record variables, we identified a group of survivors who matched on the following four variables and replaced the missing values with the values of a randomly sampled survivor in the group. The matching variables were original cancer (eight categories as in Table 1), age at diagnosis (5-year age groups), calendar year of diagnosis (4-year calendar periods), and the institution that treated the original cancer. This imputation was repeated 10 times, creating 10 complete datasets without missing values. Each analysis was conducted 10 times using the 10 datasets, and the results were summarized by the standard method for combining multiple-imputation analyses.[32] By repeating the imputation and analysis 10 times, we properly represent uncertainties of missing values in between-imputation variability. A single imputation would have filled in missing values once, without acknowledging uncertainties, and would have resulted in an overstatement of precision levels.

RESULTS

Among the cohort of 20,227 5-year survivors, 2,030 patients (10.0%) died before December 31, 1996. Surrogate interviews were completed for 1,133 (56%); 410 (20%) surrogates refused participation; 29 (1%) are pending contact; and 458 (23%) surrogates were lost to follow-up.

Table 1. Number of Deaths and SMRs* in CCSS

	Alive (no. of patients)	Deaths (no. of patients)	SMR	95% CI
Total no. of patients	18,197	2,030	10.8	10.3-11.3†
Sex				
Male	9,961	1,216	8.5	8.0-9.0†
Female	8,236	814	18.2	17.0-19.5†
Age at diagnosis				
0-4 years	7,416	601	14.0	12.9-15.1†
5-9 years	4,101	446	10.8	9.8-11.8†
10-14 years	3,642	468	9.2	8.4-10.1†
15-20 years	3,038	515	9.7	8.9-10.6†
Year of diagnosis				
1970-1973	2,434	520	9.7	8.9-10.5†
1974-1977	3,726	547	9.6	8.8-10.5†
1978-1981	4,784	488	10.7	9.8-11.7†
1982-1986	7,253	475	14.8	13.5-16.2†
Survival after diagnosis				
5-9 years	—	1,130	22.6	21.3-24.0†
10-14 years	—	556	8.6	7.9-9.4†
15-19 years	—	241	4.9	4.3-5.6†
20-24 years	—	89	4.0	3.2-4.9†
25-29 years	—	14	6.2	3.4-10.4†
Diagnosis				
Leukemia	5,927	722	15.5	14.3-16.6†
CNS tumors	2,443	377	15.7	14.1-17.3†
Hodgkin's disease	2,383	328	8.3	7.4-9.2†
Non-Hodgkin's lymphoma	1,391	93	5.1	4.1-6.2†
Kidney (Wilms)	1,617	65	6.2	4.8-7.9†
Neuroblastoma	1,281	59	7.8	5.9-10.1†
Soft tissue sarcoma	1,641	171	8.6	7.4-10.0†
Bone tumors	1,514	215	10.1	8.8-11.5†

*Age- and sex-adjusted according to National Center for Health Statistics criteria.

†$P < .01$ for SMR.

Of the 2,030 deaths, death certificate information was requested on 1,891 individuals who were United States residents at the time of death; 1,727 (91%) of these certificates were obtained. Classification of cause of death was possible in 1,848 (91%) of all deaths when also using information available through medical records and surrogate interviews.

Overall SMRs and Survival in CCSS Cohort

Overall, deaths occurred in this population almost 11 times more often than expected (SMR = 10.8; 95% confidence interval [CI], 10.3 to 11.3) (Table 1). Increased SMRs were seen in both females (18.2; 95% CI, 17.0 to 19.5) and males (8.5; 95% CI, 8.0 to 9.0). SMRs were highest in subjects diagnosed with their initial malignancy 0 to 4 years

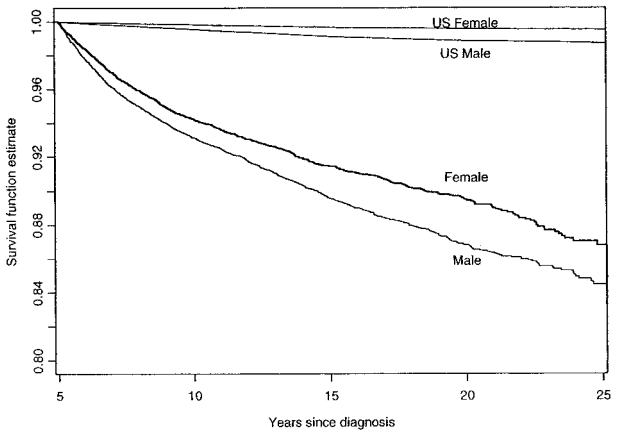
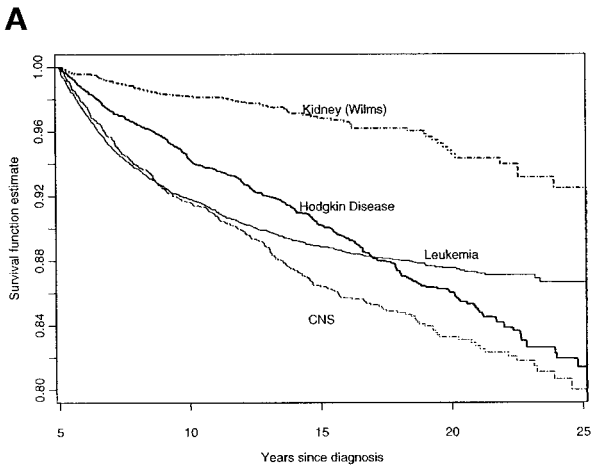


Fig 1. All-cause mortality—sex-specific survival.



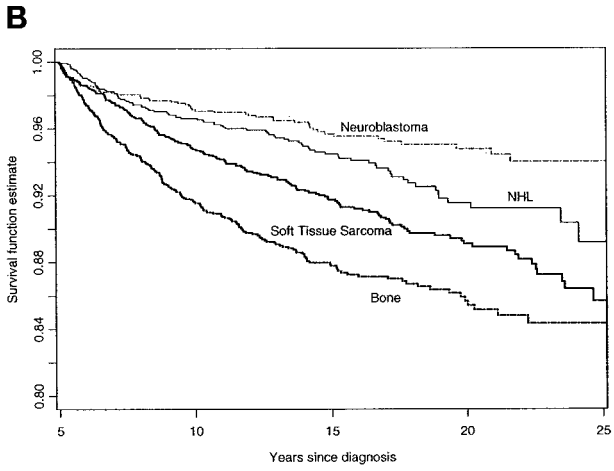


Fig 2. All cause mortality—survival by original cancer diagnosis in CCSS: (A) kidney disease, Hodgkin's disease, leukemia, CNS tumors; (B) neuroblastoma, non-Hodgkin's lymphoma, soft tissue, bone.

of age (14.0; 95% CI, 12.9 to 15.1). Relative mortality was also highest in the 5 to 9 year period after diagnosis of their initial malignancy (SMR = 22.6; 95% CI, 21.3 to 24.0), and was fairly stable after 15 years (SMR 4.0 to 6.2). SMRs were high in all diagnoses, with highest values among individuals with an initial diagnosis of leukemia (15.5; 95% CI, 14.3 to 16.6) and CNS tumors (SMR = 15.7; 95% CI, 14.1 to 17.3).

Subjects diagnosed more recently (1982 to 1986) had a higher SMR (14.8; 95% CI, 13.5 to 16.2) than those diagnosed in earlier years (SMR = 9.6 to 10.7). When adjusted for years since diagnosis, however, earlier years of diagnosis showed a higher relative risk (RR) of death, compared with the years of 1982 to 1986 (RR = 1.4, 1.2, 1.0, and 1.0, for 1970 to 1973, 1974 to 1977, 1978 to 1981, and 1982 to 1986, respectively).

All-cause mortality experience from 5 years after initial cancer diagnosis was compared with age-adjusted expected survival rates for the United States population (Fig 1). Overall, cumulative mortality was 6.4% at 10 years from diagnosis, 9.3% at 15 years, 11.4% at 20 years, and 14.0% at 25 years, and individuals remained at excessive risk of death throughout this period. Individuals with an original diagnosis of kidney tumors and neuroblastoma had the best overall survival, with cumulative mortality proportions of approximately 5.0% at 20 years (Fig 2). Individuals with an original diagnosis of CNS tumors had the poorest overall survival, with a cumulative mortality rate of 16.8% at 20 years.

Specific Causes of Death

Table 2 shows the distribution of specific causes-of-death categories. Recurrent disease was the leading cause, with 1,246 patient deaths (67.4%) attributed to a recurrence of the original childhood cancer. Death was attributed to treatment-related consequences in 394 patients (21.3%), including 235 (12.7%) with secondary or subsequent cancer, 83 (4.5%) with cardiac toxicity, 33 (1.8%) with pulmonary complications, 13 (0.7%) with infections, and 30 (1.6%) with other treatment-related sequelae. Death due to other causes accounted for 208 deaths (11.3%), including 94 (5.1%) external causes of death and 13 (0.7%) deaths due to AIDS-related causes.

The cumulative cause-specific mortality was highest for cancer recurrence (7% at 25 years from diagnosis) (Fig 3). Death rates due to subsequent cancers and other causes increased more rapidly in the time period 15 to 25 years after diagnosis.

Table 2. Specific Causes of Death in CCSS

Specific Cause of Death	No. of Patients
Recurrence	1,246
Treatment-related consequences	394
Subsequent neoplasm	
Lip, oral cavity, pharynx, lung	7
Digestive organs and peritoneum	20
Bone and articular cartilage	22
Connective and other soft tissue	25
Melanoma and other skin	3
Breast	14
Genitourinary organs	9
Brain and other parts of nervous system	58
Lymphatic and hematopoietic	65
Other subsequent cancer	12
Cardiac	
Ischemic heart disease	20
Cardiomyopathy	38
Congestive heart failure	8
Other cardiac	17
Pulmonary	
Pulmonary fibrosis	17
Other pulmonary	16
Other sequelae	
Infectious disease	13
Other sequelae	30
Non–treatment-related causes of death	208
External causes	
Motor vehicle accident	43
Other accident	20
Suicide	20
Homicide	11
Medical conditions	
Human immunodeficiency virus	13
Pneumonia	13
Other bacterial/viral infection	5
Heart disease	6
Cerebrovascular disease	6
Other medical condition	71

Death Due to Recurrence

The overall mortality rate for death as a result of recurrence in this cohort is 0.6% per year (Table 3). A statistically significant difference was seen for all categories of sex, age at diagnosis, years of diagnosis, years survived since diagnosis, and diagnosis. Mortality rates for deaths due to recurrence varied across diagnostic categories, with the highest rates for individuals diagnosed with CNS tumors (0.9% per year), leukemia (0.8% per year), and bone tumors (0.8% per year) and the lowest rates for those with kidney tumors (0.1% per year). Rates were also higher in individuals who were older at initial cancer diagnosis. The mortality rate for recurrence in those aged 15 to 20 at diagnosis was 0.8% per year; for those diagnosed at age 0 to 4, it was 0.5% per year. The highest annual rate of death due to recurrence was in the first interval between 5 and 9 years after diagnosis (1.1% per year); rates decreased with time from diagnosis, with the lowest rates in the intervals between 20 to 24 and 25 to 29 years from diagnosis (0.1% and 0.2% per year, respectively).

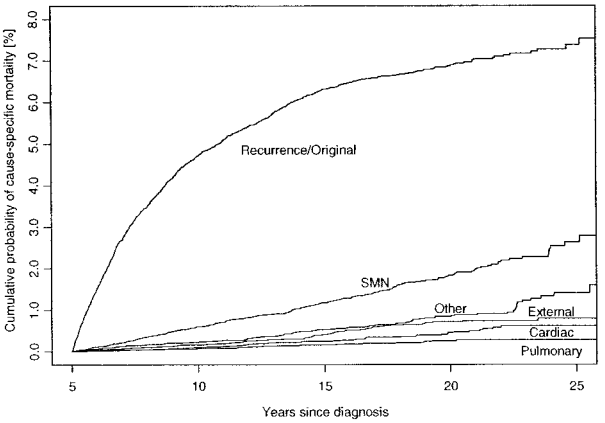


Fig 3. Cumulative cause-specific mortality.

Table 3. Yearly Mortality Rates for Deaths Due to Recurrence in CCSS

	Deaths (no. of patients)	Rate (%)	95% CI
Total	1,246	0.60	0.56-0.63
Sex			
Male	750	0.65	0.61-0.70
Female	496	0.53	0.48-0.57
Age at diagnosis*			
0-4 years	386	0.47	0.42-0.52
5-9 years	289	0.61	0.54-0.68
10-14 years	272	0.64	0.57-0.72
15-20 years	299	0.82	0.73-0.92
Year of diagnosis*			
1970-1973	293	0.60	0.53-0.67
1974-1977	315	0.54	0.48-0.60
1978-1981	303	0.56	0.50-0.63
1982-1986	335	0.71	0.63-0.79
Survival after diagnosis*			
5-9 years	841	1.08	1.01-1.15
10-14 years	315	0.42	0.38-0.47
15-19 years	70	0.17	0.14-0.22
20-24 years	18	0.12	0.07-0.19
25-29 years	2	0.16	0.02-0.58
Diagnosis*			
Leukemia	532	0.83	0.76-0.90
CNS tumors	247	0.91	0.80-1.03
Hodgkin's disease	136	0.44	0.37-0.52
Non-Hodgkin's lymphoma	36	0.23	0.16-0.32
Kidney (Wilms)	22	0.12	0.08-0.18
Neuroblastoma	38	0.26	0.18-0.35
Soft tissue sarcoma	97	0.48	0.39-0.58
Bone tumors	138	0.78	0.66-0.92

*$P < .01$ for difference in rate within variable.

Table 4. Cause-Specific SMRs and 95% Confidence Intervals by Sex and Cancer Diagnosis in CCSS (excluding deaths due to recurrences)

	Subsequent Cancer*		Cardiac		Pulmonary		External Causes†		Other Deaths	
	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
All cases	19.4	17.2-21.8‡	8.2	6.4-10.4‡	9.2	6.5-12.5‡	0.8	0.7-1.0§	3.3	2.8-3.9‡
Sex										
Male	17.1	14.5-20.1‡	8.0	5.9-10.7‡	9.7	6.3-14.2‡	0.8	0.7-1.0	2.5	2.0-3.1‡
Female	22.5	18.9-26.6‡	8.7	5.5-13.0‡	8.5	4.7-13.9‡	0.7	0.4-1.1	5.2	4.0-6.6‡
Diagnosis										
Leukemia	17.4	13.3-22.2‡	3.8	1.5-7.6‡	8.2	4.1-16.3‡	0.6	0.4-0.9§	3.7	2.6-5.2‡
CNS	18.5	12.8-25.7‡	7.5	3.2-14.4‡	16.5	8.2-32.9‡	1.0	0.6-1.6	4.7	3.0-6.9‡
Hodgkin's disease	24.0	19.2-29.7‡	13.8	9.3-19.4‡	12.0	6.5-22.4‡	0.9	0.5-1.3	2.7	1.8-3.9‡
Non-Hodgkin's lymphoma	15.6	9.6-23.7‡	6.5	2.3-14.0‡	14.7	6.1-35.4‡	1.1	0.6-1.8	2.1	1.0-4.0§
Kidney (Wilms)	22.9	14.1-34.8‡	18.0	7.1-36.4‡	0.0	0.0-12.1	0.7	0.3-1.5	4.5	2.1-8.3‡
Neuroblastoma	12.6	5.7-23.4‡	8.4	1.4-25.8‡	0.0	0.0-16.0	1.2	0.5-2.4	2.3	0.6-5.9
Soft tissue sarcoma	19.5	13.3-27.3‡	5.7	2.0-12.2‡	7.3	2.4-22.6‡	0.5	0.2-1.0	3.7	2.2-5.8‡
Bone	18.5	12.6-25.9‡	4.9	1.8-10.5‡	4.7	1.2-18.6§	0.9	0.5-1.5	2.8	1.6-4.5‡

*Subsequent cancers included for survivor population. Cancer deaths resulting from progression of the original cancer are not included in the observed number of events.

†Includes accidents, homicides, and suicides.

‡$P < .01$ for SMR.

§$P < .05$ for SMR.

SMR and Multiple Regression for Cause-Specific Mortality

SMRs were calculated for deaths as a result of specific causes (Table 4). Relative to the United States population, individuals in this cohort were 19.4 times more likely to have died of a subsequent cancer (after exclusion of the original diagnosis), 8.2 times more likely to die from cardiac-related events, and 9.2 times more likely to die due to pulmonary disease. Females demonstrated higher SMRs for deaths as a result of subsequent cancers and other causes. Most striking was the increase in subsequent cancer deaths, with SMRs of 22.5 (95% CI, 18.9 to 26.6) and 17.1 (95% CI, 14.5 to 20.1) for females and males, respectively.

Cause-specific SMRs differed according to the primary cancer diagnosis, with death as a result of subsequent cancers associated with a 24-fold excess among subjects originally diagnosed with Hodgkin's disease (SMR = 24.0; 95% CI, 19.2 to 29.7). A total of 69 deaths occurred from subsequent cancers among Hodgkin's disease cases. These subsequent cancers included 22 lymphatic/hematopoietic malignancies, six breast cancers, six soft tissue sarcomas, five CNS tumors, and 30 other malignancies. The largest excess for cardiac mortality was seen among kidney (Wilms) tumor patients (SMR = 18.0; 95% CI, 7.1 to 36.4); CNS tumor patients had the greatest excess of pulmonary mortality (SMR = 16.5; 95% CI, 8.2 to 32.9).

There was a statistically significant deficit in the number of deaths due to external causes (SMR = 0.8; 95% CI, 0.7 to 1.0). There were no statistically significant excesses in deaths from motor vehicle accidents (SMR = 0.9; 95% CI, 0.7 to 1.2), other accidents (SMR = 0.9; 95% CI, 0.6 to 1.4), suicide (SMR = 0.9; 95% CI, 0.6 to 1.5), or AIDS-related causes (SMR = 1.1; 95% CI, 0.6 to 1.8). A statistically significant increase was seen in the number of deaths as a result of other causes (not recurrences of original cancers) (SMR = 3.3; 95% CI, 2.8 to 3.9). Death due to other causes was highest in CNS tumor patients (SMR = 4.7; 95% CI, 3.0 to 6.9).

Table 5 summarizes the results from the multiple regression analysis, adjusted for sex, age at diagnosis, and years since diagnosis. For each cause of death category, the relative risk of mortality decreased as years since diagnosis increased. Risk of mortality was increased in females due to both subsequent cancers and in deaths due to other causes (RR = 1.4, 95% CI, 1.1 to 1.8, and RR = 1.9, 95% CI, 1.5 to 2.4, respectively).

Risk of death from a secondary or subsequent cancer decreased with years since diagnosis (RR = 0.5; 95% CI, 0.3 to 0.8, for $\geq$ 20 years since diagnosis). Risk was also increased among individuals who received radiation (RR = 2.5; 95% CI, 1.6 to 3.9), a higher dose of alkylating agents (RR = 2.1; 95% CI, 1.5 to 3.1, for a score $\geq$ 5), and a higher dose of epipodophyllotoxins (RR = 2.7; 95% CI, 1.5 to 4.9, for doses 983 to 4,108 mg/m^2). Increased relative risks were seen for cardiac-related deaths, particularly in individuals who had received chest/spinal radiation (RR = 2.2; 95% CI, 1.2 to 4.4). Deaths due to pulmonary complications were associated with the use of bleomycin (RR = 1.7; 95% CI, 0.6 to 4.5, for doses $>$ 118 mg/m^2), although the association was not statistically significant. Relative

Table 5. Summary of Poisson Regression Model for Deaths Not From Recurrence

	Subsequent Cancer		Cardiac		Pulmonary		Other Deaths	
Independent Risk Factor	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Reference group SMR	6.1	3.4-11.2*	5.1	2.3-11.3*	5.3	0.7-43.3	0.7	0.3-1.4
Sex								
Male	1.0		1.0		1.0		1.0	
Female	1.4	1.1-1.8*	1.1	0.8-1.4	0.9	0.5-1.4	1.9	1.5-2.4*
Age at diagnosis								
< 1 year	0.8	0.4-1.8	0.6	0.2-1.8	0.0	0.0	1.6	0.6-4.4
1-3 years	1.8	1.1-2.8†	1.1	0.7-1.9	3.2	0.7-14.6	4.3	2.3-8.0*
4-6 years	1.0	0.6-1.7	1.3	0.8-2.0	3.1	0.7-14.0	3.3	1.8-6.3*
7-9 years	0.9	0.5-1.7	0.5	0.3-1.0†	3.7	0.7-18.3	4.4	2.3-8.4*
10-12 years	0.9	0.5-1.5	0.5	0.3-0.9†	3.7	0.8-16.8	2.7	1.4-5.1*
13-15 years	1.2	0.8-1.9	0.4	0.3-0.7*	3.1	0.7-13.8	3.5	1.9-6.4*
16-18 years	0.8	0.5-1.3	0.6	0.4-0.9†	5.3	1.2-22.7†	1.9	1.0-3.6
19-20 years	1.0		1.0		1.0		1.0	
Years since diagnosis								
5-9 years	1.0		1.0		1.0		1.0	
10-14 years	0.8	0.6-1.1	1.2	0.8-1.7	1.1	0.6-1.9	0.7	0.5-0.9*
15-19 years	0.7	0.5-0.9†	0.7	0.5-1.0	0.9	0.5-1.7	0.5	0.3-0.6*
20+ years	0.5	0.3-0.8*	0.6	0.4-1.0	0.4	0.1-1.1	0.4	0.3-0.6*
Radiation‡								
No	1.0		1.0		1.0		1.0	
Yes	2.5	1.6-3.9*	2.2	1.2-4.4†	1.1	0.5-2.4	2.1	1.4-3.4*
Alkylating agent score								
Not exposed	1.0		1.0		1.0		1.0	
1-2	1.4	1.0-2.2	1.1	0.6-1.9	—		1.1	0.7-1.7
3-4	1.3	0.8-2.0	1.1	0.7-1.8	—		0.9	0.6-1.6
5+	2.1	1.5-3.1*	1.3	0.8-2.1	0.4	0.2-1.0§	1.3	0.9-2.0
Anthracycline								
Not exposed	1.0		1.0		1.0		1.0	
1-100 mg/m^2	0.9	0.5-1.6	0.8	0.4-1.8	—		1.1	0.6-1.9
101-400 mg/m^2	1.2	0.8-1.9	1.3	0.6-2.8	—		1.3	0.8-2.1
401+ mg/m^2	1.2	0.8-1.8	1.4	0.8-2.2	1.6	0.8-2.9§	1.5	1.1-2.2†
Epipodophyllotoxin								
Not exposed	1.0		1.0		1.0		1.0	
1-982 mg/m^2	1.7	0.8-4.0	2.2	0.9-5.6	—		0.9	0.3-2.2
983-4,108 mg/m^2	2.7	1.5-4.9*	0.0	0.0-—	—		0.1	0.0-10^3
4,109+ mg/m^2	2.0	1.0-4.1†	1.2	0.4-3.6	1.4	0.4-4.5§	0.0	0.0-—
Bleomycin								
Not exposed	1.0		1.0		1.0		1.0	
1-59 mg/m^2	1.2	0.6-2.4	2.7	1.2-6.1†	—		1.3	0.6-3.0
60-118 mg/m^2	1.3	0.6-3.1	1.6	0.4-6.0	—		0.0	0.0-—
119+ mg/m^2	1.4	0.6-3.5	1.5	0.4-5.6	1.7	0.6-4.5§	0.0	0.0-—

*$P < .01$.

†$P < .05$.

‡Radiation is overall radiation for subsequent cancer; chest/spine/total-body irradiation for cardiac; chest/total-body irradiation for pulmonary.

§Signifies drug use, any dose.

risks were statistically significantly elevated by radiation treatment for deaths from other causes (RR = 2.1; 95% CI, 1.4 to 3.4).

For cause-specific mortality, potential interactions between specific chemotherapy and radiation with sex and age at diagnosis were examined (data not shown). No statistically significant interaction was observed in this analysis.

Absolute Excess Risk

Among the CCSS cohort, the overall all-cause absolute excess risk was 8.8 deaths per 1,000 person-years. Within treatment-related cause-specific categories (ie, excluding recurrences and non–treatment-related deaths), the absolute excess risk was 1.26, 0.27, and 0.015 deaths per 1,000

person-years for secondary and subsequent cancers, cardiac causes, and pulmonary causes, respectively.

DISCUSSION

The CCSS is the largest and most extensively studied cohort of individuals established to date for the study of late effects of therapy in children who were treated for cancer between 1970 and 1986 and survived at least 5 years from diagnosis. This time period represents a relatively modern era of therapy in which children and young adults were exposed to treatment modalities, including radiation and multiple chemotherapeutic agents, that in most cases continue to be used. Many of these agents have been shown to be related to late effects that may result in excess mortality and morbidity. The CCSS is unique in that the cohort under study has been extensively characterized according to previous cancer therapy and occurrence of outcomes of interest. Moreover, the population is sufficiently heterogeneous with respect to therapeutic exposures and demographic characteristics to allow for investigation of a wide range of risk factors that may be associated with specific long-term outcomes. Lastly, because of the size of the cohort and the large number of person-years of observation, the study provides an excellent opportunity to define more precisely the rate and magnitude of risk for outcomes, such as late mortality.

In the United States, deaths in most states are reported on a death certificate standardized by the National Center for Health Statistics, and the underlying cause of death is described using the ninth revision of the ICD coding rules. The validity and accuracy of death certificates has been questioned in other studies addressing cancer mortality, because the physician completing the form may not be familiar with the deceased's medical history.[33,34] This inaccuracy may lead to an incorrectly assigned cause of death. In an effort to minimize this potential bias in our cohort, each death certificate was reviewed at the University of Minnesota, along with information from the surrogate respondent, to categorize the cause of death in relation to the diagnosis of the original cancer. Cause of death was not able to be determined in 9% of our cohort. For these missing causes, the absolute risk (shown in Tables 3 and 4) was underestimated by about 9% and therefore yielded conservative results. The relative risk calculations (Table 5), however, were expected to be unbiased because missing records should occur at random.

In this study of 5-year survivors of childhood and adolescent cancer, we found that the overall SMR was 10.8 times greater than that of the United States population. The major cause of death in this cohort of 5-year survivors of cancer was recurrence of the original cancer (67%). This finding is consistent with those of other studies, where death due to recurrence ranges from to 61% to 75% of deaths,[6-11] depending on the era of treatment (pre-1970 *v* after 1970) and the distribution of the initial cancer diagnosis. These studies also noted that deaths from recurrence were highest 5 to 9 years after diagnosis, as in our study.

Even after death as a result of recurrence or progression of the original disease was excluded, mortality rates were higher than expected given the general population rates. Increased risks of death were evident from subsequent neoplasms. These deaths are consistent with previous studies of late effects, specifically in the increased proportion of new solid tumors within irradiated fields[27] and increased proportion of second primary leukemias following the use of alkylating agents[35] and epipodophyllotoxins.[36] Previous mortality studies, with limited data on treatment of original primary malignancies, have also found an increase in death as a result of secondary or subsequent malignancies. These increases were associated with the original diagnosis,[7,8] radiation,[6,10] and combination chemotherapy and radiation.[9] Our study found a 19-fold increased risk in deaths due to a secondary or subsequent cancer, which was related to radiation, alkylating agents, and epipodophyllotoxins. When considering the occurrence of subsequent cancers, whether within the context of incidence or mortality, it is always important to consider not only the potential role of therapeutic exposures but also the possible contribution of genetic predisposition. In the current analysis of mortality, we were not able to evaluate genetic factors. The incidence of secondary and subsequent malignancies in this cohort is a topic of a separate publication.[37]

Anthracyclines[18,19,38] and mediastinal radiation[17] are known to produce substantial long-term cardiac morbidity. Other mortality studies of 5-year survivors noted an excess of cardiac deaths. Our study also identified a 10-fold increased risk, which was associated with exposure to chest irradiation.

Results from analysis of the CCSS cohort found that the proportion of deaths did not differ appreciably by sex (12% for males, 10% for females), but SMRs were more than twice as high for females compared with males. Since SMR calculations are based on the observed and expected numbers of deaths, the difference in the SMR is partly due to the overall higher expected numbers of deaths for males in these age groups compared with females. Another source of increased SMRs in females was an increase in the number of subsequent cancers of the breast (data not shown). No statistically significant interactions between sex and treatment exposure were present in this study. This difference will need to be studied further, as the individuals in this cohort age further from the time of diagnosis.

The pattern of deaths in 5-year survivors is key to understanding late relapse and the late effects of treatment. By studying mortality rates within specific therapeutic modalities as well as within clinical and demographic subgroups, we will be able to gain insights into (1) therapeutic modalities associated with higher mortality, (2) which patients require special attention in follow-up, and (3) interventions that may be considered to reduce excess mortality among childhood cancer survivors, particularly focussing on strategies that maintain the vastly improved overall survival in those diagnosed with childhood cancer while lowering the likelihood of the late consequences of disease and therapy.

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APPENDIX
CCSS Institutions and Investigators

University of California-San Francisco, CA (Arthur Ablin, MD*); University of Alabama, Birmingham, AL (Roger Berkow, MD*); International Epidemiology Institute, Rockville, MD (John Boice, ScD‡); University of Washington, Seattle, WA (Norman Breslow, PhD‡); University of Texas–Southwestern Medical Center at Dallas, TX (George R. Buchanan, MD*); Dana-Farber Cancer Institute, Boston, MA (Lisa Diller, MD*), Holcombe Grier, MD,† Frederick Li, MD‡); Texas Children's Center, Houston, TX (Zoann Dreyer, MD*); Children's Hospital and Medical Center, Seattle, WA (Debra Friedman, MD, MPH,* Thomas Pendergrass, MD†); Roswell Park Cancer Institute, Buffalo, NY (Daniel M. Green, MD*‡); Hospital for Sick Children, Toronto, Ontario, Canada (Mark Greenberg, MB, ChB*); St Louis Children's Hospital, St Louis, MO (Robert Hayashi, MD*, Teresa Vietti, MD†); St Jude Children's Research Hospital, Memphis, TN (Melissa Hudson, MD*‡); University of Michigan, Ann Arbor, MI (Raymond Hutchinson, MD*); Stanford University School of Medicine, Stanford, CA (Michael P. Link, MD,* Sarah S. Donaldson, MD‡); Children's Hospital of Philadelphia, PA (Anna Meadows, MD,*‡ Bobbie Bayton‡); Children's Hospital, Oklahoma City, OK (John Mulvihill, MD‡); Children's Hospital, Denver, CO (Lorrie Odom, MD*); Children's Health Care, Minneapolis, MN (Maura O'Leary, MD*); Columbus Children's Hospital, Columbus, OH (Amanda Rauck, MD*, Frederick Ruymann, MD†, Stephen Qualman, MD‡); Children's National Medical Center, Washington, DC (Gregory Reaman, MD*, Roger Packer, MD‡); Children's Hospital of Pittsburgh, PA (A. Kim Ritchey, MD*, Julie Blatt, MD†); University of Minnesota, Minneapolis, MN (Leslie L. Robison, PhD,*‡ Ann Mertens, PhD‡, Joseph Neglia, MD, MPH‡, Mark Nesbit, MD‡, Stella Davies, MD, PhD‡); Children's Hospital, Los Angeles, CA (Kathy Ruccione, RN, MPH*); Memorial Sloan-Kettering Cancer Center, New York, NY (Charles Sklar, MD*‡); National Cancer Institute, Bethesda, MD (Malcolm Smith, MD,‡ Martha Linet, MD‡); Mayo Clinic, Rochester, MN (W. Anthony Smithson, MD,* Gerald Gilchrist, MD†); University of Texas M.D. Anderson Cancer Center, Houston, TX (Louise Strong, MD*‡, Marilyn Stovall, PhD‡); Riley Hospital for Children, Indianapolis, IN (Terry A. Vik, MD*, Robert Weetman, MD†); Fred Hutchinson Cancer Center, Seattle, WA (Yutaka Yasui, PhD*, John Potter, MD, PhD†‡); University of California-Los Angeles, CA (Lonnie Zeltzer, MD*‡).

*Institutional principal investigator.
†Former institutional principal investigator.
‡Member CCSS steering committee.

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