Impact of temporal changes in therapeutic exposure on self-reported health status in childhood cancer survivors

Kirsten K. Ness, PhD[1,*], **Melissa M. Hudson, MD**[2,*], **Kendra E. Jones, MS**[1], **Wendy Leisenring, ScD**[3], **Yutaka Yasui, PhD**[1], **Yan Chen, MS**[12], **Marilyn Stovall, PhD**[4], **Todd M. Gibson, PhD**[1], **Daniel M. Green, MD**[1], **Joseph P. Neglia, MD**[5], **Tara O. Henderson, MD**[6], **Jacqueline Casillas, MD**[7], **Jennifer S. Ford, PhD**[8], **Karen E. Effinger, MD, MS**[10], **Kevin R. Krull, PhD**[1], **Gregory T. Armstrong, MD, MSCE**[1], **Leslie L. Robison, PhD**[1], **Kevin C. Oeffinger, MD**[9,**], and **Paul C. Nathan, MD**[11,**]

[1]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, Tennessee 38105

[2]Department of Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, Tennessee 38105

[3]Clinical Research and Public Health Sciences Divisions, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue, Seattle, Washington 98109

[4]Department of Radiation Physics, Division of Radiation Oncology, The University of Texas, MD Anderson Cancer Center, 1220 Holcombe Boulevard, Houston, Texas 77030

[5]Department of Pediatrics, University of Minnesota Medical School, 100 Church Street South East, Minneapolis, Minnesota

[6]Department of Pediatrics, University of Chicago, 5801 South Ellis Avenue, Chicago, Illinois 60637

[7]Pediatrics, Hematology & Oncology, David Geffen School of Medicine at University of California at Los Angeles and Jonsson Comprehensive Cancer Center, 10833 Le Conte Avenue, Los Angeles, California 90095

Corresponding Author: Kirsten K. Ness, PT, PhD, FAPTA, Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS-735, Memphis, Tennessee 38105, T: 901-595-5157, F: 901-595-5845, kiri.ness@stjude.org.
*Co-first authors
**Co-senior authors

[8]Department of Psychiatry and Behavioral Sciences, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10065

[9]Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10065

[10]Pediatrics, Hematology & Oncology, Emory University, 201 Dowman Drive, Atlanta, Georgia 30322

[11]Hematology & Oncology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8

[12]University of Alberta, 116 Street, Edmonton, Alberta T6G 2R3

Abstract

Background—The impact of temporal changes in cancer therapy on health status among childhood cancer survivors has not been evaluated.

Objective—Compare proportions of self-report of adverse health status outcomes across three decades among childhood cancer survivors.

Design—Cross-sectional

Setting—27 North American institutions

Participants—14,566 adults, 5 year survivors (median age 27, range 18-48 years) treated 1970-1999

Measurements—Patient-report of poor general or mental health, functional impairment, activity limitation, cancer-related anxiety or pain were evaluated as a function of treatment decade, cancer treatment exposures, chronic health conditions, demographics, and health habits.

Results—Despite reductions in late-mortality and proportions with severe, disabling or life threatening chronic health conditions (33.4% among survivors treated 1970-79, 21.0% among those treated 1990-99), proportions reporting adverse health status did not decrease by treatment decade. When compared to those diagnosed 1970-79, survivors diagnosed 1990-99 were more likely to report poor general health (11.2% vs. 13.7%, $p < 0.001$) and cancer-related anxiety (13.3% vs. 15.0%, $p < 0.001$). From 1970-79 to 1990-99, the proportions reporting adverse outcomes were higher ($p < 0.001$) among leukemia (9.5% vs. 13.9%, poor general health) and osteosarcoma (23.9% vs. 36.6%, pain) survivors. Temporal changes in treatment exposures were not associated with changes in proportions reporting adverse health status. However, smoking, not meeting physical activity guidelines, and being either underweight or obese were associated with poor health status.

Limitations—The considerable improvement in survival among children diagnosed with cancer in the 1990s compared to those diagnosed in the 1970s makes it difficult to definitively determine the impact of risk factors on later self-reported health status without considering their impact on mortality itself.

Conclusions—Because survival rates following a diagnosis of childhood cancer have improved substantially over the past thirty years, this population now includes persons who would have died

in earlier eras. Unfortunately, self-reported health status among those that do survive has not improved. This is despite evolution of treatment designed to reduce toxicities, and is an important reminder that even in the modern era, cancer cure is not without consequences."

Introduction

Progress in treatment and supportive care for children with cancer has improved survival resulting in increasing numbers of childhood cancer survivors (1, 2). Unfortunately, a substantial number of survivors have chronic medical conditions resulting from cancer and/or therapy that alter health status and interfere with daily life (3-6). Ten to 25% of survivors of childhood cancer in their twenties and thirties report adverse health status including poor general health, poor mental health, functional impairment, activity limitation, cancer-related pain and cancer-related anxiety (4, 7-9). Of concern, these estimates are not static; longitudinal data indicate increased risk for adverse health status outcomes as survivors age (9, 10).

Since adverse health status outcomes are associated with specific treatment exposures, data describing risk of late effects have been used to modify clinical trials for newly diagnosed patients with the goals of maximizing survival, decreasing late effects of cancer therapy and improving overall health status (11-14). The Childhood Cancer Survivor Study (CCSS), a multi-institutional cohort study of childhood cancer survivors, has provided a wealth of information on prevalence and predictors of adverse health status that directly apply to survivors treated in North America between 1970 and 1986 (15, 16). Analysis of the recently expanded CCSS cohort to include individuals diagnosed between 1987 and 1999 demonstrates that survivors treated in more recent decades have reduced risk for late mortality (17), due in part to reduction in therapeutic exposures. However, the proportions reporting adverse health status among survivors treated with more contemporary therapy is not known.

Given this extension in lifespan for more contemporary survivors, the aims of this analysis were to: 1) determine the proportions of adult survivors of childhood cancer reporting adverse health status outcomes by treatment decade (1970-79, 1980-89, 1990-99) compared to rates in siblings; and 2) evaluate associations between diagnosis, temporal changes in treatment, chronic health conditions, demographic characteristics and health habits on adverse health status as a function of treatment decade. We hypothesized that survivors from the 1990s, treated with contemporary therapy, would report better health status compared to survivors from the 1970s.

Methods

These analyses included childhood cancer survivors participating in the CCSS treated from 1970-1999 at 27 institutions in North America. Survivors eligible for these analyses were diagnosed when < 21 years and had survived 5 years from original diagnosis. Analyses were restricted to survivors who completed a baseline questionnaire when 18 years and consented to medical record abstraction, and siblings 18 years when they completed the baseline questionnaire (see Supplemental Figure 1) (15, 16). Study documents were

approved by institutional review boards at each site; informed consent was obtained from participants. Data for these analyses were restricted to participants' responses on the first ("baseline") questionnaire.

Health status

Adverse health status was determined using established definitions in four domains for survivors and siblings and two additional domains for survivors (7). Participants were considered to have *poor general health* if they answered poor or fair when asked "Would you say that your health is excellent, very good, good, fair or poor?", and *poor mental health* if responses on the Brief Symptom Inventory-18 (BSI-18) (18) resulted in a sex-specific T-score of 63 or higher on the Global Severity Index or depression, anxiety, or somatization subscales. *Functional impairments* were considered present among participants reporting needing help with personal care, routine needs, or difficulty attending school or work. *Activity limitations* were considered present among participants reporting limitations in moderate activities (e.g. walking one block) in 3 months of the past two years. Survivors also rated *pain related to cancer or treatment* (adverse status defined as medium, a lot or very bad, excruciating pain) and *fears/anxiety related to cancer or treatment* (adverse status defined as medium, a lot or very many, extreme fears/anxiety).

Chronic conditions

Chronic health conditions were categorized using the Common Terminology for Adverse Events version 4.03 as none (Grade 0), mild/asymptomatic (Grade 1), or moderate/minimal local or non-invasive intervention indicated (Grade 2), versus severe, medically significant, disabling (Grade 3), and life-threatening (Grade 4) (19).

Decade, diagnosis, cancer therapy

Information related to diagnosis and treatment modalities/doses was obtained from medical records. Treatment decade (1970-79, 1980-89, 1990-99) was assigned based on diagnosis date. Time from diagnosis to survey completion was treated as a continuous variable. Diagnosis-specific (ALL, astrocytoma, medulloblastoma, HL, NHL, neuroblastoma, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma and osteosarcoma) surgery, radiation and chemotherapy variables were selected for evaluation (Supplemental Table 1) based upon changes in treatment standards over time (20, 21), or because of previously established associations with adverse health status outcomes (7, 10, 22). To illustrate treatment changes over time, a variable, "treatment score", was calculated using multivariable piecewise exponential models to estimate risk of any chronic condition grade 3, with an offset of the logarithm of person years at risk, terminated at the onset of any chronic condition grade 3 or censoring, and diagnosis-specific treatment exposures as risk factors (Supplemental Table 1). Specifically, this value is the standardized logarithm (those from 1970-1979 had mean 0.0, standard deviation 1) of fitted risk of having any grade 3 chronic health condition (Supplemental Table 2), based on diagnosis-specific treatment exposures. Therefore, survivors with greater risk of grade 3 chronic conditions have a higher treatment score (17).

Demographic characteristics, health habits

Attained age, sex, race/ethnicity, smoking history, alcohol-intake history, body mass index (BMI) and physical activity levels were determined from questionnaire responses. Age was treated as a continuous variable and race/ethnicity as a dichotomy ("non-Hispanic white"; "other"). Smoking status (>100 cigarettes) was categorized as never, past or current (23). Heavy drinking was defined as > 4 drinks/day or >14 drinks/week for males and >3 drinks/day or >7 drinks/week for females (24). BMI was categorized as underweight (<18.5 kilograms per square meter (kg/m^2)), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) or obese (30 kg/m^2) (25). Inactivity was defined as <the equivalent of 150 minutes of moderate/75 minutes of vigorous weekly physical activity (26).

Statistics

Descriptive statistics were compared between survivors and siblings and across decades with Chi-square or t-tests. Proportions reporting adverse health status were compared between siblings and survivors by treatment decade in generalized linear regression models adjusted for attained age, race and sex. Among survivors, associations between decade of treatment and adverse health status outcomes were examined within diagnosis-specific groups by contrasting relative risks (RR) from three multivariable models for each outcome, adjusted for attained age, time since diagnosis, race and sex. The first models evaluated associations between treatment decade (decade) and adverse health status. The second (decade-treatment) models were additionally adjusted for treatment variables (Supplemental Table 1), and the third (decade-chronic condition) for any grade 3-4 chronic health condition. We hypothesized that attenuation of RR from the decade-only to the decade-treatment model would suggest that treatment exposures explain, at least partially, associations between treatment decade and adverse health status. Similarly, attenuation of RR from the decade-only to the decade-chronic condition model would indicate that chronic health conditions explain, at least partially, associations between treatment decade and adverse health status. Regression was also used to evaluate associations between treatment decade, demographic characteristics and health habits with health status outcomes among survivors. Because of the availability of large numbers of ALL survivors, to reduce study costs, while still preserving statistical power, and to assure adequate numbers of less commonly diagnosed childhood cancer types, ALL survivors diagnosed 1987-1999 were under sampled. Sampling weights were applied in all modeling. SAS 9.3 (Cary, N.C.) was used for analyses.

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Results

Characteristics of the study population are shown in Table 1. Survivors included 4,618 diagnosed 1970-79; 4,669 diagnosed 1980-89; and 5,279 1990-99. Among those eligible for these analyses, participation rates did not differ by treatment decade: 66% for 1970-79; 61% for 1980-89, and 64% for 1990-99 (p=0.22). Participation differed by diagnosis and was

highest among survivors of ALL (73%) and lowest among survivors of neuroblastoma (50%). At the time they responded to the baseline survey, survivors treated 1970-79 were slightly older and further from diagnosis than those treated 1990-99, more likely to report non-Hispanic white race, less likely to be obese or report heavy drinking, and more likely to report current smoking. Siblings were more likely than survivors to be female, have health insurance and report current smoking.

Temporal changes-exposures

Provided in Table 2 (Supplemental Tables 3-12) are decade-specific distributions of survivors by diagnosis and therapeutic exposure (17, 27). The percentage of survivors exposed to cranial radiotherapy (CRT) decreased across time, primarily due to the declining use of prophylactic CRT in dose ranges 1800-2400 centigray (cGy) for ALL. Therefore, those exposed to CRT in the 1990s were primarily those with CNS tumors who received higher mean doses. The percentage of survivors exposed to chest radiation also decreased from the 1970s to the 1990s (17.3% decrease HL, 13.3% decrease neuroblastoma). Use of amputation for local control of osteosarcoma decreased from 80.3% in the 1970s to 22.8% in the 1990s. Over the three decades, the percentage of survivors exposed to nearly every type of chemotherapy agent increased, but with lower cumulative doses.

Temporal changes-chronic health conditions

A decrease in proportions with severe, medically significant, disabling or life-threatening chronic health conditions is shown in Table 2, with 33.4%, 25.8%, and 21.0% of survivors (mean±SD age 26.1±6.1 years) diagnosed from 1970-79, 1980-89, and 1990-99, respectively, reporting at least one grade 3-4 chronic health condition.

Temporal changes-health status

Despite an overall decrease in radiation exposure, reduced mean chemotherapy doses, and a decline in proportions with grade 3-4 chronic health conditions, in general, patient-reported health status did not improve across treatment decades (Supplemental Table 13, Figure 1). The percentage of survivors reporting poor general health and cancer-related anxiety was highest among survivors treated 1990-99 and lowest in those treated 1970-79 (13.7% vs. 11.2% and 15% vs 13.3% respectively). Patient-reported poor general health, poor mental health, functional impairment, activity limitation or an adverse outcome in any of these four domains did not improve, with survivors more likely than siblings to report adverse health status outcomes in each (or any) domain.

Treatment decade (1970s, 1980s, 1990s) was associated with changes in proportions reporting adverse health status primarily among ALL, astrocytoma, medulloblastoma, and osteosarcoma survivors (Figure 2, Supplemental Table 14). The percentage of ALL survivors reporting poor general health (9.5%, 9.9%, 13.9%) and cancer-related pain (7.5%, 9.5%, 13.7%) or anxiety (11.3%, 12.2%, 16.1%) increased across treatment decades. After adjusting for treatment exposures, associations between treatment decade and both poor general health and cancer-related pain became non-significant. However, adjusting for presence of any grade 3-4 chronic health condition did not influence these associations. The association between treatment decade and cancer-related anxiety was not attenuated by

including treatment exposures or chronic conditions in multivariable models. The percentage of astrocytoma survivors reporting functional impairment (33.4%, 28.9%, 18.1%) and activity limitation (21.1%, 15.4%, 12.5%) decreased across time. Adjusting for treatment exposure or chronic health conditions did not impact associations between treatment decade and functional impairment. However, the association between treatment decade and activity limitation became non-significant when treatment exposures or grade 3-4 chronic health conditions were included in models. The percentage of medulloblastoma survivors reporting functional impairment also decreased over time (45.8%, 28.6%, 26.5%), although treatment decade was not associated with this change. The proportion of osteosarcoma survivors reporting poor general health (12.8%, 9.4%, 16.3%), poor mental health (16.8%, 17.3%, 24.8%) and cancer-related pain (23.9%, 23.4%, 26.6%) increased across time. The effects of treatment decade remained significant for pain, but were attenuated for poor general and mental health when treatment exposures were included in models. Including chronic health conditions in models did not influence associations between treatment decade and poor general health, poor mental health or cancer-related pain.

Table 3 shows relative risks for adverse health status outcomes among survivors by treatment decade, demographic characteristics and health habits. In multivariable models, when compared to those treated 1970-79, those treated 1990-99 had an increased risk for poor general health and anxiety. Female sex, other race, BMI < 18.5 kg/m^2 or > 24.9 kg/m^2, physical inactivity and smoking were associated with increased risk for poor general health, functional impairment, poor mental health and anxiety. Heavy drinking was inversely associated with functional impairments and activity limitations, but was not associated with chronic disease status (16.6% among those with no vs. 13.1% among those with any grade 3-4 chronic condition).

Conclusions

While contemporary therapy for certain childhood cancers has resulted in reduction of late mortality, extending the lifespan of survivors (17), our findings suggest that there is not concurrent improvement in patient-reported health status among survivors. This is important as perceived health and well-being have been associated with long-term mortality in other adult cohorts (28-30). Overall, we observed increases in the percentages of childhood cancer survivors treated from 1990-99 who reported poor general health and anxiety, and found that accounting for specific treatment exposures, in most instances, did not explain effects of treatment decade on adverse health status outcomes. Demographic characteristics and high-risk health behaviors were associated with an increased risk for adverse health status. Thus, while the results of our analysis do not generally support anticipated benefits to health status expected from reductions in therapy, they do provide potential targets for clinical counseling and intervention among the increasing number of long-term survivors of childhood cancer.

There are several potential explanations for lack of improvement in health status outcomes reported by survivors treated over three decades. First, there has been a substantial increase in survival among children diagnosed with cancer. Estimates indicate that five-year survival rates for children diagnosed with cancer improved from 62.8% in 1975 to 79.8% in 1999 (2). It is possible that those who would have died in the earliest era, but lived in the most recent

era, are those that on average, would report worse later health outcomes. It is likely that contemporary cohorts contain a greater proportion of survivors cured of higher risk disease, who would have previously died because of their cancer or treatment complications. Risk-adapted therapy minimized treatment intensity for children with low-risk disease in the 1990s, whereas children with high risk for relapse or mortality continued to receive more intensive treatment (31). This is exemplified among ALL survivors, for whom we found a small but consistent increase in the percentage reporting adverse outcomes in three of six health status domains. Among children with ALL, gains in survival over the study period were realized with evolution of therapies designed to cure children with high-risk disease (32), whereas decreases in long-term morbidity resulted from reduction of therapies to minimize late-effects in those with low-risk disease (33). Our data suggest that a smaller proportion of ALL survivors have medically significant, detectable chronic conditions (treated for high-risk disease), whereas a more sizable proportion may have subclinical chronic conditions that interfere with daily function. Second, there has been a decrease in late mortality among childhood cancer survivors (1), potentially because surveillance and identification allows for earlier medical management of subclinical health conditions. Early screening and disease management may reduce mortality, but may not positively influence perception of health status (34), which may result in survivors rating their health as worse. Finally, it is possible that survivors of childhood cancer treated in a more recent era who were more likely to have access to organized follow-up care (35) and educational materials about medical late effects (36), and who were treated when disclosure of mental health issues and pain were more acceptable, developed different internal standards (expectations) upon which to judge health status outcomes. Thus, those treated 1990-99 may be more likely to anticipate and/or report adverse outcomes than those treated 1970-79.(37)

In previous reports from the CCSS, the highest proportions of functional limitations were among CNS and bone tumor survivors (7). Since treatment approaches for these disease groups evolved over the decades to minimize adverse events, we expected rates of functional limitation to decrease over time. We observed improvement among astrocytoma and medulloblastoma survivors, where changes in treatment included improved surgical techniques and reductions in CRT dose/volume (20, 38, 39). However, there was no improvement among osteosarcoma survivors, where the biggest change in treatment was replacement of amputation with limb-sparing surgery. Our findings are consistent with literature that indicates a dose-response association (7% (1-13%) per Gray) between CRT dose and risk for adverse events among childhood brain tumor survivors (40), and with meta-analyses that report no difference in long-term disability among childhood sarcoma survivors who require amputation compared to those who had limb-sparing surgery (41).

The increase from the 1970s to the 1990s in percentage of ALL and osteosarcoma survivors who report cancer-related pain years after diagnosis is concerning. Among ALL survivors, this may be related to increased use of intrathecal therapy to treat CNS disease in the more recent era. Data indicate that back pain is a frequent complaint of adult survivors of ALL (42), and that back pain and neuropathy are associated with the number of intrathecal chemotherapy administrations (43). In osteosarcoma survivors, this may be due to increases in numbers of younger patients eligible for limb-sparing related to availability of expandable prostheses in the 1990s, many of whom required multiple surgeries to manage orthopedic

complications. Dotan et al (44) reported an average of 6.2 complications, requiring 83 additional surgeries, among 22/38 children. Likewise, Ruggieri et al (45) reported implant-related complications among 17/32 children (72 months of follow-up) with lower extremity sarcoma who had limb-sparing using expandable prostheses.

As in the general population (46), smoking, body composition, inactivity, non-white race and female sex were associated with adverse health status outcomes among childhood cancer survivors. This indicates that survivors may be able to influence health status outcomes by modifying high-risk personal behaviors. Survivors who smoke, are inactive or obese should be directed to interventions designed to eliminate smoking (47), increase activity (48) and achieve a healthy weight (48). In addition, clinicians who treat female and non-white survivors and researchers designing interventions should consider these factors (49, 50) when counseling patients or developing targeted strategies to improve health status. Of note, we found an association between heavy drinking and functional impairments and activity limitations in our cohort. These data seem implausible, but are consistent with other studies among middle age adults where the highest odds for physical limitations are among never-drinkers and among individuals who quit drinking because of illness (51). Because we did not collect data on drinking history in our cohort, we were unable to directly evaluate this. However, there were no differences in the percentages of individuals who reported heavy drinking by chronic condition status.

These results should be considered in the context of potential study limitations. First of all, these analyses include many parallel comparisons, not adjusted for multiplicity. Chance alone could account for some of our findings. Second, not every survivor eligible for CCSS agreed to participate. Even though we stratified our analyses by diagnoses, participants may have been healthier or sicker than non-participants which could bias estimates either toward or away from the null. Third, the considerable improvement in survival among children diagnosed with cancer in the 1990s compared to those diagnosed in the 1970s makes it difficult to definitively determine the impact of risk factors on later self-reported health status without considering their impact on mortality itself. Finally, our evaluation of the impact of personal risk factors was concurrent with ascertainment of health status making it impossible to determine the temporality of this association.

Improved survival following a diagnosis of childhood cancer is a success story in modern medicine. Surprisingly, our data demonstrate lack of improvement in health status among childhood cancer survivors over thirty years of changing cancer therapy, an important reminder that cancer cure is not without some consequences. Current long-term follow-up guidelines are primarily focused on screening for chronic disease and do not give specific recommendations for surveillance of perceived health status. Fortunately, there has been recent recognition of the importance of patient-reported outcomes as part of curative therapy trials (48). These data may be important in providing opportunities to modify treatments with extreme toxicity and directing early intervention during survivorship for survivors who report adverse health status. Evaluations of associations between changes in specific treatment exposures and health status outcomes for individual primary cancer types, and the development and validation of risk prediction models to better determine who needs screening (52), are important next steps. In addition, because data indicate that risk for

adverse health status increases with age, including measures of perceived health status should be considered in long-term follow-up settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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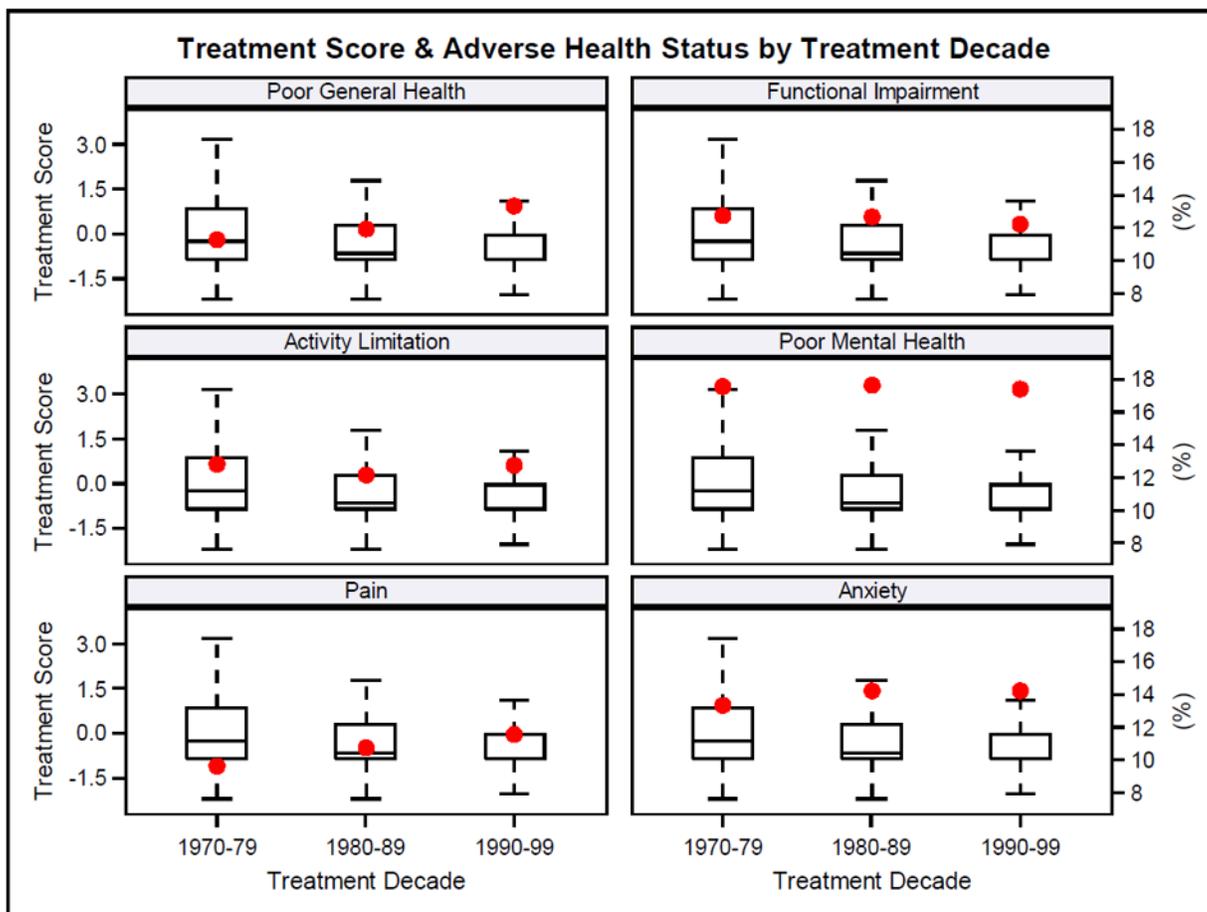
Figure 1.
Treatment score (box and whisker plot – left y axis) and percent with adverse health status outcome (large dots – right y axis) by treatment decade.

A) Acute Lymphoblastic Leukemia
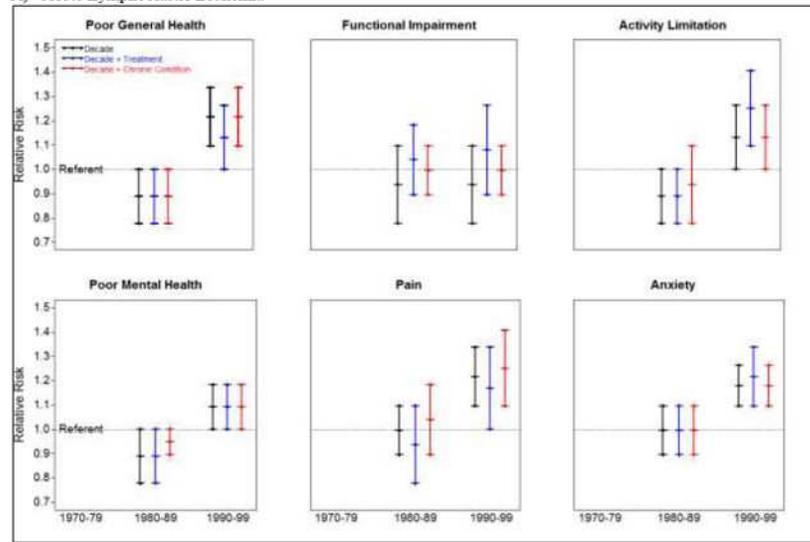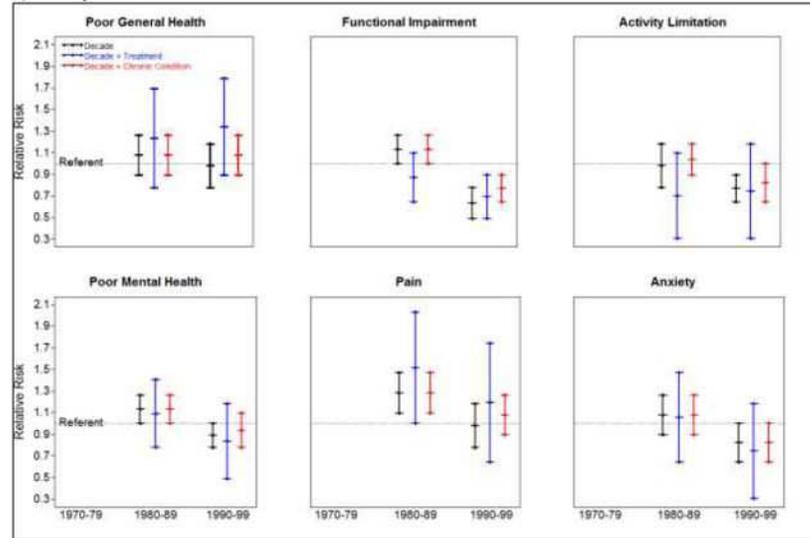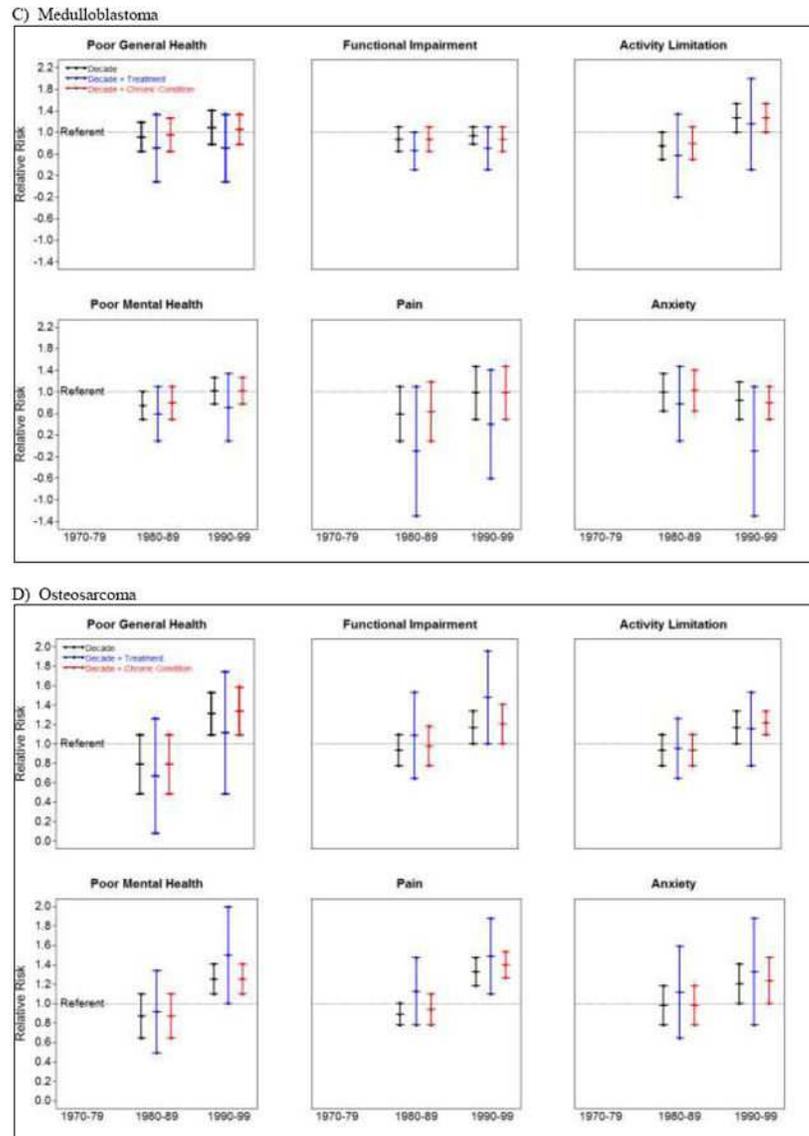
B) Astrocytoma

Figure 2.
Relative risk for adverse health status by treatment decade, adjusted for treatment and chronic conditions among survivors of A) acute lymphoblastic leukemia, B) astrocytoma, C) medulloblastoma, and D) osteosarcoma.

Table 1

Characteristics of the study population

Characteristic		Siblings	Survivors		
		N=3149	1970-1979 N=4618	Survivors 1980-1989 N=4669	1990-1999 N=5279
Attained age at questionnaire (years)	Mean (SD)	29.6 (7.3)	28.5 (6.4)	26.9 (6.0)	25.7 (5.8)
	Median (Range)	29.0 (18.0, 56.0)	28.0 (18.0, 47.0)	26.0 (18.0, 48.2)	24.9 (18.0, 42.4)
Age at diagnosis (years)	Mean (SD)		8.7 (5.8)	10.1 (5.8)	9.0 (6.1)
	Median (Range)		7.7 (0.0, 21.0)	10.3 (0.0, 21.0)	8.5 (0.0, 21.0)
Survival time (years)	Mean (SD)		20.3 (3.0)	17.0 (5.6)	16.8 (3.5)
	Median (Range)		20.1 (12.9, 30.2)	15.6 (6.4, 27.3)	16.9 (8.4, 23.9)
		%	%	%§	%§
Sex	Male	47.2	51.1	52.3	50.6
	Female	52.8	48.9	47.7	49.4
Race/ethnicity	Non-Hispanic White	88.3	90.5	83.4	74.0
	Non-Hispanic Black	2.5	2.8	4.8	8.2
	Hispanic	3.4	4.3	7.0	11.9
	Asian	0.9	0.6	1.7	1.9
	Other/Unknown	4.9	1.8	3.2	4.0
High school graduate	Yes	94.1	91.7	92.7	91.5
	No	5.9	8.3	7.3	8.5
Health insurance	Yes	89.0	84.7	83.2	79.8
	No	11.0	15.3	16.8	20.2
Body mass index [*]	Underweight	3.6	6.3	5.4	3.8
	Normal	51.4	52.1	51.0	47.2
	Overweight	29.1	27.7	27.4	27.6
	Obese	15.9	13.9	16.2	21.3
Smoking status	Never	58.3	69.9	68.2	67.6
	Former	17.1	11.5	14.8	16.1
	Current	24.6	18.6	16.9	16.3

Characteristic		Siblings	Survivors		
		N=3149	1970-1979 N=4618	Survivors 1980-1989 N=4669	1990-1999 N=5279
Heavy drinking [†]	Yes	13.3	10.1	16.2	22.5
	No	86.7	89.9	83.8	77.5
Meets physical activity guidelines[‡]	Yes	40.4	34.7	42.4	46.2
	No	59.6	65.3	57.6	53.8

SD=standard deviation, %=percent, N=number, kg=kilogram, m=meter

[*] Underweight: <18.5 kilograms/square meter (kg/m^2), Normal: 18.5-24.9 kg/m^2, Overweight: 25-29.9 kg/m^2, Obese: 30kg/m^2;

[†] Consuming > 4 drinks/day or > 14 drinks/week for males and consuming > 3 drinks/day or > 7 drinks/week for females,

[‡] 150 minutes of moderate or 75 minutes of vigorous physical activity per week;

[§] Sampling weights applied

Table 2

Cancer diagnosis and treatment changes by decade

	1970-1979 (N=4618)	1980-1989 (N=4669)	1990-1999 (N=5279)
Parameter	%	%[*]	%[*]
Leukemia	32.5	36.8	41.9
Central Nervous System	11.5	14.2	17.8
Hodgkin Lymphoma	17.8	15.6	11.3
Non-Hodgkin Lymphoma	7.5	9.8	8.3
Wilms Tumor	8.6	4.9	6.2
Neuroblastoma	6.3	3.3	3.6
Rhabdomyosarcoma	6.2	4.4	3.4
Bone tumor	9.5	10.9	7.5
Cranial radiation	37.5	29.3	20.4
Mean (SD) dose (cGy)	3053 (1332)	3083 (1871)	3310 (2164)
Chest radiation	31.6	24.2	18.7
Mean (SD) dose (cGy)	3156 (1087)	2872 (1216)	2403 (1150)
Abdominal radiation	31.7	19.2	15.6
Mean (SD) dose (cGy)	3017 (988)	2689 (1185)	2169 (1194)
Pelvic radiation	25.2	15.6	13.2
Mean (SD) dose (cGy)	3057 (1111)	2838 (1340)	2297 (1364)
Alkylating agent[†]	47.9	59.6	58.1
Mean (SD) (mg/m^2)	10491 (10257)	8301 (8265)	8418 (9323)
Anthracycline[‡]	31.0	55.9	66.1
Mean (SD) (mg/m^2)	335 (290)	248 (163)	193 (139)
High dose methotrexate[§]	5.1	13.8	21.3
Prednisone	47.4	49.4	48.1
Dexamethasone	3.1	13.0	25.5
Vincristine	72.3	71.3	72.0
Bleomycin	2.3	10.7	7.6
Cisplatin	0.9	9.0	8.9
Amputation	35.3	26.7	12.0
Splenectomy	74.7	57.9	9.3
Hematopoietic stem cell transplant	0.2	1.9	2.9
Grade 3-4 chronic condition with onset prior to baseline	33.4	25.8	21.0

N=Number, %=Percent, mg=milligrams, m^2=square meter, cGy=centigray, SD=standard deviation

[*] % adjusted for sampling weights;

[†] alkylating agent dose in cyclophosphamide equivalents (27)

[‡] anthracycline dose in doxorubicin equivalents (17);

§ high dose methotrexate defined as intravenous ≥ 4300 mg/m^2

Table 3

Relative risk for adverse health status outcomes by treatment decade and by demographic characteristics and health habits among survivors.

			Poor General Health		Functional Impairment		Activity Limitation		Poor Mental Health		Cancer-related Pain		Cancer-related Anxiety	
		N	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)
Treatment decade	1970-1979	4618	11.2	1.0	12.8	1.0	12.8	1.0	17.5	1.0	9.6	1.0	13.3	1.0
	1980-1989	4669	11.8	1.2 (1.0, 1.4)	12.2	1.1 (0.9, 1.2)	11.6	0.9 (0.8, 1.0)	17.3	1.0 (0.9, 1.1)	10.6	1.1 (1.0, 1.3)	14.0	1.0 (0.9, 1.1)
	1990-1999	5279	13.3	**1.3 (1.1, 1.5)**	11.3	1.0 (0.9, 1.2)	11.9	1.0 (0.9, 1.2)	17.8	1.0 (0.9, 1.1)	11.3	**1.3 (1.1, 1.5)**	14.4	1.0 (0.9, 1.1)
Sex	Male	7492	11.5	1.0	11.0	1.0	9.6	1.0	16.6	1.0	9.7	1.0	11.0	1.0
	Female	7074	13.0	**1.3 (1.1, 1.4)**	13.0	**1.6 (1.4, 1.7)**	14.7	**1.9 (1.7, 2.1)**	18.6	1.1 (1.0, 1.2)	11.7	**1.3 (1.2, 1.5)**	17.2	**1.5 (1.4, 1.7)**
Non-Hispanic white	Yes	12062	11.2	1.0	11.4	1.0	11.7	1.0	17.1	1.0	10.3	1.0	13.9	1.0
	No	2504	17.1	**1.7 (1.5, 1.9)**	14.7	**1.3 (1.2, 1.5)**	13.8	**1.3 (1.1, 1.4)**	19.6	**1.2 (1.1, 1.3)**	12.2	**1.2 (1.1, 1.4)**	14.6	1.1 (1.0, 1.2)
Smoking status	Never	9936	9.7	1.0	10.8	1.0	10.9	1.0	14.2	1.0	8.5	1.0	11.9	1.0
	Former	2074	13.1	**1.4 (1.2, 1.6)**	11.8	1.2 (1.0, 1.4)	13.8	**1.2 (1.1, 1.4)**	19.3	**1.4 (1.2, 1.5)**	12.7	**1.4 (1.2, 1.6)**	17.5	**1.4 (1.2, 1.5)**
	Current	2472	21.9	**2.8 (2.5, 3.1)**	16.9	**1.8 (1.6, 2.1)**	14.9	**1.5 (1.3, 1.7)**	29.7	**2.1 (1.9, 2.2)**	17.2	**2.2 (2.0, 2.5)**	19.4	**1.6 (1.4, 1.7)**
Heavy drinking *	No	12252	12.1	1.0	12.7	1.0	12.2	1.0	16.9	1.0	10.4	1.0	12.9	1.0
	Yes	2311	13.2	0.9 (0.8, 1.1)	8.7	**0.5 (0.4, 0.6)**	11.5	**0.7 (0.6, 0.8)**	20.7	1.1 (1.0, 1.2)	11.9	1.0 (0.8, 1.1)	19.6	1.2 (1.0, 1.3)
Body mass index †	Normal	7129	8.5	1.0	10.0	1.0	10.2	1.0	15.9	1.0	8.9	1.0	13.6	1.0
	Underweight	758	16.3	**2.0 (1.6, 2.5)**	19.7	**2.1 (1.7, 2.6)**	19.7	**2.1 (1.7, 2.5)**	20.4	**1.3 (1.1, 1.5)**	14.1	**1.8 (1.4, 2.2)**	14.9	1.1 (0.9, 1.3)
	Overweight	3905	11.2	**1.3 (1.2, 1.5)**	10.4	1.0 (0.9, 1.2)	11.3	**1.1 (1.0, 1.3)**	17.2	1.1 (1.0, 1.2)	10.7	**1.2 (1.1, 1.4)**	12.8	1.0 (0.9, 1.1)
	Obese	2394	22.3	**2.7 (2.4, 3.1)**	17.2	**1.7 (1.5, 1.9)**	15.9	**1.5 (1.3, 1.7)**	22.0	**1.3 (1.2, 1.5)**	14.3	**1.5 (1.3, 1.8)**	16.6	**1.2 (1.1, 1.3)**
Meets physical activity guidelines ‡	Yes	5777	7.8	1.0	9.1	1.0	8.4	1.0	15.5	1.0	9.6	1.0	13.7	1.0
	No	8348	15.3	**1.9 (1.7, 2.2)**	13.9	**1.4 (1.3, 1.6)**	14.7	**1.7 (1.5, 1.9)**	19.1	**1.2 (1.1, 1.3)**	11.3	1.1 (1.0, 1.2)	14.2	1.0 (0.9, 1.0)

N=number, %=percent, RR=relative risk, CI=confidence interval

Regression models used a binomial distribution with a log link. Adjusted for sampling weights, attained age and survival time in years which were not significant.

*
Consuming > 4 drinks/day or > 14 drinks/week for males and consuming > 3 drinks/day or > 7 drinks/week for females,

†Underweight: <18.5 kilograms/square meter (kg/m^2), Normal: 18.5-24.9 kg/m^2, Overweight: 25-29.9 kg/m^2, Obese: 30kg/m^2.

‡
150 minutes of moderate or 75 minutes of vigorous physical activity per week.

Bold text indicates RR estimates with p < 0.05