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Stephanie Dixon Date

Impact of Risk-Stratified Therapy on Health Status in Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study

By

Stephanie Dixon, MD

Degree to be awarded: Master of Public Health

Executive MPH program, Applied Epidemiology Track

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Ann Mertens, PhD, MS

Committee Chair

_____

Gregory Armstrong, MD, MSCE

Committee Member

_____

Yutaka Yasui, PhD

Committee Member

Impact of Risk-Stratified Therapy on Health Status in Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study

By

Stephanie Dixon

MD
University of Michigan Medical School
2012

BSE
University of Michigan College of Engineering
2008

Thesis Committee Chair: Ann Mertens, PhD, MS

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
2019

Abstract

Impact of Risk-Stratified Therapy on Health Status in Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study

By: Stephanie Dixon, MD

Purpose To evaluate the impact of changes in risk-stratified therapy on health status among adult survivors of childhood acute lymphoblastic leukemia (ALL).

Methods We estimated the self-reported prevalence of adverse health status, including poor general or mental health, functional impairment, activity limitations, and cancer-related pain or anxiety among 5119 survivors of childhood ALL diagnosed from 1970-1999. Therapy combinations defined treatment groups representative of 1970s therapy (70s), standard- and high-risk 1980s and 1990s therapy (80sSR, 80sHR, 90sSR, 90sHR), and relapse/bone marrow transplant (R/BMT). To compare outcomes between groups, log-binomial models adjusted for clinical and demographic factors estimated prevalence ratios (PR) with 95% confidence intervals (CI).

Results Overall, survivors were more likely than siblings to report increased risk for all health status outcomes including poor general health (13.5% vs. 7.4%; PR 1.97 95% CI 1.73-2.24). Compared to 70s, 90sSR were less likely to report functional impairment (PR [95% CI] 0.55 [0.41-0.75]), activity limitations (0.63 [0.45-0.87]) and cancer-related pain (0.65 [0.45-0.94]); however, although a lower proportion reported poor general health (90sSR 12.2% vs 70s 16.5%), a 22% reduction in likelihood (PR 0.78 [0.59-1.03]), this was not statistically significant. Compared to 70s, 90sHR were less likely to report poor general health (0.61 [0.40-0.92]), functional impairment (0.61 [0.40-0.91]) and activity limitations (0.63 [0.40-0.98]). Compared to 70s, a higher proportion of survivors from R/BMT reported adverse health status outcomes, albeit PR was not statistically significantly different. Compared to siblings, 90sSR reported no difference in activity limitations (PR 1.25 [0.96-1.62]).

Conclusion Risk-stratified ALL therapy has succeeded in reducing risk for certain components of adverse health status compared to 70s. Further, 90sSR had no increase in risk for activity limitations compared to siblings.

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I would like to first acknowledge the survivors and families who participate in the Childhood Cancer Survivor Study (CCSS) and make this research possible. I also would like to acknowledge my thesis committee, Dr. Greg Armstrong, Dr. Yutaka Yasui and Dr. Ann Mertens, and my collaborators in my work utilizing the CCSS for their support of my thesis study, but also my research career. The involvement in collaborative research in cancer survivorship through my thesis study and other studies I have had the opportunity to participate in from the CCSS have been invaluable to my understanding of epidemiology and biostatistics which will help to shape my future career as a pediatric oncologist and researcher in the field of pediatric cancer survivorship.

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Chapter I: Introduction

Self-reported health status began appearing in medical research in the 1980s predominately as a single question of how an individual viewed their health compared to that of same-aged peers. This single question, asked in different formats, was repeatedly shown to be associated with mortality.[1] In fact, one of the first studies to demonstrate a clear association showed that self-reported health status was a better predictor of seven-year mortality than available medical records or self-report of medical conditions.[2] Additionally, health status served as a more holistic measure of individual health, focused on the individuals perception of their well-being, not simply an assessment of the number or severity of medical conditions documented. In the decades following, the assessment of health status became widely used and often included multiple attributes of physical and emotional health, as well as functional measures of activity and self-care.

One of the first studies evaluating health status in childhood cancer survivors utilized a multi-attribute classification system to evaluate sensation, mobility, emotion, cognition, self-care, pain and fertility as assessed by pediatric oncologists.[3] This did little to include the perception of the individual in the scoring system, but could be applied to younger participants. A subsequent study in the late 1990s primarily focused on self-reported toxicities and associations with health-related quality of life (HRQL).[4] This study offered some of the first descriptions of associations between therapy intensity and comorbid conditions with self-reported HRQL among long-term survivors of childhood cancer.

However, childhood cancer survivors not only suffer complex medical sequelae as a result of cancer therapy,[5,6] but also may experience general anxiety and fears after cancer treatment.[7] Additionally, although the majority of survivors are well adjusted, an increased proportion of survivors experience emotional distress compared to siblings.[7-10] These physical and psychological sequelae may also impact perceived health and quality of life. Because of this, investigators describing health status of childhood cancer survivors in the Childhood Cancer Survivor Study (CCSS) felt that it was important to include general health, mental health, functional impairment, limitations in activity as well as pain and anxiety related to cancer in the comprehensive assessment of survivor health status.[11]

From the methods of Hudson et al., the six domains of health status measured in the original publication on this topic from the CCSS included general health, mental health, functional status, activity limitations, cancer-related pain and cancer-related anxiety. All measures were self-reported by survey questionnaire. General health was defined by a single question from the 36-Item Short Form Survey Instrument (SF-36), “In general, would you say your health is excellent, very good, good, fair, or poor?” Mental health was assessed using the 18-item Brief Symptom Inventory (BSI-18).[12] Questions assessing activity limitations and functional status included in the CCSS questionnaires had been adapted from the National Health Interview Survey and the Behavioral Risk Factor Surveillance System Survey Questionnaires. Specifically, functional impairment was assessed by questions that asked respondents about the presence of a health problem that

resulted in the need for help with personal care, activities of daily living or difficulty keeping a job or attending school. Activity limitations were determined by report that a health problem(s) limited specific activities (walking 1 block, walking upstairs, moderate activities such as carrying groceries) for at least 3 months of the past 2 years. Survivors were also asked about pain, “Do you have pain as a result of your cancer or its treatment?”, and to quantify the amount on a 5-point Likert scale. Similarly, survivors were asked if they experienced fear or anxiety related to cancer, and to quantify the amount. Using these criteria, an analysis of nearly 10,000 survivors of childhood cancer in the original CCSS cohort, diagnosed from 1970-1986, identified that a higher proportion of survivors reported adverse health status outcomes than siblings. Among survivors, 10.9% reported poor general health compared to only 4.9% of siblings. Overall, 43.6% of survivors reported poor health status in at least one domain. Within survivors, increased risk for adverse health status in any domain was associated with female sex, and older age was associated with adverse outcomes in the physical domains (general health, functional status, activity limitations and pain). Additionally, specific therapy exposures were associated with adverse health status. This work provided a systematic approach to assessing self-reported health status among a large cohort of adult survivors of pediatric cancer, however, it did not explore health status by cancer diagnosis in detail.

My thesis work focuses on health status of survivors of acute lymphoblastic leukemia (ALL) and a basic understanding of this disease and its treatment is

necessary to understand the motivation for this work. ALL is the most common childhood cancer, accounting for 20% of all malignancies among children <20.[13] Dramatic improvements in five-year survival from only 10% in the 1960s to near 90% by the early 2000s have been achieved with risk-stratification to tailor intensity of chemotherapy regimens to clinical and biologic variables as well as treatment response.[14-21] These efforts have been led through cooperative group trials as well as a handful of single-institutions with independent clinical trials. Although therapy variations across cooperative groups and institutions exist, there have been major trends in therapy changes over this time including increased use of dexamethasone and asparaginase,[22] increased use of anthracyclines[23] with variation in cumulative dose by risk-group, increase in high-dose methotrexate exposure,[17] increased use of alkylating agents with a decrease in the cumulative dose received,[23] and a successive decline in the proportion of patients receiving cranial radiation therapy (CRT).[21,24-26] Risk-stratified therapy for ALL was primarily introduced into therapeutic protocols in the 1980s. The criteria for risk-group assignment have varied over time (and protocol) based on improved understanding and discovery of clinical presentation and features of the patient, biologic and genetic features of the leukemia cells, and early response to treatment which predict risk of relapse.

While the majority of ALL patients treated in the current era are expected to be cured of their disease, many will go on to experience excess morbidity and mortality as a result of their cancer experience. These adverse outcomes impact

self-reported health status, as described above. All-cause late mortality in the entire CCSS cohort, including those diagnosed from 1970-99, was most recently evaluated by Armstrong et al. In this analysis, they reported that the 15-year cumulative mortality conditioned on 5-year survival was reduced from 13.3% for ALL survivors treated in the 1970s to 4.7% for those treated in the 1990s. [27]

ALL survivors are also known to be at increased risk for subsequent neoplasms compared to the general US population.[28,29] Although recent studies have described a decrease in the rate of subsequent malignant neoplasms in cancer survivors overall who received treatment in later decades, this trend toward improved outcomes was not observed in the subgroup of ALL survivors by decade.[29] ALL survivors are at an increased risk for chronic health conditions compared to siblings. Among ALL survivors diagnosed 1970-1986, survivors were 3.7 times as likely as siblings to report a severe or life-threatening condition, with a cumulative incidence among ALL survivors 25 years from diagnosis of 21.3%.[28] A recent analysis of temporal trends in chronic health conditions among the entire CCSS cohort, diagnosed 1970-1999, observed no significant difference across treatment decades in the 15-year cumulative incidence of any severe, disabling, life-threatening or fatal chronic health condition for ALL survivors (15.7% for 1970s vs. 14.5% for 1980s vs. 14.6% for 1990s).[30]

Specifically focusing on health status of ALL survivors. Prior studies evaluating the original cohort of the CCSS (survivors diagnosed 1970-1986) have identified that ALL survivors more frequently reported poor general health status, mental health problems, activity limitations and functional impairment compared to siblings;[28] however, Essig et al. observed that in the subset of survivors treated most similarly to contemporary ALL therapy (without cranial radiation, with low to moderate anthracycline doses and low overall alkylating agent exposure), differences from siblings health status were seen only with regards to functional limitations.[31] However, a recent analysis of the overall CCSS cohort by Ness et al. observed an increase in the percentage of ALL survivors reporting poor general health, cancer-related pain and cancer-related anxiety by treatment decade, meaning ALL survivors diagnosed in the 1990s had worse health status outcomes in these domains than those diagnosed in the 1970s.[23] Further, although differences in poor general health and cancer-related pain became non-significant after adjustment for treatment exposures, they were not changed by adjustment for grade 3 or 4 chronic health conditions.

Previous studies have identified that among ALL survivors in their 20s, 30s and 40s, approximately 10-20% report adverse health status in each domain assessed (general health, mental health, functional impairment, activity limitations, cancer-related pain and anxiety).[23,28,32] Additionally, because adverse health status outcomes are associated with specific therapy exposures,[11,23,32] we would anticipate improvement in health status as therapy has evolved to modify

chemotherapy intensity and eliminate cranial radiation for standard-risk ALL patients.[15,17,21,33] As detailed above, while studies of survivors across decades have reported a decrease in premature mortality for survivors of ALL treated in more recent eras,[27] they have not observed consistent reductions in rates of subsequent malignant neoplasms (SMN)[29] or chronic health conditions[34] and, in fact, identified an increase in the proportion of survivors reporting poor general health, cancer-related pain and anxiety.[23]

Although prior work has detailed late effects of specific therapeutic exposures or era of therapy on health status outcomes of survivors of childhood ALL, none have analyzed reported health status of adult survivors of ALL stratified by groups representative of risk-stratified therapy as it has evolved over time. However, practically, a survivor received a therapy combination (including dosage) reflective of the era and risk-group in which they were treated, and therefore, likely has a late effects risk profile reflective of this combined therapy, not simply the individual agents received. Because therapy varies significantly not only across treatment eras but also across risk groups with increasing intensity of therapy received by survivors of high-risk therapy compared to standard-risk therapy, this knowledge of late-health outcomes for risk-stratified groups would inform life-long clinical care of these survivors. Essig et al. utilized review of ALL protocols from the early 2000s to determine treatment exposures that would define treatment most similar to contemporary standard-risk ALL therapy. They applied these criteria (no cranial radiation, anthracycline dose

≤120 mg/m^2, cyclophosphamide dose ≤1000 mg/m^2) to CCSS participants diagnosed from 1970-1986 to estimate late-effect risk among contemporary standard risk survivors. Building on these methods, I carefully reviewed ALL therapeutic protocols utilized across cooperative groups and independent treating institutions from 1970-1999 and consulted with experts in the field of pediatric leukemia, remaining mindful of the specific treatment exposure information available in the CCSS, to categorize survivors of ALL in the CCSS into treatment groups representative of risk-stratified therapy changes from 1970-1999. With these treatment categories, I was able to utilize data from the largest cohort of survivors of childhood ALL in North America, to provide health status outcomes across 30-years of treatment and describe these findings in the context of risk-stratified therapy changes of this timespan.

Purpose of the study

To evaluate the association between risk-stratified treatment over time and self-reported health status among adult survivors of childhood ALL utilizing the CCSS cohort.

Public health purpose of the study

To better characterize expected long-term health status of ALL survivors based on the risk-stratified therapy they received to inform clinical care of these survivors beyond what is available from studies focused on individual therapy exposures.

Goals of the Study

1) Identify prevalence of adverse health status outcomes among adult survivors of childhood ALL by treatment groups

2) Compare prevalence of adverse health status outcomes between treatment groups and to a sibling control group to determine the impact of risk-stratified therapy changes over time

Chapter II: Manuscript

Results contained in this article to be submitted either independently or with additional outcomes not included in this thesis work for publication, formatted for the Journal of Clinical Oncology

Impact of Risk-Stratified Therapy on Health Status in Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study

Stephanie B. Dixon, M.D.

Yan Chen, M.Sc.

Yutaka Yasui, Ph.D.

Ann C. Mertens, Ph.D.

Gregory T. Armstrong, M.D., M.S.C.E.

From the Departments of Oncology (S.B.D), Epidemiology and Cancer Control (Y.Y, G.T.A.), St. Jude Children's Research Hospital, Memphis; School of Public Health, University of Alberta, Edmonton, Alberta, Canada (Y.C.); Department of Pediatrics (A.C.M.) Emory University School of Medicine, Atlanta, GA;

Corresponding Author: Stephanie B. Dixon, MD
Department of Oncology
St. Jude Children's Research Hospital
262 Danny Thomas Place Mail Stop 260
Memphis, TN 38105
Phone: (901) 595-0531
Fax: (901) 595-5845
E-mail: stephanie.dixon@stjude.org

Running Head: Risk-Stratified ALL Therapy and Health Status.

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This research will be presented in October at The International Society of Paediatric Oncology (SIOP) Annual Meeting 2019, Lyon, France.

ABSTRACT

Purpose To evaluate the impact of changes in risk-stratified therapy on health status among adult survivors of childhood acute lymphoblastic leukemia (ALL).

Methods We estimated the self-reported prevalence of adverse health status, including poor general or mental health, functional impairment, activity limitations, and cancer-related pain or anxiety among 5119 survivors of childhood ALL diagnosed from 1970-1999. Therapy combinations defined treatment groups representative of 1970s therapy (*70s*), standard- and high-risk 1980s and 1990s therapy (*80sSR*, *80sHR*, *90sSR, 90sHR*), and relapse/bone marrow transplant (*R/BMT*). To compare outcomes between groups, log-binomial models adjusted for clinical and demographic factors estimated prevalence ratios (PR) with 95% confidence intervals (CI).

Results Overall, survivors were more likely than siblings to report increased risk for all health status outcomes including poor general health (13.5% vs. 7.4%; PR 1.97 95% CI 1.73-2.24). Compared to *70s*, *90sSR* were less likely to report functional impairment (PR [95% CI] 0.55 [0.41-0.75]), activity limitations (0.63 [0.45-0.87]) and cancer-related pain (0.65 [0.45-0.94]); however, although a lower proportion reported poor general health (*90sSR* 12.2% vs *70s* 16.5%), a 22% reduction in likelihood (PR 0.78 [0.59-1.03]), this was not statistically significant. Compared to *70s*, *90sHR* were less likely to report poor general health (0.61 [0.40-0.92]), functional impairment (0.61 [0.40-0.91]) and activity limitations (0.63 [0.40-

0.98]). Compared to *70s*, a higher proportion of survivors from *R/BMT* reported adverse health status outcomes, albeit PR was not statistically significantly different. Compared to siblings, *90sSR* reported no difference in activity limitations (PR 1.25 [0.96-1.62]).

Conclusion Risk-stratified ALL therapy has succeeded in reducing risk for certain components of adverse health status compared to *70s*. Further, *90sSR* had no increase in risk for activity limitations compared to siblings.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for 20% of all malignancies among children <20.[13] Improvements in five-year survival from 10% in the 1960s to near 90% by the early 2000s have been achieved with improved risk-stratification to tailor intensity of chemotherapy regimens to clinical and biologic risk as well as treatment response.[14-21] Although differences in treatment approaches across cooperative groups and institutions existed, major trends over this time included increased use of dexamethasone and asparaginase,[22] increased use of anthracyclines[23] with variation in cumulative dose by risk-group, increase in high-dose methotrexate exposure,[17] and a successive decline in the proportion of patients receiving cranial radiation therapy (CRT).[21,24-26]

However, many survivors of childhood ALL go on to experience premature mortality and excess morbidity in the form of subsequent neoplasms, chronic health conditions, neurocognitive impairment and poor health status as a result of their cancer treatment.[23,27-29,34-36] Previous studies have identified that among ALL survivors in their 20s, 30s and 40s, approximately 10-20% report adverse health status in each domain assessed (general health, mental health, functional impairment, activity limitations, cancer-related pain and anxiety).[23,28,32] Adverse health status outcomes in the physical domains (general health, functional impairment and activity limitations), are known to be associated with aging.[32,37] Additionally, because adverse health status is associated with specific therapy

exposures,[11,23,32] we anticipate improvement in health status as therapy has evolved to modify intensity and eliminate cranial radiation for standard-risk ALL patients.[15,17,21,33] While studies of survivors across decades reported a decrease in premature mortality for survivors of ALL treated more recently,[27] they have not observed consistent reductions in rates of subsequent malignant neoplasms (SMN)[29] or chronic health conditions[34] and, in fact, identified an increase in the proportion of survivors reporting poor general health, cancer-related pain and anxiety.[23]

Although prior work has detailed late effects of specific therapeutic exposures and era of treatment on health status outcomes of survivors of childhood ALL, none have analyzed reported health status of adult survivors of ALL stratified by groups representative of risk-stratified therapy as it has evolved over time. Because therapeutic agents and intensity vary significantly not only across treatment eras but also risk groups, this knowledge would inform clinical care of these survivors. Using the largest cohort of survivors of childhood ALL in North America, we provide health status outcomes across 30-years of treatment and describe these findings in the context of therapeutic changes over this time span, focused on characterizing the impact of treatment most similar to contemporary standard-risk therapy across the lifespan of survivors.

Methods

Study Population

The Childhood Cancer Survivor Study (CCSS) is a retrospective, multi-institutional, cohort study with longitudinal follow-up of survivors of childhood cancer diagnosed and treated at 31 institutions across the US and Canada. Study eligibility included diagnosis of cancer before age 21 years, initial treatment between January 1, 1970 and December 31, 1999, and alive at five years after diagnosis of leukemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma or a bone tumor. The CCSS was approved by institutional review boards at participating centers. Participants or guardians provided informed consent. A detailed description of the cohort methodology and study design have been previously published.[38]

Outcome Measures

Adverse health status across four domains in survivors and siblings (poor general or mental health, functional impairment and activity limitations) and two additional domains in survivors only (cancer-related pain or anxiety) were evaluated using established definitions.[23,39] Poor general health was defined as a response of “poor” or “fair” to a single question rating participant health on a 5-point Likert scale. Poor mental health was defined as participants whose responses on the Brief Symptom Inventory 18 (BSI-18) resulted in a sex-specific T-score of 63 or higher on the Global Severity Index or any two of the depression, anxiety or somatization subscales.[12] Functional impairment was defined by report of a health problem that resulted in the need for help with

personal care, activities of daily living or difficulty keeping a job or attending school. Activity limitations were assigned to participants who reported that health limited their ability to participate in moderate activities (i.e. walking upstairs, climbing a few flights of stairs, or walking one black) three or more months of the past two years. With the exception of mental health, health status questions were adapted from the National Health Interview Survey and Behavioral Risk Factors Surveillance System Survey Questionnaire.[40,41] For cancer-related pain, survivors were dichotomized as having medium, a lot, or very bad/excruciating pain related to their cancer or cancer treatment versus none or a small amount of pain. For cancer-related anxiety, survivors were dichotomized as having medium, a lot, or many/extreme fears or anxiety related to their cancer or treatment versus none or a small amount. Analyses of health status outcomes were limited to participants ≥18 years of age at the time of outcome response and excluded proxy reports.

Cancer Treatment Information and Treatment Groups

For the 6148 survivors of childhood ALL who provided authorization, cancer diagnosis including age at diagnosis and treatment data including chemotherapy cumulative doses and body region-specific radiation dosimetry were abstracted from medical records at the treating institutions utilizing standardized methods within the CCSS.[42,43] Survivors who were <18 years at the time of last assessment or with outcomes reported by proxy (n=1029) were excluded from this study. Anthracycline and alkylating drug doses were standardized as

doxorubicin-equivalent dose and cyclophosphamide-equivalent dose respectively.[44,45] We generated clinically meaningful and mutually exclusive treatment groups representative of risk-stratified therapy across different eras using multi-modal therapy exposures and dose cut-points detailed in Table 1. Survivors assigned a group received treatment representative of 1970s therapy (*70s*), 1980s and 1990s standard and high-risk therapy (*80sSR, 80sHR, 90sSR, 90sHR)* and therapy for relapse or with bone marrow transplant (*R/BMT*).

Demographic Characteristics

Questionnaire responses were used to determine attained age, sex and race/ethnicity. For all analyses, age at the time of questionnaire response was treated as a continuous variable. Race/ethnicity was categorized into four mutually exclusive groups (non-Hispanic white, non-Hispanic black, Hispanic and Other).

Statistical Analysis

The prevalence of adverse health status outcomes was estimated stratified by treatment group. Reports of adverse health status were compared between siblings and survivors and among survivors by treatment group using multivariable log-binomial regression. Analyses comparing all survivors to siblings included adjustment for attained age, race/ethnicity and sex. Analyses among survivors examined the associations between treatment group and adverse health status outcomes adjusted for attained age, age at diagnosis,

race/ethnicity and sex. Because prior analyses demonstrated significant associations with overall health status and decade of diagnosis, a second model added an adjustment for decade of diagnosis to the treatment group comparison. As ALL is the most common pediatric cancer, survivors of ALL were under-sampled at the time of CCSS cohort expansion to include survivors diagnosed in 1987-1999 to reduce study costs without sacrificing statistical power. Therefore, sampling weights were applied to all modeling. Potential intra-family correlation between survivors and siblings and among weighted survivors was accounted for using generalized estimating equation (GEE). For all analyses, SAS, version 9.4 (SAS Institute) was used.

Results

Among 8,551 survivors eligible for participation with a diagnosis of ALL, 5119 completed the baseline survey and had at least one evaluable self-reported health status outcome. For treatment group analyses, the 437 survivors for whom treatment information was not available or was incomplete were excluded and 3499 (75%) of the 4682 ALL survivors with complete treatment information were assigned a treatment group (Table 2, Data Supplement). There were 4693 siblings with evaluable self-reported health status outcomes for comparison. Overall, the median age at last follow-up was 32.8 years (range 18.0 – 61.9) for survivors and 36.7 years (range 18.0-68.9) for siblings.

Treatment groups demonstrated expected differences in age at last assessment with *70s* having an older median age at last follow-up (40.3 years). Additionally,

treatment groups demonstrated concordance with anticipated year of diagnosis with the majority of survivors assigned to a representative treatment group being diagnosed in the corresponding decade. For example, 85% of *70s* were diagnosed in the 1970s. Overall, 52% of survivors were male, however both *90sHR and R/BMT* had a higher proportion of male participants (58% and 65% respectively) while *70s* and *90sSR* had a lower proportion of male participants, both with 46%. Overall, 6.1% of survivors reported Hispanic ethnicity, however, a higher proportion of *90sSR, 90sHR* and *R/BMT* reported Hispanic ethnicity (10.7%, 10.9% and 13.9% respectively).

Many between group differences in treatment exposure were defined by assigned treatment groups, including cranial radiation, dexamethasone and anthracycline dose. Notable exposure differences between groups included 55% of *90sHR* and 23% of *R/BMT* received no cranial radiation therapy, and 24% of *R/BMT* and 28% of *90sSR* received dexamethasone. Although all survivors in a high-risk treatment group received >120mg/m^2 anthracycline, *90sHR* received a lower cumulative dose with <250 mg/m^2 received by 93% of survivors compared to *80sHR* where only 44% of survivors received <250 mg/m^2. A larger proportion of 80s treatment groups received at least 4000 mg/m^2 cyclophosphamide (36% in *80sSR* and 65% in *80sHR*) compared to <25% in other non-relapse/transplant groups. Finally, a larger proportion of *90sSR* received high-dose methotrexate (43%) compared to <25% of all other treatment groups.

Survivors with a median age 33 years (range 18-62), had a high prevalence of adverse health status outcomes in every domain with 13.5% reporting poor general health, 9.3% poor mental health, 12.7% functional impairment and 10.7% activity limitations. (Table 3) After adjustment for attained age, sex and race/ethnicity, survivors were more likely than siblings to report adverse health status across all domains. Specifically, survivors were twice as likely to report poor general health (PR 1.97, 95% CI 1.73-2.24) and three times as likely to report functional impairment (2.98, 2.55-3.49).

When stratified by treatment group, we identified differences in the proportion of survivors experiencing adverse health status across treatment groups. For health status outcomes related to physical health, a lower percentage of survivors of *90sHR* and *90sSR* reported adverse outcomes compared to other groups. Specifically, 10.1% of *90sHR* and 12.2% of *90sSR* reported poor general health compared to 13.2-16.5% among other treatment groups and only 8.8% and 7.9%, respectively, reported activity limitations compared to 12.1-14.7% among other groups. (Table 4) However, no similar trend was observed for poor mental health and cancer-related anxiety. Multivariable analyses adjusted for age at diagnosis, attained age, sex, race/ethnicity and treatment group found no evidence of worsening health status for survivors of more modern treatment exposures compared to *70s* as was previously suggested in earlier work. Specifically, a lower proportion *90sSR* reported poor general health (12.2% vs 16.5% respectively), although this was not statistically significantly different (PR

[95% CI] 0.78 [0.59-1.03]), and there was no difference in reported cancer related anxiety (1.0 [0.73-1.36]). Further, compared to *70s,* a lower proportion of *90sSR* survivors reported functional impairment (0.55 [0.41-0.75]), activity limitations (0.63 [0.45-0.87]), and cancer-related pain (0.65 [0.45-0.94]). (Table 4, Figure 1) Compared to *70s*, *90sHR* was also associated with a decreased likelihood to report functional impairment (PR [95% CI] 0.61 [0.40-0.91) and activity limitations (0.63 [0.40-0.92]). Further, while a higher percentage of *90sHR* and *R/BMT* than *70s* survivors reported cancer-related pain (12.4%, 13.3%, 10.6%, respectively) and anxiety (15.4%, 13.2%, 11.4%), these differences were not statistically significant (PR [95% CI] Pain: *90sHR* 1.03 [0.70-1.52], *R/BMT* 1.23 [0.86-1.78]; Anxiety: *90sHR* 1.20 [0.81-1.79], *R/BMT* 1.12 [0.78-1.63]).

Because a recent study observed a significant impact of decade of therapy on health status outcomes,[23] a second model explored this association. After adjustment for decade of diagnosis, effect sizes for observed associations between treatment groups changed slightly, but, apart from functional impairment, significance of associations did not. In the treatment group-decade model, compared to *70s*, our data showed a 30% reduction in the likelihood of functional impairment among *90sHR*, although this was no longer statistically significant (PR [95% CI] 0.69 [CI 0.44-1.08]), it was similar to the 35% reduction among *90sSR,* which remained statistically significant (0.64 [0.45-0.90]). Compared to *70s,* there was a 35% increased likelihood of functional impairment among R/BMT which was now significant (1.35 [1.0-1.8]). (Supplemental Table 1)

Finally, when compared to siblings after adjustment for attained age, sex and race/ethnicity, survivors of *90sSR* were no more likely to report activity limitations (PR [95% CI] 1.25 [0.96-1.62]). However, for all other outcomes across treatment groups survivors reported worse health status than sibling controls. (Table 5)

Discussion

Survivors of childhood ALL, overall and within treatment groups, report a high prevalence of adverse health status outcomes. Although prior studies in the CCSS reported that survivors treated in the 1990s experienced worse health-status than those treated in the 1970s, we identified that when stratified by treatment group, there was no evidence for worsening outcomes among *90sSR* or *90sHR* compared to *70s*. In fact, our study identified some domains of improved health status for *90sHR* and *90sSR* survivors including in the domains of functional impairment and activity limitations. Not surprisingly, a larger proportion of *R/BMT* survivors experienced functional impairment, activity limitations and cancer-related pain than any other treatment group. Notably, one-third of these survivors were treated in the 1990s and just less than one-quarter in the 1970s. In many domains, *R/BMT* survivors showed a trend towards worse health status outcomes compared to *70s*, although none met significance after adjustment for age at diagnosis and demographic factors.

Treatment groups were representative of risk-stratified therapy by decade of treatment, however, each group included survivors treated in multiple decades.

Knowing this and that prior studies observed a significant impact of decade on health status outcomes,[23] a second model included an adjustment for decade of treatment in addition to treatment group. The added adjustment for decade had a small impact on effect sizes of association, which may represent improvements in supportive care over time and other unmeasured factors. However, there was no change in the significance of outcomes for *90sSR.* Even after adjustment for decade, *90sSR* survivors were less likely to report functional impairment, activity limitations and cancer-related pain when compared to *70s*. However, compared to *70s, R/BMT* survivors were now more likely to report functional impairment, and improvements in functional status previously observed in *90sHR* were no longer significant. This suggests that risk-stratification was successful in improving certain health status outcomes for survivors treated with contemporary standard-risk therapy. In addition, survivors who received higher-intensity therapy, particularly in the relapse/transplant setting, may be responsible for previous reports of worse health outcomes of ALL survivors treated in the 1990s overall. Clearly, the ability to assess modern (1990s) survivors based on treatment exposure provides further insight into risk for adverse health status for this population.

There are many potential reasons health status differed between risk-stratified groups. First, survival of childhood ALL has improved dramatically with treatment advances occurring over the time examined in this study.[15-18,21] This has led to increased numbers of survivors, particularly those who received more intensive

therapy that cured their high risk disease.[46] Children with high-risk ALL who may have died after receiving *70s* therapy or earlier era relapse/transplant treatment, more often survived treatment with *90sHR* therapy or later era relapse/transplant treatment. These survivors of high-risk disease may report worse health outcomes and are likely under-represented in the *70s* cohort. Additionally, although contemporary standard-risk therapy may decrease risk for chronic health conditions;[31] high-risk therapy, with more intensive chemotherapy regimens, and therapy for relapse or transplant may increase the burden of comorbidities experienced by survivors of these groups. This is suggested by results of a recent analysis of the entire CCSS identifying that the 15-year cumulative incidence of severe, life-threatening or fatal chronic health conditions experienced by survivors of ALL has not changed between survivors treated in the 1970s and those treated in the 1990s.[34] Survivors with a higher prevalence of severe health conditions may be more likely to report adverse health status, as is seen in the general population with other chronic conditions.[47-49]

Limitations of this study exist. First is the potential influence of participation bias. Not all survivors eligible for the CCSS chose to participate. While we stratified our analysis by treatment group, even within a given treatment group, participants may have reported different health status outcomes than non-participants. Second, because many health status outcomes are not easily observable, proxy reports could not be used. This eliminates outcomes for some of the most vulnerable populations of survivors, those with significant

neurocognitive impairment. Therefore, results reported in this analysis are potentially an under-estimate of the true prevalence of adverse health status among survivors of ALL.

Despite encouraging improvements across many domains in health status among survivors treated most similar to contemporary standard- and high-risk ALL therapy, all treatment groups reported worse health status compared to siblings. The only exception was for activity limitations, where survivors of *90sSR* reported no difference from siblings. Further, while a clear trend toward improved outcomes in the domain of functional impairment is seen with more recent risk-stratified therapy, evidenced by the decreasing effect sizes compared to siblings, this trend is not observed in reported mental health and is unclear for general health. This is concerning because self-reported health status has repeatedly been demonstrated to predict mortality,[1,2,50] including when examined independent of traditional risk-factors for specific conditions such as cardiovascular disease.[47] Further, health status has been associated with care utilization and, specifically, decreased uptake of population based cancer screening among adults reporting poor mental health,[51,52] as well as poor general health.[53] We know that survivors, as a whole, have increased risk for late-mortality and chronic conditions associated with their cancer treatment, however, disparities in health care utilization exist within the population,[54,55] and less than one-third of survivors report survivor-focused care and counseling, including late effects screening.[54,56] It is unknown if similar associations between perceived

health status and mortality or care utilization exist in childhood cancer survivors, and further research into this relationship may provide new opportunities to identify survivors at high-risk of late morbidity and mortality. However, we are encouraged that our findings indicate that risk-stratification is successful in improving aspects of health status outcomes for survivors treated with contemporary standard-risk therapy.

Table 1. Therapeutic exposures defining mutually exclusive treatment groups

Therapy Exposure	Treatment Group					
	70s	**80sHR**	**80sSR**	**90sHR**	**90sSR**	**R/BMT**
Cranial radiation therapy (Gy)	>20	>0	0<CRT≤20	-	None	-
Dexamethasone exposure	No	No	No	Yes	-	-
Anthracycline cumulative dose (mg/m2)	-	>120	≤120	>120	≤120	-
Cyclophosphamide cumulative dose (mg/m2)	-	-	-	>1000	≤1000	-
Cytarabine, IV	No	Yes	-	-	-	-
Relapse or bone marrow transplant	No	No	No	No	No	Yes

CRT: Cranial radiation therapy, IV: Intravenous
Therapy exposures, including relapse or bone marrow transplant, occurred within the first 5 years from diagnosis of ALL.
A – indicates that the variable is not a differentiator for the group, the cell can assume any value.
Anthracycline dose reported as doxorubicin equivalent dose where conversions are idarubicin x 3, daunorubicin x 0.5, mitoxantrone x 10 and epirubicin x 0.67

Table 2. Demographic and Treatment Characteristics of 5-Year Survivors and Siblings

Characteristic	Overall		Treatment Groups					
	All survivors	Siblings	70s	80s HR	80s SR	90s HR	90s SR	Relapse/ BMT
	no. (%)							
All participants	5119	4693	675	342	591	368	1028	495
Sex								
Male	2674 (52.3)	2191 (46.7)	314 (46.4)	181 (51.5)	298 (50.4)	208 (58.2)	462 (45.8)	319 (64.9)
Female	2445 (47.7)	2502 (53.3)	361 (53.6)	161 (48.5)	293 (49.6)	160 (41.8)	566 (54.2)	176 (35.1)
Race/Ethnicity								
White, NH	4244 (80.3)	4104 (87.5)	618 (91.6)	288 (82.3)	519 (85.1)	306 (80.9)	857 (79.7)	389 (75.8)
Black, NH	231 (3.4)	132 (2.8)	14 (2.1)	13 (5.0)	23 (5.6)	13 (2.9)	40 (4.7)	22 (4.9)
Hispanic/Latino	429 (6.1)	184 (3.9)	27 (4.0)	28 (8.5)	25 (5.6)	32 (10.9)	91 (10.7)	61 (13.9)
Other	215 (2.9)	273 (5.8)	16 (2.3)	13 (4.2)	24 (3.7)	17 (5.3)	40 (4.8)	23 (5.4)
Age at last follow-up (yr), median (range)	32.8 (18.0-61.9)	36.7 (18.0-68.9)	40.3 (19.1-61.9)	35.6 (18.6-55.3)	33.8 (18.3-60.3)	30.7 (18.0-48.4)	29.5 (18.0-58.7)	33.1 (18.2-59.5)
Age at diagnosis (yr)								
0-4	2461 (51.0)		346 (51.4)	135 (41.7)	318 (55.0)	95 (34.6)	593 (59.3)	228 (48.6)
5-9	1382 (29.7)		196 (29.1)	101 (32.0)	146 (25.8)	80 (28.5)	307 (33.3)	138 (29.9)
10-14	882 (13.8)		102 (15.0)	71 (17.5)	85 (13.7)	134 (26.7)	92 (5.4)	78 (13.2)
15-21	394 (5.5)		31 (4.5)	35 (8.8)	42 (5.5)	59 (10.3)	36 (1.9)	51 (8.3)
Treatment era								
1970-1974	577 (7.3)		260 (38.0)	8 (1.9)	47 (6.0)	1 (0.1)	63 (2.9)	50 (7.4)
1975-1979	1016 (12.9)		319 (46.7)	101 (23.4)	129 (16.3)	5 (0.7)	63 (2.9)	106 (15.8)
1980-1984	1361 (17.3)		83 (12.1)	125 (29.0)	253 (32.0)	61 (9.0)	230 (10.7)	161 (23.9)
1985-1989	982 (21.3)		9 (1.7)	63 (23.6)	125 (30.8)	87 (19.5)	295 (26.3)	84 (19.4)
1990-1994	630 (23.3)		3 (0.9)	26 (14.6)	33 (13.7)	83 (26.2)	226 (34.5)	47 (17.1)
1995-1999	553 (17.9)		1 (0.5)	19 (7.6)	4 (1.2)	131 (44.4)	151 (22.7)	47 (16.4)
Therapy Exposure								
Cranial Radiation (Gy) †								
None	2020 (55.8)		0 (0.0)	0 (0.0)	0 (0.0)	145 (54.5)	1028 (100.0)	92 (23.4)
>0-20	1337 (25.3)		0 (0.0)	255 (74.6)	591 (100.0)	189 (40.4)	0 (0.0)	133 (30.0)
>20	1219 (18.9)		675 (100.0)	87 (25.4)	0 (0.0)	24 (5.1)	0 (0.0)	212 (46.6)
Anthracycline exposure (mg/m^2) †§								
None	2030 (35.2)		520 (77.7)	0 (0.0)	401 (52.6)	0 (0.0)	685 (52.5)	109 (22.4)
>0-120mg/m2	1162 (36.8)		43 (6.4)	0 (0.0)	190 (47.4)	0 (0.0)	343 (47.5)	122 (35.3)

>120-<250mg/m2	838 (18.8)		22 (4.1)	168 (44.4)	0 (0.0)	337 (93.3)	0 (0.0)	89 (24.4)
≥250mg/m2	485 (9.2)		79 (11.8)	174 (55.6)	0 (0.0)	31 (6.7)	0 (0.0)	77 (17.9)
Cyclophosphamide Exposure (mg/m^2) †								
None	2167 (46.9)		548 (84.1)	34 (17.2)	382 (56.5)	0 (0.0)	884 (82.0)	104 (30.3)
>0-1000	240 (7.4)		9 (1.4)	13 (3.0)	8 (1.0)	0 (0.0)	144 (18.0)	17 (5.8)
>1000-<4000	838 (19.3)		26 (4.8)	56 (14.4)	36 (6.3)	278 (78.0)	0 (0.0)	74 (25.3)
≥4000	1176 (26.4)		63 (9.7)	235 (65.4)	160 (36.2)	90 (22.0)	0 (0.0)	140 (38.6)
IV Methotrexate (mg/m^2) †								
None	2506 (49.6)		482 (73.8)	214 (53.5)	420 (56.5)	233 (68.8)	491 (44.3)	183 (41.8)
>0-<4300	1043 (21.2)		164 (24.7)	100 (36.0)	109 (22.0)	109 (26.2)	136 (12.4)	140 (33.7)
≥4300	961 (29.1)		10 (1.5)	24 (10.5)	60 (21.5)	24 (5.0)	384 (43.4)	75 (24.5)
IT Methotrexate (mg/m^2) †								
None	253 (4.1)		100 (16.0)	0 (0.0)	28 (4.0)	2 (0.7)	37 (2.2)	12 (2.8)
>0-<230	2669 (53.9)		493 (79.0)	244 (71.2)	457 (71.6)	229 (47.0)	451 (41.6)	160 (49.9)
≥230	1342 (42.0)		26 (5.0)	88 (24.4)	88 (24.4)	133 (52.3)	502 (56.2)	128 (47.3)
Dexamethasone†								
Yes	946 (28.3)		0 (0.0)	0 (0.0)	0 (0.0)	368 (100.0)	206 (28.3)	68 (24.3)
No	3641 (71.7)		675 (100.0)	591 (100.0)	342 (100.0)	0 (0.0)	812 (71.7)	345 (75.7)
Epipodophyllotoxin†								
Yes	945 (27.3)		1 (0.2)	73 (18.5)	129 (36.8)	13 (3.7)	196 (26.7)	164 (42.4)
No	3715 (72.7)		674 (99.8)	269 (81.5)	460 (63.2)	355 (96.3)	831 (73.3)	291 (56.6)
Cytarabine†*								
Yes	2875 (71.8)		56 (8.2)	342 (100.0)	207 (50.4)	365 (98.8)	575 (70.7)	360 (83.4)
No	1768 (28.2)		619 (91.8)	0 (0.0)	383 (49.6)	3 (1.2)	451 (29.3)	89 (16.6)

Cranial radiation excludes body site scatter.

IV=intravenous; IT=intrathecal

Weighting of ALL survivors due to differences in sampling in the expansion cohort (1987-1999) were accounted for in the percentage calculation with a weight of 1.21 for ALL age 0 or 11–20 at diagnosis, and a weight of 3.63 for those age 1–10.

Included survivors and siblings have an outcome for the OHS analysis at age ≥18 years and excluding proxy reports.

†percentage is based on available information.

†*Any administration includes intravenous or intrathecal.

§ Anthracycline dose reported as doxorubicin equivalent dose where conversions are idarubicin x 3, daunorubicin x 0.5, mitoxantrone x 10 and epirubicin x 0.67

Table 3. Prevalence ratios of adverse health outcomes in ALL survivors, compared to siblings.

	N*	Poor General Health		Poor Mental Health		Functional Impairment		Activity Limitations	
		%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)
Survivor Status									
Sibling	4693	7.4	1.0	4.7	1.0	4.5	1.0	7.9	1.0
Survivors	5119	13.5	**1.97 (1.73-2.24)**	9.3	**1.81 (1.52-2.14)**	12.7	**2.98 (2.55-3.49)**	10.7	**1.63 (1.43-1.85)**
Sex									
Male	4865	10.3	1.0	7.1	1.0	8.4	1.0	7.3	1.0
Female	4947	12.2	**1.19 (1.04-1.36)**	7.9	1.16 (0.96-1.39)	10.9	**1.34 (1.15-1.57)**	12.1	**1.64 (1.41-1.90)**
Age at follow-up									
Every 5 years over 18			**1.09 (1.05-1.12)**		**0.93 (0.89-0.98)**		**1.06 (1.01-1.10)**		**1.13 (1.09-1.17)**
Race/ethnicity									
White, NH	8348	10.3	1.0	7.2	1.0	9.1	1.0	9.6	1.0
Black, NH	363	21.6	**2.07 (1.60-2.68)**	10.1	1.22 (0.79-1.87)	14.3	**1.44 (1.02-2.02)**	19.1	**2.02 (1.53-2.67)**
Hispanic	613	16.3	**1.52 (1.20-1.91)**	10.0	1.19 (0.86-1.66)	13.2	1.29 (0.98-1.70)	8.0	0.85 (0.61-1.18)
Other	488	10.8	1.14 (0.83-1.56)	6.8	0.94 (0.60-1.46)	8.9	1.05 (0.71-1.56)	5.9	0.67 (0.45-1.00)

PR = Prevalence Ratio; CI = Confidence Interval; NH = Non-Hispanic

*Count does not reflect weight and is limited to survivors with at least one outcome response at age 18 years or older and excluding proxy reports. Percentages and PR in table reflect sampling weight

PR adjusted for all covariates in the table with attained age as a continuous variable.

Table 4. Prevalence ratios of adverse health outcomes among ALL survivors, according to treatment groups.

	N*	Poor General Health		Poor Mental Health		Functional Impairment		Activity Limitations	
		%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)
Treatment group									
70s	675	16.5	1.0	7.9	1.0	16.1	1.0	14.1	1.0
80s HR	342	14.5	0.87 (0.61-1.22)	9.9	1.08 (0.65-1.80)	11.2	0.66 (0.43-1.02)	12.2	0.85 (0.57-1.27)
80s SR	591	13.2	0.82 (0.60-1.12)	8.3	0.92 (0.59-1.45)	15.6	0.93 (0.69-1.26)	12.1	0.90 (0.64-1.26)
90s HR	368	10.1	**0.61 (0.40-0.92)**	10.4	1.02 (0.63-1.64)	10.7	**0.61 (0.40-0.91)**	8.8	**0.63 (0.40-0.98)**
90s SR	1028	12.2	0.78 (0.59-1.03)	10.1	1.05 (0.73-1.51)	9.4	**0.55 (0.41-0.75)**	7.9	**0.63 (0.45-0.87)**
R/BMT	495	14.8	0.91 (0.67-1.23)	6.6	0.73 (0.45-1.19)	19.5	1.19 (0.90-1.59)	14.7	1.17 (0.85-1.61)
Sex									
Male	1782	12.2	1.0	7.8	1.0	11.2	1.0	8.2	1.0
Female	1717	14.1	1.16 (0.95-1.42)	10.5	**1.36 (1.03-1.79)**	14.2	**1.34 (1.09-1.66)**	13.1	**1.68 (1.33-2.11)**
Age at diagnosis, yrs									
0-4	1715	11.2	1.0	8.0	1.0	11.8	1.0	8.3	1.0
5-9	968	14.8	**1.32 (1.04-1.68)**	10.6	**1.42 (1.04-1.95)**	12.7	1.10 (0.85-1.42)	11.5	**1.42 (1.07-1.87)**
10-14	562	17.8	**1.52 (1.14-2.02)**	11.7	**1.78 (1.20-2.64)**	15.6	1.29 (0.95-1.74)	14.7	**1.60 (1.16-2.20)**
15-21	254	12.2	1.05 (0.70-1.56)	6.3	1.09 (0.63-1.92)	13.9	1.21 (0.82-1.77)	18.1	**2.11 (1.46-3.05)**
Age at evaluation									
Every 5 years over 18			1.03 (0.97-1.10)		**0.90 (0.83-0.98)**		0.97 (0.91-1.03)		1.01 (0.94-1.08)
Race/ethnicity									
White, NH	2977	12.1	1.0	8.7	1.0	12.4	1.0	10.7	1.0
Black, NH	125	20.9	**1.81 (1.18-2.76)**	14.3	1.58 (0.90-2.80)	16.5	1.35 (0.80-2.25)	22.5	**2.11 (1.39-3.22)**
Hispanic	264	18.0	**1.55 (1.12-2.15)**	11.7	1.29 (0.84-1.99)	14.8	1.21 (0.84-1.74)	7.4	0.70 (0.43-1.12)
Other	133	15.2	1.34 (0.84-2.14)	7.7	0.85 (0.41-1.78)	9.6	0.81 (0.44-1.48)	4.0	**0.40 (0.17-0.97)**

Table 4 continued. Prevalence ratios of adverse health outcomes among ALL survivors, according to treatment groups.

	Cancer-Related Pain		Cancer-Related Anxiety	
	%	**PR (95% CI)**	**%**	**PR (95% CI)**
Treatment group				
70s	10.6	1.0	11.4	1.0
80s HR	10.8	0.91 (0.59-1.40)	14.3	1.15 (0.77-1.74)
80s SR	11.8	1.06 (0.72-1.54)	10.6	0.87 (0.60-1.26)
90s HR	12.4	1.03 (0.70-1.52)	15.4	1.20 (0.81-1.78)
90s SR	6.6	**0.65 (0.45-0.94)**	13.1	1.00 (0.73-1.36)
R/BMT	13.3	1.23 (0.86-1.78)	13.2	1.12 (0.78-1.63)
Sex				
Male	8.7	1.0	9.5	1.0
Female	10.8	**1.34 (1.05-1.72)**	16.4	**1.79 (1.43-2.24)**
Age at diagnosis, yrs				
0-4	7.0	1.0	11.3	1.0
5-9	10.6	**1.50 (1.10-2.05)**	15.6	**1.43 (1.12-1.84)**
10-14	16.4	**2.05 (1.44-2.91)**	14.1	1.32 (0.94-1.84)
15-21	15.5	**2.03 (1.34-3.07)**	10.5	1.12 (0.72-1.74)
Age at evaluation				
Every 5 years over 18		0.99 (0.92-1.06)		0.94 (0.88-1.00)
Race/ethnicity				
White, NH	9.2	1.0	12.4	1.0
Black, NH	20.0	**2.13 (1.34-3.38)**	17.2	1.35 (0.80-2.27)
Hispanic	9.0	0.98 (0.62-1.57)	14.2	1.08 (0.74-1.57)
Other	10.4	1.19 (0.65-2.17)	15.3	1.21 (0.73-1.98)

PR = Prevalence Ratio; CI = Confidence Interval; NH = Non-Hispanic
*Count does not reflect weight. Percentages and PR in table reflect sampling weight.
Analysis was limited to survivors with at least one outcome response at age 18 years or older and excluding proxy reports
PR adjusted for all covariates included in the table with attained age as a continuous variable.

Table 5. Prevalence ratios of adverse health outcomes comparing ALL survivors to siblings, according to treatment groups.

	N*	Poor General Health		Poor Mental Health		Functional Impairment		Activity Limitations	
		%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)
Siblings	4693	7.4	1.0	4.7	1.0	4.5	1.0	7.9	1.0
70s	675	16.5	**2.20 (1.80-2.68)**	7.9	**1.71 (1.28-2.29)**	16.1	**3.49 (2.79-4.35)**	14.1	**1.70 (1.37-2.09)**
80s HR	342	14.5	**1.99 (1.46-2.72)**	9.9	**2.02 (1.30-3.13)**	11.2	**2.52 (1.68-3.80)**	12.2	**1.79 (1.19-2.43)**
80s SR	591	13.2	**1.85 (1.40-2.44)**	8.3	**1.65 (1.14-2.41)**	15.6	**3.53 (2.69-4.63)**	12.1	**1.72 (1.30-2.29)**
90s HR	368	10.1	**1.50 (1.04-2.15)**	10.4	**2.03 (1.37-3.00)**	10.7	**2.56 (1.76-3.74)**	8.8	**1.47 (1.01-2.13)**
90s SR	1028	12.2	**1.76 (1.41-2.20)**	10.1	**1.88 (1.44-2.46)**	9.4	**2.18 (1.67-2.84)**	7.9	1.25 (0.96-1.62)
R/BMT	495	14.8	**2.05 (1.58-2.66)**	6.6	**1.33 (0.87-2.03)**	19.5	**4.64 (3.61-5.95)**	14.7	**2.33 (1.79-3.03)**

PR = Prevalence Ratio; CI = Confidence Interval; NH = Non-Hispanic

*Count does not reflect weight. Percentages and PR in table reflect sampling weight.

Analysis was limited to survivors with at least one outcome response at age 18 years or older and excluding proxy reports

PR adjusted for all covariates included in the table with attained age as a continuous variable.

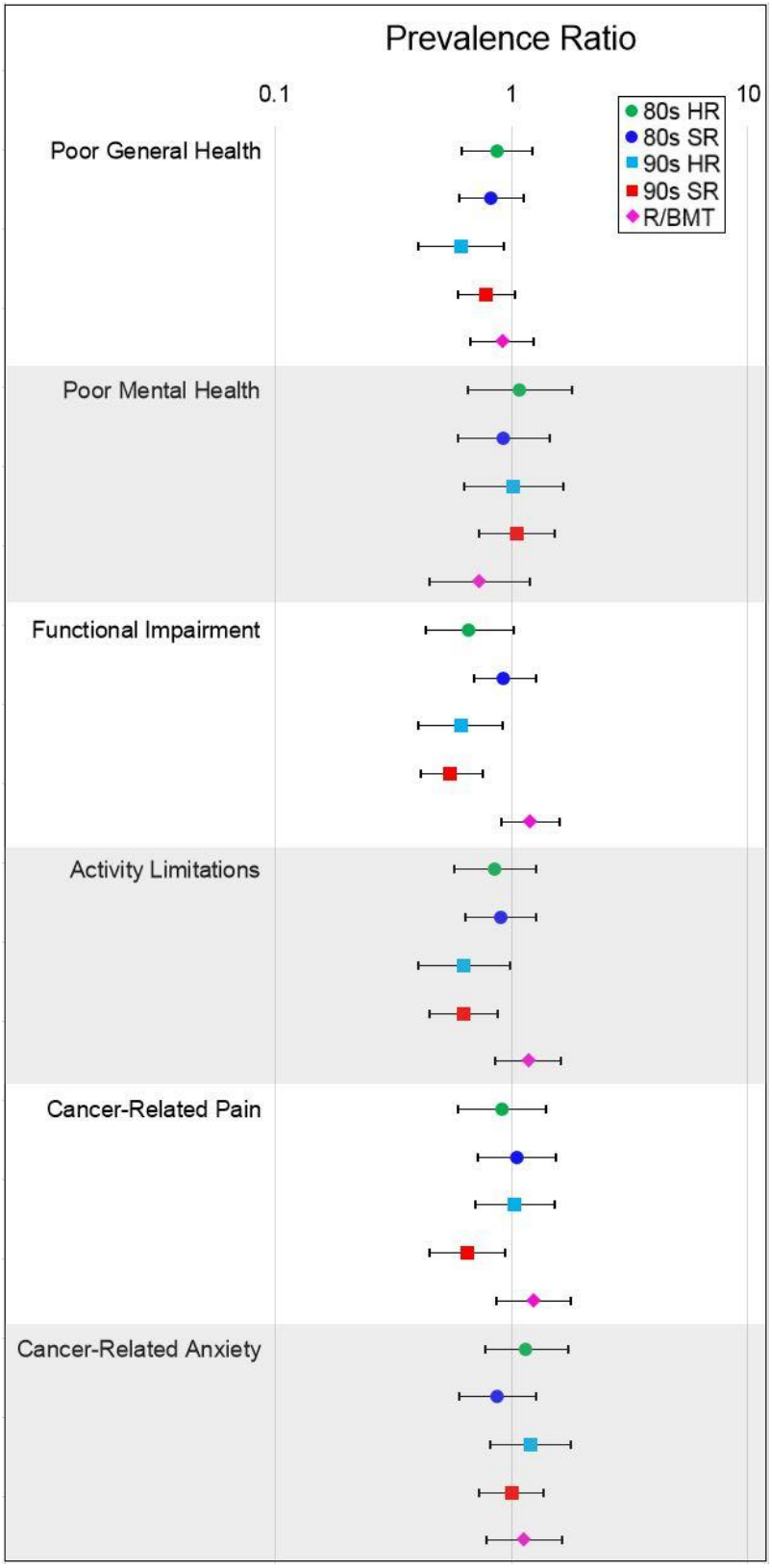
Supplemental Table 1. Prevalence ratios of adverse health outcomes among ALL survivors by treatment group, adjusted for decade of diagnosis.

	N*	Poor General Health		Poor Mental Health		Functional Impairment		Activity Limitations	
		%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)
Treatment group									
70s	675	16.5	1.0	7.9	1.0	16.1	1.0	14.1	1.0
80s HR	342	14.5	0.91 (0.64-1.30)	9.9	1.11 (0.67-1.84)	11.2	0.75 (0.49-1.15)	12.2	0.87 (0.58-1.31)
80s SR	591	13.2	0.87 (0.63-1.19)	8.3	0.97 (0.62-1.53)	15.6	1.09 (0.80-1.48)	12.1	0.94 (0.67-1.32)
90s HR	368	10.1	**0.64 (0.41-0.99)**	10.4	0.97 (0.57-1.66)	10.7	0.69 (0.44-1.08)	8.8	**0.62 (0.38-0.99)**
90s SR	1028	12.2	0.82 (0.61-1.12)	10.1	1.02 (0.67-1.54)	9.4	**0.64 (0.45-0.90)**	7.9	**0.63 (0.43-0.90)**
R/BMT	495	14.8	0.95 (0.69-1.30)	6.6	0.74 (0.45-1.22)	19.5	**1.35 (1.00-1.81)**	14.7	1.20 (0.86-1.67)
Decade of diagnosis									
1970-1979	1152	15.5	1.0	7.6	1.0	16.3	1.0	13.4	1.0
1980-1989	1576	12.5	0.89 (0.70-1.14)	7.7	0.93 (0.65-1.33)	11.4	**0.75 (0.59-0.96)**	10.0	0.94 (0.71-1.23)
1990-1999	771	12.5	0.93 (0.66-1.32)	11.4	1.22 (0.77-1.93)	12.0	0.86 (0.61-1.21)	9.7	1.10 (0.75-1.62)

	Cancer-Related Pain		Cancer-Related Anxiety	
	%	PR (95% CI)	%	PR (95% CI)
Treatment group				
70s	10.6	1.0	11.4	1.0
80s HR	10.8	0.80 (0.51-1.27)	14.3	1.16 (0.76-1.78)
80s SR	11.8	0.95 (0.64-1.42)	10.6	0.89 (0.60-1.32)
90s HR	12.4	0.81 (0.51-1.28)	15.4	1.15 (0.73-1.81)
90s SR	6.6	**0.51 (0.33-0.80)**	13.1	0.96 (0.66-1.40)
R/BMT	13.3	1.08 (0.73-1.59)	13.2	1.12 (0.76-1.66)
Decade of diagnosis				
1970-1979	9.3	1.0	11.4	1.0
1980-1989	9.2	1.21 (0.88-1.66)	11.6	0.97 (0.72-1.31)
1990-1999	10.4	**1.57 (1.10-2.52)**	15.0	1.16 (0.79-1.71)

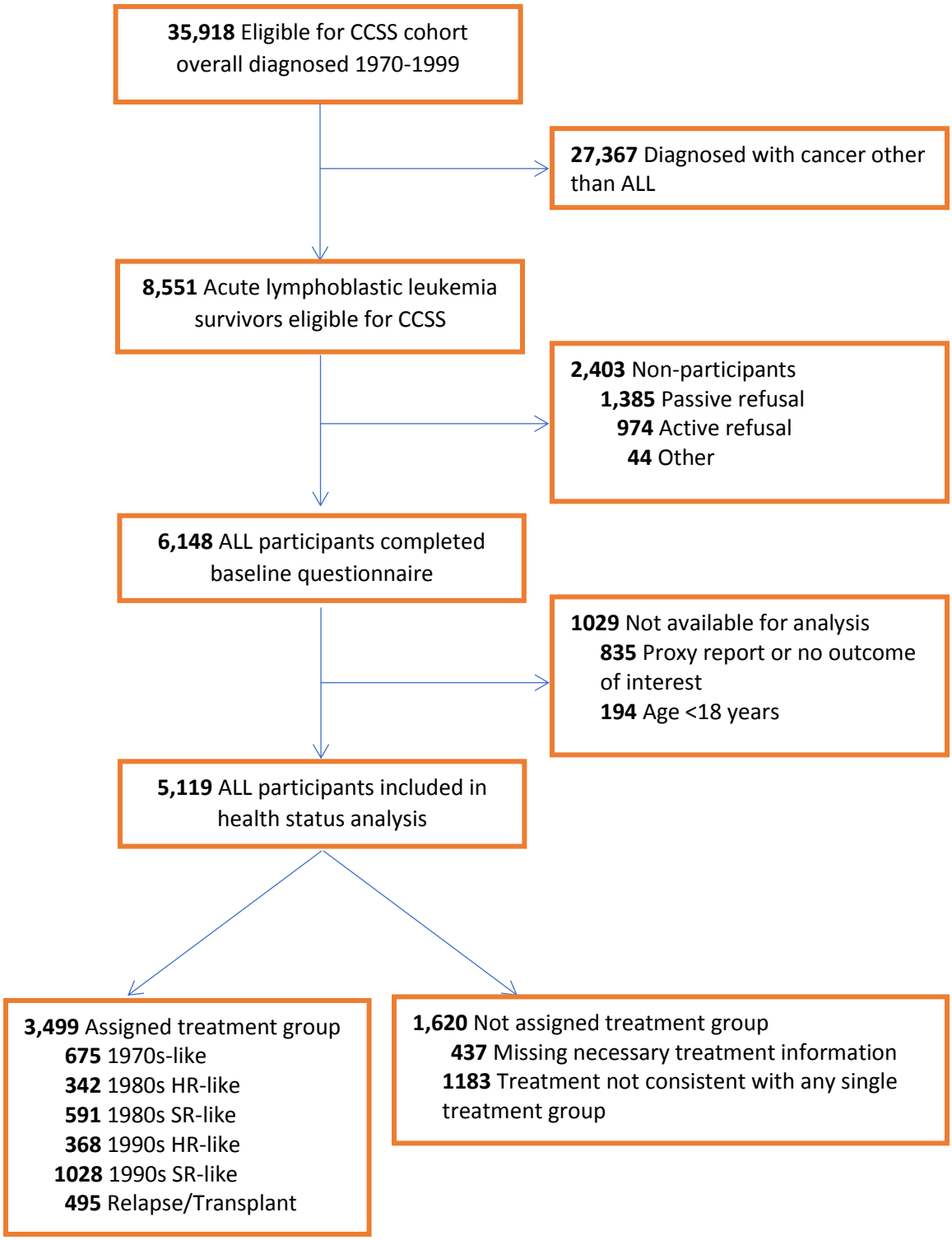
PR = Prevalence Ratio; CI = Confidence Interval; NH = Non-Hispanic
*Count does not reflect weight. Percentages and PR in table reflect sampling weight.
Analysis was limited to survivors with at least one outcome response at age 18 years or older and excluding proxy reports
PR adjusted for age at diagnosis, attained age, sex, race/ethnicity and covariates included in the table.

Figure 1. Patient-reported health status outcomes of survivors by treatment group compared to *70s.*



Data Supplement

CONSORT diagram for study participants. CONSORT = Consolidated Standards of Reporting Trials.



Chapter III: Expanded Discussion and Public Health Implications

Through this analysis, I was able to demonstrate that, while survivors of childhood ALL have a high prevalence of adverse health status outcomes compared to siblings, there is not a trend toward worse outcomes among survivors of more contemporary, standard-risk ALL therapy, which previous publications had suggested. Further, our results suggest that the previously observed associations with worse health status in more recent decades of survivors of childhood ALL,[23] were at least partially explained by worse health status among survivors of higher intensity therapy including high-risk therapy and therapy for relapse or with bone marrow transplant. Additionally, our study builds on health-status outcomes reported by prior CCSS studies. I examined the cohort at a later time-point than the study by Ness et al., the most recent follow-up, and therefore the median age of each treatment group ranges from 29.5 to 40.3 years whereas the median age at assessment for previous work in the expansion cohort was 24.9 to 28.0 years (depending on decade of treatment). This later time-point also allowed us to include a larger number of survivors, specifically, after applying survivor weights, an additional 2000 survivors of ALL were included, the majority of whom were treated in the 1980s or 1990s. Given the assessment at a later timepoint, where survivors are farther from their cancer-treatment, and the increased number of survivors evaluated, I am not surprised that the same trend in results was not observed. However, within the treatment group-decade model, it is notable that decade, even after adjustment for treatment group, had a significant impact on the report of cancer-related pain,

with survivors diagnosed in the 1990s more likely to report this than those in other eras.

It is unclear what is driving this association between cancer-related pain and later decade of treatment. Perhaps it is differential expectations among different generations of survivors. Another change was the introduction of dexamethasone, and although this is partially controlled for by the treatment group analysis where *90sHR*, some survivors of *90sSR* and *R/BMT* also received dexamethasone. Dexamethasone is known to be associated with osteonecrosis, particularly when administered in continuous doses, a complication that is potentiated by asparaginase.[57,58] Osteonecrosis is a debilitating complication that can often involves multiple joints and may necessitate surgical intervention including decompression or joint replacement. Some of the increase in cancer-related pain experienced by the 1990s group may be attributable to the increased use of dexamethasone in this era. Further, although no other significant associations between decade and health status outcomes were seen for the 1990s when adjusted for treatment group, there was a trend toward worse mental health and cancer-related anxiety, though a relatively small effect size.

I expect that high-risk therapy, with its more intensive chemotherapy regimens, and therapy for relapse or transplant has increased the burden of comorbidities experienced by survivors of these groups over time. This is suggested by results of a recent analysis identifying that the cumulative incidence of severe, life-

threatening or fatal chronic health conditions experienced by survivors of ALL has not changed between survivors treated in the 1970s and 1990s.[34] This would imply that if survivors of 1990s standard-risk therapy experience fewer chronic conditions, survivors of high-risk and relapse/transplant therapy treated in the 1990s must experience more. This is currently being assessed in the CCSS cohort using methods similar to those utilized in the analysis of overall health status. And, if in fact, survivors of *90sHR* and *R/BMT* experience a higher incidence of chronic conditions than *70s,* while *90sSR* have a lower incidence, it may provide further insight into the differential health status reported between these groups. As, survivors with a higher prevalence of severe health conditions may be more likely to report adverse health status, as is seen in the general population with cardiovascular disease, diabetes or both.[47-49]

A comparison not addressed directly in the manuscript was the difference in prevalence of poor mental health compared to prior CCSS studies. Previous studies by Hudson et al. and Ness et al. reported much higher prevalence of poor mental health among ALL survivors of 15-20% compared to our study reporting a prevalence of 7-10%. This is because previous studies utilized a different definition to categorize poor mental health as participants whose responses on the Brief Symptom Inventory 18 (BSI-18) resulted in a sex-specific T-score of 63 or higher on the Global Severity Index or any ***one*** of the depression, anxiety or somatization subscales. However, during the development of this study concept in consultation with the chair of the Psychology working group of the CCSS, it

was recommended to use the definition described with poor mental health defined by any ***two*** subscales or the Global Severity Index. This is felt to be more consistent with the current literature on perceived mental health and will be used in CCSS studies moving forward. Because of this, the prevalence values reported in our study are lower than prior studies for poor mental health, however, we would not expect this change to significantly impact the findings from comparisons between groups.

When discussing limitations above, I stated that due to exclusion of proxy reports, these results may represent an under-estimation of poor health status among ALL survivors. To expand on this when considering treatment group associations, because survivors in the *90sSR* treatment group could not have received CRT, the expectation from prior studies of ALL survivors treated with chemotherapy alone is that they would have less neurocognitive impairment (and therefore little need for proxy reports).[59] The group most likely to be biased due to exclusion of proxy reports would be *R/BMT*. Finally, although all analyses adjusted for attained age, survivors of the *70s* group were older, and as physical measures of health status (general health, functional impairment, activity limitations, and cancer-related pain) are known to be associated with aging, it is possible that the model was unable to completely adjust for the full impact of this across treatment groups.

Public Health Implications

ALL is the most common cancer of childhood and approximately 3000 new cases are diagnosed in the United States annually,[60] of these, approximately 90% will be cured and require survivor related care into adulthood.[61] Survivors of childhood ALL are known to experience an increased risk for late-morbidity and mortality as a result of their cancer treatment. [23,27-29,34-36] As such, they constitute a growing population of adult patients with likely multi-morbidity care needs. It is important to continue to better understand the impact of our therapy changes not only on 5-year survival, but also on late health outcomes in this large population of childhood cancer survivors. This can help both to inform future up-front therapy decisions during protocol development and to guide survivorship care and counseling on the individual patient level based on the risk-stratified therapy received.

Future Directions

Additional information is needed regarding the impact of perceived health status on future outcomes of childhood cancer survivors. Because of the well described association of self-reported health status on mortality across many diverse populations of adults with and without known comorbidities, I believe it would be informative to study whether poor health status, independent of treatment exposures or risk-stratified therapy received, was predictive of future mortality among adult survivors of childhood cancer.

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