Cumulative Burden of Cardiovascular Morbidity among Pediatric, Adolescent and Young Adult Hodgkin Lymphoma Survivors: An Analysis from the St. Jude Lifetime Cohort Study

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Abstract

Background—The magnitude of cardiovascular morbidity among survivors of pediatric, adolescent, and young adult Hodgkin lymphoma is not known. Using medically ascertained data, we applied the cumulative burden metric to compare chronic cardiovascular health conditions among Hodgkin survivors and general population controls.

Methods—Among 670 survivors treated at St. Jude Children’s Research Hospital, who survived ≥10 years and became 18 years old, 348 were clinically assessed in the St. Jude Lifetime Cohort Study (SJLIFE). Age-sex-frequency-matched SJLIFE community-controls (n=272) were used for comparison. All SJLIFE participants underwent evaluation for 22 chronic cardiovascular health conditions. Direct assessments, combined with retrospective clinical reviews, were used to assign severity to conditions using a modified Common Terminology Criteria of Adverse Events (CTCAE) grading schema. Occurrences and CTCAE-grades of the conditions for 322 eligible
non-SJLIFE participants were accounted for by multiple imputation. The mean cumulative count (treating death as a competing risk) was used to estimate cumulative burden.

Findings—At 50 years of age, the cumulative incidence of survivors experiencing at least one grade 3-5 cardiovascular condition was 45.5%. The survivor cohort experienced, on average, 430·6 (95% confidence interval, 380·7-480·6) grade 1-5 and 100·8 (77·3-124·3) grade 3-5 cardiovascular conditions per 100 survivors. At age 50, the grade 1-5 and 3-5 cumulative burdens of community-controls were appreciably lower at 227·4/100 (192·7-267·5) and 17·0/100 (8·4-27·5), respectively. Myocardial infarction and structural heart defects were the major contributors to the excess grade 3-5 cumulative burden among survivors. Higher cardiac radiation dose (≥35 Gy) was associated with an increased grade 3-5 cardiovascular burden.

Interpretation—The true impact of cardiovascular morbidity among pediatric Hodgkin lymphoma survivors is reflected in the cumulative burden. 50-year-old Hodgkin survivors will experience over two times the number of chronic cardiovascular health conditions compared community-controls and, on average, have one severe/life-threatening/fatal cardiovascular condition. The cumulative burden metric provides a more comprehensive approach to evaluating overall morbidity and will assist clinical researchers when designing future trials and refining general practice screening guidelines.

Introduction

Over the past 40 years, children and adolescents diagnosed with Hodgkin lymphoma (HL) have experienced a 5-year relative survival above 80%. Today, extended survival into adulthood exceeds 90%1 with an estimated 36,000 survivors of pediatric/adolescent HL in the U.S.2 Due to treatments such as chest radiation and anthracyclines, however, these survivors may develop multiple life-long cardiovascular health conditions and have a higher likelihood of premature mortality.3-7

The established associations between therapy-related exposures and risk for individual cardiovascular chronic health conditions among childhood cancer survivors have been well characterized.8-15 Investigators have developed risk prediction models for congestive heart failure and optimized screening guidelines for survivors based on single-disease-specific toxicity-related trade-offs and exposure-based risk profiles.16-18 However, much of what is known is based on the cumulative incidence or, in some instances, the absolute number, of individual chronic cardiovascular health conditions in a given cohort.19,20 The total magnitude of cardiovascular morbidity among survivors, accounting for the severity of multiple types of conditions and recurrent events, has not been precisely described. Incorporating these event data may change established associations between therapy-related exposures and chronic illness, thereby improving pre-clinical decision-making for late-effects research. The objective of this investigation was to determine and characterize the cumulative burden of cardiovascular disease among a clinically assessed population of long-term survivors of pediatric/adolescent HL and compare their outcomes to a group of age-sex-frequency-matched general population controls.
Methods

Study design and participants

Data were obtained through two ongoing cohort studies at St. Jude Children’s Research Hospital (SJCRH) approved by the SJCRH institutional review board (IRB): the St. Jude Lifetime Cohort Study (SJLIFE) and the St. Jude Long-term Follow-up Study (SJLTFU). SJLIFE is a cohort study initiated in 2007 to facilitate longitudinal clinical evaluation of health outcomes of childhood cancer survivors treated or followed at SJCRH. Recruitment strategy, study design, data abstraction methods, screening for organ dysfunction and validation of medical events for SJLIFE have been previously reported. Written consent was obtained from all SJLIFE participants. Demographic, mortality and therapy-related exposure data for survivors who died prior to recruitment into SJLIFE or had not completed a clinical assessment visit were retrospectively obtained using an IRB approved waiver of consent obtained through SJLTFU, an administrative-system-based study initiated in 2000 to collect outcome and late toxicity data on all SJCRH patients treated for childhood cancer. Methods of treatment-exposure data abstraction in SJLTFU are the same as those in SJLIFE.

The patient cohort for our analysis was defined as those treated at SJCRH who reached 18 years of age and at least 10 years post-diagnosis of pathologically confirmed primary HL, representing a fix sample number. All survivors who met these criteria were included in this study, regardless of presenting comorbidities. Patients who presented to SJCRH for consultative evaluation but received no therapy (i.e., no radiation, chemotherapy or surgical intervention beyond biopsy) and were not followed at SJCRH were excluded (Figure 1). Outcomes among the HL survivors were compared to a sample of 272 SJLIFE community-control participants, consisting of individuals 18 years of age or older at the time of assessment, frequency-matched based on strata defined by 5-year age blocks within each sex, who were selected regardless of past medical history. Exclusion criteria included first-degree relatives of SJCRH patients, individuals with a history of childhood cancer, and pregnant females. The community-controls were assessed for the potential of a healthy participant bias by utilizing the National Health and Nutrition Examination Survey data on the general U.S. population. The age-sex-race standardized prevalence rates of cardiovascular conditions that were defined comparably by the two data sources agreed overall (Supplement, Page 19).

Procedures

Using a structured protocol, cumulative doses of chemotherapeutic agents were abstracted from medical records by trained research staff. Radiation dosimetry calculations of maximum heart field dose estimations were performed by the Radiation Physics Center at the University of Texas MD Anderson Cancer Center (n=484 survivors) or estimated using the maximum cumulative mantle or mediastinal dose from the abstracted radiation therapy record (n=186). The radiation exposure to the heart and anthracycline dose categories used in the analysis were based on risk groups defined by the International Late Effects of Childhood Cancer Guideline Harmonization Group.
All SJLIFE survivors and community-control participants completed at least one comprehensive clinical assessment at SJCRH that included surveys of medical and psychosocial outcomes, a history and physical exam by a health practitioner, a battery of laboratory tests including lipids, a formal evaluation of neuromuscular function, and an electrocardiogram. In addition to the initial SJLIFE clinical evaluation, 64% of survivors completed more than one prospective evaluation (164 [47·1%] two assessments, 55 [15·8%] three assessments, 2 [0·6%] four assessments). Community-control participants completed a one-time SJLIFE clinical evaluation. Echocardiograms were obtained on every community-control participant and on HL survivor participants exposed to anthracyclines or chest radiation. Medical records were obtained from SJLIFE survivors and community-control participants and reviewed to validate diagnoses and age at onset of self-reported health conditions.

Outcomes

Twenty-two chronic cardiovascular health conditions for SJLIFE survivors and community-controls were classified using a SJCRH-modification of the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) [mild (grade 1), moderate (grade 2), severe/disabling (grade 3), life-threatening (grade 4) or death (grade 5)].25 Definitions and CTCAE modifications for each of the cardiovascular conditions included in our analysis are detailed in Supplement, Pages 4-11. Modifications to the CTCAE were made to: (1) define how clinical data (e.g., medical or surgical interventions) were used in severity grading; (2) define more conservative diagnostic ranges with the objective of avoiding over-diagnosis of specific conditions; and (3) conform to diagnostic practice at SJCRH. The 22 conditions were further summarized into six disease groups for presentation (Table 1).

To define recurrent events without overestimating multiply assessed chronic illness, each of the 22 cardiovascular conditions was further categorized into three clinically defined sub-types (Supplement, Pages 4-11). “Chronic, non-recurrent” conditions were defined as ongoing events that could not happen recurrently (e.g., hypercholesterolemia). When estimating cumulative burden, chronic, non-recurrent events were counted only once and at the earliest time of onset for each subject. For “single, recurrent” conditions (e.g., thrombus), all events were independently counted using corresponding grades and dates of onset. Finally, “chronic, recurrent” conditions (e.g., cardiomyopathy) included elements of both prior categories: based on the clinical characteristics of the condition, lower grades were counted only once and at the time of onset per subject, similar to “non-recurrent” conditions; however, higher-grade events (such as surgical interventions that could occur more than once) were assigned “recurrent” and individually counted. As part of our counting algorithm for these types of conditions, “non-recurrent” lower grades that occurred after a “recurrent” higher grade were not counted. All data were formatted in compliance with the above definitions prior to statistical analysis.

A search of the National Death Index (NDI) was conducted (June 2013) of all SJLTFU patients. Cause of death was recorded using ICD 9 and 10 codes obtained from the NDI. Deaths occurring after the NDI search cut-off date (December 31, 2011) were ascertained by
the SJCRH Cancer Registry. Cause of death was assigned as cardiac versus non-cardiac, based upon information obtained from the NDI cause of death/death certificates, medical records, and next-of-kin. Cardiac grade 5 events were further sub-categorized into one of the 22 chronic cardiovascular health conditions where appropriate.

Statistical analysis

Survivors entered the analysis cohort when they became 18 years old or 10 years from HL diagnosis, whichever occurred later. Since survivors entered the cohort at different ages, cumulative incidence estimation by age accounted for left truncation. At-risk status for developing cardiovascular conditions ended on June 30, 2014 (censoring), or on the date of death for patients who died. Community-control participants entered the analysis cohort at age 18 and censored one day after the completion of their clinical assessment. All ascertained cardiovascular conditions according to the unified ascertainment/grading scheme above were included in this analysis.

There were 322 survivors who were eligible but did not participate in SJLIFE by the time of the current analysis (Figure 1), including 102 who died after having met the SJLIFE eligibility criteria. Chi-square and t-tests were used to describe the differences between SJLIFE and non-SJILFE survivors.

Multiple imputation was used to minimize potential bias related to missing chronic cardiovascular health condition data among the 322 non-SJLIFE survivors; a complete description of the imputation method is provided in Supplement, Page 1. To determine the impact of imputation on final outcomes, a post-hoc sensitivity analysis comparing the HL SJLIFE participants and all HL SJLIFE eligible survivors (participants and non-participants) was conducted (Supplement, Page 2). Grade 1-4 events were imputed independent of the knowledge of survivors' vital status, recognizing the independence assumption between death and cardiovascular conditions would yield a conservative estimate of cumulative burden. This approach is based on a weaker, more tenable assumption than the complete-data-only analysis that requires the assumption of "missing completely at random."

The cumulative burden was estimated using the method of mean cumulative count (MCC) which estimates the mean number of recurrent/multiple health events a cohort experiences over time in the presence of competing risk events. Estimates are presented as the average number of events occurring per 100 individuals. Cumulative burden of each of the 22 chronic health conditions was estimated and then summed to reflect both the total cumulative burden and those of the six grouped condition categories. The bootstrap percentile method was used to calculate 95% confidence intervals. Cumulative burden was compared to cumulative incidence graphically. A sensitivity analyses excluding conditions with no difference between the HL survivors and community-controls was also completed (Supplement, Page 3).

Marked-point-process regression was performed to estimate the association of cumulative anthracycline dose and radiation dose to the heart with the cumulative burden of chronic cardiovascular health conditions, adjusting for gender, treatment era, race, and attained age using cubic splines. This method separates the associations into one with the overall rate of
developing a condition and the other with the propensity for a condition to be of a higher grade (given the condition has developed). We used SAS (version 9·4) and R (version 3·2·3) for all statistical analyses.

Role of Funding Source

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Results

Of the 6,038 survivors who survived 10 years and became 18 years of age, 694 were HL survivors and 670 were included in the analysis (Figure 1). The 24 (3·5% of 694) were excluded as they were consult-only patients who were never treated or followed at SJCRH. The first survivor met eligibility for cohort entry on October 15, 1971. Demographic and relevant therapy-related exposures of SJLIFE participants, SJLIFE non-participants, all eligible survivors and SJLIFE community-control participants up through June 30, 2014 are presented in Table 2. Of the 568 living SJLIFE-eligible survivors (excluding the 102 deceased survivors from the 670 SJLIFE-eligible survivors), 381/568 (67·1%) enrolled and 348/568 (61·3%) had completed an on-campus clinical assessment. The mean, median (IQR) and range of time from Hodgkin lymphoma diagnosis to first on-campus SJLIFE clinical assessment was 23·1, 22·2 (16·1 – 28·5) and 10·9 – 45·4 years, respectively. The prevalence of the maximum grade for each of the 22 graded chronic cardiovascular health conditions is presented in Supplement, Page 12. An additional post-hoc analysis comparing the prevalence of multiple cardiovascular conditions in our community-control population to that of the National Health and Nutrition Examination Survey (NHANES) was conducted. Overall our community-control population in SJLIFE has similar prevalence rates of cardiovascular conditions compared to those of the general U.S. population (Supplement, Page 19).

The grade 1-5 and grade 3-5 cumulative incidence and cumulative burden estimates are presented in Figure 2 for the cohorts of all SJLIFE-eligible survivors and community-controls. The difference in Grade 3-5 SJLIFE eligible participants and the entire HL survivor cohort is presented in the Supplement, Page 2. By age 50, the cumulative incidence of grade 1-5 and grade 3-5 chronic cardiovascular health conditions among 10-year adult survivors of HL was estimated to be 89·2% (95% confidence interval, 85·3-93·2%) and 45·5% (36·6-54·3%), respectively. In the community-control group, the grade 1-5 cumulative incidence was no different at 85·8% (80·1-91·6%), while the grade 3-5 cumulative incidence was substantially lower at 15·7% (7·0-24·4%). In contrast to the cumulative incidence, the grade 1-5 cumulative burden among 50-year-old survivors was nearly twice that of the control cohort (430·6, 380·7-480·6 vs 227·4, 192·7-267·5), and the grade 3-5 cumulative burden at the same time point was over five times greater (100·8, 77·3-124·3 vs 17·0,
8-4-27.5). Cumulative incidence and cumulative burden grades 1-5 and 3-5 results by demographics and exposures are presented in 5-year increments in Supplement, Pages 13-16.

The estimates of average annual increase of the cumulative burden are presented in Figure 3. While the average annual increase of grade 1-5 conditions is higher among all SJLIFE-eligible survivors between the ages of 30-55, by age 45, the average annual increase of grade 1-2 conditions among community-controls equals and surpasses that of the survivors. For grade 3-5 conditions, the rate of increase in cumulative burden among survivors remains greater than that of community-controls over the entire range of attained age of the cohort. The cumulative burden of the six grouped categories and their contribution to the total grade 1-5 and grade 3-5 cumulative burden at 30 and 50 years of age are presented in Figure 4 (and Supplement, Pages 17-18) for all SJLIFE-eligible survivors and community-controls. Survivors have a higher total grade 1-5 and grade 3-5 cumulative burden compared to community-controls at 30 and 50 years of age. The total grade 3-5 cumulative burden of survivors at 30 years of age is similar to that of community-controls at 50 years of age. There is no difference between 50-year-old survivors and community-controls for grade 1-5 or 3-5 cumulative burden of dyslipidemia and essential hypertension. The contributions to cumulative burden from each of the five other categories were, however, greater among survivors with myocardial infarctions and structural defects contributing the most to the difference. A post-hoc sensitivity analysis was conducted to verify whether the difference in cumulative burden between HL survivors and community-controls persisted after the exclusion of chronic health conditions that did not differ between the two groups. We found that excluding the dyslipidemias and essential hypertension events did not alter the difference in cumulative burden between the two groups. The cumulative incidence of the community-controls, however, did require a longer time (older age) to equal that of the HL survivors when these conditions were excluded (Supplement, Page 3).

Figure 5 shows the multivariable regression results for anthracycline dose and heart radiation exposure after adjusting for each other and gender, treatment era, race, time-dependent attained age and age at diagnosis. Results are presented as the adjusted rates (counts per 10,000 person years) by cumulative dose of anthracycline and radiation dose to the heart. There was a dose-response relationship of developing a cardiac condition (i.e., grades 1-5) with increasing exposure to anthracyclines, but exposure was not significantly associated with the grade distribution: i.e., each grade is similarly increased. The overall rate of developing any cardiovascular condition did not increase significantly with dose of radiation to the heart. However, in contrast to anthracyclines, radiation dose to the heart of ≥35 Gy was significantly associated with higher grade of cardiovascular conditions.

Discussion

Our analysis highlights that, while there are no significant differences in cumulative incidence beyond age 50, significant differences in cumulative burden between HL survivors and community-controls persist beyond age 60 and are comprised of a heterogeneous combination of morbidities. Using a clinically well-characterized cohort of childhood HL survivors and community-controls, we demonstrate a novel and more clinically meaningful
method of estimating the magnitude and trajectory of treatment-related morbidity. It is well accepted that long-term survivors of pediatric HL are at a marked excess risk of cardiovascular morbidity and mortality related to specific therapeutic exposures.\textsuperscript{3-6,10-12,14,15} To estimate the severity of these outcomes, prior analyses have generally used the cumulative incidence of individual or grouped conditions. Although this approach is routinely applied, relying on cumulative incidence alone underestimates the total disease morbidity by counting only the time to first event. The cumulative burden metric overcomes this limitation by considering recurrences or, when grouped, multiple health conditions, in relation to age or time from diagnosis and the severity of chronic and late health events. These outcomes data more accurately characterize the spectrum of cardiovascular disease and periods of increased cardiovascular health vulnerability among at risk survivors.

From a clinical research perspective, the cumulative burden provides clinical investigators additional data when prioritizing study aims. For example, our results show that reducing anthracycline dose in frontline clinical trials of pediatric/adolescent/young adult HL survivors will result in a lower rate of Grade 1-5 chronic cardiovascular health conditions, while not appreciably affecting the distribution of grade severity among patients who develop a condition. In contrast, reductions in heart radiation dose will not significantly lower the rate of Grade 1-5 chronic cardiovascular health conditions but will result in fewer higher grade events at the lower dose. By measuring all cardiovascular outcomes simultaneously, which may be affected to different degrees by various treatment exposures, our multivariable analysis highlights the types of trade-offs between late-effects that must be weighed when designing new interventions.

In the general practice setting, our results support prior findings from other childhood cancer studies suggesting survivors of childhood HL experience an accelerated onset of chronic cardiovascular health conditions compared to that of the general population.\textsuperscript{20,30} In contrast to cumulative incidence-based analyses, however, the cumulative burden of community-controls neither “catches up” nor approaches that of the survivor population. These results were verified after conducting a sensitivity analysis where chronic cardiovascular health conditions with no differences in cumulative burden between the HL survivor cohort and community-controls were excluded (Supplement, Page 3). Additionally, while the rate of increase for grade 1-2 conditions among our controls appears to attain and surpass that of survivors by 45 years of age, and thus closing the burden gap for lower-grade conditions, the average annual increase in grade 3-5 chronic cardiovascular health conditions always remains greater among survivors. These data, combined with the different distribution of disease for both survivors and controls at 30 and 50 years of age, indicate that community physicians should develop unique care-plans for younger survivors and maintain an increased index of suspicion for complex illness compared to even older adult populations. Moreover, it is important for clinicians to recognize these risks when screening survivors treated with historic protocols when higher radiation doses of \( \geq 35 \) Gy were routinely used.

There are a number of methodological limitations that need to be considered in the interpretation of our findings. The aim of SJLIFE is to make in-person clinical and diagnostic assessments of all chronic health conditions, regardless of known treatment
related associations, in a long-term survivor cohort with sufficient granularity in order to identify new associations and quantify excess (or similar) morbidity associated with childhood cancer therapy relative to a community-control cohort. In order to provide generalizable cohort data with the most clinical relevance, our presented analysis includes all long-term survivors ever treated at SJCRH and not just the survivors who were able to return to SJCRH for an on-campus clinic visit. By not including the SJLIFE eligible non-participants, we would have reported outcomes for only a subset of the SJLIFE eligible population that both survived until 2007 and were able to return to campus for clinical assessment. This subset’s data are, however, difficult to generalize and interpret because of the additional criteria of survival to 2007 and return to campus. In Supplement, Page 2, we provide the plot of Grade 3-5 cumulative burden curves with and without the SJLIFE eligible non-participants. With the inclusion of non-participants, the cumulative burden was appreciably lower in older ages, but slightly higher before age 40. Without knowing the true cardiovascular health conditions of the non-participants, it is impossible to know whether the combined estimate or the participant-only estimate is closer to the truth. Given our concerns with generalizability, we report the complete eligible cohort data but acknowledge our results are likely to represent a conservative lower bound of disease burden in the HL survivor population.

Additionally, the current analysis utilized data collected from prospective as well as retrospective clinical assessments. Use of retrospectively ascertained data (i.e., that prior to SJLIFE study activation) to calculate cumulative burden likely results in a conservative lower bound of the actual cumulative burden for several reasons. Due to the low incidence of mortality in the SJLIFE cohort, grade 1-4 chronic conditions were imputed independent of grade 5 conditions. As a result, we expect our analysis also underestimates the true cumulative burden in this subset of survivors. Furthermore, prior to activation of the SJLIFE protocol, the majority of survivors were followed for several decades in the SJCRH late-effects clinic when knowledge of and surveillance practices for late-effects were evolving. We anticipate that inconsistent screening practices likely resulted in systematic underestimation of grade 1-2 chronic health conditions in particular as it is often difficult to diagnose asymptomatic or mild disease without routine diagnostic screening. As technology and screening guidelines continue to evolve, we also expect newer, more sensitive screening modalities such as computerized tomography angiography, which can detect both changes, thickening, and irregularities of vascular wall and thickening in the vascular lumen, will identify cardiovascular disease at earlier time points. This may further highlight the potential advantage of using the cumulative burden as a metric when reporting disease burden. At the same time, the degree of diagnostic underestimation between survivors and community-controls is also likely different. While both groups provided a retrospective medical history and underwent at least one SJLIFE clinical evaluation, there is more clinical surveillance data available for the survivor population because of their longer period of follow-up and greater attention to documentation of cardiovascular events due to known exposures to cardiotoxic therapies. This enhanced level of surveillance would be expected to result in an earlier ascertainment of cardiovascular events among survivors compared to controls. Beyond ascertainment concerns, data regarding social and behavioral factors such as smoking status or nutrition that may modify cardiovascular disease risk were also not
available for eligible patients who had died prior to the initiation of the SJLIFE study. Prospective evaluation of these data among SJLIFE participants may inform future intervention research targets aiming to preserve cardiovascular health.

Finally, although the cumulative burden is a powerful analytic tool, it is a count statistic that must be clinically contextualized based on the types and distribution of chronic conditions contributing to its total sum. This is particularly important as the metric is agnostic to patient perceptions and treats conditions of the same grade exchangeably as if they contribute equally to patient health. Although the general grading schema of the CTCAE is based on an ordinal grading schema ranging from asymptomatic to life-threatening, it may not accurately reflect survivors' perception. For example, a survivor with grade 3 hypercholesterolemia presumably will not rate his or her disease-related decrement in health the same as another survivor with grade 3 cardiomyopathy. Thus, although we have shown the cumulative burden of cardiovascular conditions among 30-year-old survivors and 50-year-old control participants was no different, the composition of the total cumulative burden was different and suggests, from a clinical perspective, that there may be differences in health-related quality of life between the two groups. Furthermore, in our multivariable analysis, we report the combined outcome of multiple chronic cardiovascular health conditions without accounting for potential variations in the dose-risk relationship. Given the heterogeneity of the pathophysiologic factors driving disease, further methodologic research will be required to take this variation of dose-risk relationship into account when quantifying dose-specific burden.

In summary, we applied the cumulative burden metric to quantify the added magnitude and trajectory of total cardiovascular morbidity among HL survivors compared to a control population. To our knowledge, our approach represents the first application of this metric to study both recurrent and multiple events in a setting where death represents a significant competing risk and different pathophysiologic processes occur. As frontline pediatric clinical cancer trials continue to include late-effect objectives and survivor screening guidelines continue to evolve, we propose that incorporation of the cumulative burden metric into future survivorship analyses will provide a more clinically relevant assessment of treatment-related morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

Due to curative therapy-related exposures, long-term survivors of childhood Hodgkin lymphoma have a substantially increased risk of cardiovascular disease. We searched the terms “Hodgkin lymphoma” and “childhood or adolescent” and “long-term or survivors” and “cardiovascular or cardiac or vascular or valvular or blood pressure” for publications describing cardiovascular morbidity in this population. Multiple studies have described subsets of cardiac outcomes among childhood Hodgkin lymphoma survivors with most focusing predominantly on the cumulative incidence of individual chronic cardiovascular health conditions.

Added value of the study

To our knowledge, this study is the first to describe and apply the cumulative burden metric to characterize total morbidity from multiple and recurrent therapy-associated late-effects. This contrasts with the popular “cumulative incidence” measure which only accounts for the first occurrence of late-effect conditions.

Implications of all the available evidence

Using cardiovascular disease among childhood Hodgkin lymphoma survivors, a known high-morbidity, high-survival group, as a model population, we have applied a new metric that can provide both descriptive and inferential insights into pediatric cancer survivorship. In cohorts such as ours where detailed clinical information results in a near 100% cumulative incidence for many chronic health conditions, the cumulative burden metric provides a more comprehensive approach for evaluating both the magnitude and trajectory of disease morbidity. Applying this approach, we provide a comprehensive quantitative measure of the exceptionally high rate and pattern of morbidity experienced by survivors of pediatric Hodgkin lymphoma. Incorporation of the cumulative burden metric into routine analyses of populations at risk for recurrent/multiple morbidities will provide a more complete characterization of health-related outcomes. Moreover, knowledge of the cumulative burden, particularly among cancer survivors, will better inform the development of future clinical trials aimed at limiting potential late-effects or evaluating the benefit of general practice screening guidelines by providing a broader perspective of the potential trade-offs among chronic health conditions resulting from therapeutic decision-making.
Figure 1.
Hodgkin Lymphoma Survivors Treated or Followed at St. Jude Children’s Research Hospital
Figure 2. Cumulative Incidence and Cumulative Burden of Chronic Cardiovascular Health Conditions among Hodgkin Lymphoma Survivors and Community-Controls

Technical note: The atypical pattern of the 95% confidence limits of survivors’ curves is due to application of left-truncation and multiple imputation in the estimation of cumulative incidence and cumulative burden. Furthermore, the atypical pattern of the numbers at risk for cumulative incidence and cumulative burden is due to the following reasons:

**Cumulative incidence:** For controls, everyone started the at-risk period at birth (age 0). At this beginning of the start of the at-risk period, the number of our community controls at risk is 272 (the total number of our community controls). Until the first censoring, death, or the first occurrence of cardiovascular conditions of interest, the number at risk remains at 272. For survivors, the start of the at-risk period is 10 years post Hodgkin lymphoma diagnosis or age of 18 years whichever comes later, i.e., the SJLIFE cohort entry. Thus, age at the start of the at-risk period differs across survivors, which led to the number of survivors at risk increasing over age up to about 30 years old and then decreasing. There are a total of 670 survivors and the latest age at the cohort entry was 35 years old. Because some people were censored before age 35, there is no time point at which the number at risk was 670.

**Cumulative burden:** For cumulative burden, people stay at risk during their length of follow-up. Unlike cumulative incidence which stops the at-risk period at the occurrence of the event of interest, cumulative burden keeps subjects who have events of interest at risk: the two methods are equal in their handling of censoring at the end of follow-up and deaths.
Figure 3.
Average Annual Increase in Cardiovascular Cumulative Burden
Figure 4.
Contributions to Cumulative Burden by Cardiovascular Disease Group
Figure 5.
Multivariable Analysis of Cardiovascular Burden by Grade for Anthracycline and Heart Radiation Exposure. Multivariable models included adjustment for gender, race, treatment era, time-dependent attained age and age at diagnosis.
| Grouped Categories | CTCAE Graded Chronic Cardiovascular Health Conditions |
|-------------------|------------------------------------------------------|
| Myocardial infarction | Myocardial infarction |
|                   | Atrioventricular heart block |
|                   | Conduction abnormalities |
|                   | Prolonged QT interval |
| Arrhythmias       | Cardiac dysrhythmia |
|                   | Sinus bradycardia |
|                   | Sinus tachycardia |
|                   | Cardiomyopathy |
| Cardiovascular dysfunction | Right ventricular systolic dysfunction |
|                   | Cor pulmonale |
|                   | Pulmonary hypertension |
|                   | Heart valve disorder |
| Structural defects | Pericarditis |
|                   | Aortic root aneurysm |
|                   | Atrial myxoma |
|                   | Arteriovenous malformation |
|                   | Raynaud phenomenon |
| Vascular disease  | Thrombus |
|                   | Stenosis/occlusion of vessel |
| Dyslipidemia and essential hypertension | Hypertriglyceridemia |
|                   | Hypercholesterolemia |
|                   | Essential hypertension |
Table 2
Characteristics of SJLIFE Eligible Hodgkin Lymphoma Survivors and Community-Controls

| SJLIFE Eligible Survivors | Participants (n=348) | Non-Participants (n=322) | P-Value | All Eligible Survivors (n=670) | Community-Controls (n=272) |
|---------------------------|----------------------|-------------------------|---------|------------------------------|---------------------------|
| Gender                    |                      |                         | 0·012   |                              |                           |
| Male                      | 185 (53%)            | 202 (37%)               |         | 387 (58%)                    | 142 (52%)                 |
| Female                    | 163 (47%)            | 120 (63%)               |         | 283 (42%)                    | 130 (48%)                 |
| Age at HL Diagnosis (Years) |                      |                         | 0·72    |                              |                           |
| Mean                      | 13·8                 | 13·9                    |         | 13·9                         |                           |
| Median (IQR)              | (11·5-17·0)          | (11·2-17·0)             |         | (11·4-17·0)                  |                           |
| Range                     | 3·0 - 22·7           | 3·6 - 25·4              |         | 3·0 - 25·4                   |                           |
| Age at Censor or Death (Years) |                      |                         | <0·0001 |                              |                           |
| Mean                      | 40·6                 | 37·1                    |         | 38·9                         | 35·1                      |
| Median (IQR)              | (33·4-46·8)          | (29·8-44·2)             |         | (31·7-45·7)                  | (28·0-42·3)               |
| Range                     | 21·1 - 67·3          | 18·7 - 64·6             |         | 18·7 - 67·3                  | 18·3 - 70·2               |
| Race                      |                      |                         | 0·83    |                              |                           |
| White                     | 295 (85%)            | 271 (84%)               |         | 566 (85%)                    | 238 (87%)                 |
| Other                     | 53 (15%)             | 51 (16%)                |         | 104 (15%)                    | 34 (13%)                  |
| Treatment Era             |                      |                         | 0·0060  |                              |                           |
| Before 1980               | 80 (23%)             | 100 (31%)               |         | 180 (27%)                    |                           |
| 1980-1994                 | 177 (51%)            | 125 (39%)               |         | 302 (45%)                    |                           |
| After 1995                | 91 (26%)             | 97 (30%)                |         | 188 (28%)                    |                           |
| Heart Radiation Exposure  |                      |                         | 0·76    |                              |                           |
| Yes                       | 320 (92%)            | 294 (91%)               |         | 614 (92%)                    |                           |
| No                        | 28 (8%)              | 28 (9%)                 |         | 56 (8%)                      |                           |
| Heart Radiation Dose      |                      |                         | 0·0080  |                              |                           |
| <15 Gy                    | 82 (24%)             | 51 (16%)                |         | 133 (20%)                    |                           |
| ≥15 to <35 Gy             | 194 (56%)            | 178 (55%)               |         | 372 (55%)                    |                           |
| ≥35 Gy                    | 72 (21%)             | 93 (29%)                |         | 165 (25%)                    |                           |
| Anthracycline Dose        |                      |                         | 0·15    |                              |                           |
| None                      | 124 (36%)            | 131 (41%)               |         | 255 (38%)                    |                           |
| 1-249 mg/m²               | 191 (55%)            | 153 (46%)               |         | 344 (51%)                    |                           |
| ≥250 mg/m²                | 33 (9%)              | 38 (12%)                |         | 71 (11%)                     |                           |
| Any Death                 |                      |                         |         |                              |                           |
| Rate per 10,000 Person Years (95% Confidence Interval) | 51·2 (34·6-73·1) | 240·0 (195·6-291·2) | <0·0001 | 130·6 (109·3-154·9) |                           |
| Cardiovascular Death (Grade 5 Event) |                |                         | 0·0001  |                              |                           |
| Rate per 10,000 Person Years (95% Confidence Interval) | 6·8 (1·9-17·5) | 42·3 (25·1-66·9) | <0·0001 | 21·8 (13·6-32·9) |                           |