Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Incidence of chronic disease among childhood cancer survivors by treatment era and temporal trends in treatment exposure

Working Group & Investigators: Chronic Disease Working Group (Secondary: Epi/Biostats)

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Background & Rationale

The 5-year survival rate for most childhood malignancies has increased dramatically over the past five decades to over 80%, due largely to advances in treatment and supportive care.[1] As a result, there were an estimated 420,000 childhood cancer survivors in the United States in 2013, with that number expected to exceed 500,000 by 2020.[2] Unfortunately, progress in survival has been accompanied by increasing recognition of the high burden of treatment-related late mortality and morbidity experienced by survivors. Results from the Childhood Cancer Survivor Study (CCSS) and similar pediatric cancer survivor cohorts around the world have clearly demonstrated increased risks of mortality and morbidity due to late effects.[3-6] In response, pediatric oncologists have modified therapeutic approaches and utilized risk-stratified treatment plans to decrease treatment exposures for many, but not all, more recent patients.[7, 8] The recent expansion of the CCSS to include participants diagnosed with childhood cancer from 1987-1999 provides the unique opportunity to examine late effects occurring in survivors who received treatment regimens that evolved over three decades (1970-99).

A recent analysis including the CCSS expanded cohort by Armstrong et al. showed that mortality due to health-related causes, a category that includes death due to late effects of treatment, decreased significantly from 3.1% in those treated in the 1970s to 1.9% in those treated in the 1990s.[9] Significant decreases in death due to second malignant neoplasms and cardiac or pulmonary causes contributed to this reduction in mortality. Furthermore, for specific diagnoses (acute lymphoblastic leukemia, Wilms tumor) decreases in health-related cause mortality followed demonstrable temporal reductions in therapeutic intensity. Notably, temporal changes in mortality varied substantially by primary cancer diagnosis. This is exemplified by survivors of neuroblastoma, for whom late mortality rates increased in more recent treatment decades, likely reflecting increased therapeutic intensity that has resulted in increased 5-year survival among high risk patients.[9] The study by Armstrong et al. provides clear evidence that changes in childhood cancer therapy that occurred between 1970 and 1999 successfully translated to a reduction in mortality due to late effects and extension of lifespan for at least some groups of survivors.

However, the question remains whether these changes in therapy resulted in a reduced burden of therapy-related chronic health conditions as well as lifespan (or, conversely, increased burden of chronic conditions in subgroups such as neuroblastoma where intensive treatment resulted in improved 5-year survival). An analysis by Ness et al. (*submitted*) of self-reported health status by treatment decade in CCSS provides some initial insights into this question. The primary finding among survivors treated from 1970-1999 was that the risk for self-reported adverse health status did not diminish over time. In fact, within some diagnostic groups the prevalence of reported poor general health and anxiety was higher among those treated in the 1990s compared to earlier decades. Potential reasons for the lack of improvement or worsening in health status include a) changes in the population of childhood cancer survivors such that more high-risk patients, who received high-intensity therapies, survived at least 5 years and thus were evaluable for late health status in more recent decades; b) self-reported health status is subjective, thus an increased recognition and detection of late effects in more recent decades could result in improved mortality but more negative perceptions of health; or c) higher expectations regarding long-term health in more recently treated survivors.

In the context of these recent findings of temporal improvements in mortality but not health status, there is a clear need to examine objective measures of morbidity to better understand how the experience of childhood cancer survivors has changed over time. One such measure that has proven to be a useful indicator of disease burden is the incidence and severity of chronic health conditions as classified under the Common Terminology Criteria for Adverse Events (CTCAE).[10]

An initial study by Oeffinger et al. of survivors diagnosed from 1970-1986 found that 62% of survivors had at least one chronic condition, and that survivors had an elevated risk (RR=3.2) of any chronic condition compared to siblings.[6] The relative risk of severe/disabling or life-threatening (CTCAE grade 3 or 4) chronic conditions was even higher (RR=8.2), and 28% of survivors had at least one such condition. More recently, Armstrong et al. examined the cumulative incidence of CTCAE grade 3-5 chronic conditions in survivors across the age spectrum, which reached 54% by age 50 years.[3] Risk of grade 3-5 chronic conditions was increased compared to siblings at all ages, and further increased among survivors as they aged into their fourth and fifth decades of life. Numerous other CCSS studies have examined

specific chronic conditions and/or diagnostic groups to further clarify relationships between treatment and late effects, but these analyses have been limited to participants diagnosed from 1970-1986.

Classification and coding of chronic conditions according to CTCAE version 4.0 was recently completed for outcomes reported on the baseline questionnaire for the expansion of the CCSS cohort. An ongoing high priority analysis by Oeffinger et al. examining temporal changes in late effects among Hodgkin lymphoma (HL) survivors will include analysis of this chronic conditions data and should yield important insights into the impact of changes in HL treatment. Additional detailed disease-specific analyses will likely follow. However, there is a clear opportunity to provide an overview of temporal trends in the cumulative incidence and cumulative burden of chronic conditions for the entire cohort, providing context for the prior overall analyses of changes in mortality and health status, as well as the diagnosis-specific analyses that will follow.

Specific Aims:

1. Examine the cumulative incidence and cumulative burden of chronic health conditions (overall and by organ system) in childhood cancer survivors by treatment era (defined by 5 year or 10 year intervals of diagnosis), and compare cumulative incidence and cumulative burden between survivors of each era and a sibling comparison group from the same time period.
2. Evaluate temporal patterns in cumulative incidence and cumulative burden of chronic health conditions, overall and stratified by diagnosis group, according to temporal changes in treatment exposure.

Hypotheses:

- Overall cumulative incidence of chronic health conditions will be lower in more recent eras, although patterns will differ across diagnostic groups.
- Differences by treatment era and for survivors versus siblings will be more pronounced when examining cumulative burden by the method of mean cumulative count.
- Reductions in cumulative incidence and cumulative burden of chronic health conditions may be identified in certain cancer diagnoses where historical reduction in therapeutic intensity has occurred, such as ALL, HL and Wilms tumor.
- Increases in cumulative incidence and cumulative burden of chronic health conditions may be identified in certain cancer diagnoses where historical increases of therapeutic intensity have resulted in higher rates of 5-year survival for high risk patients, such as neuroblastoma.
- Changes in the relative risk of chronic health conditions across treatment eras can be at least partially attributed to changes in treatment exposures, although this may vary by organ system.

Analysis Framework:

A. Population of Interest: All CCSS participants (survivors diagnosed 1970-1999); siblings of original and expanded cohort survivors who provided a baseline questionnaire.

B. Outcome Measures: Self-reported outcomes at baseline and follow-up questionnaires (≥5 years after cancer diagnosis) have been categorized and coded according to the CTCAE version 4.0, which

grades conditions as mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4), or fatal (grade 5). Chronic conditions were further categorized by organ system (hearing, vision, speech, endocrine, respiratory, cardiac, gastrointestinal, renal, musculoskeletal, neurological, other hematologic, other infectious/immunologic, and second malignant neoplasms).

C. Explanatory Variables: To capture global changes in treatment among all survivors across potential treatment eras, we propose to examine survivors stratified by decade of cancer diagnosis (1970-79, 1980-89, 1990-99). In addition to reporting cumulative incidence and cumulative burden by decade, a three-level variable for treatment era can be included in multivariable regression models to evaluate the impact of temporal changes. We will further examine more detailed time intervals (e.g. 1970-74, 1975-79, 1980-84, etc.) to explore whether potentially important signals are missed using treatment decades. For analyses restricted to specific diagnosis groups, we will consider specific treatment variables that represent known changes in treatment patterns over time (e.g. reduced rates of cranial radiotherapy for ALL, abdominal radiotherapy for Wilms' tumor, or chest radiotherapy for Hodgkin lymphoma).

D. Statistical Approach:

Basic participant characteristics, including primary cancer, treatment exposures and demographics will be described using means and proportions for continuous and categorical variables, respectively. Survivors will be described by decade of cancer diagnosis, and similarly siblings will be described by decade according to the date of diagnosis of their related cancer survivor. For sibling analyses, we will investigate the existence of secular trends by decade (according to diagnosis of their related survivor), but will plan to combine siblings for analysis as a single group in the absence of such trends to maximize statistical power. It is important to note that by the time this analysis is underway, we expect to be able to reference the paper by Leisenring et al. that describes in detail the changes in therapy of CCSS survivors over time. Broad examples of these changes include a decrease in the proportion of survivors who received radiotherapy and an increase in the proportion who received anthracyclines, but with overall reductions in doses administered.

Aim 1: Examine the cumulative incidence and cumulative burden of chronic health conditions (overall and by organ system) in childhood cancer survivors by treatment era, and compare cumulative incidence and cumulative burden between survivors of each era and a sibling comparison group.

Cumulative incidence of chronic conditions will be estimated by age at first occurrence, with deaths due to causes other than Grade 5 CTCAE conditions considered as competing risks. In exploratory analyses, similar plots of cumulative incidence by time since primary cancer diagnosis will be generated to check for any substantial differences from the trends by age. Cumulative incidence plots will be stratified by decade of cancer diagnosis, and siblings will be similarly stratified by decade of diagnosis of their related survivor as described above. A series of cumulative incidence plots will be generated, as outlined below. We recognize that the proposal includes a large number of specific analyses, but feel that being able to see a comprehensive picture of chronic conditions by numerous subgroupings will be critical for identifying and conveying the most important overall messages. For example, readers will likely be interested in seeing analyses of grade 1-5 chronic conditions to show overall morbidity in the

population, and grade 3-5 chronic conditions to show key drivers of severe morbidity. However, it will also be important to examine grade 1-2 conditions, as some temporal trends may manifest as decreased severity of conditions over time as opposed to a strict reduction in incidence of those conditions. Analyses focused on grade 1-2 events only may need to account for development of grade 3-5 events or death as competing risks. For final presentation of the results in a manuscript, it may be most appropriate to present cumulative incidence of grade 1-5 events and grade 3-5 events, with the difference between these two curves representing the percentage of participants developing ONLY grade 1-2 events.

a) Grade 1-5 conditions (overall and by organ system) for all survivors and siblings (stratified by decade)

b) Grade 1-2 conditions (overall and by organ system) for all survivors and siblings (stratified by decade)

c) Grade 3-5 conditions (overall and by organ system) for all survivors and siblings (stratified by decade)

d) Grade 1-5 conditions for survivors (overall only) by diagnostic group (stratified by decade)

e) Grade 1-2 conditions for survivors (overall only) by diagnostic group (stratified by decade)

f) Grade 3-5 conditions for survivors (overall only) by diagnostic group (stratified by decade)

We will also examine the overall burden of chronic conditions, including multiple conditions suffered by the same participant. To assess cumulative burden, we will employ the method of mean cumulative count, as described by Dong et al. and employed by Bhakta et al. (*in press*) for an analysis of cumulative burden of cardiac late effects in the St. Jude Lifetime Cohort study.[11, 12] As described above for cumulative incidence, plots of mean cumulative count (overall and by organ system), stratified by decade of diagnosis, will be generated for survivors and siblings (grade 1-5; grade 1-2; grade 3-5) and then for each diagnostic group (overall chronic conditions only) among survivors (grade 1-5; grade 1-2; grade 3-5). Given the novelty of the cumulative burden approach, we believe readers may be interested in seeing analyses by both cumulative incidence and cumulative burden. When reporting results of cumulative burden analyses, we will need to acknowledge the limitations imposed by data collection in CCSS, where for the majority of conditions questionnaire-based assessment only identifies the first occurrence of any specific condition. Thus cumulative burden will provide insights into the burden of multiple different conditions, but will fail to capture multiple occurrences of a particular condition type (with the notable exception of second neoplasms, particularly non-melanoma skin cancers).

To further examine potential differences by diagnosis decade, we will calculate 15-year cumulative incidence and cumulative burden of chronic conditions (grade 1-5; grade 1-2; grade 3-5) by organ system (Tables 2-7), and also by diagnosis group (Tables 8-13). Because not all survivors diagnosed from 1990-99 have completed 15 years of follow-up, a sensitivity analysis examining 10-year cumulative incidence will need to be done for any noteworthy results. Examination of organ-specific chronic conditions within distinct diagnostic groups will be reserved for diagnosis-specific analysis concepts, many of which are already in development. Statistical inference based on these analyses will rely on bootstrap-based confidence intervals and permutation tests.[11]

Piecewise exponential models (overall, by specific organ system, and by primary diagnosis; Tables 14-15) with age as the underlying time scale will be employed to estimate rate ratios (RRs) and 95% confidence intervals (95% CIs) comparing the risk of incident chronic conditions of all grades between survivors and

siblings, as well as trends across treatment eras. We will use generalized linear mixed models with robust variance estimation to account for potential correlation due to inclusion of survivors and siblings from the same family and multiple events per person (recurrent events). This will be the first of the two stages of modeling – this first stage focuses on the description of the overall rates of chronic conditions. In the second stage, we will describe changes in distribution of grades over treatment era (conditioned on incident chronic conditions) employing logistic regression models for the binary outcome of grade 3-5 vs. grade 1-2 events in association with survivor/sibling status and its trend over treatment era, similarly accounting for potential within-family correlation as above. These two models will be jointly referred to as "marked point process models" for incident chronic health conditions where each incident event is "marked" by its CTCAE grade.[11, 13] By combining the results from the two stages of modeling, we will be able to examine both trends in the overall incidence of chronic conditions and potential changes in the distribution of severity (CTCAE grades) of these conditions. Standard large sample statistical inference will be used in these models. Models will be adjusted for sex and race/ethnicity. Specific parameters of interest will be those comparing decades of treatment era, such that survivors diagnosed from 1970-79 will be compared to siblings whose related survivor was diagnosed during the same time period, and similarly for 1980-89 and 1990-99. Examination of risk over time among siblings may inform the appropriateness of this strategy, and if risks do not differ by decade we will consider combining siblings to create a single comparison group.

Aim 2: Evaluate temporal patterns in incidence of chronic health conditions according to temporal changes in treatment exposure.

Relative risks of developing a chronic health condition (grade 1-5; grade 1-2; grade 3-5) will be compared across decades of diagnosis using multivariable piecewise exponential models with a three-level variable for treatment era, using survivors diagnosed in 1970-79 as the reference group. Initial models will be adjusted for age (as the time scale in the models), sex and race/ethnicity only. A second set of models will then be fit that include specific treatment variables (varying based on diagnostic group or organ system), with the goal being to determine the impact of accounting for treatments (and their changes) on the association between treatment era and risk of chronic conditions. Separate analyses will be done for grade 1-5 chronic conditions (Table 16), grade 1-2 chronic conditions (Table 17) and grade 3-5 chronic conditions (Table 18), for the overall cohort of survivors, by diagnostic group, and by organ system (but not by organ system within a particular diagnostic group). Specific treatments included in each model will be determined based on clinical knowledge, literature review, and changes highlighted by Leisenring et al., and will be similar to those used by Armstrong et al. in their mortality analysis. An example for survivors of acute lymphoblastic leukemia and Hodgkin lymphoma is shown in Table 19. In recognition of this already extensive analysis concept, we propose saving any examination of separate models for chronic conditions related to each organ system within specific diagnostic groups for future analyses. Choice of whether to use incidence or burden of chronic conditions to model the impact of treatment on the association between treatment era and chronic conditions will be made after viewing the results of the previous analyses proposed above.

Finally, we will explore the possibility of including a graphical presentation of treatment score, as has been done in the mortality and health status papers (the figure utilized by Ness et al. is included below as a reference, Figure 7). As in these previous papers, the treatment score would be generated as a

method of providing a visual illustration of changes in the treatment related risk of the outcome over time. Briefly, the method employed by Ness et al. in the health status analysis involved using multivariable piecewise exponential models to estimate risk of any chronic condition ≥ grade 3, with diagnosis-specific treatment exposures as risk factors. The treatment score was the standardized logarithm (those from 1970-1979 had a mean 0.0 and standard deviation 1) of fitted risk of having any ≥ grade 3 chronic health condition, based on diagnosis-specific treatment exposures. We will work closely with Drs. Yasui and Leisenring to determine the precise methodology to be employed for construction and visualization of treatment scores.

References:

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Table 1. Participant characteristics, overall and by decade of primary cancer diagnosis for survivors

	Childhood Cancer Survivors								Siblings[1]	
	Total		Diagnosed 1970-1979		Diagnosed 1980-1989		Diagnosed 1990-1999		Total	
	N	%	N	%	N	%	N	%	N	%
All Survivors										
Sex										
Male										
Female										
Race/Ethnicity										
Non-Hispanic white										
Non-Hispanic black										
Hispanic										
Non-Hispanic Asian or Pacific Islander										
Non-Hispanic American Indian/Alaskan Native										
Age at Diagnosis (years)										
0-4										
5-9										
10-14										
15-20										
Age at questionnaire (years)										
5-19										
20-29										
30-39										
40-49										
50+										
Time since diagnosis (years)										
0-9										
10-19										
20-29										
30+										
Diagnosis										

Leukemia										
Acute lymphoblastic leukemia										
Acute myeloid leukemia										
Other leukemia										
Hodgkin lymphoma										
Non-Hodgkin lymphoma										
CNS tumors										
Medulloblastoma										
Ependymoma										
Glioma										
Other CNS										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Bone tumors										
Ewing sarcoma										
Osteosarcoma										
Other bone tumors										
Treatment exposure										
Any radiation										
Yes										
No										
Chest radiation										
Yes										
No										
Central nervous system radiation										
Yes										
No										
Abdominal radiation										
Yes										
No										

Pelvic radiation										
Yes										
No										
Alkylating agent (CPM equivalents, mg/m^2)										
None										
0 - <4,000										
≥4000-<8000										
≥8000-12,000										
≥12,000-<16,000										
≥16,000-<20,000										
≥20,000										
Anthracycline (mg/m^2)										
None										
0-100										
101-250										
251-400										
>400										
Epipodophyllotoxin (mg/m^2)										
Yes										
No										
Bleomycin										
Yes										
No										
Platinum										
Yes										
No										
Education										
High school or less										
More than high school										
Household Income ($ per year)										
<20,000										

20,000-59,999										
≥60,000										
Health Insurance Status										
Yes										
No										

[1] Siblings will be examined separately by decade as well, and presented as separate groups if there are significant differences in incidence of chronic conditions across decades.

Figure 1. A) Cumulative incidence of grade 1-5 chronic conditions for childhood cancer survivors and siblings by treatment era (overall and by diagnosis group).

A. Grade 1-5 overall
B. Grade 1-5 ALL
C. Grade 1-5 HL
D. Grade 1-5 kidney

Etc.

Figure 2. A) Cumulative incidence of grade 1-2 chronic conditions for childhood cancer survivors and siblings by treatment era (overall and by diagnosis group).

A. Grade 1-2 overall
B. Grade 1-2 ALL
C. Grade 1-2 HL
D. Grade 1-2 kidney

Etc.

Figure 3. A) Cumulative incidence of grade 3-5 chronic conditions for childhood cancer survivors and siblings by treatment era (overall and by diagnosis group).

A. Grade 3-5 overall
B. Grade 3-5 ALL
C. Grade 3-5 HL
D. Grade 3-5 kidney

Etc.

(Example figure for illustration only)

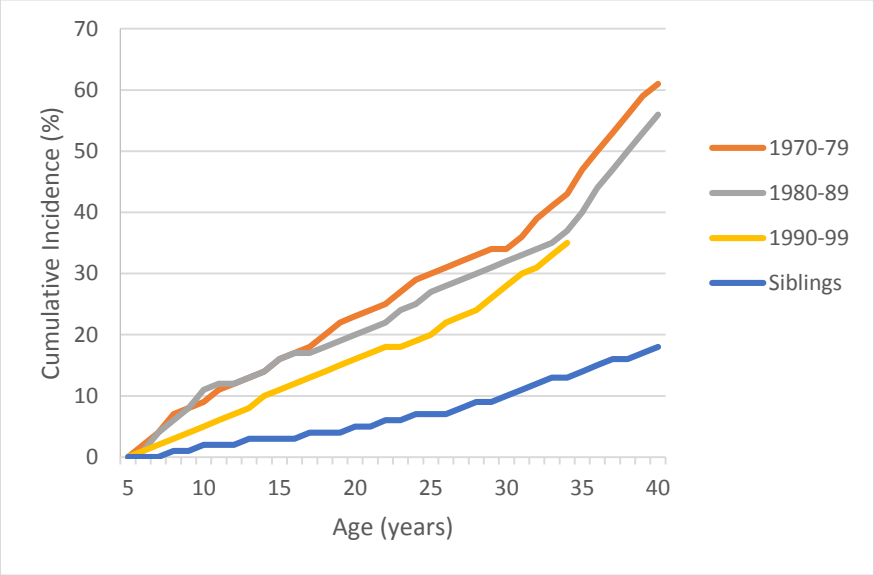

Figure 4. Estimated mean cumulative count curves for grade 1-5 chronic conditions in childhood cancer survivors and siblings by treatment era (overall and by diagnosis group).

A. Grade 1-5 overall
B. Grade 1-5 ALL
C. Grade 1-5 HL
D. Grade 1-5 kidney

Etc.

Figure 5. Estimated mean cumulative count curves for grade 1-2 chronic conditions in childhood cancer survivors and siblings by treatment era (overall and by diagnosis group).

A. Grade 1-2 overall
B. Grade 1-2 ALL
C. Grade 1-2 HL
D. Grade 1-2 kidney

Etc.

Figure 6. Estimated mean cumulative count curves for grade 3-5 chronic conditions in childhood cancer survivors and siblings by treatment era (overall and by diagnosis group).

E. Grade 3-5 overall
F. Grade 3-5 ALL
G. Grade 3-5 HL
H. Grade 3-5 kidney

Etc.

(Example figure for illustration only)

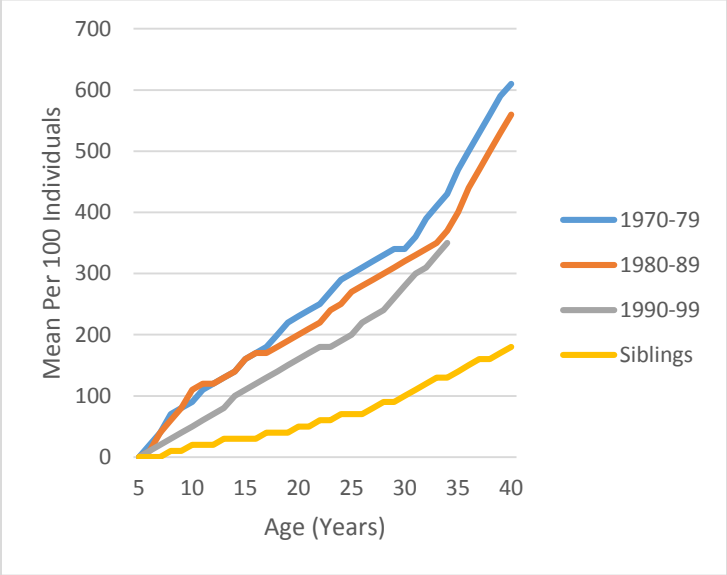

Table 2. Cumulative incidence of grade 1-5 chronic health conditions by organ system at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	
Any grade 1-5										
Hearing										
Vision										
Speech										
Endocrine										
Respiratory										
Cardiac										
Gastrointestinal										
Renal										
Musculoskeletal										
Neurologic										
Other Hematologic										
Other Infectious/ Immunologic										
SMN										

Table 3. Cumulative incidence of grade 1-2 chronic health conditions by organ system at 15 years from primary cancer diagnosis among survivors

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	
Any grade 1-2										
Hearing										
Vision										
Speech										
Endocrine										
Respiratory										
Cardiac										
Gastrointestinal										
Renal										
Musculoskeletal										
Neurologic										
Other Hematologic										
Other Infectious/ Immunologic										
SMN										

Table 4. Cumulative incidence of grade 3-5 chronic health conditions by organ system at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	
Any grade 3-5										
Hearing										
Vision										
Speech										
Endocrine										
Respiratory										
Cardiac										
Gastrointestinal										
Renal										
Musculoskeletal										
Neurologic										
Other Hematologic										
Other Infectious/ Immunologic										
SMN										

Table 5. Cumulative burden of grade 1-5 chronic health conditions by organ system at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	
Any grade 1-5										
Hearing										
Vision										
Speech										
Endocrine										
Respiratory										
Cardiac										
Gastrointestinal										
Renal										
Musculoskeletal										
Neurologic										
Other Hematologic										
Other Infectious/ Immunologic										
SMN										

Table 6. Cumulative burden of grade 1-2 chronic health conditions by organ system at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	
Any grade 1-2										
Hearing										
Vision										
Speech										
Endocrine										
Respiratory										
Cardiac										
Gastrointestinal										
Renal										
Musculoskeletal										
Neurologic										
Other Hematologic										
Other Infectious/ Immunologic										
SMN										

Table 7. Cumulative burden of grade 1-2 chronic health conditions by organ system at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	
Any grade 3-5										
Hearing										
Vision										
Speech										
Endocrine										
Respiratory										
Cardiac										
Gastrointestinal										
Renal										
Musculoskeletal										
Neurologic										
Other Hematologic										
Other Infectious/ Immunologic										
SMN										

Table 8. Cumulative incidence of grade 1-5 chronic health conditions by diagnosis group at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	
ALL										
AML										
Other leukemia										
Hodgkin lymphoma										
NHL										
CNS tumors										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										

Table 9. Cumulative incidence of grade 1-2 chronic health conditions by diagnosis group at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	
ALL										
AML										
Other leukemia										
Hodgkin lymphoma										
NHL										
CNS tumors										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										

Table 10. Cumulative incidence of grade 3-5 chronic health conditions by diagnosis group at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	At risk	Cumulative incidence (%)	95% CI	
ALL										
AML										
Other leukemia										
Hodgkin lymphoma										
NHL										
CNS tumors										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										

Table 11. Cumulative burden of grade 1-5 chronic health conditions by diagnosis group at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	
ALL										
AML										
Other leukemia										
Hodgkin lymphoma										
NHL										
CNS tumors										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										

Table 12. Cumulative burden of grade 1-2 chronic health conditions by diagnosis group at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	
ALL										
AML										
Other leukemia										
Hodgkin lymphoma										
NHL										
CNS tumors										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										

Table 13. Cumulative burden of grade 3-5 chronic health conditions by diagnosis group at 15 years from primary cancer diagnosis among survivors.

	1970-1979			1980-1989			1990-1999			*P*
	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	At risk	Mean Cumulative Count	95% CI	
ALL										
AML										
Other leukemia										
Hodgkin lymphoma										
NHL										
CNS tumors										
Kidney tumors										
Neuroblastoma										
Soft tissue sarcoma										
Ewing sarcoma										
Osteosarcoma										

Table 14. Comparison of risk of incident grade 1-5 chronic health conditions by organ system between siblings and survivors, stratified by treatment era for survivors.

	1970-1979					1980-1989					1990-1999					*P*
	Siblings		Survivors			Siblings		Survivors			Siblings		Survivors			
Organ System	**N[1]**	**RR[2]**	**N**	**RR**	**95% CI**	**N**	**RR**	**N**	**RR**	**95% CI**	**N**	**RR**	**N**	**RR**	**95% CI**	
All Conditions		1.00					1.00					1.00				
Hearing		1.00					1.00					1.00				
Vision		1.00					1.00					1.00				
Speech		1.00					1.00					1.00				
Endocrine		1.00					1.00					1.00				
Respiratory		1.00					1.00					1.00				
Cardiac		1.00					1.00					1.00				
GI		1.00					1.00					1.00				
Renal		1.00					1.00					1.00				
Musculoskeletal		1.00					1.00					1.00				
Neurological		1.00					1.00					1.00				
Other Hematologic		1.00					1.00					1.00				
Other Infectious/ Immunologic		1.00					1.00					1.00				
SMN		1.00					1.00					1.00				

[1] N = number of events

[2] Rate ratio from piecewise exponential models adjusted for age, sex and race

Table 15. Comparison of risk of incident grade 1-5 chronic health conditions by diagnosis group between siblings and survivors, stratified by treatment era for survivors.

	1970-1979					1980-1989					1990-1999					*P*
	Siblings		Survivors			Siblings		Survivors			Siblings		Survivors			
Diagnosis Group	**N[1]**	**RR[2]**	**N**	**RR**	**95% CI**	**N**	**RR**	**N**	**RR**	**95% CI**	**N**	**RR**	**N**	**RR**	**95% CI**	
ALL		1.00					1.00					1.00				
AML		1.00					1.00					1.00				
Other leukemia		1.00					1.00					1.00				
Hodgkin lymphoma		1.00					1.00					1.00				
NHL		1.00					1.00					1.00				
CNS tumors		1.00					1.00					1.00				
Kidney tumors		1.00					1.00					1.00				
Neuroblastoma		1.00					1.00					1.00				
Soft tissue sarcoma		1.00					1.00					1.00				
Ewing sarcoma		1.00					1.00					1.00				
Osteosarcoma		1.00					1.00					1.00				

[1] N = number of events

[2] Rate ratio from piecewise exponential models adjusted for age, sex and race

Table 16.

This example represents a summary table focused on the RRs for the treatment era variable and risk of incident grade 1-5 chronic conditions. Each diagnostic group will be examined in a separate model. In preliminary analyses we would want to see the full multivariable regression analysis results for each diagnostic group, so potentially 8 separate tables. Specific treatment variables will vary based on diagnostic group.

	1970-1979	1980-1989				1990-1999			
Diagnosis Group	**RR**	**Model 1 RR[*]**	**95% CI**	**Model 2 RR[#]**	**95% CI**	**Model 1 RR[*]**	**95% CI**	**Model 2 RR[#]**	**95% CI**
All Primary Cancers	1.00								
Leukemia	1.00								
Hodgkin lymphoma	1.00								
NHL	1.00								
CNS	1.00								
Kidney	1.00								
Neuroblastoma	1.00								
Soft tissue sarcomas	1.00								
Bone tumors	1.00								

[*] Rate ratio from piecewise exponential models adjusted for age, sex and race

[#] Model 2 includes the variables in Model 1 plus relevant treatment variables

Table 17.

This example represents a summary table focused on the RRs for the treatment era variable and risk of incident grade 1-2 chronic conditions. Each diagnostic group will be examined in a separate model. In preliminary analyses we would want to see the full multivariable regression analysis results for each diagnostic group, so potentially 8 separate tables. Specific treatment variables will vary based on diagnostic group.

	1970-1979	1980-1989				1990-1999			
Diagnosis Group	**HR**	**Model 1 RR***	**95% CI**	**Model 2 RR#**	**95% CI**	**Model 1 RR***	**95% CI**	**Model 2 RR#**	**95% CI**
All Primary Cancers	1.00								
Leukemia	1.00								
Hodgkin lymphoma	1.00								
NHL	1.00								
CNS	1.00								
Kidney	1.00								
Neuroblastoma	1.00								
Soft tissue sarcomas	1.00								
Bone tumors	1.00								

* Rate ratio from piecewise exponential models adjusted for age, sex and race

Model 2 includes the variables in Model 1 plus relevant treatment variables

Table 18.

This example represents a summary table focused on the RRs for the treatment era variable and risk of incident grade 3-5 chronic conditions. Each diagnostic group will be examined in a separate model. In preliminary analyses we would want to see the full multivariable regression analysis results for each diagnostic group, so potentially 8 separate tables. Specific treatment variables will vary based on diagnostic group.

	1970-1979	1980-1989				1990-1999			
Diagnosis Group	**RR**	**Model 1 RR***	**95% CI**	**Model 2 RR#**	**95% CI**	**Model 1 RR***	**95% CI**	**Model 2 RR#**	**95% CI**
All Primary Cancers	1.00								
Leukemia	1.00								
Hodgkin lymphoma	1.00								
NHL	1.00								
CNS	1.00								
Kidney	1.00								
Neuroblastoma	1.00								
Soft tissue sarcomas	1.00								
Bone tumors	1.00								

* Rate ratio from piecewise exponential models adjusted for age, sex and race

Model 2 includes the variables in Model 1 plus relevant treatment variables

Table 19. Example of treatment exposures to be examined in diagnosis-specific models of associations between treatment era and incidence of chronic conditions.

Acute lymphoblastic leukemia	
Anthracycline (mg/m2)	None
	1 - <150
	≥150 - <300
	≥300 - <450
	≥450 - <600
	≥600
Steroid	Prednisone
	Dexamethasone
	Both
	None
Epipodophyllotoxin	Yes
	No
Cranial radiotherapy	None
	1-19.9 Gy
	≥20 Gy
Hodgkin lymphoma	
Chest radiotherapy	None
	≥1 - <20 Gy
	≥20 - <30 Gy
	≥30 Gy
Splenectomy	Yes
	No
Cyclophopsphamide equivalent dose (mg/m2)	None
	0 - <4000
	≥4000 - <8000
	≥8000 - <12000
	≥12000 - <16000
	≥16000 - <20000
	≥20000
Anthracycline (mg/m2)	None
	1 - <150
	≥150 - <300
	≥300 - <450
	≥450 - <600
	≥600

Figure 7. *From Ness et al. (submitted)* Treatment score (box and whisker plot – left y axis) and percent with adverse health status outcome (large dots – right y axis) by treatment decade.