Childhood Cancer Survivor Study
Analysis Concept Proposal

Original title: Changes in Long-Term Outcomes in Hodgkin Lymphoma Survivors with Contemporary Risk-Adapted Therapy

Working Group & Investigators: Chronic Disease (Primary), Second Malignancy, Cancer Control, Psychology, and Epidemiology / Biostatistics

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Background and Rationale:

Over the last five decades, Hodgkin lymphoma (HL) has served as an oncologic model for the "maximize cure, minimize cost" paradigm. Due to the radiosensitivity of this malignancy, very favorable cure rates were achieved with HL earlier than most cancers. Donaldson et al reported that children diagnosed with HL prior to age 15 and treated at Stanford from 1962 through 1972 had a 5-year actuarial survival rate of 89%.[1] Data from the Surveillance, Epidemiology, and End Results (SEER) Program reported that the 5-year survival rate for children in the U.S., aged 0-19 years, and diagnosed with HL (all stages) from 1975 through 1977 was 86.2%.[2] Indeed, while 5-year survival rates have continued to improve, now exceeding 95%, much of the change in therapy in recent years has focused on minimizing the cost or risk of long-term and late effects.[2]

This therapeutic evolution occurred over several overlapping periods, or eras, characterized by inconsistent use of combination chemotherapy designed to minimize radiation-related side effects. Thus, there has been significant practice variation across the U.S., and even within specific centers, over the past decades.

Several recent reviews have detailed these changes in therapy.[3,4] Briefly, in the 1960s and 1970s, treatment decisions with regard to radiation fields and dose were based in part upon the extent of infradiaphragmatic disease as determined by a staging laparotomy, liver and para-aortic biopsies and splenectomy. Children and adolescents (hereafter, collectively referred to as 'children') with supradiaphragmatic disease were treated with high-dose (35-44 Gy) mantle field radiotherapy, including the cervical, supra/infraclavicular, mediastinal and axillary nodes. Those with only infradiaphragmatic disease, representing less than 10% of the newly diagnosed children, were treated with para-aortic fields often including the splenic pedicle, and depending upon extent of disease, extending to include the iliac and inguinal nodes (creating the 'inverted-Y' field). Lastly, those with supra and infradiaphragmatic disease were treated with extended field, or total lymphoid irradiation (i.e., mantle plus inverted-Y field). Radiation was initially delivered via Cobalt-60. A fascinating description of the delivery of Co-60 mantle radiotherapy, including details about doses and pertubations in the field, and an early treatise on the changes to normal tissues are provided by Svahn-Tapper and Landberg.[5,6] This is pertinent, as many of the early CCSS HL participants were treated with Co-60. In the mid to late 1970s, depending upon institution, the use of linear accelerators (and, for a short time period, betatrons) became more common. Importantly, while the prescribed radiation dose and field may have been similar between Co-60 and linear accelerators, the absorbed dose varied greatly, with Co-60 generally producing more damage to normal surrounding tissue, often resulting in significant aberrations in the musculoskeletal development of a child.[7,8]

With the introduction of multi-agent chemotherapy in the late 1960s, beginning with MOPP (mechlorethamine, vincristine [Oncovin], procarbazine, and prednisone), efforts were made to reduce the dose of radiation and determine the efficacy of combined modality therapy. It was soon apparent, however, that MOPP therapy commonly led to gonadal dysfunction and infertility[9,10] and occasionally to secondary leukemia.[11,12] In hopes of avoiding these adverse outcomes, the next combination to be tested was ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine). Again, it was soon observed that one set of late effects was simply being traded for another, as ABVD conferred a risk for cardiomyopathy and pulmonary disease, particularly when combined with mantle field radiotherapy.[13-17] Thus, in an effort to reduce short-term and long-term toxicity while increasing survival rates, multiple hybrids have been used, such as COPP/ABV where cycles of COPP (cyclophosphamide substituted for mechlorethamine) were alternated with ABV. As CT scanning was introduced in the 1970s and resolution improved, staging laparotomy with splenectomy was abandoned (thus avoiding the persistent risk of overwhelming sepsis). Paralleling these improvements in therapeutic approaches, the dose and the size of the field of radiation was gradually reduced.[4,18,19] Advances in diagnostic imaging, particularly with the advent of functional imaging such as 18-fluorodeoxyglucose positron-emission tomography (PET), have allowed risk-adapted and response-adapted approaches that seek to tailor the intensity of therapy based upon the baseline risk factors and chemotherapy sensitivity, with the hope of avoiding both undertreatment (and subsequent relapse) and overtreatment (with its associated risks of long-term and late effects).

So, what have we learned from the CCSS and similar cohorts about pediatric HL survivors treated in the 1970s and 1980s? In the initial CCSS cohort of HL survivors treated from 1970 through 1986, 76% had a splenectomy, 94% received radiation to some dose or extent and 61% received chemotherapy in combination with radiation and 6% received chemotherapy alone.[20] We know that when compared to other cancer groups and/or non-cancer populations, HL survivors, depending on their treatment exposures, have substantially elevated risks for late mortality,[20-24] overall and serious morbidity,[20,25-28] second malignant neoplasm (SMN; primarily

solid tumors in the radiation field[29-38]) cardiac disease,[14,39,40] stroke,[41,42] pulmonary disease,[20] infertility and gonadal dysfunction,[43-45] diabetes and other endocrinopathies.[20,46,47]

While some studies suggest that more contemporary risk-adapted therapy will be associated with less long-term morbidity, this remains understudied. It is imperative that we determine if these changes in therapy have led not only to an increase in 5-year survival rates (as evidenced in the SEER reports) but also to improvements in long-term survival (or decreases in late mortality) and a parallel reduction in serious morbidity. In other words, it is important to determine if more contemporary therapy has improved long-term outcomes or just resulted in a set of trade-offs.

NOTE: there will be some overlap with the ongoing mortality study led by Greg Armstrong. We have discussed this and will use the same analytic approach for consistency. Notably, whereas the Armstrong analysis will evaluate mortality across all cancers and with some key treatment exposures, this analysis will focus solely on HL survivors and evaluate treatment exposures in much greater detail.

Specific Aims & Hypotheses:

Aim 1. Estimate all-cause and cause-specific mortality for 5+ year survivors of childhood and adolescent Hodgkin lymphoma diagnosed from 1970 through 1999 and compare by era of therapy (1970-1979, 1980-1989, and 1989-1999) and by major treatment groupings (see below for description).

Hypotheses:

In HL survivors who have survived at least 5 years after diagnosis,
10- and 15-year all-cause mortality will be lower for survivors

- diagnosed 1990-1999 compared with those diagnosed 1970-1979
- treated with multiagent chemotherapy without radiation compared to all other groups
- treated with multiagent chemotherapy with involved field radiotherapy in comparison to those treated with only mantle and/or extended field radiotherapy

Cause-specific mortality will be lower for recurrence/progressive disease, cardiac-mortality, and SMN-mortality for survivors:

- diagnosed 1990-1999 compared with those diagnosed 1970-1979
- treated with multiagent chemotherapy with involved field radiotherapy in comparison to those treated with only radiotherapy

Importantly, we will work closely with Greg Armstrong and the working group focused on mortality so that the information we publish is not redundant and also benefits from the methods used in the analysis.

Aim 2. Determine the incidence of chronic health conditions (any condition, grade 3-5 conditions, multiple grade 3-5 conditions, and selected conditions [e.g., SMN, cardiovascular disease, etc) and compare by era of therapy (1970-1979, 1980-1989, and 1989-1999) and by major treatment groupings (see below for description).

Hypotheses:

The hazard of a grade 3-5 chronic condition will be significantly lower for HL survivors:

- diagnosed 1990-1999 compared with those diagnosed 1970-1979
- treated with multiagent chemotherapy without radiation compared to all other groups
- treated with COPP-ABV-like hybrid regimens with involved field radiotherapy in comparison to those treated with only mantle radiotherapy

Aim 3. Estimate risks of chronic health conditions (any condition, grade 3-5 conditions, multiple grade 3-5 conditions) with contemporary HL therapy.

For this aim, we will use data from CCSS to create groups with similar exposures to two contemporary Children's Oncology Group (COG) protocols – AHOD 0031 and AHOD 0431. See below for more detail.

Analytic Framework:

There are a few caveats to note. First, the evolution of HL therapy was not consistent across, and sometimes within, institutions. Some institutions adopted therapies that were intended to have a lower risk of long-term complications and continued this approach for many years. In contrast, some institutions were late adopters, reducing doses and fields of radiation years after other institutions and/or varied their approach depending upon the primary treating oncologist's preference. Thus, we anticipate that there will be a reasonable amount of heterogeneity and variation in practice by using the treatment era approach.

Lastly, a key limitation in our analysis will be that we cannot fully describe the trade-offs and improvements since the analysis will be based on 5-year survivors and we do not have mortality (or treatment) data for those who were diagnosed with HL at one of the 26 institutions but did not survive to 5-years.

Recognizing these caveats, what we really want to know is whether more contemporary therapy, with chemotherapy alone or with lower doses and smaller fields of radiation, has resulted in less long-term morbidity and late mortality. While we will assess differences by treatment eras, our primary comparisons will be based upon (major) treatment groupings for 5+ year survivors.

1. Population of interest:

For the mortality analysis, we have two options. First, we can assess all-cause and cause-specific mortality for all HL survivors <u>eligible</u> for the CCSS cohort (diagnosed 1970-1999, n=4349 minus Canadians). Note, however, that we can only compare by diagnostic eras, not by treatment groups, for the eligible population. Since our primary goal is to assess changes due to therapy, our main analysis will focus on all Hodgkin lymphoma survivors <u>participating</u> in the CCSS cohort (diagnosed 1970-1999, n=2959). It is likely that we will only report results from the latter analysis, but for completeness sake and to determine if there is an important trend or potential bias in mortality rates among the participant group, we will also conduct the mortality analysis using the eligible population.

The chronic condition analysis will be restricted to HL survivors participating in the CCSS.

2. Outcome measures:

a. Mortality:

Vital status (alive/dead) to identify a) cumulative incidence of mortality, and 2) standardized mortality ratios (SMR) and excess absolute risk (EAR). The National Death Index will be the source for vital status. The CCSS currently has NDI data updated through 2008. This is the same NDI data used during the recruitment of the expansion cohort. Standardized mortality ratios will be calculated using age-sex- and calendar year specific mortality rates for the U.S. population from the National Center for Health Statistics to evaluate expected counts.. Information on the underlying cause of death was obtained from death certificates for cases that resided in the U.S. Cause of death has been determined from death certificates and for this analysis will be categorized as:

- Recurrence/progression of primary childhood malignancy
- External cause (e.g. accidents, injuries, suicide)
- Non-recurrence/non-external cause (attributable to chronic health conditions): SMN, cardiac, pulmonary, infection, other

b. Chronic conditions:

We will use our standard approach of identifying chronic conditions and scoring the severity of each condition. The chronic conditions reported by HL survivors in the expansion cohort are currently being scored.

- No chronic condition
- Any grade 1-5 condition
- At least one grade 3-5 condition
- Multiple grade 3-5 conditions

3. Explanatory variables:

a. Treatment era: 1970-1979, 1980-1989, and 1990-1999. Shorter treatment eras blocks (five year blocks) will be considered if sufficient data exist within diagnostic sub-groups. Individuals will be assigned to a given treatment era based on their date of diagnosis.

b. Treatment groups:

Surgery: splenectomy (yes/no)

The following radiation fields will be used:

- Total Lymphoid Irradiation (TLI): mantle + inverted-Y
- Mantle
- Involved field radiotherapy (IFRT) - we will construct multiple groupings based upon what areas were involved (neck, mediastinum, right axilla, left axilla)
- Para-aortic radiotherapy with and without splenic pedicle / spleen irradiation
- Inguinal / iliac / femoral nodes
- Inverted-Y: para-aortic + inguinal / iliac / femoral nodes
- Other radiation fields

We will consider maximal radiation dose to a field, boost, and energy source used to deliver radiotherapy.

Chemotherapy: we will assess both common regimens as well as specific agents, particularly doxorubicin, bleomycin, and cyclophosphamide-equivalent dose of alkylators.

Multi-agent regimens will include:

- MOPP
- ABVD
- COPP-ABV
- Stanford V - mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone
- Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine)
- Other regimens that will be considered, based upon the number of HL survivors treated on them include: COPP, COPDAC, OPPA, OEPA, VAMP, DBVE, ABVE-PC, and CVP. For information on the agents, doses, and schedules for each of these regimens, please refer to Table 4 of: http://www.cancer.gov/cancertopics/pdq/treatment/childhodgkins/HealthProfessional/page4#Section_570

Individual agents will include: mechlorethamine, vinblastine, vincristine, doxorubicin, bleomycin, cyclophosphamide, etoposide, procarbazine, dacarbazine, prednisone, and chlorambucil.

We will begin to group therapies by using a cross-tab approach with radiation fields and chemotherapeutic agents. This will allow us to determine the frequency of the above combinations in the CCSS cohort. We anticipate that the number of HL survivors treated with infradiaphragmatic RT (i.e., para-aortic field) without supradiaphragmatic RT (i.e., mantle field) will be relatively small. This will keep our radiation combinations somewhat smaller.

We then will likely need to collapse the regimens into a smaller number for analysis, while paying particular attention to the most common combinations. Thus, based upon the cross tabs, we might further collapse into the following approaches:

- Major therapeutic regimens (based upon the numbers):
    - Total Lymphoid Irradiation without chemotherapy
    - Mantle RT without chemotherapy
    - Mantle RT + MOPP
    - Mantle RT + ABVD
    - IFRT + COPP-ABV
    - IFRT + other hybrids
    - MOPP without radiation
    - ABVD without radiation
    - COPP-ABV or other hybrids without radiation
    - Other regimens

- Key exposures
    - Supradiaphragmatic RT - 3 regions (yes/no; maximal dose; dose categories): neck, mediastinum, axilla (at least one side) - NOTE: combination of neck + mediastinum + axilla = mantle
    - Infradiaphragmatic RT - 3 regions (yes/no; maximal dose): para-aortic, spleen / splenic pedicle, inguinal/iliac
    - Doxorubicin (yes/no; cumulative dose)
    - Bleomycin (yes/no; cumulative dose)
    - Cyclophosphamide equivalent dose (CED)
    - Procarbazine (yes/no; cumulative dose)
    - Etoposide (yes/no; cumulative dose)
    - Vinca alkaloid agents (yes/no)

c. For Aim 3 (Estimate risks of chronic health conditions (any condition, grade 3-5 conditions, multiple grade 3-5 conditions) with contemporary HL therapy), we will create groups with similar treatment exposures to COG protocols AHOD 0031 (intermediate risk HL) and AHOD 0431 (low risk HL). These will be compared with some of the early therapies for HL, including radiation only and radiation + MOPP.

AHOD 0031 (intermediate risk)

- Doxorubicin 200 mg/m^2
- Cyclophosphamide 3200 mg/^{2}
- Prednisone 1120 mg/m^2
- Vincristine 11.2 mg/m^2
- With and without 21 GY IFRT

AHOD 0431 (low risk)

- Doxorubicin 150 mg/m^2
- Cyclophosphamide 3600 mg/^{2}
- Bleomycin 60 IU/m^2
- Etoposide 1500 mg/m^2
- Prednisone 840 mg/m^2
- Vincristine 8.4 mg/m^2
- With and without 21 GY IFRT

4. Covariates

a. Age at cancer diagnosis
b. Gender
c. Race, ethnicity
d. Interval from cancer diagnosis (either as time-scale of model or time dependent covariate)
e. Attained Age (either as time-scale of model or time dependent covariate)t
f. Recurrence prior to 5-yr time-point (post diagnosis)

5. Statistical analysis

a. Mortality:

To accomplish the first aim of assessment of mortality by treatment era and by treatment groupings, a descriptive analysis of the entire HL cohort based on treatment era will be performed. Overall survival probabilities will be estimated using the product-limit estimate and will be presented separately by treatment era and by major treatment groupings. A nonparametric estimate of the cumulative incidence function will be used to estimate cause-specific mortality by treatment era and by major treatment groupings accounting for the competing risk of death from other causes.

Standardized mortality ratios (SMR) and excess absolute risk (EAR) by treatment era will be calculated for all-cause and cause-specific mortality. To compare CCSS mortality with that expected in the US population, an expected number of deaths each year since diagnosis will be calculated based on US age-, year- and sex-specific mortality rates. To assess the trend over time of all-cause mortality and cause-specific mortality rates, we will use joinpoint methods similar to linear splines.[48] Multivariable Poisson regression will be used to assess the simultaneous impact of multiple factors on the cause-specific SMRs, potentially adjusting for sex, age at diagnosis, year of diagnosis, current age and/or years since diagnosis. With the logarithm of expected numbers of deaths from the US mortality rates incorporated in the models as offset terms, these models will allow for comparisons of SMRs between levels of specific factors of interest, such as treatment era.

In addition to comparing mortality outcomes across treatment eras and major treatment groupings, additional models will evaluate the impact of specific treatment exposures as separate variables in a model.

b. Chronic health conditions:

Cox proportional hazards models will be used to compare any grade, grade 3-5, and multiple grade 3-5 chronic conditions across treatment era and major treatment grouping and reported as hazard ratios. We will use age as the time scale.

Survivors will enter the analysis at an age equivalent to 5 years post diagnosis (or the age equivalent with age as the time scale). Because participants could have reported multiple grade 3 to 5 conditions, the models will use a counting-process approach, using all reported unique conditions for each participant, and accounting for intra-participant correlations using sandwich SE estimates.

The cumulative incidence of any grade, grade 3-5, and multiple grade 3-5 chronic conditions will be estimated nonparametrically treating deaths due to conditions other than those qualifying as a grade 5 fatal chronic condition as a competing risk event (i.e. death due to recurrence of primary cancer or external causes such as accidents, injuries, or suicide). For each outcome, the cumulative incidence will be computed based on time to the earliest reported occurrence of the event of interest.

In addition to looking at mortality outcomes by treatment era and major treatment groupings, additional models will look at handling specific treatment exposures as separate variables in a model.

c. Missing data

We will explore the magnitude and patterns of missingness in the data. Differences between survivors with complete data and those with missing data will be described, focusing particularly on missing treatment exposure data. Depending on what is observed, methods for handling missing data such as multiple imputation or inverse probability weighting may be used.

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Table 1. Demographic and treatment characteristics by treatment era and life status of five-year survivors of childhood HL									
	1970-1979		1980-1989		1990-1999		Total	Alive	Dead
	N	%	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									
Survival after diagnosis (years)									
5-9									
10-14									
15-19									
20-24									
25-29									
30-34									
Treatment exposure									
Any radiation									
Yes									
No									
Total lymphoid irradiation									
Yes									
No									
Mantle radiation									
Yes									
No									
Para-aortic with and without spleen/splenic pedicle									
Yes									
No									
Inguinal/iliac/femoral radiation									
Yes									
No									
Any chemotherapy									
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									
Procarbazine									
Yes									
No									
Bleomycin									
Yes									
No									
Vinca alkaloid agents									
Yes									
No									
Etoposide									
Yes									
No									

Note: Depending upon quality of data, we may assess cumulative dose of bleomycin, procarbazine, etoposide, and other agents. Also, the combinations of therapy listed above are not exhaustive and will not all be included in the final table.

Table 2. 10-year cumulative incidence of mortality among five-year survivors of childhood Hodgkin lymphoma based on historical changes in treatment										
	All Cause			Recurrence/Progression of primary malignancy			Nonrecurrence, Non-external Cause			
	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	P*
Splenectomy										
Yes										
No										
Radiation										
Yes										
No										
Mantle (Gy)										
None										
1-10										
11-20										
21-30										
>30										
Inverted Y (Gy)										
None										
1-10										
11-20										
21-30										
>30										
TLI (Gy)										
None										
1-10										
11-20										
21-30										
>30										
Chemotherapy										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										
Alkylator (CPM equiv. in grams)										
≥20										
≥16 - <20										
≥12 - <16										
≥8 - <12										
≥4 - <8										
0 - <4										
None										
Multimodal therapy										
Mantle RT + MOPP										

Mantle RT + ABVD										
IFRT + COPP-ABV										
IFRT + other regimens										
MOPP alone										
ABVD alone										
COPP-ABV/other regimens alone										

Table 3. All-cause and cause-specific standard mortality ratios in five-year survivors of childhood HL by treatment era and treatment exposure															
	All Causes			Subsequent Malignancy			Cardiac Causes			Pulmonary Causes			Other nonrecurrent/non-external causes		
	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
All survivors															
Treatment era															
1970-1979															
1980-1989															
1990-1999															
Splenectomy															
Yes															
No															
Radiation															
Yes															
No															
TLI irradiation															
≥30															
20-29															
10-19															
1-9															
None															
Mantle radiation															
≥30															
20-29															
10-19															
1-9															
None															
Inverted Y radiation															
≥30															
20-29															
10-19															
1-9															
None															
Chemotherapy															

Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
Alkylator (CPM equiv. in grams)															
≥20															
≥16 - <20															
≥12 - <16															
≥8 - <12															
≥4 - <8															
0 - <4															
None															
Multimodal therapy															
Mantle RT + MOPP															
Mantle RT + ABVD															
IFRT + COPP-ABV															
IFRT + other regimens															
MOPP alone															
ABVD alone															
COPP-ABV/other regimens alone															

Table 4. Hazard (and 95% CI) of having a grade 3-5 chronic condition

Note: this table is intended as an example only. Other variable / therapy combinations will be assessed as above. Also, in the multivariate analysis, some of the variables are collinear or correlated and thus we will determine which variable to include in the final model.

	Univariate	**Multivariate**
Variables	**HR (95% CI)**	**HR (95% CI)**
All survivors		
Treatment era		
1970-1979	reference	reference
1980-1989		
1990-1999		
Splenectomy		
Yes		
No	reference	reference
Radiation		
Yes		
No		
TLI irradiation		
≥30		
20-29		
10-19		
1-9		
None	reference	reference
Mantle radiation		
≥30		
20-29		
10-19		
1-9		
None	reference	reference
Inverted Y radiation		
≥30		
20-29		
10-19		
1-9		
None	reference	reference
Chemotherapy		

Anthracycline (mg/m^2)		
≥600		
≥450-<600		
≥300-<450		
≥150-<300		
1-<150		
None		
Alkylator (CPM equiv. in grams)		
≥20		
≥16 - <20		
≥12 - <16		
≥8 - <12		
≥4 - <8		
0 - <4		
None	reference	reference
Multimodal therapy		
Mantle RT + MOPP	reference	reference
Mantle RT + ABVD		
IFRT + COPP-ABV		
IFRT + other regimens		
MOPP alone		
ABVD alone		
COPP-ABV/other regimens alone		

Figure 1 – Hypothetical example of a figure displaying cumulative all-cause and cause-specific mortality of childhood HL 5-year survivors by treatment era.

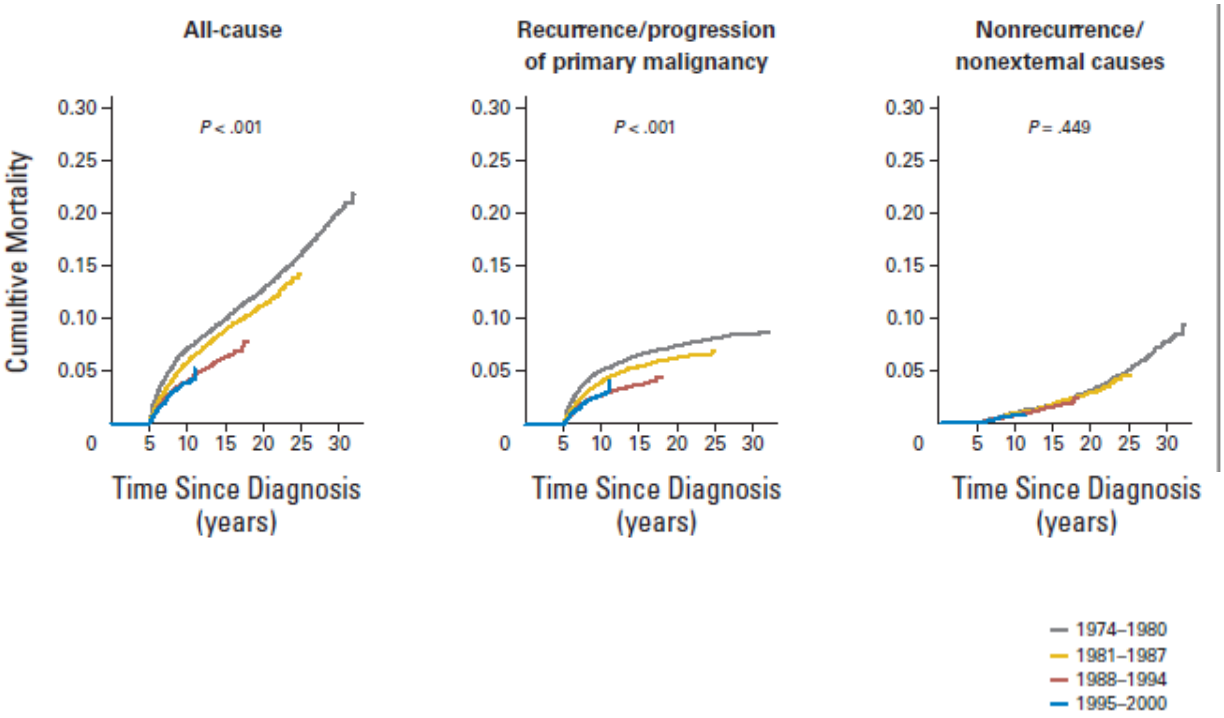
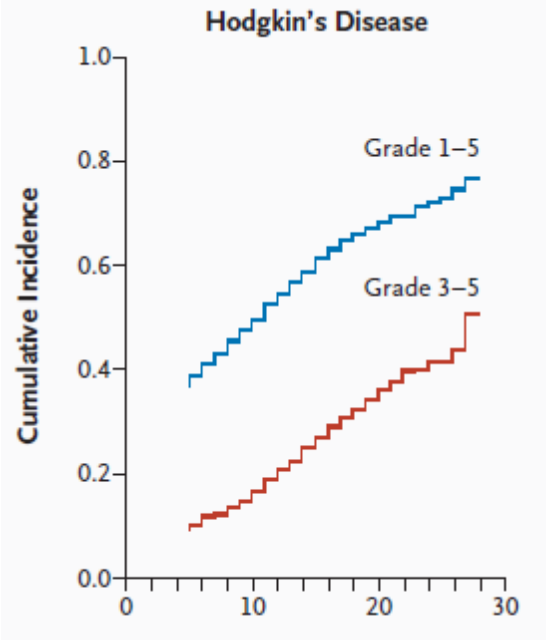
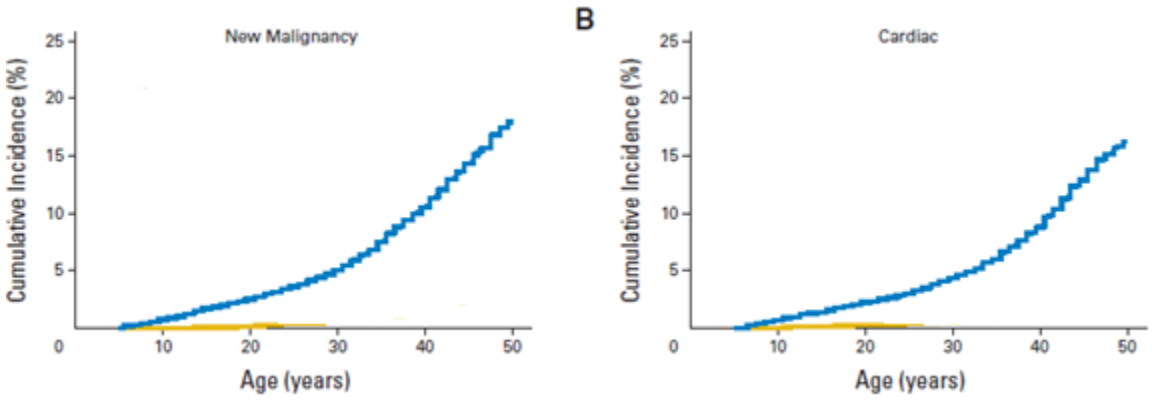


Figure 2 – Cumulative incidence of chronic health conditions among survivors of childhood Hodgkin lymphoma, according to the severity of the later condition.



Note, this is a snapshot of the original Figure 1 in Oeffinger KC, et al. N Engl J Med, 2006 for the Hodgkin lymphoma population. For this analysis, we will provide cumulative incidence curves for the entire HL cohort, by gender, by era of therapy, and by key therapeutic combinations. A similar panel (or separate figure) will show the cumulative incidence for contemporary therapy (Aim 3 – two risk groups)

Figure 3 – Cumulative incidence of specific chronic conditions among Hodgkin lymphoma survivors



Note, as above, these are two examples of specific outcomes that will be evaluated in a figure similar to this format. Panels may include second malignant neoplasms, cardiac, pulmonary, renal, musculoskeletal, and endocrine disease.