Childhood Cancer Survivor Study: Analysis concept proposal

Study title: Comparison of excess risk of late mortality and subsequent malignant neoplasms after Hodgkin lymphoma: a Childhood Cancer Survivor Study and Dutch Hodgkin lymphoma Survivor Study collaboration

Working groups and investigators:

Working groups: Primary: Epidemiology and Biostatistics
Secondary: Second Malignancy
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Background and Rationale:

Advances in treatment and supportive care have substantially improved the survival rate for most childhood cancers such that 85% will now become five-year survivors of their cancer [1-3]. Being a particularly radiosensitive malignancy, Hodgkin lymphoma (HL) diagnosed during childhood and adolescence has favorable cure rates with 5-year survival rates exceeding 95% in both the United States and the Netherlands [3, 4]. However, in contradistinction to this excellent five-year survival, it is well established that the rate of subsequent malignant neoplasms (SMNs) and cardiovascular disease experienced as late effects of cancer therapy by survivors of HL are elevated beyond that of the general population and beyond that experienced by survivors of many other primary pediatric malignancies, leading to an increased risk of late (≥5 years from diagnosis) mortality and excess deaths compared with the general population [5-7]. Given the growing and aging population of childhood HL survivors, it is imperative to further investigate the long-term sequelae in order to reduce excess deaths that occur beyond the commonly used benchmark of 5-year survival [7, 8].

The long-term morbidity and mortality associated with the treatment of childhood cancer have been investigated in multiple international cohorts with different demographics, treatment

exposures, follow-up times, and lifestyle habits [9]. However, few investigations have compared outcomes internationally across cohorts. Möller et al. (2004) observed a difference in late mortality between Nordic countries that decreased over time, possibly as a result of increased collaborative efforts resulting in the use of similar treatment protocols across these Nordic countries; however, treatment exposures were not available to directly evaluate associations [10]. Fidler-Benaoudia et al. (2021) compared the North American Childhood Cancer Survivor Study (CCSS) and the British Childhood Cancer Survivor Study (BCCSS) [11]. Their results identified that North American survivors (overall and also observed among all lymphoma survivors) initially experienced a lower 10-year cumulative mortality attributable to reduced risk of death from recurrence or progression of the primary cancer. However, they had a higher risk of mortality 40 years after diagnosis, primarily attributable to an increased risk of death due to SMNs and other health-related causes such as cardiopulmonary disease. The authors *hypothesized* that the observed differences may be partially explained by differences in treatment practices such that an increased intensity of primary cancer treatment would lead to the observed improved 10-year cumulative mortality at the cost of higher rates of long-term, treatment-related mortality. *Unfortunately, detailed treatment exposure information for the BCCSS cohort was not available, preventing direct investigation into whether differences in treatment exposures across the two cohorts were associated with these disparate outcomes*.

Treatment of HL has evolved through the years with the goal of maximizing cure and minimizing adverse events from therapy. Risk-adapted therapy was introduced in the 1990s and was associated with decreasing long-term morbidity in both CCSS and the Dutch cohort [11, 12]. However, in earlier years, treatment regimens were less standardized with each of the two cohorts following different guidelines (CCSS: largely treated in centers offering children oncology group studies; Dutch: European Organization for Research and Treatment of Cancer), particularly in cases of recurrence when treatment tended to be provider dependent [13]. Thus, whether differences in treatment exposure are associated with differential risk for late mortality between European and North American survivors remains largely unknown.

In addition to treatment, health outcomes and mortality in survivors are associated with a number of clinical and nonclinical factors. Social determinants of health, including sociodemographic and healthcare system factors, which vary within and between countries, may affect this association [14, 15]. As an example, while the Netherlands has a universal healthcare system, no single nationwide system of health insurance is available in the United States, with adult survivors of childhood cancer in the US reporting lower rates of health insurance and more difficulties in obtaining coverage compared with their siblings [16]. Similarly, behavioral risk factors, including obesity, physical activity, smoking, and alcohol use have an important impact on long-term childhood cancer survivorship [17-20]. Rates of people engaging in these behaviors differ in the general population of the United States and the Netherlands, with the US population having higher rates of alcohol dependence and obesity, and lower rates of physical activity and smoking compared with the Dutch general population [21-25]. Chronic cardiovascular conditions including hypertension, diabetes, and dyslipidemia, are also important and modifiable contributors to health outcomes as survivors age. These conditions vary in prevalence among the general population in North America and Europe [21, 22, 26-29].

Significance:

Building on the results from Fidler-Benaoudia et al. (2021), a collaborative analysis comparing CCSS and Dutch HL survivors will provide a better understanding of the reasons for international differences in the magnitude of long-term risks for survivors of HL. *Understanding how treatment exposures and cardiovascular risk factors (CVRF; including hypertension, diabetes, dyslipidemia,*

and smoking) differentially affect the long-term outcomes across childhood cancer survivor cohorts will contribute to strategies to mitigate late effects that are specific to the differences in geographical treatment preferences or cardiovascular risk factors. These findings could also have important implications for policy and practice changes in the United States and the Netherlands and advance the need and priority for global survivorship efforts to elucidate outcomes in underdeveloped countries.

Specific aims and hypotheses:

Aim 1.1: To compare the rates of death, the absolute excess risk (AER), and standardized mortality ratios (SMRs) for all-cause and cause-specific late (death ≥5 years from cancer diagnosis) mortality among adult survivors of HL diagnosed ages 15-<21 years, the age range comparable between CCSS and Dutch cohorts.

Hypothesis 1.1: Survivors treated in North America will experience higher standardized rates of death from health-related causes (which includes deaths attributable to late effects but excludes death due to primary cancer or external/accidental causes) compared to survivors of the Dutch cohort.

Aim 1.2: To identify treatment exposures and modifiable CVRF associated with the observed differences in late mortality between the CCSS and Dutch cohorts.

Hypothesis 1.2: We hypothesize that differences in treatment exposures (such as anthracycline dose and proportion of survivors that received radiation) and a greater burden of modifiable CVRF are associated with increased standardized rates of death (all-cause and cardiac-specific) in survivors from North America compared to the Dutch survivors.

Aim 2.1: To compare the rate, AER, and standardized incidence ratios (SIRs) of SMNs (overall and type-specific) among survivors of HL diagnosed between the age of 15-<21 years in the CCSS and the Dutch cohorts.

Hypothesis 2.1: Survivors treated in North America will have higher standardized incidence rates of SMNs compared to survivors of the Dutch cohort.

Aim 2.2: To identify treatment exposures associated with the observed differences in the incidence rate of developing SMNs between the CCSS and Dutch cohorts.

Hypothesis 2.2: We hypothesize that differences in treatment exposures drive the observed increase in the standardized incidence rate of SMNs in survivors from North America compared to the Dutch cohort.

Exploratory aim 1.1: We aim to compare the cumulative incidence and rate of myocardial infarction (MI) among survivors of HL diagnosed between the age of 15-<21 years in the CCSS and the Dutch cohorts. This is exploratory as we acknowledge limitations due to the lack of a population-based registry for MI in the US, which will prevent calculation of AERs and SIRs.

Hypothesis: Survivors treated in North America will have a higher incidence rate of MI compared to survivors of the Dutch cohort.

Exploratory aim 1.2: To identify treatment and modifiable cardiovascular risk factors associated with the observed differences in the rate of developing an MI between the CCSS and Dutch cohorts.

Hypothesis: We hypothesize that differences in treatment exposures and a greater burden of modifiable cardiovascular risk factors drive the difference observed in the rate of MI between the two cohorts.

Methods:

I. Study Population

North American Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional retrospective cohort that includes 5-year childhood cancer survivors diagnosed under the age of 21 from 1970-1999 in the United States or Canada (https://ccss·stjude·org/). The CCSS protocol was approved by the institutional review boards of each participating institution. A detailed description of the study design and methodology has been published [30, 31].

Dutch Late-Effects Hodgkin lymphoma Study (van Leeuwen, PI)

The Dutch Late-Effects Hodgkin lymphoma study is a multicenter cohort that includes 5-year HL survivors diagnosed between the ages of 15 and 51 from 1965-2000. Data were collected by review of medical records, linkage with nationwide registries, and questionnaires sent to general practitioners. Patient selection and data collection were previously described [13, 32]. We will be submitting an application to the Netherlands Cancer Institute IRB for secondary use of the de-identified data.

Study participants

For this study, participants fulfilling the following eligibility criteria will be included: (1) diagnosis of HL; (2) age at diagnosis between 15-<21 years (overlapping age range between cohorts to insure comparability); (3) diagnosis period 1970-1999. CCSS participants from Canadian institutes will be excluded from mortality analyses due to the absence of information on the specific cause of death. For mortality analysis, all eligible CCSS (n=2,116; mortality rate 32%) and an estimated 1100 survivors from the Dutch cohort will be included. For subsequent analyses, all eligible Dutch cohort survivors and the subset of CCSS participants (n=1,484) who completed a survey including the potentially modifiable risk factors of interest will be included. A descriptive comparison of eligible vs. ineligible participants will be provided to assess for potential bias.

II. Outcome Measures

Mortality

Date and cause of death for eligible CCSS participants were ascertained through linkage with the US National Death Index (NDI) through December 2017. For deaths predating the NDI (1975-1978), state death certificates will be used. For the Dutch cohort date of death was ascertained by linkage with the Dutch Central Office of Genealogy through January 2018. Cause of death was obtained from hospital medical records, general practitioners, and through cause-of-death registry at Statistics Netherlands and classified using the International Classification of Disease 10th revision [ICD-10] [4].

Cause-specific mortality will be classified using the ICD-10 include categorization as 1) recurrence/progression of primary cancer; 2) external cause (e.g., accidents, injuries, suicides); and 3) health-related cause (including deaths due to SMNs, cardiac, pulmonary, and other health-related causes, excludes deaths due to primary cancer). Causes of death will also be described by specific ICD-based causes of death.

Subsequent malignant neoplasm

Subsequent malignant neoplasm (SMN) will be defined as all subsequent invasive neoplasms, excluding non-melanoma skin cancer, and classified as International Classification of Disease for Oncology (ICD-O)[33].

For CCSS, SMNs were identified by self- or next-of-kin proxy report or death certificate and confirmed by pathology report, or if unavailable, death certificate and/or medical records. For the Dutch cohort, information on SMNs was collected from medical records, questionnaires administered to general practitioners, and through record linkage with the Netherlands Cancer Registry[34].

Myocardial infarction (Exploratory)
For both cohorts, we will consider MI CTCAE grade 3-5, self- or proxy-reported (CCSS) or reported by general practitioners/cardiologist (Dutch cohort) [35].

III. Explanatory variables

Demographic/Diagnosis related variables

- Sex
- Race and ethnic group (for CCSS cohort only)
- Age at HL diagnosis
- Treatment era by 5-year interval (1970-1974, 1975-1979, 1980-1984, 1985-1989, 1990-1994, 1995-1999)
- Follow-up duration.

Treatment-related variables

(To note that the final decision on treatment-related variables inclusion and categorization will depend on how similar the data collection was performed in the two cohorts studied.)

- Radiotherapy: exposure by body region (chest, pelvic, abdomen) + maximal dose. In the case that treatment significantly mediates the studied relationship, we will further explore exposure by radiation field, dose, and volume.
- Splenectomy (Y/N)
- Chemotherapy:
    i. Anthracyclines (Y/N) and cumulative dose received. We will explore associations using dose as a continuous variable (propose reporting per 100 mg/m^2) and by categories (None, 1-250 mg/m^2; ≥250 mg/m^2)
    ii. Alkylating agents (Y/N) and cumulative dose received. We will explore associations by:
        ➔ Specifics agents (Procarbazine, Cyclophosphamide, Nitrogen mustard, and Dacarbazine), as continuous variables with any categorizations to be determined by the distribution of doses within the cohorts.
        ➔ Alkylator dose reported as cyclophosphamide equivalent dose (CED) with conversions as follows: ifosfamide x 0.244, procarbazine x 0.857, BCNY x 15, CCNU x 16, melphalan x 40, Thio-TEPA x 50, nitrogen mustard x 100 and Busulfan x 8.823 [36]. We will explore this variable as a continuous variable by 1 g/m^2 and by categories (None, 1-4 g/m^2, 4-8 g/m^2, >8 g/m^2).
    iii. Bleomycin (Y/N) and cumulative dose received. We will explore associations as a continuous variable (propose reporting per 50 IU/m^2) and by categories (none, 1-119 IU/m^2; ≥120 IU/m^2)
    iv. Etoposide (Y/N)
    v. Platinum (Y/N)
    vi. Vinca alkaloid (Y/N)

For CCSS survivors who consented to participate, information on treatment was abstracted from medical records [31]. Imputation of treatment information for CCSS non-participants with missing treatment information will be employed, consistent with previous CCSS mortality publications [37]. For the Dutch cohort, information on treatment was collected from medical files. The dose of Procarbazine was estimated from the dose of alkylating agents received as they were almost

always administered together in combination. Missing number of cycles was estimated according to the average number of cycles given within the specific treatment period [38].

Modifiable cardiovascular risk factors

- Hypertension (Y/N)
- Diabetes (Y/N)
- Dyslipidemia (Y/N)
- Smoking (never/ever-[current; former]).

Data retrieved from medical records and by contacting general practitioners for the Dutch survivors; self-report for CCSS participants.

We acknowledge that obesity, physical activity, and alcohol use may further exacerbate the long-term health risks of survivors. Unfortunately, data on these behavioral factors were only collected on a subset of the Dutch cohort participating in nested case-control studies, precluding the ability to compare their effects on the outcomes of this study.

Healthcare systems may also affect health surveillance and outcomes. We may explore a sensitivity analysis of the effect of insurance on outcomes while considering all Dutch participants as insured through the country's universal health care system.

IV. Statistical analysis framework

Cohort follow-up will start 5 years from diagnosis and end at date of death, date of study exit or emigration (Dutch cohort only). Study exit date will be defined as the date of the most recent vital status linkage for each cohort (CCSS: December 2017; Dutch cohort: January 2018) for late mortality outcomes and date of last survey or data collection for SMNs and MI. Descriptive analysis summarizing and comparing characteristics of the CCSS and Dutch cohorts will be performed on the following measures: sex, age at diagnosis, year of diagnosis (5-year band), follow-up time, treatment, vital status, and CVRF (Table 1-3). Mortality analysis will follow the same framework used in Fidler-Benaoudia et al. (2021) and will include imputation or inverse-probability-weighting of eligible non-participants using factors available for all eligible survivors (HL diagnosis year, age at diagnosis, sex, country) [9].

Aim 1.1: *To compare the rate of death, the absolute excess risk (AER), and standardized mortality ratios (SMRs) for all-cause and cause-specific late-mortality among adult survivors of HL diagnosed ages 15-<21 years in the CCSS and Dutch cohorts.*

Vital status will be used to estimate:
a) Cumulative mortality with 95% confidence intervals (CI) for all-cause and cause-specific mortality for the entire CCSS eligible cohort and the Dutch cohort. Comparison stratified by follow-up time will be explored.
b) Rates of death (all-cause and cause-specific) per 1,000 person-years with 95% CI. Comparison stratified by follow-up time (Table 5), treatment exposure (Table 8), and CVRF will be explored (Table 9).
c) Standardized mortality ratio (SMR): defined as the ratio of observed over expected number of deaths, with 95% CI, for all-cause and cause-specific mortality (Table 6).
d) Absolute excess risk (AER): defined as observed minus expected number of deaths divided by person-years at risk multiplied by 10,000, with 95% CI for all-cause and cause-specific mortality (Table 7).
Relative measures of mortality will be standardized to, and expected counts of death will be calculated from, the respective general population mortality rates using strata defined jointly by 5-year age-, sex-, race- (for CCSS only), calendar-year, and country (CCSS: National Death

Index; Dutch: Statistics Netherlands). Comparison stratified by follow-up time (Tables 6-7), treatment exposure (Tables 10 & 12), and CVRF (Tables 11 & 13) will be explored.

Aim 1.2: *To identify treatment exposures and modifiable CVRF associated with the observed differences in late mortality between the CCSS and Dutch cohorts.*

To understand the difference in SMRs between the two cohorts, we will perform a mediation analysis using multivariable piecewise-exponential models to estimate the relative rates (RR) and 95% CI of death under the framework depicted in Figure 1. Specifically, to further describe the effect of treatment and CVRF, we will perform a mediation analysis of the cohort-mortality association with both treatment and CVRF as mediators analyzed in a sequential manner. This analysis will adjust for sex, age at diagnosis, and follow-up time (Table 14). We will explore adjusting for treatment through three models:
(1) by treatment era (1970-1979; 1980-1989; 1990-2000)
(2) by treatment group (chemotherapy without radiation, chemotherapy and low dose radiation, chemotherapy and high dose radiation, radiation only, salvage and extended)
(3) In case adjusting by treatment group significantly mediated the association studied, we will explore adjusting by specific treatment exposure.
We will also explore adjusting this analysis for insurance status.

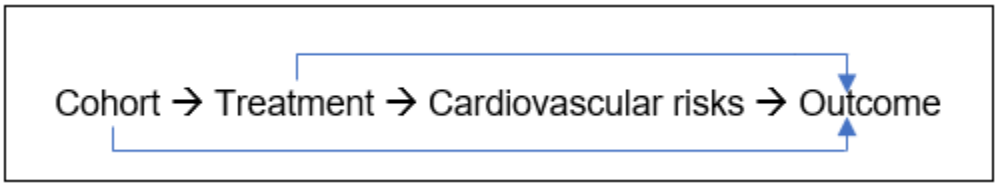

Figure 1 Mediation analysis framework

Aim 2.1: *To compare the rate, AER, and standardized incidence ratios (SIRs) of SMNs (overall and type-specific) among survivors of HL diagnosed between the age of 15-<21 years in the CCSS and the Dutch cohorts.*

We will estimate:
a) Cumulative incidence of SMNs with 95% CI for overall and type-specific (using ICD-O codes), for the CCSS participants and the Dutch cohort. Comparison stratified by follow-up time will be explored.
b) Incidence rate of SMNs (overall and type-specific) per 1,000 person-years with 95% CI. Comparison stratified by follow-up time (Table 16) and treatment exposure (Table 19) will be explored.
c) Standardized incidence ratio (SIR): defined as the ratio of observed over expected number of SMNs, with 95% CI, for overall and type-specific.
d) AER of SMNs (overall and type-specific).
Relative measures of SMNs will be standardized to, and expected counts of death will be calculated from, the respective general population rates of neoplasms using strata defined jointly by 5-year age-, sex-, race- (for CCSS only), calendar-year, and country. Comparison stratified by follow-up time (Tables 17-18) and treatment exposure (Tables 20-21) will be explored. Multiple SMNs within individual survivors will be accounted for in the models using generalized estimating equations.

Aim 2.2: *To identify treatment exposures associated with the observed differences in the incidence rate of developing SMNs between the CCSS and Dutch cohorts.*

To understand the difference in SIR of SMNs between the two cohorts, we will perform mediation analysis using multivariable piecewise-exponential models to estimate the relative rates (RR) and 95% CI of SMN. Specifically, we will perform a mediation analysis of the cohort-SMNs association with treatment as a mediator. This analysis will adjust for sex, age at diagnosis, follow-up time, and smoking (Table 22). We will explore adjusting for treatment through three models:

(1) by treatment era (1970-1979; 1980-1989; 1990-2000)
(2) by treatment group (chemotherapy without radiation, chemotherapy and low dose radiation, chemotherapy and high dose radiation, radiation only, salvage and extended)
(3) In case adjusting by treatment group significantly mediated the association studied, we will explore adjusting by specific treatment exposure.

Exploratory aim 1.1: *We aim to compare the cumulative incidence and rate of myocardial infarction (MI) among survivors of HL diagnosed between the age of 15-<21 years in the CCSS and the Dutch cohorts. This is exploratory as we acknowledge limitations due to the lack of a population-based registry for MI in the US, which will prevent calculation of AERs and SIRs.*

We will estimate:

a) Cumulative incidence of MIs with 95% CI for CCSS participants and the Dutch cohort.
b) Incidence rate by MIs per 1,000 person-years.

Comparison stratified by follow-up time (Table 23), treatment exposure (Table 24), and CVRF (Table 25) will be explored.

Exploratory aim 1.2: *To identify treatment and modifiable cardiovascular risk factors associated with the observed differences in the rate of developing an MI between the CCSS and Dutch cohorts.*

To understand the difference in the rate of MI between the two cohorts, we will perform a mediation analysis using multivariable piecewise exponential models to estimate the relative rates (RR) and 95% CI of MI under the framework depicted in Figure 1. Specifically, to further describe the effect of treatment and CVRF, we will perform a mediation analysis of the cohort-MI association with both treatment and CVRF as mediators analyzed in a sequential manner. This analysis will adjust for sex, age at diagnosis, and follow-up time (Table 26). We will explore adjusting for treatment through three models:
(1) by treatment era (1970-1979; 1980-1989; 1990-2000)
(2) by treatment group (chemotherapy without radiation, chemotherapy and low dose radiation, chemotherapy and high dose radiation, radiation only, salvage and extended)
(3) In case adjusting by treatment group significantly mediated the association studied, we will explore adjusting by specific treatment exposure.

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Tables and figures

Table 1. Descriptive characteristics of the study population by cohort.

Characteristics	CCSS eligible n (%)	CCSS participants n (%)	P-value	Dutch eligible n (%)	P-value
Overall	2,116	1,484		~1,100	
Sex					
Male					
Female					
Race/ethnicity				**N/A**	
Non-Hispanic white					
Non-Hispanic black					
Hispanic					
Other					
Unknown					
Age at diagnosis (years; mean, SD)					
Treatment period					
1970-1974					
1975-1979					
1980-1984					
1985-1989					
1990-1994					
1995-1999					
Time from diagnosis (years)					
Median (IQR)					
5-9					
10-14					
15-19					
20-24					
25-29					
30+					

Age at last follow-up (years)					
Median (IQR)					
20-24					
25-29					
30-34					
35-39					
40-44					
45+					
Vital status					
Alive					
Dead					
Survival after diagnosis (years)					
5-9					
10-19					
20-29					
30-39					
≥40					

Table 2. Treatment characteristics of 5-year survivors of childhood cancer.

	CCSS eligible n (%)	CCSS participants n (%)	Dutch eligible n (%)
HL treatment			
RT alone			
CT alone			
RT+CT			
RT field			
No RT			
Chest radiation			
None			
Median dose (IQR)			
Abdomen radiation			
None			

Median dose (IQR)			
Pelvis radiation			
None			
Median dose (IQR)			
Splenectomy			
Anthracyclines (mg/m^2)			
Any exposure			
Median dose (IQR)			
Procarbazine (g/m^2)			
Any exposure			
Median dose (IQR)			
Cyclophosphamide (g/m^2)			
Any exposure			
Median dose (IQR)			
Nitrogen mustard (mg/m^2)			
Any exposure			
Median dose (IQR)			
Dacarbazine (mg/m^2)			
Any exposure			
Median dose (IQR)			
Alkylating agents-CED (g/m^2)			
Any exposure			
Median dose (IQR)			
Bleomycin (IU/m^2)			
Any exposure			
Median dose (IQR)			
Etoposide			
Any exposure			
Platinum			
Any exposure			
Vinca alkaloid			
Any exposure			

Figure 1. Changes in HL treatment over 3 decades by cohort.

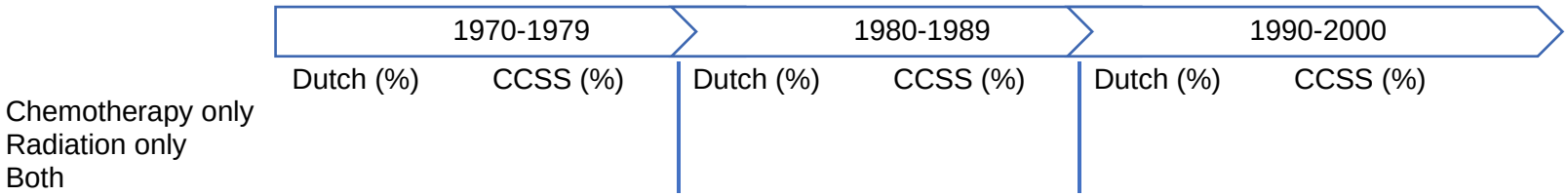

Table 3. Cardiovascular risk factors of participants

Lifestyle factor	CCSS participants n(%)	Dutch participants n (%)
Smoking		
Never		
Ever-current		
Ever-former		
Hypertension		
Diabetes		
Dyslipidemia		

Table 4. Frequency of death by cause in eligible CCSS and dutch participants.

Cause of death	ICD-10 Code	CCSS		Dutch	
		N	%	N	%
Total known					
Recurrence/progression of disease					
External causes					
Motor vehicle accident					
Other accidents					
Suicide					
Homicide					
Other injury					
Medical causes of death					

Subsequent neoplasm					
Lip, oral cavity, pharynx					
Digestive organs and peritoneum					
Respiratory and intrathoracic organs					
Bone, connective tissue, skin					
Breast					
Genitourinary organs					
Brain and nervous system					
Lymphatic and hematopoietic					
Other					
Endocrine, nutritional, metabolic disease					
Disease of blood and blood-forming organs					
Mental health disorders					
Diseases of the nervous system and sensory organs					
Diseases of the circulatory system					
Ischemic heart disease					
Cardiomyopathy					
Heart failure					
Cerebrovascular diseases					
Other cardiac					
Diseases of the respiratory system					
Pneumonia					
Pulmonary fibrosis					
Other pulmonary					
Diseases of digestives system					
Diseases of genitourinary system					
Infectious diseases					
Complications of the puerperium					
Diseases of musculoskeletal system and connective tissues					
Congenital anomalies					

Symptoms, signs, and ill-defined conditions					
Unknown cause of death					

Table 5. Mortality rates (death/1,000) by cause of death in all eligible CCSS and Dutch cohorts.

	All-cause		Recurrence/progression		External		Health-relates	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
All survivors								
Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								
30+								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
All survivors								
Time from diagnosis (years)								
5-9								

10-14								
15-19								
20-24								
25-29								
30+								

Table 6. Standardized mortality ratios (SMR) in eligible survivors.

	All-cause		Recurrence/progression		External		Health-relates	
	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch
All survivors								
Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								
30+								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch	SMR (95% CI)-CCSS	SMR (95% CI)-Dutch
All survivors								

Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								
30+								

Table 7. Absolute excess risk (AER) of death in eligible survivors.

	All-cause		Recurrence/progression		External		Health-relates	
	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95% CI)-CCSS	AER (95% CI)-Dutch
All survivors								
Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								
30+								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	AER (95%	AER (95%	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95%	AER (95% CI)-Dutch

	CI)-CCSS	CI)-Dutch					CI)-CCSS	
All survivors								
Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								
30+								

Table 8. Mortality rate by cause of death by treatment exposure

	All-cause		Recurrence/progression		External		Health-relates	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								
Chest radiation								
None								
< 15								
15-24.9								
25-34.9								
≥35								
Abdomen radiation								

Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								
Bleomycin, IU/m^2								
None								
1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								
Chest radiation								
None								
< 15								
15-24.9								
25-34.9								
≥35								
Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								

Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								
Bleomycin, IU/m^2								
None								
1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

Table 9. Mortality rate by CVRF

	All-cause		Recurrence/progression		External		Health-relates	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
Smoker								
Never								
Ever-former								

Ever-Current								
Hypertension								
Diabetes								
Dyslipidemia								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
Smoker								
Never								
Ever-former								
Ever-current								
Hypertension								
Diabetes								
Dyslipidemia								

Table 10. SMR by cause of death by treatment exposure

	All-cause		Recurrence/progression		External		Health-relates	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone								
CT alone								

RT+CT								
RT field								
No RT								
Chest radiation								
None								
< 15								
15-24.9								
25-34.9								
≥35								
Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								

(categories if possible)								
Bleomycin, IU/m^2								
None								
1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								

Chest radiation								
None								
< 15								
15-24.9								
25-34.9								
≥35								
Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								

Bleomycin, IU/m^2								
None								
1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

Table 11. SMR by cause of death by CVRF

	All-cause		Recurrence/progression		External		Health-relates	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
Smoker								
Never								
Ever-former								
Ever-current								
Hypertension								
Diabetes								

Dyslipidemia								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
Smoker								
Never								
Ever-former								
Ever-current								
Hypertension								
Diabetes								
Dyslipidemia								

Table 12. AER by cause of death by treatment exposure

	All-cause		Recurrence/progression		External		Health-relates	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								

Chest radiation								
None								
< 15								
15-24.9								
25-34.9								
≥35								
Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								

Bleomycin, IU/m^2								
None								
1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

	Health-related causes of death							
	SMN		Cardiac		Pulmonary		Other	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								
Chest radiation								
None								
< 15								
15-24.9								

25-34.9								
≥35								
Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								
Bleomycin, IU/m^2								
None								

1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

Table 13. AER by cause of death by CVRF

	All-cause		Recurrence/progression		External		Health-relates	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
Smoker								
Never								
Ever-former								
Ever-current								
Hypertension								
Diabetes								
Dyslipidemia								

	Health-related causes of death			
	SMN	Cardiac	Pulmonary	Other

	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
Smoker								
Never								
Ever-former								
Ever-current								
Hypertension								
Diabetes								
Dyslipidemia								

Table 14. Mediation analysis: cohort-mortality

Cohort	RR (95% CI)	p-value	% mediation
Dutch	1.0 (ref)		
CCSS adjusted for demographics			
CCSS adjusted for demographics + treatment			
CCSS adjusted for demographics+ CVRF			
CCSS adjusted for demographics+ CVRF+trearment			

Demographics= sex, age at diagnosis, and follow-up time.

Table 15: Overall and type-specific subsequent malignant neoplasms in the CCSS and Dutch cohort HL survivors

Overall and type-specific SMNs	ICD-O	CCSS		Dutch	
		N	%	N	%
All types					
Any solid cancer					
Lip, oral cavity, pharynx					
Lower respiratory system					
Lung or bronchus					
Mesothelioma					
GI tract					
Esophagus					
Stomach					
Colon					
Rectum or rectosigmoid junction					
Pancreas					
Thyroid gland					
Skin					
Melanoma					
Non-Melanoma					
Soft-tissue sarcoma					
Female breast					
Female genital organ					
Male genital organ					
Urinary tract					
Kidney					
Urinary bladder					
Blood, bone marrow, or lymphatic system					
Non-Hodgkin’s lymphoma					
Leukemia					
Other					

Table 16. Rates of SMN (per 1,000) overall and type-specific in participants CCSS and Dutch cohort.

	All-cause		Breast		Thyroid		Lung	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
All survivors								
Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								
30+								

Note: Final type-specific choice depends on the numbers in Table 15

Table 17. Standardized incidence ratios (SIR) of overall and type-specific SMNs by follow-up time

	All-cause		Breast		Thyroid		Lung	
	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch
All survivors								
Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								

30+								

Table 18. AER of SMNs by follow-up time

	All-cause		Breast		Thyroid		Lung	
	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95% CI)-CCSS	AER (95% CI)-Dutch	AER (95% CI)-CCSS	AER (95% CI)-Dutch
All survivors								
Time from diagnosis (years)								
5-9								
10-14								
15-19								
20-24								
25-29								
30+								

Table 19. SMN rate by treatment exposure

	All-cause		Breast		Thyroid		Lung	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								

Chest radiation								
None								
< 15								
15-24.9								
25-34.9								
≥35								
Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								

Bleomycin, IU/m^2								
None								
1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

Table 20. SIR of SMNs by treatment exposure

	All-cause		Breast		Thyroid		Lung	
	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								
Chest radiation								
None								
< 15								

15-24.9								
25-34.9								
≥35								
Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								
Bleomycin, IU/m^2								
None								

1-119								
≥120								
Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

Table 21. AER of SMNs by treatment exposure

	All-cause		Breast		Thyroid		Lung	
	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch	SIR (95% CI)-CCSS	SIR (95% CI)-Dutch
RT alone								
CT alone								
RT+CT								
RT field								
No RT								
Chest radiation								
None								
< 15								
15-24.9								
25-34.9								
≥35								

Abdomen radiation								
Pelvis radiation								
Splenectomy								
Anthracyclines, mg/m^2								
None								
1-250								
≥250								
Procarbazine, g/m^2								
None								
1-4.2								
4.3-8.4								
>8.4								
Alkylating agents, mg/m^2								
Any exposure								
(categories if possible)								
Bleomycin, IU/m^2								
None								
1-119								
≥120								

Etoposide (Any exposure)								
Platinum (any exposure)								
Vinca alkaloid (any exposure)								

Table 22. Mediation analysis: cohort- SMN

Cohort	SIR (95% CI)	p-value	% mediation
Dutch	1.0 (ref)		
CCSS adjusted for demographics			
CCSS adjusted for demographics + treatment			
CCSS adjusted for demographics+ smoking+trearment			

Table 23. Rates of MI by follow-up time

	MI	
	Rate (95% CI)- CCSS	Rate (95% CI)- Dutch
All survivors		

Time from diagnosis (years)		
5-9		
10-14		
15-19		
20-24		
25-29		
30+		

Table 24. Rate of MI by treatment exposure

	MI	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
RT alone		
CT alone		
RT+CT		
RT field		
No RT		
Chest radiation		
None		
< 15		
15-24.9		
25-34.9		
≥35		
Abdomen radiation		
Pelvis radiation		

Splenectomy		
Anthracyclines, mg/m^2		
None		
1-250		
≥250		
Procarbazine, g/m^2		
None		
1-4.2		
4.3-8.4		
>8.4		
Alkylating agents, mg/m^2		
Any exposure		
(categories if possible)		
Bleomycin, IU/m^2		
None		
1-119		
≥120		
Etoposide (Any exposure)		

Platinum (any exposure)		
Vinca alkaloid (any exposure)		

Table 25. Rate of MI by CVRF

	MI	
	Rate (95% CI)-CCSS	Rate (95% CI)-Dutch
Smoker		
Never		
Ever-former		
Ever-current		
Hypertension		
Diabetes		
Dyslipidemia		

Table 26. Mediation analysis: cohort-MI

Cohort	Hazard ratio (95% CI)	p-value	% mediation
Dutch	1.0 (ref)		
CCSS adjusted for demographics			

CCSS adjusted for demographics + treatment			
CCSS adjusted for demographics+ CVRF			
CCSS adjusted for demographics+ CVRF+trearment			