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Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study

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Key words: survivors, childhood cancer, Hodgkin lymphoma, second malignancies, cardiovascular disease, sex differences

For a complete list of Childhood Cancer Survivor Study (CCSS) participants, please see the supplemental appendix.

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ABSTRACT

The contribution of specific cancer therapies, co-morbid medical conditions, and host factors to mortality risk after pediatric Hodgkin lymphoma (HL) is unclear. We assessed leading morbidities, overall and cause-specific mortality, and mortality risks among 2742 survivors of HL in the Childhood Cancer Survivor Study, a multi-institutional retrospective cohort study of survivors diagnosed from 1970 to 1986. Excess absolute risk (EAR) for leading causes of death, and cumulative incidence and standardized incidence ratios of key medical morbidities were calculated. Cox regression models were utilized to estimate hazard ratios (HR) and 95% confidence intervals (CI) of risks for overall and cause-specific mortality. Substantial EAR of mortality per 10,000 person-years was identified: overall 95.5; death due to HL 38.3, second malignant neoplasms (SMN) 23.9, and cardiovascular disease 13.1. Risks for overall mortality included: radiation dose > 30 gray [supra-diaphragm: HR 3.8; 95%CI 1.1, 12.6; infra+supra-diaphragm: HR 7.8; 95%CI 2.4, 25.1]; exposure to anthracycline (HR 2.6; 95%CI 1.6, 4.3) or alkylating agents (HR 1.7; 95%CI 1.2, 2.5); non-breast SMN (HR 2.6; 95%CI 1.4, 5.1); or a serious cardiovascular condition (HR 4.4; 95%CI 2.7, 7.3). Excess mortality from second neoplasms and cardiovascular disease vary by sex, and persist over more than 20 years of follow-up in childhood HL survivors.

INTRODUCTION

Current 5-year survival rates for people treated for Hodgkin lymphoma (HL) in childhood exceed 90%.[1,2] Approximately 31,500 childhood HL survivors live in the United States, and this population increases annually.[3] Long-term HL survivors commonly experience treatment-related morbidity that impairs thyroid, pulmonary, gonadal, cerebrovascular and cardiovascular (CV) function.[4-13] In addition, their curative therapy has been linked to an excess risk of developing second malignant neoplasms (SMN).[14-21] These late treatment sequelae can negatively impact survivor's health and predispose to premature death.[22-25]

Despite extensive characterization of mortality in HL survivors, the literature contains some important limitations. Prior study populations have mixed survivors of adult and childhood HL.[25,26] Additionally, studies have included multiple childhood cancer diagnoses,[27] or reported on few mortality events,[10,23] and had median follow-up time less than 20 years from diagnosis. Finally, studies have lacked detailed cancer treatment data to establish risk models for mortality.[10,23,25,26] Specifically, neither the Childhood Cancer Survivor Study (CCSS) nor any other study of childhood HL survivors have evaluated the association between mortality, patient characteristics, treatment, and treatment mediated co-morbid medical conditions.[4,6,13,27,28]

Elucidation of factors influencing mortality risk is important to inform clinical care and future interventions aimed at preventing premature death in HL survivors. To address these gaps in knowledge, we sought to 1) delineate cause-specific mortality in a cohort of pediatric HL survivors; 2) characterize the incidence and latency of key morbidities underlying mortality in survivors of childhood HL; and 3) investigate predictors of overall and leading cause-specific mortality.

PATIENTS and METHODS

Characteristics of Study Participants

The CCSS is an ongoing multi-institutional study of individuals who survived > 5 years following treatment for childhood cancer. Subjects for this analysis met the following eligibility criteria: a) diagnosis of HL; b) diagnosis and initial treatment at one of 26 collaborating CCSS institutions; c) diagnosis date between January 1, 1970 and December 31, 1986; d) age younger than 21 years at diagnosis; and e) survival at least five years from diagnosis. A detailed description of the methodology and cohort characteristics has been reported previously.[29] The CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. Among the 2,742 eligible HL subjects, 1,927 (70.3%) enrolled survivors represent 13% of the CCSS respondent cohort. Figure 1 summarizes HL survivors eligible for mortality analysis, versus those enrolled in the cohort, and with available treatment data.

Data Sources and Definitions

The data sources for this CCSS analysis include: the U.S. National Death Index (NDI); self-report questionnaires administered to the survivors or parent proxy; and treatment data for the initial HL, abstracted by the survivor's treating institution.

Mortality was evaluated among non-Canadian HL subjects eligible for CCSS as described previously.[27] The vital status and cause of death of all subjects eligible for CCSS was ascertained as of December 31, 2002, linking to the NDI, and followed up with a death certificate request from the state where the death occurred.[27,30]

Eligible subjects (or a legal proxy for subjects who had died or were ≤18 years of age) who agreed to participate completed a baseline questionnaire at entry into the cohort. For traceable living subjects, follow-up questionnaires were collected at three subsequent times.

Copies of all questionnaires and the treatment abstraction form are available for review at http://ccss.stjude.org. Questionnaire items specific to this analysis included: demographic information; cardiovascular (CV), pulmonary or thyroid conditions diagnosed by a physician; cancer recurrence; and development of a benign neoplasm, second malignant neoplasm (SMN) or non-melanoma skin cancer (NMSC). For medical conditions, subjects were asked to provide an age at first occurrence of the condition. Self-report of all SMNs was collected at each questionnaire and validated by pathology review of the report as previously described.[19,21] Histology for invasive SMNs was coded and classified with the use of the International Classification Diseases for Oncology (ICD-O). Recurrences are captured by participant self-report and verified by review of medical records.[31]

Chronic condition data were collected and scored based on baseline questionnaire response. Scoring of severity of chronic conditions was based on the Common Terminology Criteria for Adverse Events (version 3) system developed through the National Cancer Institute (http://ctep.cancer.gov). Conditions are graded as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5) as previously described.[4] The current analysis utilized grade 3-5 CV conditions including: congestive heart failure requiring medication; myocardial infarction; angina or coronary heart disease on anti-angina medication, or requiring cardiac catheterization, angioplasty or coronary artery bypass graft surgery; heart transplantation; or cerebrovascular accident. Grade 3-5 pulmonary conditions included: emphysema on medication; pulmonary fibrosis on oxygen; pulmonary embolism and infarction.[4,32] Thyroid chronic conditions included: thyroid nodules, hypothyroidism, or hyperthyroidism.[6,33]

For HL participants who signed a medical record release, a detailed summary of cancer treatment was abstracted by CCSS trained staff at the treating institution as previously described.

[4,29] Cumulative anthracycline or alkylating agent chemotherapy exposure was expressed as a total score (0-3) based on the tertile of cumulative doses received, according to methods reported previously.[34] Radiation therapy (RT) records were submitted to CCSS by the treating institution, and centrally abstracted with calculation of absorbed dose coordinated through the Department of Radiation Physics, the University of Texas M.D. Anderson Cancer Center, Houston.[29] RT exposure was divided into five categories by treatment field in reference to the diaphragm (supra-diaphragmatic, versus infra- or infra- plus supra-diaphragmatic) and dose (< 30 Gy, or > 30 Gy).

Statistical Analyses

The primary outcomes for this analysis were overall and cause-specific mortality. Secondary outcomes included key chronic conditions, including SMNs. Descriptive statistics are presented by sex. To compare demographic and cancer treatment variables between genders, Pearson chi-square tests were performed.

Follow-up time was defined as the interval from entry into the CCSS cohort (5 years after original cancer diagnosis) to the date of death from any cause, or censored at date of NDI search (12-31-2002). Standardized mortality ratios (SMR) were calculated for overall and cause-specific death in U.S. residents in the HL cohort (Figure 1) and compared to the U.S. resident cohort. SMR was computed as the number of observed deaths divided by the expected number of deaths in an age, sex and calendar year matched general population, based on US mortality rates from the National Center for Health Statistics. A 95% confidence interval (CI) of each SMR was calculated based on Poisson probability models, and differences between groups were evaluated using likelihood ratio tests from these models.[35]

Because the SMR only reflects the relative increase in risk, excess adverse risk (EAR)s were also calculated to illustrate the absolute increase in risk for a young population that has low expected mortality rates. EAR per 10,000 person-years was determined by subtracting the expected number of events from the observed number, dividing the difference by total person-years of follow-up, and multiplying by 10,000. Cause of death was missing for 44 people; these were not included in cause-specific calculations. Estimated probabilities of overall survival were calculated by the method of Kaplan-Meier with associated 95% CI based on Greenwood's formula. Cumulative incidence and 95% CI were estimated for each cause-specific mortality, treating other causes of death as competing risks and conditioned on survival of 5, 10, 15 and 20 years since the original diagnosis.[36]

The remaining analyses utilize questionnaire and treatment data from the respondent HL cohort (Figure1). Cumulative incidence and 95% CI were estimated for each of the following events: first recurrence of HL, histologically confirmed SMN, NMSC, grade 3-5 CV condition, grade 3-5 pulmonary condition, thyroid chronic conditions. Death was treated as a competing risk event and participants were censored at date of last questionnaire at which the outcome was ascertained. Events dated prior to cohort entry were included as prevalent at 5 years from diagnosis. All SMNs and recurrences reported up to and including the follow-up 2005 Questionnaire were included in this analysis. Excess risk of SMN (exclusive of NMSC) was evaluated using standardized incidence ratio (SIR) and EAR. SIR was calculated in a similar manner to that described above for SMR, utilizing U.S. Surveillance Epidemiology and End Results (SEER) age, sex and race-specific rates to calculate the expected number of cases.[19,37] All multiple SMNs were counted in the numerator of SIRs. EAR was determined as described above for mortality.

Cox proportional hazards regression, with age as the time scale, was used to assess the effects of demographics, cancer treatment, and medical conditions of interest (recurrence, SMN, CV event, NMSC, thyroid disease, pulmonary condition) on overall or cause-specific mortality risk.[38] Regression diagnostics to assess the proportional hazards assumption for key variables (such as sex) were assessed and appeared valid. Initial regression models were constructed to screen treatment and co-morbidity explanatory variables of interest, testing each factor individually while controlling for age at diagnosis, race, sex, household income, and education, which were *a priori* included in all models. Risk factors significant at alpha=0.1 level in initial adjusted models were eligible for evaluation in the final multivariable model. The ultimate set of factors was determined from step down procedures, using p-value < 0.05 as inclusion criteria. Recurrence of HL, occurrence of a SMN and report of grade 3-5 cardiac condition (inclusive of cerebrovascular events), an NMSC, grade 3-5 pulmonary condition and thyroid chronic condition were each examined as time-dependent covariates for the all cause-mortality model. Of these, recurrence of HL, thyroid chronic condition and NMSC occurrence were also evaluated as time-dependent covariates for the SMN mortality model. Interactions between sex and treatment variable, between sex and co-morbidity variables, and between anthracycline exposure and RT field were also tested in all mortality and SMN-mortality models. An interaction was found between sex and SMN in the overall mortality model; hence the final Cox model was stratified on sex to evaluate separate sex-specific effects of SMN. Due to the smaller number of cardiac deaths, a more parsimonious model (including sex, household income, and anthracycline score) was fit for CV mortality and a log rank test of RT was performed. Hazard ratios (HR), 95% CI, and p-values are reported.

Data were analyzed with SAS version 9.0 (SAS Institute, Cary, NC) and Tibco-Spotfire® S+ version 8.0 (Tibco Software Inc.), using 2-tailed statistical tests at the alpha = 0.05 level.

RESULTS

Characteristics of Childhood HL Survivors

Figure 1 delineates the HL survivors included in: mortality analysis, those enrolled in CCSS, and those with treatment data used for models to predict mortality. Among all 2,633 US HL survivors eligible for the analysis, 57% were male and 58% were treated from 1970-1979 (Table1). Of the 1,927 HL survivors participating in CCSS, the median age at diagnosis was 14.0 years (range, 2.0-20.0 years). Most participants were white. The median follow-up for these participants is 23.8 years (range 16.0-33.0) and 16.1years (range 5.0- 31.5) from diagnosis for those alive and deceased, respectively. Participants treated in the early treatment era versus the later treatment era did not differ significantly by sex (p=0.30) or race/ethnicity (p=0.20), but differed by age at diagnosis (p=< 0.001).

Treatment records available for 1,675 HL participants show 6% received chemotherapy alone for their initial HL treatment, while the rest received RT alone (33%) or combined with chemotherapy (61%). Chemotherapy included anthracyclines in 24% and alkylating agents in 56% of participants.

Mortality

Among 2,633 U.S. members of the eligible cohort, the 500 observed deaths are due to: HL (N= 175; 35%); SMN (N= 116; 23%); benign neoplasms (N= 4, <1%); cerebrovascular and heart disease (CV disease) (N=70; 14%); non-malignant respiratory disease (N=22; 4%); external cause (N=33; 7%); other (N=40; 8%); and unknown causes (N= 44; 9%) (Table 2).

Overall survival at 30 years post diagnosis is 74.1% (95% CI 71.8, 76.6), and differs by sex (p=0.007, Cox regression model results not shown) (Figure 2a). The SMR differs by sex (p<0.001) and is 6.3 (95% CI: 5.6- 7.1) for males and 12.0 (95% CI: 10.4-13.8) for females. The EAR for overall death is 95.5 per 10,000 person-years (95% CI: 86.1-105.5). The EAR for the leading causes of death was 38.3 for HL, 23.9 for non-HL SMN, and 13.1 for cardiovascular disease (all per 10,000 person-years).

Estimates of cause-specific mortality and EAR for cause-specific mortality change when conditioned on time from initial diagnosis (Figure 2b; Table 2). Notably, the EAR of death from relapse decreases over the follow-up period, while the EAR from solid tumors, cerebrovascular disease and all heart disease increases over time.

Subsequent Neoplasms

Recurrent HL, SMN and non-invasive second neoplasms indicative of morbidity in 5-year HL survivors were delineated. The prevalence of recurrent HL was 8.1% (95% CI: 6.8-9.3) at cohort entry, with an increase to 11.9% (95% CI: 10.5-13.4) at 10 years and 15.0% (95% CI: 13.2-16.7) at 30 years from diagnosis (Figure 3a).

The incidence of invasive SMN surpasses the risk of relapse by 20 years from diagnosis (Figure 3a). There have been 277 invasive SMNs among 257 HL 5-year survivors (Table 3). The median time to first SMN is 18.7 years from diagnosis (range 5.0-33.5). The gender difference in 30-year cumulative incidence of any SMN of 10.9% (95% CI: 8.3-13.4) among males and 26.1% (95% CI 22.4-29.8) in females (log rank test, $p<0.001$) is driven by the incidence of invasive breast cancer (Figure 3b). Compared to the general US population, SIRs are highest for solid epithelial cancers: bone cancer 22.3(95% CI: 10.0-49.6), thyroid cancer 17.6 (95% CI: 13.0-24.0), breast cancer 17.0 (95% CI: 14.0-21.7) per 10,000 person-years, respectively (Table 3). Cumulative incidence of invasive breast SMN at 30 years post diagnosis is 18.3% (95% CI: 16.0-20.6), with no apparent plateau in incidence within the cohort at this time (Figure 3b). The median time to occurrence of invasive breast SMN is 21.0 years (range 6.7-33.5 years) from diagnosis.

Non-invasive neoplasms (NMSC; other benign neoplasms) also confer morbidity. Cumulative incidence of NMSC at 30 years post diagnosis is 16.7% (95% CI 14.5, 19.4) (Figure

3a). Eighty two additional non-invasive neoplasms were reported, including non-infiltrating intraductal carcinoma of the breast (n=41), other breast histologies (n= 12) non-invasive meningioma (n= 2), neurilemmoma (n=3), noninvasive female genitourinary cancer (n=8), and other histologically unspecified neoplasms (n=16).

Chronic Medical Conditions

At least one chronic condition (grade 1-4) was reported by 70% (1348/1927) of survivors by baseline questionnaire response. Serious chronic conditions (grade 3-4) were enumerated in 27% (516/1927). Of these, 34% (174/516) were present at cohort entry, and 63% (327/516) were incident events after 5 years from diagnosis. Multiple morbidities were reported by HL survivors, with 44% having > 2 and 28% reporting > 3 chronic health conditions. The 30-year cumulative incidence of grade 3-5 CV conditions reported by the cohort is 11.1% (95% CI 8.5, 13.8) (Figure 3c). There is no sex difference in incidence of reported CV conditions (log rank test, p=0.20). Specific CV conditions of concern among the 1,927 participants included: coronary artery disease requiring medication (2%, N=39); myocardial infarction (1.2%, N=24); congestive heart failure (1.5%, N=28); heart transplant for cardiomyopathy (0.1%, N=2); cerebrovascular accident (0.78%, N=15); and other (0.57%, N= 11).

The 30-year cumulative incidence of grade 3-5 pulmonary conditions or any thyroid conditions was 5.1% (95% CI: 3.3-6.9) and 51.1% (95% CI: 44.6-57.7), respectively (Figure 3c). Among these, 72% (38/53) of grade 3-5 pulmonary conditions and 52% (334/639) of thyroid conditions occurred after cohort entry.

Risks for Overall and Cause-Specific Mortality

Adjusting for demographics, and key medical conditions, overall mortality was independently associated with initial cancer treatment (Table 4). Infra-diaphragmatic and supra-diaphragmatic extended field RT together increased risk at any dose (< 30 Gy: HR 3.9 [95% CI: 1.1-13.8]; > 30 Gy: HR 7.8 [95% CI: 2.4-25.1]), as did supradiaphragmatic RT at > 30 Gy (HR 3.8 [95% CI: 1.1-12.6]). Overall mortality also was associated with any alkylating agent exposure (HR 1.7 [95% CI: 1.2-2.5]) and risk increased with increasing exposure to anthracycline chemotherapy (highest cumulative dose score, HR 4.4 [95% CI 1.9-10.1]). There were no interactions between sex and treatment variables.

In evaluating leading morbidities driving overall mortality risk, there was a statistically significant interaction of sex with the type of SMN. Separation of effects of SMN type showed overall mortality was not associated with female breast cancer, but rather was associated with other SMN in both males and females (Table 4). Finally, report of a grade 3-5 cardiac condition was also an independent risk factor for mortality (HR 4.4 [95% CI 2.7-7.3]). The occurrence of recurrent HL was evaluated in mortality models, and was neither significant nor was a confounder on treatment or key medical condition effect; hence recurrent HL was not included in final models.

A similar model for risk of death from SMN also showed independent associations of treatment with death (Table 5), including RT over 30 Gy (HR 7.4 [95% CI 1.8, 30.3]) to any site, alkylating agent exposure (HR 2.3 [95% CI 1.4, 3.9]), or any anthracycline dose (highest cumulative dose score, HR 6.6 [95% CI 2.6, 16.2]).

Males had a higher risk of cardiac-specific death (HR of 3.2; 95% CI 1.4, 7.7) compared to females (adjusted Cox regression model, data not shown). There was no significant effect of anthracycline or alkylating exposure on cardiac mortality. The RT effect was not estimable, as all cardiac deaths occurred in those who received > 30 Gy to any field. However, due to the small number of cardiac deaths, in a log rank test, RT was not significant (p= 0.81).

DISCUSSION

Despite excellent 5-year survival rates for HL treated in childhood, the overall EAR of death after 5 years is significantly elevated at 95.5 /10,000 PY in a cohort treated between 1970-1986. Underlying this excess are second malignant neoplasms (SMN) and cardiovascular (CV) disease, both of which are elevated above population norms. Consistent with previous studies, death in the first 10 years after diagnosis is largely attributable to HL. [10,23,25,26] With extended follow-up beyond 10 years, treatment complications, predominantly SMN and CV disease, emerge as leading causes of excess death, and exhibit novel gender relationships in this young cohort. Notably, despite the 17-fold elevated incidence of breast cancer in this cohort and with the current length of follow-up, women with breast cancer do not appear to have an excess risk of overall mortality. Longer follow-up will be important to know if this observation persists. Yet, non-breast SMNs in both men and women confers an excess independent risk for mortality after adjustment for treatment effects. Overall and SMN-specific mortality is associated with both RT and chemotherapy.

Importantly, 20 years after initial HL treatment, the excess death risk from CV disease rivals that from solid tumor SMN. The EAR for a CV mortality of 13.1 per 10,000 person-years is comparable to the estimate of 9.5 and 17.7 per 10,000 person-years in those treated at < 20 years age in the Dutch and Stanford cohorts, respectively,[25,39] and to the myocardial infarction-specific mortality of 12.6 per 10,000 PY in a British cohort of both pediatric and adult HL survivors.[9] We noted an elevated incidence of congestive heart failure, coronary artery disease and cerebrovascular events in the cohort. The rates of fatal SMN in our cohort differ by site/histology from previous literature. Breast cancer mortality is similar to that in the Dutch experience, but we found lower EAR of fatal respiratory or gastrointestinal SMN at > 20 years of follow-up.[25]

Our regression model, adjusted for attained age, indicates no effect of age at treatment on overall, SMN, or CV specific mortality within a cohort treated during childhood. This does not negate prior findings in cohorts of combined pediatric and adult HL that noted increased mortality risk from SMN or CV disease in patients treated at < 21 years of age compared to those older at diagnosis.[25,40] Following adjustment for key chronic medical conditions, initial cancer treatments (including RT exceeding 30 Gy, any anthracycline, or alkylating agent chemotherapy exposure) remain significant independent risks for overall and SMN-specific mortality. The lack of significance for anthracycline dose as a independent predictor of CV specific mortality in our cohort must be interpreted in the context of 94% of the CCSS cohort having received RT as initial therapy.[9] The effects of anthracycline and other chemotherapy (such as alkylating agents) will need to be distinguished from that of RT in childhood HL cohorts treated with contemporary approaches that minimize or avoid RT.

Sex affects multiple dimensions of health following childhood cancer therapy.[41] We show that male survivors of HL have a higher overall mortality compared to females, echoing previous single-institution and cohort studies with smaller event numbers among those treated in childhood.[23,25,39] This finding parallels mortality excess for males in the general population of North America, where CV events are the leading cause of death. While Ng *et al.* noted no sex effect in their multivariable model of survival among low stage HL patients, unadjusted for treatment or co-morbidities,[26] Dutch investigators reported similar findings to ours in a cohort of adult and childhood HL patients. They found male sex conferred a HR of 2.4 for CV-specific mortality, unadjusted for treatment factors.[25] Conversely, some studies among survivors who received anthracyclines find females to have an increased risk for cardiotoxicity compared to males.[41] Importantly, the reported incidence of grade 3-5 CV conditions in our cohort was not significantly higher in male survivors, yet their risk of mortality from CV disease was 3-fold that of their female counterparts. Possible explanations for our findings are that male survivors are twice as likely to receive no medical care.[42] An alternate explanation is that perception of CV risk or the symptom complex of CV events may differ between the sexes.

The steep rise in the cumulative incidence of serious CV conditions begins at 10 years after diagnosis, highlighting the temporal window for modifiable injury regardless of gender.[12,39] Hence, investigation for biomarkers of subclinical CV injury and related interventions to preserve CV health should target this critical period. This is germane to HL which often presents in adolescence and necessitates transition from pediatric oncology to community primary medical care providers who may not be familiar with cancer-related health risks.

Our EAR estimates for breast cancer are consistent with the well-described elevated risk of breast cancer and its association with RT in female HL survivors.[16-18,20,28,40] We now show that despite the high rates of non-invasive and invasive breast neoplasms, HL survivors with breast malignancies in the CCSS cohort have a comparable mortality risk to females with no history of SMN. Continued follow-up of this cohort will be important to evaluating this mortality effect over time. Although one could postulate that lower mortality is due to better surveillance and treatment options for breast cancer compared to the other second tumor types noted in the cohort, previous investigations have demonstrated suboptimal adherence to mammography screening recommendations in the CCSS cohort.[43] Alternately, an index invasive or non-invasive breast neoplasm may lead to better overall health surveillance for these women. Our data support the current practice guidelines for heightened breast cancer surveillance, and the potential benefit associated with early detection in female childhood cancer survivors treated with chest RT.[44-46] Although organ-targeted cancer screening programs (analogous to breast screening in women) may not be feasible in male survivors, regular health surveillance may allow increased awareness and modification of health behaviors to modify risk of RT associated malignancies.

The rates of NMSC and non-invasive breast neoplasms in HL survivors underscore the morbidity of these "low grade" entities, which often require multiple surgical procedures for surveillance and management.[47] While development of an NMSC within the RT field is a recognized risk, it portends increased tissue sensitivity to RT. Therefore, the decreased risk of overall mortality in cohort members who developed an NMSC was unexpected. Our finding could be explained by the fact that the occurrence of a NMSC serves as a gateway diagnosis for better overall health surveillance. Conversely, this population, who already has regular medical care, may be more likely to have an NMSC diagnosed. It is also possible that the mechanisms leading to RT-associated invasive or life threatening SMNs are independent from those for development of an NMSC.

While the CCSS cohort of 5-year survivors of HL is rich in treatment and co-morbidity data, results must be interpreted in light of limitations of its unique retrospective-prospective design. The current analysis utilized a mixture of well-validated variables (death, SMN, treatment, RT dose and field), and variables based on self-report, which have not been fully adjudicated (pulmonary, CV condition). In addition, multivariable models constructed on information from the 87% of the cohort with full available treatment data may reflect participants with more serious illness. However, the Nordic cohort comparable to the CCSS treatment era, with 94% follow-up of all survivors and outcomes verified by physician exam, reported chronic illness rates similar to that of the CCSS.[48] Lastly, risks derived primarily from rare events that occur late in follow-up may be inaccurate predictors of the outcome of more contemporary therapy.

Regardless, the CCSS remains the largest available cohort with the most extended follow-up, making it a rich resource for understanding childhood cancer survivors' long-term outcomes. The expanded CCSS cohort, currently being assembled will have the ability to evaluate HL survivors treated with contemporary chemotherapy only and combined modality approaches, as it encompasses children treated from 1987-1999. While it is anticipated that more targeted contemporary approaches (i.e. risk- and response-based chemotherapy, immunotherapy; anti-angiogenic agents, involved and targeted nodal RT) will minimize the incidence of SMN and CV disease in the next generation of survivors, decades of follow up will be required to document the magnitude of impact of such approaches delivered to the growing child. The strong association of RT with SMN, and CV morbidity and mortality substantiates current and future cooperative group strategies to minimize and obviate the use of RT while maintaining disease free survival in the treatment of childhood HL. However, given the radiosensitivity of HL, it remains that some proportion of patients will ultimately require RT to optimize disease control.

In summary, HL survivors continue to be at risk for treatment-related mortality for decades beyond their initial disease. SMN and CV conditions represent the leading morbidities underlying the risk of premature death; sex and specific treatment modality influence this risk. HL survivors and clinicians supervising their medical care should be vigilant for these gender- and therapy-specific health risks. Research is needed to evaluate if health surveillance programs that facilitate early diagnosis of cancer-related morbidity can optimize long-term health outcomes in childhood cancer survivors.

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AUTHOR CONTRIBUTIONS

Contribution: S.M.C. designed and performed analyses and wrote the manuscript; W.M.L., J.A.T. and P.G. performed and oversaw all analyses; A.M.G., A.C.M.; M.M.H contributed to interpretation of data; M.M.H, A.M.G. and L.L.R. edited the paper; M.S. performed radiation dosimetry analyses; P.G. prepared figures; A.C.M collected data; L.L.R. is the Principal Investigator of the CCSS project and designed and assembled the study.

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CONFLICT OF INTEREST

None of the authors have conflicts of interest to disclose relevant to this work.

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Table 1. Characteristics of 5-year survivors of childhood Hodgkin lymphoma (HL) in the CCSS

	HL Cohort N (%)[7]	Male N (%)[7]	Female N (%)	P-value[8]
All-Eligible CCSS Survivors[1]	n=2633	1507 (57)	1126 (43)	
Treatment Era				0.63
1970-1979	1546 (59)	879 (58)	667 (59)	
1980-1986	1087 (41)	628 (42)	459 (41)	
Age (years) at Diagnosis				<0.001
0-9	476 (18)	379 (25)	100 (90)	
10-14	884 (34)	490 (33)	394 (35)	
15-21	1273 (48)	641 (43)	632 (56)	
Participants[2]	n= 1927	n= 1049	n=878	
Treatment Era				0.30
1970-1979	1097 (57)	586 (56)	511 (58)	
1980-1986	830 (43)	463 (44)	367 (42)	
Age (years) at Diagnosis				<0.001
0-9	329 (17)	244 (23)	85 (10)	
10-14	663 (34)	350 (33)	313 (36)	
15-21	935 (49)	455 (43)	480 (55)	
Race/Ethnicity[3]				0.20
White, non Hispanic	1653 (86)	892 (85)	761 (87)	
Other	268 (14)	156 (15)	112 (13)	
Missing	6	1	5	
Household Income[3]				0.12
0-19,999	288 (17)	167 (18)	121 (15)	
20,000+	1423 (83)	753 (82)	670 (85)	
Missing	216	129	87	
Education [3]				<0.001
Through High school	503 (27)	323 (32)	180 (22)	
Post High School	1339 (73)	691 (68)	648 (78)	
Missing	85	35	50	
Treatment Group[4]				0.77
Radiation only	548 (33)	285 (32)	263 (33)	
Chemotherapy + radiation	1024 (61)	552 (62)	472 (60)	
Chemotherapy only	98 (6)	52 (6)	46 (6)	
Missing	257	160	97	
Splenectomy (yes)	1441 (76)	760 (74)	681 (79)	0.02
Chemotherapy Categories[5]				0.10
Radiation only	548 (33)	285 (32)	263 (34)	
Chemo, no anthracycline	689 (41)	355 (40)	334 (43)	
Chemo, including anthracycline	428 (26)	247 (28)	181 (23)	
Missing	262	162	100	
Anthracycline Score[5]				0.21
0	1237 (76)	640 (74)	597 (78)	
1	174 (11)	98 (11)	79 (10)	
2	166 (10)	99 (12)	67 (9)	
3	47 (3)	25 (3)	22 (3)	
Missing	303	187	116	

Alkylating Agents Score[5]				0.02
0	606 (44)	317 (43)	289 (44)	
1	118 (9)	58 (8)	60 (9)	
2	108 (8)	45 (6)	63 (10)	
3	555 (40)	316 (43)	239 (37)	
Missing	540	313	227	
RT field by Dose				<0.01
Chemotherapy only	98 (6)	52 (6)	46 (6)	
Supra-diaphragmatic, <30Gy	156 (10)	104 (12)	52 (7)	
Supra-diaphragmatic, >30Gy	406 (25)	201 (24)	205 (27)	
Infra-+ Supra-diaphragmatic, <30Gy[6]	147 (9)	82 (10)	65 (9)	
Infra-+ Supra-diaphragmatic, >30Gy[6]	790 (49)	409 (48)	381 (51)	
Missing	330	201	129	

[1] All U.S. survivors with HL, who met eligibility criteria for CCSS study and were included in national death index search (Figure 1).

[2] HL survivors who participated in the study [at baseline]

[3] Race, income and education not reported at baseline by some participants

[4] Summary data on treatment data for first diagnosis of HL available in 1675 respondents. Other specific treatment factors have varying numbers of missing values as indicated

[5] Chemotherapy categories are mutually exclusive. Exposure to anthracycline and alkylating agents was expressed as a total score based on the tertiles of various alkylating agents received, according to methods reported previously. A score of 0 indicates no exposure to the agent [34]

[6] Includes 49 subjects with field limited to infra-diaphragmatic sites only

[7] Percentages are calculated based on the number of non-missing values for each factor as the denominator

[8] Comparisons based on 2-tail Chi square for categorical variables

Table 2. Excess absolute risk (EAR) and standardized mortality ratio (SMR) for leading causes of death by time since diagnosis in 5-year survivors of Hodgkin lymphoma (n= 2633)

	Years Post Diagnosis								
	5-9 years		10-19 years		> 20 years		Over-All		
Cause of Death	**N**	**EAR /10000 PY (95%CI)**	**N**	**EAR /10000 PY (95%CI)**	**N**	**EAR/10000 PY (95%CI)**	**N**	**EAR/10000 PY (95%CI)**	**SMR/1000 PY (95% CI)**
All Deaths[1]	148	10.5 (8.7 - 12.6)	205	7.6 (6.8 - 9.0)	147	12.6 (10.3 - 15.1)	500	95.5 (86.1 - 105.5)	7.8 (7.2 - 8.5)
Hodgkin Lymphoma	89	69.6 (55.9 - 85.7)	64	28.1 (21.6 - 35.8)	22	21.7 (13.6 - 32.9)	175	38.3 (32.4 - 44.4)	779.2 (668.0 - 903.5)
All Other Malignant Neoplasms	21	15.8 (9.6 - 24.5)	48	19.9 (14.4 - 26.8)	47	43.1 (30.7 - 58.4)	116	23.9 (19.5 - 29.0)	16.8 (13.9 - 20.1)
Leukemia	7	5.3 (2.0 - 11.1)	4	1.6 (0.3 - 4.3)	0	.	11	2.3 (1.0 - 4.2)	15.5 (7.7 - 27.7)
All Other Hematopoietic	3	2.3 (0.4 - 6.8)	8	3.4 (1.4 - 6.8)	10	9.7 (4.5 - 18.0)	21	4.5 (2.7 - 6.9)	42.5 (26.3 - 64.97)
Solid Tumors	11	8.2 (3.9 - 15.0	36	14.9 (10.2 - 21.0)	37	33.6 (22.7 - 47.4)	84	17.2 (13.4 - 21.5)	14.9 (11.9 - 18.4)
Breast	1	0.8 (0.0 - 4.3)	9	3.8 (1.7 - 7.4)	11	10.3 (4.9 - 18.9)	21	4.4 (2.6 - 6.8)	22.3 (13.8 - 34.1)
Buccal Cavity/ Pharynx	0	.	2	0.9 (0.1 - 3.2)	0	.	2	0.4 (0.0 - 1.6)	17.9 (2.01 - 64.5)
Lung/Bronchus/Trachea	1	0.8 (0 - 4.3)	4	1.7 (0.4 - 4.4)	10	9.3 (4.2 - 17.6)	15	3.1 (1.7 - 5.2)	19.4 (10.9 - 32.0)
Digestive Organs/ Peritoneum	2	1.5 (0.1 - 5.6)	10	4.2 (1.9 - 7.9)	9	8.2 (3.4 - 16.2)	21	4.4 (2.6 - 6.8)	18.7 (11.6 - 28.6)
CNS	2	1.5 (0.1 - 5.6)	4	1.6 (0.4 - 4.4)	1	0.8 (-0.2 - 5.3)	7	1.4 (0.5 - 3.0)	12.0 (4.89 - 24.6)
Kidney	0	.	1	0.4 (0.0 - 2.4)	0	.	1	0.2 (0.0 - 1.2)	8.4 (0.1 - 46.8)
Melanoma	1	0.8 (0 - 4.3)	0	.	1	0.9 (-0.1 - 5.4)	2	0.4 (0.0 - 1.5)	6.3 (0.7 - 22.9)
Others	4	3.1 (0.8 - 7.9)	6	2.5 (0.8 - 5.6)	5	4.6 (1.3 - 11.2)	15	3.1 (1.7 - 5.3)	21.4 (12.0 - 35.3)
Benign Neoplasms	2	1.5 (0.1 - 5.6)	1	0.4 (0 - 2.4)	1	0.9 (0.0 - 5.5)	4	0.8 (0.2 - 2.2)	23.7 (6.4 - 60.6)
Cerebrovascular Disease		.	2	0.7 (0.1 - 3.0)	3	2.4 (0.1 - 8.1)	5	0.9 (0.1 - 2.3)	4.6 (1.5 - 10.7)
All Heart Disease	7	5.1 (1.8 - 10.9)	30	12.3 (8.0 - 18.0)	28	25.0 (15.7 - 37.3)	65	13.1 (9.9 - 17.0)	12.7 (9.8 - 16.2)
Ischemic Heart Disease	4	3.1 (0.8 - 7.9)	20	8.5 (5.1 - 13.3)	13	11.4 (5.4 - 20.5)	37	7.6 (5.2 - 10.7)	16.5 (11.6 - 22.8)
Chronic Endocardial, Other Myocardial Insufficiency	2	1.5 (0.2 - 5.6)	5	2.1 (0.7 - 5.1)	8	7.8 (3.3 - 15.5)	15	3.2 (1.8 - 5.4)	62.4 (34.9 - 102.92)
Non Malignant Respiratory Disease	5	3.7 (1.1 - 8.9)	12	5.0 (2.4 - 8.9)	5	4.4 (1.0 - 10.9)	22	4.5 (2.7 - 7.0)	14.2 (8.9 - 21.5)

[1.] Cause of death not detailed in the table include: external causes (n=33); other (n=40); unknown causes (n=44)

Table 3. Standardized incidence ratio (SIR) and excess absolute risk (EAR) of invasive second malignant neoplasm (SMN) among 5-year survivors of childhood Hodgkin lymphoma

Second Cancer Diagnosis	Observed	Expected	SIR	95% CI	EAR/10,000 PY	95%CI
All SMN	277	31.9	8.7	7.7 - 9.8	69.2	60.3 - 79.3
All SMN in Males	82	13.0	6.3	5.0 - 8.0	37.0	27.9 - 48.4
All SMN in Females	195	18.9	10.3	8.9 - 11.8	105.1	89.8 - 122.7
Hematopoietic						
Leukemia	13	1.0	12.7	7.4 - 21.9	3.4	1.8 - 6.0
Non Hodgkin Lymphoma	15	1.9	8.1	4.6 - 14.3	3.7	1.9 - 7.0
Solid Tumors						
Breast	109	6.4	17.0	14.0 - 21.7	29.0	23.5 - 35.7
Thyroid	42	2.4	17.6	13.0 - 24.0	11.2	8.1 - 15.5
Head and Neck	10	0.9	11.7	6.3 - 21.7	2.6	1.3 - 5.0
Lung/Bronchus	7	1.1	6.3	3.0 - 13.2	1.7	0.6 - 3.8
Small intestine/Colorectal	11	1.7	6.6	3.7 - 12.0	2.6	1.3 - 5.1
Bone Cancer	6	0.3	22.3	10.0 - 49.6	1.6	0.7 - 3.7
Soft Tissue Sarcomas	22	2.0	10.9	7.2 - 16.3	5.6	3.5 - 8.9
CNS	7	1.2	6.1	2.9 - 12.7	1.7	0.6 - 3.8
Kidney	5	0.7	7.2	3.0 - 17.3	1.2	0.4 - 3.2
Melanoma	13	3.3	4.0	2.3 - 6.8	2.8	1.2 - 5.4
Female genital	4	3.0	1.3	0.5 - 3.54	0.3	-0.4 - 2.2
Others	12	4.5	2.7	1.5 - 4.7	2.1	0.6 - 4.7

Table 4. Multivariable model of predictors of mortality from any cause in 5-year survivors of childhood Hodgkin lymphoma[1]

Variable	HR of Death from Any Cause	95% CI	P-value
Age at Diagnosis (years)			
<10 (reference)	1.0	.	.
10-14	0.9	0.5 - 1.6	0.68
15-21	1.1	0.6 - 2.0	0.82
Race			
Other (reference)	1.0	.	.
White not Hispanic	1.3	0.8 - 2.3	0.26
Household Income			
$20,000+ (reference)	1.0	.	.
$< 20,000	2.4	1.6 - 3.5	<0.01
Education			
Post High school (reference)	1.0	.	.
< High school	1.6	1.1 - 2.2	0.01
Radiation Field + Dose			
No Radiation (reference)	1.0	.	.
Supra-diaphragm, < 30Gy	0.9	0.2 - 4.6	0.92
Supra-diaphragm, >30Gy	3.8	1.1 - 12.6	0.03
Infra- or Infra+supra-diaphragm, <30Gy	3.9	1.1 - 13.9	0.04
Infra- or Infra+supra-diaphragm,>30Gy	7.8	2.4 - 25.1	<0.01
Chemotherapy			
Anthracycline Score			
0 (reference)	1.0	.	.
1	1.9	1.1 - 3.2	0.02
2	2.6	1.6 - 4.3	<0.01
3	4.4	1.9 - 10.1	<0.01
Alkylating Agent			
No (reference)	1.0	.	.
Yes	1.7	1.2 - 2.5	<0.01
Grade 3-5 Cardiac Condition			
No (reference)	1.0	.	.
Yes	4.4	2.7 - 7.3	<0.01
NMSC			
No (reference)	1.0	.	.
Yes	0.1	0.04-0.40	<0.01
SMN within Sex Stratum			
Female No SMN (Female Reference)	1.0	.	.
Female with Breast cancer	0.7	0.3 - 1.6	0.38
Female with Non Breast Ca SMN	2.6	1.4 - 5.1	<0.01
Male, No SMN (Male reference)	1.0	.	.
Male with SMN	2.3	1.4 - 3.9	<0.01

[1] Chronic cardiac conditions, non-melanoma skin cancer (NMSC) and second malignant neoplasms (SMN) are adjusted as time dependent covariates. There was no significant effect of pulmonary or thyroid condition or recurrent HL on overall mortality in univariate or multivariable modeling; hence they were not included in the final

model. SMN effects differed within sex stratum, with differences primarily due to lower risks due to breast cancer. Effects are presented within sex stratum to illustrate this phenomenon. There was no interaction between sex and chronic cardiac condition. Exposure to anthracycline was expressed as a total score based on the tertile of cumulative dose received; a score of '0' indicates no exposure to the agent. [34]

Table 5. **Multivariable model of predictors of mortality from a second malignant neoplasm (SMN) in 5-year survivors of childhood Hodgkin lymphoma**[1]

Variable	HR for fatal SMN	95% CI	p-value
Age at diagnosis (years)			
<10 (reference)	1.0	.	.
10-14	0.9	0.4 - 1.9	0.68
15-21	1.6	0.7 - 3.6	0.28
Sex			
Female (reference)	1.0	.	.
Male	1.3	0.9 - 2.0	0.15
Race			
Other (reference)	1.0	.	.
White not Hispanic	1.8	0.9 - 3.7	0.10
Household Income			
$20,000+ (reference)	1.0	.	.
$< 20,000	2.4	1.5 - 3.9	<0.01
Education			
Post High school (reference)	1.0	.	.
< High school	1.5	1.0 - 2.3	0.05
Radiation Dose			
No Radiation (reference)	1.0	.	.
< 30Gy	1.9	0.4 - 8.7	0.43
> 30Gy	7.4	1.8 - 30.3	<0.01
Chemotherapy Anthracycline Score			
0 (reference)	1.0	.	.
1	2.3	1.2 - 4.2	0.01
2	5.0	2.9 - 8.7	<0.01
3	6.6	2.6 - 16.2	<0.01
Alkylating Agent			
No (reference)	1.0	.	.
Yes	2.3	1.4 - 3.9	<0.01
NMSC			
No (reference)	1.0	.	.
Yes	0.3	0.1 - 1.0	0.04

[1] Neither recurrence of HL, nor the occurrence of a chronic cardiac condition was significant in models adjusted for treatment effects, and was therefore not included in final model. Occurrence of NMSC was included as a time-dependent covariate. Exposure to anthracycline was expressed as a total score based on the tertile of cumulative dose received; a score of 0 indicates no exposure to the agent. [34]

Figure 1. Consort diagram of 5-year Survivors of Childhood Hodgkin Lymphoma in the Childhood Cancer Survivor Study

Figure 2. Overall Survival in 5-year Survivors of Childhood Hodgkin Lymphoma by Sex A) Expected based on US population mortality. B) 30- year cumulative incidence of mortality varies when conditioned on time since diagnosis: 26.7% (95% CI 24.2, 29.2) in 5-year survivors, 22.3% (95% CI 19.7, 24.9) in 10-year survivors, and 14.9% (95% CI 12.3, 17.5) in 20-year survivors. Pattern of mortality differs with recurrent disease in the early years (C) and non-recurrence causes in later years (D)

Figure 3. Cumulative Incidence of Leading Chronic Medical Conditions in 5-year Survivors of Childhood Hodgkin Lymphoma: A) all neoplasms; B) invasive second malignant neoplasms (SMN) by sex (logrank for women with no breast SMN vs. male SMN; p =0.05); C) other non-neoplastic conditions.

Figure 1.

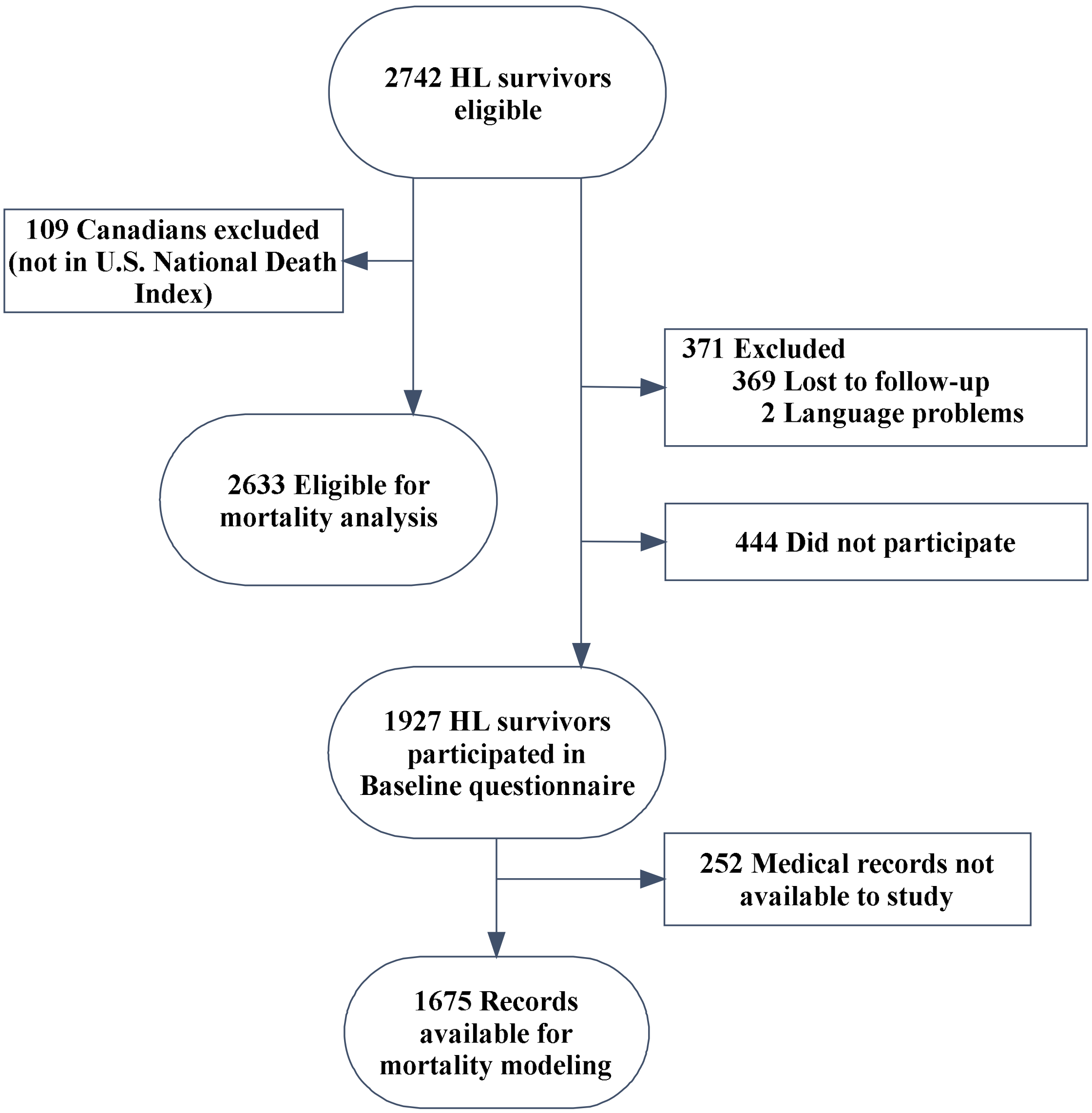
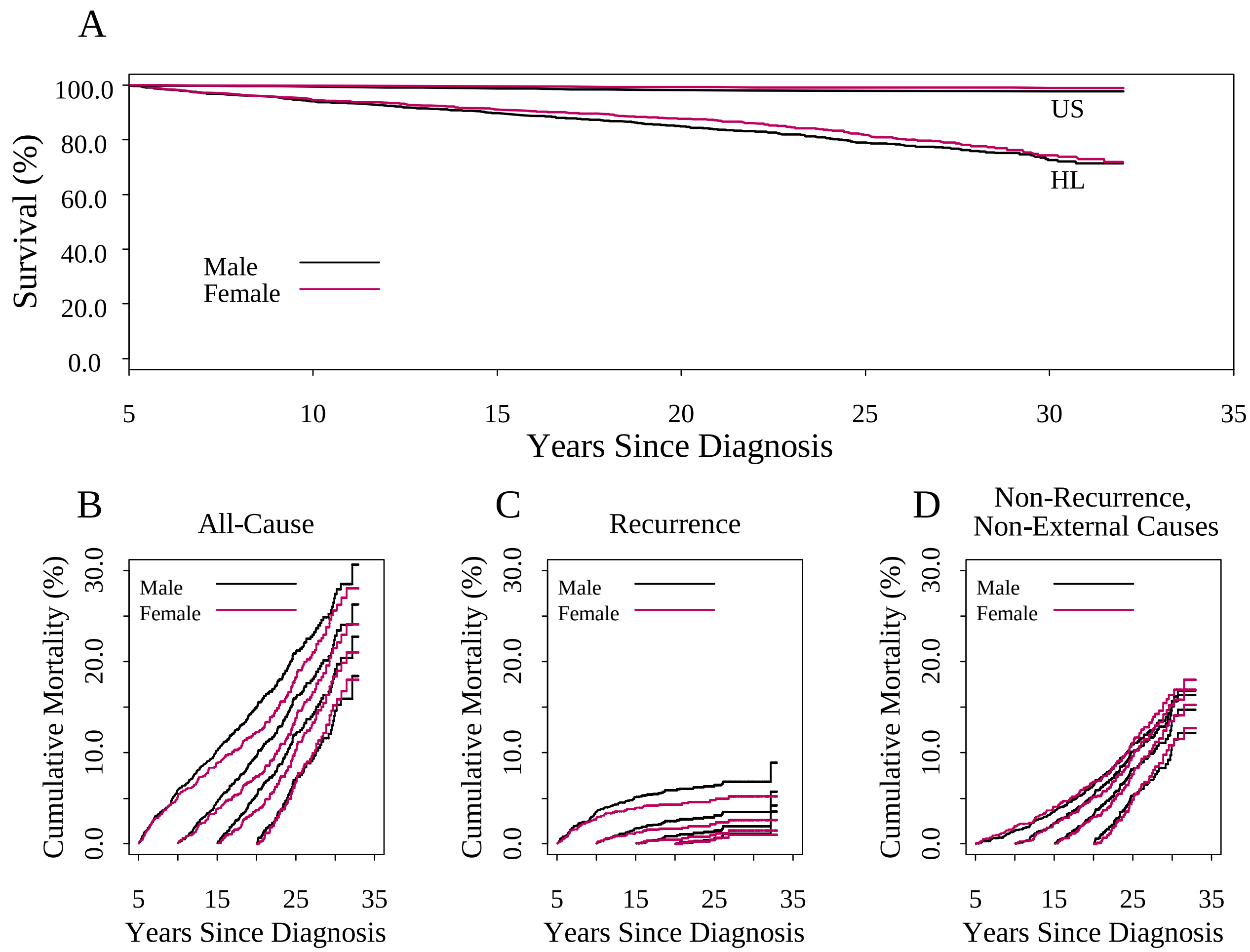
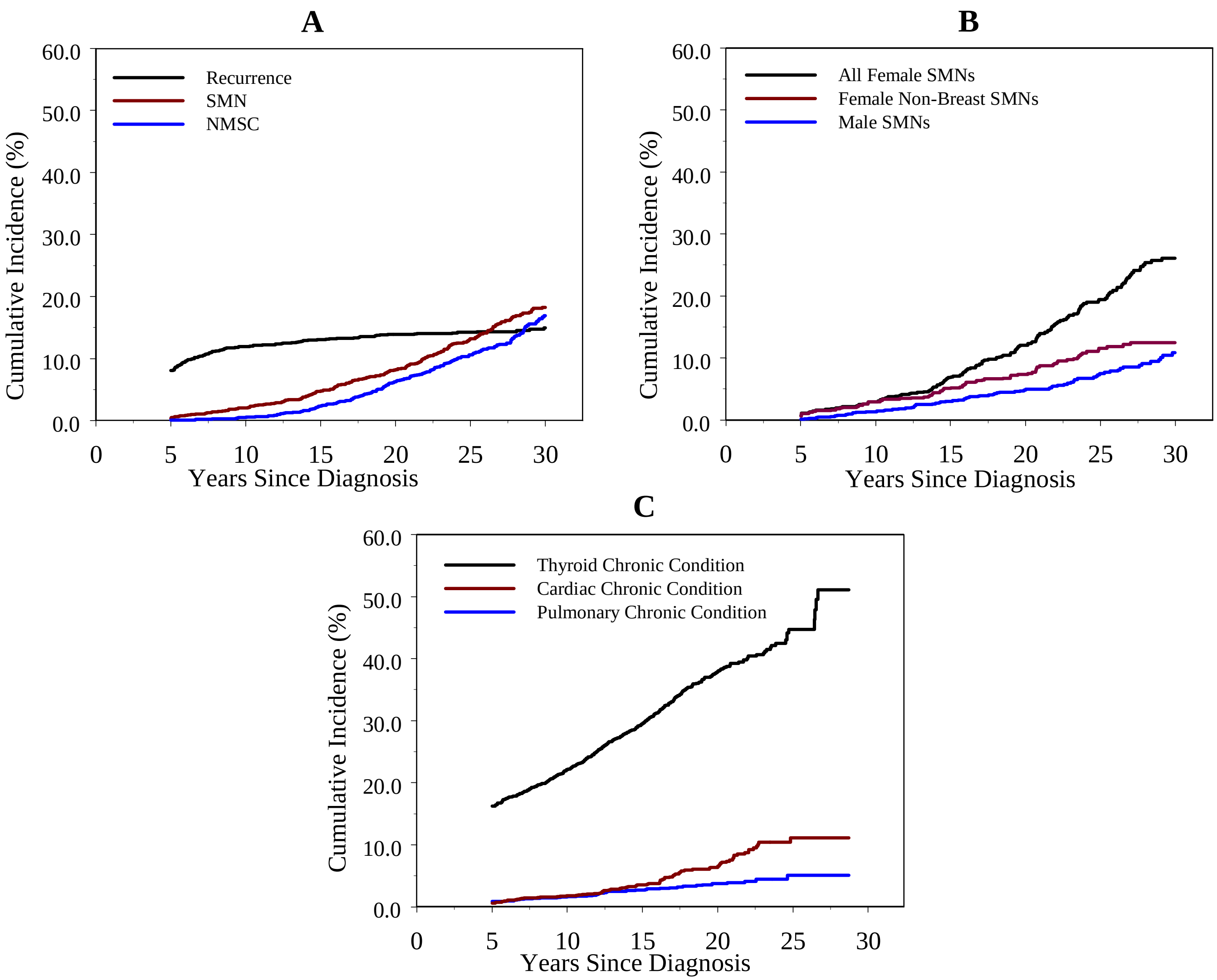

2742 HL survivors eligible
109 Canadians excluded (not in U.S. National Death Index)
371 Excluded
369 Lost to follow-up
2 Language problems
2633 Eligible for mortality analysis
444 Did not participate
1927 HL survivors participated in Baseline questionnaire
252 Medical records not available to study
1675 Records available for mortality modeling

Figure 2.



A
100.0
80.0
60.0
40.0
20.0
0.0
Survival (%)
US
HL
Male
Female
5
10
15
20
25
30
35
Years Since Diagnosis
B
All-Cause
Cumulative Mortality (%)
0.0
10.0
20.0
30.0
Male
Female
5
15
25
35
Years Since Diagnosis
C
Recurrence
Cumulative Mortality (%)
0.0
10.0
20.0
30.0
Male
Female
5
15
25
35
Years Since Diagnosis
D
Non-Recurrence,
Non-External Causes
Cumulative Mortality (%)
0.0
10.0
20.0
30.0
Male
Female
5
15
25
35
Years Since Diagnosis

Figure 3.


A
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Cumulative Incidence (%)
Recurrence
SMN
NMSC
0
5
10
15
20
25
30
Years Since Diagnosis
B
All Female SMNs
Female Non-Breast SMNs
Male SMNs
C
Thyroid Chronic Condition
Cardiac Chronic Condition
Pulmonary Chronic Condition