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Long-term cardiac morbidity in adolescent and young adult survivors of classical Hodgkin lymphoma: the British Columbia experience

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The data that support the findings of this study are available on request from the corresponding authors [KCM, KJS). The data are not publicly available due to restrictions, including data that could compromise the privacy of research participants. Access to data provided by the Data Stewards is subject to approval but can be requested for research projects through the Data Stewards or their designated service providers. The following data sets were used in this study: BC Chronic Disease Registry, BC Cancer Registry, BC Cancer Radiotherapy database. All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not reflect the opinions or policies of the Data Steward(s). This Data was provisioned under Information Sharing Plan (ISP) 16-118.

ABSTRACT

Adolescents and young adults (AYA) with classic Hodgkin lymphoma (cHL) have excellent survival outcomes, however the late effects of treatment, including cardiovascular disease (CVD), can impact long-term disease-free morbidity and mortality. Using population-level administrative data, we evaluated rates of CVD in 2-year AYA survivors of cHL, aged 16-39 years, treated with ABVD or equivalent chemotherapy, with or without radiotherapy (RT). With a median follow up of 17 years (range 2.3-29 years), risk of CVD was 2.9-fold higher relative to controls, with a 5.2-fold risk of heart failure (HF) and 2.4-fold risk of ischemic heart disease (IHD). Risk of HF was associated with anthracycline-containing chemotherapy regimens alone or with combined modality therapy; whereas higher IHD risk was identified only in those treated with RT. At 20 years after the most recent cHL diagnosis or relapse, the cumulative incidence (CI) of HF was 4.3% in cases vs 0.8% in controls; and for IHD was 8.3% in cases vs 2.8% in controls. Treatment after 2005 using a PET scan guided approach reduced the overall use of RT (56.0% < 2005 vs 14.9% $\geq$ 2005), and was associated with a lower 15-year CI of IHD (< 2005: 3.4% (95% CI 1.8-5.1%), > 2005: 0.7% (95% CI 0-1.7%) with the latter era comparable to controls; (1.6% (95% CI 1.3-1.9%)). cHL survivors had increased 20-year cumulative mortality above that of age-matched controls (5.0% vs 2.0%). These results can inform surveillance strategies, screening guidelines, and recommendations for risk factor modification for AYA cHL survivors.

INTRODUCTION

Classic Hodgkin lymphoma (cHL) is one of the most commonly diagnosed malignancies in adolescents and young adults (AYA) with a peak incidence between ages 15-34 years[1,2]. ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) was first introduced 50 years ago[3] and has been a standard therapy since that time. With five-year overall survival greater than 90%[4,5], there is a significant population of long-term survivors. The late effects of chemotherapy and radiation therapy (RT) used in cHL are well documented in children and adolescents with significant burden of chronic health disease compared to healthy peers[6].

The incidence of late morbidity secondary to treatment rises rapidly 10 years after diagnosis; by 20 years after diagnosis, the mortality due to secondary causes surpasses that due to relapse of cHL[6]. In all ages, cardiovascular disease (CVD) has been reported as the third leading cause of mortality in cHL survivors[7,8], with a 19-fold increased risk of CVD-related mortality in AYAs relative to controls[9]. Development of CVD secondary to exposure to anthracycline chemotherapy or mediastinal RT is one of the better characterized late effects in pediatric cohorts, with reports of 16-fold increased risk of heart failure (HF)[10] , 5-fold increased risk of ischemic heart disease (IHD) in those exposed to 15 Gy of cardiac radiation or more[11], and a 5-fold increase in cardiac-related mortality[12], compared to age-and sex-matched controls. In recognition of these risks, life-long surveillance for cardiac disease is recommended in survivors of childhood cancer, with risk-based guidelines to guide modality and frequency of screening[13].

The risk of CVD late effects for young adults is less well characterized. Existing studies support that young adults treated for cHL in earlier eras between 1965-1995 have an excess risk of CVD[14] and mortality[9] similar to pediatric patients, including a 25-year cumulative risk of congestive HF as high as 33%[14]. The latent onset of late effects makes it challenging to extrapolate the impact of historic treatments to modern clinical practice. Given the excellent survival outcomes in cHL, treatment protocols have evolved in the more modern era to reduce treatment intensity and particularly RT field and dose, without compromising outcomes[15–18], however how this has impacted overall CVD risk in this age group remains unknown.

In British Columbia (BC), province-wide treatment guideline modifications have included reduced exposure to RT through use of smaller volumes using involved-field RT (IFRT) as of 1997, and use of

involved-nodal RT (INRT) < or =5cm as of 2001[19]. In 2005, PET-guided elimination of RT was introduced for advanced stage cHL patients in a complete metabolic response on PET scan following 6 cycles of ABVD chemotherapy, including those with bulky disease[20] and similarly, for limited stage disease, RT is only given in those with a positive scan after 2 cycles[21]. We are only now reaching the early time points at which we can measure the impact of reduced-intensity strategies. Of concern, studies of other late effects, such as secondary cancers, over sequential treatment eras in young adult survivors of HL suggest that these risks may not have decreased as anticipated[22].

Using population-based administrative data, we evaluated the incidence of CVD (HF and IHD) in a cohort of AYA cHL survivors with a focus on young adults, treated using ABVD or equivalent chemotherapy with or without RT in BC.

METHODS

AYA patients with cHL newly diagnosed between 1992-2013 to ensure sufficient follow-up for late effects, and treated with curative intent ABVD or equivalent therapy (eg. COPP (or MOPP)/ABV) in BC, Canada were identified in the BC Cancer Lymphoid Cancer Database. AYA was defined as ages 16-39 years aligning with the National Cancer Institute definition[23] and commonly used standards from publications in cancer survivors[24,25]. Cases must have survived to an index date defined as 2 years from the most recent cHL event (primary diagnosis or, if applicable, most recent relapse) and have had a minimum follow-up of 1 year beyond their index date. Index date of 2 years from most recent cHL event was selected based on our prior study describing a very low rate of recurrence in patients event-free at 2 years[5]. Limited stage disease was defined as stage IA, IB (included as of January 1, 2000 and later) or IIA, non-bulky disease (bulk =any mass size ≥10cm); all others had advanced stage disease. Standard treatment guidelines for this era in BC have been published previously with ABVD or equivalent chemotherapy used during this time period[5]. A PET-adapted approach was introduced in 2005 for limited stage[21] and advanced stage[20] to limit use of RT. Cases were linked to the provincial BC Cancer Radiation Therapy database to identify the types and doses of radiation treatments received.

A control population was derived from the BC Ministry of Health (MOH) Chronic Disease Registry (CDR). The CDR is a population-based registry that captures the chronic disease status of every individual in BC annually. The CDR uses the following administrative health databases to identify chronic conditions (e.g. HF): physician claims through Medical Services Plan (MSP) Payment Information; medical drug claims

submitted to Pharmacare; and hospital admission records through Discharge Abstract Database. Chronic diseases are identified based on validated case algorithms adapted from the Canadian Chronic Disease Surveillance System[26] (Supplemental Table 1). The date of the first event that contributed to the case definition captured in the CDR was used as date of onset of the chronic disease outcome. A 10:1 individually-matched control population was identified from the CDR based on age, sex, and health authority region on the index date of the matched case. Controls were excluded if they had a pre-existing invasive malignancy or in-situ bladder malignancy (as determined by the BC Cancer Registry), HF, or IHD prior to the study window.

Both the cHL and control cohorts were further linked to the CDR to determine the cumulative incidence CVD over the study follow-up period. Individual outcomes were collected from the index date of the matched case until December 31, 2018 or until an individual was censored due to loss to follow-up or death. Individuals no longer registered with MSP for a period of ≥2 years during the study period; or with a gap of <2 years during the study period but who had less than 2 years of follow-up time after regaining MSP registration, were censored as lost to follow-up due to potential for misidentification of an outcome event.

Descriptive statistics were used to characterize the study population. The cumulative incidence approach and Gray's test were used to derive and compare estimates of CVD outcomes at 15 and 20 years of follow-up. A competing risk regression analysis was used to evaluate relative risk (RR) of primary outcomes in survivors relative to age-, sex- and region-matched controls. A multivariable analysis of RR was performed adjusting for patient factors (stage and age at diagnosis, and era of treatment < or ≥ 2005); treatment-related factors (anthracycline cumulative dose, mediastinal RT); and the presence of pre-existing cardiovascular risk conditions captured in the CDR (limited to hypertension (HTN), diabetes mellitus (DM), or chronic obstructive pulmonary disease (COPD) as a surrogate for smoking). To capture only pre-existing CV risk conditions, the date of onset of the CV risk condition must have been prior to that of the primary outcome in the CDR for both cases and controls. A sensitivity analysis was performed, including only patients who had received front line treatment and their matched controls. In all analyses, *p*-values less than 0.05 were considered statistically significant. This study was approved through the University of British Columbia/BC Cancer Research Ethics Board.

RESULTS

With a median follow-up time of 16.9 years (range 2.3-29) from the date of diagnosis of cHL or most recent relapse, 806 AYA 2-year survivors were eligible for analysis and compared against age-, sex- and region-matched controls (N=8058). 602 (75%) patients were 2-year survivors from the initial diagnosis and 204 (25%) were 2-year survivors from relapse, 47% of which received autologous stem cell transplantation. The proportion of limited and advanced stage disease at diagnosis was 34% and 66%, respectively, and 51% were male (Table 1). At the end of study period, the age of survivors ranged from 22 to 67 years (median 44 years). In total, 487 patients (39.6%) received mediastinal RT. Fifty-two percent received a cumulative anthracycline dose ≥300 mg/m^2. Of patients with limited stage disease, the median dose of anthracyclines was 100 mg/m^2 and 53.3% received mediastinal RT. For those with advanced stage disease, the median dose was 300 mg/m^2 and 32.7% received mediastinal RT.

At 20 years after most recent cHL event, survivors had an increased risk of CVD with a cumulative incidence of 10.1% (95% CI 7.2-12.9%) compared to 3.2% (95% CI 2.7-3.7%) among controls (Figure 1). Survivors had an increased incidence of all-cause mortality, with 20-year cumulative mortality of 5.0% (95% CI 3.2-7.0%) relative to 2.0% (95% CI 1.7-2.4%) in controls (Figure 1B).

The cumulative incidence of both HF and IHD was significantly higher at 20 years after most recent cHL event in all cases relative to controls (HF: 4.3% in cases vs 0.8% in controls; IHD: 8.3% in cases vs 2.8% in controls) (Figure 2, and Supplemental Table 2). Compared to chemotherapy alone, combined modality treatment had a numerically higher incidence of HF (20-year incidence 3.3% chemotherapy alone vs 5.4% combined modality; *p*-value = 0.28) and a trend was observed for incidence of IHD (20-year incidence 6.0% chemotherapy alone vs 10.7% combined modality; *p*-value = 0.08) at 20-years. The incidence of IHD was not significantly increased at 20 years in those treated with chemotherapy alone without RT, relative to controls. The incidence of HF among those with limited stage disease (2.0%) and advanced disease (5.2%) were both higher than among controls (0.8%). IHD incidence was similarly higher among those with limited (6.7%) and advanced disease (9.2%) compared to the control group (2.8%). Notably, in comparison to controls, a higher incidence of CVD was also seen in those diagnosed at age 30 years or older (18.5%, 95% CI 12.1-24.8%) compared to those aged less than 30 years (5.5%, 95% CI 2.9-8.0%) and controls (3.2%, 95% CI 2.7-3.7%) which was most notable for IHD (20 year incidence $\geq$ 30 y 15.3% (95% CI 9.3%-21.4%); < 30 y 4.4% (95% CI 2.1-6.7%) (Figure 3E) but also elevated for HF (7.4% (95% CI 3.1-11.6%) (Figure 3A). The incidence of HF was increased in both males and

females, relative to controls (5.9%, 95% CI 2.7-9.2%; 2.5%, 95% CI 0.6-4.5%; and 0.8%, 95% CI 0.5-1.0%; respectively) (Figure 3B). However, only males had a statistically significant increase in incidence of IHD relative to both females and controls (13.1%, 95% CI 8.6-17.6%; 2.9%, 95% CI 0.5-5.3%; and 2.8%, 95% CI 2.4-3.3%; respectively) (Figure 3E).

The incidence of IHD has decreased with a more modern therapy approach, a management era in which RT use was significantly reduced (56.0% < 2005 and 14.9% $\geq$ 2005). At a shorter time-point of follow-up available, the 15-year cumulative incidence of IHD was 0.7% (95% CI 0-1.7%) for those treated after 2005, and 3.4% (95% CI 1.8-5.1%) for those treated prior to 2005, compared with 1.6% (95% CI 1.3-1.9%) in controls (Figure 3F). However, the 15-year cumulative incidence of HF was the same before and after 2005 (1.7% for both), but overall elevated relative to 0.4% in controls (Figure 3C).

Overall, cHL survivors had a 2.9-fold increased risk of CVD relative to controls (Table 2). The relative risk was greatest for onset of HF (RR=5.18, 95% CI 3.09-8.66) compared with the RR estimated for IHD (RR=2.38, 95% CI: 1.73, 3.29) (Table 2). Independent co-variates that were associated with increased risk of HF included age >30 y at diagnosis and the presence of cardiac comorbidities. Treatment with chemotherapy alone or with combined therapy with RT was significantly associated with risk of HF compared to controls (Table 3). Of treatment related factors, significantly increased risk of IHD was identified only in patients who had mediastinal RT compared to patients treated with chemotherapy alone, with RR 3.6 (95% CI 2.44-5.31) vs 1.42 (95% CI 0.84-2.40), respectively. In multi-regression analysis, the era of treatment was no longer a significant risk factor when adjusted for RT exposure (Table 3). Cumulative dose of anthracycline did not significantly impact RR of IHD (Table 3). Other risk factors for IHD included male sex, age >30 at diagnosis, and diagnosis with diabetes and hypertension (Table 3).

In this population of patients that had survived more than 2 years from their most recent treatment, 204 had undergone treatment for relapsed disease and received additional therapy, including 47% that received autologous stem cell transplantation. However, the frequency of mediastinal RT was only slightly higher for those treated for relapsed disease (42.6%) relative to the frequency in those who received it as part of their primary therapy only (38.5%). Further, the exposure to anthracycline was unchanged. A sensitivity analysis was performed for survivors who had received front-line treatment only (Table 2, Supplemental Table 3). The results demonstrate a similar pattern of associated CV risks to

that observed in the full cohort of patients, with a small reduction in the strength of the association. The relative risk remained greatest for onset of HF (RR=4.09, 95% CI 2.14-7.84) compared with the RR estimated for IHD (RR=1.80, 95% CI: 1.16-2.78). Similar to findings from the full cohort analysis, factors male sex, age >30 at diagnosis, and diagnosis with diabetes and hypertension were all associated with an increased CV risk.

DISCUSSION

Adolescents and young adults with cHL have excellent disease-specific long-term survival outcomes but their therapy may be associated with late treatment-related morbidity and mortality. Given the young population at risk, the impact of treatment decades later remains a significant concern. Using population-level administrative data, we demonstrate that AYA survivors of cHL have an excess risk of late onset cardiac disease, with 5.2-fold increased risk of HF and 2.4-fold increased risk IHD relative to matched population controls, contributing to the increase in overall mortality in long-term survivors of cHL.

Cardiotoxicity is a well-recognized late effect of therapy for pediatric cancers[13,27,28]. Extensive data from pediatric cohorts demonstrate an excess risk of dose-dependent anthracycline-related cardiomyopathy, with a synergistic impact of combined modality therapy[13]. Mediastinal RT confers additional risk of IHD and valvular disease. The Childhood Cancer Survivor Study, a large multi-institutional study of self-reported outcomes between 5-year survivors and siblings, reported that the rate of grade 3-5 CVD in pediatric HL survivors at 30 years is 11.1%[6], with a hazard ratio of 6.8 for HF and 12.2 for myocardial infarction, relative to siblings[11]. The pediatric DAL-HD trial consortium reported a 25-year incidence of 14% for all cardiac disease and reported a dose-dependent relationship between the dose of RT used and rates of CVD[29]. Female sex and younger age at treatment are commonly reported independent risk factors for HF in the pediatric age cohort[13,30], whereas male sex is reported as a risk factor for IHD, also observed in our study[30].

Compared to the pediatric age group, there is far less data regarding the risk of CVD in AYA survivors with a history of cHL, especially those treated as young adults. We demonstrate that age $\geq$30 years at diagnosis is associated with higher risk of CV disease highlighting that age-specific outcomes are essential to ensure appropriate guidelines are in place. Van Nimwegen et al previously reported

outcomes of 2524 AYA 5-year survivors aged ≤50 years treated during 1965-1995[31]. In this cohort, 81% had received mediastinal RT, and of those, 30% had also received anthracycline-based chemotherapy. They found 6.8-fold increased standardized incidence ratio (SIR) of HF and 3.2-fold increased SIR of coronary heart disease. Both mediastinal radiation and exposure to anthracyclines were associated with an increased risk of CVD[31], with a dose-response and synergistic impact demonstrated for risk of HF; both mean left ventricle dose of RT, and escalating dose of anthracyclines[32]. At 40 years after cHL, the cumulative incidence (CI) of CVD was 49.5%, and in those treated with mediastinal RT, the 40-year incidence was 54.6% compared to 24.7% in those treated with chemotherapy alone[31]. The 25-year CI of HF in those treated with anthracyclines and RT >21 Gy was 32.9%; and was 13.3% for those treated with RT alone[32]. Interestingly, they identified a significant increase in SIR for those treated at a younger age, in contrast to our results. Maraldo et al evaluated cardiac outcomes in 6039 patients treated on sequential LYSA HL clinical trials (all ages, median age 29 years), treated between 1964 and 2009[33]. Only mean heart dose of RT and cumulative dose of anthracyclines had a statistically significant effect on risk of CVD. The 25-year cumulative incidence of IHD and HF were 6.0% and 7.1%, respectively. Aleman et al[7] reported on survivors of HL, 95% of whom were treated with RT. The 25-year CI of HF was 6.8% for those treated with RT alone; and 7.9% if combined modality with anthracycline-based chemotherapy. 30-year CI of myocardial infarction was 12.9% for those treated with mediastinal RT.

These prior studies primarily reflect treatment eras when there was a high rate of RT use and wider RT fields such as mantle and extended-field RT. Given the evolution of treatment, our study provides important data on the impact of modern therapy approaches on the rate of CVD with the use of reduced volumes and dose of RT as well a PET-guided approach to reduce RT use since July 2005. The rate of mediastinal RT use in our cohort was only 40% overall, considerably lower than the range of 80-95% reported in other studies of CV outcomes in HL survivors[7,31,34]. Further, from 2005 onwards, RT use dropped from 56% to 15% following a treatment policy change recommending integration of a PET scan to guide RT in both advanced and limited stage cHL[20,21]. For patients treated with a risk-adapted approach after 2005, we found a reduced incidence of IHD, which was similar to the incidence in population controls. In multi-regression analysis, the era of treatment was no longer a significant risk factor when adjusted for RT exposure, suggesting that the change in radiation use was an important factor in reducing the risk of IHD. Although longer follow-up is needed, these data suggest that reduction of RT in the management of HL has impacted CVD risk. Similar trends have been documented

in pediatric populations, with a trend of reduced rates of both IHD and HF in more recent clinical trials with decreased radiation exposure and with the use of cardio-protectants such as dexrazoxane[30].

Evaluation of late effects of therapy is challenged by the long latency, and because patients are discharged from follow-up well before the onset of late effects. The use of population-level administrative data enabled us to capture clinically significant CVD in a cHL survivor cohort that had been discharged from oncologic follow-up, and for whom the association with previous cancer therapy might not have been recognized. However, our study was limited to the data available in the chronic disease registry and dependent on surrogate standardized case definitions derived for disease surveillance purposes to identify endpoints rather than clinical diagnostic measures. Data regarding other forms of cardiac disease such as valvular disease, and additional cardiac risk factors, such as family history, obesity and dyslipidemia, were not available, and COPD was used as a surrogate for smoking. Furthermore, given the young age of survivors of cHL, young patients are often very mobile, moving out of province for personal, educational, or occupational opportunities. Our analysis can only follow patients using provincial health data for the duration of their follow-up within their time living in BC and those that emigrate from the region are thus lost to follow-up.

Despite these limitations, similar to prior studies, we found an increased risk of CVD starting 10 years after completion of treatment, long after patients have typically been discharged from follow-up care. The risk was particularly striking in males and those $\geq$ 30 years. Our data support the need for informed risk counseling at the time of discharge from oncological care and clear communication to primary care practitioners regarding the potential long-term risks. Patients require counseling regarding their risk of late effects, including written treatment summaries and detailed guides for surveillance and for secondary prevention strategies through management of modifiable risk factors[35]. For risk of CVD, this would include lifestyle counseling and monitoring for hypertension, diabetes and smoking, which we confirmed are independent risk factors for onset of cardiac disease in survivors of cHL. Given that follow-up is transferred to primary care providers, it is essential that this is communicated to both patient and practitioner. A recent comparison of US survivorship guidelines in lymphoma suggests a wide variation in screening approaches when comparing pediatric and adult recommendations as well as across guidelines[35]. Pediatric guidelines recommend lifelong surveillance with 2-D echocardiogram for early identification of asymptomatic heart disease dose to prevent or delay disease progression, with screening every 2-5 years based on risk stratification by anthracycline dose and/or mediastinal RT

exposure[13]. No guidelines have been published for AYA and adult survivors, with only expert opinion advocating for surveillance[36]. Our data would also support extension of echocardiogram surveillance beyond the pediatric age group. Trials are underway in pediatric cancer survivors to evaluate if cardiac remodeling with agents such as carvedilol may reverse or delay progression and symptomatic disease[37].

The landscape of treatment of cHL is rapidly changing with the integration of novel therapies into upfront treatment. Brentuximab vedotin (BV)-AVD demonstrated improved PFS and OS compared to ABVD in stage 3/4 cHL[38] and more recently, nivolumab with AVD demonstrated superior PFS compared to BV-AVD[39]. These therapies have improved the cure rates of front-line therapy, reducing the need for RT in subsequent salvage therapy, which likely will further impact CV risk. However, anthracycline exposure will remain, and patients with advanced stage disease will continue to receive at least a cumulative doxorubicin dose of 300 mg/m2. Further, immune checkpoint inhibitors have recently been associated with an increased risk of CVD by worsening atherosclerosis, further highlighting the need for long term data on CVD with newer therapies[40]. Regardless, our data further support the need for refined surveillance strategies, screening guidelines, recommendations for risk factor modification, and counseling for AYA cHL survivors.

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Table 1: Classical Hodgkin lymphoma case cohort characteristics at diagnosis and treatment history

	N	%
Total	**806**	
Period of Diagnosis		
Prior to July 1, 2005	484	60.0
After July 1, 2005	322	40.0
Sex		
Male	408	50.6
Female	398	49.4
Age at Diagnosis of HL		
16-29 y	527	65.4
≥ 30 y	279	34.6
Diagnosis		
Nodular Sclerosing	675	83.7
Mixed Cellularity	55	6.8
Lymphocyte Rich	9	1.1
Lymphocyte Deficient	4	0.5
Not Otherwise Specified	63	7.8
Ann Arbor Stage		
I	54	6.7
II	496	61.5
III	156	19.4
IV	99	12.3
Not available	1	0.1
B Symptoms		
Yes	330	40.9
No	476	59.1
Bulk ≥10 cm		
Yes	244	30.3
No	555	68.9
Not available	7	0.9
Stage Group		
Limited	272	33.7
Advanced	532	66.0
Not available	1	0.1
IPS Score Group (Advanced Stage Group only)		
Low (0-3)	371	89.0
High (4-7)	46	11.0
Cumulative Anthracycline Dose (Front-line therapy)		
1-299 mg/m2	366	45.4
300 mg/m2	361	44.8
>300 mg/m2	63	7.8
Mediastinal radiotherapy		
No	487	60.4
Yes	319	39.6

Radiotherapy Dose		
0 Gy	487	60.4
≤ 35 Gy	273	33.9
> 35 Gy	46	5.7
Mediastinal radiotherapy		
Limited Stage		
No	127	46.7
Yes	145	53.3
Advanced Stage		
No	358	67.3
Yes	174	32.7
Mediastinal Radiotherapy by Period of Diagnosis		
Prior to July 1, 2005		
No	213	44.0
Yes	271	56.0
As of July 1, 2005		
No	274	85.1
Yes	48	14.9
Relapse		
Yes	204	25.3
No	602	74.7
Mediastinal radiotherapy in patients treated for recurrence	117	57.4
No	87	42.6
Yes		
Autologous stem cell transplantation		
Yes	95	11.8
No	711	74.7
Diagnosis of Cardiac Comorbidity after cHL Treatment		
Diabetes Mellitus	69	8.4
Hypertension	103	12.7
COPD	19	2.2

Table 2: Relative risk of cardiovascular (CV) disease in adolescent and young adult survivors with classic Hodgkin lymphoma (cHL) versus age-, sex- and region-matched population controls

	RR of CV disease All Cases			**RR of CV disease** Patients treated with front-line therapy only		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
cHL survivors (Cases)	2.88	2.19 - 3.78	<0.001	2.26	1.57 - 3.23	<0.001
Male	1.65	1.30 - 2.08	<0.001	2.01	1.51 - 2.69	<0.001
Advanced stage	0.98	0.78 - 1.24	0.884	0.91	0.69 - 1.19	0.492
Era of Treatment After 2005	1.00	0.70 - 1.44	0.981	0.96	0.62 - 1.48	0.840
Age >30 y at diagnosis	2.27	1.79 - 2.86	<0.001	2.25	1.70 - 2.98	<0.001
Diabetes	2.33	1.63 - 3.34	<0.001	3.07	2.04 - 4.62	<0.001
Hypertension	2.82	2.11 - 3.78	<0.001	2.51	1.74 - 3.61	<0.001
COPD	1.87	1.04 - 3.36	0.037	1.70	0.81 - 3.57	0.164

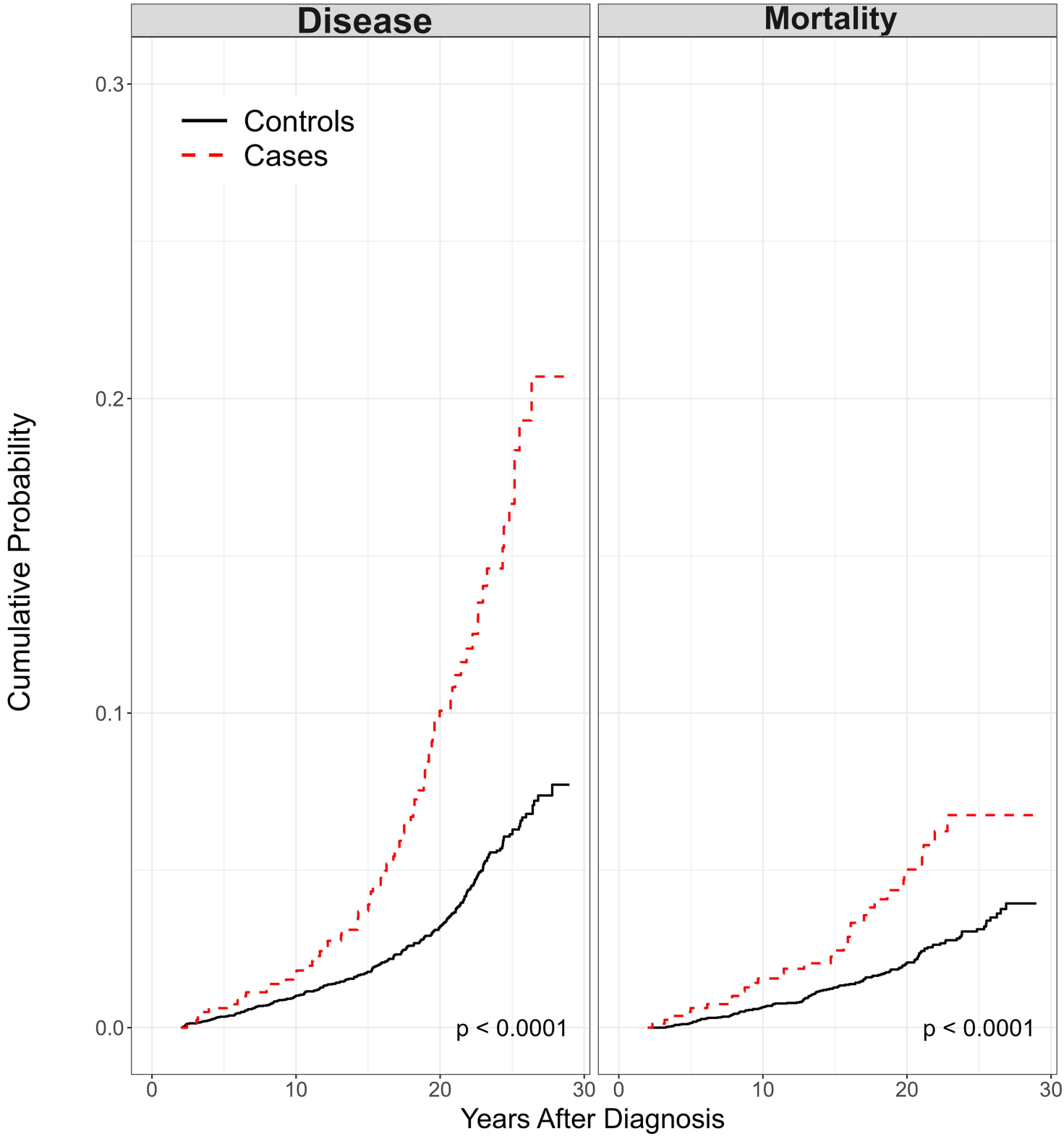
Table 3: Multi-regression analysis of relative risk of heart failure (HF) and ischemic heart disease (IHD) in adolescent and young adult survivors with classical Hodgkin lymphoma versus age-, sex- and region-matched population controls

	HF			IHD		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Radiation and anthracycline <300 mg/m2	5.77	2.49 - 13.40	<0.001	4.00	2.54 - 6.32	<0.001
Radiation and anthracycline ≥300 mg/m2	6.40	2.29 - 17.92	<0.001	2.84	1.39 - 5.80	0.004
No radiation and anthracycline <300 mg/m2	5.46	2.28 - 13.08	<0.001	1.23	0.53 - 2.87	0.624
No radiation and anthracycline ≥300 mg/m2	3.79	1.48 - 9.70	0.005	1.57	0.82 - 3.01	0.176
Male	1.11	0.70 - 1.78	0.649	1.91	1.46 - 2.50	<0.001
Advanced stage	1.19	0.70 - 2.02	0.514	1.01	0.77 - 1.33	0.916
Era of Treatment After January 1, 2005	1.00	0.48 - 2.07	0.996	1.13	0.75 - 1.70	0.544
Age >30 y at diagnosis	2.40	1.47 - 3.90	<0.001	2.31	1.77 - 3.00	<0.001
Diabetes	3.21	1.69 - 6.12	<0.001	2.07	1.35 - 3.16	<0.001
Hypertension	3.06	1.77 - 5.32	<0.001	2.87	2.05 - 4.03	<0.001
COPD	5.87	2.69 - 12.79	<0.001	0.80	0.29 - 2.22	0.663

Figure 1: Cumulative incidence of combined cardiovascular disease and cumulative mortality in 2-year survivors of classical Hodgkin lymphoma relative to age-, sex-, and region-matched controls

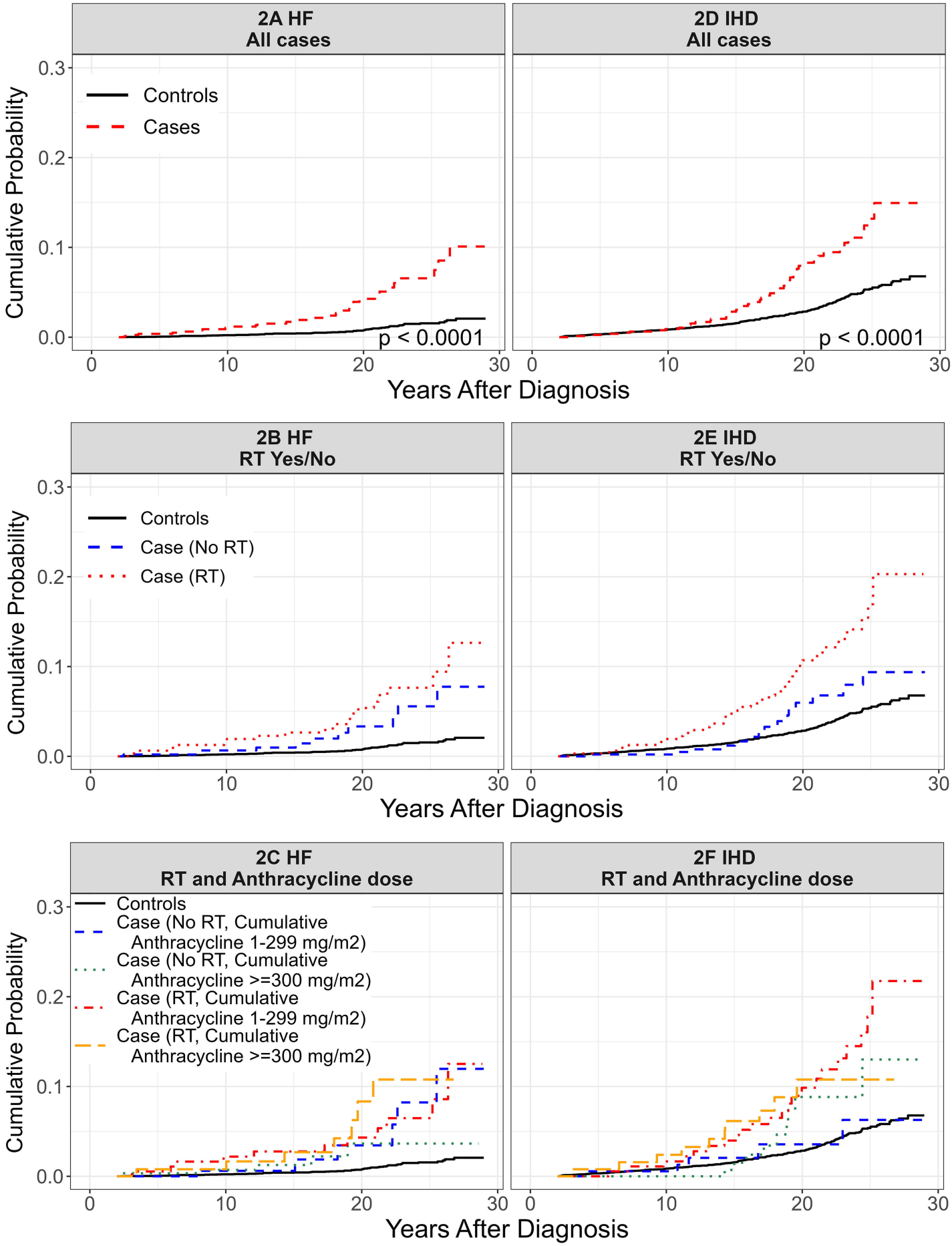
Figure 2: Cumulative incidence of heart failure (HF) and ischemic heart disease (IHD) in all cases and by treatment exposure in 2-year survivors of classical Hodgkin lymphoma (cHL) relative to age-, sex-, and region-matched controls

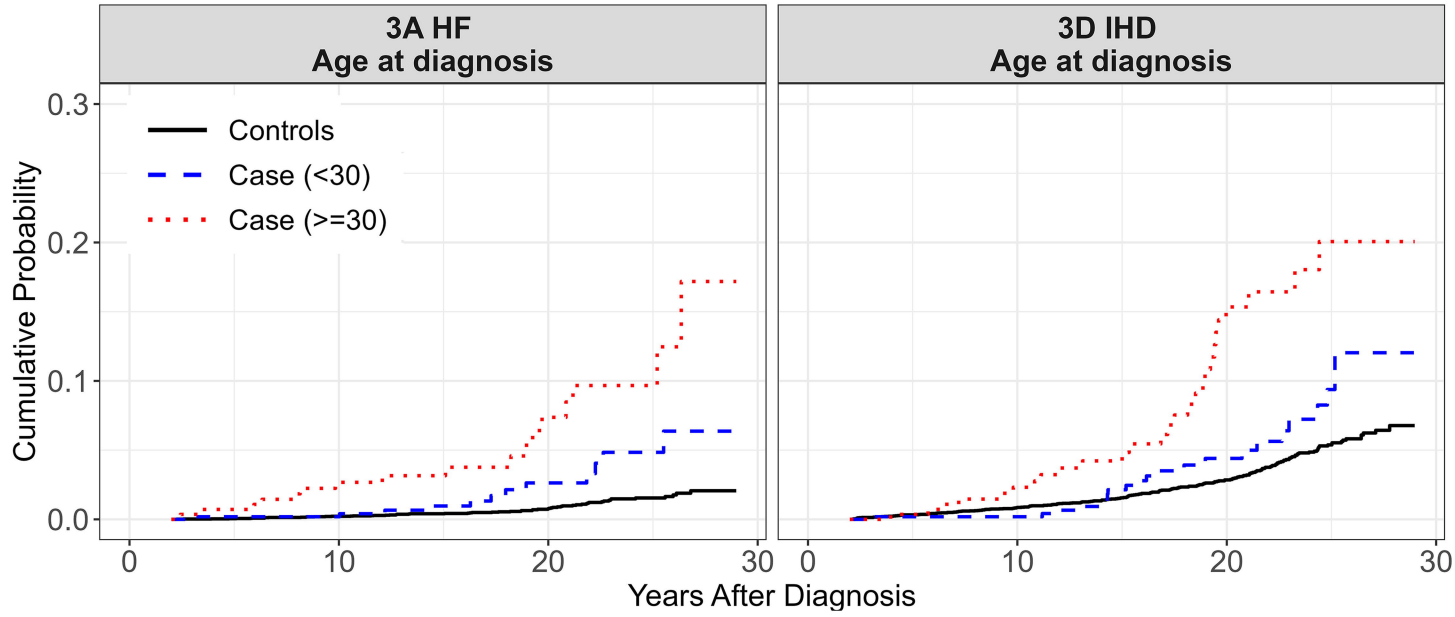
Figure 3: Cumulative incidence of heart failure (HF) and ischemic heart disease (IHD) by sub-group in 2-year survivors of classical Hodgkin lymphoma relative to age-, sex-, and region-matched controls

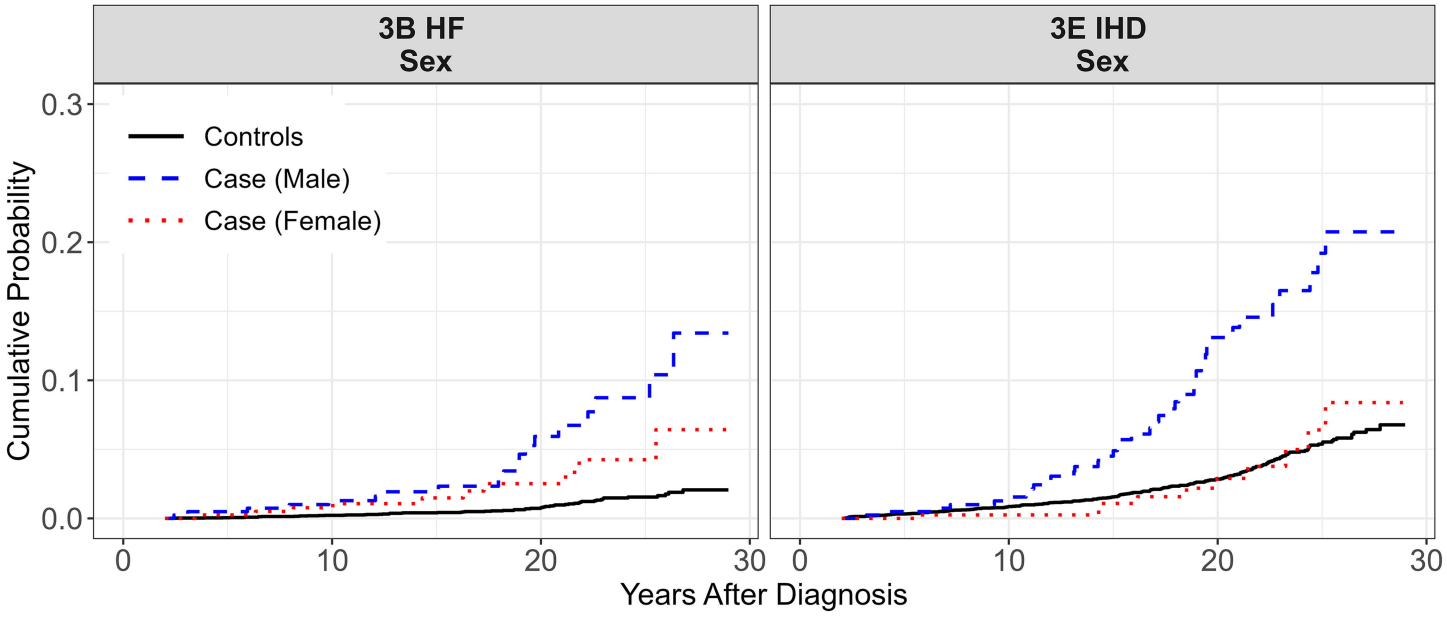


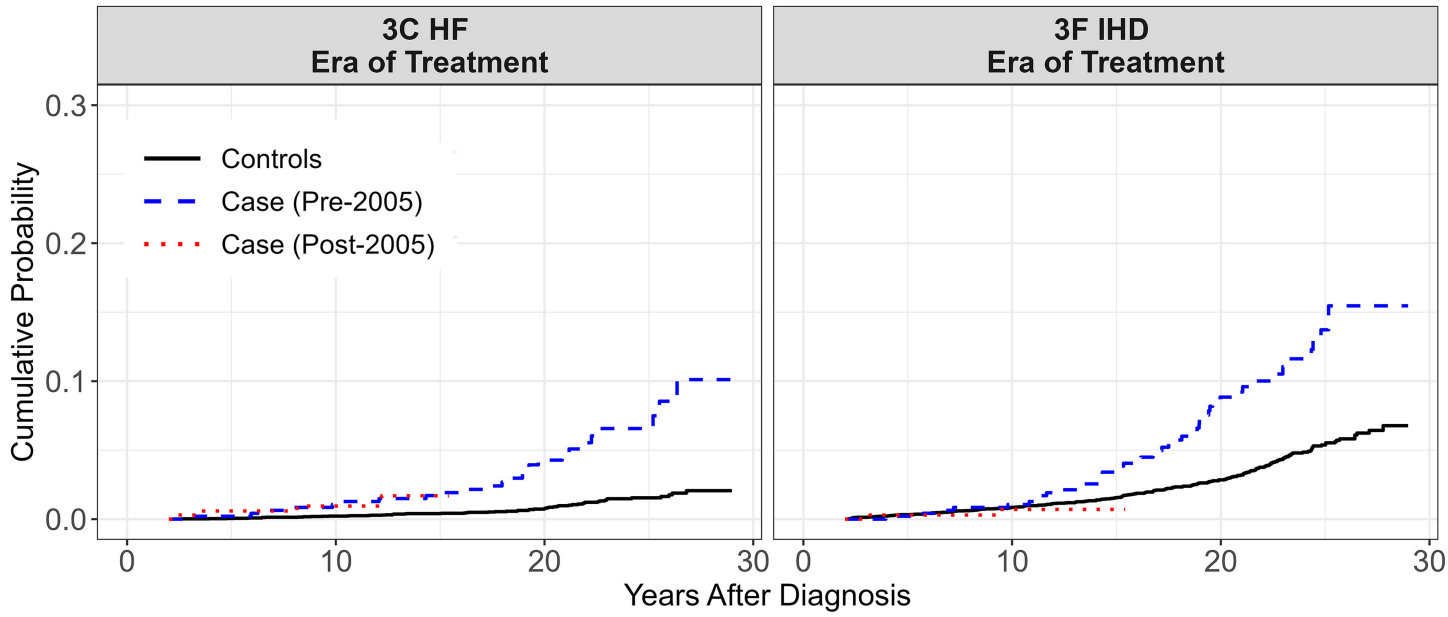
Numbers at Risk by years since diagnosis of relapse of classical Hodgkin lymphoma

Years	0	7	12	15	17	20
Cases	806	777	589	452	376	252
Controls	8058	7836	5985	4670	4010	2875


2A HF
All cases
2D IHD
All cases
Controls
Cases
p < 0.0001
p < 0.0001
Cumulative Probability
Years After Diagnosis
2B HF
RT Yes/No
2E IHD
RT Yes/No
Controls
Case (No RT)
Case (RT)
Cumulative Probability
Years After Diagnosis
2C HF
RT and Anthracycline dose
2F IHD
RT and Anthracycline dose
Controls
Case (No RT, Cumulative Anthracycline 1-299 mg/m2)
Case (No RT, Cumulative Anthracycline >=300 mg/m2)
Case (RT, Cumulative Anthracycline 1-299 mg/m2)
Case (RT, Cumulative Anthracycline >=300 mg/m2)
Cumulative Probability
Years After Diagnosis


3A HF
Age at diagnosis
3D IHD
Age at diagnosis
Controls
Case (<30)
Case (>=30)
Cumulative Probability
0.0
0.1
0.2
0.3
0
10
20
30
Years After Diagnosis


3B HF
Sex
3E IHD
Sex
Controls
Case (Male)
Case (Female)
Cumulative Probability
0.0
0.1
0.2
0.3
0
10
20
30
Years After Diagnosis


3C HF
Era of Treatment
3F IHD
Era of Treatment
Controls
Case (Pre-2005)
Case (Post-2005)
Cumulative Probability
0.0
0.1
0.2
0.3
0
10
20
30
Years After Diagnosis

Long-term cardiac morbidity in adolescent and young adult survivors of classical Hodgkin lymphoma: the British Columbia experience

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Supplementary Table 1: Chronic Disease Registry (CDR) definitions for diagnosis

Condition	Definition	ICD 9/10 Code
Chronic Obstructive Pulmonary Disease	One hospitalization or two physician visits in one year, with ICD code(s) specified.	J41 Simple and mucopurulent chronic bronchitis; J42 Unspecified chronic bronchitis; J43 Emphysema; J44 Other chronic obstructive pulmonary disease; 491 Chronic bronchitis; 492 Emphysema; 496 Chronic airways obstruction, not elsewhere classified
Diabetes Mellitus	One hospitalization or two physician visits in one year with diagnostic code(s) specified below; or two or more insulin prescriptions in one year; or two	E10 Type 1 diabetes mellitus; E11 Type 2 diabetes mellitus; E13 Other specified diabetes mellitus; E14 Unspecified diabetes mellitus; 250 Diabetes mellitus Gestational

	or more oral antihyperglycemic (not including metformin) prescriptions in one year; or one insulin and one oral antihyperglycemic (including metformin) in one year; or 2 metformin prescriptions and 1 physician visit in one year with ICD code(s) specified. Cases of suspected gestational diabetes in women aged 10-54 are not included by excluding hospitalizations, physician claims or prescriptions within the time period 120 days preceding or 180 days after hospital records containing birth-related diagnostic codes.	
Heart Failure	One hospitalization or two physician visits in one year with diagnostic code(s) specified.	I50 Heart Failure; 428 Heart Failure
Hypertension	One hospitalization or two physician visits in one year with diagnostic code(s) specified.	I10 Essential (primary) hypertension; I11 Hypertensive heart disease; I12 Hypertensive renal disease; I13 Hypertensive heart and renal disease; I15 Secondary hypertension; 401 Essential hypertension; 402 Hypertensive heart disease; 403 Hypertensive renal disease; 404

		Hypertensive heart and renal disease; 405 Secondary hypertension
Ischemic Heart Disease	Two physician visits with Angina ICD-9 code 413 plus one prescription (as specified in drug list) in one year; or one specialist visit with Angina ICD-9 code 413 plus one prescription (as specified in drug list) in one year; or two physician visits with two ICD9 410, 411, 412, 413, 414 in one year; or 1 CABG,PCI/PCTA procedure code specified; or one hospitalization with any IHD code specified.	I20 Angina pectoris; I21 Acute myocardial infarction; I22 Subsequent myocardial infarction; I23 Certain current complications following acute myocardial infarction; I24 Other acute ischaemic heart diseases; I25 Chronic ischaemic heart disease; 410 Acute myocardial infarction; 411 Other acute and subacute forms of ischaemic heart disease; 412 Old myocardial infarction; 413 Angina pectoris; 414 Other forms of chronic ischaemic heart disease; CCI/CCP Procedure Code Description 1IJ57LA Extraction, coronary arteries using open approach; 1IJ57VS Extraction, coronary arteries using open approach with placement/implant of stent; 1IJ76 Bypass, coronary arteries (endoscopic or open approach); 1U50 Dilation, coronary artery; 1IJ57G Extraction, coronary arteries using percutaneous transluminal arterial approach; 48.11 Aortocoronary Bypass For Heart Revascularization, Unqualified; 48.12 Aortocoronary Bypass Of One Coronary Artery; 48.13 Aortocoronary Bypass Of Two Coronary

		Arteries; 48.14 Aortocoronary Bypass Of Three Coronary Arteries; 48.15 Aortocoronary Bypass Of Four Or More Coronary Arteries; 48.16 Single (Internal) Mammary-Coronary Artery Bypass; 48.17 Double (Internal) Mammary-Coronary Artery Bypass; 48.19 Single (Internal) Mammary-Coronary Artery Bypass; 48.02 Percutaneous Transluminal Coronary Angioplasty Without Mention; 48.03 Percutaneous Transluminal Coronary Angioplasty With Thrombolytic

Supplemental Table 2: 20-year cumulative incidence of heart failure and ischemic heart disease in 2-year survivors of classic Hodgkin lymphoma relative to age-, sex- and region-matched controls

	Combined CVD		**HF**		**IHD**	
	20-y cumulative incidence	95% CI	20-y cumulative incidence	95% CI	20-y cumulative incidence	95% CI
Controls	3.2%	2.7-3.7%	0.8%	0.05-0.1%	2.8%	2.4-3.3%
All cases	10.1%	7.2-12.9%	4.3%	2.3-6.2%	8.3%	5.6-11.0%
Mediastinal RT						
Yes	12.0%	7.8-16.2%	5.4%	2.4-8.3%	10.7%	6.7-14.7%
No	8.5%	4.6-12.5%	3.3%	0.8-5.8%	6.0%	2.5-9.4%
Anthracycline dose						
RT Yes, A <300	11.5%	6.4-16.7%	4.3%	1.1-7.5%	9.9%	5.0-14.7%
RT Yes, A ≥300	11.4%	4.6-18.3%	8.3%	1.4-15.3%	10.8%	4.0-17.5%

RT No, A <300	7.0%	1.5-12.4%	3.4%	0-7.5%	3.6%	0-7.3%
RT No, A ≥300	10.9%	4.5-17.2%	3.6%	0-7.3%	8.8%	2.7-14.9%
Stage						
Limited	7.4%	3.5-11.4%	2.0%	0.3-3.8%	6.7%	2.9-10.6%
Advanced	11.3%	7.5-15.1%	5.2%	2.4-8.0%	9.2%	5.7-12.8%
Age at Diagnosis						
<30 y	5.5%	2.9-8.0%	2.6%	0.7-4.5%	4.4%	2.1-6.7%
≥30 y	18.5%	12.1-24.8%	7.4%	3.1-11.6%	15.3%	9.3-21.4%
Sex						
Male	15.1%	10.4-19.7%	5.9%	2.7-9.2%	13.1%	8.6-17.6%
Female	4.6%	1.7-7.4%	2.5%	0.6-4.5%	2.9%	0.5-5.3%

Supplementary Table 3: Multi-regression analysis of relative risk of heart failure (HF) and ischemic heart disease (IHD) in adolescent and young adult survivors with classical Hodgkin lymphoma treated with upfront therapy only versus age-, sex- and region-matched population controls

	HF			**IHD**		
	RR	95% CI	p-value	RR	95% CI	p-value
Radiation and anthracycline <300 mg/m2	4.95	1.86 - 13.16	0.001	3.03	1.67 - 5.47	<0.001
Radiation and anthracycline ≥ 300 mg/m2	4.63	1.12 - 19.21	0.035	2.53	1.02 - 6.30	0.045
No radiation and anthracycline <300 mg/m2	3.01	0.68 - 13.25	0.146	1.63	0.64 - 4.16	0.305

No radiation and anthracycline ≥ 300 mg/m2	3.75	1.26 - 11.11	0.017	0.25	0.03 - 1.78	0.166
Male	1.60	0.90 - 2.85	0.111	2.23	1.59 - 3.12	<0.001
Advanced stage	1.09	0.60 - 1.98	0.776	0.96	0.69 - 1.32	0.785
Era of Treatment After January 1, 2005	1.18	0.48 - 2.87	0.721	1.02	0.62 - 1.70	0.932
Age >30 y at diagnosis	3.27	1.77 - 6.05	<0.001	2.08	1.52 - 2.86	<0.001
Diabetes	5.36	2.67 - 10.76	<0.001	2.55	1.54 - 4.24	<0.001
Hypertension	2.44	1.22 - 4.89	0.012	2.58	1.68 - 3.97	<0.001
COPD	4.67	1.82 - 11.97	0.001	0.65	0.15 - 2.76	0.558