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Temporal trends in treatment-related incidence of diseases of the circulatory system among Hodgkin lymphoma patients

Running head: Trends in excess incidence of circulatory system disease after Hodgkin lymphoma

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Novelty and Impact

The risk of diseases of the circulatory system (DCS) in Hodgkin lymphoma (HL) patients was separated into “excess” (related to the HL and its treatment) and “expected” (in the absence of HL), complementing reports showing high risks of DCS without disentangling the risk patients would have faced also in the absence of HL. The risk of a treatment-related DCS persists for up to 10 years among patients who completed their treatment in the new millennium.

Abstract

While Hodgkin lymphoma (HL) survival has improved, treatment-related complications remain a concern. As a measure of treatment-related diseases of the circulatory system (DCS) we report excess incidence of DCS and absolute risks among HL patients diagnosed in the modern treatment era. From the Swedish Cancer Register, we identified all HL patients diagnosed 1985 through 2013, at ages 18-80 years. Excess incidence rate ratios (EIRRs) with 95% confidence intervals (CIs) comparing excess DCS incidence between calendar periods were estimated overall, and at five- and ten years after diagnosis using flexible parametric models. Model-based predictions were used to obtain probabilities of being diagnosed with DCS, in the presence of competing risks. During follow-up, 726 (16%) of the 4,479 HL patients experienced DCS. Overall, the excess DCS incidence was lower during all calendar periods compared to the first (2009-2013 versus 1985-1988: EIRR=0.63, 95% CI: 0.42-0.95). The five- and ten-year excess incidence of DCS decreased between 1985 and 1994 for 25-year-olds (5-year-$EIRR_{1994}$=0.32, 95% CI: 0.12-0.92) and 60-year-olds (5-year-$EIRR_{1994}$=0.45, 95% CI: 0.24-0.88), but remained stable thereafter. No improvements were observed among 75-year-olds. The probability of excess DCS remained the same throughout the study period. In 2009, the percentage of patients aged 25, 60, and 75 experiencing excess DCS within five years was 3.4%, 15.0%, and 17.0% (males) and 2.3%, 10.8%, and 12.6% (females). Treatment-related incidence of DCS has declined since the mid-1980s, but more recent improvements are absent and an excess risk remains. Continued efforts towards less toxic treatments are warranted, alongside primary prevention strategies.

Introduction

For Hodgkin lymphoma (HL), the survival improvements following the introduction of new therapeutic chemotherapy agents, advances in radiotherapy (RT), and clinical work-up, are a success story[1-3]. However, while approximately 90% of young HL patients today will be cured from their lymphoma[4,5], treatment toxicity remains a concern[6-8]. Morbidity from diseases of the circulatory system (DCS) among patients treated for HL includes, e.g., coronary heart disease, congestive heart failure, valvular heart disease, and stroke[9-18]. Furthermore, the forty-year cumulative incidence of cardiovascular disease has been shown to be above 50% among HL survivors[19]. However, although the overall risk of cardiovascular disease is high, the proportion of the all-cause risk that is specifically related to the HL therapy and the underlying disease, is seldom reported.

In Sweden, excess DCS mortality (that is, the DCS-specific mortality attributable to the HL and its treatment) has decreased among survivors since the mid-1980s[20]. Standard of care, as described in the National Care Programs for HL, has been revised regularly since 1985 to accommodate risk-adapted therapy that aims to maximize the chances of cure, while reducing treatment toxicity. More thorough clinical follow-up for late effects among survivors has likely also contributed to the reduction in excess DCS mortality, as it potentially leads to earlier detection and improved management of patients who show signs of circulatory system disease. Another potential reason for the observed decrease in excess mortality due to DCS is that this group of diseases is less fatal today than in the past. Taken together, the decrease in mortality does not necessarily reflect a decrease in incidence.

To complement the literature on late effects of HL treatment with a measure that specifically captures the DCS risk attributable to the disease and its treatment, we here present temporal trends in excess incidence rates and absolute risks of DCS among HL survivors. These trends are also useful to better understand if the previously reported reduction in excess DCS mortality is explained by a decrease in excess incidence or improved management among affected patients. Lastly, by presenting trends that capture the transition to modern HL treatment, we also aim to advance the understanding of the circulatory system disease burden associated with more intensive chemotherapy and less RT in a large

unselected cohort of HL patients. The results for contemporarily treated patients may serve as a benchmark for further improvements of the clinical follow-up and treatment concepts/care of HL survivors.

Material and methods

Data sources and study population

All patients with a primary diagnosis of HL registered in the nationwide Swedish Cancer Register (SCR) between 1985 and 2013, aged 18-80 years at diagnosis, were included (n=4,668). The SCR contains information on incident primary malignancies in Sweden since 1958. Notification of new cancers to the register is mandatory by law and the register has close to complete coverage of HL[21]. Autopsy findings (n=140, mainly during the earlier calendar period) and diagnoses with uncertain morphological confirmation (n=49) were excluded. No patients were excluded based on previous cancer or DCS. The patients were followed for DCS by linking to data from the Swedish Inpatient Register (IPR), originating in 1964. Since 1987 the coverage is nationwide, however, the register has coverage above 90% since 1985. Dates of death or loss to follow-up due to emigration were identified by linking the cohort to the Swedish Cause of Death Register (CDR) and the Register of Total Population and Population Changes, respectively. The final study population comprised 4,479 patients.

General population

To enable comparison to the baseline DCS risk in the Swedish general population, a cohort of individuals included in either the nationwide Multi-Generation Register (all Swedish residents born after 1931 who were still alive and living in Sweden at some point after 1961, and their parents) or any Swedish census 1960-1990, was constructed. Population incidence rates of DCS in this cohort of approximately 10 million individuals (n=10,020,472) were calculated via record linkage to all other registers in the same manner as for the HL patients. The last year for which incidence data in the general population was available was 2010. For later years (2011-2014) the DCS rates were assumed to remain unchanged.

Definition of DCS diagnoses and non-DCS death

An incident case of DCS was defined as either a hospitalization recorded in the IPR with DCS as the main diagnosis, or a death recorded in the CDR with DCS as the underlying cause (both defined via codes I00 to I99 in the 10th revision of the International Classification of Disease (ICD), or equivalent in earlier versions). A non-DCS death was defined as a death with any underlying cause other than DCS. Patients with an incident case of DCS who later died (from DCS or any other cause) were only followed until the DCS diagnosis, and only that event was considered in the statistical analyses.

Treatment principles of HL during the study period

In Sweden, diagnosis and treatment of HL has been uniform since the introduction of the National treatment recommendations for HL in 1985[4,5,22-25] and resemble those in other high-income countries. The most influential shift, from a cardiac- and cerebral-toxicity risk perspective, in HL therapy during the time period of the present study was the abandonment of mantle field RT around 1995. Also the transition from chemotherapy combinations including MOPP (mechlorethamine, vincristine, procarbazine, prednisone) to either ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for patients with low-risk features, or BEACOPP-14/escalated (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) for patients with high-risk features (International Prognostic Score, IPS≥3), during the late 1990s is specifically relevant for the study at hand. Furthermore, to minimize late effects of treatment, tailored therapy has been introduced. For example, since 2004, patients initially treated with BEACOPP who become FDG-PET (fluorodeoxyglucose-positron emission tomography) negative after two courses, continue with ABVD.

Statistical analysis

Patients were followed from date of HL diagnosis until a first admission date of DCS, date of death, emigration date, or December 31, 2014, whichever occurred first. Follow-up was furthermore restricted to the first eleven years (ten years plus one additional year to improve the stability of the estimates). The time scale in all analyses was time since diagnosis. The excess incidence rate of DCS was defined as the difference between the observed DCS incidence rate in the patient population and the incidence rate in

the general population (assumed free from HL) matched on age, sex and year. Differences in excess incidence were assumed to be attributable to HL therapy, and referred to as "treatment-related DCS incidence". This includes direct effects of radiation and chemotherapy and indirect effects of lifestyle interventions (e.g., smoking cessation advice).

Excess incidence rate ratios (EIRR) of DCS were estimated using a flexible parametric survival model adapted to relative survival[26]. Time to non-DCS death was simultaneously modelled as a second outcome. Separate baseline excess incidence rates were estimated for the two distinct outcomes (DCS diagnosis/death and non-DCS death) using restricted cubic splines[27] with 3 degrees of freedom. The final model included sex, calendar year of diagnosis, and age at diagnosis, with calendar year and age modelled using restricted cubic splines with 4 degrees of freedom. An interaction term between diagnosis year and age was further included (with 2x2 degrees of freedom). All covariates were allowed to have separate effects on the two outcomes, and non-proportional hazards were estimated for all main effects.

As a measure of absolute risk, predictions from the flexible parametric model were used to obtain cumulative probabilities of DCS, partitioned into treatment-related (excess) and not treatment-related (i.e., events that were expected also in the absence of HL), in the presence of competing risks[28] (i.e., non-DCS death).

All statistical analyses were done using Stata (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Role of the funding source

The funders had no role in study design, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

The study was approved by the regional ethics review board in Stockholm, Sweden.

Results

Among the 4,479 HL patients, 726 (16%) were hospitalized or died from DCS during follow-up (Table 1). The overall excess incidence decreased between 1985-1988 and 1989-1993 (adjusted EIRR = 0.66, 95% CI: 0.44-1.00) but remained on the same level after that. The majority of DCS events were identified from hospitalizations (n=648, 89%), while the remaining 78 (11%) events were found via death certificates in the CDR (Supplementary Table 1). Overall, ischemic heart disease (25.3%) and other forms of heart diseases (27.7%; including heart failure, atrial fibrillation, and acute pericarditis) were the most commonly recorded diagnoses. Cerebrovascular diseases accounted for 16.7% of all DCS events.

In total, 876 (20%) patients experienced the competing event of a non-DCS death (prior to a potential DCS event) (Table 1). Among these patients, the major cause of death was HL (59%) (data not shown).

Figure 1 shows EIRRs of DCS comparing patients diagnosed in 1994, 1999, 2004, 2009, and 2013 to patients diagnosed in 1985. The results are presented for three selected ages at diagnosis, representing patients from the first (25-year-olds) and second (60-year-olds) incidence peaks, as well as elderly patients (75-year-olds). At five years after diagnosis, the excess incidence rate of DCS was lower, and remained at approximately the same level, after 1994 for patients aged 25 (e.g., $EIRR_{1994}$=0.32; 95% CI: 0.12-0.92 and $EIRR_{2009}$=0.16; 95% CI: 0.03-0.96) and 60 years at diagnosis (e.g., $EIRR_{1994}$=0.45; 95% CI: 0.24-0.88 and $EIRR_{2009}$=0.37; 95% CI: 0.17-0.84). Similar trends were observed at ten years for 25- and 60-year-old males. For elderly patients (aged 75 at diagnosis), no significant changes over calendar time were observed. All EIRRs (with 95% CIs) are listed in Supplementary Table 2.

The corresponding trends expressed as absolute risks of DCS, i.e., cumulative probabilities of DCS (in the presence of the competing risk of death) subdivided into treatment-related (excess) and not treatment-related (expected), are presented for males in Figure 2 and for females in Figure 3. The

temporal trend was very similar for both sexes when including interactions with sex, so results are based on a model assuming the same shape for both males and females. For male 25-year-olds, the treatment-related risk of DCS within five years of diagnosis was 5.2% (95% CI: 1.8-8.6) in 1985 and 3.4% (95% CI: 1.5-5.2) in 2009. For females of the same age, the corresponding numbers were 3.2% (95% CI: 1.2-6.0) and 2.3 (95% CI: 1.0-3.6). The DCS risk unrelated to treatment remained stable at around 0.5% for both sexes. For 60-year-old male patients, the treatment-related risk remained approximately at the same level throughout (1985: 15.0%, 95% CI: 8.5-21.5, 2009: 15.0%, 95% CI: 10.4-19.7) while the expected risk decreased (from 10.4% in 1985 to 7.1% in 2009). For females aged 60 years, the treatment-related risk was 11.6% (95% CI: 6.3-17.0) in 1985 and 10.8% (95% CI: 7.0-14.6) in 2009. Among 75-year-olds of both sexes, the risk for DCS unrelated to treatment was similar in all three calendar years. The five-year risk for treatment-related DCS among male patients diagnosed in 1985 was 11.8% (95% CI: 3.7-20.0), compared to 17.0% (95% CI: 9.0-25.1) among those diagnosed in 2009. For female 75-year-olds, the increase was less pronounced (9.8% with 95% CI: 3.0-16.6 in 1985, and 12.6% with 95% CI: 6.2-18.9 in 2009).

The temporal trends in five- and ten-year absolute risks of treatment-related DCS are shown for males in Figure 3 and for females in Supplementary Figure 1 (as the shapes were very similar for both sexes). For 25-year-old male patients the cumulative probabilities remained stable and low throughout the study period. For patients aged 60 years at diagnosis they also remained relatively constant over time, with a five-year risk of approximately 15% and a ten-year risk of around 20%. For 75-year-olds, the temporal trend was increasing until year 2005 (irrespective of timing in relation to the diagnosis date).

Discussion

In this study on Swedish HL patients diagnosed between 1985 and 2013, including patients treated with modern HL therapy, no dramatic changes in short-term (≤10 years after diagnosis) treatment-related DCS morbidity were observed. The five- and ten-year excess incidence rate of DCS decreased from 1985 to the 1990s among young and middle-age patients. The decrease did not continue into the new millennium. For elderly patients, no significant decrease in treatment-related DCS incidence rate was

seen. In contrast to previously published trends in excess DCS mortality in Sweden, a decrease in the absolute risk of a treatment-related DCS (in terms of proportion of affected patients) within five years of HL diagnosis was not observed.

As the excess risk of a treatment-related DCS remains among all patients, irrespective of age at diagnosis, reducing toxicity from first- and second line HL therapy continues to be important. Efforts to raise awareness, promote primary prevention activities, together with continuous systematic clinical follow-up, are warranted. Existing national guidelines for HL treatment in Sweden recommend that patients treated with anthracyclines corresponding to six to eight cycles of ABVD and no cardiac RT exposure, should be followed up with echocardiography and heart evaluation in case of pregnancy or if the patient is an athlete. Patients treated with more than 30 Gy of mediastinal RT together with anthracyclines are to be followed up for treatment-associated late cardiac effects, starting at ten years after finished treatment.

While the refinement of treatment options for HL has significantly improved the prognosis for affected patients, including patients diagnosed in advanced stage, late effects (encompassing also cerebrovascular conditions) from treatment toxicity remain a concern. Results from existing literature have contributed to an enhanced understanding of the timing and magnitude of very late treatment effects, especially in relation to RT, but are primarily based on patients treated with outdated therapy (including extensive field RT)[9-18,29-32]. Furthermore, several previous studies have reported increased cumulative probabilities of cardiac late effects among HL patients, such as heart failure[18], coronary heart disease[17] and valvular heart disease[16], showing an up to 50% risk of being diagnosed with cardiovascular disease within forty years after diagnosis (taking the competing risk of death into account)[19]. As the purpose typically has been to illustrate differences within a cohort (e.g., for different amounts of irradiation towards the heart) these cumulative probabilities have been estimates of the observed overall risk. Although this is an important measure, it does not capture the risk for DCS that is attributable to the HL and its treatment. For cardiovascular diseases, where the observed risk increases with age and decreases with calendar time, this separation is of particular importance, especially for understanding

the effect of changes in standard of care, or the efficacy of primary prevention activities on the risk for treatment toxicity.

The observed decrease in the five- and ten-year excess incidence rate among young and middle-aged patients could in part be explained by the abandonment of extended field RT, particularly the mantle field RT. Modern involved site or node RT often reduces the dose to the carotid arteries and the heart as compared to mantle field RT, and thus decreases the risk of stroke[33] and cardiovascular disease[34]. While reductions in RT volumes, as well as the introduction of more advanced techniques, has most probably reduced the risk for RT-associated DCS, contemporary chemotherapy treatment still involves high cumulative doxorubicin doses. Unlike with radiation-induced cardiac sequelae, which usually manifest later (although can be seen already after five to ten years after treatment), cardiotoxicity from chemotherapy can be observed at different intervals after therapy[35]. Anthracyclines can induce both acute and late cardiomyopathy, which in turn can lead to congestive heart failure. Other anti-lymphoma drugs that may lead to cardiac sequelae are alkylating agents (cyclophosphamide in BEACOPP and MOPP) and vinca alkaloids[35] (vincristine in BEACOPP and MOPP, and vinblastine in ABVD). The fact that no additional improvements of treatment-related DCS incidence was observed in our study after the 1990s might reflect that the toxicity profile of HL therapy was more or less unchanged during this period. The results of this investigation indicates that treatment-related DCS remains a dilemma, and that further fine tuning of treatment concepts is needed. Novel targeted drugs[36] could potentially lower the mortality and morbidity of DCS in the future if they can replace drugs that have the most cardiotoxic potential. However, this could also introduce a novel panorama of late adverse effects.

Even though the excess incidence rate declined during the first half of the study period for all but elderly patients, no improvements in temporal trends of treatment-related DCS were observed in terms of absolute risks that also accommodate the competing risk of death. This is possibly influenced by more patients surviving their HL and therefore being at risk for late effects. A similar lack of reduction in risk was seen in a study by van Nimwegen from 2015[19], where it was observed that the cumulative

probability of cardiovascular disease did not decline throughout the study period in a cohort of five-year survivors diagnosed 1965-1995.

HL treatment practice in Sweden has moved towards administering full curative treatment to a broader group of patients, including older patients[37]. This could explain the lack of reductions in excess DCS incidence rate and absolute risk observed among elderly patients (aged 75 years at diagnosis), as they are now surviving to a larger degree and are increasingly exposed to potentially cardiotoxic therapy.

The major strength of this study is the use of novel statistical methodology enabling a separation between the treatment-related risk of DCS and what is expected in the absence of HL. The method obviates the need to enumerate all possible cardiovascular and cerebrovascular conditions that may contribute to the excess incidence and provides a less subjective selection of the study outcome. However, the results need to be interpreted in the context of the observational nature of the study. Incident cases of DCS were ascertained using the Swedish IPR and CDR. As such, only more severe cases were included. While the lack of individual-level information on treatment in this study is a limitation, compliance with national guidelines has been high in Sweden during the study period. As no information on relapses was available it was not possible to associate the excess risk of DCS by first- and second line treatment. Lastly, despite the long follow-up (>25 years) for patients diagnosed in the 1980s, follow-up was restricted to the first decade to avoid residual confounding by follow-up time. The risk for long-term adverse effects of modern chemotherapy protocols (and reduced RT fields) remain to be evaluated.

Conclusions and clinical significance

The treatment-related incidence and risk of DCS among HL patients has seen a slight decrease since the mid-1980s. However, as the excess risk remains, and at a relatively high level, there is still a need for additional improvements in first- and second line treatment (towards a more cardio-protective profile) in both younger and older HL patients.

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TABLE 1 Demographic features and distribution of DCS cases and non-DCS deaths during follow-up (restricted to the first eleven years after diagnosis), and excess incidence rate ratios (EIRR) with confidence intervals (CIs) among patients diagnosed with Hodgkin lymphoma (HL) in Sweden between 1985 and 2013 at ages 18 to 80.

Calendar period	1985-1988	1989-1993	1994-1998	1999-2003	2004-2008	2009-2013	Total
All patients (row %)	661 (14.8)	733 (16.4)	721 (16.1)	743 (16.6)	767 (17.1)	854 (19.1)	4,479 (100)
Patients with DCS* (col %)	146 (22.1)	138 (18.8)	116 (16.1)	135 (18.2)	116 (15.1)	75 (8.8)	726 (16.2)
Patients with non-DCS death (col %)	218 (33.0)	192 (26.2)	154 (21.4)	119 (16.0)	110 (14.3)	83 (9.7)	876 (19.6)
*EIRR** (CI)*	*1.00*	*0.66 (0.44-1.00)*	*0.65 (0.43-0.97)*	*0.69 (0.47-1.02)*	*0.70 (0.48-1.02)*	*0.63 (0.42-0.95)*	-
Age at diagnosis (years) (col %)							
18-35	227 (34.3)	280 (38.2)	326 (45.2)	339 (45.6)	325 (42.4)	337 (39.5)	1,834 (41.0)
36-50	138 (20.9)	153 (20.9)	131 (18.2)	124 (16.7)	149 (19.4)	170 (19.9)	865 (19.3)
51-65	126 (19.1)	130 (17.7)	122 (16.9)	142 (19.1)	150 (19.6)	191 (22.4)	861 (19.2)
66-80	170 (25.7)	170 (23.2)	142 (19.7)	138 (18.6)	143 (18.6)	156 (18.3)	919 (20.5)
Sex (col %)							
Male	388 (58.7)	419 (57.2)	418 (58.0)	399 (53.7)	436 (56.8)	480 (56.2)	2,540 (56.7)
Female	273 (41.3)	314 (42.8)	303 (42.0)	344 (46.3)	331 (43.2)	374 (43.8)	1,939 (43.3)

Due to rounding, not all percentages add up to 100. Abbreviations; DCS, diseases of the circulatory system.

** A hospitalization with DCS as main diagnosis, or a death with DCS as the underlying cause of death*

*** Estimated from a flexible parametric relative survival main effects model adjusted for age at diagnosis and sex.*

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FIGURE 1 Excess incidence rate ratios (EIRRs) with 95% confidence intervals (CI) at five- and ten years after diagnosis, comparing excess incidence of DCS (diseases of the circulatory system) among Hodgkin lymphoma patients diagnosed in 1994, and onwards in five-year intervals, to those diagnosed in 1985, aged 25, 60, and 75 at diagnosis.

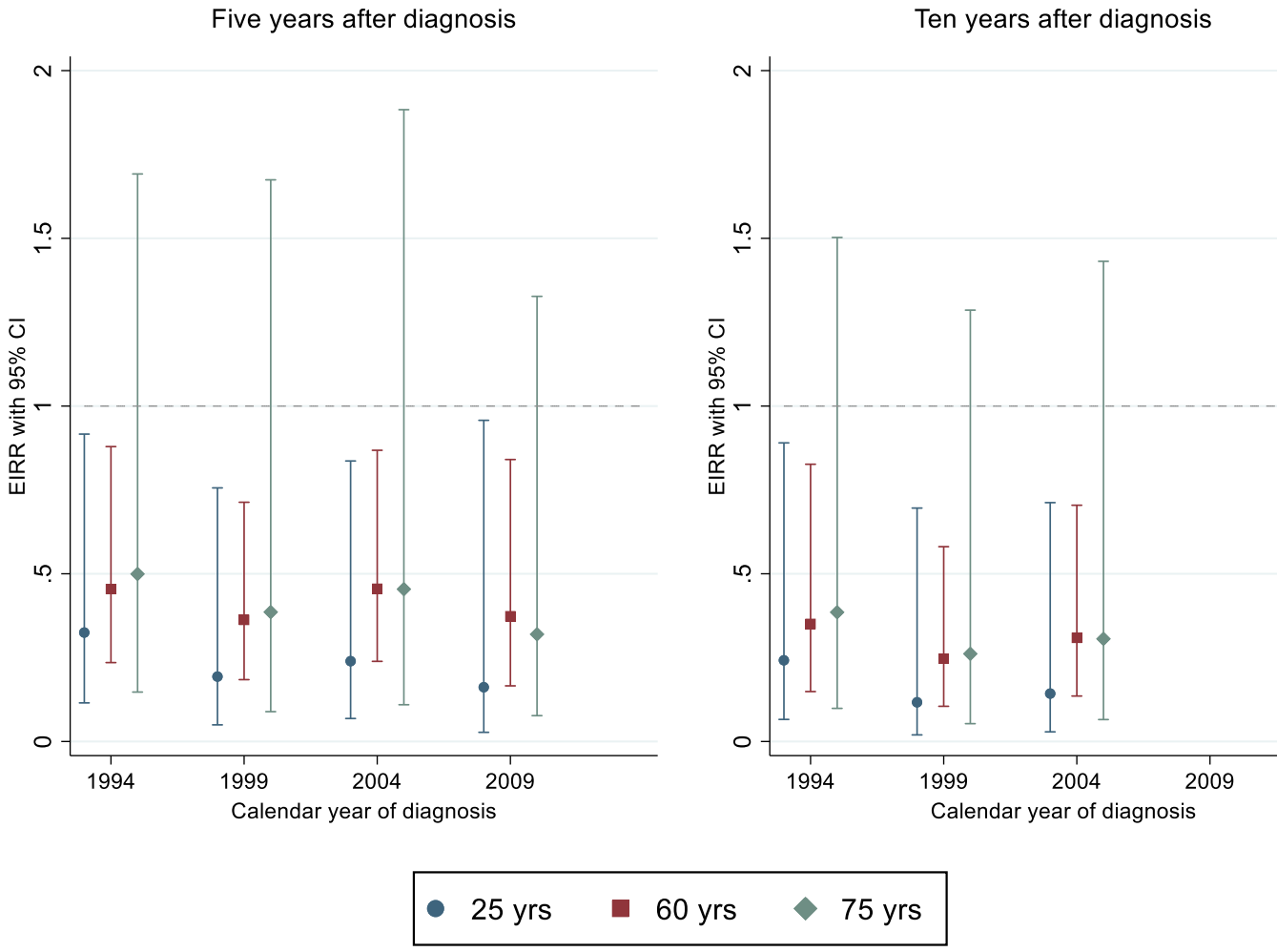
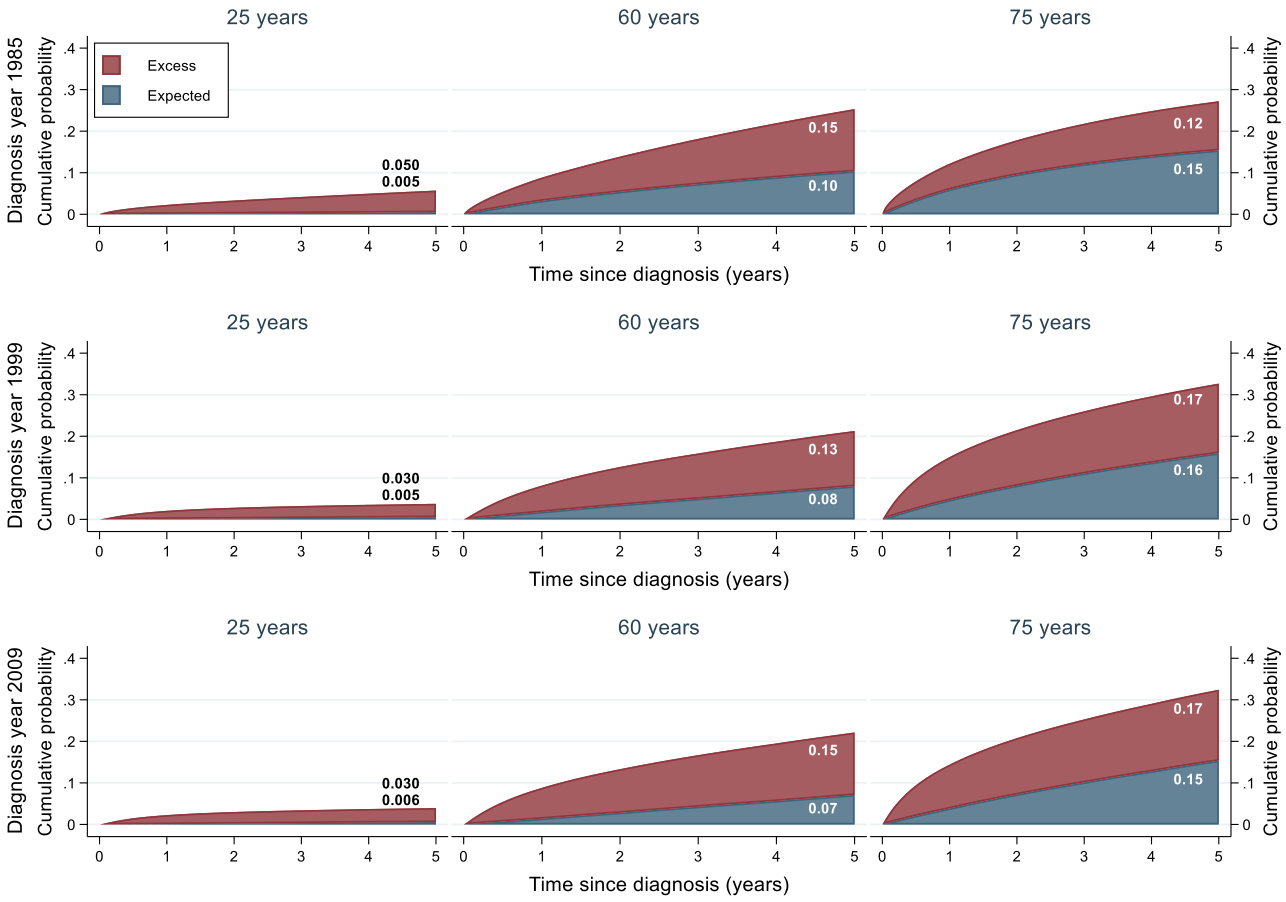


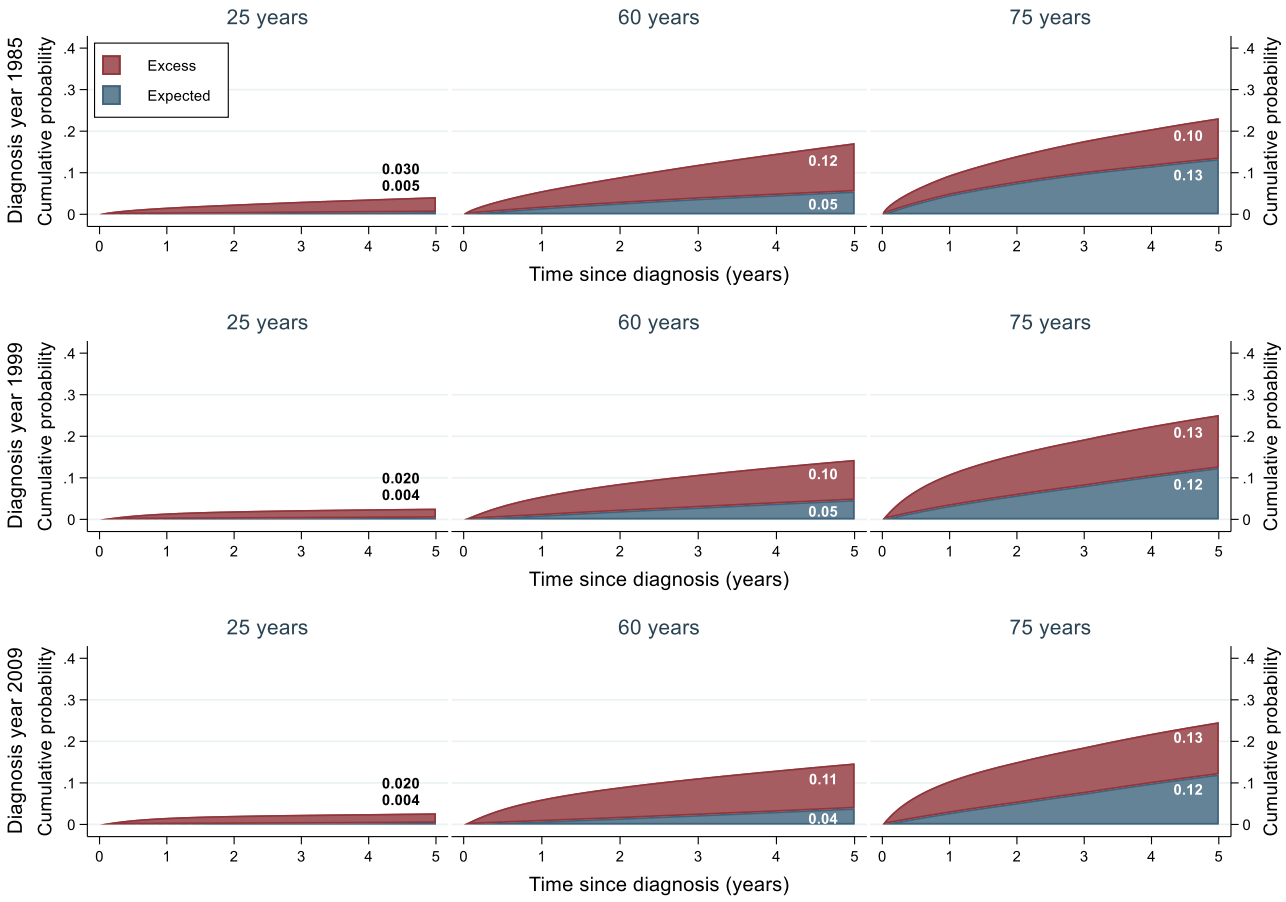
FIGURE 2 Five-year cumulative probability of diseases of the circulatory system (DCS), partitioned into treatment-related ("excess") and expected in the absence of HL ("expected"), among male Hodgkin Lymphoma patients diagnosed in 1985, 1999, and 2009, aged 25, 60, and 75 at diagnosis. The numbers in the figure indicate the exact excess and expected proportions, and the below table show these numbers with 95% confidence intervals (CIs).



Percentage (%) with 95% CI of male patients who experienced a DCS within 5 years after diagnosis.

	25 years		60 years		75 years	
	Excess % (CI)	**Expected** %	**Excess** % (CI)	**Expected** %	**Excess** % (CI)	**Expected** %
1985	5.2 (1.8 to 8.6)	0.5	15.0 (8.5 to 21.5)	10.4	11.8 (3.7 to 20.0)	15.4
1999	3.2 (1.7 to 4.8)	0.5	13.3 (8.8 to 17.7)	8.0	16.7 (9.5 to 23.9)	16.0
2009	3.4 (1.5 to 5.2)	0.6	15.0 (10.4 to 19.7)	7.1	17.0 (9.0 to 25.1)	15.4

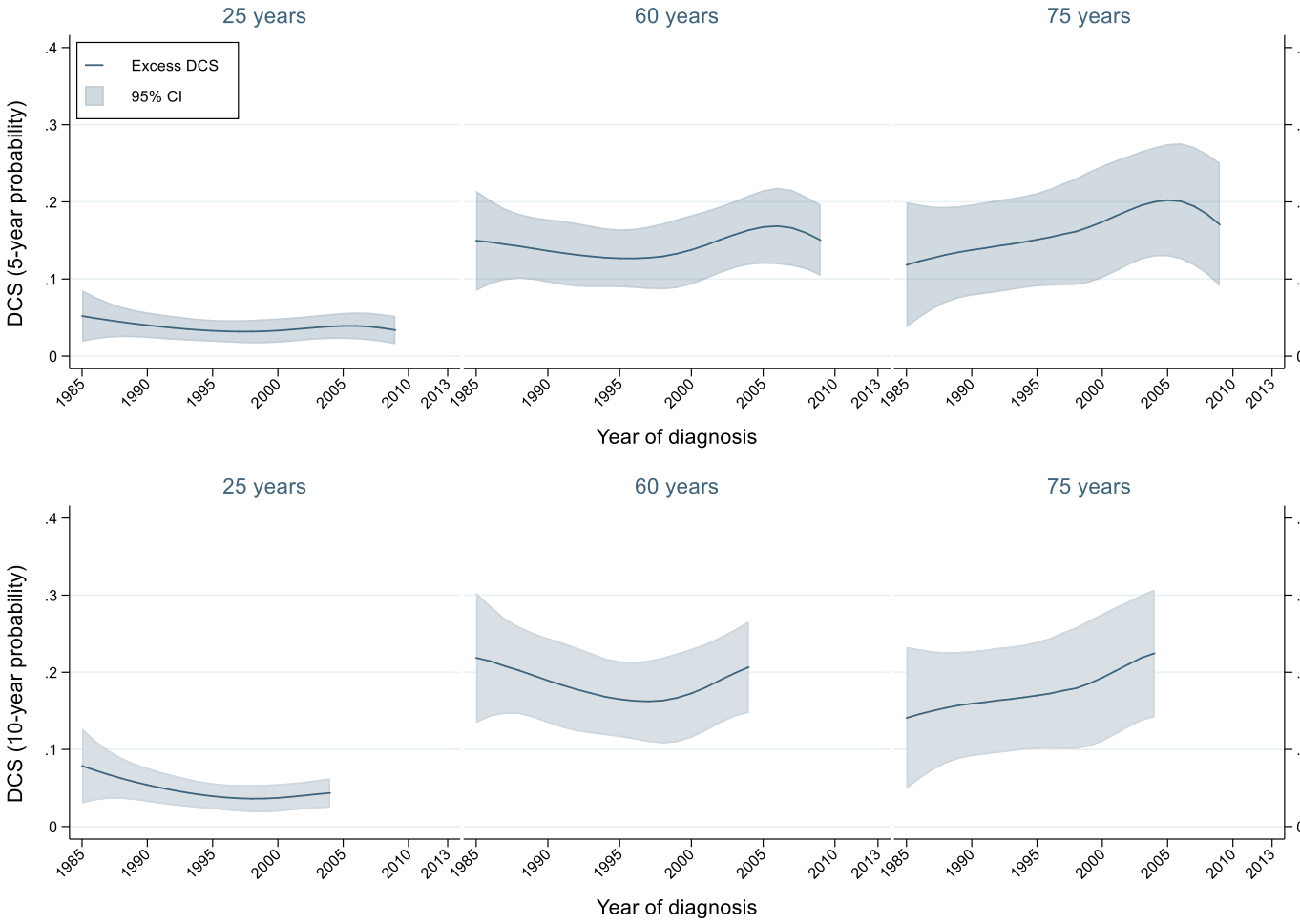
FIGURE 3 Five-year cumulative probability of diseases of the circulatory system (DCS), partitioned into treatment-related ("excess") and expected in the absence of HL ("expected"), among female Hodgkin Lymphoma patients diagnosed in 1985, 1999, and 2009, aged 25, 60, and 75 at diagnosis. The numbers in the figure indicate the exact excess and expected proportions, and the below table show these numbers with 95% confidence intervals (CIs).



Percentage (%) and 95% CI of female patients who experienced a DCS within 5 years after diagnosis.

	25 years		60 years		75 years	
	Excess % (CI)	**Expected** %	**Excess** % (CI)	**Expected** %	**Excess** % (CI)	**Expected** %
1985	3.2 (1.2 to 6.0)	0.5	11.6 (6.3 to 17.0)	5.5	9.8 (3.0 to 16.6)	13.3
1999	2.2 (1.1 to 3.3)	0.4	9.7 (6.0 to 13.3)	4.7	12.7 (7.1 to 18.4)	12.4
2009	2.3 (1.0 to 3.6)	0.4	10.8 (7.0 to 14.6)	3.9	12.6 (6.2 to 18.9)	12.1

FIGURE 4 Five- and ten-year cumulative probability of treatment-related ("excess") diseases of the circulatory system (DCS) as a function of year of diagnosis among male Hodgkin Lymphoma (HL) patients diagnosed between 1985 and 2013, aged 25, 60, and 75 at diagnosis.



SUPPLEMENTARY TABLE 1 Distribution of DCS cases in 726 Hodgkin lymphoma (HL) patients diagnosed between 1985 and 2013 at ages 18 to 80, who experience a DCS during follow-up (restricted to the first eleven years after diagnosis), by source of identification (a diagnosis in the Inpatient Register or from death certificate in the Cause of Death Register).

	ICD-10 code	Identified in the IPR **N (%)**	Identified in the CDR **N (%)**
	I00-I99	648 (100)	78 (100)

er	I00-I02, I05-I09	1 (0.2)	0 (0.0)
liseases	I10-I15	5 (0.8)	2 (2.6)
diseases	I20-I25	148 (22.8)	36 (46.2)
rt disease and diseases of pulmonary circulation	I26-I28	45 (6.9)	3 (3.9)
heart disease	I30-I52	186 (28.7)	15 (19.2)
rditis	*I30*	*16 (2.5)*	*0 (0.0)*
tion	*I48*	*58 (9.0)*	*0 (0.0)*
	I50	*51 (7.9)*	*5 (6.4)*
ar diseases	I60-I69	108 (16.7)	13 (16.7)
eries, arterioles and capillaries	I70-I79	46 (7.1)	6 (7.7)
ns, lymphatic vessels and lymph nodes, not elsewhere	I80-I89	105 (16.2)	3 (3.9)
pecified disorders of the circulatory system	I95-I99	4 (0.6)	0 (0.0)

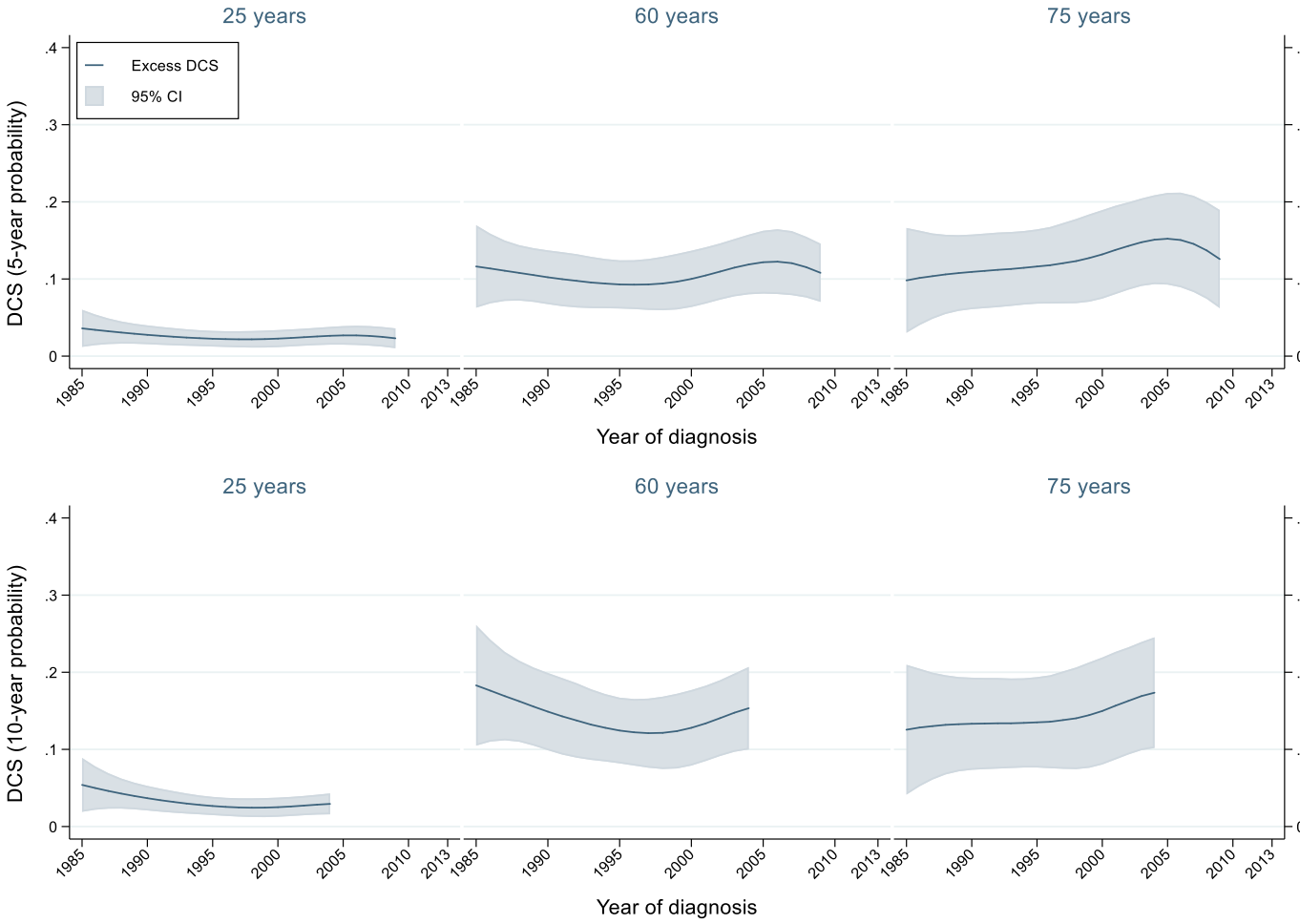
Due to rounding, not all percentages add up to 100. Abbreviations; DCS, diseases of the circulatory system; IPR, Inpatient Register; CDR, Cause of Death Register.

SUPPLEMENTARY TABLE 2 Excess incidence rate ratios (EIRRs) with 95% confidence intervals (CI) from Figure 1.

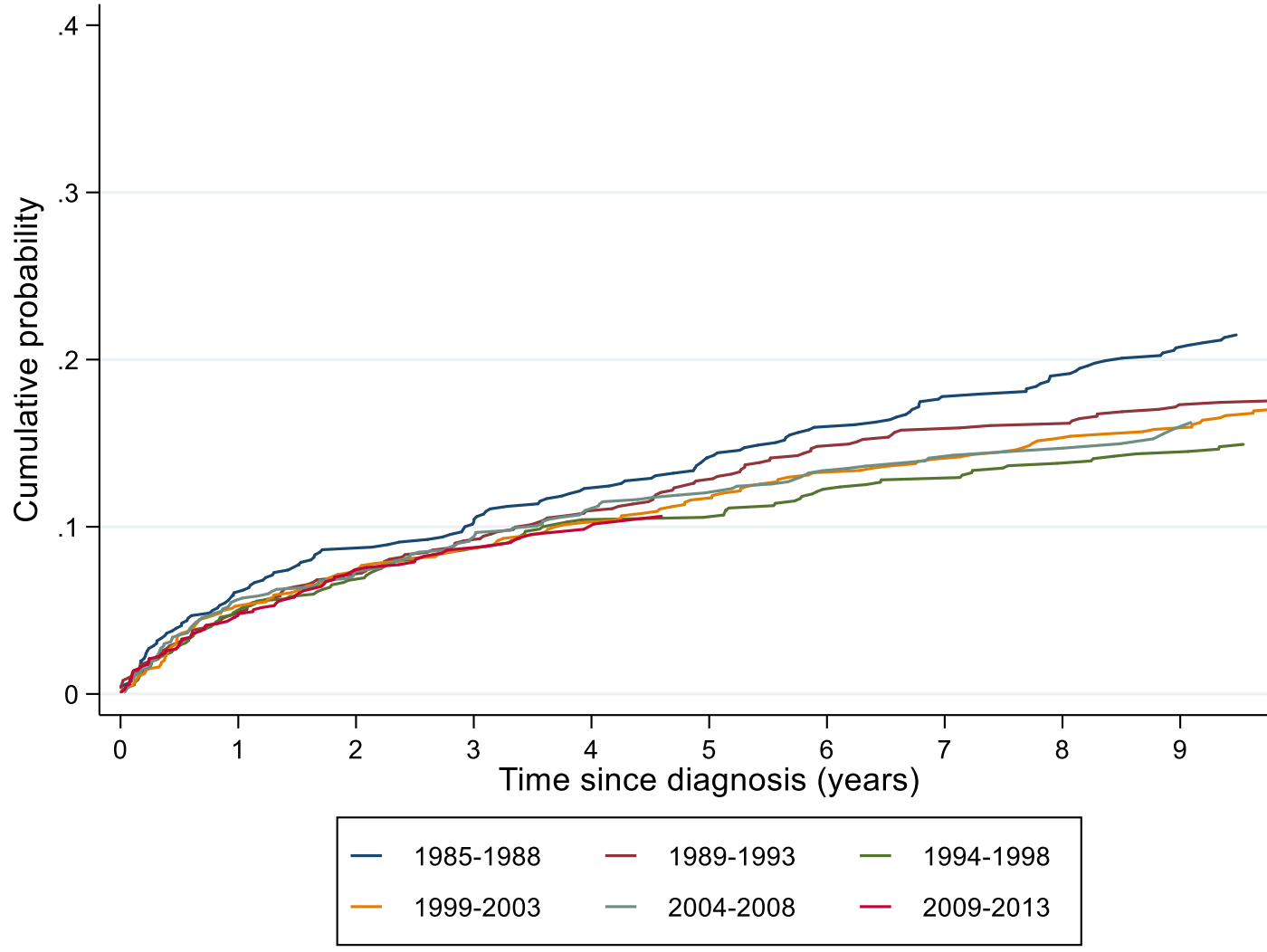
Five years after diagnosis				**Ten years after diagnosis**			
Age at diagnosis	Year of diagnosis	EIRR	95% CI	Age at diagnosis	Year of diagnosis	EIRR	95% CI
25	1994	0.32	(0.12-0.92)	25	1994	0.24	(0.07-0.89)
25	1999	0.19	(0.05-0.76)	25	1999	0.12	(0.02-0.70)
25	2004	0.24	(0.07-0.84)	25	2004	0.14	(0.03-0.71)
25	2009	0.16	(0.03-0.96)	25	2009	-	-
60	1994	0.45	(0.24-0.88)	60	1994	0.35	(0.15-0.83)
60	1999	0.36	(0.18-0.71)	60	1999	0.25	(0.10-0.58)
60	2004	0.46	(0.24-0.87)	60	2004	0.31	(0.14-0.70)

60	2009	0.37	(0.17-0.84)	60	2009	-	-
75	1994	0.50	(0.15-1.69)	75	1994	0.39	(0.10-1.50)
75	1999	0.39	(0.09-1.67)	75	1999	0.26	(0.05-1.29)
75	2004	0.45	(0.11-1.88)	75	2004	0.31	(0.07-1.43)
75	2009	0.32	(0.08-1.33)	75	2009	-	-

SUPPLEMENTARY FIGURE 1 Five- and ten-year cumulative probability of treatment-related ("excess") diseases of the circulatory system (DCS) as a function of year of diagnosis among female Hodgkin Lymphoma (HL) patients diagnosed between 1985 and 2013, aged 25, 60, and 75 at diagnosis.



SUPPLEMENTARY FIGURE 2 Observed cumulative incidence of diseases of the circulatory system (DCS) for the different calendar periods, estimated non-parametrically in the presence of the competing event of dead.


.4
.3
.2
.1
0
Cumulative probability
0
1
2
3
4
5
6
7
8
9
Time since diagnosis (years)
1985-1988
1989-1993
1994-1998
1999-2003
2004-2008
2009-2013

46

47