Original Investigation

Cardiovascular Disease After Hodgkin Lymphoma Treatment
40-Year Disease Risk

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IMPORTANCE Hodgkin lymphoma (HL) survivors are at increased risk of cardiovascular diseases. It is unclear, however, how long the increased risk persists and what the risk factors are for various cardiovascular diseases.

OBJECTIVES To examine relative and absolute excess risk up to 40 years since HL treatment compared with cardiovascular disease incidence in the general population and to study treatment-related risk factors for different cardiovascular diseases.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included 2524 Dutch patients diagnosed as having HL at younger than 51 years (median age, 27.3 years) who had been treated from January 1, 1965, through December 31, 1995, and had survived for 5 years since their diagnosis.

EXPOSURES Treatment for HL, including prescribed mediastinal radiotherapy dose and anthracycline dose.

MAIN OUTCOMES AND MEASURES Data were collected from medical records and general practitioners. Cardiovascular events, including coronary heart disease (CHD), valvular heart disease (VHD), and cardiomyopathy and congestive heart failure (HF), were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

RESULTS After a median follow-up of 20 years, we identified 1713 cardiovascular events in 797 patients. After 35 years or more, patients still had a 4- to 6-fold increased standardized incidence ratio of CHD or HF compared with the general population, corresponding to 857 excess events per 10 000 person-years. Highest relative risks were seen in patients treated before 25 years of age, but substantial absolute excess risks were also observed for patients treated at older ages. Within the cohort, the 40-year cumulative incidence of cardiovascular diseases was 50% (95% CI, 47%-52%). Fifty-one percent of patients with a cardiovascular disease developed multiple events. For patients treated before 25 years of age, cumulative incidences at 60 years or older were 20%, 31%, and 11% for CHD, VHD, and HF as first events, respectively. Mediastinal radiotherapy increased the risks of CHD (hazard ratio [HR], 2.7; 95% CI, 2.0-3.7), VHD (HR, 6.6; 95% CI, 4.0-10.8), and HF (HR, 2.7; 95% CI, 1.6-4.8), and anthracycline-containing chemotherapy increased the risks of VHD (HR, 1.5; 95% CI, 1.1-2.1) and HF (HR, 3.0; 95% CI, 1.9-4.7) as first events compared with patients not treated with mediastinal radiotherapy or anthracyclines, respectively. Joint effects of mediastinal radiotherapy, anthracyclines, and smoking appeared to be additive.

CONCLUSIONS AND RELEVANCE Throughout their lives, HL survivors treated at adolescence or adulthood are at high risk for various cardiovascular diseases. Physicians and patients should be aware of this persistently increased risk.

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Hodgkin lymphoma (HL) is the prototype of a curable malignant neoplasm, with 10-year survival rates currently exceeding 80%.[1] Consequently, the number of long-term survivors is increasing every year. Treatment for HL has been associated with adverse late effects, such as increased risks of secondary malignant neoplasms and cardiovascular diseases.[2-5] Late cardiovascular complications may arise as a consequence of radiotherapy and chemotherapy and cause substantial excess morbidity and mortality in long-term HL survivors.[2,6-8]

Several studies[2,9-12] observed high risks of cardiac mortality in HL survivors after 15 to 25 years of follow-up. Survivors treated before 21 years of age appeared to have the highest relative risk of death from cardiovascular diseases.[2,9] We and others also found that HL survivors have an increased risk of cardiac morbidity.[7,8,13] Few studies[8,13] have compared cardiovascular disease incidence in HL survivors and the general population.

In studies published so far, follow-up rarely exceeded 20 to 25 years. Because most patients with HL are young at diagnosis and cure rates are high, patients in previous reports had often not yet reached the ages at which cardiovascular diseases become more common in the general population. Therefore, studies with prolonged follow-up are needed to assess long-term effects of treatment (eg, when patients with HL enter their sixth or seventh decade of life). Furthermore, the interaction between mediastinal radiotherapy and anthracycline-containing chemotherapy in patients with HL across a broad range of ages at treatment has hardly been studied because follow-up of anthracycline-treated patients was short in most published studies.

This study examined relative and absolute excess cardiovascular disease risk up to 40 years after treatment for HL compared with cardiovascular disease incidence in the general population. In addition, this study examined treatment-related cardiovascular disease risk factors in a cohort of patients with HL treated from January 1, 1965, through December 31, 1995.

Methods

Cardiovascular disease risk was studied in a multicenter, hospital-based cohort (N = 2604) of patients treated for HL in 5 Dutch university hospitals or cancer centers. Patient selection has been described in detail previously.[2,4,13-15] Briefly, patients received their first treatment for HL from January 1, 1965, through December 31, 1995, before the age of 51 years and had survived 5 years or more after HL diagnosis.

From the medical records, data on dates of birth and HL diagnosis, histologic findings, stage, and primary and recurrence treatment (radiation fields, prescribed radiotherapy dose, chemotherapy regimens, and number of cycles) were collected. In addition, follow-up information on cardiovascular events and smoking was retrieved by contacting general practitioners and cardiologists in 2004 (complete follow-up for 94%)[13,14] and in 2013 (complete follow-up for 83%). Vital status and dates of death were obtained up to July 2013 by linkage with the Dutch Central Bureau of Genealogy. This study was exempt from institutional review board approval according to Dutch law because existing data from medical files were used.

The following cardiovascular events were included: coronary heart disease (CHD), including myocardial infarction and angina pectoris; valvular heart disease (VHD); and heart failure (HF), including congestive heart failure and cardiomyopathy. Fatal incident cardiovascular events are registered by general practitioners in the Netherlands and were also included as events in the analyses. All events were defined and graded according to a slightly adapted version of the Common Terminology Criteria for Adverse Events, version 4.0 (eAppendix in the Supplement).[16] The data abstraction forms and coding instructions were developed in collaboration with physicians, and the Common Terminology Criteria for Adverse Events can be used to properly grade cardiovascular events from medical records.[17] The any cardiovascular event analyses were used to assess the burden of disease, whereas the first cardiovascular event analysis was performed to study risk factors for the event concerned.

Over time, a wide variety of treatment regimens was used in the study population. Most patients were treated according to European Organisation for Research and Treatment of Cancer Lymphoma Group protocols.[18-22] Frequently used treatments and changes over time have been described in detail previously.[13,23] In the 1960s, patients were treated with orthovoltage therapy or cobalt 60; from the 1970s onward, linear accelerators were used. Individual blocks were used to shield normal tissues as much as possible. Patients usually received 40 Gy in fractions of 1.5 to 2.0 Gy when they were treated with radiotherapy only and 30 to 36 Gy when they also received chemotherapy. Mantle field irradiation (including mediastinal, axillary, and neck nodes) was the most commonly applied radiation from the early 1970s to the late 1980s. Since the late 1980s, an increasing number of patients received more limited radiation fields (involved fields). Three-dimensional planning was not used in the current study population. Prescribed radiation dose to the mediastinum was used as a proxy for radiation dose to the heart.

From the 1960s to the 1980s, chemotherapy consisted mainly of mechlorethamine hydrochloride, vincristine sulfate [Oncovin], procarbazine, and prednisone (MOPP). In the 1980s, anthracycline-containing regimens, such as MOPP and doxorubicin hydrochloride [Adriamycin], bleomycin sulfate, and vinblastine sulfate (ABV) and ABV and dacarbazine (ABVD), were introduced as part of primary treatment. Anthracycline dose was estimated in milligrams of anthracycline per square meter of body surface based on number of cycles received times the standard anthracycline dose in the corresponding chemotherapy regimen during that period. Standard doses of anthracycline per regimen per cycle were 25 mg/m^2 at days 1 and 15 for ABVD and hybrid MOPP-ABV and 35 mg/m^2 at day 8 for alternating MOPP-ABVD.

Statistical Analysis

Comparison With the General Population

The incidence of CHD and HF in the cohort was compared with age-, sex-, and calendar period–specific cardiovascular dis-

ease incidence rates for the Dutch population, accounting for person-years of observation. No reference incidence data were present for VHD. Cardiovascular disease incidence data from the Continuous Morbidity Registration Nijmegen of general practices were used as a reference for the calendar period of 1971 to 2001.[24,25] For 2002 to 2011, we used reference data from the Netherlands Institute for Health Services Research Primary Care Database.[26] Standardized incidence ratios (SIRs) were calculated as the ratios of the observed and expected numbers of cardiovascular events in our cohort. Because expected numbers were based on the registration of multiple events per patient, observed numbers were calculated accordingly. Absolute excess risk was calculated as the observed number of events minus the number expected divided by the number of person-years at risk multiplied by 10 000.

Time at risk of cardiovascular diseases began 5 years after the start of first treatment for HL and ended at the date of diagnosis of cardiovascular disease, the date of most recent medical information, the date of migration, or the date of death, whichever came first. Patients diagnosed as having cardiovascular diseases before HL diagnosis (n = 18) or less than 5 years after HL diagnosis (n = 62) were excluded. The 95% CIs of the SIRs and tests for heterogeneity were performed according to standard methods.[27] Generalized linear models with Poisson distributions were used to test for heterogeneity and trends.

Within-Cohort Comparisons

The cumulative incidence of cardiovascular diseases was estimated in the presence of death from any cause as a competing risk.[28] When specific cardiovascular diseases occurring as a first event were analyzed separately, all other cardiovascular events were considered competing risks as well. Multivariable Cox proportional hazards regression analyses were performed to quantify the effects of different treatments and smoking on cardiovascular disease risk within the patient group, adjusting for confounders. Model fit and model assumptions were assessed using graphic and residual-based methods. All Cox proportional hazards regression models were stratified for age at HL diagnosis because hazards were nonproportional by age. Interactions between mediastinal radiotherapy and anthracycline dose and between mediastinal radiotherapy and smoking at HL diagnosis were tested using standard methods. All analyses were performed using STATA statistical software (Stata Corp). $P < .05$ was considered statistically significant.

Results

Patient characteristics are listed in **Table 1**. In total, 2524 patients were included in the analyses. Median age at HL diagnosis was 27.3 years. A total of 2052 patients (81.3%) had received mediastinal radiotherapy, and 773 (30.6%) had received anthracycline-containing chemotherapy. After a median follow-up of 20.3 years (range, 5-47 years), we identified 1713 cardiovascular events in 797 patients; 410 patients (51.4%) developed 2 events or more. The most frequently occurring cardiovascular disease was CHD, with 401 patients developing CHD as their first event (eTable 1 in the Supplement), followed by VHD (374 events) and HF (140 events). A total of 1321 cardiovascular events (77.1%) could be graded. Of the VHDs, 429 (67.0%) were grade 2 or higher, and 243 (38.0%) were grade 3 or higher. Of HFs, 140 (77.0%) were grade 3 or higher (eTable

Table 1. Patient Characteristics[a]

Characteristic	Total Cohort	Patients With Cardiovascular Disease
All patients	2524 (100)	797 (31.6)
Sex		
Male	1370 (54.3)	440 (55.2)
Female	1154 (45.7)	357 (44.8)
Age at first HL treatment, median (IQR), y	27.3 (21.3-35.1)	28.8 (22.0-36.3)
Age at first HL treatment, y		
3-17	296 (11.7)	81 (10.2)
18-24	732 (29.0)	216 (27.1)
25-29	454 (18.0)	133 (16.7)
30-39	678 (26.9)	239 (30.0)
40-50	364 (14.4)	128 (16.0)
Treatment period		
1965-1969	323 (12.8)	117 (14.7)
1970-1974	381 (15.1)	150 (18.8)
1975-1979	433 (17.2)	160 (20.1)
1980-1984	444 (17.6)	153 (19.2)
1985-1990	465 (18.4)	137 (17.2)
1990-1995	478 (18.9)	80 (10.0)
Time of follow-up or to cardiovascular disease, median (IQR), y	20.3 (14.0-26.6)	20.6 (14.6-26.7)
Time of follow-up or to cardiovascular disease, y		
5-9	352 (14.0)	78 (9.8)
10-19	876 (34.7)	298 (37.4)
20-29	893 (35.4)	102 (12.8)
30-39	357 (14.1)	102 (12.8)
≥40	46 (1.8)	10 (1.2)
Treatment of HL[b]		
No radiotherapy		
Chemotherapy without anthracyclines	111 (4.4)	18 (2.3)
Chemotherapy with anthracyclines	58 (2.3)	6 (0.8)
Radiotherapy only below diaphragm		
No chemotherapy	68 (2.7)	9 (1.1)
Chemotherapy without anthracyclines	120 (4.8)	18 (2.3)
Chemotherapy with anthracyclines	111 (4.4)	19 (2.4)
Mediastinal radiotherapy, with or without radiotherapy below diaphragm		
No chemotherapy	677 (26.9)	304 (38.3)
Chemotherapy without anthracyclines	771 (30.6)	262 (33.0)
Chemotherapy with anthracyclines	604 (24.0)	158 (19.9)

(continued)

Table 1. Patient Characteristics (continued)[a]

Characteristic	Total Cohort	Patients With Cardiovascular Disease
Prescribed mediastinal radiotherapy dose in patients receiving mediastinal radiotherapy, median (IQR), Gy	37 (30-40)	39 (35-40)
Prescribed mediastinal radiotherapy dose, Gy[c]		
0 (No mediastinal radiotherapy received)	471 (18.6)	72 (9.0)
10-29	57 (2.3)	17 (2.1)
30-35	177 (7.0)	92 (11.6)
≥36	534 (21.2)	286 (35.9)
Unknown	1285 (50.9)	330 (41.4)
Prescribed anthracycline dose in patients receiving anthracyclines, median (IQR), mg/m^2	210 (210-300)	210 (210-300)
Prescribed anthracycline dose, mg/m^2[d]		
0 (No anthracyclines received)	1751 (69.4)	614 (77.0)
35-200	180 (7.1)	40 (5.0)
201-325	428 (16.9)	110 (13.8)
326-880	131 (5.2)	27 (3.4)
Unknown	34 (1.4)	6 (0.8)
Smoking		
Smoking at HL diagnosis	1110 (44.0)	393 (49.3)
Ever smoking	1057 (41.9)	407 (51.1)
Attained age, median (IQR), y	49.4 (41.0-57.0)	50.9 (43.6-57.2)
Vital status at date of last contact		
Alive	1435 (56.9)	406 (50.9)
Deceased	1089 (43.1)	391 (49.1)

Abbreviations: HL, Hodgkin lymphoma; IQR, interquartile range.

[a] Data are presented as number (percentage) of patients unless otherwise indicated. Numbers may not total 100% because of missing values.

[b] Treatment includes primary and relapse treatment for HL.

[c] Total prescribed dose, usually applied in fractions of 2 Gy for 5 fractions per week (range, 10-80 Gy).

[d] Total prescribed dose based on number of cycles: 6 cycles of ABVD (doxorubicin hydrochloride [Adriamycin], bleomycin sulfate, vinblastine sulfate, and dacarbazine) (300 mg/m^2), 6 alternating cycles of MOPP (mechlorethamine hydrochloride, vincristine sulfate [Oncovin], procarbazine, and prednisone) and ABVD (300 mg/m^2), and 6 hybrid cycles of MOPP and ABV (doxorubicin hydrochloride [Adriamycin], bleomycin sulfate, and vinblastine sulfate) (210 mg/m^2) (range, 35-880 mg/m^2).

1 in the Supplement). Median intervals between HL treatment and first events were 18, 24, and 19 years for CHD, VHD and HF, respectively.

Comparison With the General Population

Survivors of HL had a 3.2-fold increased SIR (95% CI, 3.0-3.5) of developing a CHD and a 6.8-fold increased SIR (95% CI, 5.9-7.6) of developing HF compared with the general population, corresponding to 70 and 58 excess cases of CHD and HF per 10 000 person-years, respectively (**Table 2**). When only considering first CHD or HF events, SIRs were substantially elevated as well (eTable 2 in the Supplement).

Although SIRs were significantly increased for all age categories, patients treated at a younger age had higher SIRs than patients treated for HL above the age of 35 years. Patients treated before 25 years of age experienced a 4.6- to 7.5-fold increased risk of CHD and a 10.9- to 40.5-fold increased SIR of HF depending on their attained age (*P* for trend across attained age categories <.001 and <.001, respectively). Patients treated at 35 to 50 years of age experienced a 2.0- to 2.3-fold increased risk of CHD and 3.1- to 5.2-fold increased risk of HF depending on their attained age (*P* for trend across attained age categories = .17 and .15, respectively) (Table 2). The risks of CHD and HF remained significantly increased beyond 35 years after HL treatment (SIR, 3.9; 95% CI, 2.6-5.6; and SIR, 5.8; 95% CI, 3.8-8.5; respectively), resulting in high absolute excess risks of 475 and 382 per 10 000 person-years, respectively (Table 2 and eFigure 1 in the Supplement). When only considering first CHD and HF events, the SIR for CHD remained significantly increased up to 30 years or more after HL treatment compared with the general population (eTable 2 and eFigure 2 in the Supplement). The SIR for HF remained elevated as well although not statistically significantly so from more than 30 years after HL treatment.

Within Cohort Comparisons

At 40 years after HL, the cumulative incidence of any cardiovascular disease amounted to 49.5% (95% CI, 46.6%-52.4%). Patients treated with mediastinal radiotherapy had a 40-year cumulative incidence of any cardiovascular disease of 54.6% (95% CI, 51.2%-57.9%) compared with 24.7% (95% CI, 17.2%-32.9%) in patients not treated with mediastinal radiotherapy or anthracyclines (**Figure 1**A). Cumulative incidence curves appeared similar for patients treated in 1965 through 1974, 1975 through 1984, and 1985 through 1995 (eFigure 3 in the Supplement). Forty-year cumulative incidences for CHD and VHD as first events were 22.9% (95% CI, 20.7%-25.1%) and 25.9% (95% CI, 23.4%-28.5%), respectively (Figure 1B). Heart failure most frequently occurred as a subsequent event; the cumulative incidence of HF as a first event was only 8.1% (95% CI, 6.7%-9.7%) after 40 years, whereas the 40-year cumulative incidence for any HF was 24.8% (95% CI, 21.4%-28.4%) 40 years after HL treatment.

Patients treated before 25 years of age had a higher cumulative incidence of cardiovascular diseases at any attained age (**Figure 2**). Patients treated before 25 years of age reached a given cumulative incidence 10 to 20 years earlier than patients treated at an older age. For example, a 50-year-old survivor treated before 25 years of age experienced the same absolute risk as a 61-year-old survivor treated at 35 to 50 years of age (Figure 2A).

Adjusted for year of HL diagnosis, sex, and ever smoking, mediastinal radiotherapy and anthracycline-containing chemotherapy were associated with increased risk of any cardiovascular disease (hazard ratio [HR] for mediastinal radiotherapy, 3.6; 95% CI, 2.8-4.6; HR for anthracycline chemotherapy, 1.5; 95% CI, 1.2-1.8) (**Table 3**). Radiation below the diaphragm or vincristine-containing chemotherapy did not influence the risks of any cardiovascular disease. The association between mediastinal radiotherapy and cardiovascular disease risk appeared to be strongest for VHD when evaluating risk for a first event (HR, 6.6; 95% CI, 4.0-10.8) (Table 3) and

Table 2. SIRs and AERs for Any Coronary Heart Disease and Heart Failure Event[a]

Characteristic	Any CHD[b]				Any HF[c]			
	Observed, No.	SIR (95% CI)	*P* for Heterogeneity or Trend	AER	Observed, No.	SIR (95% CI)	*P* for Heterogeneity or Trend	AER
Total	480	3.2 (3.0-3.5)		70	251	6.8 (5.9-7.6)		58
Sex								
Male	313	3.1 (2.8-3.5)	.19	101	112	6.9 (5.8-8.2)	.68	62
Female	167	3.5 (3.0-4.1)		59	139	6.6 (5.4-7.9)		54
Treatment								
No mediastinal radiotherapy, no anthracyclines	35	1.1 (0.8-1.6)	<.001	7	11	1.3 (0.7-2.4)	<.001	5
Anthracyclines, no mediastinal radiotherapy	16	2.1 (1.2-3.3)		40	6	4.0 (1.5-8.7)		22
Mediastinal radiotherapy, no anthracyclines	348	3.8 (3.4-4.2)		99	175	7.3 (6.3-8.5)		69
Mediastinal radiotherapy and anthracyclines	81	4.5 (3.6-5.6)		86	59	16.9 (12.8-21.8)		77
Age at treatment, y								
<18	35	8.8 (6.3-12.3)	<.001	53	25	38.9 (25.2-57.4)	<.001	48
18-24	118	5.4 (4.5-6.5)		72	70	18.7 (14.5-23.6)		59
25-29	81	4.1 (3.3-5.1)		84	40	10.4 (7.5-14.2)		56
30-39	154	2.8 (2.4-3.3)		94	71	5.7 (4.4-7.2)		61
40-50	92	2.0 (1.6-2.4)		100	45	2.7 (2.0-3.7)		67
Age at treatment <25 years								
Attained age <45 years	79	7.5 (5.9-9.3)	<.001	43	54	40.5 (30.4-52.9)	<.001	41
Attained age 45-59 years	64	4.6 (3.6-5.9)		161	36	13.8 (9.7-19.2)		97
Attained age ≥60 years	10	6.9 (3.3-12.7)		478	5	10.9 (3.5-25.4)		207
Age at treatment 25-34 years								
Attained age <45 years	42	3.5 (2.5-4.7)	.001	40	11	9.2 (4.6-16.4)	<.001	18
Attained age 45-59 years	111	3.7 (3.0-4.4)		145	52	8.9 (6.7-11.7)		78
Attained age ≥60 years	13	1.5 (0.8-2.5)		53	10	2.9 (1.4-5.4)		66
Age at treatment 35-50 years								
Attained age <45 years	4	2.0 (0.6-5.2)	.17	28	1	5.2 (0.1-29.2)	.15	17
Attained age 45-59 years	95	2.3 (1.9-2.8)		97	33	5.1 (3.5-7.2)		56
Attained age ≥60 years	62	2.2 (1.7-2.8)		161	49	3.1 (2.3-4.1)		129
Follow-up period, y								
5-9	54	2.3 (1.7-3.0)	.02	26	12	4.8 (2.5-8.3)	.49	13
10-14	82	2.9 (2.3-3.6)		53	26	6.1 (4.0-8.9)		26
15-19	109	3.7 (3.0-4.4)		97	51	8.0 (5.9-10.5)		55
20-24	96	3.6 (2.9-4.4)		127	66	8.7 (6.7-11.0)		97
25-29	72	3.5 (2.7-4.4)		155	45	6.5 (4.7-8.7)		101
30-34	38	3.1 (2.2-4.3)		152	25	5.1 (3.3-7.5)		101
≥35	29	3.9 (2.6-5.6)		475	26	5.8 (3.8-8.5)		382

Abbreviations: AER, absolute excess risk; CHD, coronary heart disease; HF, heart failure; SIR, standardized incidence ratio.

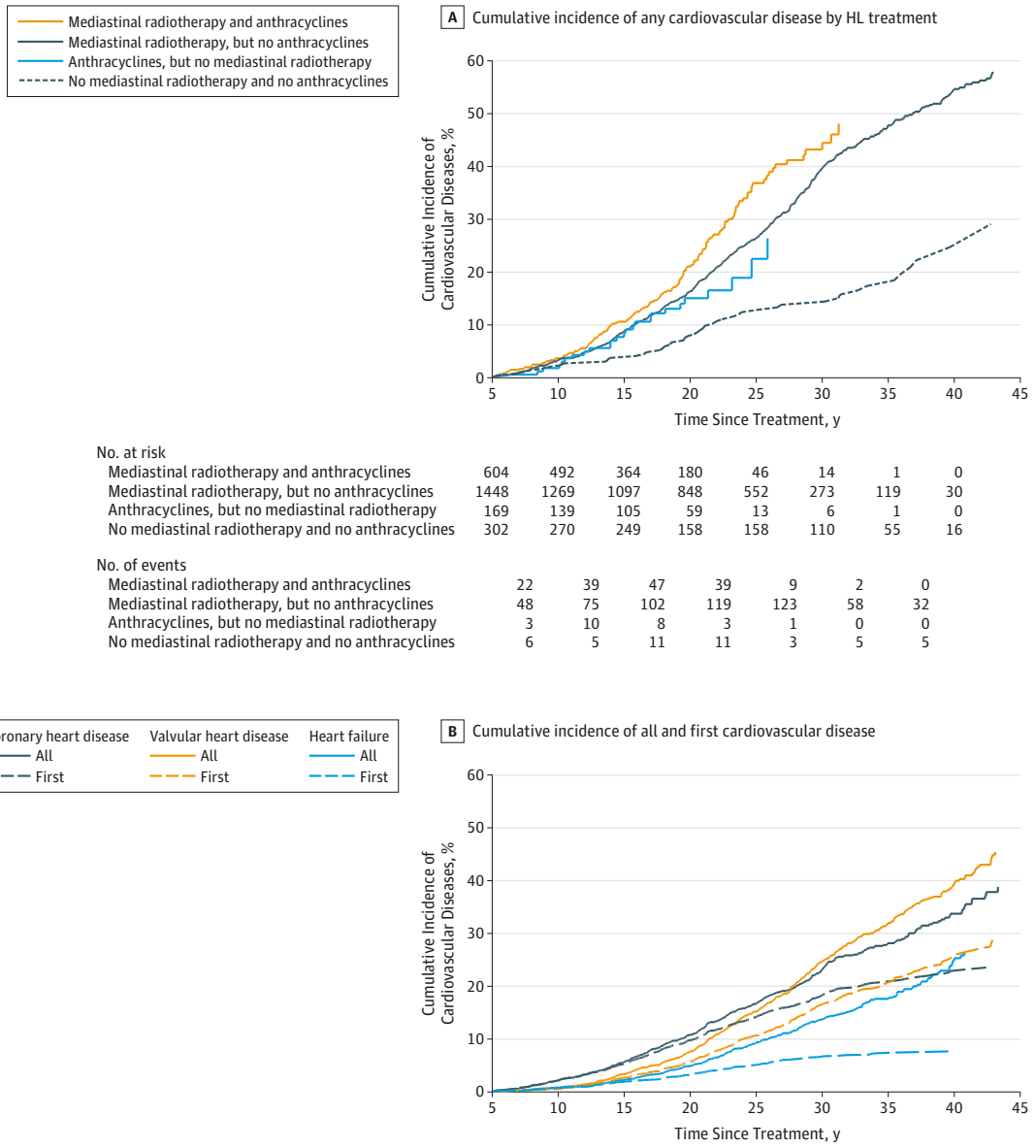
[a] Reference data from 1971 through 2001 originated from the Continuous Morbidity Registration Nijmegen, and data from 2002 through 2011 originated from the Netherlands Institute for Health Services Research because of a larger source population of general practices. These data are derived from routine electronic health records from 85 general practices.

[b] CHD includes both acute myocardial infarction and angina pectoris.

[c] HF includes both cardiomyopathy and congestive heart failure (HF was left censored before January 1, 1989).

risk of any VHD event (HR, 5.2; 95% CI, 3.6-7.6) (eTable 3 in the Supplement). Mediastinal radiotherapy was also associated with an increased risk of CHD (HR, 2.7; 95% CI, 2.0-3.7) and HF (HR, 2.7; 95% CI, 1.6-4.8) as a first event. Risk of all cardiovascular diseases combined and of VHD and HF as first events increased with a higher prescribed mediastinal radiation dose (*P* for trend = .003, .02, and .03, respectively). Anthracycline-containing chemotherapy was associated with increased risks of VHD (HR, 1.5; 95% CI, 1.1-2.1) and HF (HR, 3.0; 95% CI, 1.9-4.7) as first events but not with CHD (Table 3). Risk of VHD increased with higher anthracycline dose (*P* = .04). No clear dose-response relationship could be identified for HF as a first event; risk of HF was already strongly increased for low anthracycline doses (Table 3).

Figure 1. Cumulative Incidence of Cardiovascular Diseases With Death From Any Cause as a Competing Risk



HL indicates Hodgkin lymphoma.

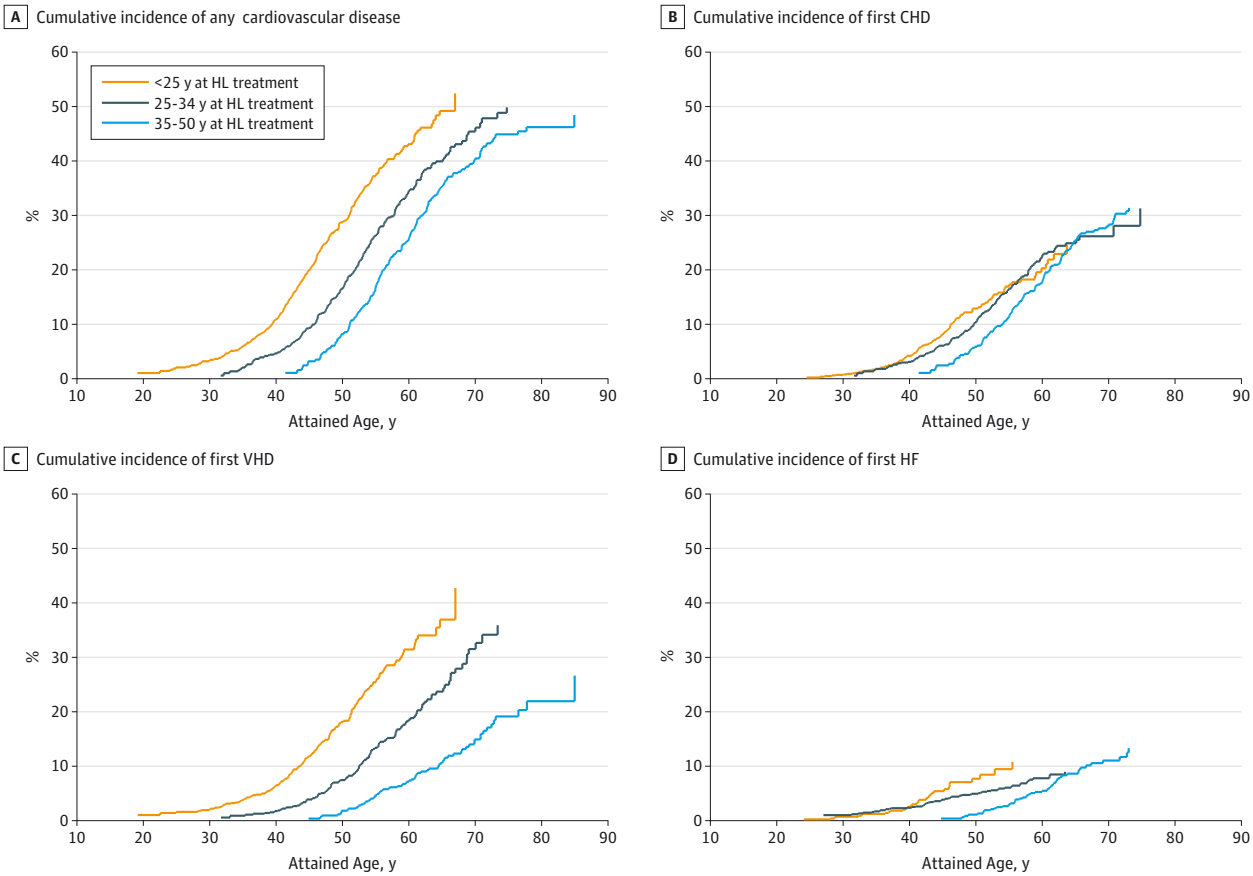
No interactions on a multiplicative scale were found between mediastinal radiotherapy and anthracycline dose or mediastinal radiotherapy and smoking; the joint effects of these outcomes appeared to be additive rather than multiplicative (Table 3).

When examining whether treatment-related cardiovascular disease risk changed in the course of follow-up, we observed that the risks for any cardiovascular disease and first CHD after mediastinal radiotherapy were statistically significantly higher after 20 to 47 years of follow-up than in the 5 to 20 years of follow-up interval (*P* for interaction = .002 and .01, respectively) (eTable 4 in the Supplement). Anthracycline-associated risk did not seem to alter with increasing follow-up time (*P* for interaction >.05). However, after 20 years of follow-up, anthracycline-associated risk was still significantly elevated for any cardiovascular disease and VHD and HF as first events (eTable 4 in the Supplement).

Discussion

To the best of our knowledge, our study is the first to report cardiovascular disease incidence for such a long period after HL treatment, to examine combined effects of age at treatment and attained age, and to evaluate interactions between anthracycline dose and mediastinal radiotherapy in a large cohort treated across a broad age range. We observed that HL survivors experience increased risks of cardiovascular diseases up

Figure 2. Cumulative Incidence of Any and Different Cardiovascular Diseases by Attained Age for Different Groups of Age at Hodgkin Lymphoma (HL) Diagnosis (With Death From Any Cause as a Competing Risk)



CHD indicates coronary heart disease; HF, heart failure; and VHD, valvular heart disease.

to at least 40 years after initial HL treatment. Compared with the general population, 4- to 7-fold increased risks of CHD or HF are observed 35 years or more after HL treatment, resulting in 857 excess cardiovascular events per 10 000 person-years. The cumulative incidence of any type of cardiovascular disease amounted to 50% at 40 years after HL diagnosis. Patients who received mediastinal radiotherapy experienced increased risk of not only CHD but also VHD and HF. Anthracycline-containing chemotherapy was associated with increased HF and VHD risk. Half of the patients with a cardiovascular disease developed multiple cardiovascular events. Although patients treated at younger ages had the highest relative risk of cardiovascular disease compared with age-matched peers in the general population, substantial absolute excess risks were also seen for patients treated at 40 years or older.

Only a few studies[13,29] observed an association between anthracyclines and VHD. The pathophysiologic mechanism behind this association is still unclear. Because anthracycline-containing chemotherapy has been associated with HF[13,30,31] and HF can result in valvular dysfunction by dilation of the ventricles,[32,33] asymptomatic HF may underlie this association. Another possibility is that anthracyclines damage the papillary muscles of the valves, causing valvular regurgitation. Allen et al[33] suggest that anthracycline-related papillary muscle dysfunction, which is too subtle to be detected by changes in fractional shortening, may result in mitral regurgitation.

We did not find evidence of multiplicative interaction between mediastinal radiotherapy and anthracycline-containing chemotherapy for any cardiovascular disease. Our analysis examining risks for various combinations of anthracycline dose, mediastinal radiotherapy, and smoking suggests additive effects of these risk factors. This finding is in line with the results of Myrehaug et al,[11] who found a nonsignificant supra-additive interaction between mediastinal radiotherapy and anthracyclines for cardiac morbidity in a cohort of 615 HL survivors. Studies[29,34-37] in childhood cancer survivors and survivors of other cancers, such as breast cancer, did not address this issue in depth or had insufficient power to study interactions between treatment modalities.

The risk of cardiovascular diseases did not appear to decrease in the more recent decades: high risk of cardiovascular diseases was also found in patients treated in the 1990s. This finding may be attributable to the large number of patients undergoing mediastinal radiotherapy with cardiac

Table 3. Risk of First Cardiac Event After Hodgkin Lymphoma (HL) Treatment

Characteristic	Any Cardiovascular Event		First Events, HR (95% CI)[a]		
	No./Total No.	HR (95% CI)	CHD[b]	VHD	HF[c]
No. of events		797	400	358	139
Univariate models					
Mediastinal radiotherapy (yes vs no)	724/2052	2.9 (2.3-3.7)[d]	2.0 (1.5-2.7)[d]	5.9 (3.7-9.5)[d]	2.3 (1.3-3.9)[d]
Mediastinal radiotherapy dose (prescribed), Gy					
No mediastinal radiotherapy	72/471	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1-29	17/57	2.1 (1.2-3.6)[d]	1.2 (0.6-2.7)	4.2 (1.8-9.8)[d]	1.7 (0.5-5.7)[d]
30-35	92/177	3.1 (2.3-4.2)[d]	2.3 (1.1-3.4)[d]	4.8 (2.7-8.4)[d]	2.4 (1.0-4.8)[d]
≥36	286/534	3.8 (3.0-5.0)[d]	2.2 (1.6-3.1)[d]	7.2 (4.4-11.8)[d]	4.0 (2.3-7.0)[d]
Anthracycline-containing chemotherapy (yes vs no)	183/773	1.6 (1.3-1.9)[d]	1.2 (0.9-1.5)	2.0 (1.5-2.6)[d]	2.2 (1.5-3.2)[d]
Anthracycline dose, mg/m^2					
No anthracycline-containing chemotherapy	614/1751	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
35-200	40/180	1.5 (1.1-2.1)[d]	1.4 (0.9-2.2)	1.3 (0.8-2.4)	1.7 (0.8-3.6)
210-325	110/428	1.6 (1.3-1.9)[d]	1.1 (0.8-1.4)	2.2 (1.6-2.9)[d]	2.2 (1.4-3.4)[d]
350-880	27/131	2.3 (1.3-3.9)[d]	1.0 (0.4-2.7)	3.7 (1.7-8.0)[d]	4.5 (1.8-11.2)[d]
Sex (female vs male)	357/1154	0.8 (0.7-0.95)[d]	0.5 (0.4-0.6)[d]	1.3 (1.1-1.6)[d]	1.0 (0.7-1.3)
Ever smoking (yes vs no)	407/1057	1.4 (1.3-1.7)[d]	1.7 (1.4-2.1)[d]	0.9 (0.8-1.1)	1.5 (1.1-2.1)[d]
Model 1[e]					
Mediastinal radiotherapy (yes vs no)	724/2052	3.6 (2.8-4.6)[d]	2.7 (2.0-3.7)[d]	6.6 (4.0-10.8)[d]	2.7 (1.6-4.8)[d]
Model 2[e]					
Mediastinal radiotherapy dose, Gy					
No mediastinal radiotherapy	72/471	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1-29	17/57	2.3 (1.3-3.8)[d]	1.5 (0.7-3.3)	4.2 (1.8-9.7)[d]	1.6 (0.5-5.6)
30-35	92/177	3.7 (2.7-5.0)[d]	2.8 (1.9-4.2)[d]	5.7 (3.2-10.2)[d]	2.8 (1.2-5.7)[d]
≥36	286/534	4.6 (3.5-6.0)[d]	2.8 (2.0-4.0)[d]	8.4 (5.0-13.9)[d]	4.7 (2.6-8.4)[d]
Model 3[f]					
Anthracycline-containing chemotherapy (yes vs no)	183/773	1.5 (1.2-1.8)[d]	1.0 (0.8-1.4)	1.5 (1.1-2.1)[d]	3.0 (1.9-4.7)[d]
Model 4[f]					
Anthracycline dose, mg/m^2					
No anthracycline-containing chemotherapy	614/1751	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
35-200	40/180	1.4 (1.01-2.0)[d]	1.2 (0.8-1.9)	1.1 (0.6-2.0)	2.4 (1.1-5.0)[d]
210-325	110/428	1.4 (1.1-1.7)[d]	0.9 (0.6-1.3)	1.5 (1.1-2.2)[d]	3.1 (1.9-5.2)[d]
350-880	27/131	2.1 (1.2-3.5)[d]	0.8 (0.3-2.3)	3.3 (1.5-7.1)[d]	4.8 (1.9-12.1)[d]
Joint effects of risk factors					
Mediastinal radiotherapy and anthracycline chemotherapy					
No mediastinal radiotherapy or anthracyclines	47/302	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Anthracycline dose, mg/m^2					
<250 (No mediastinal radiotherapy)	15/83	3.1 (1.8-5.5)[d]	3.1 (1.6-6.0)[d]	4.0 (1.3-12.6)[d]	1.6 (0.3-7.5)
≥250 (No mediastinal radiotherapy)	8/77	2.1 (0.9-4.9)	0.6 (0.1-2.4)	3.9 (0.9-17.5)	4.5 (1.2-16.8)[d]
Mediastinal radiotherapy					
No anthracyclines	566/1448	3.5 (2.6-4.8)[d]	2.4 (1.6-3.4)[d]	7.1 (4.0-12.7)[d]	2.6 (1.3-5.2)[d]
Mediastinal radiotherapy and anthracycline dose, mg/m^2					
<250	77/338	4.9 (3.4-7.1)[d]	2.2 (1.4-3.6)[d]	12.3 (6.4-23.9)[d]	5.4 (2.5-11.9)[d]
≥250	77/241	6.5 (4.4-9.5)[d]	2.9 (1.8-4.8)[d]	17.3 (8.8-33.9)[d]	6.5 (2.8-15.1)[d]

(continued)

Table 3. Risk of First Cardiac Event After Hodgkin Lymphoma (HL) Treatment (continued)

Characteristic	Any Cardiovascular Event		First Events, HR (95% CI)[a]		
	No./Total No.	HR (95% CI)	CHD[b]	VHD	HF[c]
Smoking at HL diagnosis and mediastinal radiotherapy					
No mediastinal radiotherapy, no smoking at HL diagnosis	26/258	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Mediastinal radiotherapy, no smoking at HL diagnosis	364/1209	4.3 (2.8-6.6)[d]	2.9 (1.7-5.0)[d]	6.7 (3.4-13.1)[d]	3.7 (1.4-10.2)[d]
No mediastinal radiotherapy, smoking at HL diagnosis	46/213	2.4 (1.5-4.0)[d]	2.8 (1.5-5.2)[d]	1.1 (0.4-2.9)	2.8 (0.9-8.9)
Mediastinal radiotherapy and smoking at HL diagnosis	360/843	5.9 (3.8-9.0)[d]	4.8 (2.8-8.2)[d]	6.4 (3.2-12.5)[d]	5.4 (2.0-14.9)[d]

Abbreviations: CHD, coronary heart disease; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.

[a] For first event analyses, only those cardiac events that occurred as a first cardiac event in a patient were included.

[b] CHD includes both acute myocardial infarction and angina pectoris.

[c] HF includes both cardiomyopathy and congestive heart failure.

[d] $P < .05$.

[e] Adjusted for year of HL diagnosis, sex, anthracycline-containing chemotherapy, and ever smoking.

[f] Adjusted for year of HL diagnosis, sex, mediastinal radiotherapy, and ever smoking.

exposure, albeit with somewhat more limited radiation fields and doses, and to combined treatment with cardiotoxic chemotherapy. Modeling studies by Maraldo et al,[38,39] however, predict reduced cardiac morbidity and mortality with modern radiotherapy techniques introduced since the late 1990s.

A strength of our study is the use of general practitioner- and cardiologist-reported outcomes instead of patient-reported outcomes, reducing potential misclassification bias. The high response rate from the general practitioners renders selection bias unlikely. Furthermore, we were able to grade most cardiovascular events. Most graded events were moderate to severe (grade ≥2, 83%), confirming that this population was not routinely screened for cardiovascular diseases. There is no cardiovascular screening program for HL survivors in the Netherlands. However, a subpopulation (a part of the females treated with mediastinal radiotherapy) was recalled for breast cancer screening (not for cardiovascular screening). Physical examination probably frequently included auscultation of the heart, possibly leading to identification of asymptomatic cardiovascular disease. However, no striking differences were seen in cardiovascular disease incidence between males and females, and no effect modification was found by sex, rendering it unlikely that breast cancer surveillance led to increased incidence of cardiovascular diseases.

Our results have important implications for long-term HL survivors. Screening guidelines for childhood cancer survivors treated with mediastinal radiotherapy and anthracyclines have been developed[40-42] and should be extended to survivors of adult HL. Our results are also important for patients with HL treated to date because anthracyclines continue to be used as standard treatment for HL and various other cancers, such as breast cancer. Furthermore, mediastinal radiotherapy is still indicated for substantial numbers of patients with HL,[43,44] although smaller radiation fields and more modern radiotherapy techniques are used. Currently applied doses (20-30 Gy for 10-15 fractions) are lower than in our study but may still be cardiotoxic. Consistent with other studies, we found a dose-response relationship for prescribed mediastinal radiotherapy dose and cardiovascular disease risk. A limitation of this study is, however, that radiation dose-response relationships could not be studied in more depth because radiation dosimetry could not be performed for the entire study population. Future studies of radiation dose-response relationships using doses to specific cardiac structures can guide modern radiotherapy planning in patients with newly diagnosed HL by providing specific dose constraints.

Conclusions

Survivors of HL remain at substantially increased risk of various cardiovascular diseases for at least 40 years after HL diagnosis. A sizeable proportion of HL survivors develop multiple events over time. Treating physicians and patients should be aware of the persistently increased risk of cardiovascular diseases throughout life, and the results of our study may direct guidelines for follow-up of patients with HL.

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Invited Commentary

Caring for the Adult Survivor of Hodgkin Lymphoma
Highlighting the Need for Care Coordination

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There are currently more than 13 million individuals with a history of cancer living in the United States.[1] Of these, an estimated 400 000 are adult survivors of childhood cancer[2]; with ongoing progress in cancer treatment and supportive care, that estimate is expected to increase. Cardiovascular events, including coronary heart disease (CHD), cardiomyopathy and congestive heart failure (HF), and valvular heart disease, are the leading noncancer causes of morbidity and mortality in this population.[3] Furthermore, we know that few adult survivors of childhood cancer return to their cancer center for adult care,[4] and care for older adult cancer survivors is often fragmented, such that care for these medically complex patients is typically in the hands of primary care physicians who treat adults.

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In this issue of *JAMA Internal Medicine*, van Nimwegen and colleagues[5] from the Netherlands describe the results of a large retrospective cohort study to assess the long-term risk of clinical diagnosis of CHD, valvular heart disease, and HF among survivors of Hodgkin lymphoma (HL) compared with age-matched general population controls. Patients included survivors of HL diagnosed before 51 years of age and treated in 1 of 5 Dutch university hospitals or cancer centers from 1965 through 1995. Cardiovascular outcomes were identified from medical records and primary care physicians and cardiologists for both the survivors and controls.

van Nimwegen et al report that individuals who were treated for HL were at a significantly higher risk of developing CHD (standardized incidence ratio, 3.2) and HF (standardized incidence ratio, 6.8) than population controls. These estimates correspond to absolute excess risks of 70 and 58 cases of CHD and HF per 10 000 person-years, respectively. Furthermore, the risks were higher with longer follow-up; absolute excess risks for CHD and HF were 475 and 382 events per 10 000 person-years more than 35 years after treatment. The highest risks were among those who were treated at a younger age for their HL. Adjusting for year of diagnosis, sex, and smoking history, mediastinal radiotherapy and anthracycline chemotherapy were identified as relevant risk factors, with overall hazard ratios of 3.6 and 1.5, respectively, for any cardiovascular disease diagnosis. With this work, van Nimwegen and colleagues have expanded our understanding of this high-risk population.

What implications does this study have for the primary and secondary prevention of heart disease in individuals with nontraditional risk factors? This study is important because it adds to the increasing body of evidence regarding risk factors in cancer survivorship that do not fit into traditional cardiovascular risk models. It highlights a population (individuals living with a history of HL) for whom the natural history of cardiovascular disease is only beginning to be understood. The authors note that, in this study, individuals were not routinely screened for cardiovascular disease. Furthermore, we do not know the status of other important comorbidities, such as hypertension, obesity, diabetes mellitus, or dyslipidemia. Therefore, these results do not reveal whether screening or early intervention with traditional approaches would be effective at reducing morbidity or mortality from cardiovascular disease. In addition, the pathophysiologic mechanism of cardiovascular disease among these cancer survivors may be different than the general population; although traditional risk reduction strategies are recommended,[6,7] effectiveness is not fully known. Ultimately, we will need large, long-term prospective studies and randomized clinical trials to guide evidence-based practice in regard to defining the best approaches, taking into account potential benefits and harms. How we incorporate additional risk factors attributable to past exposures into consideration of treatment recommendations for our patients and use of currently available guidelines needs to be tailored to each clinical scenario and to take into account patient preferences. However, we are learning more about important long-term risks associated with past cancer treatment and which individuals may be at higher risk.

A considerable strength of this study is that individuals diagnosed as having HL as young adults or adults were included in the cohort, building on what we have learned from