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Mortality is persistently increased in Hodgkin's lymphoma survivors

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ABSTRACT

Background: Negative health outcomes of chronic fatigue (CF) in disease-free cancer survivors are mainly unexplored. Aims of this study were to examine mortality and causes of death in Hodgkin's lymphoma survivors (HLSs) compared to controls from the general population, and to explore if CF was associated with increased mortality.

Methods: HLSs ($n = 557$) invited to participate in a survey on late effects in 1994 were divided into three groups: participants without CF ($n = 329$), participants with CF ($n = 113$), non-participants ($n = 98$). Controls matched for gender and age were drawn from the general population (five per HLSs, $n = 2785$). Observation time was calculated from 1st January 1994 until date of death or cut-off at 1st January 2007. Kaplan–Meier plots were used for univariate analyses and Cox models for multiple covariates.

Results: Compared to controls HLSs had nearly five times higher mortality (HR = 4.93; 95% confidence interval [CI]: 3.91–6.21) and the mortality rate of HLSs was higher than the rate of their controls for the entire observation period. Mortality was increased in all groups: participants with CF: HR = 4.85 (95% CI: 3.02–7.77), participants without CF: HR = 4.35 (95% CI: 3.16–6.00), non-participants: HR = 9.45 (95% CI: 5.44–16.41).

Compared to the controls HLSs had over six times increased mortality of cancer (HR: 6.6, 95% CI: 4.7–9.2) and almost five times increased mortality of cardiovascular diseases (HR: 4.9, 95% CI: 3.1–7.9).

Conclusions: HLSs had almost five-time increased mortality compared to controls. CF was not associated with increased mortality rate. The high mortality among the non-participating HLSs indicates that serious health problems are underestimated in this group. This has implications for the interpretation of surveys in cancer survivors.

1. Introduction

Long-term survivors after Hodgkin's lymphoma (HL) are at increased risk of different morbidities after treatment, such as second cancers, cardiovascular diseases, hormonal dysfunction and infertility.[1–9] Previous studies have shown that Hodgkin's lymphoma survivors (HLSs) also have increased mortality when compared to expected death rates in the

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general population.[2,10–12] Few studies have examined mortality in HLSs observed for more than 12 years from diagnosis.[2] Patients treated for HL before the age of 41 years in the period 1965–1987 (median follow-up 17.8 years, $n = 1261$) were reported to have a 6.8 times higher relative risk (RR) of death from all causes other than HL compared to the general population.[2] Another survey reported that the RR of mortality from all causes remained significantly elevated more than 20 years after treatment for stage IA-IIB HL ($n = 1080$).[10] The most common causes of deaths are reported to be relapse of HL, second cancers, cardiovascular diseases and infections.[2,10]

In questionnaire based surveys, HLSs have reported lower general and physical health compared to controls from the general population.[13,14] In addition, HLSs have increased levels of fatigue persisting several years after treatment.[15,16]

The present study is based on a cohort of 557 HLSs included in a survey in 1994 on long-term effects including the presence of chronic fatigue (CF).[17,18] The HLSs were treated at the Norwegian Radium Hospital (NRH) from 1971 to 1991 and were considered to be in complete remission when included in the survey in 1994. The main finding among the responding HLSs was that 26% had CF after a median observation time of 13 years, compared to 11% of controls representative of the general Norwegian population.[18] Uncertainty exists as to the causes of CF in HLSs, and one might speculate whether it reflects aspects of the disease itself such as altered cytokine levels or immune dysfunction which can exert long-term negative health effects. Knowledge about possible negative impact of CF upon somatic health outcomes is lacking, and no study has investigated the association between CF and future significant health events such as mortality in cancer survivors. In addition, to our knowledge, no studies in cancer survivors have investigated mortality in participants versus non-participants in questionnaire surveys.

Thus, the main objectives of this study were as follows:

1. To examine mortality and causes of death in a defined cohort of HLSs who were considered to be disease-free when surveyed in 1994[17,18] and compare the mortality to a control group from the general population matched for age and gender.
2. To examine whether HLSs with CF in 1994 display increased mortality compared to HLSs without CF and the non-participants from the same survey.[18]

2. Patients and methods

2.1. Subjects

The present study was performed to analyse the mortality among $\geqslant 3$ years survivors after HL, and to assess if mortality was influenced by the presence of CF or by not participating in the 1994-survey.Therefore only HLSs alive at inclusion for the 1994-survey was included.

The eligibility criteria for the cross-sectional survey in 1994 were HLSs treated at the NRH from 1971 to 1991, aged 15–61 years at diagnosis and aged 19–74 at the time of the survey, alive and in complete remission by the end of 1993.[17,18] Fifty-seven (10%) of the HLSs had experienced a relapse, seven within the two years preceding the 1994-study.[18] In the period 1970–1980 the treatment of HL in Norway was centralised to the NRH, with 92% of patients aged 15–39 years and 80% of patients aged 40–59 years admitted to the hospital. Since 1981 four other national oncological centres gradually began to treat HL.[19] After 1985 all HL patients from a defined region constituting about 50% of the Norwegian population have been referred to the hospital. The treatment of HL at the NRH in the period 1971–1991 followed international guidelines and have been described previously.[1,17,18,20] Stage I/II was treated with extended radiation fields (Mantle/Inverted-Y field) alone or after chemotherapy. Stage III/IV was treated with eight chemotherapy courses, with radiation to sites of initial bulky tumour or residual masses from 1980. Chemotherapy was given as MVPP/ChlVPP, gradually replaced by ABVD from 1985.

In 1994, 557 patients were contacted by mail and 459 returned the completed questionnaire. The main outcome was self-reported health status including fatigue.[17,18] Fatigue was assessed by Fatigue Questionnaire (FQ)[21] which measures physical fatigue (7 items) and mental fatigue (4 items). The sum of all items is designated total fatigue. Two additional items cover the duration and extent of fatigue. The prevalence of CF was assessed as described and required substantial fatigue for 6 months or more at time of assessment.[18]

Based on findings from the 1994-survey the HLSs were categorised in three groups: participants without CF (No-CFgroup, $n = 329$), participants with CF (CFgroup, $n = 113$), and non-participants who did not return the questionnaire (Non-Partgroup, $n = 98$), 17 patients had invalid FQ and were not categorised. Medical information on all the HLSs was retrieved from the lymphoma database of the NRH.

2.2. Controls

A control group was constructed by randomly drawing five controls per patient from the general population matched for gender and age. The draw was performed by Statistics Norway (SSB). The controls had to be alive on 31st December 1993, as were the HLSs at inclusion in the 1994-survey. For all the HLSs and the controls date of death and causes of death were retrieved from the Statistics for Causes of Deaths, Statistics Norway (SSB). Causes of deaths were categorised into three groups: (1) tumour (all malignant diagnosis), (2) cardiovascular disease and (3) other (including infections, diabetes, pulmonal diseases, gastrointestinal diseases, traumas, diseases in the urinary system, diseases in the musculo-skeletal system, psychiatric diseases. In case of deaths from tumours, these were subdivided in two: (1) malignant lymphomas and (2) other malignancies, including solid tumours, multiple myeloma and leukaemias.

2.3. Statistics

Continuous variables were described using median and range, whereas categorical data were described with proportions. Crude differences in categorical variables were assessed with Chi-square tests, whereas continuous variables were analysed with Mann–Whitney–Wilcoxon tests. Observation time for survival analyses was calculated from 1st January 1994

until date of death or to cut-off at 1st January 2007. Crude cumulative probability of survival was calculated using the Kaplan–Meier method and the three groups of HLSs (No-CFgroup, CFgroup and Non-Partgroup) compared with log-rank tests. Cox proportional hazard regression models were used for univariate and multivariate analyses. When analysing the mortality of the HLSs versus the controls the analyses was stratified by the matched group; the five controls for each HLSs. The proportionality of hazards assumption was investigated using log minus log plots.

The three groups of HLSs were compared to their matched control groups in separate analyses. Considering the HLSs only, possible predictors of death were first investigated in univariate analyses. Secondly, statistically significant variables (age at diagnosis, period of treatment, treatment and patient group [No-CFgroup, CFgroup, Non-Partgroup]) were entered into a multiple model.

The cumulative probability of dying was computed using a competing risk approach[22] with death causes divided into four categories: (1) malignant lymphomas; (2) other cancers; (3) cardiovascular diseases and (4) other causes of death.

A p-value $\leqslant 0.05$ (two-sided) was considered statistically significant. All analyses were performed with SPSS 16 and Stata version 10.

2.4. Ethical considerations

The Regional Committee for Medical Research Ethics, Health Region South, Norway approved the study.

3. Results

3.1. Patients' characteristics

Of the 557 HLSs who were approached in 1994, 43% were female. Median age at diagnosis was 30 years (range 15–60) and median age at survey in 1994 was 43 years (range 19–74) (Table 1). The median observation time from diagnosis to the survey in 1994 was 13 years (range 2.3–23.0 years). Seventy-eight percent were treated with mantle field or mediastinal radiotherapy with or without chemotherapy. The CFgroup had a higher median age at diagnosis than the two other subgroups ($p < 0.01$), whereas there were no statistically significant differences in gender, period of diagnosis, median time from diagnosis to inclusion in the 1994-survey, primary stage or treatment group among the three groups of HLSs. For further details on the patient cohort, see previous publications.[17,18]

3.2. All cause mortality in HLSs versus controls

By 1st January 2007 death had occurred in 149 of the 557 HLSs (27%), 72 deaths in the No-CFgroup (22%), 35 deaths in the CFgroup (31%) and 38 deaths in the Non-Partgroup (39%). In comparison, 197 (7%) deaths had occurred among the controls (Table 1). Mortality among all HLSs was significantly increased compared to the controls, the HLSs were almost five times more likely to die (HR: 4.93, 95% confidence interval [CI]: 3.91–6.21). The mortality rate of the patients was higher than the rate of their controls throughout the entire observation period. The 10 year cumulative mortality from 1994 was 20% (95% CI: 18–23%) for the HLSs and 5% (95% CI: 4–6%) for the controls.

When comparing each patient group to its matched control group, the CFgroup had an increased mortality rate of 4.85 (95% CI: 3.02–7.77), whereas the No-CFgroup had an increased mortality rate of 4.35 (95% CI: 3.16–6.00). The comparable figures for the Non-Partgroup were 9.45 (95% CI: 5.44–16.41) (Fig. 1).

3.3. Factors associated with mortality within the HLSs

In univariate analyses both the CFgroup (HR: 1.54, 95% CI: 1.03–2.31) and the Non-Partgroup (HR: 2.04, 95% CI: 1.37–3.02) had increased mortality rate compared to No-CFgroup (Table 2). When comparing overall mortality in the Non-Partgroup to all participants (with and without CF) the HR for the Non-Partgroup was almost doubled (HR: 1.8, 95% CI: 1.24–2.60).

Patients treated with mantle field or mediastinal radiotherapy had a twofold increased mortality rate compared to patients treated with chemotherapy only (HR: 2.02, 95% CI: 1.09–3.74). Compared to those diagnosed in the period 1981–1990, patients diagnosed in 1971–1980 had increased mortality rate (HR: 2.46, 95% CI: 1.76–3.44).

Multivariate analysis revealed that the Non-Partgroup had a twofold increased risk of mortality (HR: 1.99, 95% CI: 1.33–2.98) compared to the No-CFgroup. No statistically significant difference was observed between the participants with and without CF. Treatment group remained significant with patients treated with radiotherapy with or without chemotherapy having about two and a half times higher mortality risk than those treated with chemotherapy only. Patients diagnosed before 1981 had increased risk of mortality compared to those diagnosed from 1981 onwards (HR: 2.80, 95% CI: 1.97–3.98).

3.4. Causes of deaths

Among the HLSs 83 of the 149 (56%) deaths were caused by malignant disease and 36 (24%) were caused by cardiovascular diseases. Among the controls 41% (81/197) of the deaths were caused by malignant diseases and 25% (50/197) by cardiovascular diseases (Table 3). Overall, the risk of dying of cancer or all other causes was always higher for HLSs compared to their controls, as depicted in Fig. 2. Compared to the controls, the HLSs had more than six times increased mortality of cancer (HR: 6.6, 95% CI: 4.7–9.2) and almost five times increased mortality of cardiovascular disease (HR: 4.9, 95% CI: 3.1–7.9). For the other causes of death the HLSs had almost three times increased mortality compared to the controls (HR: 2.9, 95% CI: 1.9–4.7). No differences between the predefined patient groups in regard to causes of deaths were observed (data not shown).

Among the HLSs who died of malignant diseases, 33 of these deaths were caused by malignant lymphomas (of which 21 by HL) and 50 by other cancer types (pulmonary cancer: $n = 20$, cancer in the gastrointestinal tract: $n = 11$, breast cancer: $n = 3$, leukaemia/multiple myeloma: $n = 3$). Deaths

Table 1 – Patients characteristics, Hodgkin lymphoma sample $n = 557$, control sample $n = 2785$.

	All HLSs, $n = 557$	No-CFgroup, $n = 329$	CFgroup, $n = 113$	Non-Partgroup, $n = 98$	Controls, $n = 2785$
Age at diagnosis[a]					
Median (range) (years)	30 (15–60)	28 (15–60)	33 (15–60)	28 (15–60)	
Age at survey 1994[b]					
Median (range) (years)	43 (19–74)	41 (19–74)	46 (21–74)	41 (20–72)	
Follow-up from diagnosis to the survey in 1994					
Median (range) (years)	13 (3–23)	12 (3–23)	13 (3–23)	14 (3–23)	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Gender					
Male	320 (57)	187 (57)	60 (53)	65 (66)	
Female	237 (43)	142 (43)	53 (47)	33 (34)	
Period of diagnosis					
1971–1980	242 (43)	132 (40)	50 (44)	50 (51)	
1981–1991	315 (57)	197 (60)	63 (56)	48 (49)	
Treatment group					
1. Chemotherapy only	73 (13)	40 (12)	15 (13)	16 (17)	
2. Radiotherapy including mediastinum ± chemotherapy	429 (78)	256 (80)	88 (79)	73 (76)	
3. Radiotherapy not including mediastinum ± chemotherapy	45 (8)	26 (8)	9 (8)	7 (7)	
Chemotherapy regimens[c]					
ChlVPP	174 (31)	93 (28)	39 (34)	34 (35)	
ChlVPP/ABOD alternating	95 (17)	63 (19)	19 (17)	12 (12)	
ABOD/EBVP	53 (10)	37 (11)	9 (8)	6 (6)	
Primary stage					
I/IIA	269 (48)	165 (50)	50 (44)	45 (46)	
I/IIB	67 (12)	32 (10)	21 (19)	13 (13)	
III/IV A	104 (19)	61 (19)	24 (21)	16 (16)	
III/IV B	117 (21)	71 (22)	18 (16)	24 (25)	
Mortality[d]					
Alive	408 (73)	257 (78)	78 (69)	60 (61)	2588 (93)
Dead	149 (27)	72 (22)	35 (31)	38 (39)	197 (7)

CF: chronic fatigue; No-CF group: participants without CF; CF group: participants with CF; Non-Partgroup: non-participants.
ABOD: doxorubicin, bleomycin, vincristin, dacarbazine; ChlVPP: chlorambucil, vinblastine, procarbazine, prednisone; EBVP: epirubicin, bleomycin, vinblastine, prednisolone.
[a] Participants with CF higher median age at diagnosis than the two other subgroups of HLSs ($p < 0.01$).
[b] Participants with CF higher median age at survey 1994 than participants without fatigue ($p < 0.001$).
[c] Chemotherapy courses ± radiotherapy.
[d] Mortality at cut-off 1st January 2007.

due to malignant lymphomas occurred significantly earlier than deaths by secondary solid tumours (data not shown).

4. Discussion

In the present study mortality and causes of death were examined in an unselected cohort of disease-free survivors after HL, alive ⩾ 3 years after diagnosis, included in a previous questionnaire survey.[18] The present study provides new information on mortality and causes of death in HLSs due to a substantially longer follow-up period than previous studies,[10–12] with a median observation time of 13 years from diagnosis to the survey in 1994, and thereafter observation until 2007. Compared to the controls, the HLSs had almost five times higher mortality, and the mortality rate of patients was higher than the rate of their controls throughout the entire observation period. In the multivariate analysis, the presence of CF was not significantly associated with increased mortality among the HLSs who participated in the 1994-survey, but the Non-Partgroup displayed a twofold increased mortality compared to the No-CFgroup.

Previous studies investigating mortality after treatment for HL have set the observation time from time of diagnosis or from end of treatment.[2,10,11] When investigating 1261 patients treated for HL in the period 1965–1987, Aleman et al reported a ten year overall survival of 75%,[2] whereas Ng et al. found a somewhat higher 15-year survival rate of 84% in their patients treated for early-stage HL at age 50 or younger.[10] The present study was constructed specifically to analyse mortality and causes of death in survivors of HL ⩾ 3 years after diagnosis. The cross-sectional nature of the 1994-survey makes this patient group biased with regard to survival compared to the

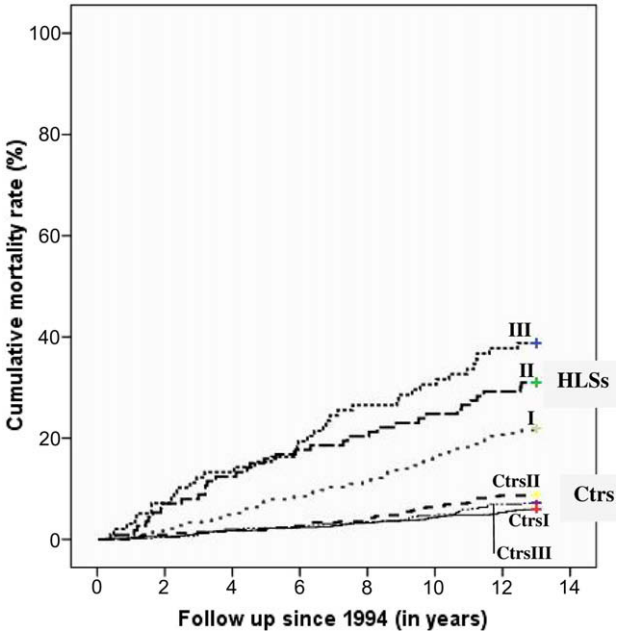

Fig. 1 – Cumulative mortality rate in HLSs related to patient group and the relevant control groups. All patient groups displayed increased mortality compared to their controls ($p < 0.001$). HLSs: (I) participants without chronic fatigue (CF) $n = 329$. (II) Participants with CF, $n = 113$. (III) Non-participants, $n = 98$. Ctrs: controls. CtrsI: controls to participants without CF, $n = 1645$; CtrsII: controls to participants with CF, $n = 565$; CtrsIII: controls to non-participants, $n = 490$.

previous studies,[2,10,11] because only HLSs alive in 1994 were included. Thus, the ten year cumulative mortality can not be directly compared to the mortality rates in the other studies.[2,10,11] The 10 year cumulative mortality from 1994 (20%) therefore represents an underestimation compared to studies including patients from diagnosis. This is emphasised in the figures recently extracted from the lymphoma database of the NRH showing that of 970 HL patients registered in the inclusion period and with the same age criteria as the 1994-survey, 344 had died in the period 1971–1993. The strength of the present design is that the results give the mortality rates for the survivors at the expense of direct comparability with previous studies thus limiting the generalisiability. So far as we know, no other studies have examined mortality in a similar cohort of HLSs as presented here.

There was almost a fivefold increase in mortality risk among the HLSs compared to the control group from the general population. This number is slightly lower than the increased RR of mortality of 6.4 and 6.8 found by others,[2,10] whereas Provencio et al. reported the mortality rate among patients treated for HL to be >10-fold higher than mortality rates from the general population.[11] The difference between our result and the other studies is probably explained by the survival bias in our cohort as previously explained. However, it is remarkable that even among $\geqslant 3$ years survivors of HL the increased risk of mortality are as high as five times higher than in the controls. There are also methodological differences to be illustrated; the earlier studies explored the standardised mortality ratio; the ratio between the observed deaths in the cohort and the expected number of deaths if the cohort had the same mortality rate as the general population.[2,10,11] In contrast, our control group was constructed by drawing five persons per HLSs from the general population matched for age and gender, and both the HLSs and controls were followed to either death or time for cut-off. The use of matched controls selected from the general population provides an intuitively understandable interpretation of the results. Moreover, having five controls per patient ensured a high level of efficiency and precision of our estimates.[23]

At inclusion in the 1994-survey, the patients were considered to be in complete remission. However, the observation time from diagnosis to inclusion in 1994 had a wide time span from 2–23 years (median 12 years) and makes the patient group heterogeneous, with patients with the shortest

Table 2 – Uni- and Multivariate analyses of predictors for deaths among HLSs ($n = 540$).

Within the cohort of HLSs ($n = 540$)				
Variable	Univariate Cox model		Multivariate Cox model	
	HR univariate Cox	95% CI	HR multivariate Cox	95% CI
Patient groups				
No-CFgroup	Reference		Reference	
CFgroup	1.54	1.03–2.31	1.24	0.82–1.87
Non-Partgroup	2.04	1.37–3.02	1.99	1.33–2.98
Treatment groups				
Chemotherapy only	Reference		Reference	
Radiotherapy including mediast ± chemotherapy	2.02	1.09–3.74	2.68	1.43–5.03
Radiotherapy not including mediast ± chemotherapy	1.88	0.81–4.33	2.59	1.12–6.00
Period of diagnosis				
1971–1980	2.46	1.76–3.44	2.80	1.97–3.98
1981–1991	Reference		Reference	
Age at diagnosis	1.05	1.03–1.06	1.06	1.05–1.08

Non-Partgroup: non-participants; CFgroup: participants with CF; No-CF group: participants without CF; CF: chronic fatigue; HLSs: Hodgkin's lymphoma survivors.

Table 3 – Causes of deaths in HLSs (n = 557) and controls (n = 2785).

Group	Malignant disease		Cardiovascular disease	Other
Controls (n = 2785)				
Dead by 1st January 2007, n = 197 (7%)	81 (3%)		50 (2%)	66 (2%)
% of this group				
All HLSs (n = 557)				
Dead by 1st January 2007, n = 149 (27%)	83 (15%)		36 (6%)	30 (5%)
% of this group	Malignant lymphoma	Other cancers		
	33	50		
	21 HL/12 NHL			
No-CFgroup (n = 329)				
Dead by 1st January 2007, n = 72 (22%)	46 (14%)		16 (5%)	10 (3%)
% of this group	Malignant lymphoma	Other cancers		
	19	27		
CFgroup (n = 113)				
Dead by 1st January 2007, n = 35 (31%)	15 (13%)		11 (10%)	9 (8%)
% of this group	Malignant lymphoma	Other cancers		
	3	12		
Non-Partgroup (n = 98)				
Dead by 1st January 2007, n = 38 (39%)	20 (20%)		7 (7%)	11 (11%)
% of this group	Malignant lymphoma	Other cancers		
	10	10		

Non-Partgroup: non-participants; CF group: participants with CF; No-CF group: participants without CF; CF: chronic fatigue; HLSs: Hodgkin's lymphoma survivors.

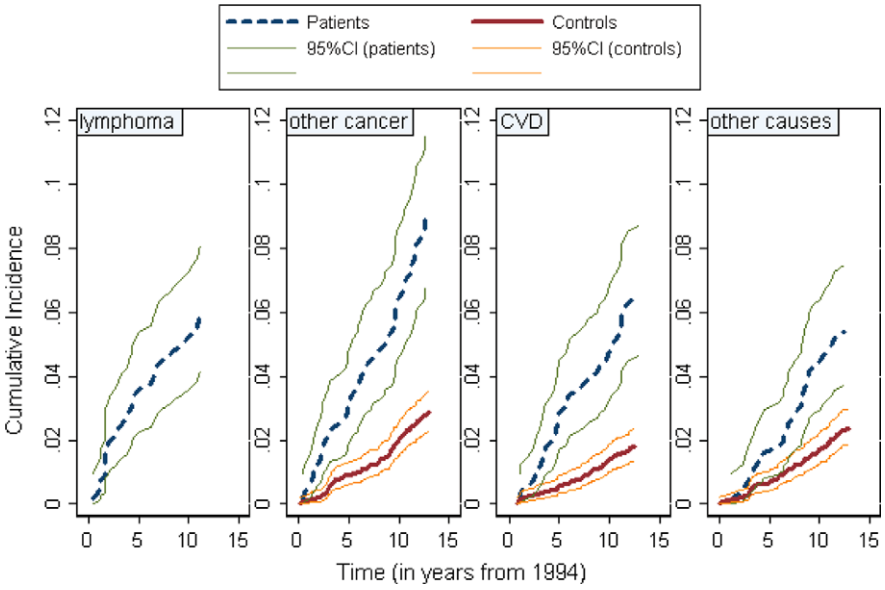

Fig. 2 – Plot of competing causes of deaths among HLSs and controls.

observation time from diagnosis to the 1994-survey having higher risk for relapse than patients with longer observation time.

Of particular interest, a twofold increased risk of mortality among the Non-Partgroup compared to the No-CFgroup was observed. To our knowledge, such an association between the willingness/ability to respond to a questionnaire survey and a central health outcome has not been described in cancer survivors earlier. However, epidemiological studies have indicated impaired health status and higher mortality in groups of non-responders.[24,25] The observation of increased mortality among the Non-Partgroup indicates that impaired health may explain why some HLSs did not respond to the questionnaire survey in 1994. A possible burden in the Non-Partgroup as to having more symptoms and impaired physical health may imply that adverse health effects in HLSs might be underestimated in follow-up surveys. This finding needs to be confirmed and explored by further examinations, also in other groups of cancer survivors.

In univariate analysis, increased mortality in the CFgroup compared to the No-CFgroup was observed. However; this difference disappeared in the multivariate analysis, probably

reflecting confounding by age, since, in 1994, the CFgroup were significantly older than the No-CFgroup. The finding of similar mortality in HLSs with and without CF is of clinical importance, as it indicates that CF itself is not associated with life-threatening somatic morbidity. Theoretically, HLSs with CF might have had more intense follow-up due to their condition than the HLSs without CF with possible beneficial effects upon morbidity and mortality. However, no special programs for HLSs with CF have been running during the observation period, and in our opinion a possible bias related to this can therefore be excluded.

Patients diagnosed in the period 1971–1980 had increased mortality rate compared to those diagnosed in the period 1981–1991 both in univariate and multivariate analyses, which is comparable to earlier findings.[11] This observation may be due to more toxic treatment in the first period, particularly caused by the use of larger radiation fields, and/or better treatment options in the latter period. Another explanation is improved histopathological diagnosis; some lymphomas classified as HL in the earliest period, especially of the lymphocyte depleted and unclassified subtypes in the elderly (considered to be associated with poor prognosis), probably have been classified as NHL during the second period.[19]

Malignant diseases and cardiovascular diseases were the most frequent causes of deaths among the HLSs, which is similar to earlier reports.[2,10] Mortality of cancer was more than six times higher in HLSs compared to the control group, and almost five times higher for cardiovascular diseases. This is comparable to the RR of deaths resulting from solid tumours reported to be 6.6 and cardiovascular disease reported to be 6.3 in 1261 patients treated for HL before age 41.[2] In comparison, Ng et al reported the RR of excess mortality from second tumours to be 11.2 and 3.2 from cardiovascular diseases in their cohort of 1080 HLSs.[10]

The treatment of the patients in the described cohort is no longer standard therapy, as the treatment for HL has been modified in order to avoid long-term effects without reducing the very good survival rates. Mantle field irradiation is no longer used as standard therapy, and for chemotherapy, MOPP-like regimens have to a large extent been abandoned. Nevertheless, it is of importance to study the morbidity and mortality after treatment with these regimens because a large number of survivors after such treatment are still alive. In addition, patients today still receive radiotherapy, albeit to smaller volumes and with lower doses, and chemotherapy regimens used today, such as ABVD and BEACOPP, still contain many of the same compounds as did earlier regimens. In a recently published study comparing overall survival (OS) after treatment for advanced stage HL (median follow-up 111 months), OS was significantly improved after treatment with escalated-dose BEACOPP compared to COPP/ABVD and standard BEACOPP.[26] However, a higher number of acute myeloid leukaemia and myelodysplastic syndrome in the dose-escalated BEACOPP arm was observed, whereas there were no differences in the total number of secondary malignancies between the treatment arms.[26] This emphasises the importance of clinicians being aware of possible long-term complications after curative treatment for HL and provides the best follow-up care as possible. As current treatment regimens for HL in general are less toxic than earlier treatment regimens, future HL survivors will hopefully not have such increased mortality compared to the general population as found in the present sample.

The underlying cause of death was recorded in this study. Comorbidities may have contributed to death, especially in the older patients, but this was not taken into account in the present analyses.

Overall, we showed that in this cohort of HLSs, assumed to be in complete remission in 1994, the overall mortality risk was almost five times higher than for matched controls from the general population. This raises the question whether the total long-term mortality is a better estimate of successful treatment of HL, than specific mortality of HL.

Conflict of interest statement

None declared.

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