Late and very late mortality in 5-year survivors of childhood cancer: changing pattern over four decades. Experience from the Nordic countries.

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Running head of the title:

Late and very late mortality in childhood cancer survivors

Abstract

Long-term survivors of childhood cancer suffer from a higher mortality than the general population. Here we evaluate late and very late mortality, and patterns of causes of death, in five year survivors after childhood and adolescent cancer in cases diagnosed during four decades in the five Nordic countries.

The study is population-based and uses data of the nationwide cancer registries and the cause of death registers. There were in all 37,515 incident cases, diagnosed with cancer before the age of 20 years, between 1960 and 1999. The 5-year survivor cohort used in the mortality analyses consisted of 21,984 patients who were followed-up for vital status until December 31, 2005 (Norway, Sweden) or 2006 (Denmark, Finland, Iceland).

At the latest follow-up, 2,324 patients were dead. The overall standardized mortality ratio was 8.3 and the absolute excess risk was 6.2 per 1,000 person-years. The pattern of causes of death varied markedly between different groups of primary cancer diagnosis**,** and was highly dependent on time passed since diagnosis. With shorter follow-up the mortality was mainly due to primary cancer, while with longer follow-up, mortality due to second cancer and non-cancer causes became more prominent. Mortality between 5 and 10 years after diagnosis continued to decrease in patients treated during the most recent period of time, 1990-99, compared to previous periods, while mortality after 10 years changed very little with time period.

We conclude that improvement of definite survival demands not only reducing early but also late and very late mortality.

Introduction

Traditionally, clinicians have used 5-year survival from the time of diagnosis as a general benchmark for cure, and late mortality has thus been defined as death occurring beyond this point of time. Moreover, most therapeutic protocols are designed to monitor patients only for assessing clinical efficacy (typically 5 to at most 10 years from diagnosis) and pediatric oncology programs are usually not structured to systematically follow survivors into adulthood. For these reasons, assessment of late mortality is generally dependent on epidemiologic studies.

The most recent report on late mortality from the Childhood Cancer Survivor Study (CCSS) [1] included 2,821 deaths occurring among 20,483 five-year survivors. When all-cause mortality rates were compared with those for the United States population, the standardized mortality ratio showed a substantially increased risk of dying that persisted 30 years after diagnosis. Data from two large population-based studies, one in the United Kingdom [2] reporting 3,049 deaths among 17,981 survivors and one in the Nordic countries [3] with 1,422 deaths among 13,711 patients, indicate that approximately 10 to 17% of 5-year survivors of childhood and adolescent cancer will subsequently die at a young age. Overall, long-term survivors of childhood cancer experience in average about 11-fold greater death rates than the background population. These, and a couple of other smaller studies [4, 5, 6, 7, 8, 9] show that within 5 – 10 years after diagnosis the main cause of death is relapse of the primary cancer, while later on second primary and cardiac and pulmonary causes are more prominent. Cancer treatments are the likely cause of excess mortality after a very long follow-up (more than 15 years after diagnosis) [7] but a number of aspects of this relationship have not been satisfactorily investigated, partly due to cohort size constrains and relatively short follow-up.

In all the Nordic countries there is an excellent possibility to study cancer incidence, mortality and survival because of their nationwide population-based cancer registration and causes of

death registers. Thus NORDCAN [10] published a series of papers concerning trends in survival of patients diagnosed with cancer in different topographic sites, but childhood and adolescent cancer was not accounted for separately.

Here we report changing patterns of late and very late mortality after childhood cancer in the Nordic countries over four decades for overall mortality as well as for different causes of death.

Patients and methods

Nordic childhood cancer (NCC) cohort

Patient data were obtained from the population-based cancer registries and cause of death registers in the five Nordic countries: Denmark, Finland, Iceland, Norway, and Sweden. The NCC cohort was formed of all 37,515 incident cases (20,651 males and 16,864 females) diagnosed with a malignant tumor before 20 years of age during the time period 1960 – 1999. The different ICD codes for site and morphology, as originally used by the national cancer registries, were grouped according to the Birch and Marsden [11] classification scheme for childhood cancer (IARC-group). The patients were followed up through December 31, 2005 in Norway and Sweden and through December 31, 2006 in Denmark, Finland and Iceland with respect to vital status, emigration and cause of death.

Establishing the 5-year survivor (5-YS) cohort

For patients diagnosed 1960-1989, the 5-year survivor cohort from our previously published study [3] was used so that the validated causes of death through 1995 could be utilized. Follow-up from 1996 was obtained by matching with patients in the new NCC cohort that were alive on December 31 1995 and dead at latest follow-up 2005/2006. Since we did not have access to the patients´ identity the matching variables country, sex, year and month of birth, year and month of primary diagnosis, and primary diagnosis were used. All matches were unique, but 15 deaths after 1995 in the NCC cohort (about 2.5% of all deaths after 1995 in patients diagnosed before 1990) did not match with any individual in the old cohort. This may be explained by ongoing corrections and re-evaluation of originally recorded patient information in the cancer registries. Patients diagnosed 1990-1999 were taken from the NCC cohort and added to the study cohort. The resulting 5-YS cohort consisted of 21,984 individuals (11,590 males and 10,394 females). There were 6,788 individuals diagnosed at the age of 0 – 4 years,

3,839 diagnosed at 5 – 9 years, 4,191 diagnosed at 10 – 14 years, and 7,166 individuals diagnosed at the age of 15 – 19 years.

Table 1, Supportive information, shows the NCC cohort and the 5-YS cohort with distribution of patients according to decade of diagnosis and cancer type. The percentage of 5-year survivors increased rapidly and their number was almost three times as large in the last compared to the first decade. More importantly, the composition of cases in the 5-YS cohort differed markedly between decades. This is mainly due to the fact that only 4.3% of patients with leukemia survived 5 years in the first decade and thus constituted only 3.9% of the 5-YS cohort in this decade, while in the last decade 76.8% of patients with leukemia survived 5 years, constituting almost 23% of the 5-YS cohort. Totally, leukemia comprised 18.7%, Hodgkin's lymphoma 8.2% and CNS tumors 24.7% of the 5-YS cohort.

Assessment of the cause of death

For the 1,422 fatal cases, who died through December 31, 1995, and were included in the previous Nordic study, copies of death certificates were obtained in 1,402, and the cause of death was validated as described earlier [3]. For the 902 patients who died later all causes of death (underlying and contributing) were retrieved from the Cause of Death Registers' files. Based on previous experience it was considered quite adequate to determine the most probable cause of death relevant from the clinical point of view by assessing all recorded causes of death. This was done by a pediatric oncologist (SG) and a general oncologist (TRM), who had the knowledge of the date, site, and morphology of the initial and all subsequent cancer diagnoses.

All causes of death were allocated to one of the following broad categories:

Death caused by the first cancer (progression, recurrence, or metastasis);

Death caused by a second or subsequent primary cancer;

Non-cancer death.

Statistical methods

Standardized mortality ratios (SMR) and absolute excess risks (AER) were used to compare overall mortality with expected mortality. Trend tests [12] were applied to analyze SMR´s by decade of diagnosis. Expected numbers of deaths were determined by means of a Stata program (http://www.pauldickman.com/rsmodel), using country, sex, age, and calendar period specific mortality rates. Survival analysis methods were used to estimate overall mortality and cumulative incidence functions of different causes of death taking the competing risks of other causes into account [13]. Log-rank tests were used to compare overall mortality for different groups and Gray´s test [14] was used to compare cumulative incidence functions for specific causes of death. Multivariate Cox proportional hazards models were used to analyze the effect of demographic factors and primary diagnosis on all-cause mortality as well as on different cause-specific mortality hazards. Age and year of diagnosis were categorized in 5-year and 10-year groups, respectively, and they were also tested for trend. Follow-up from diagnosis was used as time scale in all survival analyses. Besides Stata, the statistical program R was also used in the analyses.

Results

Overall mortality

The 5-year survivor cohort was followed up for additional 0 - 42 years (median 13.0 years), generating 331,348 person-years at risk. Overall SMR was 8.3 with large variations depending on follow-up time and decade of diagnosis (Table 1). The SMR in the interval 5 – 9 years after diagnosis decreased from 30.2 to 18.6 for patients diagnosed in the sixties compared to those diagnosed in the nineties (trend test, P<0.001). For longer follow-up the

SMR was practically the same within the specific follow-up intervals over the whole study period (trend test, P=0.42, 0.22, 0.46, 0.30 for intervals 10-14, 15-19, 20-24 and 25-29, respectively). Considering all decades of diagnosis the SMR decreased from 9.4 in the follow-up interval 10-14 years to 2.7 for the 30+ years interval. Overall AER was 6.2 per 1000 person-years. AERs were highest after 5-9 years of follow-up and declined for this interval with every following decade; i.e. from 18.8 for patients diagnosed in the sixties to 6.3 for patients diagnosed in the nineties. Thereafter AERs were lower, in average 4.0 and they only varied between 2.9 and 5.8 with follow-up period and year of diagnosis (Table 1).

Table 1. Observed and expected number of deaths in 5-year survivors, SMR, and AER per 1000 person-years, by decade of diagnosis and follow-up interval

Follow-up	Decade of diagnosis												Total period		
	1960 - 1969			1970 - 1979			1980 - 1989			1990 - 1999					
Years	Obs/Exp	SMR	AER	Obs/Exp	SMR	AER	Obs/Exp	SMR	AER	Obs/Exp	SMR	AER	Obs/Exp	SMR	AER
5 - 9	257/8.5	30.2	18.8	340/10.3	33.0	15.9	321/13.3	24.1	9.7	233/12.5	18.6	6.3	1151/44.5	25.9	11.0
10-14	79/9.0	8.8	5.6	125/12.1	10.3	5.8	135/15.5	8.7	3.9	67/6.5	10.3	3.8	406/43.2	9.4	4.7
15-19	56/11.2	5.0	3.7	80/15.0	5.3	3.4	88/16.4	5.4	2.9	6/0.5	---	---	230/42.9	5.4	3.3
20-24	62/14.0	4.4	4.1	93/17.2	5.4	4.1	37/7.6	4.9	3.0				192/38.9	4.9	3.8
25-29	64/18.1	3.5	4.0	70/17.5	4.0	3.5	3/0.4	---	---				137/36.0	3.8	3.8
30-34	71/24.0	3.0	4.2	40/9.0	4.4	5.6							111/33.0	3.4	4.7
35-39	64/27.0	2.4	4.1	0/0.5	---	---							64/27.4	2.3	4.0
40-44	33/15.6	2.1	5.1										33/15.6	2.1	5.1
Total	686/127	5.4	6.6	748/81.6	9.2	6.8	584/53.2	11.0	5.5	306/19.5	15,7	5.6	2324/281.5	8.3	6.2

Table 2 shows the cumulative mortality in percentage at 10-, 15-, and 20-years after diagnosis for 5-year survivors, by cancer type and decade of diagnosis. For leukemia, late mortality was high in the first period and decreased markedly thereafter. The same was true for Hodgkin's lymphoma, while for CNS tumors the decrease was marked first in the last decade of diagnosis. Totally, for 5-year survivors the probability to die within the following 5 years and 10 years were 5.4% and 7.9%, respectively. Corresponding figures for 10-year survivors were 2.6% and 4.5%, respectively, and for 15-year survivors they were 2.0% and 4.3% .

Table 2. Cumulative mortality (percentage) in 5-year survivors at 10-, 15-, and 20-years after diagnosis, by cancer type and decade of diagnosis

Decade of diagnosis/	1960 - 1969			1970 - 1979			1980 - 1989			1990 - 1999			Total period		
	Years after diagnosis			*Years after diagnosis*			*Years after diagnosis*			*Years after diagnosis*			*Years after diagnosis*		
Primary cancer type	***10***	***15***	***20***	***10***	***15***	***20***	***10***	***15***	***20***	***10***	***15***	***20***	***10***	***15***	***20***
Leukemia	40.5	44.1	46.0	16.6	20.3	21.5	7.0	8.8	9.7	4.2	5.6		8.4	10.6	11.7
Hodgkin's lymphoma	22.8	29.6	33.7	10.0	15.5	19.3	5.2	7.7	11.3	1.9	5.0		7.9	12.2	16.2
Other lymphomas	5.5	5.5	8.1	3.3	3.8	5.7	2.2	4.7	6.1	1.1	3.6		2.4	3.8	5.5
Central nervous system	9.0	12.8	15.3	9.3	13.2	16.3	6.9	10.3	12.9	3.5	7.6		6.6	10.3	13.2
Sympathetic nerv. syst.	5.4	6.4	9.1	5.8	6.5	8.0	4.9	5.9	8.0	2.9	3.8		4.4	5.3	7.3
Retinoblastoma	2.1	3.4	4.1	1.2	2.4	2.4	1.3	2.0	2.7	0	0		1.1	2.1	2.5
Renal tumors	2.1	5,7	7.8	1.6	2.3	3.5	2.3	2.9	3.3	0.9	1.5		1.7	2.9	3.9
Hepatic tumors	0	0	20.0	14.3	14.3	14.3	5.7	5.7	9.3	3.1	7.7		5.6	6.8	10.6
Bone tumors	8.0	10.6	12.6	8.5	12.1	12.6	7.6	11.1	12.1	8.9	11.4		8.4	11.6	12.7
Soft-tissue sarcomas	5.7	8.4	10.1	7.5	10.5	12.4	4.1	6.2	7.7	4.3	5.6		5.2	7.5	9.2
Germ-cell tumors	2.3	3.2	3.2	2.4	5.2	6.6	2.0	2.4	3.7	1.0	1.9		1.8	3.0	4.1
Carcinomas	5.0	5.9	6.8	2.6	3.5	4.6	1.8	3.0	3.9	3.0	3.7		2.9	3.9	4.8
Other malignant neopl.	2.3	7.0	7.0	4.3	7.1	7.1	4.0	6.6	9.5	0	5.9		2.8	6.0	7.1
Total	**9.1**	**11.9**	**13.9**	**7.8**	**10.7**	**12.6**	**4.9**	**7.0**	**8.6**	**3.1**	**5.3**		**5.4**	**7.9**	**9.7**

Cause-specific mortality

At the end of follow-up 2,324 patients had died. 60.2% died of the primary tumor, 11.9% of second or subsequent tumor, and 26.9% because of other causes. For 1.0% the cause of death was unknown.

Table 2, Supportive information, shows the category of validated cause of death by cancer type. The pattern of causes of death differed depending on the primary diagnosis. In leukemia 79,4% of late deaths were attributable to initial disease, 5.9% to second cancer and 14.7% to non-cancer death, while in Hodgkin's lymphoma the corresponding figures were: 42.1%, 21.7% and 36.2%, and in CNS tumors: 65.8%, 6.5% and 27.7%, respectively.

The cumulative mortality in the 5-year survivor cohort was 5.4% at 10 years, 9.7% at 20 years, 14.1% at 30 years, and 19.9% at 40 years after diagnosis, with increasing part of mortality being due to second cancer and to other causes with longer follow-up (Figure 1). First cancer as the cause of death thus decreased continuously from 81% in the interval 5-10 years after diagnosis to 16% more than 30 years after diagnosis, while second cancer increased from 4% to 33% and non-cancer causes from 14% to 51% in the same periods.

Table 3, Supportive information, shows that when death occurred due to second cancer (totally 227 cases), it was most frequently due to tumors in the CNS (19.9%), digestive organs and peritoneum (14.8%) and in lymphatic and hematopoietic system (13.4%).

Non-cancer deaths occurred in 624 cases (Table 4, Supportive information). The most common causes were injuries, poisoning and accidents in 29.2% (including 41 suicides) followed by heart and vascular diseases in 26% (including 49 cardiomyopathies, 46 ischemic heart diseases, and 41 cerebrovascular diseases), and of respiratory tract diseases in 16.2% (including 69 pneumonias). They occurred mostly in patients with CNS tumors, who died

most often from injuries, poisoning and accidents, pneumonias and cerebrovascular diseases, and in patients with Hodgkin's lymphoma, dying predominately from ischemic heart disease, pneumonia and cardiomyopathy.

Mortality in relation to first cancer, decade and age at diagnosis

Figure 2 shows cumulative mortality for all causes and for different categories of causes of death for all primary diagnoses combined and for the three main diagnostic groups of cancer with the highest number of deaths; i.e. leukemia, Hodgkin's lymphoma and CNS tumors. Totally they contribute 2/3 of all fatal cases, as shown previously in Table 2, Supportive information. The figure demonstrates that the pattern of causes of death for late mortality differed significantly depending on primary cancer diagnosis. At 30 years of follow-up the overall cumulative mortality was 14%, the same for leukemia, 19% for CNS tumors and 27% for Hodgkin' s lymphoma. This high overall mortality for Hodgkin's lymphoma was due to second cancer (7.4% at 30 years) and to non-cancer causes (10.0% at 30 years). For CNS tumors the dominating cause of late mortality was the first primary (11.7% at 30 years).

Figure 3 shows that for 5-year survivors, the probability of dying within the next five years has decreased from 9.1% to 3.1% for patients diagnosed in the sixties compared to patients diagnosed in the nineties. The difference was especially marked for patients diagnosed during the eighties compared with those diagnosed during the seventies, but the trend continued also for patients diagnosed during the most recent decade, mainly due to reduction in death due to the primary cancer. For those surviving 10 years the probability of dying within the next 5 years decreased between 3.1% and 2.2% for the different periods of diagnosis, indicating that the very late overall mortality was only very little affected by the time of diagnosis .

Multivariate analyses of differences in late mortality depending on demographic factors and primary diagnosis are shown in table 3. For all causes of death, as well as death due to primary cancer and due to non-cancer causes, all analyzed factors (sex, age of diagnosis, year of diagnosis, and primary diagnosis) were highly significant. Thus, high age at diagnosis (trend test, $P<0.001$) and male sex increased mortality, and the decline in mortality by year of diagnosis persisted (trend test, $P<0.001$) after adjustment for demographic factors and main primary diagnoses. For second cancer as the cause of death only primary diagnosis of Hodgkin's lymphoma was significant.

In addition, we analyzed the effect of country on all cause mortality. The previous findings [15] of higher late mortality in Denmark and Finland for patients diagnosed 1960 – 1979 were confirmed. For the patients diagnosed after 1980 no country effect was found (data not shown).

Table 3. Cox regression analysis (hazard ratios, HR) of all cause mortality and cause specific mortality in 5-year survivors.

Cause of death/ *Factor*	**All causes**			**First primary**			**Second primary**			**Non-cancer causes**		
	HR	95%CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Sex												
Female (ref.)	1			1			1			1		
Male	1.28	1.18-1.39	<0.001	1.16	1.04-1.29	0.006	1.08	0.85-1.37	0.52	1.68	1.43-1.99	<0.001
Age at diagnosis												
0-4 yrs (ref.)	1			1			1			1		
5-9 yrs	1.2	1.06-1.37	0.005	1.18	1.01-1.39	0.041	0.89	0.58-1.36	0.59	1.37	1.05-1.79	0.019
10-14 yrs	1.35	1.19-1.53	<0.001	1.25	1.07-1.47	0.006	1.41	0.98-2.02	0.062	1.46	1.13-1.88	0.004
15-19 yrs	1.6	1.43-1.80	<0.001	1.59	1.37-1.84	<0.001	1.24	0.89-1.72	0.21	1.82	1.44-2.28	<0.001
Year of diagnosis												
1960-69 (ref.)	1			1			1			1		
1970-79	0.87	0.78-0.97	0.014	0.8	0.69-0.93	0.003	1.3	0.94-1.78	0.11	0.92	0.75-1.14	0.46
1980-89	0.56	0.49-0.63	<0.001	0.49	0.42-0.57	<0.001	1.06	0.70-1.62	0.77	0.64	0.50-0.82	<0.001
1990-99	0.37	0.31-0.42	<0.001	0.31	0.26-0.37	<0.001	1.37	0.82-2.30	0.23	0.42	0.30-0.60	<0.001
Primary diagnosis												
Other (ref.)	1			1			1			1		
Leukemia	2.59	2.29-2.94	<0.001	3.54	3.03-4.13	<0.001	1	0.64-1.55	0.99	1.5	1.12-2.01	0.006
Hodgkin's lymphoma	2.44	2.13-2.79	<0.001	1.87	1.54-2.28	<0.001	3.61	2.66-4.89	<0.001	3.01	2.39-3.78	<0.001
CNS	2.11	1.91-2.34	<0.001	2.6	2.27-2.97	<0.001	0.82	0.59-1.15	0.25	1.96	1.62-2.37	<0.001

Below we present in more detail causes of mortality in the three primary diagnoses, which contributed to 2/3 of the fatal cases, as shown previously.

In **leukemia** late mortality was mainly due to the primary cancer and this cause of death diminished markedly with every decade of diagnosis (Figure 1, Supportive information). Deaths due to second cancer were most common in the CNS (11 out of 26 cases, as shown in table 3, supportive information) and occurred in 7 of these after 10-15 years of follow-up. Among non-cancer death causes , 17 out of 65 were heart and vascular diseases (as shown in table 4, supportive information), occurring mainly after 5-15 years of follow-up and 16 were respiratory tract diseases, occurring mainly after 5-10 years of follow-up.

In **Hodgkin's lymphoma**, the late mortality due to the primary diagnosis also diminished markedly but at the same time second or subsequent cancer and other causes of death became more important (Figure 2, Supportive information). The three most frequent causes of death due to second cancer (totally 69 cases as shown in Table 3, supportive information) were tumors in the digestive organs, female breast and lymphatic & hematopoetic system. Death due to second cancer in the digestive organs occurred in 9 out of 12 cases in patients diagnosed in the sixties, predominantly after 25-30 years of follow-up. Death due to second cancer in female breast occurred in 8 out of 12 cases in patients diagnosed during the seventies, mainly after 25-30 years of follow-up. Death due to second cancer in the lymphatic and hematopoetic system occurred in 13 out of 15 cases after 5-15 years of follow-up without any clear pattern concerning decade of diagnosis. For non-cancer causes of death (totally 115 fatalities, as shown in Table 4, supportive information), pneumonia and other respiratory tract diseases were the most frequent cause of death among patients diagnosed during the sixties, while ischemic heart disease and cardiomyopathies dominated among deaths in patients diagnosed in the seventies and eighties.

In **CNS tumors**, late mortality due to the primary tumor did not seem to reach any plateau even after very long follow-up (Figure 3 Supportive information). Among deaths due to second cancer dominated tumors in the CNS (22 out of 50 cases, as shown in table 3, supportive information), without any clear predominance regarding the length of follow-up. At the same time cumulative mortality due to non-cancer causes increased with longer follow-up without marked difference between the decades of diagnosis of primary cancer. As shown in table 4, supportive information, the most frequent causes were injuries, poisoning and accidents (64 out of 213 cases) without any clear predominance regarding the length of follow-up. In the group of heart and vascular diseases (47 cases) most frequent were cerebrovascular diseases with fairly even distribution among the different follow-up intervals. On the contrary, deaths due to diseases in the respiratory tract (35 cases) occurred mostly in the follow-up interval 5-10 years. Similar pattern was observed for deaths due to CNS diseases (28 fatalities), where epilepsy was most prominent in the interval 5-10 years.

When multivariate analyses concerning all cause mortality were performed for the three primary diagnoses: leukemia, Hodgkin's lymphoma, and CNS tumors (Table 5, Supportive information), the previously observed importance of the year of diagnosis was confirmed for all three diagnoses (trend tests, $P<0.001$), most pronounced for leukemia and Hodgkin's lymphoma and less for CNS tumors. For sex, there was no increased risk for males with Hodgkin's lymphoma, most probably due to death because of second cancer in breast in female patients. Higher age at diagnosis was a risk factor for leukemia and for Hodgkin's lymphoma (trend tests, $P<0.001$), but not for CNS tumors.

Discussion

This study is based on all incident cases of cancer in childhood and adolescence, 0 – 19 years old at diagnosis, occurring during four decades in the five Nordic countries. It confirms that mortality among 5-year survivors decreased markedly over time.

The two other comparable cohorts of 5-year survivors for whom late mortality has been assessed include the Childhood Cancer Survivor Study (CCSS) in North America [16] and The British Childhood Cancer Survivor Study (BCCSS), a population-based cohort in Britain [17]. The composition of diagnoses in BCCSS is quite similar to our 5-year survivor cohort, while it is quite different in CCSS.

Despite these differences, the SMR:s reported in 2001 by Mertens et al. [18] for the CCSS cohort and by Möller et al. [3] for the Nordic cohort were identical: 10.8. At the follow-up of the CCSS cohort, reported by Armstrong et al. [1], the SMR decreased to 8.4. For the recently published late mortality study in the BCCSS cohort [2] the overall SMR was 10.7, being 3.1 for follow-up after 45 years from cancer diagnosis.

Perhaps the most interesting finding in our study is how the pattern of causes of late death was dependent on the primary cancer diagnosis in the first place and on the time of primary diagnosis in the second place. A major limitation of this study is lack of information on treatment which is not generally available in the Nordic cancer registries. The above mentioned parameters, however, could be regarded as a proxy for the therapy administered. At the same time it is conceivable that in addition to the specific treatments given, other factors inherent in the first cancer diagnosis such as genetic susceptibility or immunological set-up are of importance and not appreciated when analyzing only the treatment exposure.

In 2010, Armstrong et al. [19] also explored temporal trends in cause-specific late mortality among 5-year survivors of childhood cancer. Using data from the Surveillance, Epidemiology and End Results (SEER) population-based registry in the United States late mortality was

assessed among 26,643 5-year survivors, diagnosed from 1974 through 2000, and overall and cause-specific late mortality was analyzed during four consecutive periods. The SMR for all-cause mortality was 8.9, compared to 8.3 in the present study. Armstrong et al. [19] also observed a decline in all-cause mortality at 10 years from diagnosis for consecutive periods of diagnosis, mostly due to reduction in death rates due to primary malignancy. There were differences in pattern of causes of death, depending on the primary diagnosis and some demographic characteristics, like gender, age at diagnosis and ethnicity.

In the present study, the multivariate analyses confirmed the significance of decade of primary diagnosis and primary cancer type after adjusting for sex and age at diagnosis. From the clinical point of view perhaps the most important finding in our study is that almost all decrease in late mortality occurred in the interval 5 – 9 years after diagnosis, while the very late mortality (defined here as 10+ years after diagnosis) remained pretty much the same over time. The study also showed that SMR, albeit going down with longer follow-up, continued to be increased even after 30+ years after diagnosis, suggesting that the mortality of childhood cancer survivors will probably never go down to the level of the mortality in the general population. The same phenomenon is also obvious from the fact that AER was substantially elevated, 4.0 – 5.1 extra deaths per 1000 person-years for follow-up 30+ years. This means that an increasing number of individuals will need closer and practically life-long follow-up in order to avoid premature life loss. To-day's follow-up programs for childhood and adolescence cancer are clearly unsatisfactory in this respect. In 2008 a multidisciplinary pan-European network of professionals, survivors and their families (PanCare) was founded in order to ensure that every European survivor of childhood and adolescent cancer receives

optimal long-term care (www.pancare.eu). One of its ultimate goals is reducing of late mortality in this risk group.

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Figure legends

Figure 1. Accumulated cumulative mortality with the lowest curve showing cumulative mortality due to primary cancer, the middle curve cumulative mortality due to primary and second cancer, and the upper curve showing the total cumulative mortality, including other and unknown causes.

Figure 2. Cumulative late mortality due to different causes by primary diagnosis. P-values (Gray's test) refer to comparison between leukemia, Hodgkin's lymphoma and CNS tumors as primary.

Figure 3. Cumulative late mortality due to different causes by decade of primary diagnosis.

SUPPORTIVE INFORMATION: Figure 1. Cumulative late mortality for cases with leukemia as the primary diagnosis by decade of diagnosis.

SUPPORTIVE INFORMATION: Figure 2. Cumulative late mortality for cases with Hodgkin's lymphoma as the primary diagnosis by decade of diagnosis.

SUPPORTIVE INFORMATION: Figure 3. Cumulative late mortality for cases with CNS tumors as the primary diagnosis by decade of diagnosis.

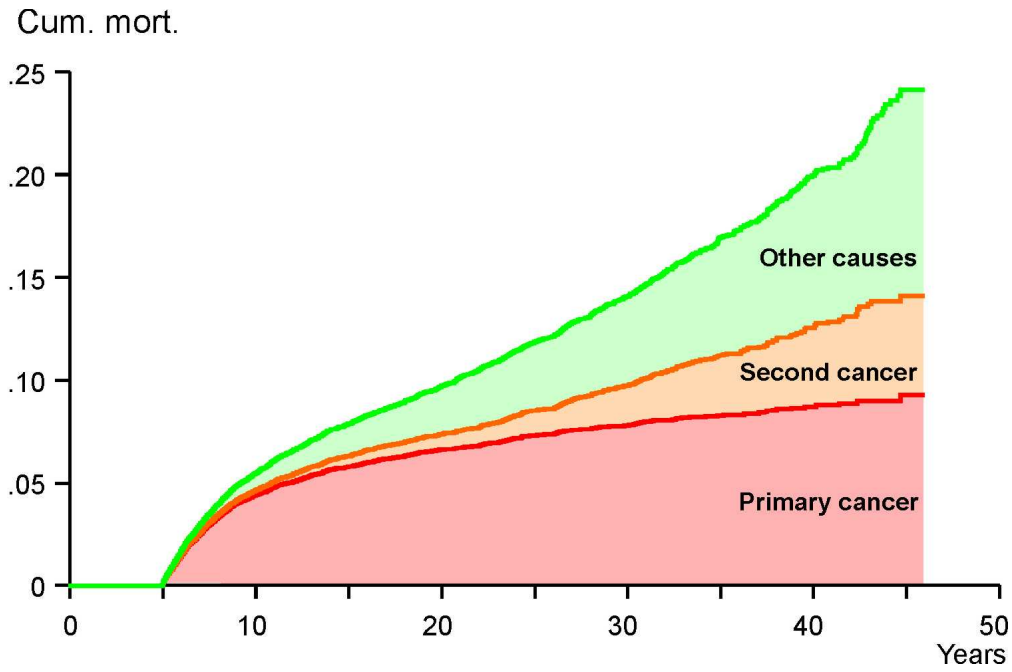


Figure 1. Accumulated cumulative mortality with the lowest curve showing cumulative mortality due to primary cancer, the middle curve cumulative mortality due to primary and second cancer, and the upper curve showing the total cumulative mortality, including other and unknown causes.
127x83mm (300 x 300 DPI)

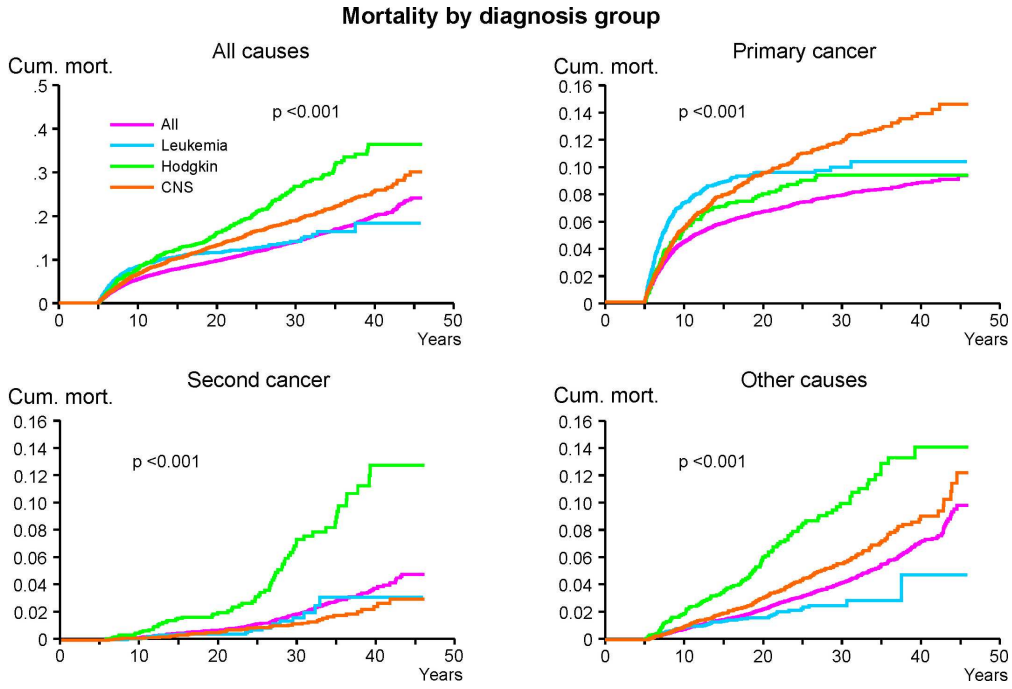


Figure 2. Cumulative late mortality due to different causes by primary diagnosis. P-values (Gray's test) refer to comparison between leukemia, Hodgkin's lymphoma and CNS tumors as primary.
181x122mm (300 x 300 DPI)

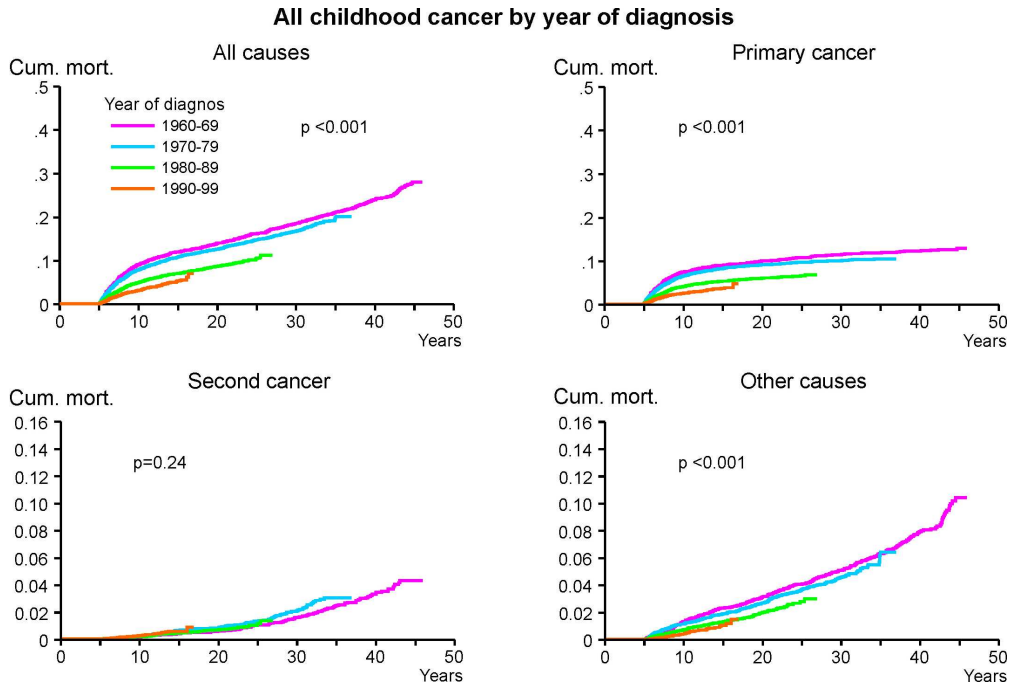


Figure 3. Cumulative late mortality due to different causes by decade of primary diagnosis.
181x122mm (300 x 300 DPI)

Late and very late mortality in 5-year survivors of childhood cancer: changing patterns over four decades. Experience from the Nordic countries.

Stanislaw Garwicz, Harald Anderson, Jørgen H Olsen, Jeanette Falck Winther, Risto Sankila, Frøydis Langmark, Laufey Tryggvadóttir, Torgil R Möller

SUPPORTIVE INFORMATION

SUPPORTIVE INFORMATION: Table 1. The Nordic childhood cancer (NCC) cohort and the 5-year survivor (5-YS) cohort by decade of diagnosis and cancer type.

Decade of diagnosis/	**1960 - 69**		**1970 - 79**		**1980 - 89**		**1990 - 99**		**Total period**			
	NCC	5-YS	*NCC*	5-YS	*NCC*	5-YS	*NCC*	5-YS	*NCC cohort*		5-YS cohort	
*Primary cancer type**	*No*	No	*No*	No	*No*	No	*No*	No	*No*	*%*	No	%
Leukemia (I)	*2,572*	111	*2,407*	700	*2,315*	1,411	*2,473*	1,899	*9,767*	*26.0*	4,120	18.7
Hodgkin´s lymphoma (II a)	*510*	281	*462*	370	*526*	480	*735*	681	*2,233*	*5.9*	1,812	8.2
Other lymphomas (II b)	*580*	163	*571*	212	*630*	406	*752*	607	*2,533*	*6.8*	1,388	6.3
Central nervous system (III)	*1,948*	823	*2,067*	1090	*2,275*	1,572	*2,554*	1.948	*8,844*	*23.6*	5,433	24.7
Sympathetic nervous system (IV)	*345*	110	*362*	139	*410*	203	*540*	329	*1,657*	*4.4*	781	3.6
Retinoblastoma (V)	*176*	146	*185*	168	*165*	150	*178*	176	*704*	*1.9*	640	2.9
Renal tumors (VI)	*396*	141	*406*	259	*397*	307	*391*	340	*1,590*	*4.2*	1,047	4.8
Hepatic tumors (VII)	*69*	5	*93*	21	*95*	35	*106*	68	*363*	*1.0*	129	0.6
Bone tumors (VIII)	*555*	151	*546*	199	*460*	224	*455*	292	*2,016*	*5.4*	866	3.9
Soft-tissue sarcomas (IX)	*495*	229	*468*	267	*583*	389	*635*	468	*2,181*	*5.8*	1,353	6.2
Germ-cell tumors (X)	*407*	189	*473*	292	*565*	493	*642*	580	*2,087*	*5.6*	1,554	7.1
Carcinomas (XI)	*623*	446	*692*	572	*873*	768	*876*	815	*3,064*	*8.2*	2,601	11.8
Other malignant neoplasms (XII)	*150*	43	*134*	70	*99*	76	*93*	71	*476*	*1.3*	260	1.2
Total (I – XII)	***8,826***	**2,838**	***8,866***	**4,359**	***9,393***	**6,514**	***10,430***	**8,273**	***37,515***	***100***	**21,984**	**100**

* *According to the Birch and Marsden [11] classification scheme for childhood cancer (IARC-group)*

SUPPORTIVE INFORMATION: Table 2. Number of deaths in broad categories of validated causes of death by cancer type of the primary tumor

Primary cancer type	Category of cause of death				**Total**
	First primary	Second primary	Non-cancer	Not known	
Leukemia	350	26	65	3	**444**
Hodgkin´s lymphoma	134	69	115	2	**320**
Other lymphomas	36	15	34	2	**87**
Central nervous system	505	50	213	11	**779**
Sympathetic nervous system	38	11	13	0	**62**
Retinoblastoma	5	15	12	0	**32**
Renal tumors	20	12	22	0	**54**
Hepatic tumors	6	1	3	0	**10**
Bone tumors	86	10	21	0	**117**
Soft-tissue sarcomas	91	20	32	2	**145**
Germ-cell tumors	28	22	38	1	**89**
Carcinomas	90	24	48	1	**163**
Other malignant neoplasms	10	2	8	2	**22**
Total	**1399**	**277**	**624**	**24**	**2324**

SUPPORTIVE INFORMATION: Table 3. Number of deaths due to second or subsequent cancer by cancer type of the first primary

Primary cancer type	Site of the second cancer											
	A	B	C	D	E	F	G	H	I	J	K	***Total***
Leukemia	*0*	*4*	*0*	*0*	*0*	*1*	*0*	*4*	*11*	*0*	*6*	***26***
Hodgkin´s lymphoma	*0*	*12*	*6*	*4*	*7*	*0*	*12*	*5*	*4*	*4*	*15*	***69***
Other lymphomas	*0*	*5*	*2*	*0*	*0*	*0*	*2*	*1*	*1*	*1*	*3*	***15***
Central nervous system	*2*	*2*	*3*	*3*	*4*	*1*	*2*	*3*	*22*	*3*	*5*	***50***
Sympathetic nervous system	*0*	*1*	*3*	*2*	*0*	*0*	*0*	*1*	*3*	*1*	*0*	***11***
Retinoblastoma	*1*	*0*	*0*	*3*	*3*	*6*	*0*	*2*	*0*	*0*	*0*	***15***
Renal tumors	*0*	*2*	*0*	*2*	*2*	*0*	*1*	*1*	*2*	*1*	*1*	***12***
Hepatic tumors	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	***1***
Bone tumors	*0*	*2*	*1*	*1*	*2*	*0*	*1*	*0*	*2*	*0*	*1*	***10***
Soft-tissue sarcomas	*0*	*0*	*0*	*4*	*2*	*2*	*0*	*3*	*3*	*4*	*2*	***20***
Germ-cell tumors	*1*	*8*	*2*	*0*	*3*	*1*	*0*	*3*	*3*	*0*	*1*	***22***
Carcinomas	*1*	*4*	*4*	*0*	*0*	*3*	*2*	*2*	*4*	*2*	*2*	***24***
Other malignant neoplasms	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1*	***2***
Total	***5***	***41***	***21***	***19***	***24***	***14***	***20***	***25***	***55***	***16***	***37***	***277***

A	Buccal cavity and pharynx
B	Digestive organs and peritoneum
C	Respiratory and intrathoracic organs
D	Bone
E	Connective and soft tissues
F	Skin
G	Female breast
H	Genito-urinary organs
I	Central nervous system
J	Other and unspecified
K	Lymphatic and hematopoietic system

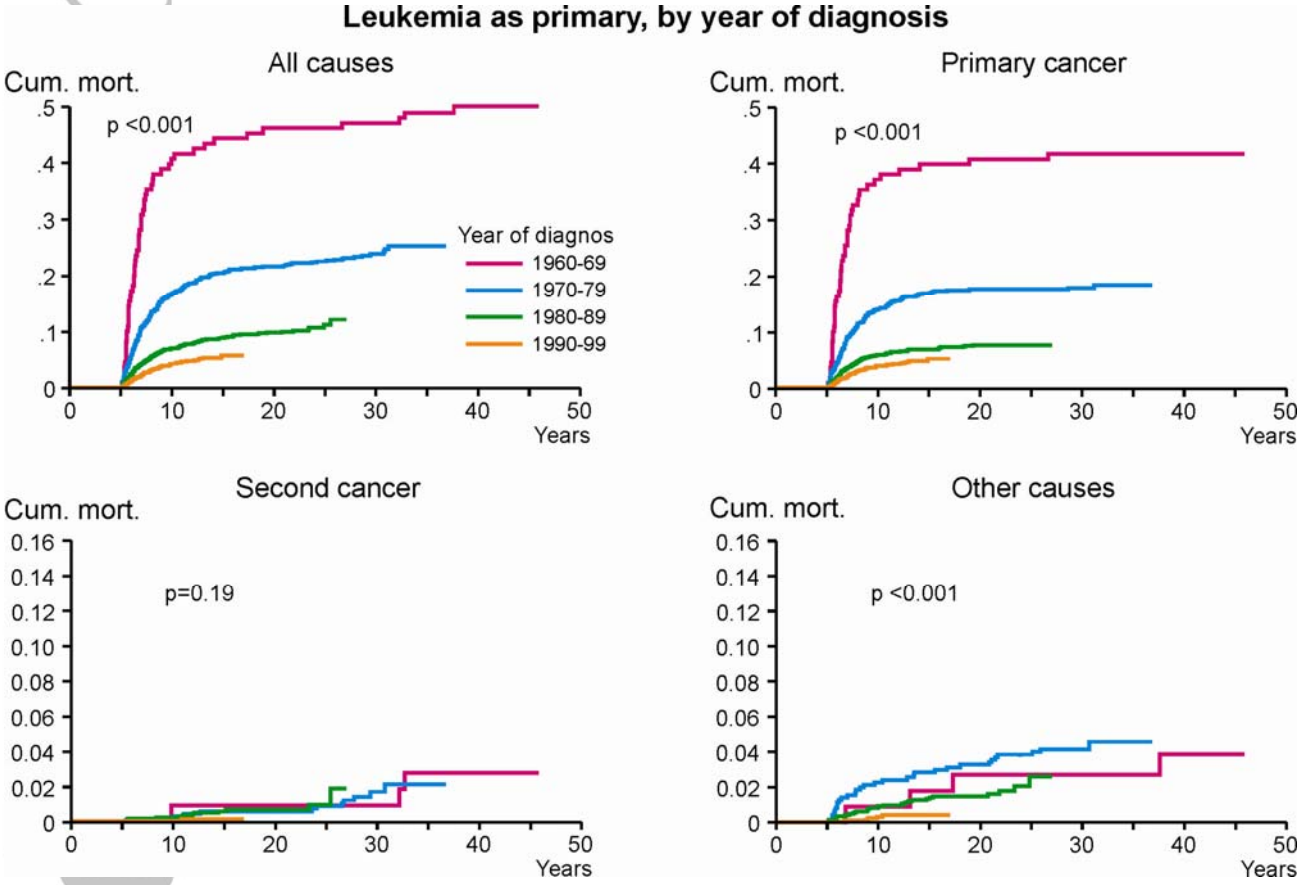
SUPPORTIVE INFORMATION: Table 4. Number of deaths due to non-cancer cause by cancer type of the first primary

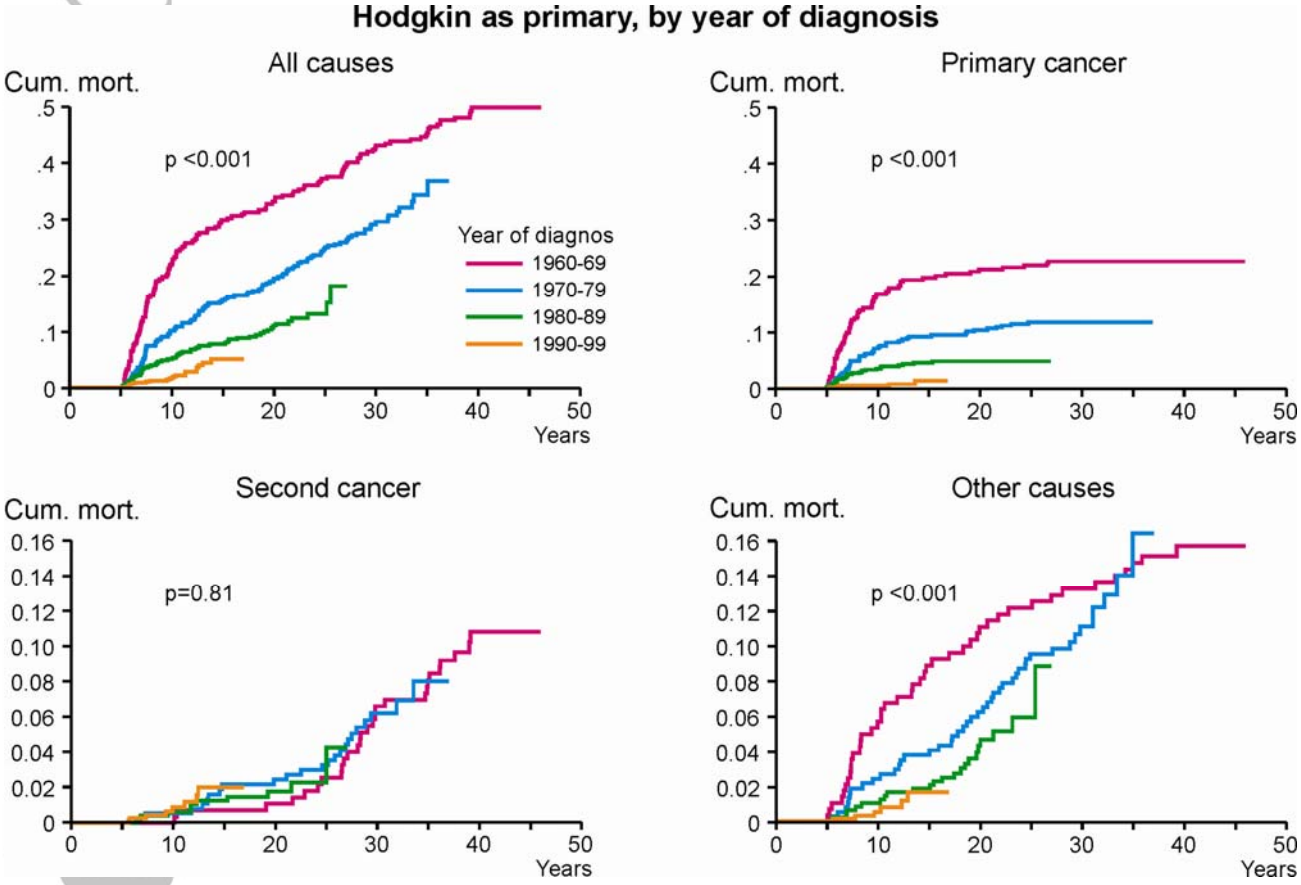
Primary cancer type	Group of non-cancer death									
	a.	b.	c.	d.	e.	f.	g.	h.	i.	***Total***
Leukemia	*6*	*0*	*2*	*8*	*17*	*16*	*3*	*3*	*10*	***65***
Hodgkin´s lymphoma	*6*	*3*	*1*	*4*	*47*	*32*	*6*	*4*	*12*	***115***
Other lymphomas	*3*	*1*	*1*	*3*	*11*	*2*	*1*	*2*	*10*	***34***
Central nervous system	*10*	*5*	*0*	*28*	*47*	*35*	*9*	*15*	*64*	***213***
Sympathetic nervous system	*1*	*0*	*0*	*5*	*2*	*2*	*0*	*1*	*2*	***13***
Retinoblastoma	*0*	*1*	*0*	*1*	*2*	*0*	*1*	*0*	*7*	***12***
Renal tumors	*0*	*1*	*0*	*0*	*3*	*2*	*1*	*2*	*13*	***22***
Hepatic tumors	*0*	*0*	*0*	*0*	*2*	*0*	*0*	*0*	*1*	***3***
Bone tumors	*0*	*0*	*0*	*0*	*5*	*3*	*0*	*3*	*10*	***21***
Soft-tissue sarcomas	*1*	*0*	*0*	*2*	*6*	*0*	*4*	*3*	*16*	***32***
Germ-cell tumors	*0*	*1*	*0*	*1*	*6*	*1*	*6*	*6*	*17*	***38***
Carcinomas	*0*	*2*	*0*	*6*	*10*	*8*	*2*	*4*	*16*	***48***
Other malignant neoplasms	*0*	*0*	*0*	*0*	*4*	*0*	*0*	*0*	*4*	***8***
Total	***27***	***14***	***4***	***58***	***162***	***101***	***33***	***43***	***182***	***624***

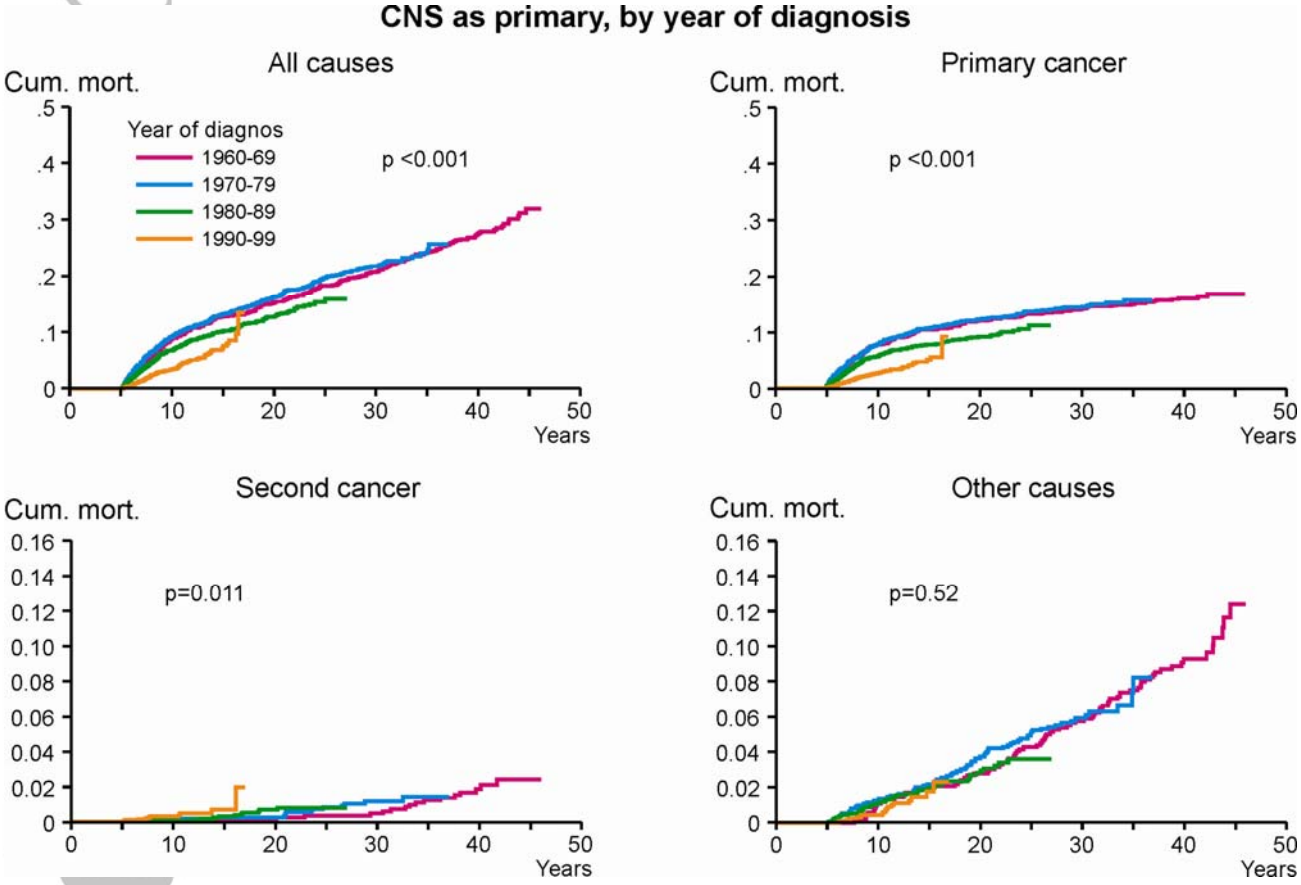
a. Infectious diseases
b. Endocrine and metabolic diseases
c. Blood diseases
d. Central nervous system diseases
e. Heart and vascular diseases
f. Respiratory tract diseases
g. Gastro-intestinal diseases
h. Other diseases and symptoms
i. Injuries and poisoning & accidents

SUPPORTIVE INFORMATION: Table 5. Cox regression analysis (hazard ratios, HR) of all cause mortality in 5-year survivors of leukemia, Hodgkin's lymphoma and CNS tumors.

Primary diagnosis/ *Factor*	**Leukemia**			**Hodgkin's lymphoma**			**CNS tumors**		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Sex									
Female (ref.)	1			1			1		
Male	1.43	1.18-1.73	<0.001	0.94	0.75-1.17	0.56	1.2	1.04-1.38	0.014
Age at diagnosis									
0-4 yrs (ref.)	1			1	1		1		
5-9 yrs	1.05	0.83-1.33	0.68	2.52	0.76-8.36	0.13	0.95	0.77-1.16	0.59
10-14 yrs	1.59	1.22-2.06	0.001	3.04	0.95-9.72	0.06	0.93	0.76-1.14	0.5
15-19 yrs	1.75	1.30-2.35	<0.001	4.14	1.32-12.97	0.015	1.1	0.90-1.34	0.35
Year of diagnosis									
1960-69 (ref.)	1			1			1		
1970-79	0.44	0.32-0.60	<0.001	0.63	0.49-0.82	<0.001	1.05	0.86-1.26	0.65
1980-89	0.18	0.13-0.25	<0.001	0.31	0.23-0.44	<0.001	0.83	0.67-1.01	0.068
1990-99	0.1	0.07-0.14	<0.001	0.13	0.08-0.21	<0.001	0.52	0.40-0.67	<0.001


Leukemia as primary, by year of diagnosis
All causes
Cum. mort.
p <0.001
Year of diagnos
1960-69
1970-79
1980-89
1990-99
Years
Primary cancer
Cum. mort.
p <0.001
Years
Second cancer
Cum. mort.
p=0.19
Years
Other causes
Cum. mort.
p <0.001
Years


Hodgkin as primary, by year of diagnosis
All causes
Cum. mort.
p <0.001
Year of diagnos
1960-69
1970-79
1980-89
1990-99
Years
Primary cancer
Cum. mort.
p <0.001
Years
Second cancer
Cum. mort.
p=0.81
Years
Other causes
Cum. mort.
p <0.001
Years


CNS as primary, by year of diagnosis
All causes
Cum. mort.
Year of diagnos
1960-69
1970-79
1980-89
1990-99
p <0.001
Years
Primary cancer
Cum. mort.
p <0.001
Years
Second cancer
Cum. mort.
p=0.011
Years
Other causes
Cum. mort.
p=0.52
Years