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Late Mortality among Five-Year Survivors of Cancer in Childhood and Adolescence

Differences between the Nordic Countries

Torgil R. Möller, Stanislaw Garwicz, Roland Perfekt, Lotti Barlow, Jeanette Falck Winther, Eystein Glattre, Gudridur Olafsdottir, Jörgen H. Olsen, Annukka Ritvanen and Risto Sankila, for the Association of the Nordic Cancer Registries (ANCR) and the Nordic Society for Paediatric Haematology and Oncology (NOPHO)

From the Department of Cancer Epidemiology (T.R. Möller, R. Perfekt) and Paediatrics (S. Garwicz), University Hospital, Lund, Sweden, Swedish Cancer Registry, Stockholm, Sweden (L. Barlow), Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (J. Falck Winther, J.H. Olsen), Cancer Registry of Norway, Oslo, Norway (E. Glattre), Icelandic Cancer Registry, Reykjavik, Iceland (G. Olafsdottir), National Research and Development Centre for Welfare and Public Health, (A. Ritvanen), and Finnish Cancer Registry (R. Sankila), Helsinki, Finland

Correspondence to: Dr Torgil R. Möller, Department of Cancer Epidemiology, Southern Swedish Tumour Registry, University Hospital, SE-221 85 Lund, Sweden. E-mail: Torgil.Moller@cancerepid.lu.se

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The present study was aimed at assessing differences between the Nordic countries, if any, in late mortality among five-year survivors of childhood cancer. All cases diagnosed before the age of 20 years, between 1960 and 1989, were collected from all Nordic cancer registries. In total, 13 689 patients were identified as five-year survivors and during the extended follow-up 12.3% of them died. Mortality was analysed by decade of diagnosis, for all sites, and for leukaemia, Hodgkin's lymphoma, and central nervous system tumours separately. Analyses were done within a Cox proportional hazards regression framework with adjustments made for gender and age at diagnosis. Hazard ratios were calculated in relation to a weighted Nordic mean based on the proportion of five-year survivors in each country. Overall late mortality was significantly higher in Denmark and Finland than in Norway and Sweden. This could not be explained by inverse differences in five-year survival. The differences diminished over time and had disappeared in the last period. The pattern was similar for both genders. The disappearance of the differences was most probably the effect of a closer collaboration between Nordic paediatric oncologists with development and implementation of common protocols for treatment of childhood cancers in all countries.

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Treatment of childhood cancer has successively become more effective, resulting in ever more patients surviving at least 5 years from diagnosis. However, several of these patients will die later on from recurrence of the primary disease. In a recently published population-based study on late mortality among 5-year survivors of cancer in childhood and adolescence in the Nordic countries (1), we found an overall standardized mortality ratio (SMR) of 10.8 (95% CI 10.3–11.5), mainly due to high excess mortality from the primary cancer. Based on validated cause of death, SMR for second cancer was 4.9 (95% CI 3.9–5.9) and it was 3.1 (95% CI 2.8–3.5) for non-cancer death. Overall late mortality was significantly lower in patients treated during the most recent period of time, and there was no increase observed in rates of deaths due to cancer treatment.

During the work on the study referred to above (1), we observed that the mortality patterns in the different Nordic countries were not as uniform as thought previously. For this reason the present study was carried out.

MATERIAL AND METHODS

Patients

Patient data were obtained from the nationwide and population-based cancer registries and cause of death registers in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). These registries have provided data for a series of studies on cancer in childhood and adolescence during the last decade (2), and a description of their procedures and completeness can be found in

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these papers or in Tulinius et al. (3), for example, and is also available at www.ncu.cancer.dk (4).

The initial cohort included 27 049 individuals (14 947 males and 12 102 females) diagnosed with a malignant neoplasm before 20 years of age during the period from 1960 to 1989. The study cohort consisted of all patients alive 5 years after the first diagnosis of cancer (survivor cohort) and included 13 689 patients or 50.6% of the initial cohort (7134 males or 47.7% of males and 6555 females or 54.2% of females in the initial cohort). The patients were followed up until 31 December 1999 for Denmark, Finland, and Iceland, until 30 June 2001 for Norway, and until 31 December 2001 for Sweden with regard to vital status by means of linking to national population and cause-of-death registers.

In the present study the causes of death were not further analysed. Cause-specific death, however, is given in our previous publication (1). All primary malignant neoplasms were classified according to the International Classification of Diseases for Oncology, ICD-O (5) and grouped according to the Birch and Marsden classification scheme for childhood cancer, proposed by the International Agency for Research on Cancer (IARC-group) (6).

Statistical methods

Non-parametric estimation of cumulative mortality was made by the Kaplan–Meier method. Unadjusted comparisons of late mortality between countries were based on the log-rank test.

For multivariate analyses taking into account possible confounding effects due to different age and/or sex distributions within countries, Cox's proportional hazards regression model was used (7). Hazard ratios for the different Nordic countries were calculated with reference to a Nordic mean. The Nordic reference value was obtained as a weighted geometric mean of the country-specific death hazards, with weights given by the proportion of 5-year survivors from each country. The particular value of the Nordic reference thus varies with the decade of diagnosis and the IARC diagnostic group chosen for a specific analysis.

All Cox regressions were adjusted for gender and stratified by age at diagnosis (four age groups; i.e. 0–4, 5–9, 10–14, 15–19). As late mortality varied quite extensively between countries with decade of diagnosis and IARC diagnostic group, we decided to apply the Cox model separately for each decade of diagnosis and each of the three primary diagnoses responsible for the largest number of fatalities, i.e. leukaemia, Hodgkin's lymphoma and central nervous system (CNS) tumours.

The proportional hazards assumption was examined both graphically and using formal testing based on Schoenfeld residuals (8). Statistical significance of estimated death hazard differences between countries was assessed using the likelihood ratio test. Confidence intervals (CI) for hazard ratios derived from the fitted Cox models have 95% coverage probability.

RESULTS

Background data

The potential median follow-up for death for the entire Nordic survivor cohort was 16.7 years (range 5–37) and the factual observed follow-up was median 14.7 years (range 0–37). During follow-up, 1681 (12.3%) of the 5-year survivors died, 981 males (13.8%) and 700 females (10.7%), while 252 individuals (1.8%) had emigrated or were otherwise lost to follow-up.

Table 1 shows the distribution of childhood cancer patients in the initial cohort diagnosed 1960–1989, the study cohort of 5-year survivors and vital status among survivors at end of follow-up for each of the Nordic countries (Table 1). As can be seen, about half of the initial cohort survived 5 years, percentages varying between 46.1 in Denmark and 55.9 in Sweden. The proportion of survivors who died during follow-up (late mortality) was highest in Denmark and Finland (14.4%) and lowest in Iceland (10.0%).

The number of 5-year survivors increased from 2841 in the first decade of diagnosis to 4346 in the second and to 6502 in the third decade, representing 32.2% in the first decade (ranging from 27.0% to 38.7% in different countries), 49.0% in the second (range 45.6–54.0%) and 69.4% in the last decade (range 64.0–72.6%), respectively. In the same period of time, estimated late mortality at 15 years from diagnosis in 5-year survivors decreased from 12% (95% CI 11–13%) to 7% (95% CI 6–8%) (not shown).

In the further analyses, taking the different IARC groups into account Iceland was excluded because of low numbers of cases.

Table 2 presents country-specific data for the entire period 1960–1989, by IARC group. The highest proportion of fatalities was observed among 5-year survivors of Hodgkin's lymphoma (22.5%), followed by patients with CNS tumours (16.3%), and leukaemia (15.0%). Together these three IARC groups accounted for more than two-thirds of all fatalities among 5-year survivors.

Cumulative late mortality by period and diagnosis

In the following, results of more detailed analyses on cumulative late mortality among 5-year survivors are given for each of the three subsequent decades for all diagnostic groups combined (Fig. 1) and for the three primary diagnoses responsible for the largest number of fatalities; i.e. leukaemia (Fig. 2 and Table 3), Hodgkin's lymphoma (Fig. 3 and Table 4), and CNS tumours (Fig. 4 and Table 5).

For *all sites combined*, there was a highly significant difference in late mortality between the Nordic countries in

Table 1

Childhood cancer patients in the initial cohort, the study cohort of 5-year survivors and vital status at end of follow-up,[1] by country

Cohorts	Denmark	Finland	Iceland	Norway	Sweden	Total
Initial cohort 1960–1989	6 110	6 064	329	5 084	9 462	27 049
5-year survivors cohort	2 817	2 917	162	2 501	5 292	13 689
Percentage 5-year survivors of initial cohort	46.1	48.1	49.2	49.2	55.9	50.6
Vital status of survivors at end of follow-up[1]						
Number dead of 5-year survivors	407	421	16	276	561	1 681
Percentage dead of 5-year survivors	14.4	14.4	10.0	11.0	10.6	12.3
Lost to follow up among 5-year survivors	52	58	5	37	100	252
Number alive at end of follow up	2 358	2 438	141	2 188	4 631	11 756
Percentage alive of the initial cohort	38.6	40.2	42.8	43.0	48.9	43.5

[1]Follow-up to December 1999 for Denmark, Finland, and Iceland, to June 2001 for Norway, and to December 2001 for Sweden.

the first (Fig. 1a, log-rank $p < 0.0001$) and second decades (Fig. 1b, log-rank $p = 0.0001$), which vanished in the last decade (Fig. 1c, log-rank $p = 0.67$). Patients diagnosed in the 1960s and 1970s in Denmark and Finland experienced a higher late mortality than patients in Sweden and Norway. In a stratified Cox regression analysis, the observed differences in mortality between countries could not be explained by differences in distributions of gender, age, or diagnostic groups (likelihood ratio test p-value less than 0.0001, equal to 0.0004 and 0.81 for 5-year survivors diagnosed during the 1960s, 1970s and 1980s, respectively).

For 5-year survivors of *leukaemia*, the unadjusted mortality comparison showed a statistically significant difference between countries in the first decade with Denmark and Finland showing higher death rates than Sweden and Norway (Fig. 2a, log-rank $p = 0.0001$). However, the differences in mortality between countries diminished for patients diagnosed during the second decade (Fig. 2b, log-rank $p = 0.64$), and seemed to have vanished in the last decade (Fig. 2c, log-rank $p = 0.72$). The corresponding age- and gender-corrected comparisons together with hazard ratio estimates from a Cox regression model are given in Table 3. The fitted regression model for the first decade showed a highly statistically significant difference in mortality between countries in the first decade ($p = 0.0007$) but only minor, and far from significant, differences in the last two decades (Table 3). Using the Nordic mean as reference, hazard ratio estimates for 5-year survivors of leukaemia diagnosed during the 1960s ranged from 0.5 for Norwegian to 2.7 for Finnish survivors.

Table 2

Number of patients in the initial cohort, 5-year survivor cohort, and subsequent deaths[1] in the period 1960–1989, by IARC group[2] and country

IARC group	Denmark			Finland			Norway			Sweden			Nordic countries		
	Initial cohort No.	Survivor cohort No.	Subs. Deaths No.	Initial Cohort No.	Survivor cohort No.	Subs. Deaths No.	Initial Cohort No.	Survivor cohort No.	Subs. Deaths No.	Initial Cohort No.	Survivor cohort No.	Subs. Deaths No.	Initial Cohort No.	Survivor cohort No.	Subs. Deaths No.
Leukaemia	1 703	455	75	1 728	502	75	1 385	437	61	2 381	803	119	7 197	2 197	330
NHL	405	151	7	389	155	9	296	122	13	667	344	32	1 757	772	61
Hodgkin's	377	268	58	329	248	75	256	195	40	506	401	77	1 468	1 112	250
CNS	1 381	734	139	1 357	713	150	1 082	541	73	2 263	1 418	194	6 083	3 406	556
SNS	297	92	11	261	108	8	241	103	10	401	189	12	1 200	492	41
Retinoblast	130	119	7	126	107	12	86	79	3	176	163	3	518	468	25
Renal	273	149	7	285	163	9	197	113	5	431	275	13	1 186	700	34
Hepatic	51	6	1	50	14	2	66	17	1	87	21	2	254	58	6
Bone	342	102	19	381	146	20	290	104	17	525	213	24	1 538	565	80
Soft-tissue	318	181	27	385	218	31	294	162	14	534	315	28	1 531	876	100
Germ-cell	370	228	21	247	150	6	333	240	11	498	340	20	1 448	958	58
Carcinoma	399	297	32	449	362	21	414	329	24	896	764	33	2 158	1752	110
Other	64	35	3	77	31	3	144	59	4	97	46	4	382	171	14
Total	6 110	2 817	407	6 064	2 917	421	5 084	2 501	276	9 462	5 292	561	26 720	13 527	1 665

[1]Follow-up to December 1999 for Denmark and Finland, to June 2001 for Norway, and to December 2001 for Sweden.
[2]Groups according to the classification of Birch and Marsden (6).
NHL = non-Hodgkin's lymphoma.
CNS = central nervous system.
SNS = sympathetic nervous system.

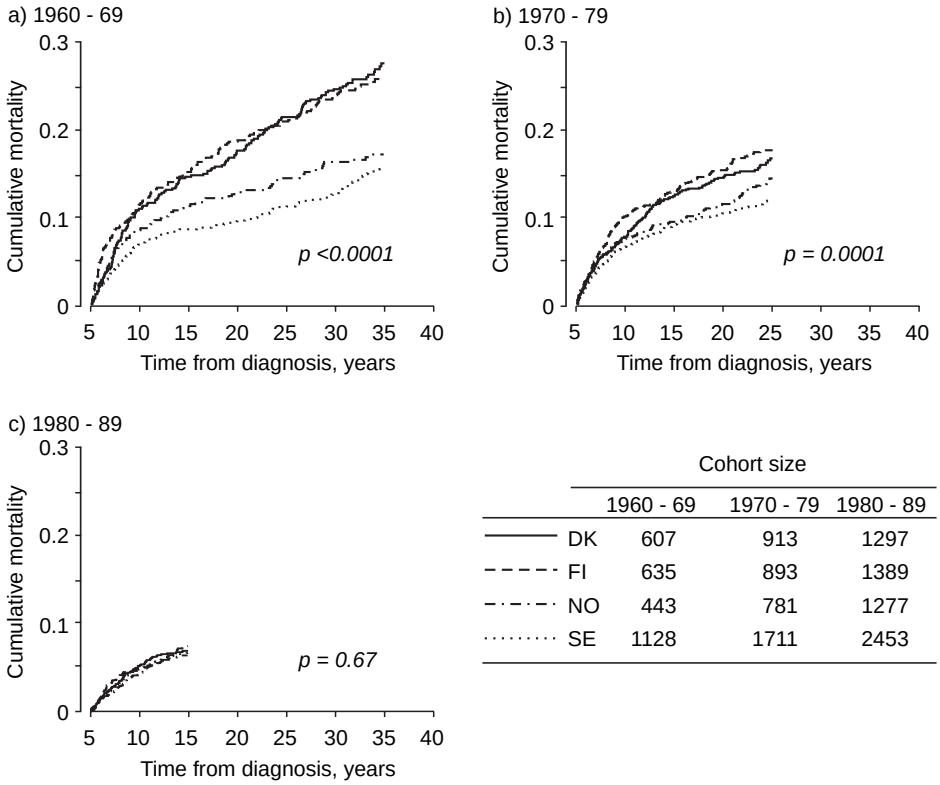

Fig. 1. Estimated cumulative mortality of 5-year survivors of all sites combined, by country in the three subsequent decades of diagnosis; i.e. (a) 1960–1969; (b) 1970–1979; and (c) 1980–1989.

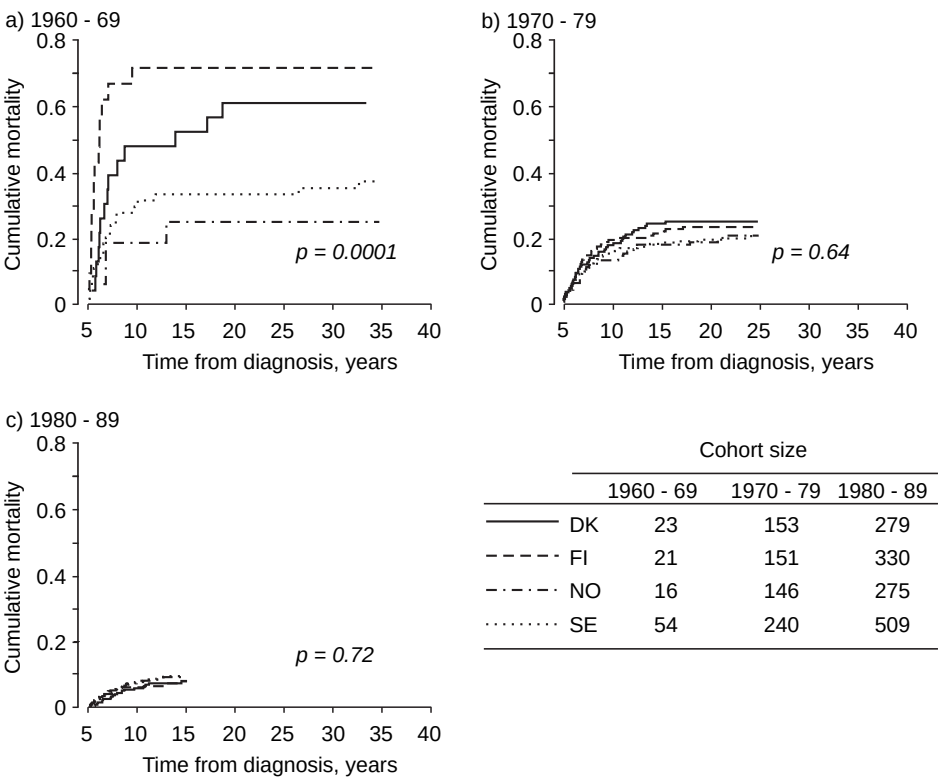

Fig. 2. Estimated cumulative mortality of 5-year survivors of leukaemia, by country in the three subsequent decades of diagnosis; i.e. (a) 1960–1969; (b) 1970–1979; and (c) 1980–1989. Associated death hazard ratios are presented in Table 3.

Table 3

Hazard ratios (HRs) for late mortality in 5-year survivors of leukaemia, by decade of diagnosis and country

	1960–1969[1]		1970–1979[2]		1980–1989[3]	
	HR	95% CI	HR	95% CI	HR	95% CI
Denmark	1.48	0.88–2.51	1.19	0.89–1.57	0.88	0.61–1.28
Finland	2.66	1.59–4.44	1.04	0.77–1.40	0.90	0.64–1.26
Norway	0.45	0.18–1.09	0.94	0.69–1.29	1.09	0.77–1.55
Sweden	0.73	0.54–1.00	0.91	0.73–1.13	1.10	0.87–1.38

[1]Significant difference between countries; p = 0.0007.
[2]No significant difference between countries; p = 0.63.
[3]No significant difference between countries; p = 0.74.

For 5-year survivors of *Hodgkin's lymphoma*, the log-rank test for late mortality differences between countries was statistically significant for patients diagnosed during the 1970s with Finnish patients presenting higher mortality figures compared with rates in the other three countries (Fig. 3b, log-rank p = 0.03). For patients diagnosed during the 1960s (Fig. 3a, log-rank p = 0.19) or 1980s (Fig. 3c, log-rank p = 0.56) the observed differences were too small in relation to cohort sizes to reach statistical significance. However, Finnish patients exhibited the highest mortality rates among 5-year survivors for all three decades. It is clear already from Fig. 3a, presenting data from the first decade, that the proportional hazards assumption in respect of mortality differences between countries is violated due to the appearance of the Danish mortality curve. Thus, excluding Danish data in the Cox modelling of late mortality of patients diagnosed during the 1960s, the difference between the remaining three countries was not statistically significant (Table 4). For the second decade, the age- and gender-corrected p-value for late mortality differences was 0.054, mainly due to Finnish data showing a significantly raised hazard ratio in comparison with the Nordic mean. For the last decade there was no significant mortality difference between the countries (Table 4).

Unadjusted comparisons of the late mortality experience among 5-year survivors of *CNS tumours* revealed clear-cut

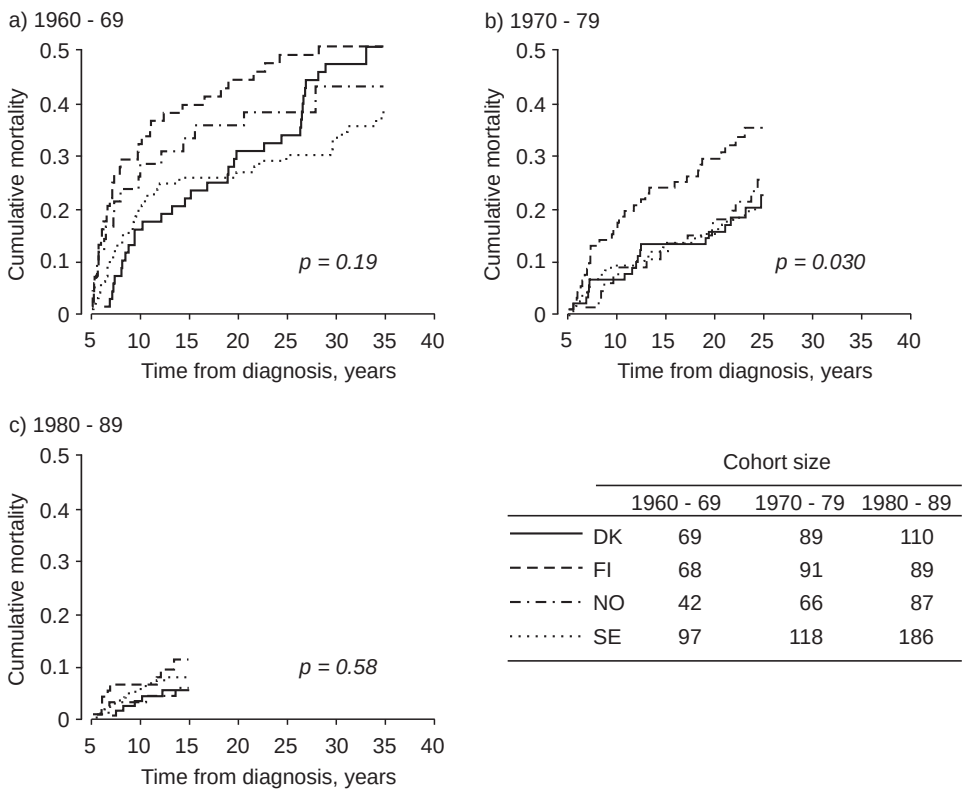

Fig. 3. Estimated cumulative mortality of 5-year survivors of Hodgkin's lymphoma, by country in the three subsequent decades of diagnosis; i.e. (a) 1960–1969; (b) 1970–1979; and (c) 1980–1989. Associated death hazard ratios are presented in Table 4.

Table 4

Hazard ratios (HRs) for late mortality in 5-year survivors of Hodgkin's lymphoma, by decade of diagnosis and country

	1960–1969[1]		1970–1979[2]		1980–1989[3]	
	HR	95% CI	HR	95% CI	HR	95% CI
Denmark	–		0.87	0.59–1.29	0.82	0.43–1.54
Finland	1.31	0.98–1.75	1.60	1.16–2.22	1.40	0.76–2.59
Norway	1.06	0.70–1.59	0.93	0.60–1.46	0.67	0.31–1.45
Sweden	0.81	0.64–1.01	0.80	0.58–1.11	1.16	0.78–1.71

[1]Danish data excluded, see text. No significant difference between countries; p = 0.13.
[2]Marginally significant difference between countries; p = 0.054.
[3]No significant difference between countries; p = 0.48.

differences for patients diagnosed both during the 1960s (Fig. 4a, log-rank p < 0.0001) and 1970s (Fig. 4b, log-rank p = 0.008). Denmark and Finland showed higher mortality than Sweden and Norway. For patients diagnosed during the 1980s, no significant differences were found (Fig. 4c, log-rank p = 0.68). For the Cox regression models, Norwegian data from the 1960s did not satisfy the proportional hazards assumption in relation to the other three countries (cf. Fig. 4a), and was therefore excluded from the analysis. However there was a highly significant difference between the remaining three countries (Table 5), with Sweden showing a lower and both Finland and Denmark showing a higher hazard ratio than the mean. The Cox model for 5-year survivors diagnosed in the 1970s again indicated a significant mortality difference between the four countries, but with only Finnish data showing a significantly raised hazard ratio in relation to the Nordic mean. We noted that there was some indication of a differential pattern for the two genders with these data (p-value for interaction country by gender = 0.03). This was mainly due to two reasons, i.e. Danish females showed a higher estimated death hazard than the corresponding female Nordic mean, while this was not true for Danish males and, in addition, Norwegian women had an estimated lower hazard in comparison with

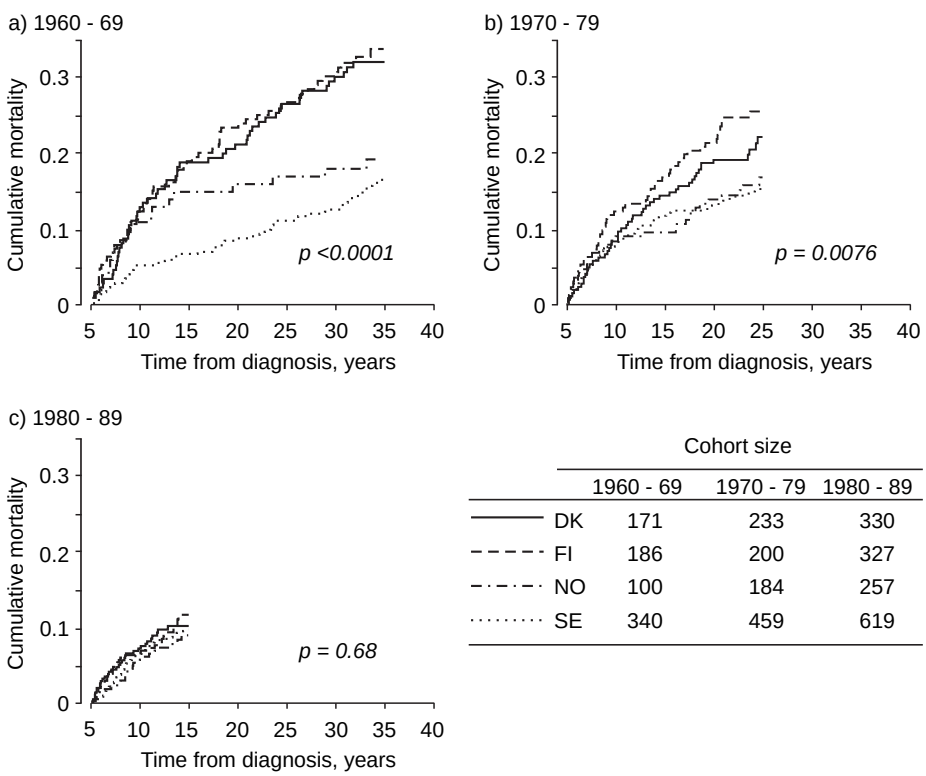

Fig. 4. Estimated cumulative mortality of 5-year survivors of CNS tumour, by country in the three subsequent decades of diagnosis; i.e. (a) 1960–1969; (b) 1970–1979; and (c) 1980–1989. Associated death hazard ratios are presented in Table 5.

Table 5

Hazard ratios (HRs) for late mortality in 5-year survivors of CNS tumours, by decade of diagnosis and country

	1960–1969[1]		1970–1979[2]		1980–1989[3]	
	HR	95% CI	HR	95% CI	HR	95% CI
Denmark	1.45	1.14–1.86	1.18	0.92–1.52	1.07	0.80–1.45
Finland	1.65	1.31–2.08	1.47	1.13–1.90	1.10	0.82–1.48
Norway			0.90	0.65–1.24	0.82	0.56–1.19
Sweden	0.63	0.53–0.74	0.81	0.69–0.96	1.00	0.82–1.20

[1]Norwegian data excluded, see text. Significant difference between countries; $p < 0.0001$.
[2]Significant difference between countries; $p = 0.009$. There is some evidence of a differential pattern between sexes, see text; $p = 0.03$.
[3]No significant difference between countries; $p = 0.70$.

the Nordic mean but this was again not true for Norwegian males (data not shown). For ease of comprehension, hazard ratio estimates from an analysis not including country by gender interaction are presented in Table 5. For the last decade there were only minor differences between the hazard ratio estimates (Table 5).

DISCUSSION

The main finding of this study is a marked difference between the Nordic countries in late mortality among 5-year childhood cancer survivors, most apparent for cases diagnosed during the 1960s. This difference diminished over time and had disappeared during the 1980s. The pattern was, however, not consistent for all cancer types. During the same time period, there was an increase in 5-year survival from 32% in the 1960s to 69% in the 1980s and decrease in late mortality at 15 years from diagnosis from 12% to 7%, indicating that more effective treatment was being employed.

Theoretically, selective under-reporting of cases with good prognosis in countries with higher mortality figures as well as under-reporting of cases with less favourable prognosis and/or incomplete ascertainment of follow-up in countries with lower mortality figures might give effects in the same direction as our observations. However, several studies have shown a high degree of completeness in all registries, and the low number of cases lost to follow-up in the present study indicates a nearly complete ascertainment of vital status. Thus, registration bias cannot explain our findings.

The higher late mortality observed for Denmark and Finland during the first decade of the study period was not associated with low early mortality. On the contrary, these countries showed high early mortality expressed as lower 5-year survival rates. The impact of the mortality in the background population was small due to the young age structure of the patients. The expected number of deaths amounted to slightly less than 1% of the study population, with minor variations between the countries, based on country-specific mortality rates. Thus, 9 out of 10 subsequent deaths among 5-year survivors represent excess mortality, mainly from first or second primary neoplasms (1). Therefore, differences in national mortality rates do not explain the observed differences in late mortality.

For all diagnoses combined, Denmark had the lowest 5-year survival and highest late mortality. This is in line with previous findings in a large Nordic study mainly concerning adult cancer, where Denmark for all cancers had a 10% lower relative 5-year survival rate than the other Nordic countries (9). This difference was small during the 1960s but increased over time, i.e. showed an opposite trend compared with that of childhood cancer, possibly an effect of management of childhood cancer becoming more and more standardized.

The case mix in the initial cohort was slightly different in the four countries and also varied over time. For example, the proportion of leukaemia during the period 1960–1969 was lower in Sweden than in the other countries (26 vs. 31%). On the other hand, during the 1980s Norway had a higher proportion of germ cell tumours. Such differences do not, however, explain the differences observed in late mortality of all sites combined.

The inter-country differences were especially marked for leukaemia. During the 1960s, very few patients did survive 5 years: 7% in Sweden vs. 4% in the other countries. Sweden also had a lower late mortality. This might to some extent be explained by the development of a standardized treatment programme (clinical guidelines) and the establishment of a Swedish Childhood Leukaemia Group in 1967. From the early 1970s onwards, all Swedish childhood patients with acute lymphoblastic leukaemia (ALL) have been treated according to such standardized treatment protocols (10). This has led to a dramatic increase in survival (11). Also on an international scene, 5-year relative survival was exceptionally high during the 1980s (12). In Norway, intermediate dose methotrexate was used from the mid-1970s in a national treatment programme for childhood ALL with good results (13). In Finland, some centres adopted the Norwegian model, but German and American

protocols prevailed. In 1974, the Danish Society for Paediatrics adopted the principle of centralization of treatment of childhood malignancies; however this was not in effect until the mid-1980s. No specific guidelines were issued then. The first Nordic treatment programme for childhood leukaemia was developed in 1981 (14), and a Nordic register for childhood leukaemia was established the same year. Since 1986, treatment of these malignancies has been uniform in the Nordic countries.

The proportion of patients with Hodgkin's lymphoma was stable over the entire period of study and approximately the same (~5%) in all countries. Sweden had the highest 5-year survival in the first period (62% vs. 47–56%) and lowest death hazard ratio. In the second period, Norway had the highest 5-year survival rate (88% vs. 79–82%) and Finland a significantly increased hazard ratio. In the latest period, the 5-year survival rate had increased further to approximately 90% (Norway 95%, Denmark 85%), which was on a par with the best European rates (15), and hazard ratios were similar. No obvious explanation could be found for the higher late mortality in Finland for patients diagnosed in the 1970s.

Approximately one-quarter of the patients in the initial cohort had CNS tumours, the proportion of such patients increasing marginally over time. In the 1960s, 5-year survival ranged from 31% in Norway to 51% in Sweden, while it improved to around 70% for all countries in the 1980s, consistent with findings of the EUROCARE-2 study (16). The only significant difference in late mortality was observed in the 1970s.

As regards management of solid childhood tumours, a multidisciplinary team was formed in Stockholm in 1961, soon followed by similar teams in the other paediatric oncology centres in Sweden. A national Planning Group for Solid Childhood Tumours (VSTB) was established in 1974, and since then treatment of childhood tumours in Sweden has been highly standardized, involving participation from a number of specialists such as paediatric oncologists, paediatric surgeons, general oncologists, pathologists, and neurosurgeons. During the following years, all the Nordic countries have increasingly been participating in the co-operative trials and programmes developed by SIOP (International Society of Paediatric Oncology) and other international organizations.

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