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Trends in survival after childhood cancer in Europe, 1978–1997: Report from the Automated Childhood Cancer Information System project (ACCIS)

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ABSTRACT

This study, originating in the Automated Childhood Cancer Information System (ACCIS), evaluated the time trend in survival after childhood cancer in Europe. The study included more than 72,000 childhood cancer cases aged 0–14 years diagnosed in 1978–1997 and followed-up in 30 population-based cancer registries with a long history of registration and follow-up, in 15 European countries. Survival was analysed using an actuarial life-table method. Five-year cumulative survival probability increased significantly over the study period for all tumour types combined, from 54% for cases diagnosed in the period 1978–1982 to 75% in 1993–1997. Significant improvement was also observed in 10-year survival. Comparing the results for the period 1993–1997 with those for 1978–1982, the largest relative increase in survival was seen for hepatic tumours (32%) and the largest reduction in mortality for non-Hodgkin's lymphomas (60%). Least progress was seen for central nervous system (CNS) tumours. The improvement was statistically significant in all European regions and was most rapid in the East. The ranking among the European regions did not change over the study period, with highest survival in the North and the West and lowest in the East. Extended data collection is necessary to evaluate future time trends and changes in differences between European regions.

1. Introduction

During the last 40 years survival after childhood malignant tumours has improved in most developed countries.[1–9] Marked decreases in cancer mortality rates were correspondingly observed in children and young adults in Europe during the period 1955–1995.[10] The improved prognosis was observed to a various extent for all major types of childhood tumours. It

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was attributed to improved treatment protocols,[11,12] diagnostic procedures[12,13] and organisation.[14]

The aim of this study is to describe the changes in long-term population-based survival of childhood cancer patients in Europe and identify further possibilities for improvement, using the large database of the Automated Childhood Cancer Information System (ACCIS).[15] The ACCIS database contains data from 78 population-based cancer registries that cover about 50% of the population aged 0–14 years living in the 35 participating countries. The present analyses of survival time trends are based on a subset of over 72,000 childhood cancer cases, diagnosed between 1978 and 1997 in 30 cancer registries, with quality data, long-term registration and follow-up, in 15 countries. The time trends are presented for childhood cancer overall and for major tumour groups; for a combined European data-set and five defined geographical regions.

2. Material and methods

All malignant neoplasms, together with non-malignant tumours of the central nervous system (CNS), diagnosed in children aged 0–14 years during the period 1978–1997 in selected registries were extracted from the ACCIS database. The registries were selected if they contributed at least 15 years of registration during 1978–1997 and comparable data-sets, as evaluated by the ACCIS Scientific Committee [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. Two other registries (Somme, and PACA – Provence, Rhone-Alps, Côte d'Azur and Corsica) were also included because of their substantial contribution to the French data despite the slightly shorter period covered. All German cancer registries were also included, since their pool did cover the required minimum 15 years. For each case, the variables included basic demographic data (age, sex, country or region of residence), information on the tumour (date of incidence, site, morphology, basis of diagnosis, grade and laterality) and on follow-up (date and vital status). Data were received and validated at the International Agency for Research on Cancer (IARC), in collaboration with the registries, using automatic[16,17] and *ad hoc* procedures to detect errors and standardise the coding [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. The tumours, coded usually according to ICD-O-2[18] were grouped according to the International Classification of Childhood Cancer (ICCC).[16] The duration of survival was calculated as the time elapsed between the date of diagnosis and the date of death (if patient died) or the date of last follow-up in the given cancer registry. In the registries with follow-up interval longer than 1 year, the survival time of the patients withdrawn before the closing date of the study (lost to follow-up) was calculated as the time interval between the date of diagnosis and the date last seen, plus half of the follow-up interval for that registry. Cases registered from death certificate only (DCO) and cases with zero survival time were excluded from the analysis of survival.

Table 1 presents the coverage and indicators of data quality and follow-up for the registries participating in this study. The largest number of cases for all categories is provided by the national paediatric cancer registries, notably England and Wales, Germany and, for leukaemia only, the Dutch Childhood Oncology Group (DCOG) in the Netherlands. The proportion of the national populations served by the regional cancer registries participating in this study differed across countries: the distribution of person-years by period showed a more complete representation from the period 1983–1987, in particular for Western and Southern regions. Participating registries provided data of good quality: for almost all registries the proportion of cases microscopically diagnosed is over 90%; the proportion of DCO cases in the Registries that used this source of data was 1% or lower (Table 1). In all registries but five the proportion of cases coded as 'lost to follow-up' was less than 5%. The proportion of non-malignant intracranial tumours was similar in the different periods and regions [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

Time trends were analysed for the following 5-year periods: 1978–1982, 1983–1987, 1988–1992 and 1993–1997. The European countries were grouped in five regions (British Islands, East, North, South and West), as shown in Table 1. The data from the National Cancer Registry of the former German Democratic Republic (GDR) for 1978–1987 contributed only to analyses of time trends for Europe as a whole, while data for 1988–1989 were pooled with German Childhood Cancer Registry (GCCR) and included in the West for geographical analyses of the period 1988–1997. Two Dutch cancer registries were included alternatively: DCOG contributed to the analyses of leukaemia, while Eindhoven contributed to all other analyses. Quality indicators by region and period are shown in Table 2.

The children were categorised by age at diagnosis in the following age-groups: 0, 1–4, 5–9, and 10–14 years. Analyses in this paper are limited to the 12 major diagnostic groups of the ICCC and to some of the more frequent diagnostic subgroups.

The actuarial life-table method was used for survival analyses.[19] Results are presented as cumulative survival probability at annual intervals from diagnosis. Five-year observed survival is the cumulative probability of surviving to the fifth anniversary of the date of incidence. Ninety-five percent confidence intervals were calculated according to Kalbfleisch and Prentice.[20] Relative survival was not computed, since mortality from competing causes of death is low in European children [Sankila and colleagues, this issue]. Differences in survival of two or more groups of patients were compared using the entire survivorship curves and tested using the log-rank test with a χ^2 distribution; the statistical significance of a trend in survival over periods was computed using the log-rank test for trend.[21] Statistical significance was set at 5%. The change over periods was also quantified using two indicators, 'rate of change in survival' (RCS) and 'percent change in cumulative probability of death' (PCD). RCS was calculated as a difference between the logarithms of cumulative 5-year survival for children diagnosed in 1993–1997 versus 1978–1982, divided by 3, the number of differences between adjacent periods. PCD is the cumulative probability of death at 5 years for the children diagnosed in 1993–1997, expressed as the percentage of the cumulative probability of death at 5 years for cases diagnosed in 1978–1982, where:

Table 1 – Data-sets, countries and registries included in the study of trends in survival of children diagnosed with cancer in 1978–1998, with indicators of coverage, data quality and follow-up. Percentages are rounded to the nearest integer (Source: ACCIS)

Region	Registry	Coverage		Non-malignant	NOS	Basis of diagnosis			Included in survival analyses		Follow-up				Notes
		Period	Cases			MV	DCO	Unknown			Closing date	Median	5+ years	Unknown	
			n	%	%	%	%	%	*n*	%		Years	%	%	
British Isles	UNITED KINGDOM, England & Wales	1978–1995	21,112	4	3	91	<1	3	20,721	98	31.1.2001	12.3	99	<1	P
	UNITED KINGDOM, Scotland	1978–1997	2436	–	3	94	<1	0	2415	99	31.12.1999	10.3	80	0	
East	ESTONIA, National	1978–1997	810	–	16	92	<1	0	768	95	31.12.1998	6.7	62	2	
	HUNGARY, National	1978–1997	4875	4	2	96	–	0	4830	99	1.1.2000	9.5	72	10	P
	SLOVAKIA, National	1978–1997	3289	2	9	93	1	0	2968	90	31.12.1997	8.6	69	0	
	GERMANY, NCR (only former East)	1978–1987	4037	4	4	98	0	0	3796	94	31.12.1987	6.3	64	5	
North	DENMARK, National	1978–1997	2775	8	10	92	<1	2	2692	97	31.12.1997	9.4	75	<1	
	FINLAND, National	1978–1997	3012	2	9	98	0	<1	2942	98	31.12.1998	8.8	74	<1	
	ICELAND, National	1978–1997	174	3	5	98	0	0	174	100	31.12.2000	11.9	85	0	
	NORWAY, National	1978–1997	2360	2	10	96	<1	<1	2357	100	1.1.2000	10.7	79	1	
South	ITALY, Piedmont paediatric	1978–1997	1970	6	6	94	<1	0	1968	100	31.12.1999	11.5	87	<1	P
	ITALY, Latina	1983–1997	152	–	13	93	0	2	150	99	31.12.1998	7.9	83	0	
	ITALY, Lombardy	1978–1997	405	–	4	92	<1	0	403	100	23.9.1999	6.9	63	0	
	ITALY, Parma	1978–1995	139	3	7	97	0	0	139	100	1.4.1999	13.4	94	<1	
	ITALY, Ragusa	1983–1997	112	–	10	94	0	0	112	100	30.3.2000	9	81	3	
	SLOVENIA, National	1978–1997	990	1	5	98	0	0	981	99	31.12.1999	10.4	77	2	
	SPAIN, Asturias	1983–1997	374	2	12	93	2	0	358	96	31.12.1997	7	65	0	
	SPAIN, Navarra	1978–1996	272	–	7	94	2	0	265	97	31.12.1997	10.9	73	1	
	SPAIN, Tarragona	1983–1997	209	–	8	95	<1	<1	199	95	31.12.1998	7.5	68	0	
	SPAIN, Zaragoza	1978–1996	403	5	7	89	8	<1	374	93	31.12.1996	8.6	70	0	
West	FRANCE, Lorraine	1983–1997	971	3	2	93	–	<1	968	100	1.1.1999	6	61	0	P
	FRANCE, PACA & Corsica	1984–1996	1473	3	1	98	–	0	1354	92	31.3.1998	3.9	44	17	P
	FRANCE, Doubs	1978–1996	262	–	8	46	–	5	243	93	1.6.2001	2.1	26	0	
	FRANCE, Bas-Rhin	1978–1996	498	–	7	97	–	0	498	100	31.12.1997	7.8	72	2	
	FRANCE, Somme	1983–1996	184	–	5	95	–	1	182	99	15.8.2000	4.6	48	11	
	GERMANY, GCCR (East and West)	1991–1997	12,153	3	2	99	–	0	10,702	88	31.12.1998	3.4	28	0	P
	GERMANY, GCCR (only former West)	1983–1990	9124	3	3	100	–	0	8845	97	31.12.1998	9.3	87	0	P
	NETHERLANDS, Eindhoven	1978–1997	478	–	6	92	–	3	475	99	1.7.1999	8.2	70	3	o
	NETHERLANDS, DCOG	1978–1997	2199	–	0	99	–	0	2181	99	1.1.2000	8.8	81	1	P o
	SWITZERLAND, Basel	1983–1997	144	–	4	98	–	0	144	100	30.6.2000	9.3	82	0	
	SWITZERLAND, Geneva	1978–1997	177	–	3	98	0	0	176	99	31.12.1999	7.7	71	8	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	202	2	6	96	<1	0	199	99	1.2.2001	2.5	46	36	

DCOG, Dutch Childhood Oncology Group, childhood leukaemia only; PACA, Provence, Rhone-Alps, Cote d'Azur.

NCR: National Cancer Registry of the former German Democratic Republic (GDR). Data for 1978–1987 contributed only to analyses of time trends for Europe as a whole. Data for 1988–1989 were pooled with GCCR and included in the West. For explanation, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue).

GCCR, National German Childhood Cancer Registry (till 1990 only West, since 1991 for reunified Germany); *n*, number of cases; MV, microscopically verified cases; DCO: registrations from death certificate only; NOS, cases with unspecified histology; P, paediatric cancer registry, age-range of the patients is 0–14 years; –, non-malignant tumours not registered systematically; o, overlapping registration areas: DCOG contributed to analyses of leukaemia only and Eindhoven to all other analyses; 5+ years, cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; –: not applicable.

Table 2 – Numbers of cases and indicators of data quality and follow-up by region and age group for time trend analyses (Source: ACCIS)

Region	Period	Cases	NOS	Basis of diagnosis			Follow-up	
				MV	DCO	Unknown	0+ days	5+ years
		n	%	%	%	%	%	%
		a	b	c	d	e	f	g
Europe	1978–1982	13,800	6	94	<1	<1	96	98
	1983–1987	20,718	4	95	<1	<1	97	87
	1988–1992	20,880	3	95	<1	2	97	87
	1993–1997	20,174	4	96	<1	<1	93	34
British Isles	1978–1982	6179	3	93	<1	1	98	99
	1983–1987	6189	3	92	<1	2	98	99
	1988–1992	6632	3	90	<1	5	98	99
	1993–1997	4548	4	92	<1	3	99	90
East	1978–1982	2129	9	93	<1	0	92	93
	1983–1987	2327	6	94	<1	0	95	84
	1988–1992	2326	5	95	<1	0	96	89
	1993–1997	2192	4	96	<1	0	98	31
North	1978–1982	1996	11	95	<1	1	97	99
	1983–1987	2042	9	96	0	<1	98	100
	1988–1992	2045	8	96	<1	<1	98	99
	1993–1997	2238	11	94	<1	1	99	26
South	1978–1982	1168	9	90	3	<1	97	98
	1983–1987	1381	7	95	<1	<1	99	99
	1988–1992	1281	6	96	<1	<1	99	96
	1993–1997	1196	5	96	<1	<1	99	34
West	1978–1982	363	8	80	0	1	99	92
	1983–1987	6707	3	98	<1	<1	98	87
	1988–1992	8596	2	99	0	<1	95	73
	1993–1997	10,000	2	99	0	<1	87	14

Europe includes the data of former GDR, that are not included in the figures by region; *n*, number of cases; MV, microscopically verified cases; DCO, registrations from death certificate only; NOS, cases with unspecified histology; 0+ days, cases followed-up for at least 1 day. The percentage refers to the number of all registered cases and describes the proportion of cases included in survival analyses.
5+ years, cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date.

cumulative probability of death at 5 years
= 1–5-year cumulative survival.
The analyses were carried out using ACCIS®, STATA® and SAS® programs.

3. Results

A total of 75,572 childhood cancer cases were registered in the 30 selected registries of 15 European countries over the study period 1978–1997. Of these, 72,398 (96%) were followed-up for a period ranging from 1 day to 22 years, and thus included in survival analyses. The proportion of cases contributing to the analyses of survival in each registry can be evaluated from Table 1. The 3174 cases with no follow-up included 239 (8%) DCO cases. In the analyses of leukaemia, the 148 leukaemia cases registered (147 followed-up) in the Eindhoven registry were replaced by the 2199 cases registered (2181 followed-up) over the same period in the DCOG, shown in Table 1.

The completeness of the follow-up at 5 years differed among registries (Table 1), regions and time periods (Table 2). These differences depended on the registration period and the timing of the closing date of the study.

Table 3 presents the distribution of cases in each tumour group over the geographical regions and 5-year periods. Almost 70% of cases resided in the British Isles or the West. Cases diagnosed in the first 5-year period 1978–1982 were under-represented in the overall data-set. Table 4 shows the distribution of each tumour group by age and gender. The distribution of tumour type by age class and the male:female ratio are representative of patterns previously observed in the European childhood cancer patients.[22] Table 4 documents the high quality of diagnosis and follow-up for each tumour group. Microscopic diagnosis was reported for 95% of cases overall, with a somewhat lower proportion for CNS tumours. The proportion of cases with no follow-up was on average around 6%.

Cumulative survival at 5, 10, 15 and 20 years from diagnosis are presented in Table 5, by period of diagnosis and tumour type. Survival improved significantly over the four quinquennia for all tumour groups, as shown in Table 5. Overall 5-year survival for 'all neoplasms' increased from 54% in 1978–1982 to 75% in 1993–1997. The improvement

Table 3 – Numbers of cases diagnosed at age 0–14 years in selected European registries in 1978–1997 included in survival analyses and percentages by European region and period, by ICCC category. Data from the former German Democratic Republic are not included in this table (see text). Percentages are rounded to the nearest integer (Source: ACCIS)

Diagnostic groups (ICCC)	Cases	European Region					Period of diagnosis			
		BRITISH	EASTERN	NORTHERN	SOUTHERN	WESTERN	1978–1982	1983–1987	1988–1992	1993–1997
	n	%	%	%	%	%	%	%	%	%
Leukaemia (I)*	25,167	30	11	10	6	43	18	26	29	27
Acute Lymphocytic Leukaemia (Ia)*	20,335	30	10	10	6	43	17	26	29	28
Acute Non-Lymphocytic Leukaemia (Ib)*	3851	31	11	9	6	43	18	26	29	26
Lymphoma (II)	8253	29	14	9	9	39	17	26	28	29
Hodgkin's Disease (IIa)	3310	30	16	8	9	38	18	26	27	29
Non-Hodgkin's Lymphomas Neoplasm (III)	15,717	35	13	14	7	31	17	26	29	28
Medulloblastoma (IIIc)	3342	35	14	9	6	37	15	26	31	28
Sympathetic System Tumours (IV)	5181	29	13	10	7	41	14	26	31	29
Retinoblastoma (V)	1855	37	10	12	6	34	15	28	32	26
Renal tumours (VI)	4215	32	13	11	6	39	16	27	29	29
Wilms' tumour (VIa)	4074	32	12	10	6	39	16	27	29	29
Hepatic neoplasm (VII)	720	28	15	14	9	35	14	29	30	27
Malignant neoplasm of the bone (VIII)	3395	33	12	10	9	38	19	27	27	27
Osteosarcoma (VIIIa)	3502	33	10	11	9	38	19	26	27	29
Ewing's sarcoma (VIIIc)	1412	33	12	7	8	40	19	29	27	25
Soft tissue sarcoma (IX)	4730	35	12	11	7	36	15	26	30	29
Rhabdomyosarcoma (IXa)	2716	36	9	10	7	38	15	26	31	28
Germ cell, trophoblastic and other gonadal neoplasm (X)	2332	33	12	11	6	37	15	26	30	29
Carcinomas and other malignant epithelial neoplasm (XI)	1712	41	11	17	10	22	19	27	28	26
Other and unspecified neoplasm (XII)	309	34	21	29	7	8	24	22	27	27
All neoplasm	71,535	33	13	12	7	36	17	26	29	28

* Figures on leukaemia are based on a slightly different data-set, whereby the data of Eindhoven Cancer Registry are replaced by the data of Dutch Childhood Oncology Group, the latter registering childhood leukaemia in The Netherlands nationwide (see text).

Table 4 – Numbers of cases diagnosed at age 0–14 years in selected European registries in 1978–1997 and included in survival analyses and their distribution by age class, gender, vital status, basis of diagnosis and ICCC category. The data from the former German Democratic Republic are not included in this table (see text). Percentages are rounded to the nearest integer (Source: ACCIS)

Diagnostic groups (ICCC)	Cases	Age class				Boys	Follow-up			Diagnosis	
		0	1–4	5–9	10–14		<1 day	Dead	Lost	MV	DCO
	n	%	%	%	%	%	%	%	%	%	%
Leukaemia (I)*	25,167	5	47	28	20	56	2	34	1	99	0
Acute Lymphocytic Leukaemia (Ia)*	20,335	3	50	29	17	56	2	28	1	99	0
Ac. Non-Lymphocytic Leukaemia (Ib)*	3851	13	32	24	31	53	5	57	0	99	0
Lymphoma (II)	8253	1	16	34	48	69	4	22	1	98	0
Hodgkin's Disease (IIa)	3310	4	14	32	50	64	1	11	1	99	0
Non-Hodgkin's Lymphomas (IIb–IIe)	4943	2	22	38	38	72	7	29	1	98	0
CNS Neoplasm (III)	15,717	6	30	35	29	55	8	37	4	86	1
Medulloblastoma (IIIc)	3342	6	33	40	21	63	7	53	2	98	0
Sympathetic System Tumours (IV)	5181	33	51	12	4	55	3	46	1	97	0
Retinoblastoma (V)	1855	38	56	5	1	52	8	7	1	90	0
Renal tumours (VI)	4215	15	61	20	4	49	2	19	1	97	0
Wilms' tumour (VIa)	4074	15	62	20	3	49	2	19	1	98	0
Hepatic neoplasm (VII)	720	33	42	11	13	61	16	46	0	95	1
Malignant neoplasm of the bone (VIII)	3395	1	6	26	67	52	1	46	1	98	0
Osteosarcoma (VIIIa)	3502	1	12	37	50	51	1	46	1	99	0
Ewing's sarcoma (VIIIc)	1412	0	10	30	59	54	1	48	0	99	0
Soft tissue sarcoma (IX)	4730	11	32	27	30	56	3	38	1	99	0
Rhabdomyosarcoma (Ixa)	2716	8	42	30	20	60	2	39	1	99	0
Germ cell, trophoblastic and other gonadal neoplasm (X)	2332	19	29	15	37	46	4	21	2	97	0
Carcinomas and other malignant epithelial neoplasm (XI)	1712	2	8	21	68	45	4	19	2	94	0
Other and unspecified neoplasm (XII)	309	21	34	22	23	50	12	30	1	53	3
All neoplasm	71,535	9	36	27	27	56	4	33	2	95	0.3

MV, microscopic verification; DCO, registrations from death certificate only.
* Figures on leukaemia are based on a slightly different data-set, whereby the data of Eindhoven Cancer Registry are replaced by the data of Dutch Childhood Oncology Group, the latter registering childhood leukaemia in The Netherlands nationwide (see text).

was also seen for survival at 10 years and 15 years after the diagnosis. Table 5 also shows the rate of change in survival (RCS), interpreted as the average change in percentage of survivors per period. For 'all neoplasm', the 5-year survival has increased by 11% per period. The 'percent change in cumulative probability of death' (PCD) at 5 years can be interpreted as the proportion of deaths avoided for children diagnosed in the last period compared with those diagnosed in the first one. Thus, for 'all neoplasm', 45% of deaths were avoided among the patients diagnosed in 1993–1997, compared with those diagnosed in 1978–1982. The reduction in mortality at 5 years of more than 50% (PCD) was observed for leukaemia (the combined group and the acute lymphocytic leukaemia), lymphomas (non-Hodgkin's lymphoma only), retinoblastoma, hepatic neoplasm and germ cell tumours (Table 5). The lowest reduction in mortality (30% or less) was seen for CNS tumours and soft tissue sarcoma. The change in cumulative survival was largest (more than 30%) for children with hepatic tumours and acute non-lymphocytic leukaemia (Table 5), the tumour groups with lowest survival in the period 1978–1982. Among the tumour groups with 5-year survival under 50% in the first 5-year period, the improvement was moderate for sympathetic nervous system tumours, bone tumours and non-Hodgkin's lymphomas and modest for primitive neuroectodermal tumors (PNET)/medulloblastoma.

Survival at 5 and 10 years by European region and period of diagnosis is presented for selected ICCC categories in Figs. 1 and 2, respectively. The improvement in survival was observed in all European regions for the majority of the tumour groups (Table 6), although inter-regional differences persisted (Figs. 1 and 2). Improvement in survival was statistically significant (P-value < 0.05) in all European regions for leukaemia (overall and the two major subtypes), lymphomas (except Hodgkin's disease), sympathetic nervous system tumours (including neuroblastoma), bone tumours (only overall, not the subtypes) and 'all neoplasm' combined. For the remaining tumour types, the trend was statistically significant for some regions only. The ranking of regions was almost constant over each of the study periods: the North and West usually had better survival than the British Isles and South, while the East was in the lowest rank. This ranking of the regions was observed for the majority of tumour types. There were hardly any differences in ranking of regions by 5-year survival (Fig. 1) or 10-year survival (Fig. 2). In the tumour groups with highest survival at the beginning of the study period, such as Hodgkin's disease, retinoblastoma or carcinomas, the relative change in survival (RCS) was lower than in the tumour groups with very low survival in the first quinquennia (Table 5).

By region, the change in survival was most remarkable for the East, with RCS of 29% and PCD of 50% for 'all neoplasm'

Table 5 – Trends in survival after childhood cancer in Europe, 1978–1997. Cumulative survival by period of diagnosis and tumour type, rate of change per period in 5-year survival (RCS) and percent change in cumulative probability of death at 5 years (PCD) between 1978–1982 and 1993–1997. P (trend) refers to the χ^2 log rank test for trend. Percentages are rounded to the nearest integer (Source: ACCIS)

	Cumulative survival probability										RCS	PCD	P (trend)
Period of diagnosis	1978–1982				1983–1987			1988–1992		1993–1997			
Years from diagnosis	5	10	15	20	5	10	15	5	10	5			
ICCC	%	%	%	%	%	%	%	%	%	%	%	%	
Leukaemia (I)*	51	45	44	43	65	60	59	72	68	77	14%	53%	<0.0001
Acute Lymphocytic Leukaemia (Ia)*	59	53	50	50	72	67	65	78	74	82	11%	57%	<0.0001
Acute Non-Lymphocytic Leukaemia (Ib)*	20	18	18	18	36	35	33	47	45	52	31%	40%	<0.0001
Lymphoma (II)	65	62	61	59	76	74	73	84	83	85	9%	58%	<0.0001
Hodgkin's Disease (IIa)	87	82	80	78	91	88	87	94	91	93	2%	44%	<0.0001
Non-Hodgkin's Lymphomas (IIb–IIe)	48	46	46	45	66	64	63	78	77	79	17%	60%	<0.0001
CNS Neoplasm (III)	52	48	46	44	59	55	52	63	59	67	8%	31%	<0.0001
Medulloblastoma (IIIc)	37	30	29	28	44	38	34	48	40	52	12%	24%	<0.0001
Sympathetic System Tumours (IV)	37	36	35	35	48	46	45	54	51	67	20%	47%	<0.0001
Retinoblastoma (V)	89	87	87	86	92	90	89	95	94	95	2%	54%	0.0001
Renal tumours (VI)	72	70	70	69	79	79	78	84	83	86	6%	49%	<0.0001
Wilms' tumour (VIa)	72	71	70	69	80	79	78	84	83	86	6%	49%	<0.0001
Hepatic neoplasm (VII)	24	21	21	21	34	32	32	56	55	64	32%	52%	<0.0001
Malignant neoplasm of the bone (VIII)	37	33	31	30	56	51	49	61	57	63	18%	42%	<0.0001
Osteosarcoma (VIIIa)	37	34	32	32	58	53	51	59	57	61	17%	38%	<0.0001
Ewing's sarcoma (VIIIc)	34	28	26	24	52	48	46	63	56	66	22%	49%	<0.0001
Soft tissue sarcoma (IX)	54	51	49	48	62	59	57	65	61	66	6%	25%	<0.0001
Rhabdomyosarcoma (IXa)	51	48	47	46	59	56	54	64	61	65	8%	29%	<0.0001
Germ cell, trophoblastic and other gonadal neoplasm (X)	64	62	61	61	75	74	73	83	82	89	11%	69%	<0.0001
Carcinomas and other malignant epithelial neoplasm (XI)	77	74	72	70	84	81	78	84	82	86	4%	38%	0.0007
All neoplasm	54	50	49	48	65	62	60	71	68	75	11%	45%	<0.0001

* Figures on leukaemia are based on a slightly different data-set, whereby the data of Eindhoven Cancer Registry are replaced by the data of Dutch Childhood Oncology Group, the latter registering childhood leukaemia in The Netherlands nationwide (see text).

(i.e. 50% of deaths avoided among the children diagnosed in the last study period, compared with the period of diagnosis 1978–1982) (Table 6). In comparison, the smallest improvement was observed for the North (PCS = 17%, PCD = 43%), reflecting high survival among the children already diagnosed in the North during 1978–1982.

4. Discussion

This study investigated the changes in survival of European children diagnosed with malignant neoplasms in 1978–1997. A considerable improvement in survival of children with cancer was observed, with an almost 50% percent reduction in mortality by 5 years over the study period. This favourable trend was seen for all tumour types and in all regions of Europe.

Using the population-based ACCIS database, only cancer registries with long registration periods were selected. The geographical variety of data sources to a certain extent permits generalising the findings to the European childhood population, although continuing data collection and extension of coverage to other parts of Europe will provide a more complete representation. Needless to say, the large size of the cohort contributed to the stability and the precision of the estimates of cumulative survival.

Various aspects of the validity of data in the individual cancer registries were considered [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. The registries contributing to the analyses of trends had relatively long and sufficiently complete follow-up, low proportion of DCO cases, and high proportion of diagnoses confirmed by microscopic examination, in agreement with the requirements for comparability of results of survival analysis.[23] The differences in data quality among the different registries and periods were small. The proportion of subjects with follow-up of 5 years or more differed between the European regions, in particular for the most recent period of diagnosis and to a lesser extent for the preceding period. Although, in theory, differences in the completeness of follow-up might affect comparability of cumulative survival, these disparities probably did not influence inter-regional comparison in this study: the ranking of regions seen for the period 1993–1997, when the completeness of follow-up differed most, was the same in the earlier periods, when follow-up was almost complete in all regions.

The increasing survival was observed at 5, 10, and 15 years since diagnosis, suggesting that increase in the most commonly reported 5-year survival is unlikely to result only from delayed death. Nevertheless, the values of survival after long-term follow-up for 10, 15 or 20 years are still slightly inferior to those observed at 5 years after diagnosis. This means that children with cancer continue to die after 5 years and long-term follow-up is therefore necessary to quantify the full extent of the excess mortality.

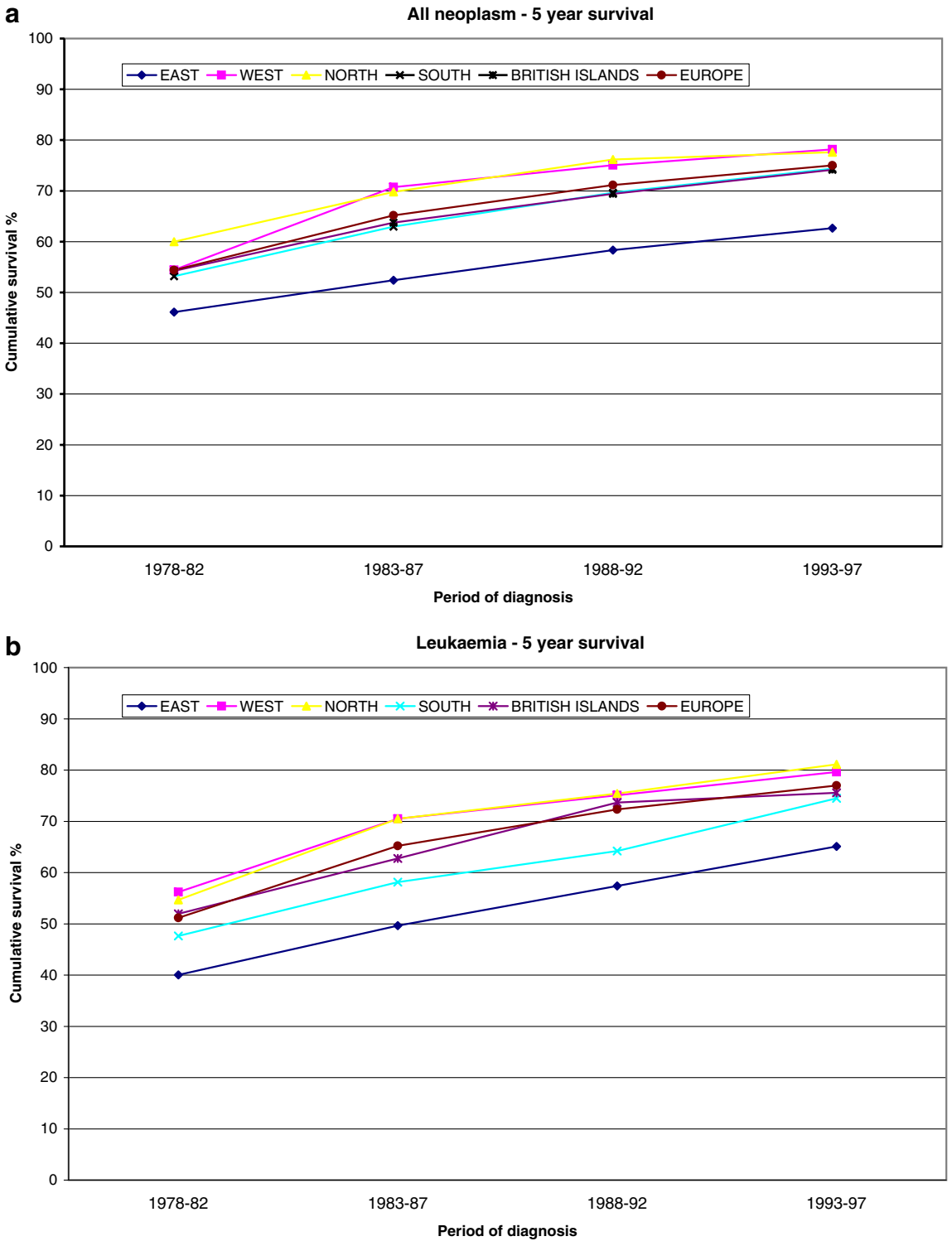
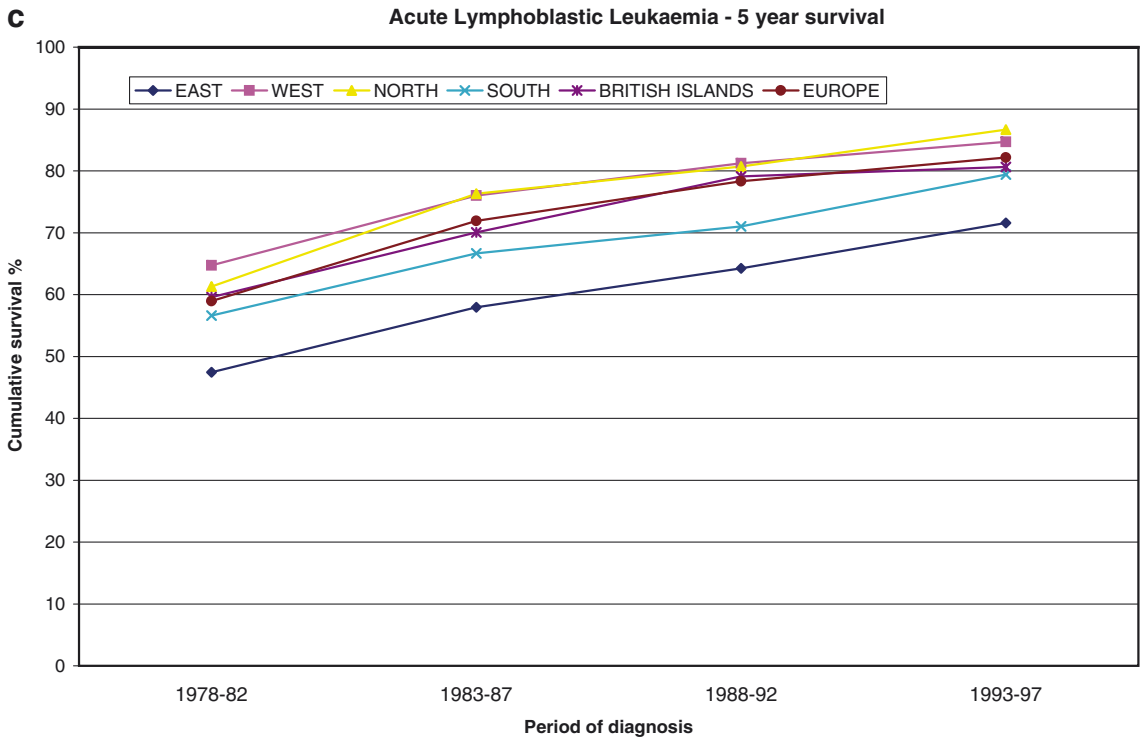


Fig. 1 – Five-year actuarial cumulative survival, by tumour type, European region and period of diagnosis. Source: ACCIS.

In order to summarise the trends in survival a measure of the rate of change in survival (RCS) was used during the study period. This index is especially sensitive for large differences in survival between compared groups of patients. Therefore, low values of RCS indicate lack of improvement in survival when either both compared values are low or both compared values are high. RCS is therefore a good indicator of progress, especially in the groups of patients with low baseline survival. Percent change in cumulative probability of death (PCD) measured the proportion of deaths avoided and therefore



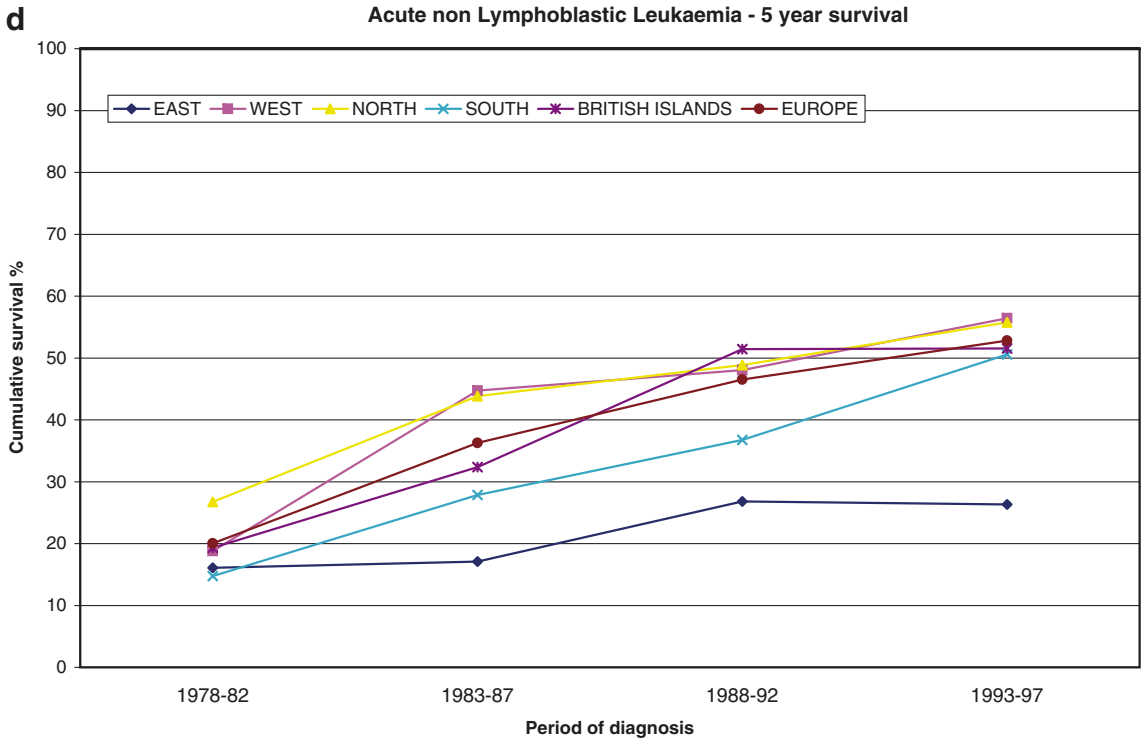
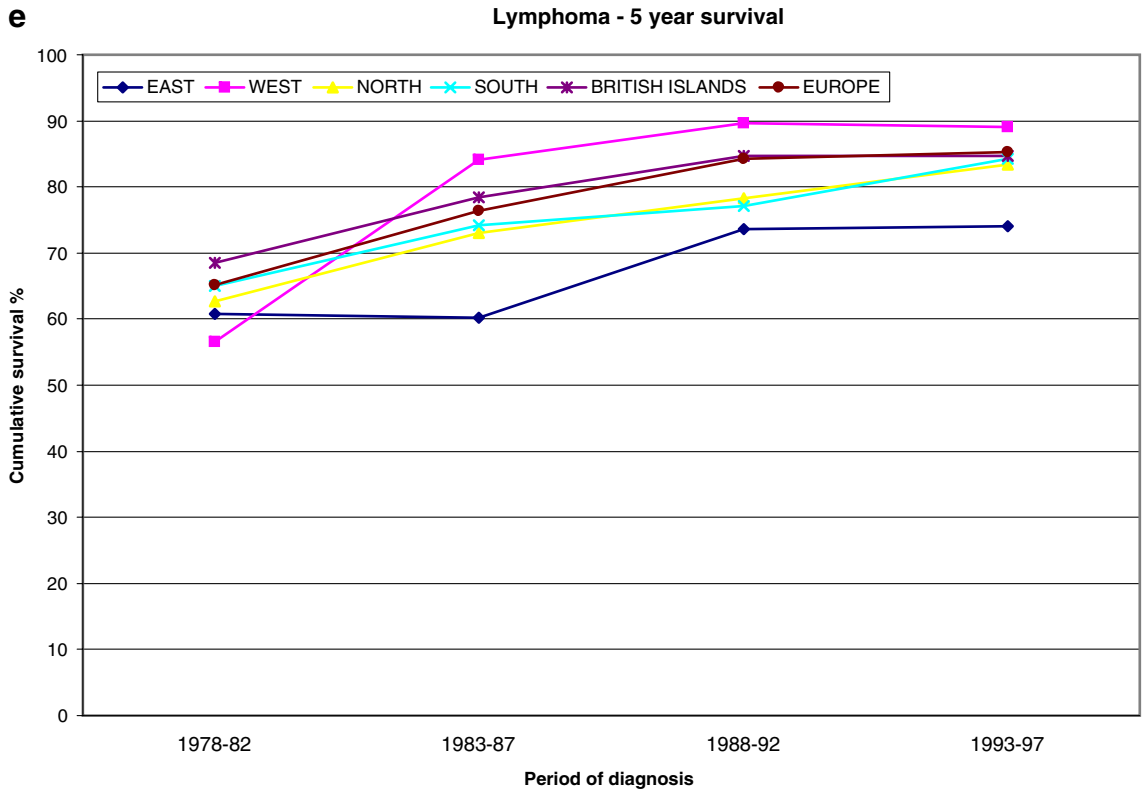
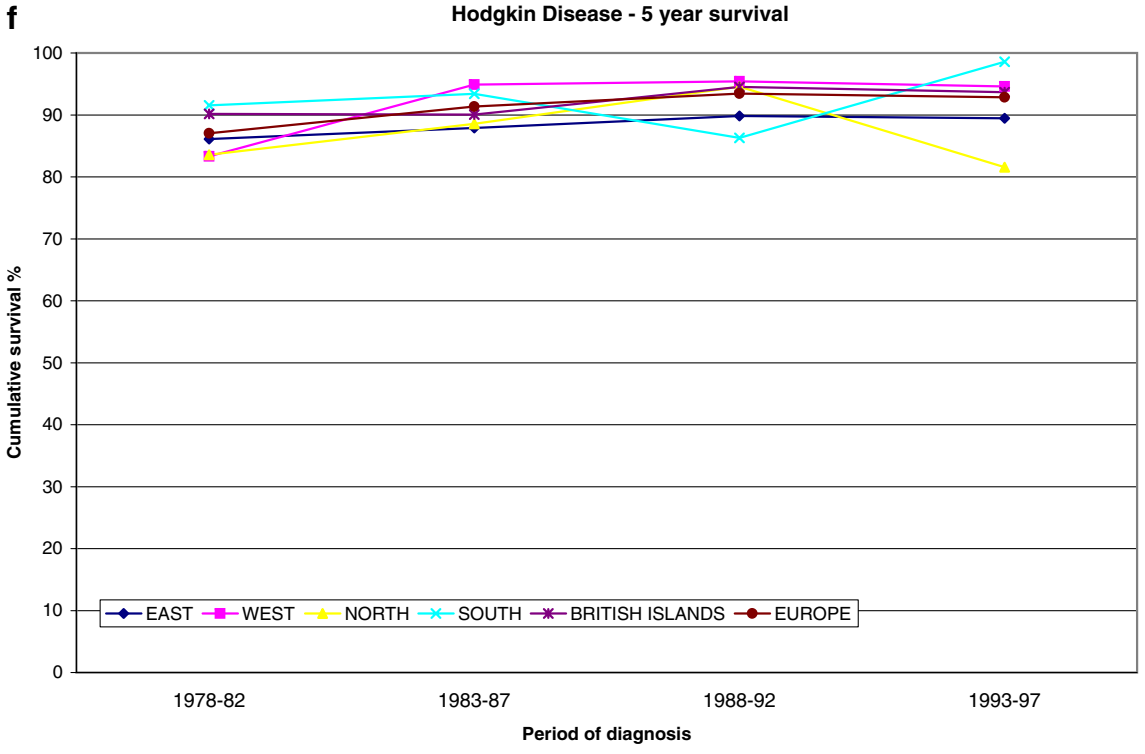


Fig. 1 – *continued*

depended less on the baseline value of survival. The two indices are complementary, RCS describing the speed and PCD the extent of change.

The results of this study are in agreement with survival figures presented for other countries[5,6] and with the analyses of mortality trends in European countries,[10] although the differences in methods, periods or geographical areas did not allow a formal comparison between these studies. Survival differed among the European regions, but the region-specific ranking stayed constant for all diagnostic groups combined and for the majority of tumour types. Similar results were observed in the Eurocare study.[8] In a recent





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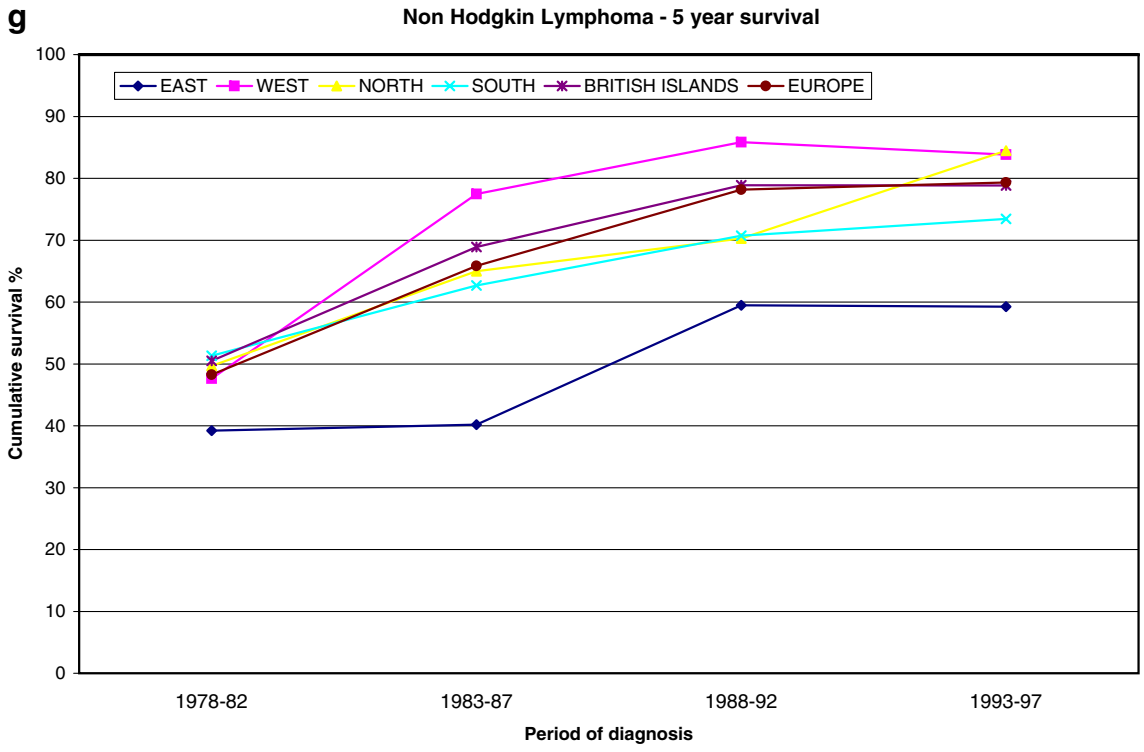
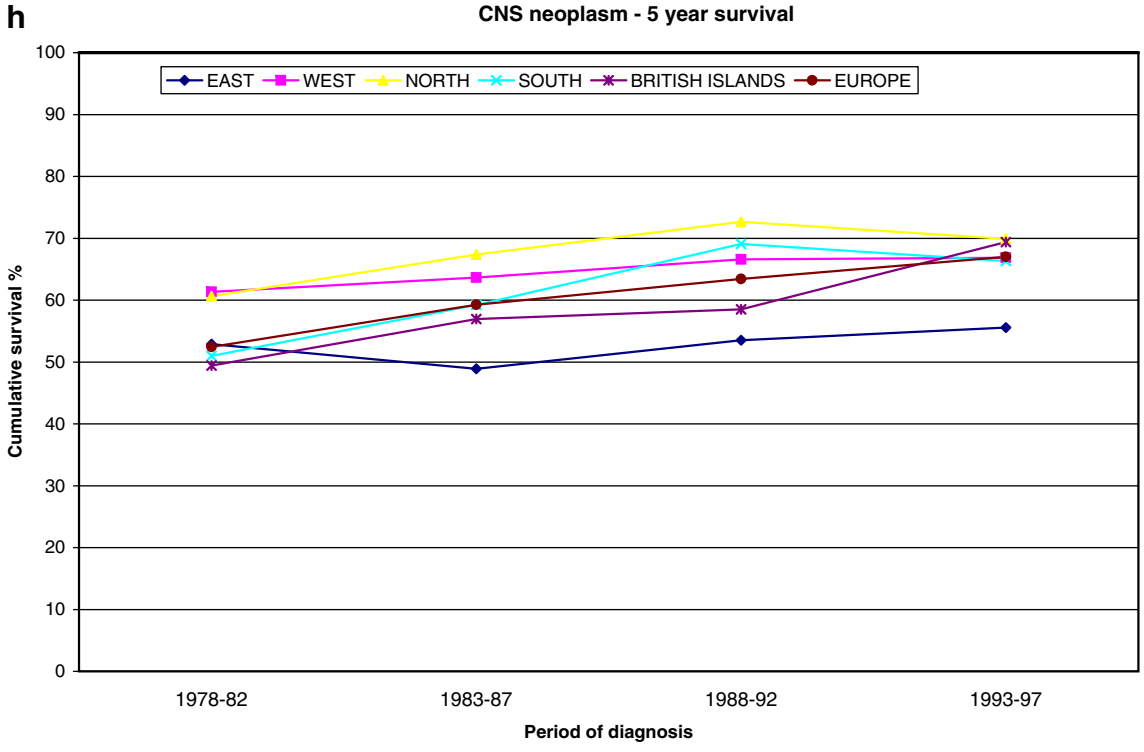
study on tumours incident in the period 1978–1994 Gatta and colleagues[9] observed a slightly narrower gap between the East and the other European regions than that seen in the present study. This difference was probably due to the different selection of the contributing registries: the Eastern region in the present study included Estonia, Hungary and Slovakia, while Eurocare included Estonia, Poland (Warsaw and Cracow), Slovenia and Slovakia. Survival for Slovenia,





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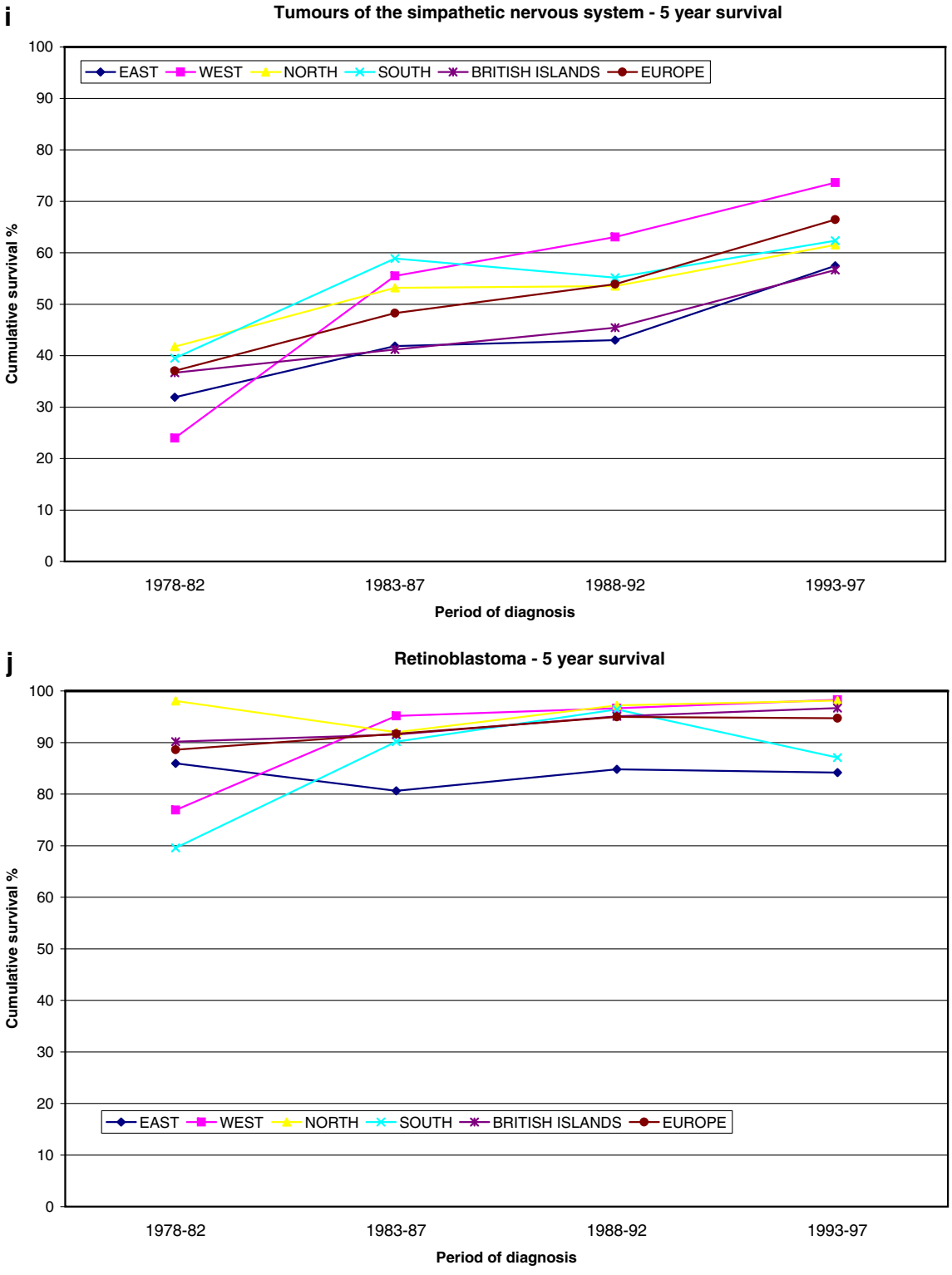
grouped with the South in this study, was superior to that of countries grouped in the East (Overview paper, this issue). However, we have observed closing of the gap: both speed (RCS) and extent (PCD) of increase in survival in the East was higher than in the other regions over the study period. Analyses of survival trends by individual country were not considered in this project.

We have limited the description of the survival time trends to clearly defined ICCC tumour groups. Small changes in tumour classification were therefore less likely



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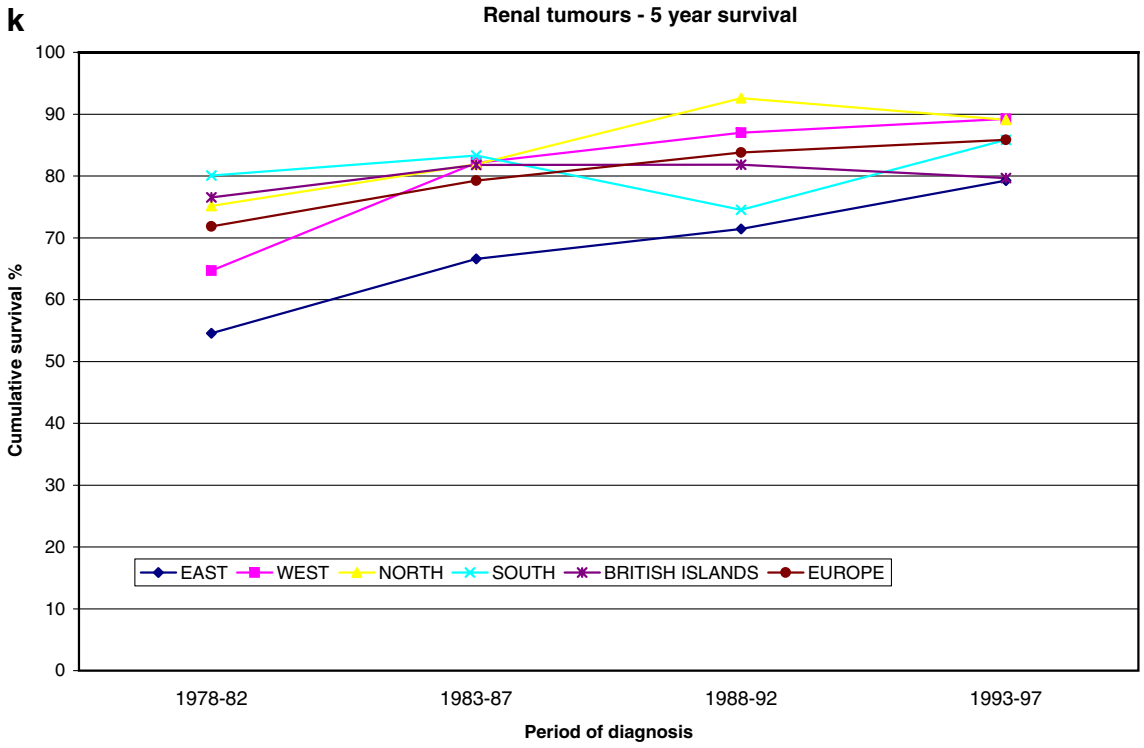
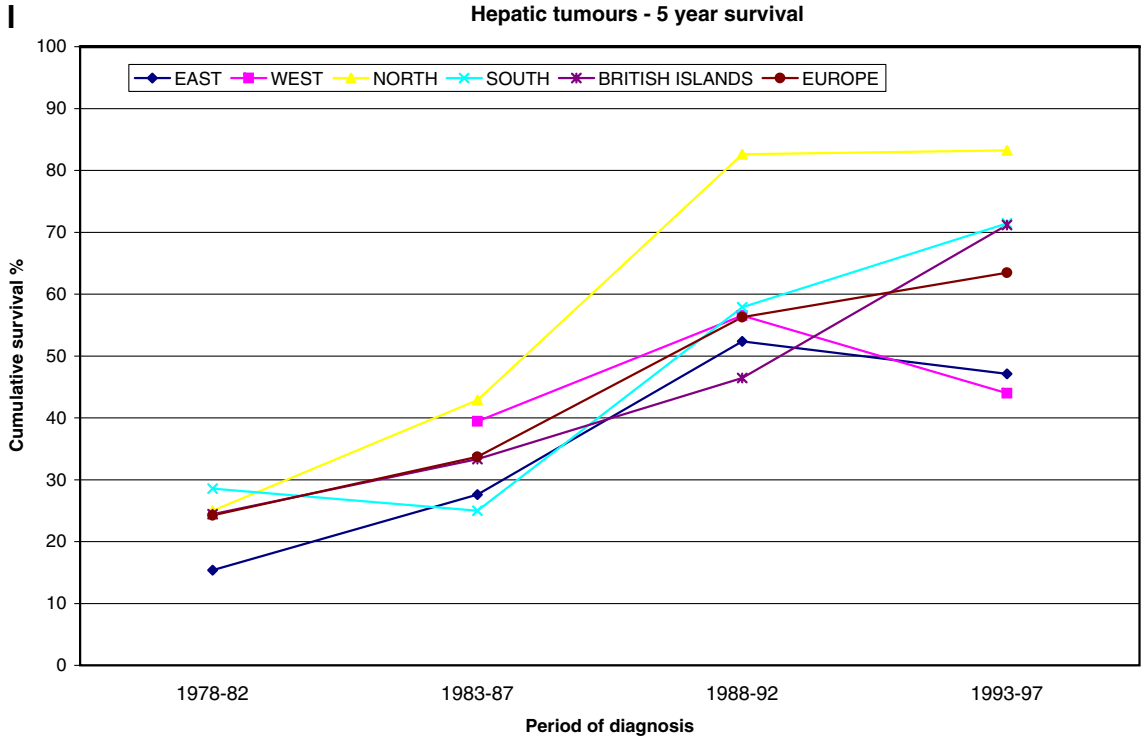
to have affected the presented results, even if they took place in different regions at different times. Some bias may only be suspected from differential diagnosis between acute lymphoblastic lymphoma (ALL) and non-Hodgkin's lymphoma. However, its extent is likely to be limited: within ACCIS, similar incidence time-trends were observed for ALL and non-Hodgkin's lymphoma [Izarzugaza and colleagues, this issue], the exchange of cases between the two groups (if any) is therefore unlikely to affect comparison of survival time trends.

In the pooled European data, a positive trend in survival was seen for all diagnostic groups, including those with rela-





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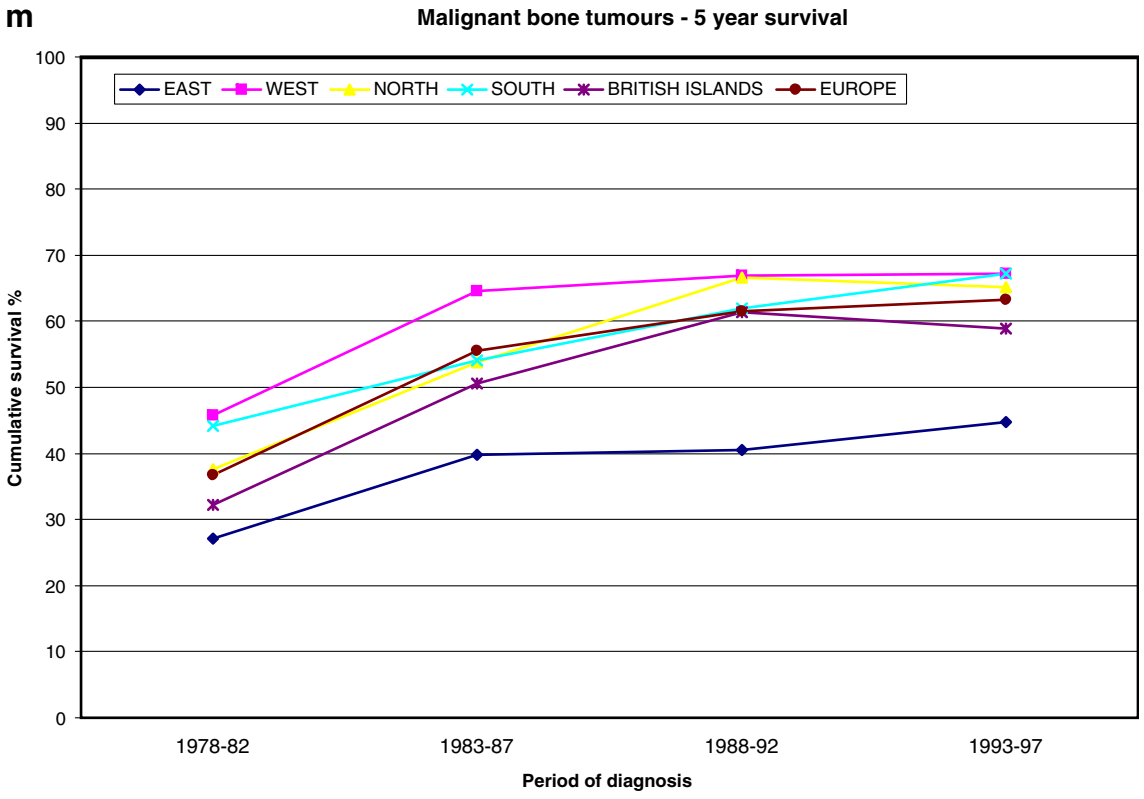
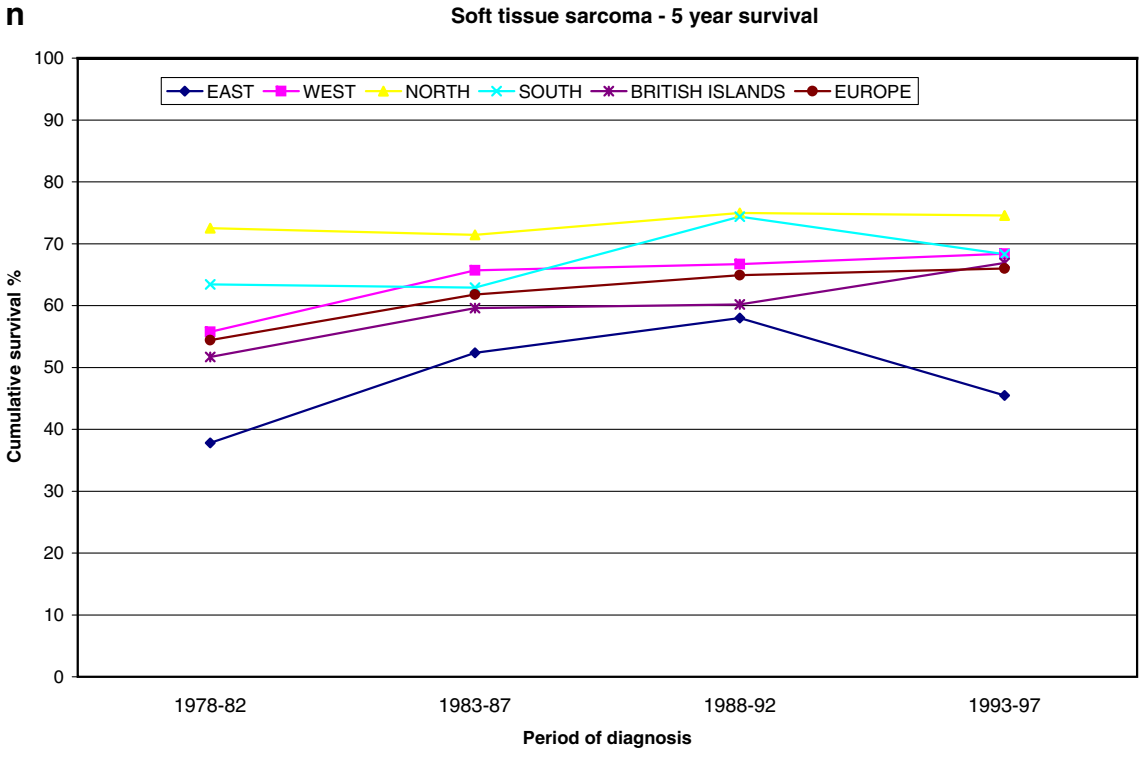
tively high survival in late 1970s, such as retinoblastoma, Hodgkin's lymphoma or carcinomas. More than 50% of deaths were avoided for large diagnostic groups of leukaemia, lymphomas, and considerable improvement was also seen for several less common tumours, notably hepatic and germ cell. On the other hand, survival of children with CNS tumours and especially PNET/medulloblastoma did not improve much and remained moderate.

Detail on tumour-specific survival can be found in other papers in this issue, we will therefore evaluate the pattern





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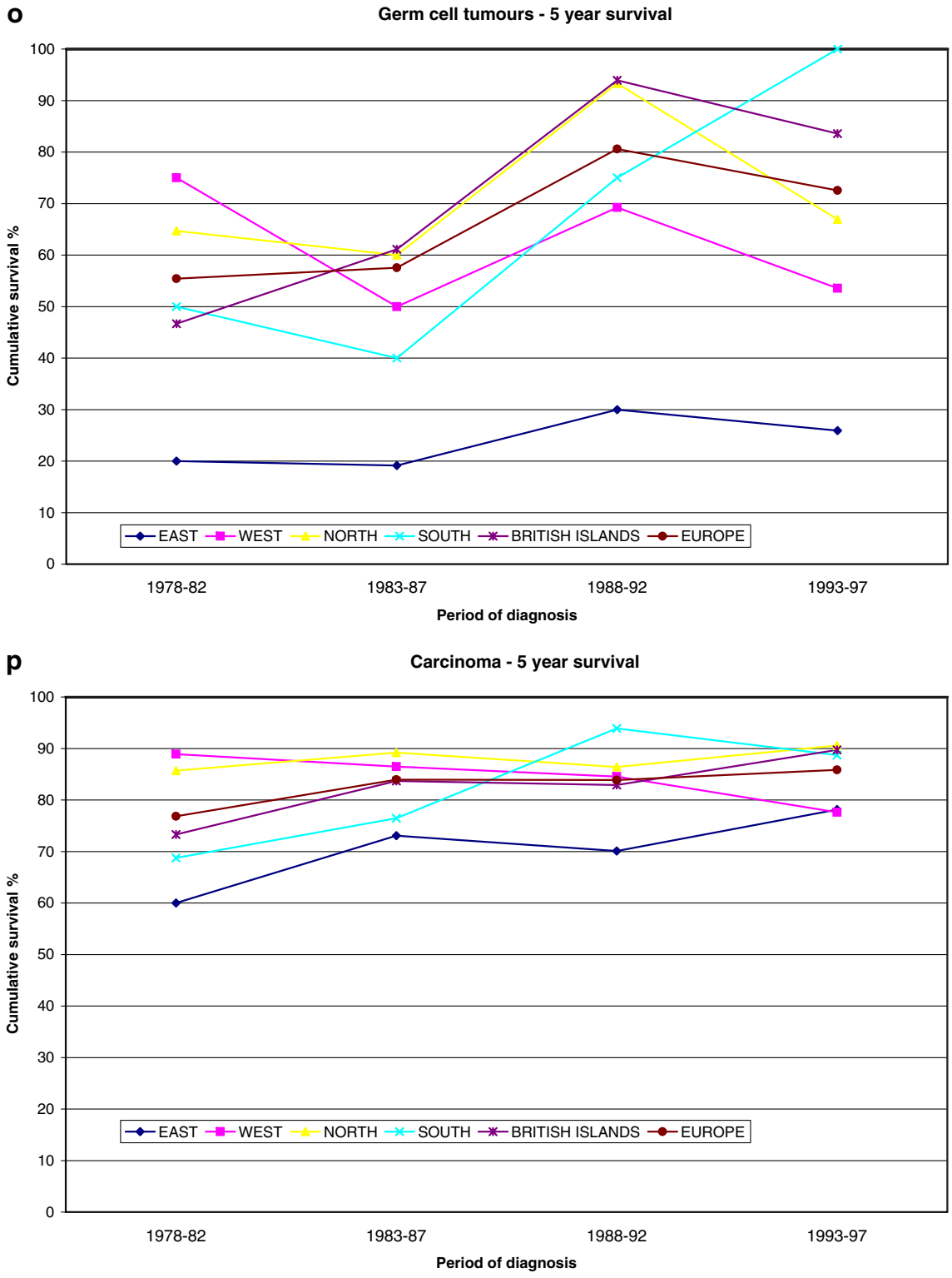
of survival trends by tumour type only briefly. Comparable trends were observed in all European regions for ALL. The significant increase in outcome for children with ALL was attributed to better diagnostic techniques and more precise risk-tailored therapeutic approaches.[24] Among the most relevant prognostic factors at diagnosis, only age class and gender could be evaluated in the ACCIS database, while others (such as number of white blood cells, immunophe-



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notype and cytogenetic analysis[25]) were not available. The survival time trends after ANLL showed a divergent pattern between the East and the other regions. In the early 1970s, less than 10% of childhood ANLL survived 5 years since diagnosis; while in the following two decades survival improved due to a prognosis-oriented classification system based on the use of monoclonal antibodies and cytogenetics and to the use of effective chemotherapy (CT), supportive therapies as well as bone marrow transplantation.[26] The region-specific trends observed in this study may therefore reflect differences in the availability of resources.

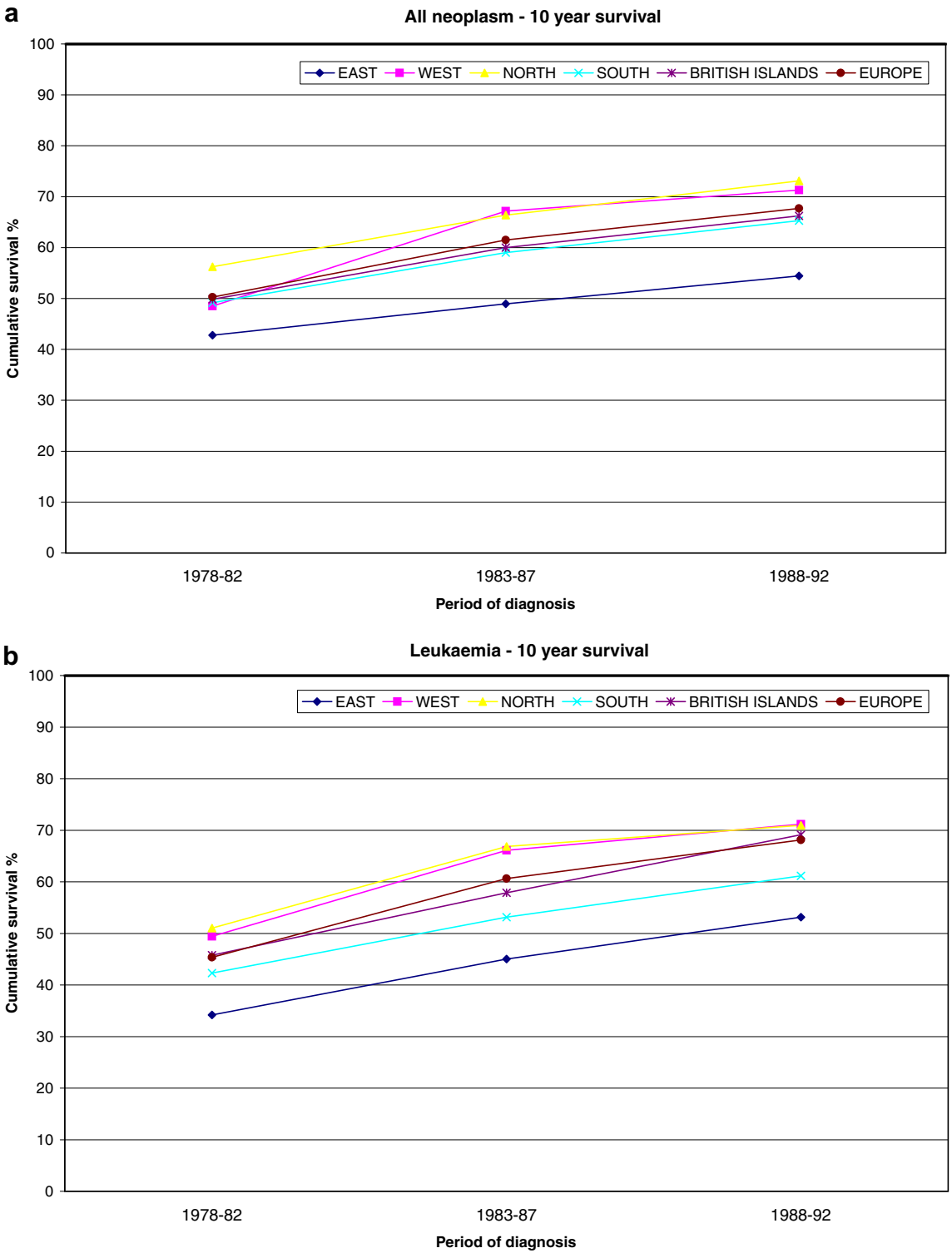
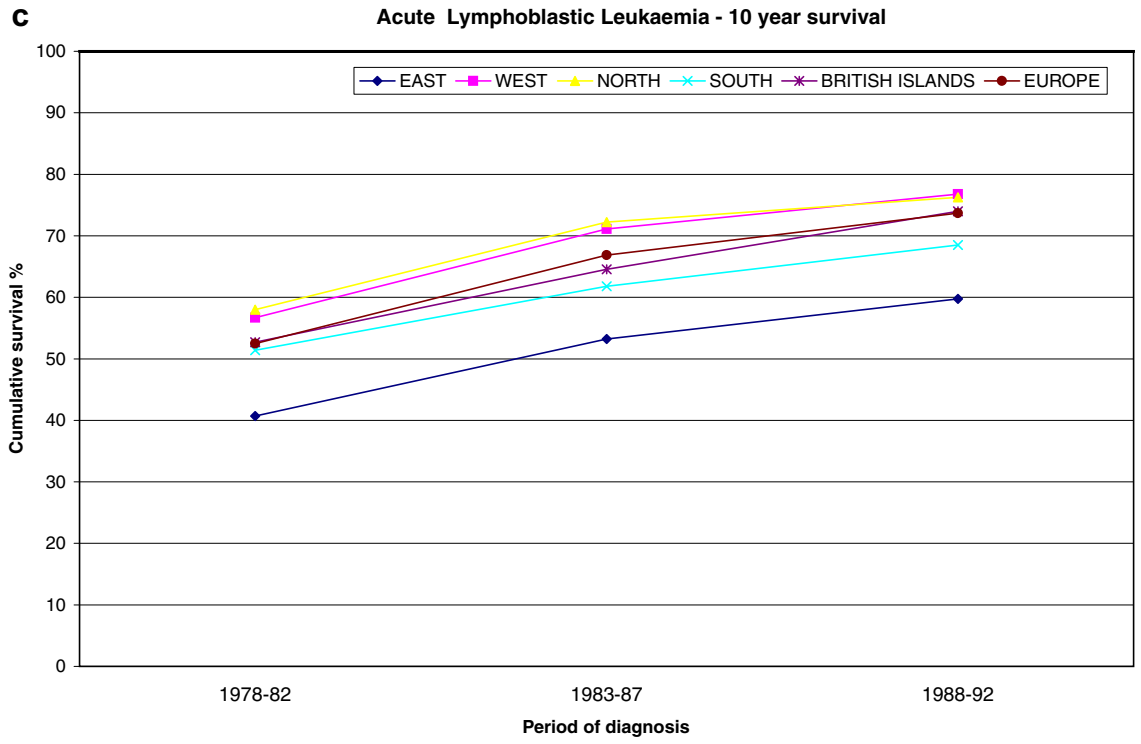


Fig. 2 – Ten-year actuarial cumulative survival, by tumour type, European region and period of diagnosis. Source: ACCIS.

This study showed good survival results for Hodgkin's disease (HD) in all European regions and over the entire study period, except rare fluctuations. Nowadays, HD can be cured in over 80% of cases with a reasonable burden of sequelae.[27] In the East, survival of children with non- Hodgkin's lymphoma was markedly lower than in the other regions. New effective treatment programs, based on high-risk ALL protocols[27] might have helped to improve the trends in the regions where these treatments were adopted.

Survival of children with CNS tumours increased to a relatively low degree and 5-year survival remained under 70%, although higher survival was observed for the subgroups of



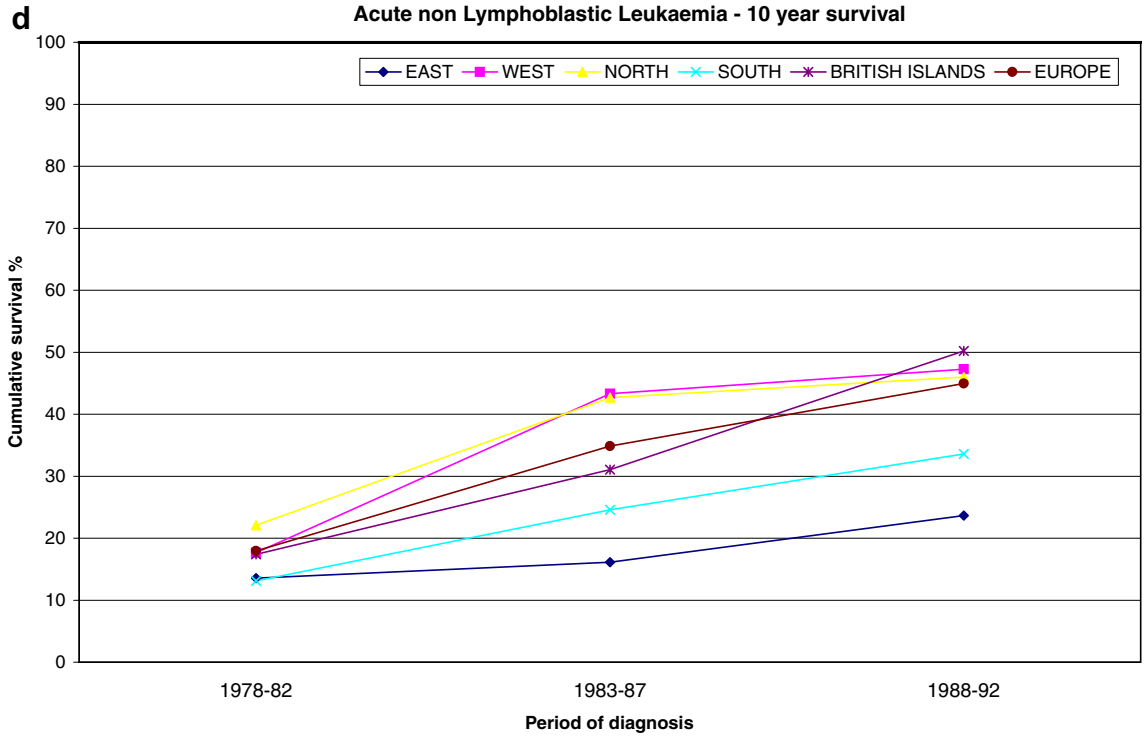
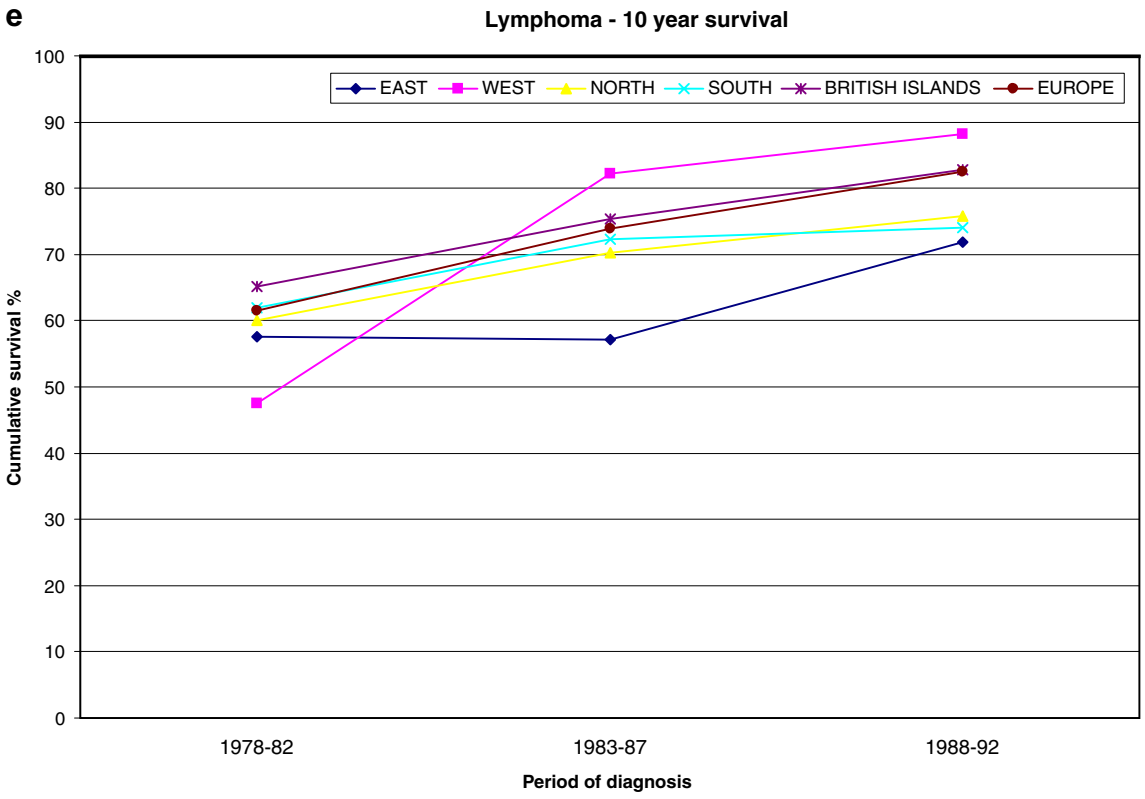


Fig. 2 – *continued*

astrocytoma and unspecified CNS tumours [Peris-Bonet and colleagues, this issue]. At the same time, the incidence rates of CNS tumours increased markedly in Europe [Kaatsch and colleagues, this issue and Peris-Bonet and colleagues, this issue], partly due to enhanced non-invasive diagnostic methods. Increasing proportion of cases diagnosed at earlier stage might contribute to the positive survival trends.[28] However, the relatively modest improvement in survival of children with CNS tumours shows extreme difficulty in reating many groups of brain tumours (PNET, some gliomas).



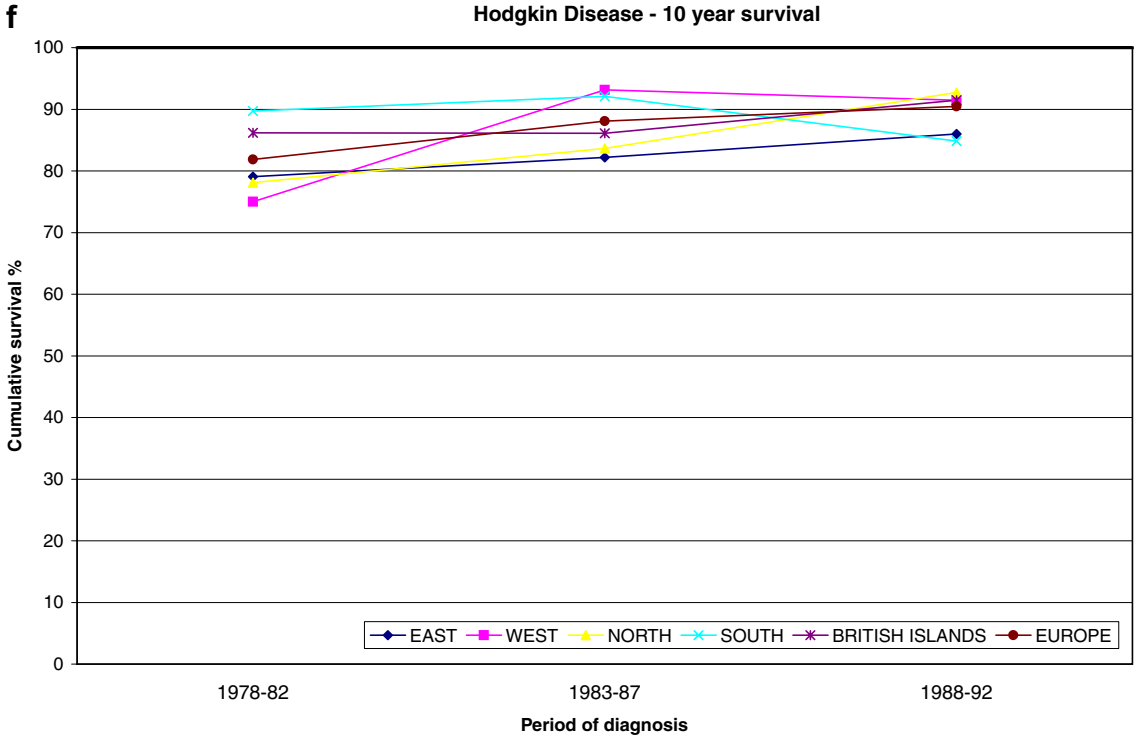
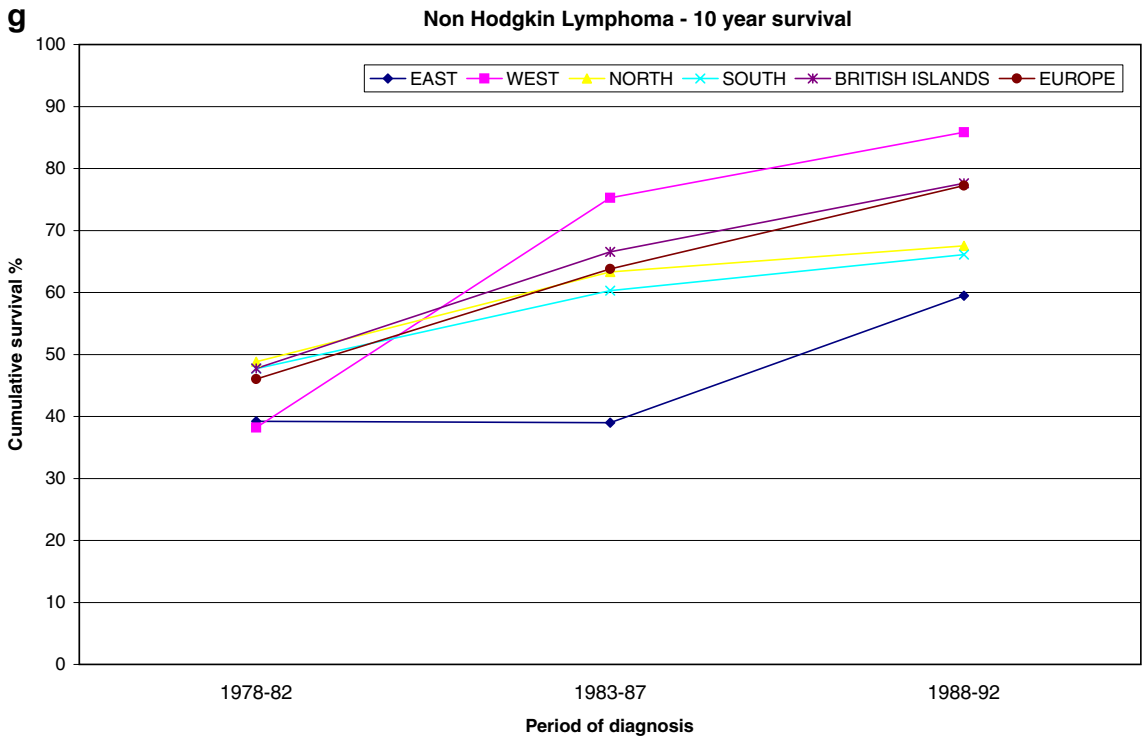
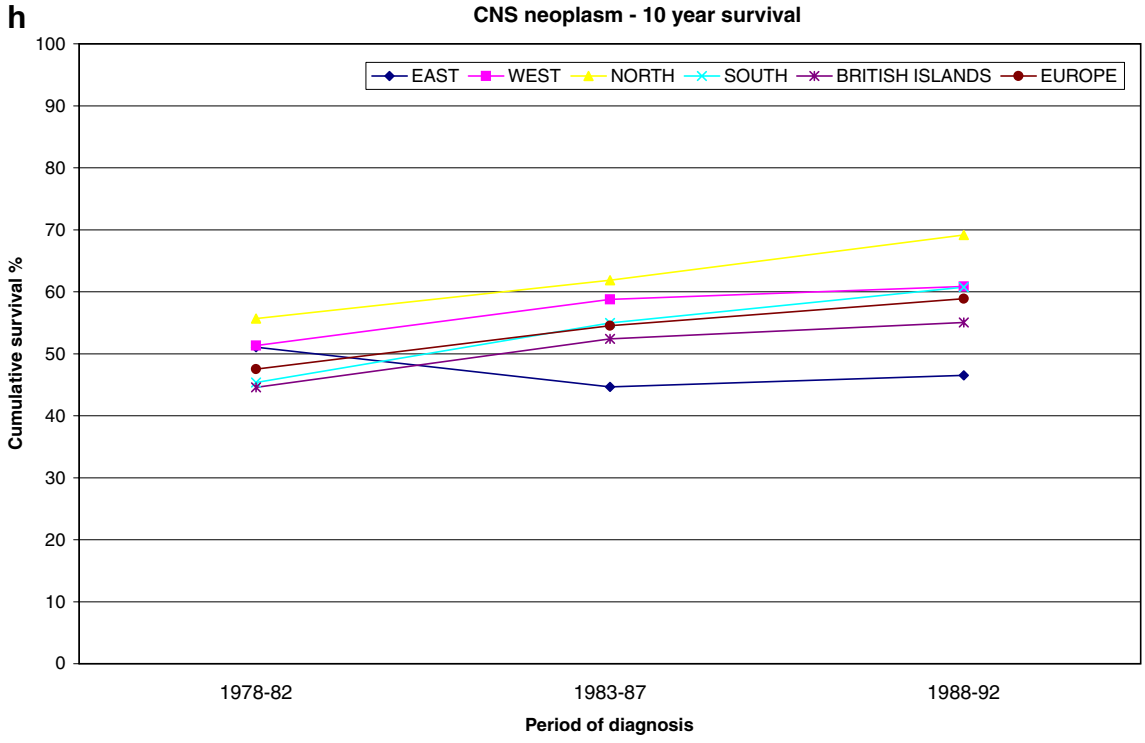


Fig. 2 – *continued*

Collection of additional data, such as extent of disease at diagnosis and clinical management (i.e. protocol, surgery and radiotherapy techniques) would be helpful to analyse further the reasons for the relative lack of improvement over time and of the observed differences among European regions.[11]

The observed trends in survival after neuroblastoma are likely to result from differences in both staging and treatment,[29] but may also be the effect of over-diagnosis of cases with good prognosis, artificially increasing both incidence and survival [Spix and colleagues, this issue]. Increasing sur-





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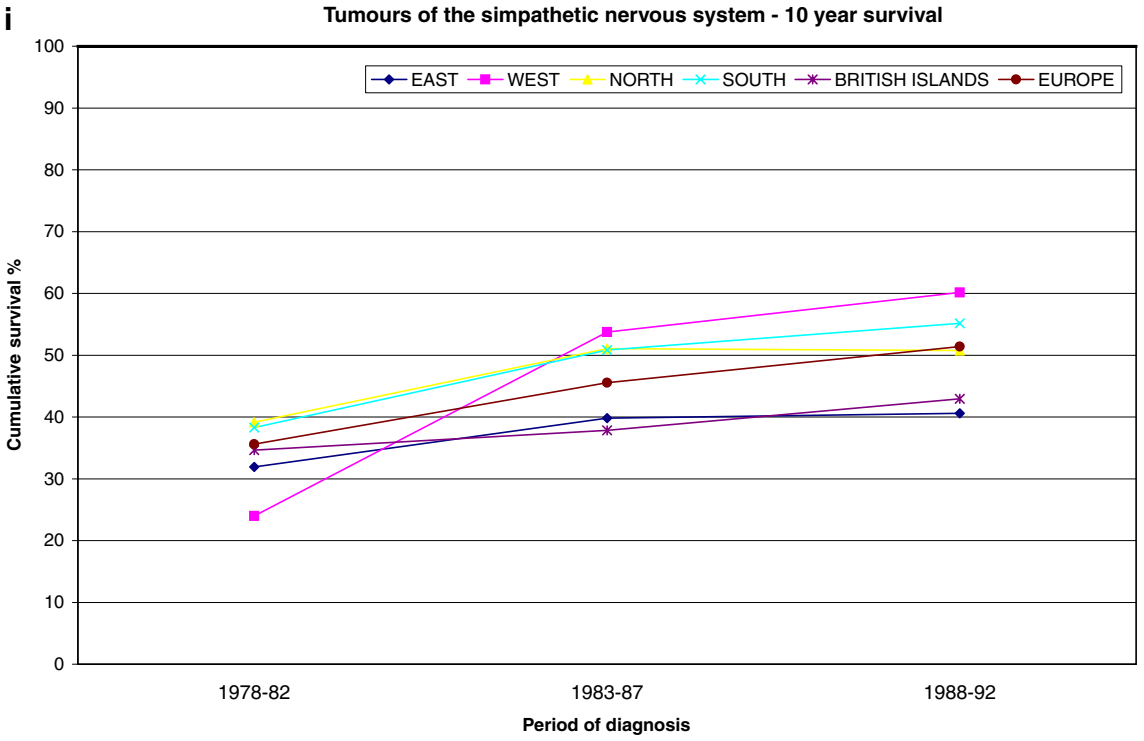
vival trends for renal tumours throughout Europe reflect the results obtained during the last decades within the multicentre randomised trials run by the Society of Paediatric Oncology (SIOP) and by the National Wilms Tumour Study Group (NWTSG): in many countries throughout Europe and the Western world the proportion of patients with Wilms' tumour treated according to these protocols has risen above 90%.[30]

In conclusion, we confirm the universally positive trend of survival after childhood cancer in Europe, over time and across the regions. We ascribe the remaining differences in population-based cumulative survival to inequalities in



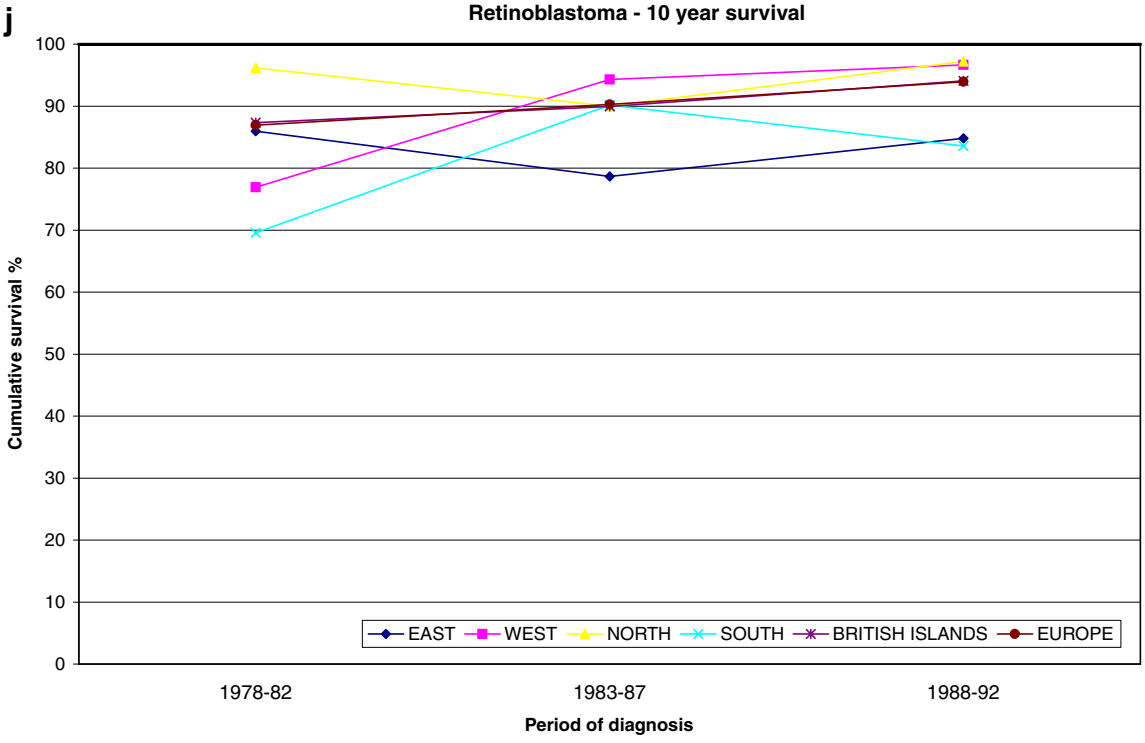
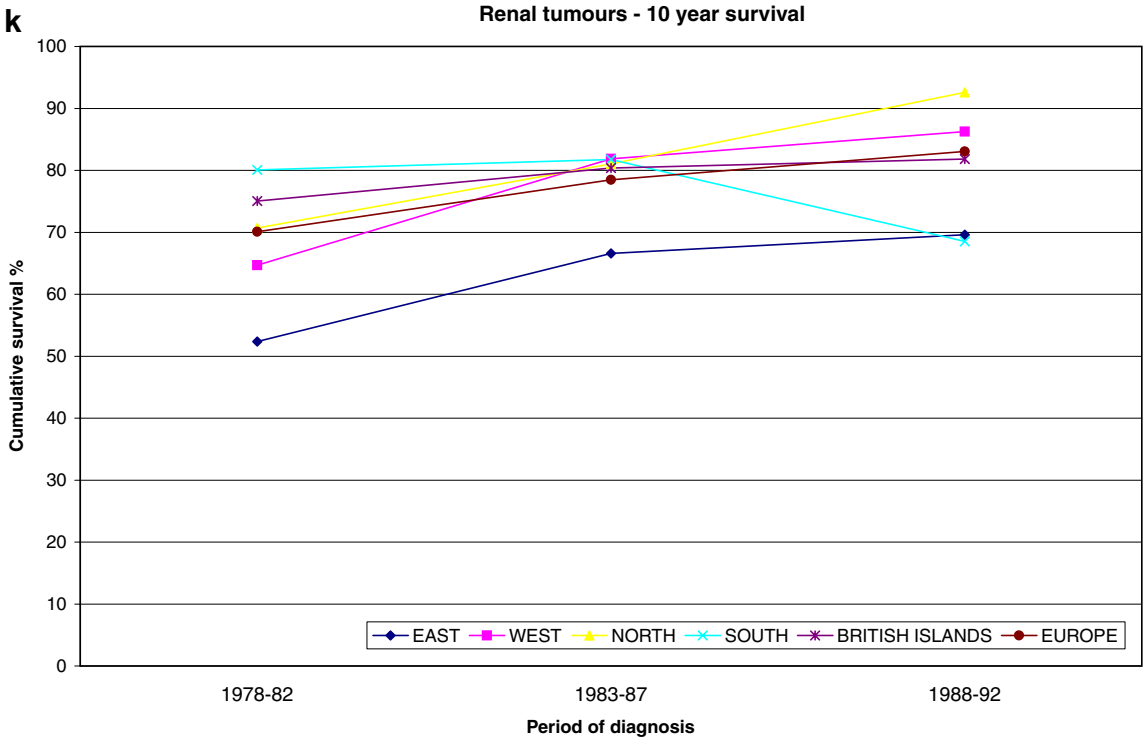
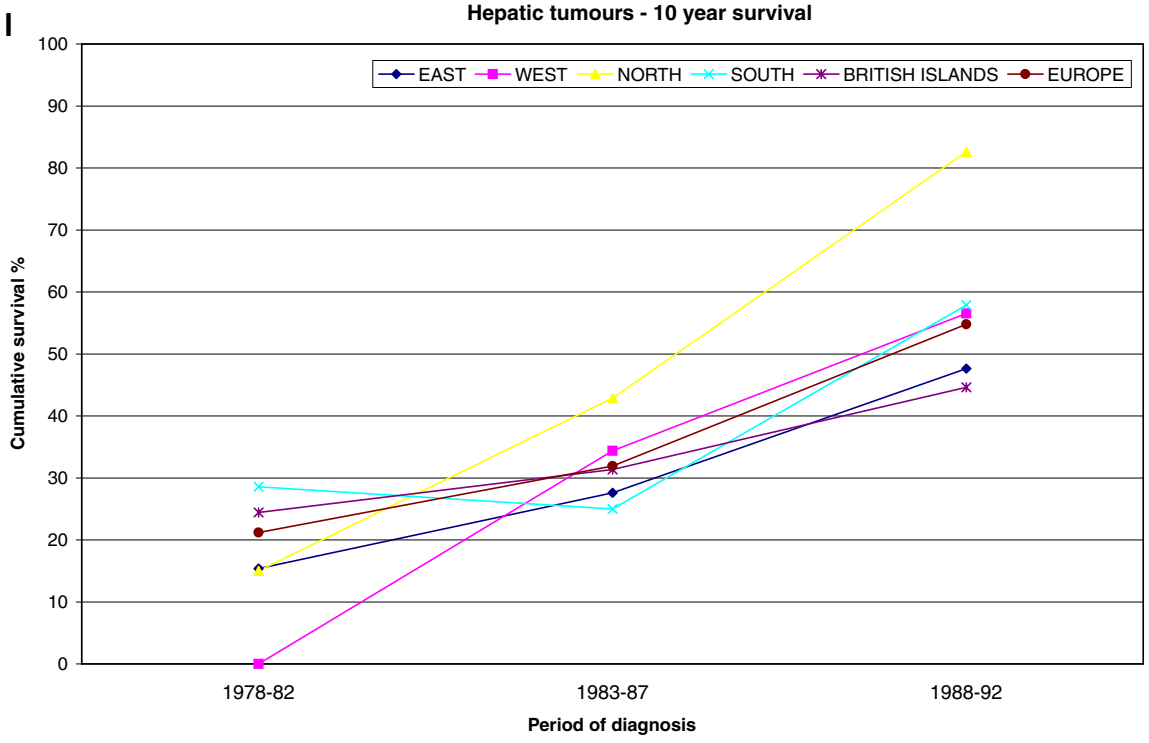


Fig. 2 – *continued*

provision of care (access to specialised cancer centres able to deal with early and late complications), in timeliness and precision of diagnosis and in application of standard treatment protocols. We emphasise the importance of childhood cancer registration for monitoring incidence, mortality and survival on population level in Europe. The systematic collection of additional variables by the European cancer registries would be useful for more precise evaluation of trends and geographical differences of population-based childhood cancer survival. The variables of interest would be number of white blood cells, immunophenotype and cytogenetics for leukaemia, staging for HD, extent of disease





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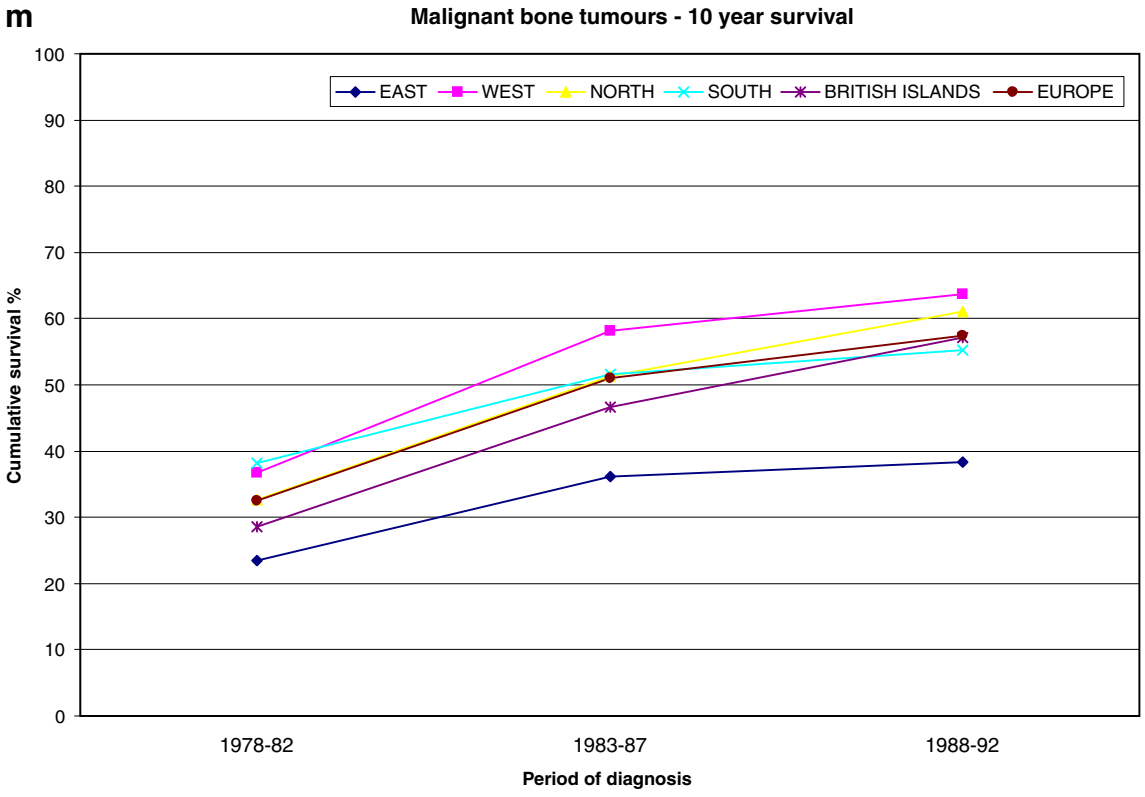
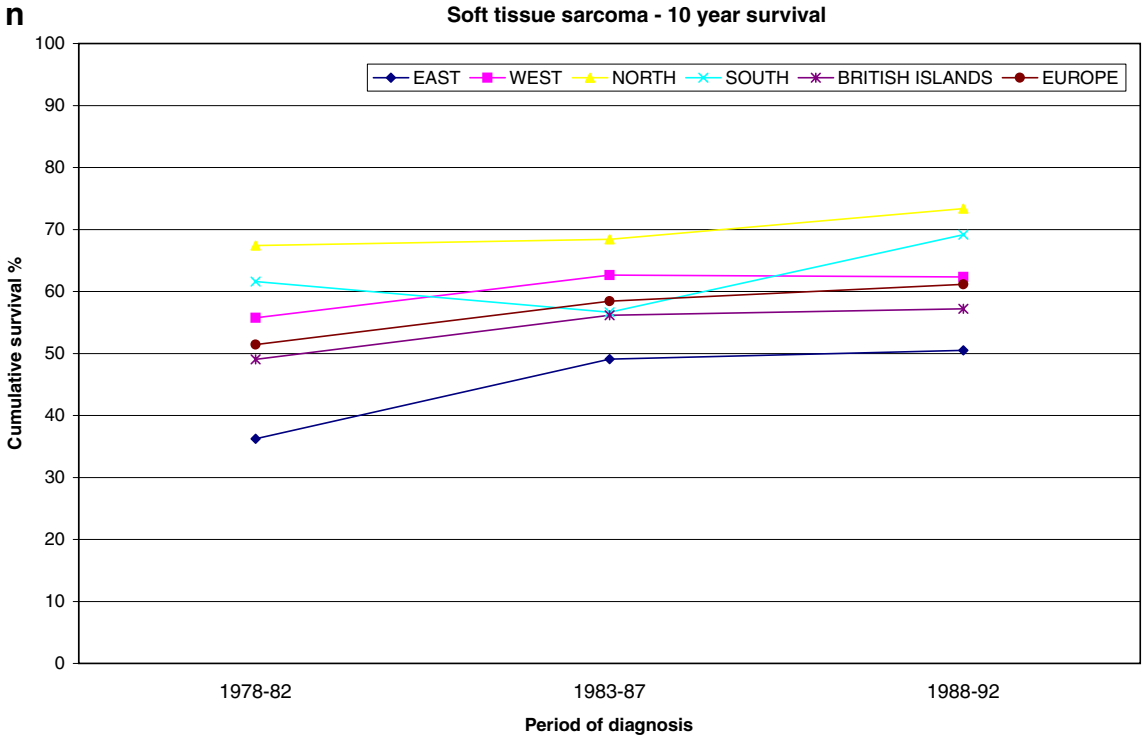
for CNS tumours, mode of diagnosis for neuroblastoma and, for all tumour types, inclusion in a clinical trial. Further improvement of follow-up of cancer patients (completeness, timeliness) would permit more up-to-date and more precise comparison of survival by period, region and tumour group. Continued collection and centralisation of detailed information on diagnosis, treatment and end-results by the cancer registries will allow the identification of specific causes of the observed differences in survival of children with cancer in Europe.

Conflict of interest statement

None declared.





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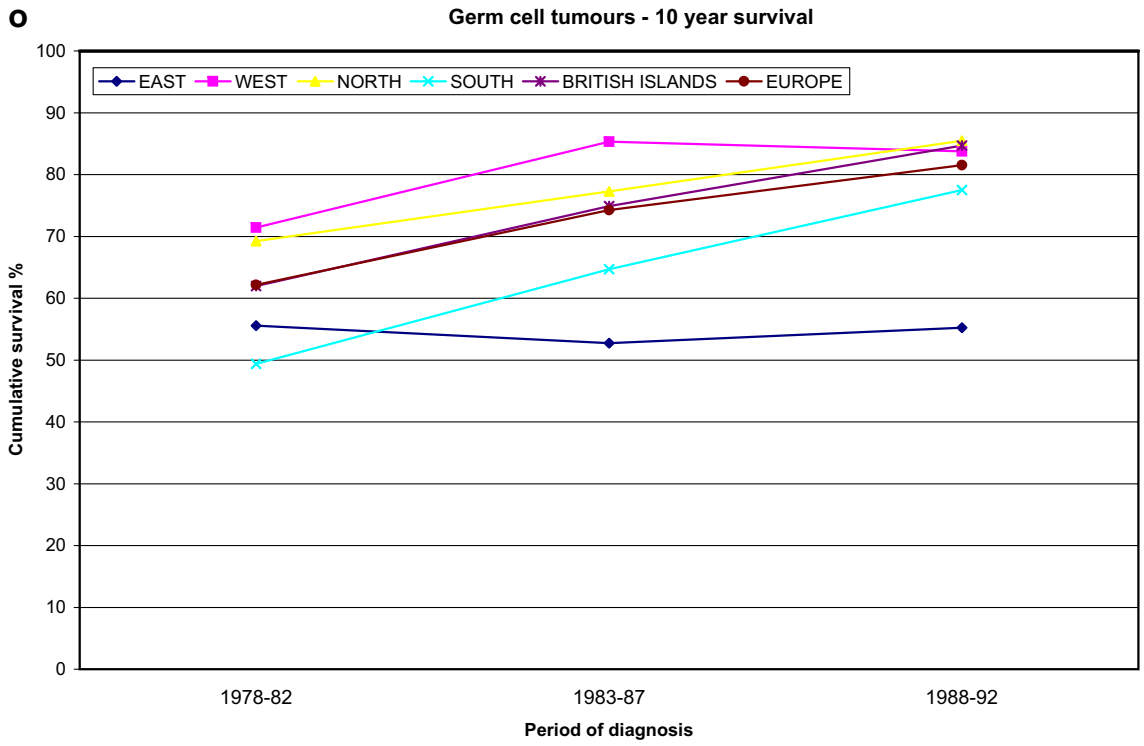

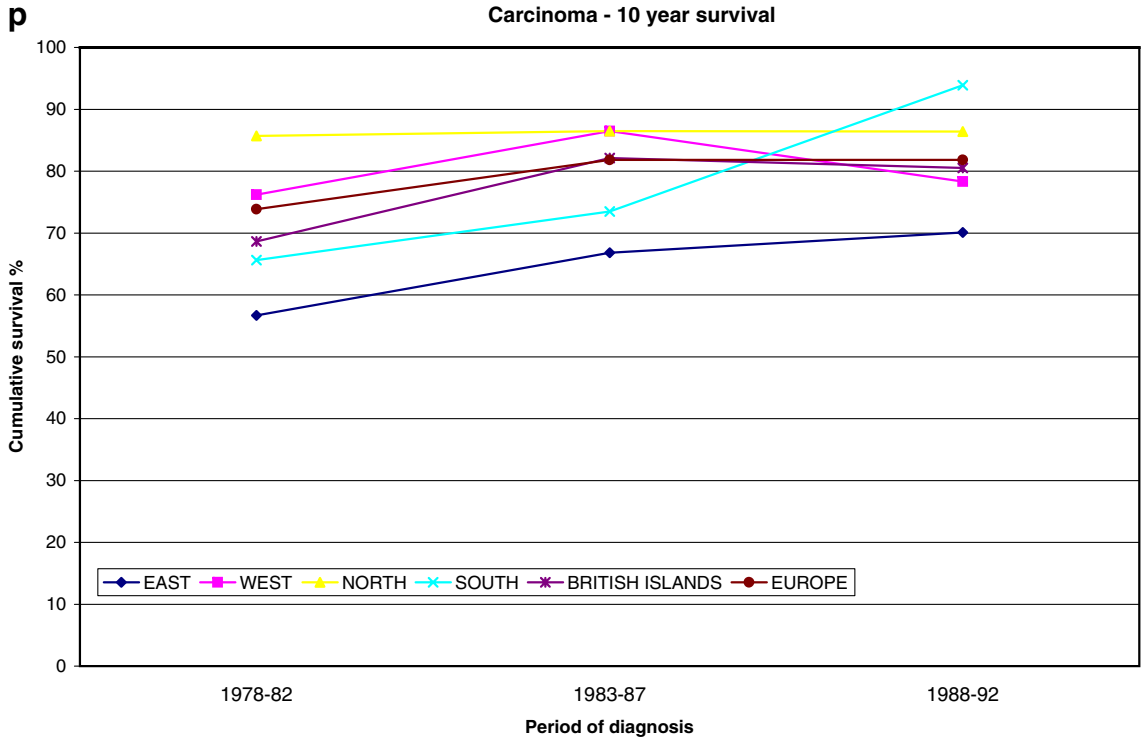

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The following collaborators from the cancer registries contributed actively to this study:

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Table 6 – Trends in survival after childhood cancer in Europe, 1978–1997. Five-year cumulative survival (CS) for 1993–1997 and the P-value of the log-rank test for trend comparing the survival curves for the periods 1978–1982, 1983–1987, 1988–1992 and 1993–1997, by tumour type and European region. Rate of change per period in 5-year survival (RCS) and percentage change between 1978–1982 and 1993–1997 in cumulative probability of death at 5 years (PCD). The data from the former German Democratic Republic only contribute to Europe as a whole (see text) (Source: ACCIS)

ICCC	EUROPE		BRITISH ISLES		EAST		NORTH		SOUTH		WEST	
	5-years CS, 1993–1997	P (trend)	5-years CS, 1993–1997	P (trend)	5-years CS, 1993–1997	P (trend)	5-years CS, 1993–1997	P (trend)	5-years CS, 1993–1997	P (trend)	5-years CS, 1993–1997	P (trend)
Leukaemia (I)*	77	<0.0001	76	<0.0001	65	<0.0001	81	<0.0001	74	<0.0001	80	<0.0001
Acute Lymphocytic Leukaemia (Ia)*	82	<0.0001	81	<0.0001	72	<0.0001	87	<0.0001	80	<0.0001	85	<0.0001
Acute Non-Lymphocytic Leukaemia (Ib)*	53	<0.0001	52	<0.0001	26	0.0095	56	<0.0001	51	0.0003	56	<0.0001
Lymphoma (II)	85	<0.0001	85	<0.0001	74	<0.0001	83	<0.0001	84	<0.0001	89	<0.0001
Hodgkin's Disease (IIa)	93	<0.0001	94	0.0121	89	0.2161	82	0.7800	99	0.3456	95	0.8761
Non-Hodgkin's Lymphomas (IIb–IIe)	79	<0.0001	79	<0.0001	59	<0.0001	84	<0.0001	73	0.0057	84	<0.0001
CNS Neoplasm (III)	67	<0.0001	69	<0.0001	56	0.1594	70	0.0001	66	<0.0001	67	0.0641
Medulloblastoma (IIIc)	52	<0.0001	50	0.0016	46	0.0630	57	0.0652	49	0.2079	55	0.9199
Sympathetic System Tumours (IV)	66	<0.0001	57	<0.0001	57	<0.0001	62	0.0001	62	0.0006	74	<0.0001
Retinoblastoma (V)	95	0.0001	97	0.0031	84	0.6267	98	0.5108	87	0.0962	98	0.0195
Renal tumours (VI)	86	<0.0001	80	0.1184	79	<0.0001	89	<0.0001	86	0.9432	89	0.0001
Wilms' tumour (VIa)	86	<0.0001	80	0.1503	80	<0.0001	90	<0.0001	85	0.9043	89	0.0001
Hepatic neoplasm (VII)	63	<0.0001	71	<0.0001	47	0.0079	83	<0.0001	71	0.0017	44	0.3302
Malignant neoplasm of the bone (VIII)	63	<0.0001	59	<0.0001	45	0.0006	65	<0.0001	67	0.0016	67	0.0286
Osteosarcoma (VIIIa)	61	<0.0001	54	<0.0001	51	0.0016	54	0.0087	63	0.1755	66	0.2151
Ewing's sarcoma (VIIIc)	66	<0.0001	67	<0.0001	34	0.1894	78	0.0082	73	0.0043	68	0.0681
Soft tissue sarcoma (IX)	66	<0.0001	67	<0.0001	45	0.0409	75	0.3273	68	0.2840	68	0.4604
Rhabdomyosarcoma (IXa)	65	<0.0001	68	<0.0001	42	0.0286	69	0.2993	70	0.3057	68	0.8343
Germ-cell, trophoblastic and other gonadal neoplasm (X)	89	<0.0001	88	<0.0001	76	0.0140	90	0.0011	84	0.0008	92	0.0851
Carcinomas and other malignant epithelial neoplasm (XI)	86	0.0007	90	0.0001	78	0.0626	91	0.3818	89	0.0021	78	0.0232
All neoplasm	75	<0.0001	74	<0.0001	63	<0.0001	78	<0.0001	74	<0.0001	78	<0.0001
RCS		17%		17%		29%		16%		19%		12%
PCD		45%		46%		50%		43%		43%		47%

* Figures on leukaemia are based on a slightly different data-set, whereby the data of Eindhoven Cancer Registry are replaced by the data of Dutch Childhood Oncology Group, the latter registering childhood leukaemia in The Netherlands nationwide (see text).

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REFERENCES

1. Stiller CA. Population based survival rates for childhood cancer in Britain 1980–91. *Br Med J* 1994;**309**:1612–6.
2. Kramarova E, Plesko I, Black R, Obsitnikova A. Improving survival for childhood cancer in Slovakia. *Int J Cancer* 1996;**65**:594–600.
3. Pannelli F, Mosciatti P, Felici L, Magnani C, Pascucci C, Pastore G. Andamento nel tempo della sopravvivenza per tumori infantili in Italia nel periodo 1978–94, primo rapporto dai registri Tumori Italiani. *Epidemiol Prev* 2001;**25**(suppl 3):354–75.
4. Viscomi S, Pastore G, Mosso ML, et al. Population-based survival after childhood cancer diagnosed during 1970–98, a report from the Childhood Cancer Registry of Piedmont (Italy). *Hematologica* 2003;**88**:974–83.
5. Ries LA, Eisner MP, Kosary CL, et al., editors. *Childhood cancer by the ICCC. SEER cancer statistics review, 1975–2001*. Bethesda, MD: National Cancer Institute; 2004.
6. Ajiki W, Tsukuma H, Oshima A. Survival rates of childhood cancer patients in Osaka, Japan. *Jpn J Clin Oncol* 2004;**34**:50–4.
7. Reedijk AMJ, Janssen-Heijnen MLG, et al. Increasing incidence and improved survival of cancer in children and young adults in Southern Netherlands, 1973–99. *Eur J Cancer* 2005;**41**:760–9.
8. Capocaccia R, Gatta G, Magnani C, Stiller C, Coebergh J-W, editors. Childhood cancer survival in Europe 1978–92, the Eurocare Study. Eur J Cancer 2001;**37** (Special Issue).
9. Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani Mand the EUROCARE Working Group. Childhood cancer survival trends in Europe. *I Clin Oncol* 2005;**23**:3742–51.
10. Levi F, La Vecchia C, Negri E, Lucchini F. Childhood cancer mortality in Europe, 1955–95. *Eur J Cancer* 2001;**37**:785–809.
11. Reddy AT. Advances in biology and treatment of childhood brain tumours. Review. *Curr Neurol Neurosci Rep* 2001;**1**:137–43.
12. Chan KW. Acute lymphoblastic leukaemia. Review. *Curr Probl Pediatr Adolesc Health Care* 2002;**32**:40–9.
13. Thornton Jr AF, Sandler HM, Ten Haken RK, et al. The clinical utility of magnetic resonance imaging in 3-dimensional treatment planning of brain neoplasm. *Int J Radiat Oncol Biol Phys* 1992;**24**:767–75.
14. Stiller CA. Centralization of treatment and survival rates for cancer. *Arch Dis Child* 1988;**63**:23–30.
15. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since 1970s, the ACCIS project. *Lancet* 2004;**364**:2087–105.
16. Kramárová E, Stiller CA, Ferlay J, et al. International classification of childhood cancer 1996. IARC technical report No.29. Lyon: International Agency for Research of Cancer; 1996.
17. Ferlay J. IARCtools. 1997. Available from: http://www-dep.iarc.fr/resour/software/iarctools.htm.
18. Percy C, Van Holten V, Muir CS, editors. *International classification of diseases for oncology*. 2nd ed. Geneva: World Health Organisation; 1992.
19. Gehan EA. Estimating survival functions from the life table. *J Chronic Diseases* 1969;**21**:629–44.
20. Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley & Sons; 1980.
21. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient, II, analysis and examples. *Br J Cancer* 1977;**35**:1–39.
22. Parkin DM, Kramarova E, Draper GJ, et al., editors. International incidence of childhood cancer, vol II. International Agency for Research on Cancer, Scientific Publication No. 144. Lyon: IARC; 1998.
23. Sant, M, Gatta G. The EUROCARE database. In: Berrino F, Sant M, Verdecchia A, et al., editors. Survival of cancer patients in Europe. The EUROCARE study. IARC Scientific Publications No. 132. Lyon: IARC; 1995, p. 15–31.
24. Working Party on Leukemia in Children. Improvement in treatment for children with acute lymphoblastic leukaemia, Medical Research Council. UK ALL trials. *Lancet* 1986;**i**:408–11.
25. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol* 1996;**14**:18–24.
26. Stiller CA, Eatock EM. Survival from acute non-lmphocytic leukemia, 1971–88, a population based study. *Arch Dis Child* 1994;**70**:219–23.
27. Pastore G, Magnani C, Verdecchia A, et al. Survival of childhood lymphomas in Europe, 1978–92, a report from the EUROCARE study. *Eur J Cancer* 2001;**37**:703–10.
28. Magnani C, Aareleid T, Viscomi S, Pastore G, Berrino Fand The EUROCARE Working Group. Variation in survival of children with CNS malignancies diagnosed in Europe between 1978 and 1992, the EUROCARE study. *Eur J Cancer* 2001;**37**:711–21.
29. Spix C, Aareleid T, Stiller C, Magnani C, Kaatsch P, Michaelis J. Survival of children with neuroblastoma time trends and regional differences in Europe, 1978–92. *Eur J Cancer* 2001;**37**:722–9.
30. Pritchard-Jones K, Pritchard J. Success of clinical trials in childhood Wilms' tumour around the world. *Lancet* 2004;**364**:1468–70.