EUROPEAN JOURNAL OF CANCER 42 (2006) 2037–2049

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Hodgkin's disease incidence and survival in European children and adolescents (1978–1997): Report from the Automated Cancer Information System project

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ARTICLE INFO

Keywords:
Hodgkin's disease
Childhood cancer
Adolescents
Europe
Registry
Incidence
Survival

ABSTRACT

This paper reports the geographical patterns and time trends of incidence and survival of Hodgkin's disease (HD) in children and adolescents in Europe over the period 1978–1997. Data on 4230 HD cases were gathered from 62 paediatric or general cancer registries in 19 European countries by the Automated Cancer Information System (ACCIS). European annual incidence rates in 1988–1997 were estimated at 5.8 per million in children (world age-standardised) and at 29.7 per million in adolescents, with higher rates in the East and South. Incidence rates increased steeply with age, while the male predominance, marked for the youngest children, vanished in the highest age groups. Over the period 1978–1997 incidence rates increased in age groups 10–14 years (+1% per year) and 15–19 years (+3.5% per year), mainly due to the nodular sclerosis subtype. Age and sex distribution of cases remained unchanged with time. The overall 5-year survival rate was higher in children (93%, 95% confidence interval (CI) 92–94) than in adolescents (89% (95% CI 87–91)) for the period 1988–1997. Five-year survival increased significantly in all regions from 87% to 93% in children and from 80% to 88% in adolescents between 1978–1982 and 1993–1997. In future, detailed documentation of cases in the cancer registries with respect to standardised diagnostic subtypes, stage of extension, and treatments, will help to refine interpretation of international and temporal variations in incidence and survival.

1. Introduction

Hodgkin's disease (HD), rare before the 10 years of age, is one of the most common cancers in adolescents. HD is characterised by the presence of Reed-Sternberg cells, which appear to be clonally developed in most cases at the expense of pre-apoptotic B-lymphocytes from the germinal centres. Distribution of HD cases over age, gender, geographical areas and socio-economic settings have long suggested that HD comprises multiple aetiologically distinct entities rather than a single disease.[1–3] Schematically, two separate entities may be described within childhood and adolescent HD, with respect to their main epidemiological features. The first is Epstein-Barr virus (EBV)-related, expressing the viral genome in Reed-Sternberg cells,[4] and is more prevalent in developing countries and under less favourable socio-economic

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doi:10.1016/j.ejca.2006.05.012

conditions. This form predominates in young children, particularly in males, and mostly presents as mixed cellularity histological subtype. The second form affects mainly older children and adolescents, and presents most often as nodular sclerosis histological subtype. This latter form was often associated with better socio-economic conditions in childhood, which might be due to a delayed exposure to common infectious agents.[2,5] To date, EBV[5,6] or other herpes virus[7] was not found to be involved in this form of HD. Genetic factors are expected to influence the risk of HD, as suggested by observations of strong concordance in occurrence of HD in monozygotic twins,[8] familial aggregations,[9] and interethnic variability of incidence.[10] The marked male predominance of HD in early childhood also suggests sex-linked predisposing factors to EBV-related HD. Associations with polymorphisms in HLA and cytokines have been reported.[11,12]

Prognosis for patients with HD has improved considerably over the past 40 years, and 5-year survival is estimated to be around 90% for children and adolescents in industrialised countries,[13–16] thanks in particular to therapeutic strategies accounting accurately for clinical stage and age, and aiming to reduce adverse immediate and late effects.

The large database of the Automated Childhood Cancer Information System (ACCIS) provides a unique source for evaluation of the geographical patterns and time trends of incidence and survival of Hodgkin's disease in children and adolescents in Europe.[16] Tthis paper reports the geographical patterns and time trends of incidence and survival of Hodgkin's disease in European children and adolescents over the period 1978–1997 and proposes priorities for further studies.

2. Material and methods

Cases of HD in people younger than 20 years registered in 19 European countries from 1978 to 1997 were extracted from the ACCIS database. With the exception of North, paediatric cancer registries were operating in all the regions. Both the paediatric and general cancer registries were used for all analyses referring to children (age 0–14 years), while the analyses for the adolescents were based on data from the general cancer registries only. All 62 included registries provided individual records of cases containing standard variables, including basic demographic data (age, gender, country or region of residence), details on diagnosis (date of diagnosis, tumour site and morphology, basis of diagnosis) and information on follow-up (date of last contact and vital status). Populations at risk for each registration area were derived from the official data from national statistical offices. Participating registries were evaluated as comparable by the ACCIS Scientific Committee, using standard and specific criteria for childhood data [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. Table 1 shows the list of data-sets included in this report, their provenance and grouping in geographical regions, the numbers of cases and the quality indicators. Five broad geographical regions were defined: British Isles, East, North, South and West Europe.

Different sets of cases were used for different analyses. Patterns of occurrence and geographical differences were derived from the 1988 to 1997 data-sets, whereas temporal trends were analysed for the period 1978–1997, using data from the registries having contributed sufficiently to at least three of the four periods of interest: 1978–1982, 1983–1987, 1988–1992 and 1993–1997. Fifty-seven registries with follow-up data contributed to the analyses of survival (Table 1). Further details on database composition can be found elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. Overall, 4230 cases of Hodgkin's disease were extracted from the ACCIS database and included in the various analyses.

Throughout this paper HD is defined as the subgroup IIa (Hodgkin's disease) of the International Classification of Childhood Cancer.[18] For detailed analyses, HD cases were classified further into six histological categories based on the ICDO-2 morphology codes:[19] unspecified HD (M9650, M9661, M9662), nodular sclerosis (M9663–M9667), mixed cellularity (M9652), lymphocyte depleted (M9653–M9655), lymphocyte rich/predominant not specified as nodular (M9657, M9658), nodular lymphocyte predominant (M9659, M9660). The two latter subgroups have been lumped together for presentation of results as 'lymphocyte rich/predominant subgroup'.

Age-specific incidence rates were estimated using standard methods for single years of age and for the age-groups 1–4 years, 5–9 years, 10–14 years and 15–19 years, no cases being diagnosed before 1 year of age. Age-standardised incidence rates (ASR) were calculated for the age-range 0–14, using the age structure of the World standard population. To assess temporal trends, incidence rates were calculated for four periods: 1978–1982, 1983–1987, 1988–1992, 1993–1997 and average annual percent changes (AAPC) of incidence rates over the period 1978–1997 were derived from Poisson regression model including calendar year as a continuous variable and adjusted for age-group, gender and region as applicable.

The duration of survival was calculated as the time elapsed between the date of diagnosis and the date of death (if patient died) or closing date of the study of the given cancer registry. Cases with zero survival time were excluded from the analysis of survival, most of them were the cases registered from death certificate only (DCO). Actuarial life-table method was used for survival analyses. The 95% confidence intervals (CI) of the cumulative survival were calculated according to Kalbfleisch and Prentice.[20] Differences in survival of two or more groups of patients were compared for the entire survivorship curves using the log-rank χ^2 statistic. Survival rates have been reported with their 95% CIs in parentheses. A log-rank χ^2 test for trend was used to assess the improvement in survival over the defined time periods.

Analyses were conducted using STATA© software.

3. Results

3.1. *Incidence*

Over the 1988–1997 period, data from 2534 children and 1319 adolescents diagnosed with a Hodgkin's disease were extracted from ACCIS database (Table 2). No childhood case and 2 adolescent cases were documented by death certificate only. Diagnosis was microscopically verified in all but 22 childhood and 16 adolescent cases (99%). Paediatric registries provided 70% of the childhood cases: 84% in the British Isles and the West regions, 75% in the East, 27% in the South,

Table 1 – Datasets included in the analyses of Hodgkin's diseases incidence and survival in children and adolescents, with indicators of coverage, data quality and follow-up (Source: ACCIS)

Region	Registry	Coverage				Basis of diagnosis			Survival analysis			Notes
		Period	Time-trend	No of cases		MV %	DCO %	unknown %	*n*	Closing date	FU > 5y %	
				0–14 years	15–19 years							
British Isles	IRELAND, National	1994–1997		17	34	100	0	0	51	31.12.1998	0	
	UNITED KINGDOM, England & Wales	1978–1995	+	883	–	97	0	2	883	31.01.2001	87	P
	UNITED KINGDOM, Northern Ireland	1993–1996		5	9	100	0	0	14	31.12.1999	7	
	UNITED KINGDOM, Scotland	1978–1997	+	102	203	95	0	0	305	31.12.1999	74	
East	BELARUS, National	1989–1997		229	–	100	0	0	229	01.09.2000	65	P
	ESTONIA, National	1978–1997	+	55	78	98	0	0	133	31.12.1998	41	
	HUNGARY, National	1978–1997	+	256	–	100	0	–	256	01.01.2000	77	P
	SLOVAKIA, National	1978–1997	+	216	207	99	<1	0	418	31.12.1997	58	
*	GERMANY, NCR (only former East)	1978–1989	+	286	530	100	0	0	699	31.12.1987	48	S
North	DENMARK, National	1978–1997	+	84	172	98	0	1	255	31.12.1997	61	
	FINLAND, National	1978–1997	+	100	183	100	0	0	282	31.12.1998	59	
	ICELAND, National	1978–1997	+	12	14	100	0	0	26	31.12.2000	69	
	NORWAY, National	1978–1997	+	74	132	100	0	0	206	01.01.2000	66	
South	ITALY, Piedmont paediatric	1978–1997	+	87	–	100	0	0	87	31.12.1999	74	P o1
	ITALY, Marche	1990–1997		13	–	100	0	–	13	30.09.2000	62	P o2
	ITALY, Ferrara	1991–1995		2	2	100	0	0	4	31.12.1998	75	
	ITALY, Latina	1983–1997	+	8	18	100	0	0	26	31.12.1998	65	
	ITALY, Liguria	1988–1995		4	12	94	0	0	16	15.04.2000	94	
	ITALY, Lombardy	1978–1997	+	23	53	99	0	0	76	23.09.1999	59	
	ITALY, Macerata	1991–1997		2	7	100	0	0	9	30.09.2000	56	o2
	ITALY, Parma	1978–1995	+	7	13	100	0	–	20	01.04.1999	70	
	ITALY, Piedmont general	1988–1997		8	22	100	0	0	30	31.05.2001	87	o1
	ITALY, Ragusa	1983–1997	+	12	11	100	0	0	23	30.03.2000	83	
	ITALY, Sassari	1992–1995		1	5	100	0	0	6	30.12.1999	50	
	ITALY, Tuscany	1988–1997		8	32	80	0	0	40	31.12.1998	60	
	ITALY, Umbria	1994–1996		3	6	100	0	0	9	31.12.1999	22	
	ITALY, Veneto	1990–1996		24	40	100	0	0	64	31.12.1998	52	
	MALTA, National	1991–1997		4	4	100	0	0	8	31.12.1999	75	
	SLOVENIA, National	1978–1997	+	77	76	100	0	0	153	31.12.1999	70	
	SPAIN, National	1990–1995		68	–	100	0	0	66	31.12.2000	88	P Z o3
	SPAIN, Albacete	1991–1997		1	4	100	0	0	5	15.09.2000	60	
	SPAIN, Asturias	1983–1997	+	27	43	100	0	0	70	31.12.1997	59	
	SPAIN, Basque Country	1988–1994		16	35	100	0	0	50	31.12.2000	88	o3
	SPAIN, Canary Islands	1993–1996		14	12	100	0	0	–	–	–	

(*continued on next page*)

Table 1 – *continued*

Region	Registry	Coverage				Basis of diagnosis			Survival analysis			Notes
		Period	Time-trend	No of cases		MV %	DCO %	unknown %	*n*	Closing date	FU > 5y %	
				0–14 years	15–19 years							
	SPAIN, Girona	1994–1997		5	7	100	0	0	12	31.12.1997	0	o3
	SPAIN, Granada	1988–1997		9	–	100	0	0	9	31.12.1999	67	G
	SPAIN, Mallorca	1988–1995		5	13	100	0	0	18	31.12.1998	78	o3
	SPAIN, Navarra	1978–1996	+	7	22	100	0	0	29	31.12.1997	52	o3
	SPAIN, Tarragona	1983–1997	+	19	20	100	0	0	39	31.12.1998	59	o3
	SPAIN, Zaragoza	1978–1996	+	16	15	100	0	0	31	31.12.1996	58	o3
	TURKEY, Izmir	1993–1996		26	7	100	0	–	–	–	–	
West	FRANCE, Brittany	1991–1997		25	–	100	0	–	25	01.01.2000	32	P
	FRANCE, Lorraine	1983–1997	+	49	–	100	0	–	49	01.01.1999	63	P
	FRANCE, PACA	1984–1996	+	53	–	100	0	–	47	31.3.1998	43	P
	FRANCE, Rhone Alps	1988–1997		51	–	100	0	–	43	01.6.2000	40	P o4
	FRANCE, Doubs	1978–1996	+	9	21	37	0	–	28	01.6.2001	32	
	FRANCE, Hérault	1988–1997		13	15	100	0	–	–	–	–	
	FRANCE, Isère	1979–1997	+	30	31	98	0	–	–	–	–	o4
	FRANCE, Manche	1994–1996		3	–	100	0	–	2	31.05.2000	0	S
	FRANCE, Bas-Rhin	1978–1996	+	22	40	100	0	–	62	31.12.1997	65	
	FRANCE, Haut-Rhin	1988–1997		11	8	100	0	–	4	31.12.1995	75	S
	FRANCE, Somme	1983–1996	+	9	16	100	0	–	25	15.08.2000	60	
	FRANCE, Tarn	1983–1997	+	2	8	100	0	–	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	647	–	100	0	–	624	31.12.1998	28	P
	GERMANY, GCCR (only former West)	1983–1990	+	410	–	100	0	–	409	31.12.1998	83	P
	NETHERLANDS, National	1989–1995		98	221	100	0	–	97	31.12.1998	60	S o5
	NETHERLANDS, Eindhoven	1978–1997	+	20	35	100	0	–	55	01.07.1999	49	o5
	SWITZERLAND, Basel	1983–1997	+	9	15	100	0	–	24	30.6.2000	75	
	SWITZERLAND, Geneva	1978–1997	+	9	19	100	0	0	28	31.12.1999	61	
	SWITZERLAND, Graubunden & Glarus	1989–1997		2	4	100	0	0	6	25.05.2000	50	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	8	14	100	0	0	22	01.02.2001	59	
	SWITZERLAND, Valais	1989–1997		3	12	100	0	0	5	01.12.1998	100	S

–, not applicable; +, included in time trend analyses; FU > 5y, cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; DCO, registrations from death certificate only; G, general cancer registry, which has only contributed data for age-range 0–14 years; GCCR, National German Childhood Cancer Registry (until 1990 covering only West and since 1991 the reunified Germany); MV, microscopically verified cases; *n*, number of cases; NCR, National Cancer Registry of the former German Democratic Republic. Data for 1978–87 contributed only to analyses of time trends for Europe as a whole. Data on children for 1988–1989 were pooled with GCCR and included in West. For explanation, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue); o1–o5, overlapping registration areas: for the overlapping years, data from the registry with larger coverage are included in each analysis, according to availability (see text); P, paediatric cancer registry; age range for all registrations is 0–14; PACA, Provence, Alps, Côte d'Azur; S, survival analyses were possible only for a restricted dataset [see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]; Unknown, registrations with unknown basis of diagnosis; Z, covers only selected areas [see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

Table 2 – Numbers of cases and indicators of data quality by region and age group used for time trend analyses of Hodgkin's disease incidence and survival in children (age 0–14 years) and adolescents (age 15–19 years) in Europe, 1978–1997 (Source: ACCIS)

Region	Period	Children (age 0–14 years)						Adolescents (age 15–19 years)					
		Cases *n*	Basis of diagnosis			Follow-up		Cases *n*	Basis of diagnosis			Follow-up	
			MV %	DCO %	Unknown %	1+ days %[1]	5+ years %[2]		MV %	DCO %	Unknown %	1+ days %[1]	5+ years %[2]
Europe*	1978–1982	712	98	0	<1	100	99	472	97	<1	0	99	98
	1983–1987	980	99	0	<1	100	89	615	99	0	<1	99	70
	1988–1992	953	98	0	1	100	90	385	99	0	0	100	97
	1993–1997	983	99	0	<1	97	28	439	99	<1	0	100	23
British Isles	1978–1982	305	98	0	<1	100	100	53	87	0	0	100	100
	1983–1987	282	97	0	2	100	99	56	98	0	0	100	100
	1988–1992	239	95	0	5	100	99	50	98	0	0	100	100
	1993–1997	159	99	0	1	100	94	44	98	0	0	100	49
East	1978–1982	130	99	0	0	100	99	56	96	4	0	95	100
	1983–1987	126	100	0	0	100	97	74	100	0	0	97	98
	1988–1992	149	100	0	0	100	98	73	100	0	0	100	98
	1993–1997	122	100	0	0	100	35	82	98	1	0	100	10
North	1978–1982	74	99	0	0	100	98	93	100	0	0	99	97
	1983–1987	62	100	0	0	100	98	97	99	0	1	99	100
	1988–1992	55	100	0	0	100	100	137	100	0	0	100	99
	1993–1997	79	95	0	3	100	28	174	100	0	0	100	20
South	1978–1982	60	100	0	0	100	93	36	100	0	0	100	91
	1983–1987	76	100	0	0	100	99	70	100	0	0	100	100
	1988–1992	74	99	0	0	100	95	80	100	0	0	100	97
	1993–1997	73	100	0	0	100	28	85	100	0	0	100	29
West	1978–1982	17	76	0	0	100	100	42	90	0	0	100	92
	1983–1987	310	100	0	0	100	96	58	90	0	2	98	86
	1988–1992	400	99	0	0	99	80	45	93	0	0	100	81
	1993–1997	550	100	0	0	95	8	54	100	0	0	100	20

1+ days, cases followed-up for 1 or more days, as a percentage of all cases in the registries with follow-up; 5+ years, cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; DCO, cases registered from death certificate only; MV, microscopically verified diagnosis; *n*, number of cases.

* Europe includes the data of the former German Democratic Republic, which are not included in any of the regions.

Table 3 – Distribution of cases and incidence rates (cases per million per year) of Hodgkin's disease by age, gender and region, Europe, 1988–1997 (Source: ACCIS)

	Children (age 0–14 years)											Adolescents (age 15–19 years)	
	Number of cases					Crude rates				ASR	Cumulative rates	No	Crude rates
	<1 y	1–4 y	5–9 y	10–14 y	0–14 y	<1 y	1–4 y	5–9 y	10–14 y	0–14 y	0–14 y	15–19 y	15–19 y
Europe													
Boys	0	173	532	899	1604	0.0	3.2	7.7	12.9	7.2	115.8	649	28.5
Girls	0	42	175	713	930	0.0	0.8	2.7	10.8	4.2	70.7	670	30.8
Both	0	215	707	1612	2534	0.0	2.0	5.2	11.9	5.8	93.5	1319	29.7
Bristish Isles													
Boys	0	23	102	155	280	0.0	1.8	6.4	10.2	5.6	90.2	66	24.6
Girls	0	6	32	102	140	0.0	0.5	2.1	7.1	2.9	48.0	71	27.8
Both	0	29	134	257	420	0.0	1.1	4.3	8.7	4.3	69.4	137	26.1
East													
Boys	0	48	114	156	318	0.0	6.7	11.7	15.1	10.2	160.8	71	25.1
Girls	0	14	35	133	182	0.0	2.0	3.7	13.4	5.7	93.5	84	30.9
Both	0	62	149	289	500	0.0	4.4	7.8	14.3	8.0	128.1	155	28.0
North													
Boys	0	9	25	54	88	0.0	2.3	5.5	11.6	5.8	94.7	162	32.3
Girls	0	1	8	37	46	0.0	0.3	1.8	8.3	3.1	51.7	149	31.1
Both	0	10	33	91	134	0.0	1.3	3.7	10.0	4.5	73.7	311	31.7
South													
Boys	0	17	59	129	205	0.0	3.6	9.1	16.6	8.9	142.9	197	33.4
Girls	0	3	17	90	110	0.0	0.7	2.7	12.2	4.6	77.3	176	31.2
Both	0	20	76	219	315	0.0	2.2	6.0	14.5	6.8	111.3	373	32.3
West													
Boys	0	76	232	405	713	0.0	3.0	7.2	12.8	7.0	112.0	153	24.3
Girls	0	18	83	351	452	0.0	0.8	2.7	11.7	4.5	75.2	190	31.4
Both	0	94	315	756	1165	0.0	1.9	5.0	12.3	5.8	94.1	343	27.8

ASR, age-standardised incidence rate (World standard); y, years.

and none in the North. The overall age-standardised incidence rate in European children (0–14 years) was estimated at 5.8 (5.5–6.0) per million per year. Incidence rate in adolescents (15–19 years) was 29.7 (28.1–31.3) per million per year (Table 3). In children, estimates of incidence rate from paediatric and general registries did not differ substantially (Fig. 1).

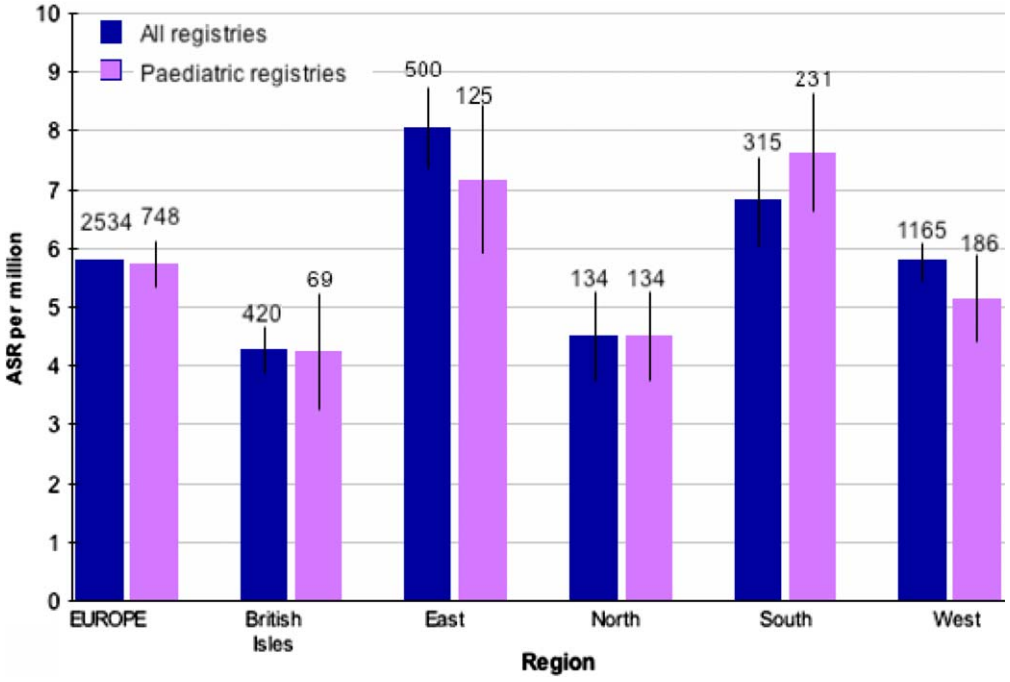

Fig. 1 – Age-standardised incidence rates (ASR) of childhood Hodgkin's disease (0–14 years), as registered in paediatric and general cancer registries in Europe, 1988–1997. 95% CI are represented by line sections. Source: ACCIS.

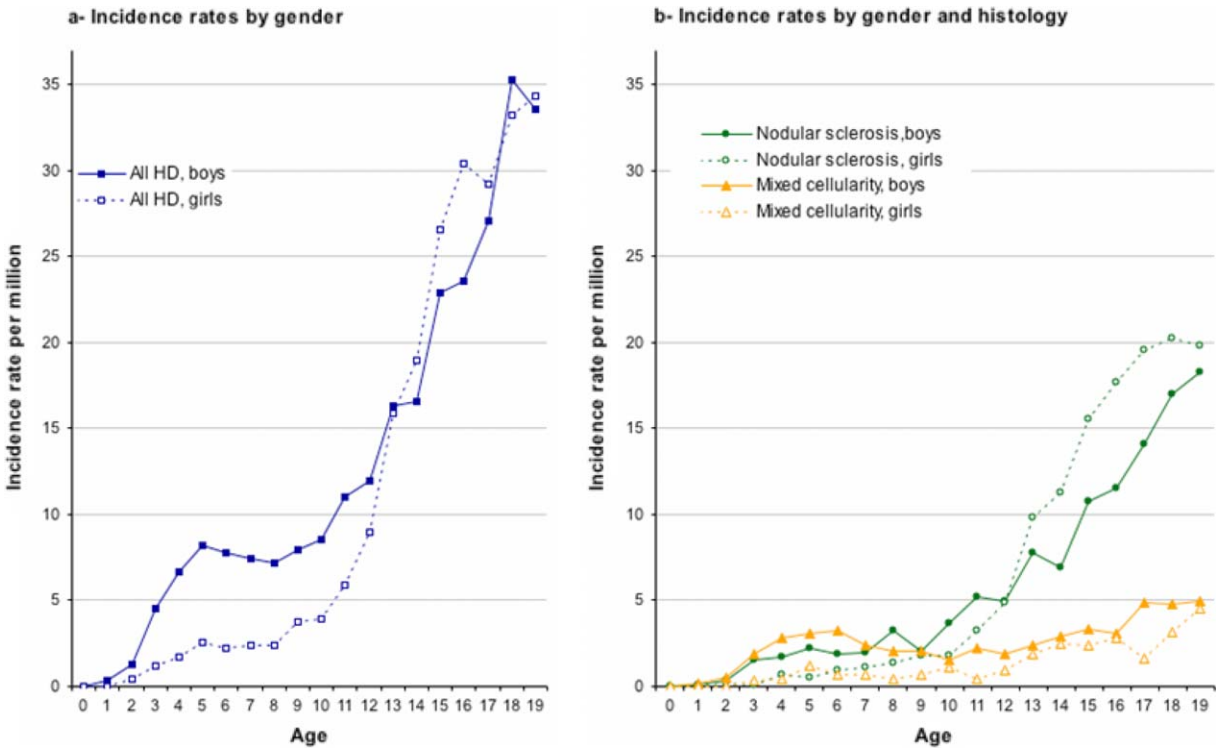

Fig. 2 – Incidence of Hodgkin's disease (HD) in children (age 0–14 years) and adolescents (age 15–19 years) (a) by age and gender and (b) by histology (selected types), Europe, 1988–1997. A total of 3853 HD cases were included in the analyses. Source: ACCIS.

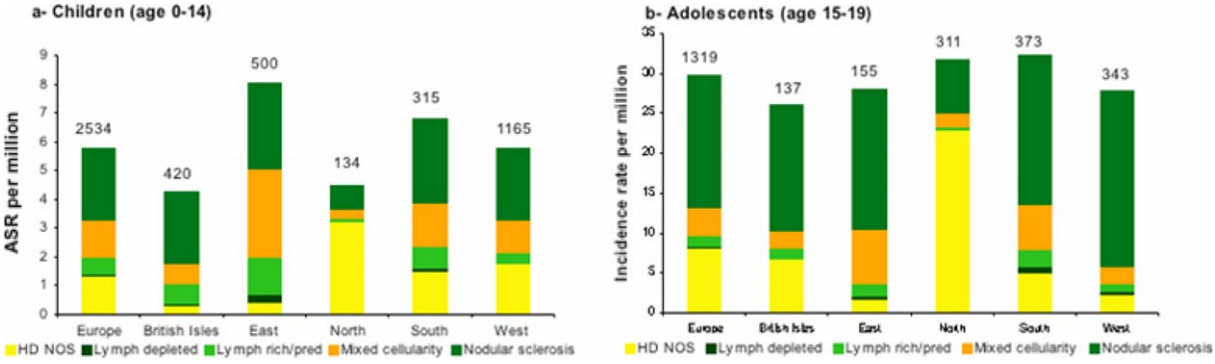

Fig. 3 – Incidence rates of Hodgkin's disease in Europe, 1988–1997, by region and histology type. (a) Age-standardised incidence rates (ASR) for children, and (b) age specific rates for adolescents. Total numbers of cases included are shown for each region. Source: ACCIS.

There was no case aged less than 1 year, and cases aged less than 5 years represented only 11% of all childhood cases (Table 3). Overall, incidence rates increased sharply with age, with different patterns for boys and girls (Fig. 2(a)). Male predominance, marked in young children, tended to vanish with age, sex ratios being 4.1, 3.0, 1.3 and 1.0 for the age groups 1–4, 5–9, 10–14, and 15–19 years, respectively. The steep rise in incidence rates after the age of 10 years in boys and girls was due mostly to the cases coded as nodular sclerosis (Fig. 2(b)). Incidence rates differed slightly between European regions: East, South and West having the rates higher than reference region (British Isles) (Table 3, Fig. 1). The age- and gender-adjusted incidence rate ratios (IRR) for the East, North, South and West regions were 1.8 (95% CI 1.6–2.1), 1.1 (95% CI 0.9–1.3), 1.6 (95% CI 1.4–1.9) and 1.4 (95% CI 1.2–1.5), respectively. The high rates observed in the East were particularly marked for boys under the age of 10 years, with a peak of incidence at the age of 5 years. In adolescents, the incidence rates were significantly higher than the reference only in the South, with IRR = 1.2 (95% CI 1.0–1.5).

There were considerable differences in the distribution of histological types of HD between the regions (Fig. 3). In the 1988–1997 period, unspecified HD represented less than 10% of the cases in the East, and more than 70% in the North.

Table 4 – Temporal variations of Hodgkin's disease incidence with age, histology and region in Europe, 1978–1997. Incidence rates are age-specific for the age groups 1–4, 5–9, 10–14 and 15–19 years and age-standardised (world standard) for all children combined (0–14 years) (Source: ACCIS)

		ASR				AAPC, 95% CI (%)	
	n	1978–1982	1983–1987	1988–1992	1993–1997	1978–1997	
Age (years)							
1–4	278	1.5	1.9	2.3	2.5	−0.05	(−2.40–2.36)
5–9	1033	5.0	4.8	5.3	5.3	0.77	(−0.44–2.01)
10–14	2317	10.4	10.7	10.4	12.6	1.30	(0.47–2.12)
0–14	3628	5.2	5.2	5.3	5.9	0.98	(0.33–1.64)
15–19	1911	22.9	29.1	27	33.1	3.49	(2.57–4.40)
Histology							
Children (0–14 years)							
NOS	834	1.2	1.1	0.88	1.8	7.19	(5.52–8.88)
Mixed cellularity	845	1.3	1.4	1.4	1.1	−2.22	(−3.58– −0.85)
Nodular sclerosis	1439	1.8	1.7	1.8	1.8	2.30	(1.24–3.36)
Adolescents (15–19 years)							
NOS	754	10.6	11.0	9.7	12.5	4.05	(2.46–5.66)
Mixed cellularity	291	3.5	5.8	3.4	3.5	−0.05	(−2.45–2.42)
Nodular sclerosis	743	7.1	10.0	12.2	16.0	4.51	(3.06–5.98)
Region							
Children (0–14 years)							
British Isles	985	4.6	4.8	4.3	4.3	−0.43	(−1.58–0.74)
East	527	6.4	5.9	7.0	6.4	0.37	(−1.14–1.91)
North	270	4.2	3.8	3.7	5.3	1.07	(−1.00–3.16)
South	283	6.0	6.3	7.1	7.7	2.41	(0.27–4.59)
West	1277	3.8	4.8	5.6	6.4	2.49	(1.23–3.77)
Adolescents (15–19 years)							
British Isles	105	23.4	25.8	27.9	28.0	0.87	(−1.54–3.34)
East	135	21.9	30.4	27.2	28.6	1.63	(−0.38–3.69)
North	279	16.8	17.7	27.1	36.7	5.72	(4.08–7.37)
South	141	21.1	26.6	30.5	36.1	3.51	(1.22–5.85)
West	98	28.1	25.2	21.6	31.6	0.82	(−1.77–3.49)

Average annual percent change (AAPC) was derived from a Poisson regression model, adjusted for age-group, sex or region, as applicable. *n*, number of cases; NOS, not otherwise specified.

Taken together, nodular sclerosis and mixed cellularity accounted for more than 80% of the specified cases in every age group, but the proportion of these two types changed with age in opposite directions: mixed cellularity decreased from 46% of the cases aged less than 5 years to 20% of the 15–19-year age group cases, whereas that of nodular sclerosis increased from 35% to 67%. In both categories the male predominance decreased with age, and in adolescents only cases with mixed cellularity remained more frequent in males than in females. Too few cases were registered with other subtypes of HD for further analysis. Overall, the mixed cellularity type was more frequent in males than in females in all age groups and in all regions. Irrespective of sex, its proportion was highest in the East (40% of specified HD in children and 26% in adolescents, compared with the respective percentage for Europe of 28% and 17%). Overall, nodular sclerosis represented 57% of specified HD in children and 76% in adolescents.

3.2. *Temporal trends in incidence*

Temporal variations in incidence over the period 1978–1997 reported in Table 4 are based on 3628 cases of Hodgkin's disease in children and 1911 in adolescents. In children, the ASR increased from 5.2 per million per year in 1978–1982 to 5.9 per million per year in 1993–1997 (AAPC = 1.0%, $P = 0.003$; adjusted for region, age and gender). By region, a significant increase was only observed in South and West and by age group, only in age group 10–14 years (AAPC = 1.3%, $P = 0.002$). In adolescents, incidence rate increased from 22.9 to 33.1 per million per year (AAPC = 3.5%, $P < 0.001$), with most of the regions affected. Incidence of nodular sclerosis type increased in both children (AAPC = 2.3%, $P < 0.001$) and adolescents (AAPC = 4.5%, $P < 0.0001$) and the increase was also observed for the unspecified type in children (AAPC = 7.2%, $P < 0.0001$) and adolescents (4.1%, $P < 0.0001$). There were no significant changes in adolescents in the incidence of other histology type. In children, incidence of mixed cellularity type decreased by 2.2% per year on average ($P = 0.002$), with no temporal change detected in the East region. The age and sex distribution of HD cases remained unchanged with time.

3.3. *Survival*

From 1988 to 1997, 2393 cases of childhood HD were followed up for at least 1 day and included in survival analyses, of whom 186 were deceased and 29 of unknown vital status by the closing date of the study. During this period, the 5-year survival was estimated at 93% (95% CI 92–94) in children and 89% (95% CI 87–91) in adolescents. Survival was inversely associated with

Table 5 – Overall 5-year survival (5y%) and 95% confidence interval (95% CI) after diagnosis of Hodgkin's disease by age group, gender and regions of residence, Europe, 1988–1997 (Source: ACCIS)

	1–4 y		5–9 y		10–14 y		1–14 years			15–19 years		
	5y%	95% CI	5y%	95% CI	5y%	95% CI	No	5y%	95% CI	*n*	5y%	95% CI
Europe												
Boys	97	92–99	94	92–96	93	91–95	1515	94	93–95	524	87	84–90
Girls	97	80–100	94	88–97	89	86–92	878	91	88–92	521	91	88–93
Both sexes	97	93–99	94	92–96	92	90–93	2393	93	92–94	1045	89	87–91
British Isles												
Boys	95	72–99	98	92–100	95	90–97	280	96	93–98	66	86	74–93
Girls	100	100–100	100	100–100	86	77–91	140	90	83–94	71	94	84–98
Both sexes	96	76–99	98	94–100	91	87–94	420	94	91–96	137	90	83–94
East												
Boys	96	84–99	90	83–94	91	84–94	318	91	87–94	71	79	65–87
Girls	93	58–99	94	76–98	83	75–89	182	86	79–90	84	86	75–93
Both sexes	95	85–98	91	85–95	87	82–91	500	89	86–92	155	83	74–88
North												
Boys	100	100–100	88	67–96	90	76–96	88	90	81–95	162	90	83–94
Girls	100	100–100	100	100–100	81	62–91	46	86	70–93	149	88	81–93
Both sexes	100	100–100	91	74–97	86	76–92	134	88	81–93	311	89	84–92
South												
Boys	100	100–100	90	77–96	94	87–97	181	93	88–96	186	89	83–93
Girls	100	100–100	100	100–100	93	85–97	92	94	87–98	168	92	87–96
Both sexes	100	100–100	91	81–96	94	89–96	273	93	89–95	354	91	87–93
West												
Boys	97	88–99	97	92–99	94	91–97	648	95	93–97	39	92	76–97
Girls	100	100–100	88	75–95	94	90–96	418	93	89–95	49	94	76–98
Both sexes	97	90–99	94	90–97	94	92–96	1066	94	93–96	88	92	82–97

age in all European regions (Table 5). It was slightly better for boys than for girls in children (94%; 95% CI 93–95) versus 91% (95% CI 88–92), $P = 0.02$), due to the 10–14 years age group. Distribution of male and female cases by age within this age group was not strictly comparable, boys being younger than girls (51% of the boys were older than 12 years versus 65% of the girls). The

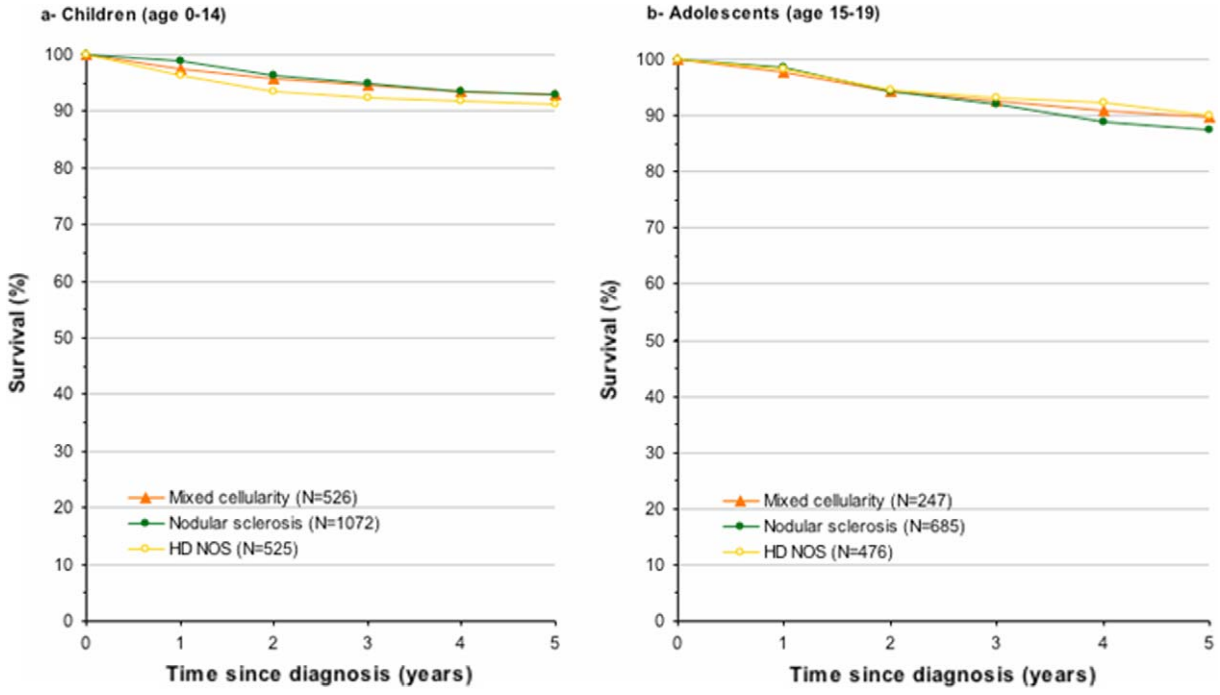

Fig. 4 – Survival curves by histological subtype of Hodgkin's disease, (a) in children and (b) in adolescents, Europe, 1988–1997. *n*, number of cases included in the analyses. Source: ACCIS.

Table 6 – Time trends in 5-year survival rates (5y%) after Hodgkin's disease by age and region, Europe, 1978–1997 (Source: ACCIS)

Region	Period	1–4 years			5–9 years			10–14 years			1–14 years			15–19 years		
		n	5y%	95% CI	*n*	5y%	95% CI	*n*	5y%	95% CI	*n*	5y%	95% CI	*n*	5y%	95% CI
Europe[a]	1978–1982	54	89	(77–95)	198	91	(86–95)	455	85	(81–88)	707	87	(84–89)	459	80	(75–83)
	1983–1987	72	92	(82–96)	264	92	(88–95)	632	91	(89–93)	968	91	(89–93)	598	81	(78–84)
	1988–1992	74	96	(87–99)	278	96	(93–98)	554	92	(89–94)	906	93	(92–95)	373	90	(86–92)
	1993–1997	66	98	(89–100)	262	94	(90–97)	619	92	(89–94)	947	93	(91–95)	432	88	(84–91)
	p for trend			0.019			0.09			<0.001			<0.001			<0.001
British Isles	1978–1982	16	94	(63–99)	84	96	(89–99)	205	87	(82–91)	305	90	(86–93)	53	83	(70–91)
	1983–1987	22	86	(63–95)	65	96	(86–98)	195	89	(83–92)	282	90	(86–93)	56	79	(65–87)
	1988–1992	17	94	(63–99)	76	100	(100–100)	146	92	(86–95)	239	95	(91–97)	50	92	(80–97)
	1993–1997	11	100	(100–100)	52	96	(85–99)	96	92	(84–96)	159	94	(89–97)	44	89	(75–95)
	p for trend			0.41			0.45			0.041			0.012			0.18
East	1978–1982	18	83	(56–94)	54	93	(81–97)	58	81	(68–89)	130	86	(79–91)	53	68	(54–79)
	1983–1987	16	88	(59–97)	45	87	(73–94)	65	89	(78–95)	126	88	(81–93)	72	68	(56–77)
	1988–1992	14	93	(59–99)	46	89	(76–95)	89	90	(81–95)	149	90	(84–94)	73	83	(73–90)
	1993–1997	8	100	(100–100)	45	95	(83–99)	69	84	(72–92)	122	89	(82–94)	82	80	(61–90)
	p for trend			0.19			0.55			0.40			0.22			0.03
North	1978–1982	3	100	(100–100)	12	92	(54–99)	59	81	(68–89)	74	84	(73–90)	92	87	(78–92)
	1983–1987	0			16	88	(59–97)	46	89	(75–95)	62	89	(78–94)	96	95	(88–98)
	1988–1992	5	100	(100–100)	16	94	(63–99)	34	94	(78–99)	55	95	(84–98)	137	90	(83–94)
	1993–1997	5	100	(100–100)	17	88	(59–97)	57	77	(59–88)	79	82	(68–90)	174	87	(78–92)
	p for trend			–			0.74			0.88			0.78			0.34
South	1978–1982	7	71	(26–92)	18	88	(61–97)	35	97	(81–100)	60	92	(91–96)	36	80	(62–90)
	1983–1987	7	100	(100–100)	24	96	(74–99)	45	91	(78–97)	76	93	(85–97)	70	84	(73–91)
	1988–1992	7	100	(100–100)	21	85	(61–95)	46	85	(71–92)	74	86	(76–92)	80	92	(84–97)
	1993–1997	0			15	100	(100–100)	58	98	(88–100)	73	99	(90–100)	85	92	(83–96)
	p for trend			0.07			0.75			0.71			0.35			0.06
West	1978–1982	0			4	75	(13–96)	8	88	(39–98)	12	83	(48–96)	34	91	(75–97)
	1983–1987	17	94	(65–99)	75	92	(83–96)	207	96	(92–98)	299	95	(92–97)	45	88	(74–95)
	1988–1992	31	97	(79–100)	119	98	(93–100)	239	94	(90–96)	389	95	(93–97)	33	93	(75–98)
	1993–1997	42	98	(84–100)	133	92	(83–96)	339	95	(92–97)	514	95	(92–97)	47	95	(80–99)
	p for trend			0.52			0.84			0.88			0.88			0.15

*P < 0.05; ***P < 0.001.

a Includes German Democratic Republic (GDR), which is not included in any other region.

slight difference in survival between adolescent boys and girls (5-year survival 87% versus 91%, Table 5) was not significant ($P = 0.20$). Five-year survival was lower in the East (89%; 95% CI 86–92) than in the rest of Europe (94%; 95% CI 92–95) $P < 0.0001$. In adolescents, the difference between the regions was non-significant ($P = 0.07$). Histological type (nodular sclerosis versus mixed cellularity) had no substantial influence on survival either in children or in adolescents (Fig. 4). Survival rates for lymphocyte rich/predominant not specified as nodular subtype in children seemed better, but the difference between the survival curve for patients with this subtype compared with that for children with all other types combined did not quite reach statistical significance ($P = 0.06$). No significant differences in survival by histological subtype were observed in adolescents ($P = 0.99$).

3.4. *Temporal trends in survival*

Analysis of temporal trends in survival were based on 3528 childhood cases and 1862 adolescent cases registered from 1978 to 1997 and followed up for at least 1 day. Among these,

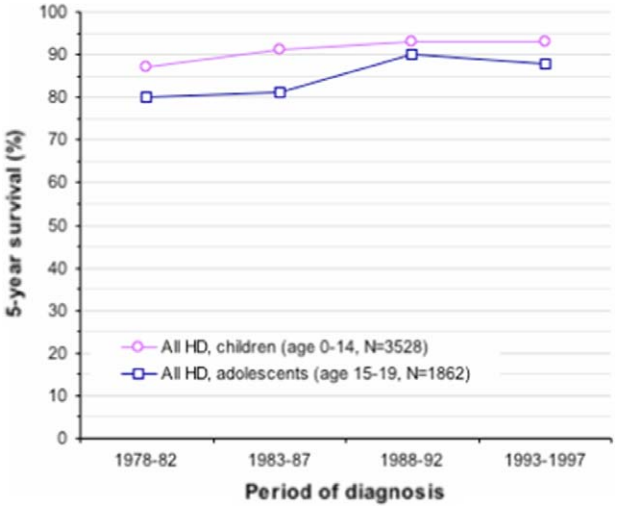

Fig. 5 – Temporal trends in 5-year survival of children and adolescents with Hodgkin's disease (HD) in Europe, 1978–1997. *n*, number of cases included in the analyses. Source: ACCIS.

393 children and 362 adolescents were deceased and 36 children and 54 adolescents were of unknown vital status by the closing date. Overall, survival increased in all age groups and for all histological subtypes, but adolescents continued to have lower survival than children (Table 6, Fig. 5). However, the increase occurred mainly before 1993–1997, except for the adolescents with mixed cellularity HD, for whom survival was increasing also between the last two periods. The increase in survival was observed in all regions except the North, where it decreased in the most recent period (Table 6).

4. Discussion

ACCIS database provided a unique set of data on HD with respect to the large number of cases included (over 4000), the age range (children and adolescents) as well as to the long period of registration available for temporal analyses (up to 20 years). The present paper is the largest report on incidence and survival of childhood HD in Europe. The good quality of the data was attested by the small proportions of DCO cases was low in the registries with the access to this source of data, of cases without microscopic verification, of subjects followed up less than 1 day and of those with unknown vital status. Most cases were provided by paediatric registries. In the European regions where paediatric and general registries coexisted they gave similar estimations for incidence rates for the common age-range.

The present data are consistent with epidemiological features of childhood HD.[2,10,13,21] HD was absent in infants and rare in young children. Annual age-standardised incidence was estimated at 5.8 (95% CI 5.5–6.0) per million in children and 29.7 (95% CI 28.1–31.3) per million in adolescents. Comparable rates of 5.5 in children and 32 in adolescents were reported in the United States of America (USA) for 1990–1994 [13] and, for children, in Australia and in Canada (4.2 per million per year and 6.0 per million per year, respectively) for 1982–1991.[22] HD was 3–4 times more frequent in boys than in girls before the age of 10 years, but this contrast between genders disappeared progressively with increasing age, together with a decreasing proportion of mixed cellularity type and increasing proportion of nodular sclerosis type (in spite of a large proportion of unspecified subtypes). In children, higher incidence rates were observed in the East, South and West than in the British Isles or the North. High incidence rates in the Mediterranean area and in some countries of Central Europe were observed previously [17] and in our study the high incidence of HD was associated with large proportion of mixed cellularity. This type represented almost 50% of cases in the childhood peak in the age-group 5–9 observed in boys in the East. These observations support the theory that HD may represent two distinct diseases with different aetiology: an EBV-related form of the disease, more prevalent in developing countries, in young children, in boys and mainly presenting as mixed cellularity HD, and a form unrelated to EBV, more prevalent in industrialised countries, in adolescents and young adults with slight female predominance and presenting as nodular sclerosis.[3,5,10]

Overall incidence rates of HD increased between 1978 and 1997 in older children and adolescents. In children under 15 years of age, the increase for the total area under study was determined by that observed in the South and West regions: withdrawing any of these two regions in turn from the total data-set resulted in a lack of overall temporal trend for the remaining area. In the childhood data-set the contribution of the West grew markedly over the study period (3% in the first period, 51% in the last). Possible under-registration of HD in paediatric cancer registries, which represented a large proportion within the West, might have resulted from missing the older children, who might have been reported less effectively in the past. The significant increase of HD in children in the West may also reflect the absorption of the area of the former German Democratic Republic (GDR) into the West region towards the end of the study period (1991–1997). This might have caused the overall childhood incidence in the West to increase.

In the West, additional years of observation and possibly separate analyses for the area of the former GDR would help to confirm or refute one of the two hypotheses (improvement in registration or contribution of the former GDR). However, the area of the former GDR has been included in the analysis of time trends for Europe overall, and the rates were also increasing in the South. The significant increase of 1% in children aged 10–14 per year within the total data-set deserves further monitoring, especially in view of the observed decrease in incidence rates of HD in children in the SEER program in the USA between 1975 and 1995, from 7.4 to 5.5 per million.[13]

In adolescents, the incidence rate was found to increase by 3.5% per year on average in the majority of the regions, reaching 33.1 per million and year for the most recent period (1993–1997). We are not aware of obvious changes in registration practices over the study period in general cancer registries providing the data on adolescents apart from, possibly, increasing specificity of diagnoses. However, the increasing concentration of care in specialised paediatric oncology departments and the development of computerised hospital files may have contributed to more exhaustive data collection and improved registration practices also within the age group 15–19 years. An increasing incidence of HD in adolescents was previously observed also in the UK.[24] In contrast, a decrease in incidence rates of HD in adolescents was seen in the SEER program in the USA between 1975 and 1995, from 36 to 32 per million.[13]

Heterogeneity in histology coding and classification, together with its improvement over time and due to advances in histology and molecular typing of tumours, hampers interpretation of variations in incidence of HD subtypes with time and between regions. For example, the unspecified HD category broadened with time in the North and shrank in the South region. In addition, it was shown in several published series, that misclassification may occur between mixed cellularity and nodular sclerosis subtypes, whereby some diagnoses of mixed cellularity HD were recoded as nodular sclerosis after a review.[10] This underlines the importance of homogeneous international coding and classification practices. Although we are aware of the limitation of the comparison by tumour type, due to regional and temporal variations in coding and classification, we cannot exclude a real secular trend with decreasing incidence of the mixed cellularity type and increasing incidence of the nodular sclerosis type. Such change may also correspond to the current

aetiological hypothesis. The increase in nodular sclerosis type may reflect increasingly later exposure to EBV (possibly due to improving socio-economic conditions), which translates into a gradually later occurrence of HD, with the morphological features changing accordingly. Incidence of nodular sclerosis type was also reported to increase from the Manchester Children's Tumour Registry over birth cohorts from 1939 to 1998.[23]

This study confirms that HD is one of the most curable cancers, with 5-year survival estimated at 93% in children and 89% in adolescents diagnosed during 1988–1997, compared with 72% for all cancers combined in children [Sankila and colleagues, this issue] and adolescents [Stiller, Desandes, Danon and colleagues, this issue]. Similar population-based data have been published by the EUROCARE study and the SEER program.[13,15,25] The moderate effect of gender on the outcome, observed in the present data for children aged 10–14 years, may be due to residual confounding by age within this age-group and should be examined in the future in multiple regression model.Results from the SEER program and EUROCARE showed no influence of gender on survival.[13] From the results of our study it appears that the different histological types do not have a prognostic importance, since at a given age, we observed similar prognoses for the main subtypes of HD mixed cellularity and nodular sclerosis. This is consistent with the results of the United Kingdom Children's Cancer Study Group (UKCCSG), which did not find any effect of histology on survival when stage was accounted for,[26] and with analyses of three clinical trials of the 1990s.[27] The lower survival of adolescents may be due to true clinical differences related to age, but it may also result from differences in medical care, since adolescents are usually treated in departments for adults, and are therefore excluded from the paediatric clinical trials.[28,29] An example of the benefit of intensive paediatric rather than adult protocol in adolescent cancers has been demonstrated for acute lymphoid leukaemia.[30] Data on stage and treatment were not available in the ACCIS database, which limits the interpretation of some patterns of survival.

In the present data, cases from the East appeared to have a lower survival than those from non-East regions, as already described in Eurocare study.[15] In our study, significant differences concerned childhood ages. Survival of children and adolescents of the East region was lower than those of other regions also for other tumours examined within ACCIS [Ref. [16] Sankila and colleagues, this issue, Stiller, Desandes, Danon and colleagues, this issue]. The reasons for this are complex and are discussed in the overview paper [Pritchard-Jones and colleagues, this issue]. However, interpretation of comparisons between regions is limited in the absence of data on stage at diagnosis, which is a major prognostic factor and an indicator of timeliness of diagnosis.

Overall, as expected from clinical trials, survival after HD has significantly improved from 87% to 93% in children and from 80% to 88% in adolescents over the period 1978–1997. The improvement was observed in all regions, although without statistical significance, but not in the North, where survival is nevertheless comparable with the other regions.

Better staging of the disease, individual adaptation of treatments, reduction of side-effects, reduction of irradiation doses by paediatric protocols and a general improvement of healthcare may explain these good results. Same improvements have been reported by the SEER program in the USA [13,31] and by the EUROCARE study in Europe.[14,15]

In conclusion, the patterns of incidence of HD by age, sex and histology described in this paper are consistent with those observed previously in industrialised countries. The clear increase in incidence after the age of 10 years may partly be due to improvement in diagnosis, classification and registration of HD in the relevant age groups. However, changes in causal risk factors, notably the overall improvement in socio-economic status within Europe, may also be involved and further study of the incidence trends is therefore necessary. Good and improving survival rates were seen in all regions, despite intra-regional variations between countries [Pritchard-Jones and colleagues, this issue]. Lower survival rates in adolescents than in children may reflect less well-adapted medical care in this transitional age group. In future, validation of diagnosis, standardisation of classification and improved documentation of cases in the cancer registries (with respect to diagnosis subtypes, extent of disease at diagnosis and possibly treatment), will help to refine interpretation of international variations in incidence and survival.

Conflict of interest statement

None declared.

Acknowledgements

The ACCIS project was funded by the European Commission from the Europe Against Cancer programme (contracts SI2.126875, SI2.321970 and SPC.2002303), jointly with the International Agency for Research on Cancer (IARC). Data analyses were partly funded by the French *Ligue Nationale Contre le Cancer, Comité du Rhône*.

The authors thank Mr Nicolas Mitton for his input in the set-up and management and exploration of the ACCIS database, the members of ACCIS Scientific Committee for steering the study and the Guest Editors for comments on earlier drafts.

The following collaborators from the cancer registries contributed actively to this study: S.V. Petrovich, O. Budanov (Belarus); H. Storm, N. Christensen (Denmark); T. Aareleid (Estonia); T. Hakulinen, R. Sankila, E. Pukkala (Finland); E. Le Gall, I. Tron (Brittany, France), B. Lacour, E. Desandes (Lorraine, France), J.L. Bernard, P. Pillon, J.C. Gentet (PACA and Corsica, France), F. Freycon, C. Berger (Rhone Alps, France), L. Remontet (Francim, France), A. Danzon, M. Mercier (Doubs, France), J.P. Daurès, B. Tretarre (Herault, France), F. Ménégoz (Isère, France), A.V. Guizard (Manche, France), M. Velten (Bas-Rhin, France), A. Buemi (Haut-Rhin, France), N. Raverdy (Somme, France), M. Sauvage, P. Grosclaude (Tarn, France); P. Kaatsch, B. Eisinger, R. Stabenow (Germany); D. Schuler, Z. Jakab, G. Borgulya (Hungary); L. Tryggvadottir, J.G. Jonasson, K. Bjarnadottir (Iceland); H. Comber, F. Dwane (Ireland); C. Magnani, G. Pastore (Piedmont, Italy), F. Pannelli, C. Pascucci (Marche, Macerata, Italy), S. Ferretti (Ferrara, Italy), E. Conti, V. Ramazzotti, M.C. Cercato (Latina Province, Italy), M. Vercelli, A. Puppo (Liguria, Italy),

P. Crosignani, G. Tagliabue, A. Tittarelli (Lombardy, Italy), V. De Lisi, P. Sgargi (Parma, Italy), R. Zanetti, S. Patriarca (Piedmont, Italy), R. Tumino (Ragusa, Italy), M. Budroni, D. Piras (Sassari, Italy), E. Paci, E. Crocetti (Tuscany, Italy), F. La Rosa, F. Stracci (Umbria, Italy), P. Zambon, S. Guzzinati (Veneto, Italy); M. Dalmas (Malta); J.W.W. Coebergh, J. van Dijck, A. Wit (Netherlands); F. Langmark, A. Johansen, A. Andersen (Norway); I. Plesko (Slovakia); M. Primic Žakelj, V. Pompe-Kirn (Slovenia); R. Peris-Bonet, B. Giner (Spain), E. Almar Marques, A. Mateos Ramos (Albacete, Spain), J. Ramon Quiros Garcia, A. Cañada Martínez (Asturias, Spain), I. Izarzugaza (Basque, Spain), A. Alemán Herrera (Canary Islands, Spain), P. Viladiu, R. Marcos, A. Izquierdo (Girona, Spain), C. Martínez Garcia (Granada, Spain), A. Obrador, I. Garau (Mallorca, Spain), E. Ardanaz (Navarra, Spain), J. Borràs, J. Galceran (Tarragona, Spain), J. de la Bárcena Guallar, M.C. Martos Jiménez (Zaragoza, Spain); G. Jundt (Basel, Switzerland), C. Bouchardy, M. Usel (Geneva, Switzerland), J. Allemann, H. Frick (Graubünden and Glarus, Switzerland), T. Fisch, S. Ess (St Gallen Appenzell, Switzerland), F. Joris, D. de Weck (Valais, Switzerland); S. Yalcin Eser (Izmir, Turkey); C.A. Stiller, M.F.G. Murphy, G.J. Draper (England and Wales, UK), A. Gavin, C. Fox, W. Hamill, R. Middleton (Northern Ireland, UK), D. Brewster, L. Bhatti, A. McDonald (Scotland, UK). We also acknowledge the collaborators from the other registries participating in ACCIS, whose data were not included in this paper.

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