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Leukaemia incidence and survival in children and adolescents in Europe during 1978–1997. Report from the Automated Childhood Cancer Information System project

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ABSTRACT

Leukaemias constitute approximately one-third of cancers in children (age 0–14 years) and 10% in adolescents (age 15–19 years). Geographical patterns (1988–1997) and time trends (1978–1997) of incidence and survival from leukaemias in children (n = 29,239) and adolescents (n = 1929) were derived from the ACCIS database, including data from 62 cancer registries in 19 countries across Europe. The overall incidence rate of leukaemia in children was 44 per million person-years during 1988–1997. Lymphoid leukaemia (LL) accounted for 81%, acute non-lymphocytic leukaemia (ANLL) for 15%, chronic myeloid leukaemia (CML) for 1.5% and unspecified leukaemia for 1.3% of cases. Adjusted for sex and age, incidence of childhood LL was significantly lower in the East and higher in the North than in the British Isles. The overall incidence among adolescents was 22.6 per million person-years. The incidence of LL was rising in children (0.6% per year) and adolescents (1.9% per year).

During 1988–1997 5-year survival of children with leukaemias was 73% (95% CI 72–74) and approximately 44% for infants and adolescents. Similar differences in survival between children and adolescents were observed for LL, much less so for ANLL. Survival differed between regions; prognosis was better in the North and West than the East. Remarkable improvements in survival occurred in most of the subgroups of patients defined by diagnostic subgroup, age, sex and geographic categories during the period 1978–1997. For children with ANLL most improvements in survival were observed in the 1990s.

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1. Introduction

Leukaemias comprise approximately one-third of all childhood cancers and one-tenth of adolescent cancers in industrialised countries.[1] As the most frequent and most prevalent childhood malignancy, leukaemias have generated much medical and societal interest. Since the late 1960s effective treatment became available for the largest leukaemic subgroup, acute lymphoblastic leukaemia (ALL),[2] which led to considerable improvement in survival in the following decades, but which varied across Europe.[3] Similar changes have been observed since the late 1980s for children with acute non-lymphocytic leukaemia (ANLL).[4]

Over the study period, several classification systems of leukaemias have been developed, based on morphological,[5] immunological[6] or cytogenetic[7] criteria. Cancer registries apply standard coding of the International Classification of Diseases for Oncology, which has been updated in 2000[8] in agreement with the WHO histological classification.[9] True comparative studies of incidence and survival were hampered by selective inclusion of cases (depending on classification criteria) and incomplete registration or follow-up related to strict interpretation of data privacy rules, especially in central and southern Europe.[4]

The increases in incidence of childhood ALL reported in many populations[10] have been attributed to a variety of factors that are often present simultaneously: higher diagnostic awareness, changing reproductive and perinatal factors, such as increasing parental age at birth, more firstborns or smaller families[11] and higher birth-weights.[12] In addition, changing socio-economic conditions may contribute to rising incidence trends in two ways. On the one hand, delayed exposure to infections, possibly due to widespread vaccinations and better housing[13] may lead to reduced immunity, counteracted by earlier attendance at day care. On the other hand, increasing mobility of populations may stimulate occurrence of childhood leukaemia as uncommon response to (probably) common infectious agent(s).[14,15] Both of these secular changes modify the response of the immune system. Lower death rates from infections may also contribute indirectly to the increase in incidence rates of common childhood leukaemia. By contrast, incidence rates of ANLL have hardly changed and the putative risk factors studied include alcohol use during pregnancy[16] and maternal history of miscarriage.[17]

Survival from leukaemia has improved in industrialised countries since the late 1960s and early 1970s, initially for ALL and since the 1980s also for ANLL.[2–4]

The Automated Childhood Cancer Information System (ACCIS), a collaborative project of European cancer registries, aims to collect, validate, present and interpret data on cancer incidence and survival of children and adolescents in Europe.[18] We now describe incidence and survival of children and adolescents registered with leukaemia in European cancer registries during 1978–1997, according to major morphological subgroups, interpret our findings and suggest avenues for research.

2. Material and methods

Detailed information on the ACCIS database is given elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. For this study, the analyses were based on data from the 62 population-based cancer registries in 19 countries listed in Table 1, which contributed to the ACCIS database and met the defined quality criteria for completeness, validity and comparability. Altogether 29,239 childhood and 1929 adolescent cases of leukaemia were extracted from the ACCIS database and included in various analyses. The analyses for children aged 0–14 years were based on data from both paediatric and general cancer registries, while those for adolescents aged 15–19 years were derived from general cancer registries (Table 1). Standard variables for each case included basic demographic data (age, sex, country or region of residence), information on the diagnosis (date and basis of diagnosis, morphology) and follow-up of the patient (date of last contact and vital status). Diagnoses were grouped according to the International Classification of Childhood Cancer (ICCC),[19] in which leukaemia is subdivided into several subgroups: lymphoid leukaemia (LL, subgroup Ia), acute non-lymphocytic leukaemia (ANLL, Ib), chronic myeloid leukaemia (CML, Ic), other specified leukaemias (Id) and unspecified leukaemias (Ie). Among children, more than 98% of the subgroup LL consisted of the acute lymphoblastic leukaemia (ALL, M-9821) and a few cases of 'unspecified lymphoid leukaemia' (M-9820, 1.2%). Subgroup Ia comprised also a few other rare types, the most common of those being chronic lymphocytic leukaemia (0.007%). We therefore used the abbreviations ALL and LL interchangeably to denote subgroup Ia.

The results are reported by gender and age-group (0, 1–4, 5–9, 10–14 and 15–19 years). To examine geographical differences in incidence and survival we grouped cancer registries into five regions (British Isles, East, North, South and West) (Table 1). The populations covered for children and for adolescents differed for all regions except the North as well as Slovenia, Slovakia and Estonia. Using data from the cancer registries with a sufficiently long registration period, time trends were studied by period of diagnosis (1978–1982, 1983–1987, 1988–1992, and 1993–1997). The distribution of cases over the periods and regions, together with selected data quality indicators are shown in Table 2. Detailed data on incidence and survival are given for the most recent period 1988–1997.

Incidence rates were calculated as the average annual number of cases per million person-years and age-standardisation (ASR) was performed by the direct method from age-specific incidence rates for age-groups 0, 1–4, 5–9 and 10–14 years, using the weights of the World standard population. Variations in incidence between the five European regions were examined in a Poisson regression model adjusted for sex and age group, as applicable, with the British Isles as the reference region. Incidence time trends were examined using Poisson regression models of rate on calendar year, adjusted for sex, age group and region (as applicable). Changes in rates were expressed as average annual percent change (AAPC).

Survival was estimated by the actuarial life-table method[20] and confidence intervals were based on computation of standard error according to Greenwood.[21] Differences between survival curves were evaluated using log-rank test or log-rank test for trend. The cases with zero follow-up time were excluded from survival analyses (mostly those registered from

Table 1 – Datasets contributed by European cancer registries for analyses of leukaemia in children (age 0–14 years) and adolescents (age 15–19 years), with indicators of coverage, data quality and follow-up (Source: ACCIS)

Region	Coverage	Cases					Basis of diagnosis			Follow-up				Notes
	Registry	Period	Time-trend	Age 0–19 years	Age 0–14 years	NOS	MV	DCO	Unknown	1+ days	5+ years	Median	Closing date	
				n	%	%	%	%	%	%	%	Years		
British Isles	IRELAND, National	1994–1997		158	80	2	100	0	0	100	0	2.8	31.12.1998	
	UNITED KINGDOM, England & Wales	1978–1995	+	6851	100	1	99	<1	<1	98	99	12.0	31.1.2001	P
	UNITED KINGDOM, Northern Ireland	1993–1996		97	76	9	85	0	0	100	4	1.5	31.12.1999	
	UNITED KINGDOM, Scotland	1978–1997	+	969	82	<1	93	<1	0	99	80	9.9	31.12.1999	
East	BELARUS, National	1989–1997		792	100	3	100	0	0	99	69	6.6	1.9.2000	P
	ESTONIA, National	1978–1997	+	265	86	22	100	<1	0	95	56	6.0	31.12.1998	
	HUNGARY, National	1978–1997	+	1499	100	<1	100	–	0	99	88	11.5	1.1.2000	P
	SLOVAKIA, National	1978–1997	+	1090	86	3	100	<1	0	93	68	8.2	31.12.1997	
	GERMANY, NCR (only former East)	1978–1989	+	1644	80	4	100	0	0	79	60	6.0	31.12.1987	S
North	DENMARK, National	1978–1997	+	999	84	2	98	<1	2	97	75	9.1	31.12.1997	
	FINLAND, National	1978–1997	+	1097	85	2	99	0	1	97	73	8.8	31.12.1998	
	ICELAND, National	1978–1997	+	62	84	5	100	0	0	98	89	12.6	31.12.2000	
	NORWAY, National	1978–1997	+	839	87	3	99	<1	0	100	77	10.9	1.1.2000	
South	ITALY, Piedmont paediatric	1978–1997	+	658	100	2	99	<1	0	100	87	11.0	31.12.1999	P o1
	ITALY, Marche	1990–1997		81	100	4	94	–	6	100	65	6.2	30.9.2000	P o2
	ITALY, Ferrara	1991–1995		12	58	17	92	8	0	92	50	5.1	31.12.1998	
	ITALY, Latina	1983–1997	+	67	81	4	100	0	0	97	71	6.7	31.12.1998	
	ITALY, Liguria	1988–1995		39	82	0	92	0	0	100	78	8.2	15.4.2000	
	ITALY, Lombardy	1978–1997	+	170	71	3	97	2	0	97	64	6.7	23.9.1999	
	ITALY, Macerata	1991–1997		18	0	11	94	–	6	100	36	4.9	30.9.2000	o2
	ITALY, Parma	1978–1995	+	60	78	13	93	0	0	100	93	11.5	1.4.1999	
	ITALY, Piedmont general	1988–1997		79	0	0	100	0	0	100	87	8.1	31.5.2001	o1
	ITALY, Ragusa	1983–1997	+	54	65	11	100	0	0	100	76	9.5	30.3.2000	
	ITALY, Sassari	1992–1995		16	75	0	100	0	0	100	71	5.3	30.12.1999	
	ITALY, Tuscany	1988–1997		89	76	6	24	0	0	100	47	4.5	31.12.1998	
	ITALY, Umbria	1994–1996		24	79	0	79	0	0	100	35	4.5	31.12.1999	
	ITALY, Veneto	1990–1996		121	72	5	95	<1	0	97	53	5.2	31.12.1998	
	MALTA, National	1991–1997		29	76	0	100	0	0	97	75	5.8	31.12.1999	
	SLOVENIA, National	1978–1997	+	351	83	2	100	0	0	100	80	9.9	31.12.1999	
	SPAIN, National	1990–1995		365	100	2	97	0	3	99	95	6.3	31.12.2000	P Z o3
	SPAIN, Albacete	1991–1997		29	90	14	93	3	0	97	68	7.8	15.9.2000	
	SPAIN, Asturias	1983–1997	+	135	77	20	96	4	0	93	64	6.4	31.12.1997	
	SPAIN, Basque Country	1988–1994		140	81	10	96	4	0	95	100	9.8	31.12.2000	o3
	SPAIN, Canary Islands	1993–1996		50	82	4	86	4	8	–	–	–	–	
	SPAIN, Girona	1994–1997		18	72	6	100	0	0	100	0	1.3	31.12.1997	o3
	SPAIN, Granada	1988–1997		54	100	0	100	0	0	100	61	6.0	31.12.1999	G
	SPAIN, Mallorca	1988–1995		49	84	2	100	0	0	94	93	7.7	31.12.1998	o3
	SPAIN, Navarra	1978–1996	+	95	88	7	95	5	0	93	72	11	31.12.1997	o3

(*continued on next page*)

Table 1 – *continued*

Region	Coverage / Registry	Cases: Period	Time-trend	Age 0–19 years *n*	Age 0–14 years %	NOS %	Basis of diagnosis: MV %	DCO %	Unknown %	Follow-up: 1+ days %	5+ years %	Median Years	Closing date	Notes
	SPAIN, Tarragona	1983–1997	+	78	78	4	99	0	1	95	63	6.8	31.12.1998	o3
	SPAIN, Zaragoza	1978–1996	+	146	79	8	93	7	0	93	78	9.0	31.12.1996	o3
	TURKEY, Izmir	1993–1996		136	85	<1	94	–	1	–	–	–	–	
West	FRANCE, Brittany	1991–1997		157	100	3	97	–	3	99	40	4.3	1.1.2000	P
	FRANCE, Lorraine	1983–1997	+	286	100	2	100	–	0	100	67	6.7	1.1.1999	P
	FRANCE, PACA	1984–1996	+	446	100	0	100	–	0	91	31	1.5	31.3.1998	P
	FRANCE, Rhone Alpes	1988–1997		419	100	<1	99	–	<1	92	55	4.9	1.6.2000	P o4
	FRANCE, Doubs	1978–1996	+	99	81	3	75	–	3	97	32	2.4	1.6.2001	
	FRANCE, Herault	1988–1997		80	85	0	100	–	0	–	–	–	–	
	FRANCE, Isere	1979–1997	+	206	85	2	99	–	0	–	–	–	–	o4
	FRANCE, Manche	1994–1996		12	83	0	100	–	0	92	50	4.1	31.5.2000	S
	FRANCE, Bas-Rhin	1978–1996	+	155	82	6	100	–	0	100	69	7.3	31.12.1997	
	FRANCE, Haut-Rhin	1988–1997		66	82	6	88	–	0	50	95	7.7	31.12.1995	S
	FRANCE, Somme	1983–1996	+	63	87	5	95	–	2	100	51	5.3	15.8.2000	
	FRANCE, Tarn	1983–1997	+	40	95	3	100	–	0	–	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	4162	100	<1	100	–	0	96	35	3.8	31.12.1998	P
	GERMANY, GCCR (only former West)	1983–1990	+	3215	100	1	100	–	0	98	91	9.8	31.12.1998	P
	NETHERLANDS, National	1989–1995		915	0	5	100	–	0	83	73	6.5	31.12.1998	S o5
	NETHERLANDS, Eindhoven	1978–1997	+	182	0	2	97	–	2	99	74	8.6	1.7.1999	o5
	NETHERLANDS, DCOG	1978–1997	+	2199	100	0	99	–	0	99	81	8.8	1.1.2000	P o5
	SWITZERLAND, Basel	1983–1997	+	51	82	4	100	–	0	100	73	10.1	30.6.2000	
	SWITZERLAND, Geneva	1978–1997	+	63	84	0	100	0	0	100	71	8.7	31.12.1999	
	SWITZERLAND, Graubunden & Glarus	1989–1997		19	79	0	100	0	0	100	50	5.0	25.5.2000	
	SWITZED, St. Gallen Appenzell	1983–1997	+	82	87	5	99	1	0	99	42	2.5	1.2.2001	
	SWITZERLAND, Valais	1989–1997		22	95	0	100	0	0	59	100	8.5	1.12.1998	S

–, not applicable; +, included in time trend analyses; 1+ days, cases followed-up for 1 or more days and included in survival analysis, 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, registrations from death certificate only; DCOG, Dutch Childhood Oncology Group (since 2003); formerly DCLSG (Dutch Childhood Leukaemia Study Group); the exclusive contributor to to all analyses in children (age 0–14 years). Data from other two Dutch registries included in analyses for adolescents only, according to data availability. See Steliarova-Foucher, Kaatsch, Lacour and colleagues [this issue]; G, general cancer registry, only contributing data for age-range 0–14 years; GCCR, National German Childhood Cancer Registry (until 1990, only West; since 1991 for reunified Germany); MV, microscopically verified cases; *n*, number of cases; NCR, National Cancer Registry of the former German Democratic Republic. Data for 1978–1987 contributed to analyses of time trends for Europe as a whole. Data on children for 1988–1989 were pooled with GCCR and included in West. See Steliarova-Foucher, Kaatsch, Lacour and colleagues [this issue]; NOS, unspecified cases (ICD-O-2 histology codes M-9800 to M-9804); o1–o5; overlapping registration areas: for the overlapping years, data from the registry with larger coverage are included i' each analysis, according to availability; P, paediatric cancer registry; age range of 0–14 for all registrations; PACA, Provence, Alps, Côte d'Azur; S, survival analyses 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 of leukaemia included in the analyses of incidence and survival and indicators of data quality by region and diagnostic period in children (0–14 years) and adolescents (15–19 years) in Europe (Source: ACCIS)

Region	Period	Children (age 0–14 years)							Adolescents (age 15–19 years)						
		Cases	Basis of diagnosis				Follow–up		Cases	Basis of diagnosis				Follow–up	
		n	NOS %	MV %	DCO %	Unknown %	1+ days %	5+ years %	*n*	NOS %	MV %	DCO %	Unknown %	1+ days %	5+ years %
Europe[a]	1978–1982	4987	2	99	<1	<1	97	99	450	12	96	<1	1	94	99
	1983–1987	7187	2	99	<1	<1	98	91	422	6	98	<1	<1	96	79
	1988–1992	7531	1	99	<1	<1	98	90	322	4	98	<1	0	97	94
	1993–1997	6985	1	99	<1	<1	97	37	297	3	96	1	<1	95	21
British Isles	1978–1982	2031	1	98	<1	<1	98	99	38	0	92	0	0	100	100
	1983–1987	1990	1	98	<1	1	99	99	40	5	98	0	0	98	100
	1988–1992	2172	<1	98	<1	<1	98	99	46	0	96	0	0	98	100
	1993–1997	1457	1	98	<1	<1	99	89	46	2	87	2	0	96	52
East	1978–1982	725	6	99	<1	0	94	100	48	17	98	2	0	88	100
	1983–1987	662	2	100	0	0	98	99	35	17	100	0	0	94	100
	1988–1992	683	1	100	0	0	99	99	53	13	98	2	0	92	100
	1993–1997	596	1	100	<1	0	97	38	52	2	98	2	0	87	0
North	1978–1982	623	3	99	<1	<1	97	99	130	5	96	0	4	95	100
	1983–1987	674	2	99	0	<1	97	99	119	6	96	2	3	97	100
	1988–1992	598	1	100	0	0	99	98	104	3	99	0	0	97	98
	1993–1997	651	3	97	<1	2	99	25	98	1	99	0	1	96	18
South	1978–1982	389	5	96	3	0	97	99	42	7	90	2	0	95	100
	1983–1987	418	6	99	<1	<1	98	99	64	6	98	2	0	94	100
	1988–1992	419	5	99	<1	0	98	97	71	4	99	1	0	99	97
	1993–1997	343	3	100	<1	0	99	39	68	9	96	3	0	97	11
West	1978–1982	687	<1	98	0	<1	99	98	31	6	90	0	0	100	75
	1983–1987	2890	1	100	<1	0	98	92	40	0	100	0	0	100	75
	1988–1992	3434	<1	100	0	0	97	81	48	2	96	0	0	100	74
	1993–1997	3938	<1	100	0	<1	96	21	33	0	100	0	0	100	10

1+ days, cases included in survival analyses, as a percentage of cases in the registries with follow-up data; 5+ years, 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; MV, microscopically verified cases; *N*, number of cases; NOS, unspecified cases, including histology codes M-9800 to M-9804.
a Europe includes data of former GDR, which are not included in any other region.

death-certificate-only, DCO), but their proportion was generally small (Table 2) in the countries with access to nominative death records. For privacy reasons death certificates did not serve as a source of registrations in France, Germany, Hungary, the Netherlands and some registries in other countries (Table 1).

3. Results

3.1. *Incidence*

Based on 17,065 cases (Table 3), the overall ASR incidence rate of leukaemia in children aged 0–14 years and diagnosed in Europe during 1988–1997 was 44 per million person years (Table 4). Lymphoid leukaemia (LL) or acute lymphoblastic leukaemia (ALL) accounted for 81% of cases, 15% of cases were ANLL, while the other three leukaemia subgroups were very rare (1.5% CML, 1.3% unspecified and less than 0.5% other specified). These proportions varied slightly with age (Fig. 1). The spectrum of the leukaemia subgroups in children was fairly constant across the regions (Fig. 1(b)). In a Poisson regression model adjusted for sex and age incidence was significantly lower in the East (incidence rate ratio, IRR = 0.9, 95% CI 0.9–1.0) and significantly higher in the North (IRR = 1.1, 95% CI 1.0–1.2) and South (IRR = 1.1, 95% CI 1.0–1.2) than in the reference region, the British Isles.

Based on 1006 adolescents registered in the contributing registries in 1988–1997 the overall age-specific incidence was 22.6 per million person-years. In adolescent boys, ALL represented approximately 60% and ANLL approximately 30% of all leukaemias, these proportions being 50% and 35%, respectively, among girls with ANLL. Across the regions, the proportion of ALL varied between 45% and 60% (Fig. 1(c)). Adjusted for sex, incidence of leukaemias was lower in the East (IRR = 0.7, 95% CI 0.5–0.9), North (IRR = 0.7, 95% CI 0.6–0.9) and West (IRR = 0.7, 95% CI 0.6–0.9) compared with the British Isles as reference region.

A geographical pattern of incidence seen for all leukaemias was also observed for the largest diagnostic subgroup, ALL in children. In adolescents, incidence rate ratio for ALL was lower only for the East (IRR = 0.6, 95% CI 0.4–0.8) and marginally for the North (IRR 0.8, 95% CI 0.6–1.0).

Incidence rates of ALL were highest among children aged 1–4 years, halving at age 5–9 years and decreasing further to approximately 25% in infants and children aged 10–14 years and slightly further in adolescents (Table 4). Age-specific incidence during 1988–1997 was remarkably similar across Europe (Fig. 2(a)), except for the ages 2–4 years, with a clearly lower incidence in the East, for both sexes (Table 3, Fig. 2(a)). Incidence in boys was generally higher than in girls, and the M/F sex ratio was increasing across the age groups from slightly under 1.0 in infants to 1.9 in adolescents (Table 4).

Incidence rates of ANLL were much lower than those of ALL (Table 4(b)), with a U-shaped age-specific curve of incidence and average rates being higher in very young children than in adolescents (Fig. 2(b)). Compared with the reference region (the British Isles), incidence of ANLL was significantly lower in the East (IRR 0.8, 95% CI 0.7–0.9) for children, and in the West (IRR 0.7, 95% CI 0.5–0.9) for adolescents. No other significant differences in incidence existed between geographical regions as delineated.

Incidence rate of chronic myeloid leukaemia was less than 1 per million in children and 1.6 per million in adolescents

Table 3 – Numbers of cases of leukaemia in children (age 0–14) and adolescents (age 15–19), diagnosed in Europe in 1988–1997 and included in the analyses of incidence (Source: ACCIS)

	All leukaemias	LL (Ia)	ANLL (Ib)	CML (Ic)	Other specified (Id)	Not specified (Ie)
Children						
Total Europe	17065	13862	2565	342	76	220
Age 0	898	447	349	40	13	49
Age 1–4 years	8043	7031	827	102	15	68
Age 5–9 years	4831	4055	630	74	23	49
Age 10–14 years	3293	2329	759	126	25	54
Boys	9551	7831	1351	212	41	116
Girls	7514	6031	1214	130	35	104
British Isles	3830	3108	587	83	10	42
East	2071	1687	269	59	19	37
North	1249	1016	174	26	7	26
South	1681	1343	231	40	17	50
West	8234	6708	1304	134	23	65
Adolescents						
Total Europe	1006	562	312	70	13	49
Boys	628	372	178	44	7	27
Girls	378	190	134	26	6	22
British Isles	146	80	48	9	2	7
East	105	49	36	9	3	8
North	202	113	67	17	1	4
South	310	176	87	21	4	25
West	243	147	74	14	3	5

LL, lymphoid leukaemia (mostly acute lymphoblastic leukaemia); ANLL, acute non-lymphocytic leukaemia; CML, chronic myeloid leukaemia.

Table 4 – Regional variation of incidence rates of leukaemias in children (age 0–14 years) and adolescents (age 15–19 years) across Europe during 1988–1997, per million person-years. ASR, age-standardised rate (Source: ACCIS)

	Children		Rate by age group				Adolescents	
	n cases	ASR	0	1–4 years	5–9 years	10–14 years	*n* cases	Rate
(a) Lymphoid leukaemia (mostly acute lymphoblastic leukaemia)								
Europe								
Boys	7831	39.4	16.7	69.5	33.7	19.5	372	16.4
Girls	6031	32.2	17.4	60.7	24.9	13.9	190	8.7
Both sexes	13862	35.9	17.0	65.2	29.4	16.8	562	12.6
British Isles								
Boys	1780	39.2	17.2	72.1	31.1	18.8	53	19.8
Girls	1328	30.9	19.0	58.1	22.7	14.1	27	10.6
Both sexes	3108	35.1	18.1	65.3	27.0	16.5	80	15.3
East								
Boys	950	35.1	14.5	59.5	31.8	18.3	27	9.5
Girls	737	28.9	20.4	50.8	23.7	13.6	22	8.1
Both sexes	1687	32.1	17.4	55.2	27.8	16.0	49	8.8
North								
Boys	541	40.4	18.3	75.3	30.5	20.1	77	15.4
Girls	475	37.7	13.9	76.1	28.1	13.7	36	7.5
Both sexes	1016	39.1	16.2	75.7	29.4	17.0	113	11.5
South								
Boys	776	42.7	19.1	75.9	37.7	19.2	110	21.5
Girls	567	33.4	14.7	66.0	21.9	16.1	66	11.7
Both sexes	1343	38.2	17.0	71.1	30.0	17.7	176	15.0
West								
Boys	3784	39.8	16.4	69.0	35.0	20.3	108	17.1
Girls	2924	32.8	16.7	61.5	26.5	13.5	39	6.5
Both sexes	6708	36.4	16.5	65.4	30.9	17.0	147	11.9
(b) Acute non-lymphocytic leukaemia								
Europe								
Boys	1351	6.6	12.5	8.0	4.8	5.6	178	7.8
Girls	1214	6.3	14.1	7.3	4.3	5.4	134	6.2
Both sexes	2565	6.5	13.3	7.7	4.6	5.5	312	7.0
British Isles								
Boys	323	6.9	11.6	8.3	5.0	6.3	24	8.9
Girls	264	6	13.2	7.1	3.7	5.5	24	9.4
Both sexes	587	6.5	12.4	7.7	4.4	5.9	48	9.2
East								
Boys	150	5.3	5.4	6.4	4.1	5.3	20	7.1
Girls	119	4.4	7.7	4.7	3.5	4.2	16	5.9
Both sexes	269	4.8	6.5	5.6	3.8	4.8	36	6.5
North								
Boys	82	6.0	8.1	9.6	3.5	4.5	36	7.2
Girls	92	7.1	21.4	9.8	3.7	4.5	31	6.5
Both sexes	174	6.6	14.6	9.7	3.6	4.5	67	6.8
South								
Boys	114	5.9	13.0	5.7	4.9	5.2	50	8.5
Girls	117	6.4	15.6	6.9	4.8	5.3	37	6.6
Both sexes	231	6.1	14.3	6.3	4.9	5.2	87	7.5
West								
Boys	622	7.1	15.4	8.5	5.1	5.6	48	7.6
Girls	682	6.8	14.8	7.8	4.8	5.8	26	4.3
Both sexes	1304	7.0	15.1	8.2	5.0	5.7	74	6.0
(c) Chronic myeloid leukaemia								
Europe								
Boys	212	1.0	1.9	1.4	0.5	1.0	44	1.9
Girls	130	0.6	1.2	0.5	0.6	0.8	26	1.2
Both sexes	342	0.8	1.5	0.9	0.5	0.9	70	1.6

(*continued on next page*)

Table 4 – *continued*

	Children		Rate by age group				Adolescents	
	n cases	ASR	0	1–4 years	5–9 years	10–14 years	*n* cases	Rate
British Isles								
Boys	51	1.1	1.5	1.9	0.6	0.7	3	1.1
Girls	32	0.7	0.6	0.6	0.5	1.0	6	2.3
Both sexes	83	0.9	1.1	1.3	0.6	0.9	9	1.7
East								
Boys	41	1.5	2.4	2.1	0.4	1.7	7	2.5
Girls	18	0.6	1.9	0.1	0.6	0.8	2	0.7
Both sexes	59	1.1	2.2	1.1	0.5	1.3	9	1.6
North								
Boys	18	1.4	5.1	2.9	0	0.4	12	2.4
Girls	8	0.6	0	0.8	0.2	0.9	5	1.0
Both sexes	26	1.0	2.6	1.9	0.1	0.7	17	1.7
South								
Boys	26	1.2	0.9	1.1	0.8	1.9	13	2.2
Girls	14	0.7	0.9	0.7	0.8	0.7	8	1.4
Both sexes	40	1.0	0.9	0.9	0.8	1.3	21	1.8
West								
Boys	58	0.8	1.6	0.8	0.5	0.8	9	1.4
Girls	76	0.6	1.5	0.4	0.6	0.6	5	0.8
Both sexes	134	0.7	1.5	0.6	0.5	0.7	14	1.1

ASR, age-standardised rate per million person-years.

(Table 4(c)). Age-specific incidence rates were highest in infants and adolescents and lowest in age group 5–9 years. Overall, CML occurred more frequently in boys, with a sex ratio of 1.6 both in children and adolescents. For the whole of Europe we observed a slight female predominance, with sex ratio of 0.8 at age 5–9 years, although the age-sex-specific pattern differed across the regions. There were some differences in overall incidence among geographical regions, but a clear pattern did not emerge, due to relatively few cases, especially among adolescents (Table 4(c)).

3.2. *Time trends*

Analyses of incidence time trends were based on 26,690 children and 1491 adolescents. Between 1978 and 1997 the incidence of leukaemia increased in children by approximately 0.6% per year on average, exclusively due to the 0.8% annual increase in acute lymphoblastic leukaemia (Table 5(a)). The ASR for all childhood leukaemia changed from 40 per million in 1978–1982 to 45 per million in 1993–1997. In adolescents, the annual incidence rates remained relatively stable at around 22 per million, while those of ALL were rising by approximately 2% per year (Table 5(b)). Clear changes in incidence rates in the other leukaemia subgroups were observed.

Table 6(a) shows that the ASRs of ALL were increasing in the age-range 0–14 years over the four periods in Europe and in each geographical region. In separate region-specific models, adjusted for age group and sex, the increase for children was observed in all regions except the North (AAPC = 0.3%, $P = 0.4$). Adjusted for region and age group, incidence increased both in boys (AAPC = 0.8%, $P < 0.0001$) and in girls (AAPC = 0.7%, $P < 0.0001$). The age-specific incidence rates of ALL were increasing relatively regularly in all age groups except infants (Table 6(a)). Among adolescents an increase was observed in boys (AAPC = 2.2%, $P = 0.01$), but not in girls (AAPC = 1.1, $P = 0.3$); based on models adjusted for region. The two regions with individually increasing rates in adolescents were the British Isles (AAPC = 3.8%, $P = 0.04$) (based on data from Scotland only) and the South (AAPC = 3.7%, $P = 0.03$); in region-specific models adjusted for sex.

Tables 5 and 6(b and c) also exhibit an absence of incidence time trend in the subgroups of ANLL and CML.

3.3. *Survival*

There were 16,166 children diagnosed with leukaemia during 1988–1997 and followed-up for vital status through the contributing cancer registries shown in Table 1. Five-year survival for these children was estimated at 73%, (95% CI 72–74), being slightly less favourable ($P < 0.0001$) for the 9075 boys (72%, 95% CI 71–73), than for the 7091 girls (75%, 95% CI 74–76). Within the age-range 0–14 years, survival of children in each age group differed significantly from that in the other age groups. Compared with the age range 1–4 years, survival rates of infants and older children were significantly lower ($P < 0.0001$): 5-year survival was 44% (95% CI 40–47) for 269 infants, 80% (95% CI 79–81) for 4731 children aged 1–4 years, 75% (95% CI 73–76) for 2592 children aged group 5–9 years and 62% (95% CI 60–64) for 1527 children of 10–14 years. Five-year survival of 1006 adolescents diagnosed with leukaemia in the same

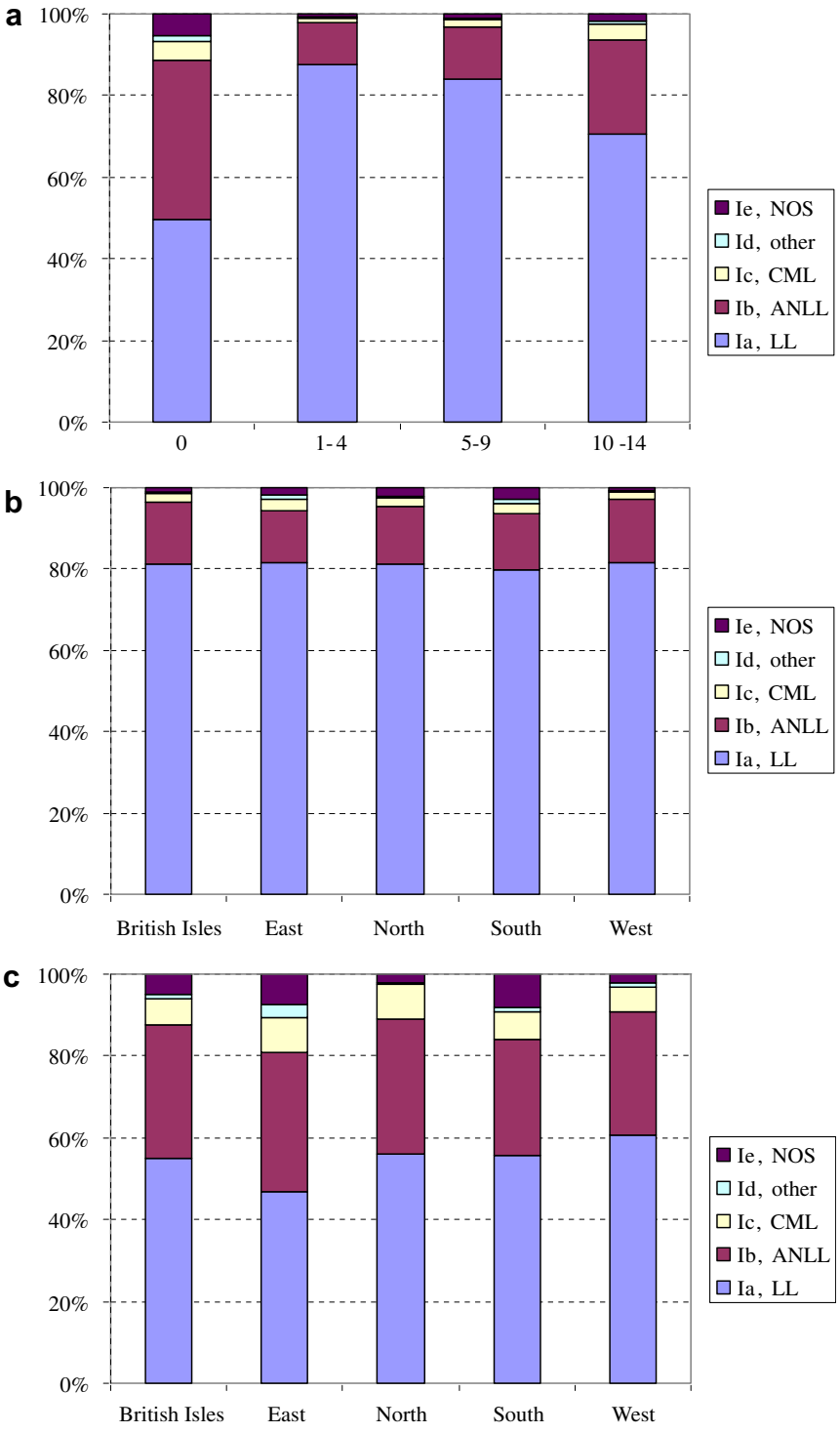

Fig. 1 – Distribution of leukaemia subgroups in Europe, 1988–1997, across (a) age groups and (b) regions in children (0–14 years) and (c) in adolescents (15–19 years) in regions. Ia, LL, lymphoid leukaemia (mostly acute lymphoblastic leukaemia); Ib, ANLL, acute non-lymphocytic leukaemia; Ic, CML, chronic myeloid leukaemia; Id, Other, other specified leukaemia; Ie, NOS, leukaemia, not specified. Source: ACCIS.

period (but somewhat different registration areas, Table 1) equalled that of infants: 44%, 95% CI 36–52).

Across Europe, survival rates of ALL diagnosed in 1988–1997 were better for children than for adolescents (Fig. 3(a and b)), yet with similar variability between the age groups as for leukaemia overall across Europe and as a whole (Table 7(a)). Survival rates in the East were generally lower than in other regions in each of the age groups. Elsewhere,

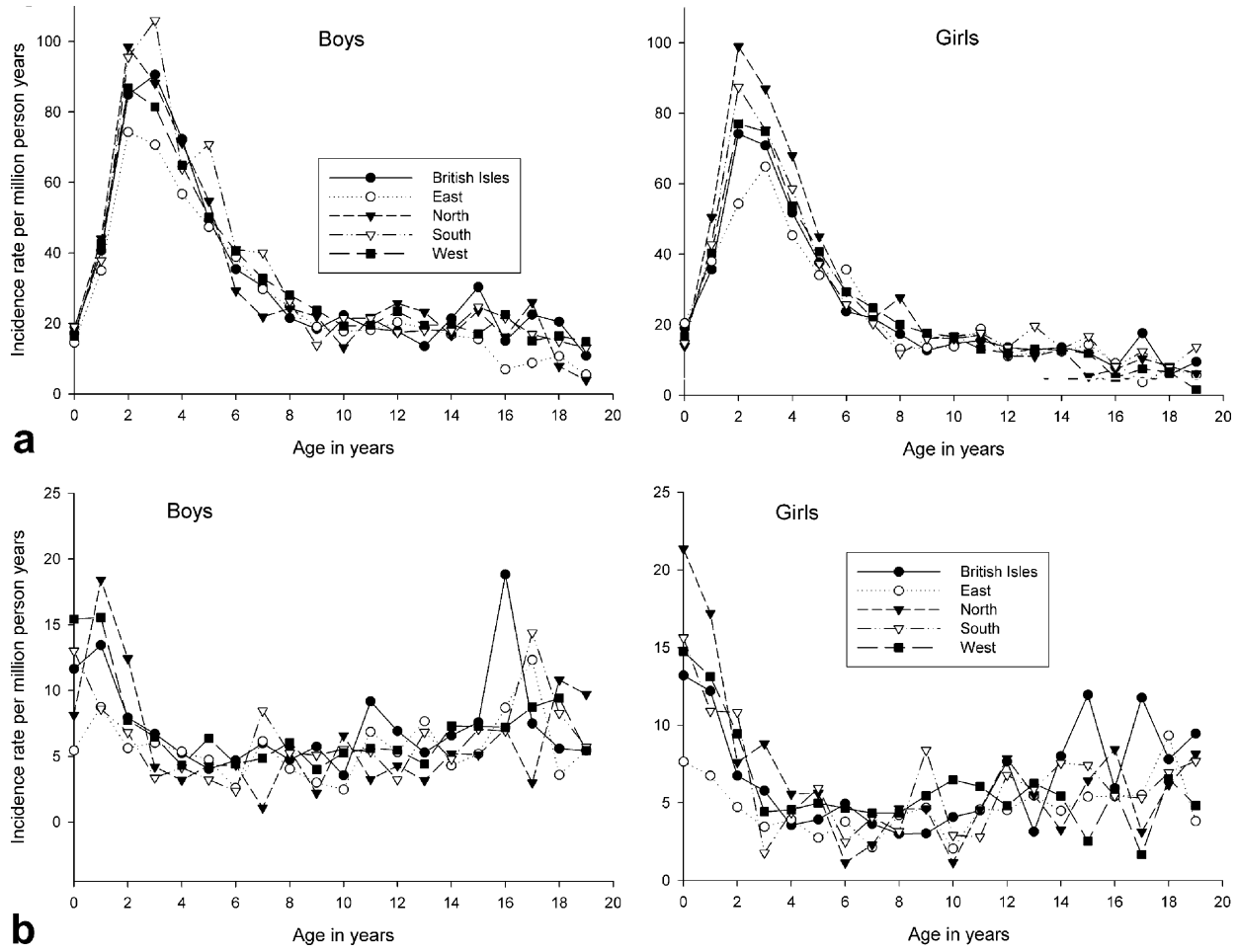

Fig. 2 – Age-specific incidence rates (per million person-years) of leukaemia among children (0–14 years) and adolescents (15–19 years) in Europe, 1988–1997; (a) lymphoid leukaemia, (b) acute non-lymphocytic leukaemia. Source: ACCIS.

Table 5 – Numbers of cases (*n*) with leukaemia registered in Europe during 1978–1997 in children (0–14 years) and adolescents (15–19 years) included in the analyses of incidence time trends, indicator of temporal change, average annual percent change (AAPC) and the probability (P) of observed AAPC being chance (Source: ACCIS)

	n	AAPC	*P*
(a) Children			
All Leukaemias	26690	0.6	<0.0001
Lymphoid leukaemia (ALL)	21552	0.8	<0.0001
Acute non-lymphocytic leukaemia	4096	0.5	0.11
Chronic myeloid leukaemia	552	–0.4	0.64
Other specified leukaemias	92	–0.6	0.78
Unspecified leukaemia	398	–1.0	0.32
(b) Adolescents			
All Leukaemias	1491	0.6	0.22
Lymphoid leukaemia (ALL)	748	1.9	0.008
Acute non-lymphocytic leukaemia	494	0.4	0.66
Chronic myeloid leukaemia	125	–0.6	0.74
Other specified leukaemias	20	–0.5	0.91
Unspecified leukaemia	104	–2.3	0.33

AAPC and P were derived from a Poisson regression model adjusted for sex and region and in children also for age group.

survival was significantly higher for children in the North and West than in the British Isles and South ($P < 0.0001$), but varied little for adolescents among these four regions ($P = 0.66$).

Survival for ANLL was lower than for ALL in both children and adolescents (Table 7(a and b)), while the prognosis for children was better than for adolescents (Fig. 3(c and d)). In

Table 6 – Numbers of cases (*n*) and incidence rates (per million person-years) of leukaemias in children (0–14 years) and adolescents (15–19 years) across Europe, 1978–1997 (Source: ACCIS)

Region	Period	Children		Rate by age group				Adolescents	
		n	ASR	0	1–4 years	5–9 years	10–14 years	*n*	Rate
(a) Lymphoid leukaemia (mostly acute lymphoblastic leukaemia)									
Europe	1978–82	3948	31.8	17.5	57.0	26.2	14.9	175	8.5
	1983–87	5799	33.8	16.6	61.2	28.1	15.6	226	10.7
	1988–92	6078	35.4	16.0	64.9	29.0	16.1	184	12.9
	1993–97	5727	37.2	17.6	67.6	30.3	17.5	163	12.3
British Isles	1978–82	1634	32.0	15.3	58.1	26.3	15.0	17	7.5
	1983–87	1596	32.5	17.5	59.4	26.3	14.7	25	11.5
	1988–92	1759	34.8	17.8	66.3	26.2	15.2	33	18.4
	1993–97	1190	35.7	18.3	63.4	28.3	18.9	19	12.1
East	1978–82	532	27.4	19.0	47.0	21.5	15.4	16	6.2
	1983–87	516	27.5	16.8	47.3	25.3	11.6	13	5.3
	1988–92	550	31.4	15.1	54.0	26.9	16.6	23	8.6
	1993–97	490	31.2	13.5	54.3	28.0	14.9	26	9.1
North	1978–82	497	35.8	23.7	64.4	27.7	17.6	69	12.5
	1983–87	552	42.7	22.3	76.4	36.7	18.9	72	13.2
	1988–92	493	39.2	14.9	77.2	30.9	15.1	52	10.3
	1993–97	523	39.0	17.4	74.3	28.5	18.9	61	12.9
South	1978–82	293	34.9	13.1	60.8	29.9	18.7	15	8.8
	1983–87	319	34.2	21.8	62.1	27.6	15.1	34	12.9
	1988–92	310	38.7	16.1	73.4	31.2	16.2	46	17.5
	1993–97	283	40.9	24.5	78.8	30.0	16.9	34	14.4
West	1978–82	564	34.8	23.8	64.6	28.1	13.4	15	10.0
	1983–87	2365	36.1	14.9	66.7	28.5	17.5	28	12.1
	1988–92	2794	36.2	15.8	64.7	31.2	17.0	30	14.4
	1993–97	3241	38.2	17.4	69.7	31.7	17.3	23	13.4
(b) Acute non-lymphocytic leukaemia									
Europe	1978—1982	769	5.8	9.7	6.6	4.7	5.2	166	8.0
	1983—1987	1112	6.2	10.8	7.6	4.3	5.7	138	6.5
	1988—1992	1185	6.7	13.8	8.3	4.6	5.6	91	6.4
	1993—1997	1030	6.5	13.4	7.7	4.5	5.6	99	7.5
British Isles	1978–1982	319	5.7	11.1	6.4	4.1	5.6	18	8.0
	1983–1987	318	6.2	8.2	8.0	4.3	5.7	11	5.1
	1988–1992	337	6.5	11.9	8.3	4.4	5.6	9	5.0
	1993–1997	220	6.4	13.9	6.7	4.2	6.7	20	12.7
East	1978–1982	123	6.3	11.0	7.6	5.1	5.1	17	6.6
	1983–1987	110	5.6	7.6	6.2	4.8	5.4	13	5.3
	1988–1992	102	5.6	8.0	6.9	4.7	4.5	16	6.0
	1993–1997	71	4.4	4.2	6.2	3.2	3.8	20	7.0
North	1978–1982	91	6.2	9.0	7.2	5.6	5.1	41	7.4
	1983–1987	94	7.3	21.1	10.0	3.9	4.6	35	6.4
	1988–1992	82	6.4	15.9	9.8	2.7	4.3	38	7.5
	1993–1997	92	6.8	13.3	8.7	4.4	4.7	29	6.1
South	1978–1982	62	6.9	6.0	7.8	6.4	6.8	18	10.5
	1983–1987	63	6.3	7.3	8.4	5.7	4.7	21	8.0
	1988–1992	71	8.4	18.1	10.1	6.4	6.2	15	5.7
	1993–1997	45	5.9	13.4	5.9	3.2	6.9	22	9.3
West	1978–1982	90	5.2	8.6	6.6	3.9	4.1	10	6.7
	1983–1987	440	6.4	12.1	7.2	4.3	6.3	10	4.4
	1988–1992	552	7.0	15.6	8.1	4.9	6.1	13	6.3
	1993–1997	602	6.9	14.9	8.2	5.0	5.6	8	4.7
(c) Chronic myeloid leukaemia									
Europe	1978–1982	125	0.97	1.2	1.5	0.49	0.90	47	2.3
	1983–1987	145	0.80	1.1	1.0	0.55	0.82	27	1.3
	1988–1992	147	0.84	1.6	1.1	0.55	0.65	30	2.1
	1993–1997	135	0.84	1.8	0.8	0.48	1.0	21	1.6

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Table 6 – *continued*

Region	Period	Children		Rate by age group				Adolescents	
		n	ASR	0	1–4 years	5–9 years	10–14 years	*n*	Rate
British Isles	1978–1982	47	0.91	1.5	1.6	0.27	0.75	2	0.9
	1983–1987	49	0.97	0.85	1.5	0.67	0.75	1	0.5
	1988–1992	49	0.95	1.1	1.4	0.74	0.66	4	2.2
	1993–1997	29	0.86	1.3	1.2	0.43	0.90	4	2.5
East	1978–1982	21	1.09	1.5	1.7	0.45	1.0	6	2.3
	1983–1987	18	0.93	1.7	1.0	0.98	0.60	2	0.8
	1988–1992	21	1.27	3.6	2.2	0.50	0.55	6	2.2
	1993–1997	21	1.18	2.1	0.7	0.7	2.0	3	1.0
North	1978–1982	11	0.69	–	0.8	0.2	1.30	11	2.0
	1983–1987	14	1.08	2.3	1.7	0.45	0.80	4	0.7
	1988–1992	11	0.88	1.1	2.0	–	0.65	10	2.0
	1993–1997	15	1.13	4.1	1.8	0.20	0.68	7	1.5
South	1978–1982	10	1.00	–	0.45	1.30	1.54	4	2.3
	1983–1987	10	0.96	1.8	1.3	–	1.49	5	1.9
	1988–1992	12	1.27	2.0	0.95	1.0	1.68	6	2.3
	1993–1997	4	0.43	–	–	0.40	1.04	5	2.1
West	1978–1982	26	1.51	1.9	2.1	1.2	1.13	3	2.0
	1983–1987	47	0.65	0.85	0.65	0.35	0.92	2	0.9
	1988–1992	47	0.60	1.3	0.70	0.41	0.54	4	1.9
	1993–1997	66	0.73	1.6	0.60	0.50	0.88	2	1.2

ASR, age-standardised rate.

the East, survival was lowest, whereas there were little to no differences between the other four regions in children ($P = 0.14$) or adolescents ($P = 0.97$). Infants and children aged 10–14 years exhibited significantly lower survival than those aged 1–9 years ($P = 0.003$). Survival was also at the lower end for adolescents with ANLL.

Survival of children and adolescents with CML was lower in the East, but did not differ among the remaining four regions. Survival was lowest at age 1–4 years, but this difference was not significant.

Survival of 25,623 children with all leukaemias diagnosed throughout 1978–1997 and followed-up for vital status, improved significantly ($P < 0.0001$) over the four periods of diagnosis. Five-year survival went from 51% (95% CI 50–53) for children diagnosed in 1978–1982, to 77% (95% CI 76–78) for those diagnosed during 1993–1997. Survival also improved significantly for 1388 adolescents ($P < 0.0001$), with the proportion of 5-year survivors doubling between the periods 1978–1982 (21%, 95% CI 17–25) and 1993–1997 (42%, 95% CI 35–49). The number of premature deaths in children in the last period was approximately 1400 for ALL and 300 for ANLL.

Table 8(a and b) show the changes in survival over time for ALL and ANLL, according to sex and age. For children with ALL, most improvements occurred in age groups with the lowest rates during 1978–1982. Such improvements did not occur in adolescents, except in the British Isles (represented by Scotland, see Table 1). Survival rates in the East improved markedly. For children with ANLL most improvements in survival were observed after 1988, but were less marked in the East than in other regions. Survival also improved for adolescents with ANLL.

4. Discussion

In this study, based on over 31,000 cases, we provide reference estimates of leukaemia incidence rates among European populations of children and adolescents. While the incidence rates differed between geographical regions (as defined in this study) by up to 30%, the differences between the age groups attained up to 300%. The most remarkable variations were observed within the largest subgroup, lymphoid leukaemia, which influenced largely the results for leukaemia overall. The amplitude of the marked age-specific incidence peak of ALL at age 2–4 years was less pronounced in the East than in the other four regions. The incidence rates of ALL increased over the period 1978–1997 by approximately 0.8% per year in children and 2% in adolescents, in agreement with previous findings.[18] Due to smaller numbers, age-specific incidence rates of ANLL and CML were less well defined and no region-specific patterns could be observed. No clear incidence time trends were seen for ANLL or CML.

The incidence rates presented here are derived from the largest population-based series of childhood cancer cases ever assembled. Consequently, incidence rates, even for relatively rare diagnostic groups and subgroups, are based on unusually large numbers of cases, allowing detecting moderate differences between regions and countries. In all the participating registries whose data were included in these analyses, there were high rates of microscopic verification and low percentages of cases registered from death certificate only (in the registries with access to relevant information sources), allowing correspondingly high reliance to be placed on the results. The proportion of unspecified diagnoses remained low during the study period.

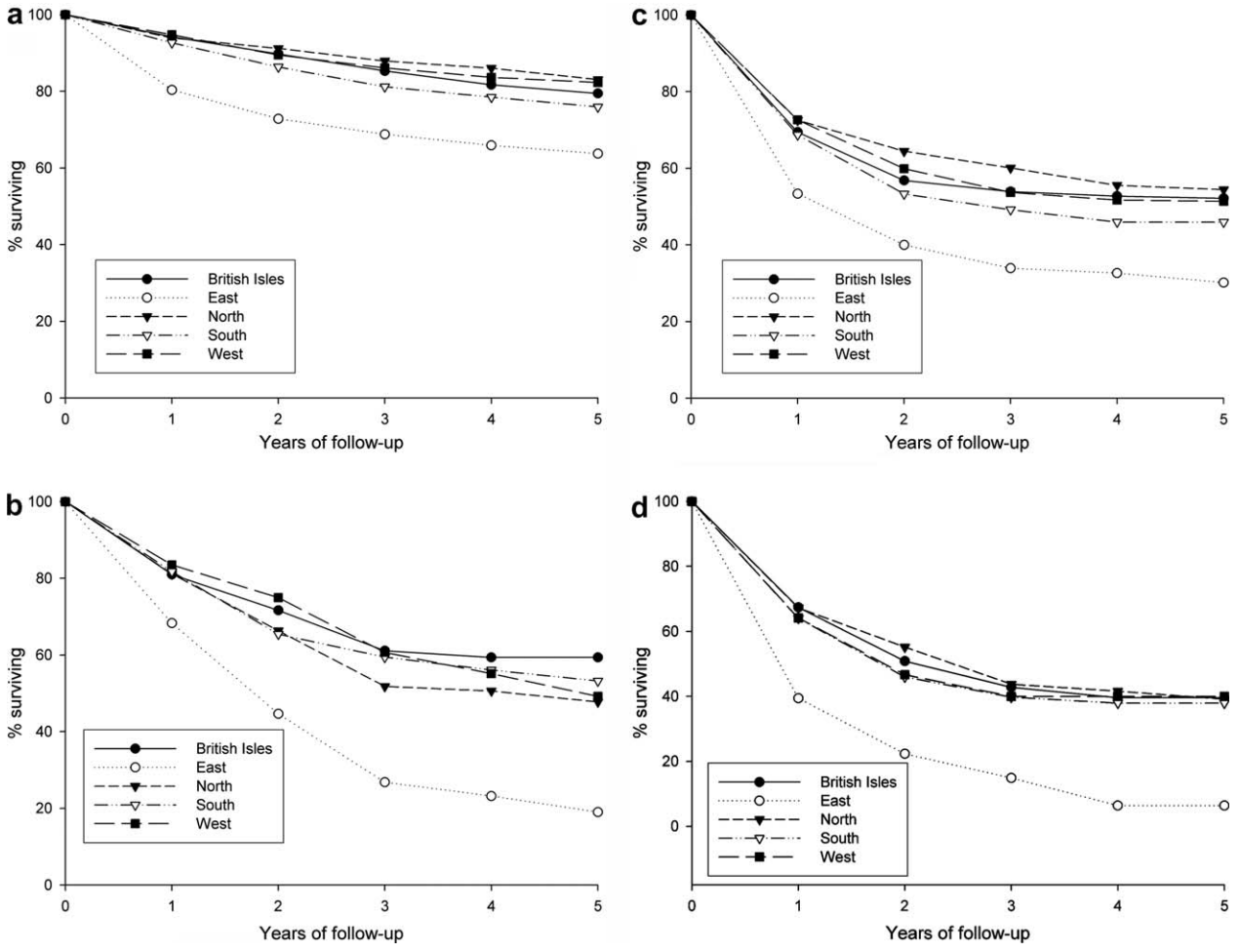

Fig. 3 – Actuarial survival probabilities for children (0–14 years) and adolescents (15–19 years) diagnosed with leukaemia in 1988–1997 in Europe. (a) ALL, children; (b) ALL, adolescents; (c) ANLL, children; (d) ANLL, adolescents. Source: ACCIS.

The geographical differences or temporal changes in the reported incidence rates may have been influenced by the development of the system of care provision through regional or national pediatric haematological networks. Centralised review of diagnoses may bias the registration rates in the direction of increase (heightened pediatric awareness, more precise diagnoses) as well as lead to a decrease. For example, a leukaemic reaction in a child with Down's syndrome may more frequently be excluded from registration in the settings with strict diagnostic criteria, which would result in a lower (increase in) incidence and a smaller improvement in survival rates. There is only anecdotal evidence to support one of these possibilities.

Changes in classification might have resulted in some overlap with high-grade non-Hodgkin's lymphomas in case of bulky disease, estimated at approximately 5% of ALL and 20% of non-Hodgkin's lymphoma (NHL) in the Netherlands during the 1980s.[22] However, this probably does not explain the increase in ALL as the incidence rates of other haematopoietic neoplasms also increased in the same populations [Izarzugaza and colleagues, this issue].

After a plethora of studies in the last 25 years, the aetiology of childhood (and adolescent) leukaemias, whether lymphoid or non-lymphoid in its many versions, remains largely unknown, although quite a few leukaemogenic events and circumstances have been well described, often as risk indicator rather than risk factor.[14] Compelling evidence suggests that childhood leukaemia largely originates *in utero*.[23–25] If some of the following exposures have been shown to be a risk factor in some studies, their prevalence has generally not increased so much that they could be considered to contribute to the rise in incidence: maternal irradiation during pregnancy[26] has decreased since the 1960s, as well as parental insecticide use[27,28] and parental medication use.[29] The role of electromagnetic fields (EMF) appears to have been none to very small in most studies.[30] On the other hand, decreasing parity,[12,13] older parental age[12] or a higher birth-weight[13] might have played a role. However, based on the studies performed, these risk factors, if relevant at all, would still contribute to only a small proportion of cases. The possibility of information bias in case-control studies derived from perceived awareness of risk factors among cases and/or controls, means that the literature about these possible risk factors is not as consistent as desired. Studies in identical twins show that a postnatal promotional event is also required.[31] A more recent hypothesis, supported by studies of leukaemia clusters,[15] is that infectious agents might play a stimulating role in the aetiology of childhood ALL, particularly for

Table 7 – Numbers (*n*) of leukaemia cases in children (0–14 years) and adolescents (age 15–19 years), diagnosed across Europe during 1988–1997, and 5-year observed survival (OS) (95% CI) by age group and region of residence at diagnosis (Source: ACCIS)

Region	Children		Five-year survival (95% CI) by age group				Adolescents	
	n	OS (95% CI)	0	1–4 years	5–9 years	10–14 years	*n*	OS (95% CI)
(a) Lymphoid leukaemia (mostly acute lymphoblastic leukaemia)								
Europe	13460	79 (78–79)	44 (39–49)	84 (83–85)	79 (77–80)	68 (66–70)	450	49 (44–54)
British Isles	3108	79 (78–81)	39 (30–47)	86 (84–87)	80 (77–82)	67 (63–71)	80	59 (47–70)
East	1687	64 (61–66)	40 (27–53)	70 (67–74)	62 (58–67)	54 (48–60)	49	19 (8–34)
North	1016	83 (80–85)	52 (32–68)	87 (84–90)	82 (76–86)	77 (69–83)	113	48 (38–57)
South	1217	76 (73–78)	57 (38–72)	81 (77–84)	78 (73–82)	64 (57–70)	159	53 (45–61)
West	6432	82 (81–83)	45 (37–52)	87 (86–88)	83 (81–85)	73 (70–76)	49	49 (33–63)
(b) Acute non-lymphocytic leukaemia								
	Children		Five-year survival (OS) by age group				Adolescents	
Europe	2482	49 (47–51)	45 (40–51)	49 (46–53)	53 (49–57)	47 (43–51)	245	34 (28–41)
British Isles	587	52 (48–56)	47 (36–58)	54 (47–61)	57 (48–65)	48 (41–55)	48	40 (25–54)
East	269	30 (25–36)	10 (2–26)	24 (15–35)	37 (26–48)	35 (25–45)	36	6 (1–20)
North	174	54 (46–62)	62 (40–77)	60 (46–70)	47 (26–66)	46 (29–61)	67	39 (26–52)
South	208	46 (39–53)	32 (16–49)	49 (35–62)	55 (41–67)	42 (30–53)	74	38 (26–49)
West	1244	51 (48–54)	49 (41–56)	50 (44–55)	55 (49–61)	51 (45–56)	20	40 (18–61)
(c) Chronic myeloid leukaemia								
Europe	324	45 (39–51)	48 (29–65)	34 (24–43)	46 (33–59)	53 (43–62)	63	37 (25–49)
British Isles	83	41 (30–52)	54 (13–83)	34 (19–51)	41 (19–63)	46 (24–65)	9	44 (14–72)
East	59	43 (29–55)	43 (10–73)	13 (2–33)	42 (11–71)	61 (38–78)	9	0
North	26	47 (26–65)	36 (3–74)	38 (14–63)	0	83 (27–97)	17	52 (27–73)
South	34	57 (38–72)	50 (0.6–91)	34 (5–68)	63 (23–86)	63 (36–82)	21	45 (23–65)
West	122	45 (35–56)	54 (18–80)	45 (24–64)	51 (28–69)	41 (25–57)	7	14 (7–47)

common ALL. In this respect, risk indicators could be paternal occupational histories (a proxy for potential exposure to infections),[32] maternal breastfeeding[33] and day care attendance.[13,34]

To conclude, the rather consistent pattern of an increasing incidence of ALL, especially in 1–4-year-old children, in populations with a rising prosperity[35] and decreasing rates of infectious disease, together with current notions on the origin of the disease suggest a role for secular and demographic changes in child bearing and (lack of) stimulation of the immune system by infection.

Survival of patients with leukaemia was more favourable for children (5-year survival 73%) than for adolescents (44%), although it was low for infants (44%), too. The lowest survival was observed in the East for children and adolescents, for leukaemia overall and for most age-sex and diagnostic subgroups. Elsewhere, 5-year survival rates for ALL were higher than 75% in children aged 0–14 years, but lower than 60% in adolescents. Survival for other diagnostic subgroups was lower in both children and adolescents, but increasing over time.

Improvements in survival occurred earlier for ALL than for ANLL. Although the extent of the improvements in survival in the five regions was inversely related to the baseline survival in 1978–1982, the geographical differences in survival persisted. The differential improvements in survival of LL and ANLL in time and place follow closely what was observed already in the EUROCARE study, both in children[3,4] and in adolescents.[36] These improvements were due to better outcomes from more (sometimes less) intensive treatment protocols and better adherence, to be considered in regional or national organisation. It is encouraging that the population-based results are in agreement with quite a few national, mostly observational clinical trials.[37–40] After the initial changes in prognosis in the 1960s and 1970s due to new treatment practices,[41] further increase in survival can be attributed to continually improved approaches to treatment. Wider dissemination of results from randomised trials probably generates more complete enrolment of patients and refines what is recognised as the 'best standard practice' by clinicians. Undoubtedly, professional discipline, development and self-regulation accompanied by dedicated planning, rising awareness and healthcare spending also contributed to this favourable trend. Developments with international impact have been reported from Nordic countries,[37] the UK,[38] the Netherlands (with a national initiative especially for childhood leukaemia in the early 1970s)[39] and (initially west) Germany.[40] In France, improvement in survival of children with ALL occurred later than in north-western Europe, notably during the 1990s.[41] Because financial resources are important for successful treatment outcome, economic development appears to be a crucial precondition, which might also explain the lower outcomes in the East until the 1990s. Yet, the accelerated increase in survival, as well as variations between these countries, also seen in the EUROCARE study of survival across Europe,[42] indicate a strong potential for further improvement [Overview paper, this issue].

Table 8 – Numbers (*n*) of leukaemia cases in children (0–14 years) and adolescents (15–19 years), diagnosed across Europe during 1978–1997, 5-year survival (5yr OS) and 10-year survival (10yr OS) with 95% CI by age group, region of residence and calendar period of diagnosis (Source: ACCIS)

	Period	Children			5–yr OS (95% CI) by age group				Adolescents		
		n	5yr OS (95% CI)	10yr OS (95% CI)	0	1–4 years	5–9 years	10–14 years	*n*	5yr OS (95% CI)	10yr OS (95% CI)
(a) Lymphoid leukaemia (mostly acute lymphoblastic leukaemia)											
Europe	1978–82	3920	59 (57–60)	52 (51–54)	25 (18–32)	66 (64–68)	60 (57–62)	47 (43–50)	172	31 (24–38)	27 (20–34)
	1983–87	5767	72 (71–73)	67 (66–68)	33 (76–80)	78 (76–80)	72 (70–74)	61 (58–64)	219	35 (29–42)	33 (26–39)
	1988–92	5848	78 (77–79)	74 (72–75)	44 (37–51)	84 (83–85)	78 (76–80)	67 (64–70)	178	49 (41–56)	47 (40–55)
	1993–97	5679	82 (81–83)	–	46 (37–54)	88 (86–89)	82 (80–84)	73 (69–76)	157	49 (38–58)	–
British Isles	1978–82	1634	60 (57–62)	53 (50–55)	25 (14–38)	66 (63–69)	61 (57–65)	47 (42–53)	17	47 (23–68)	41 (19–63)
	1983–87	1596	70 (68–72)	65 (62–67)	25 (15–36)	79 (76–81)	71 (67–75)	53 (47–59)	25	40 (21–58)	40 (21–58)
	1988–92	1759	79 (77–81)	74 (72–76)	34 (23–45)	84 (82–87)	79 (75–82)	71 (65–76)	33	59 (41–74)	56 (37–71)
	1993–97	1190	81 (78–83)	–	49 (33–63)	89 (86–91)	81 (86–85)	64 (57–70)	19	84 (59–95)	–
East	1978–82	532	47 (43–52)	41 (37–45)	17 (5–35)	52 (46–58)	52 (44–60)	34 (24–44)	16	19 (5–40)	19 (5–40)
	1983–87	516	58 (54–62)	53 (49–57)	35 (16–55)	59 (52–65)	61 (54–68)	53 (41–63)	13	46 (19–70)	31 (10–55)
	1988–92	550	64 (60–68)	60 (55–64)	47 (23–68)	73 (67–78)	60 (52–67)	54 (45–63)	23	20 (6–39)	20 (6–39)
	1993–97	490	72 (67–76)	–	46 (19–70)	78 (72–84)	69 (60–76)	62 (50–72)	26	22 (6–44)	–
North	1978–82	497	61 (57–65)	58 (53–62)	29 (12–48)	71 (64–76)	61 (52–69)	46 (35–55)	69	28 (17–39)	23 (14–34)
	1983–87	552	76 (73–80)	72 (68–76)	44 (22–65)	81 (75–85)	75 (68–81)	73 (63–81)	72	32 (21–43)	29 (19–40)
	1988–92	493	81 (77–84)	76 (72–80)	62 (31–82)	85 (80–89)	77 (69–83)	75 (63–83)	52	47 (33–60)	45 (31–58)
	1993–97	523	87 (83–90)	–	46 (21–67)	90 (84–93)	90 (83–94)	79 (67–88)	61	45 (28–60)	–
South	1978–82	293	57 (51–62)	51 (45–57)	50 (11–80)	60 (51–67)	53 (42–62)	57 (43–68)	15	33 (12–56)	27 (8–50)
	1983–87	319	67 (61–72)	62 (56–67)	33 (10–59)	74 (67–81)	70 (60–78)	49 (36–61)	34	48 (31–64)	45 (28–61)
	1988–92	310	71 (66–76)	69 (63–74)	50 (15–77)	75 (68–82)	74 (64–82)	57 (43–69)	46	56 (40–69)	56 (40–69)
	1993–97	283	79 (74–84)	–	59 (24–82)	84 (76–90)	76 (62–85)	74 (59–85)	34	56 (33–75)	–
West	1978–82	536	65 (60–69)	57 (52–61)	19 (6–38)	73 (67–78)	66 (58–73)	50 (39–60)	12	25 (6–50)	25 (6–50)
	1983–87	2333	76 (74–78)	71 (69–73)	39 (27–50)	82 (80–84)	76 (72–79)	67 (62–71)	21	43 (22–62)	43 (22–62)
	1988–92	2736	81 (80–83)	77 (75–79)	49 (37–59)	87 (85–88)	82 (79–85)	68 (64–73)	24	49 (26–68)	49 (26–68)
	1993–97	3193	85 (83–86)	–	44 (33–55)	89 (87–91)	84 (81–87)	79 (75–83)	17	36 (11–62)	–

Region	Period	Children			Adolescents		
		n	5yr OS (95% CI)	10yr OS (95% CI)	*n*	5yr OS (95% CI)	10yr OS (95% CI)
(b) Acute non-lymphocytic leukaemia							
Europe	1978–1982	766	20 (17–23)	18 (15–21)	165	7 (4–12)	5 (3–10)
	1983–1987	1103	36 (33–39)	35 (32–38)	135	15 (10–22)	14 (9–21)
	1988–1992	1136	47 (43–49)	45 (42–48)	88	33 (23–43)	33 (23–43)
	1993–1997	1017	53 (49–56)	–	98	33 (22–44)	–
British Isles	1978–1982	319	19 (15–24)	17 (13–22)	18	0	0
	1983–1987	318	32 (27–38)	31 (26–36)	11	30 (7–58)	30 (7–58)
	1988–1992	337	51 (46–57)	50 (45–56)	9	33 (8–62)	33 (8–62)
	1993–1997	220	51 (45–58)	–	20	56 (30–75)	–
East	1978–1982	123	16 (10–23)	14 (8–20)	17	0	0
	1983–1987	110	17 (11–25)	16 (10–24)	13	0	0
	1988–1992	102	27 (18–36)	24 (16–32)	16	6 (0.4–25)	6 (0.4–25)
	1993–1997	71	26 (16–38)	–	20	10 (0.7–33)	–
North	1978–1982	91	27 (18–36)	22 (14–31)	41	13 (5–25)	8 (2–19)
	1983–1987	94	44 (33–54)	43 (32–53)	35	32 (18–48)	29 (15–45)
	1988–1992	82	49 (37–59)	46 (34–57)	38	40 (24–56)	40 (24–56)
	1993–1997	92	56 (41–68)	–	29	36 (15–58)	–
South	1978–1982	62	15 (7–25)	13 (6–23)	18	12 (2–31)	12 (2–31)
	1983–1987	63	28 (17–39)	25 (15–36)	21	16 (4–35)	16 (4–35)
	1988–1992	71	37 (26–48)	34 (23–45)	15	27 (8–50)	27 (8–50)
	1993–1997	45	51 (35–65)	–	22	28 (9–52)	–
West	1978–1982	87	19 (11–28)	18 (10–26)	9	36 (6–70)	36 (6–70)
	1983–1987	431	45 (40–50)	43 (38–48)	7	0	0
	1988–1992	544	48 (44–52)	47 (43–52)	10	58 (22–82)	58 (22–82)
	1993–1997	589	56 (52–61)	–	7	11 (0.1–50)	–

The importance of improved organisation of treatment has become particularly clear when considering the relatively lower survival of adolescents with ALL. Application of the childhood ALL protocols to adolescent patients yielded better results (5-year survival rose from 40% to 80% in 15–18-year-olds) than the protocols for adults.[43–46]

In the last decade long-term surveillance has become more important because of the known (and yet unknown) side-effects in survivors. This activity may become an important part of medical care provision, because of the rising prevalence. For example, prevalence of survivors of childhood ALL in the Netherlands was estimated to increase from 30 in 1975 to 50 per 100,000 newborns of a given birth cohort in 2000.[47]

We conclude that despite stricter diagnostic and classification criteria, increases in incidence of childhood lymphoblastic leukaemia observed across Europe, seem real and largely attributable to changing demographic conditions, with respect to later age at first birth of mothers and rising birthweights, as well as less infectious stimulation in young children.

Survival improvements initially occurred in children with ALL especially in north-western Europe but clearly expanded over time and across Europe, with improvements occurring later in children with ANLL. The improved prognosis resulted from progress in organised, regionalised treatment, yet less available for adolescents.

Based on the observed changes and patterns studies of determinants of incidence, especially of ALL, should focus on interaction of demographic and secular changes, foetal growth patterns with environmental, especially microbiological, exposures. Collection of detailed information on diagnosis, including immunophenotype and genetic abnormalities, according to the most recent international classifications[8,48] and birth-weight and maternal age, as well as participation in clinical studies or protocols, would allow more conclusive interpretation of the differences in incidence and population-based survival.

Conflict of interest statement

None declared.

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