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Time trends of cancer incidence in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

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ABSTRACT

Within the framework of the Automated Childhood Cancer Information System (ACCIS), time trend analyses for childhood cancer were performed using data from 33 population-based cancer registries in 15 European countries for the period 1978–1997. The overall incidence rate based on 77,111 cases has increased significantly ($P < 0.0001$), with an average annual percentage change (AAPC) of 1.1%. The rising trend was observed in all five geographical regions and in the majority of the disease groups (in order of AAPC): soft tissue sarcomas (1.8%), brain tumours, tumours of the sympathetic nervous system, germ-cell tumours, carcinomas, lymphomas, renal tumours, and leukaemias (0.6%). No change was seen in incidence of bone tumours, hepatic tumours and retinoblastoma. The increased incidence can only partly be explained by changes in diagnostic methods and by registration artefacts. The patterns and magnitude of these increases suggest that other factors, e.g. changes in lifestyle and in exposure to a variety of agents, have contributed to the increase in childhood cancer in the recent decades.

1. Introduction

Childhood cancer is a disease that has a tremendous impact on the families affected. This is why societies with a high level of socio-economic development have devoted resources to the development of diagnostic procedures, therapeutic strategies and relevant health policies. Potential changes in childhood cancer incidence are therefore of major importance to epidemiologists, politicians and the general public. Population-based cancer registries with sufficiently long history of cancer registration can provide the means of evaluation of secular patterns of childhood cancer incidence.

Recently, incidence rates have been reported to have increased in Great Britain,[1–3] Nordic countries,[4–6] Italy,[7] Southern Netherlands,[8] United States of America (USA),[9,10] Oceania[11,12] and Japan.[13] However, the observed increase was not always interpreted concordantly. In addition, different rates of change,

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or even their direction were found for individual tumour subtypes.

Because of the rarity of the tumour types occurring in childhood, pooling data from large geographical areas and long time periods is necessary to secure sufficient power of the study of incidence time trends. A project aiming at the collection and dissemination of information on incidence and survival of children and adolescents with cancer in Europe has been set up; the Automated Childhood Cancer Information System (ACCIS). First analyses of the ACCIS database, for the last three decades of the 20th century, have shown a persistent increase in childhood cancer incidence, by 1% per year. The authors attributed this increase at least partly to an actual change in incidence rates.[14] This interpretation was challenged later as mainly imputable to improved registration,[15] but additional evidence was presented subsequently in support of the original conclusions.[16]

In this paper we describe incidence time trends of childhood cancer in Europe in more detail, using a restricted ACCIS database for the 20-year period 1978–1997, including the registries with sufficiently long registration period, and discuss the role of possible artefacts.

2. Material and methods

All malignant neoplasms, as well as non-malignant tumours of the central nervous system (CNS), registered by the 33 registries selected (Table 1) between 1978 and 1997 and in patients aged less than 15 years, were extracted from the ACCIS database and included in the analyses.

The variables available for each case included basic demographic data and information on the tumour type. Each registry provided details of registration practices and data coding. The population-at-risk for each registration area has been derived from official national statistics for each sex, calendar year and age unit.

Data were collected and validated at IARC in collaboration with the registries. To detect errors and standardise the coding, automatic and *ad hoc* procedures were used. The ACCIS Scientific Committee evaluated quality and comparability of the data-set, using standard and specific criteria for childhood data-sets. The registries included in these analyses were all classified as comparable. The selection criteria and other details related to the ACCIS database are described elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

The tumours were categorised according to the International Classification of Childhood Cancer (ICCC).[17] Here we present results for all neoplasms combined as well as for each of the 12 main ICCC groups. Additionally, all subgroups of unspecified diseases (identical with group of NOS defined in footnotes of Tables 1 and 2) were pooled for a further analysis. Countries were grouped into five regions: British Isles, East, North, South, and West.

Incidence rates were calculated as the average annual number of cases per million person-years using standard methods. The age-standardised incidence rate (ASR) is the weighted average of the age-specific incidence rates using the World standard population as a standard, specific for the age-groups 0, 1–4, 5–9, and 10–14 years. The average change of an incidence rate over time is expressed as average annual percentage change (AAPC). AAPC was derived from a Poisson regression model with year as the explanatory continuous variable coded naturally (year 1978 is year 1), adjusted for sex, age group and region, as appropriate. Any interaction influenced results only marginally. The *P*-values of the trend test report the probability of the gradient of the regression line of incidence rate over time being zero. Incidence rates were also presented for the four 5-year-periods 1978–1982, 1983–1987, 1988–1992 and 1993–1997.

3. Results

Analyses are based on a total of 77,111 cases reported from 32 registries in 15 countries. The 2181 cases from a further registry, the Dutch Childhood Oncology Group (DCOG) also shown in Table 1, replaced 148 cases of leukaemia from Eindhoven, another Dutch cancer registry, in the leukaemia-specific analyses. Table 2 shows the distribution of the numbers of cases in Europe and each of the regions over the four time periods. The sum of the numbers of cases in Table 1 ($n = 79{,}292$) differs from the total number of cases shown in Table 2 ($n = 77{,}111$) due to the partial overlap between the two Dutch registries with respect to leukaemia cases.

While in the first time period, 1978–1982, the number of cases was almost 14,000, in the following periods more than 20,000 cases per period were investigated. The West was the region with the poorest representation in the first period, since the data for the large German Childhood Cancer Registry were only included since 1983. The large cancer registry of England and Wales ended its contribution in 1995, which resulted in the drop in the number of cases in the last period for the British Isles.

The overall incidence for Europe has increased from ASR of 119.5 per 1 million children (1978–1982) to 140.9 (1993–1997) (Table 3). The average annual percentage change for the whole 20-year period was 1.1% ($P < 0.0001$). In each of the five regions the increase expressed by AAPC was significant, as shown in Table 3. While highest ASRs were found in most periods in North and South, the rate of increase was highest in the East (AAPC 1.4%). Except in the West, the ASR increased monotonously over the time in each region (Fig. 1).

For all neoplasms combined a significant increase in incidence rates was noted in all age groups ($P < 0.0001$). The rate of increase was highest for infants (AAPC 2.1%), intermediate for age-groups 1–4 and 10–14 and lowest in age group 5–9 (Table 4, Fig. 2). In infants, the fastest increase was seen for germ-cell and central nervous system (CNS) tumours. In the oldest children (age group 10–14) the highest increase was noted for soft tissue sarcomas, germ cell tumours and carcinomas. In children with age groups 1–4 and 5–9 the most prominent increases were in the incidence of tumours of nervous system and of soft tissue sarcomas (Table 4).

For all cancers combined, the incidence increased significantly for both sexes, with AAPC higher for girls (1.4%) than for boys (0.9%). This corresponds to the increase in ASR from 105.7 (in 1978–1982) to 129.0 (in 1993–1997) in girls and from 132.5 to 152.3 in boys. The faster increase in girls was seen for a majority of the diagnostic groups. The largest sex-spe-

Table 1 – List of registries included in the analyses of incidence time trends in children (age 0–14 years), with indicators of coverage and data quality (Source: ACCIS)

Region	Registry	Coverage					Cases	NOS	Carcinoid of appendix	Non-malignant	Basis of diagnosis			
		Period	Person–years											
			1978–1982 %	1983–1987 %	1988–1992 %	1993–1997 %	*n*	%	%	%	MV %	DCO %	Unknown %	Notes
British Isles	UNITED KINGDOM, England & Wales	1978–1995	29	27	27	17	21,112	3	0	4	91	<1	<1	P
	UNITED KINGDOM, Scotland	1978–1997	28	25	24	24	2436	3	0	–	94	<1	0	
East	ESTONIA, National	1978–1997	24	26	26	23	810	16	0	–	92	<1	0	
	HUNGARY, National	1978–1997	27	27	25	22	4875	2	<1	4	96	–	0	P
	SLOVAKIA, National	1978–1997	25	26	26	23	3289	9	<1	2	93	1	0	
	GERMANY, NCR (only former East)	1978–1989	42	41	17	–	4831	4	<1	4	98	0	0	
North	DENMARK, National	1978–1997	28	25	23	24	2775	10	<1	8	92	<1	<1	
	FINLAND, National	1978–1997	25	25	25	25	3012	9	1	2	98	0	<1	
	ICELAND, National	1978–1997	25	25	25	26	174	5	0	3	98	0	0	
	NORWAY, National	1978–1997	27	25	24	25	2360	10	0	2	96	<1	<1	
South	ITALY, Piedmont paediatric	1978–1997	32	26	22	20	1970	6	0	6	94	<1	0	P
	ITALY, Latina	1983–1997	–	37	33	31	152	13	<1	–	93	0	<1	
	ITALY, Lombardy	1978–1997	31	26	22	20	405	4	0	–	92	< 1	0	
	ITALY, Parma	1978–1995	35	29	24	13	139	7	0	3	97	0	0	
	ITALY, Ragusa	1983–1997	–	36	33	31	112	10	0	–	94	0	0	
	SLOVENIA, National	1978–1997	26	26	25	22	990	5	0	1	98	0	0	
	SPAIN, Asturias	1983–1997	–	41	33	26	374	12	<1	2	93	2	0	
	SPAIN, Navarra	1978–1996	32	28	24	16	272	7	0	–	94	2	0	
	SPAIN, Tarragona	1983–1997	–	38	33	29	209	8	<1	–	95	<1	<1	
	SPAIN, Zaragoza	1978–1996	31	28	24	16	403	7	0	5	89	8	<1	
West	FRANCE, Lorraine	1983–1997	–	35	33	32	971	2	0	3	93	–	<1	P
	FRANCE, PACA & Corsica	1984–1996	–	30	38	32	1473	1	<1	3	98	–	0	P
	FRANCE, Doubs	1978–1996	29	27	25	19	262	8	<1	–	46	–	<1	
	FRANCE, Isere	1979–1997	21	26	26	27	628	4	<1	1	96	–	<1	
	FRANCE, Bas-Rhin	1978–1996	27	26	25	21	498	7	<1	–	97	–	0	
	FRANCE, Somme	1983–1996	–	38	35	27	184	5	<1	–	95	–	<1	
	FRANCE, Tarn	1983–1997	–	35	33	32	117	5	2	–	97	–	0	
	GERMANY, GCCR (East and West)	1991–1997	–	–	29	71	12,153	2	0	3	99	–	0	P
	GERMANY, GCCR (only former West)	1983–1990	–	61	39	–	9124	2	0	3	100	–	0	P
	NETHERLANDS, Eindhoven	1978–1997	29	25	22	23	478	6	3	–	92	–	<1	o
	NETHERLANDS, DCOG	1978–1997	27	24	24	25	2181	0	0	–	99	–	0	P o
	SWITZERLAND, Basel	1983–1997	–	33	33	34	144	4	0	–	98	–	0	
	SWITZERLAND, Geneva	1978–1997	25	24	24	27	177	3	0	–	98	0	0	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	–	32	33	35	202	6	0	2	96	<1	0	

–, not applicable; DCOG, Dutch Childhood Oncology Group, leukaemia only; PACA, Provence, Alps, Cote d'Azur; NCR, National Cancer Registry of the former German Democratic Republic (Data for 1978–1987 contributed only to analyses for Europe as a whole. Data for 1988–1989 were pooled with GCCR and included in West. For explanation see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue); GCCR, National German Childhood Cancer Registry (till 1990 only covering the former Federal Republic of Germany, since 1991 reunified Germany); MV, microscopically verified cases; DCO, cases registered from death certificate only; NOS, cases with unspecified histology, including ICCC subgroups Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, Xe (M-8000 to M-8004 only) and XIf (C76 to C80.9 only); P, paediatric cancer registry, age-range of the patients is 0–14; o, overlapping registration areas: DCOG contributed to analyses of leukaemias only and Eindhoven to all other analyses.

Table 2 – Number of cases and indicators of data quality by region for analyses of incidence time trend in children (age 0–14 years) (Source: ACCIS)

Region	Period	Person-years	Cases	NOS	Non-malignant	Basis of diagnosis		
						MV	DCO	Unknown
		%	*n*	%	%	%	%	%
Europe[a] (*n* = 77,111)	1978–1982	20	13,907	6	3	94	<1	<1
	1983–1987	28	20,890	4	3	95	<1	<1
	1988–1992	28	21,906	4	3	95	<1	2
	1993–1997	25	20,408	4	3	96	<1	<1
British Isles (*n* = 23,548)	1978–1982	29	6179	3	3	93	<1	1
	1983–1987	27	6189	3	3	92	<1	2
	1988–1992	27	6632	3	3	90	<1	5
	1993–1997	18	4548	4	4	92	<1	3
East (*n* = 8,974)	1978–1982	26	2129	9	2	93	<1	0
	1983–1987	26	2327	6	3	94	<1	0
	1988–1992	25	2326	5	3	95	<1	0
	1993–1997	22	2192	4	3	96	<1	0
North (*n* = 8,321)	1978–1982	27	1996	11	4	95	<1	1
	1983–1987	25	2042	9	3	96	0	<1
	1988–1992	24	2045	8	4	96	<1	<1
	1993–1997	25	2238	11	5	94	<1	1
South (*n* = 5,026)	1978–1982	25	1168	9	5	90	3	<1
	1983–1987	29	1381	7	3	95	<1	<1
	1988–1992	25	1281	6	2	96	<1	<1
	1993–1997	21	1196	5	2	96	<1	<1
West (*n* = 26,411)	1978–1982	2	470	7	2	84	0	1
	1983–1987	28	6879	3	3	98	<1	<1
	1988–1992	33	8828	2	3	99	0	<1
	1993–1997	38	10,234	2	3	99	0	<1

n, number of cases ; NOS, cases with unspecified histology, including ICCC subgroups Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, Xe (M-8000 to M-8004 only) and XIf (C76 to C80.9 only); Non-malignant, includes tumours located in CNS, classified in the ICCC group III and subgroup Xa; MV, microscopically verified cases; DCO, cases registered from death certificate only.
a Europe includes the data of former German Democratic Republic (see NCR in Table 1).

cific difference in the rate of increase was seen for lymphomas, renal tumours and germ-cell tumours (Table 4).

As Fig. 3 shows, a rising trend is observed for the majority of the disease groups. Table 3 gives the ASR for all neoplasms combined and for each of the ICCC main diagnostic groups, by time period and in each of the five European regions. For Europe as a whole, significant increases were observed for the majority of the main diagnostic groups, with the exception of bone tumours, hepatic tumours and retinoblastoma. Highest AAPCs were observed for soft tissue sarcomas (1.8%), based on a steady increase from an ASR of 7.3 per 1 million (1978–1982) up to 9.6 (1993–1997), followed by CNS tumours and tumours of the sympathetic nervous system (both AAPC 1.7%), and germ-cell tumours (1.6%) (Table 3). A brief description of the time trends observed is presented below for the 12 ICCC main diagnostic groups, with reference to Tables 3 and 4 and the figures. Comprehensive tumour-specific analyses are published elsewhere in this issue.

For *leukaemia*, the most common disease group in childhood, AAPC was significant for Europe as a whole. This was mainly due to the rise in acute lymphoid leukaemia (AAPC 0.8%, $P < 0.0001$), whereas for acute non-lymphocytic leukaemia no significant increase was seen (AAPC 0.5%, $P = 0.11$). The leukaemia increase can be seen over the whole age range, apart from infants, and for both sexes in Europe. By individual region, the increase was evident only in the British Isles and the West.

Incidence of *lymphomas* increased for Europe as a whole, although a continuous increase over the 5-year periods was not seen in individual regions. For Europe as a whole, significant increase was seen in 10–14-year-old children and AAPC for girls was threefold, compared with boys. Hodgkin's disease and non-Hodgkin lymphomas showed similar AAPCs for Europe as a whole (0.7% with $P = 0.032$ and 0.9% with $P = 0.006$, respectively).

A universal increase was observed for the incidence of *CNS tumours* in all European regions (except the South), for all age groups and for both sexes. The fastest increase was seen in the East (AAPC 2.7%, $P < 0.0001$), mainly influenced by the low ASR of 20.2 per million in the first time period. North showed the highest ASRs in all four time periods and the period-specific incidence was increasing monotonously.

The AAPC in Europe for *tumours of the sympathetic nervous system* was 1.7% ($P < 0.0001$). Incidence increased markedly in the East and the West. In both regions the increase started with an ASR of about 8.5 in 1978–1982 and continued to rise

Table 3 – Age-standardised incidence rates (ASR) for childhood cancer (age 0–14 years) in Europe by time period and main diagnostic groups added by number of cases (1978–1997), average annual percent of change (AAPC) and result of trend test (*P < 0.05; **P < 0.01; ***P < 0.0001) (Source: ACCIS)

Region	Time period	ASR for diagnostic groups (per million)												Total no. of cases	Total ASR (per million)
		Leu	Ly	CNS	Symp	Ret	Ren	Hep	Bone	Soft	Germ	Ca	Oth		
Europe	1978–1982	39.7	13.1	25.9	8.6	3.2	7.6	1.0	5.6	7.3	3.9	3.0	0.8	13,907	119.5
	1983–1987	41.6	13.3	27.4	10.1	4.0	8.3	1.4	5.4	8.2	4.1	2.7	0.5	20,890	127.2
	1988–1992	43.6	14.1	29.2	11.1	4.2	8.3	1.5	5.2	9.0	4.5	2.8	0.5	21,906	134.3
	1993–1997	45.1	15.1	30.4	12.0	3.9	9.3	1.5	5.6	9.6	4.8	2.7	0.6	20,408	140.9
	No. of cases	26,690	8971	17,057	5580	1995	4549	749	3692	5111	2555	1874	339	77,111	
	AAPC	0.6%***	0.9%***	1.7%***	1.7%***	0.5%	0.8%**	0.8%	−0.3%	1.8%***	1.6%***	1.3%**	1.1%		1.1%***
British Isles	1978–1982	39.3	11.0	25.6	7.9	3.3	7.5	1.0	5.4	7.0	3.7	2.7	0.2	6179	114.5
	1983–1987	40.2	11.3	27.8	8.6	4.2	7.8	1.1	4.7	8.0	4.3	3.2	0.4	6189	121.5
	1988–1992	42.8	11.9	28.4	10.2	4.2	7.8	1.1	5.0	9.1	4.0	3.4	0.6	6632	128.6
	1993–1997	43.5	11.3	31.9	8.9	5.0	7.8	1.3	4.9	10.6	4.1	3.7	1.1	4548	134.0
	No. of cases	7650	2373	5451	1528	691	1338	202	1105	1633	774	697	106	23,548	
	AAPC	0.7%**	0.5%	1.4%***	1.6%**	2.4%**	0.3%	0.6%	−0.5%	2.8%***	0.8%	2.4%**	5.8%**		1.1%***
East	1978–1982	37.3	14.8	20.2	8.7	2.0	7.7	0.8	4.3	6.8	3.8	1.7	1.1	2129	109.2
	1983–1987	35.0	15.0	31.1	9.1	3.4	7.9	2.0	4.1	6.8	4.4	2.3	1.2	2327	122.3
	1988–1992	38.9	16.4	30.2	12.2	3.2	7.7	1.6	5.1	7.9	3.6	2.1	1.1	2326	129.9
	1993–1997	37.6	14.2	33.9	13.3	3.8	9.6	2.4	5.4	9.1	4.1	2.7	0.4	2192	136.7
	No. of cases	2666	1189	2121	695	192	540	105	393	544	283	180	66	8974	
	AAPC	0.3%	−0.1%	2.7%***	2.7%***	1.3%	1.6%*	3.1%	2.9%**	2.1%**	0.6%	1.6%	1.5%		1.4%***
North	1978–1982	44.4	12.6	33.6	9.5	4.3	8.7	1.8	5.9	6.9	3.7	4.3	2.5	1996	138.1
	1983–1987	52.2	12.3	35.2	12.2	4.4	9.7	2.3	5.0	9.4	4.2	4.6	1.3	2042	152.8
	1988–1992	47.4	11.9	42.8	10.3	6.1	9.0	1.9	4.2	11.0	5.4	5.4	1.2	2045	156.5
	1993–1997	48.5	15.9	44.7	9.5	4.4	9.2	2.0	6.0	11.1	5.9	4.9	1.8	2238	163.9
	No. of cases	2546	781	2174	512	230	459	101	331	536	263	298	90	8321	
	AAPC	0.3%	1.8%**	2.0%***	−0.1%	−0.1%	0.2%	1.8%	−0.9%	2.4%**	3.2%**	1.3%	−1.3%		1.0%***
South	1978–1982	45.6	18.5	27.2	11.1	3.3	6.8	2.0	6.4	7.1	2.2	3.2	0.6	1168	133.9
	1983–1987	44.2	18.4	28.5	11.9	4.1	7.8	2.5	7.3	9.3	3.2	2.7	0.6	1381	140.2
	1988–1992	51.1	19.1	28.6	11.3	4.1	7.1	2.5	6.7	8.6	4.9	4.4	1.1	1281	149.5
	1993–1997	48.7	19.7	31.3	14.2	4.4	12.1	1.1	7.3	10.7	6.4	5.5	0.5	1196	161.8
	No. of cases	1569	730	1038	341	108	246	62	292	313	141	165	21	5026	
	AAPC	0.5%	1.3%*	0.7%	1.5%	1.7%	3.5%**	1.6%	0.5%	2.0%	5.9%***	4.2%**	−0.4%		1.2%***
West	1978–1982	41.9	15.9	26.0	8.9	4.8	7.2	0.2	6.7	9.1	2.3	3.6	0.2	470	125.9
	1983–1987	43.7	13.3	22.0	11.1	3.9	8.9	1.4	6.1	8.0	3.9	1.7	0.1	6879	124.6
	1988–1992	44.4	15.0	26.5	12.0	4.0	9.0	1.5	5.6	9.0	4.8	1.8	0.2	8828	134.6
	1993–1997	46.2	16.4	26.2	13.5	3.2	9.8	1.4	5.6	8.9	4.8	1.7	0.2	10,234	138.8
	No. of cases	10,949	3287	5088	2178	649	1685	256	1308	1745	889	400	28	26,411	
	AAPC	0.8%***	1.5%***	1.6%***	2.0%***	−3.0%**	0.8%	−1.7%	−0.9%	0.4%	2.3%**	−2.4%*	−4.3%		1.1%***

Leu, leukaemias; Ly, lymphomas; CNS, CNS tumours; Symp, tumours of the sympathic nervous system; Ret, retinoblastoma; Ren, renal tumours; Hep, hepatic tumours; Bone, malignant bone tumours; Soft, soft tissue sarcomas; Germ, germ-cell tumours; Ca, carcinomas; Oth, other and unspecified malignant neoplasms.

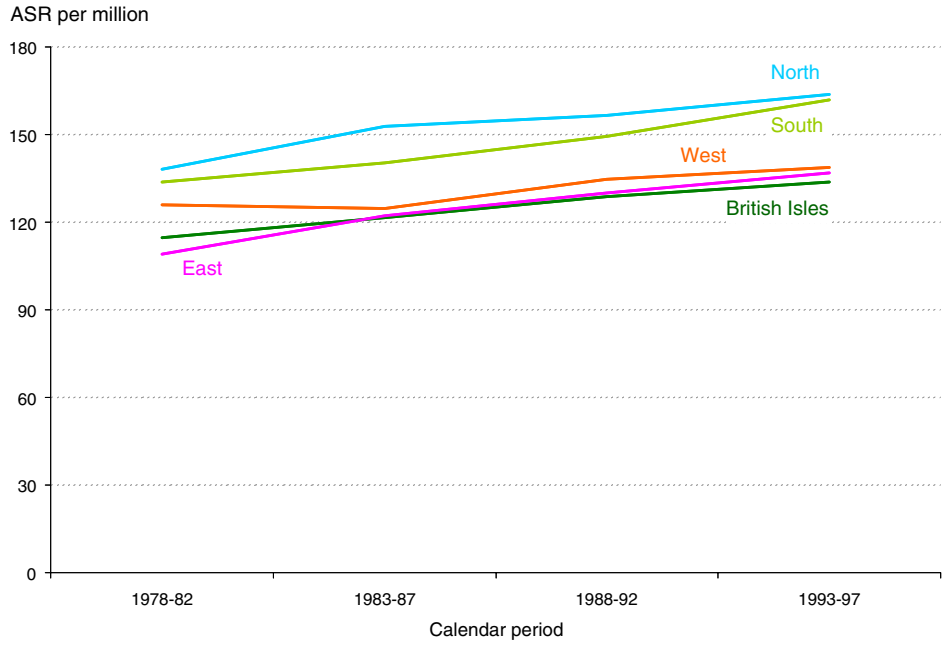

Fig. 1 – Age-standardised incidence rates (ASR, world standard) of all cancers in children aged 0–14 years, registered in the European regions in 1978–1997 (*n* = 72,280). Source: ACCIS.

Table 4 – Average annual percent of change (AAPC) and result of trend test for childhood cancer (age 0–14 years) in Europe by age groups and sex for total cancer and main diagnostic groups (*P < 0.05; ** P < 0.01; *** P < 0.0001) (1978–1997) (Source: ACCIS)

	AAPC for diagnostic groups												AAPC for total (%)
	Leu (%)	Ly (%)	CNS (%)	Symp (%)	Ret (%)	Ren (%)	Hep (%)	Bone (%)	Soft (%)	Germ (%)	Ca (%)	Oth (%)	
Age 0	0.6	−1.6	2.4***	2.2***	0.9	1.9*	1.5	−7.4	1.3	3.9***	−0.4	3.2	2.1***
Age 1–4 years	0.7***	0.6	1.8***	1.7***	0.4	0.8*	1.2	−0.5	1.9***	−0.1	0.6	−0.2	1.1***
Age 5–9 years	0.5*	0.7	1.6***	0.1	−0.6	0.5	−1.8	−1.2	1.3*	0.90	−0.9	1.0	0.8***
Age 10–14 years	0.5*	1.3***	1.7***	1.9	−6.0	0.5	0.3	0.2	2.6***	2.5***	2.2***	1.7	1.3***
Male	0.7***	0.5*	1.5***	1.5***	0.3	0.4	0.9	−0.3	1.7***	1.2*	1.2	0.2	0.9***
Female	0.6**	1.7***	2.0***	2.0***	0.7	1.3**	0.6	−0.2	2.0***	2.0***	1.3*	2.0	1.4***

Leu, leukaemias; Ly, lymphomas; CNS, CNS tumours; Symp, tumours of the sympathic nervous system; Ret, retinoblastoma; Ren, renal tumours; Hep, hepatic tumours; Bone, malignant bone tumours; Soft, soft tissue sarcomas; Germ, germ-cell tumours; Ca, carcinomas; Oth, other and unspecified malignant neoplasms.

reaching 13.5 in 1993–1997. Fig. 3 shows the relatively high difference in incidence between the beginning and the end of the period, despite temporary decreases in some years. The increase was highly significant in the two youngest age groups, where these tumours occur predominantly. The girls were affected by the increase slightly more than the boys (Table 4).

Retinoblastoma was one of the few tumours that did not show a change in incidence over time for Europe. However, region-specific AAPC ranged from 2.4% in the British Isles to minus 3.0% (West), both significant (Table 3). In the pooled European data-set we did not detect any changes by age group or sex (Table 4).

The average change of ASR of *renal tumours* for Europe was 0.8% per year. However, the increase was not apparent in all subpopulations. The only region where the incidence of renal tumours increased significantly was the South. Here, the main change had occurred between the last two quinquennia (Table 3). For Europe as a whole, the incidence increased only for girls and only for the two youngest age groups (Table 4). More detail can be found elsewhere [Pastore, Znaor, Spreafico and colleagues, this issue].

For *hepatic tumours* no change in rates was seen either for Europe as a whole or for any region-, age- or sex-specific subgroup.

The incidence of *bone tumours* did not change, with the exception of the East, where the rates increased considerably (AAPC 2.9%, $P < 0.002$).

Over the 20 years of observation the most striking increase was that of *soft tissue sarcomas*. The ASRs increased from 7.3 per 1 million in the first period to 9.6 in the last period. Results were significant for British Isles, East and West, but not for South and West (Table 3). Although the age-specific incidence rates for soft tissue sarcomas are higher in infants than in the

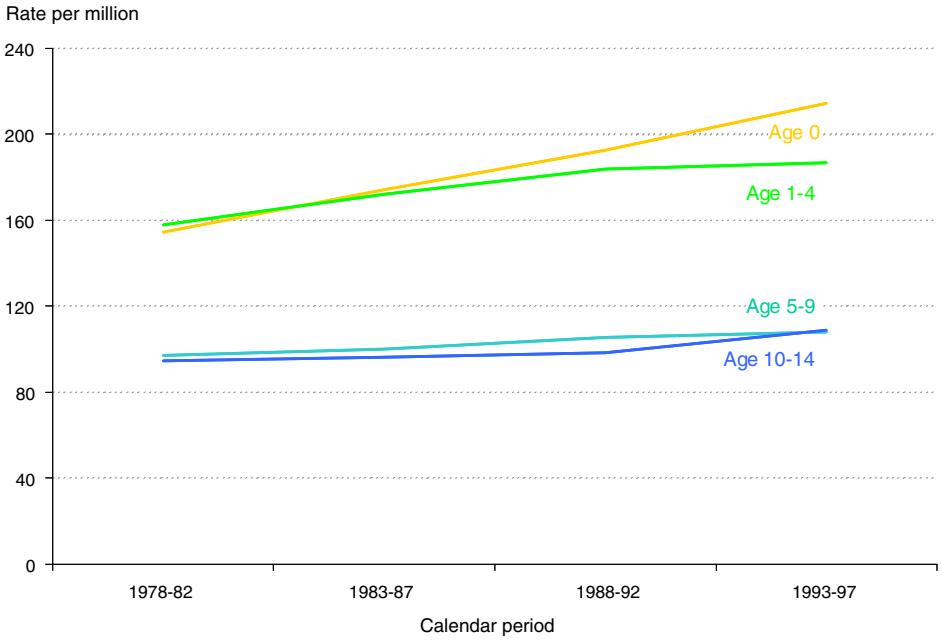

Fig. 2 – Age-specific incidence rates of all cancers in children aged 0–14 years registered in Europe in 1978–1997 (*n* = 77,111). Source: ACCIS.

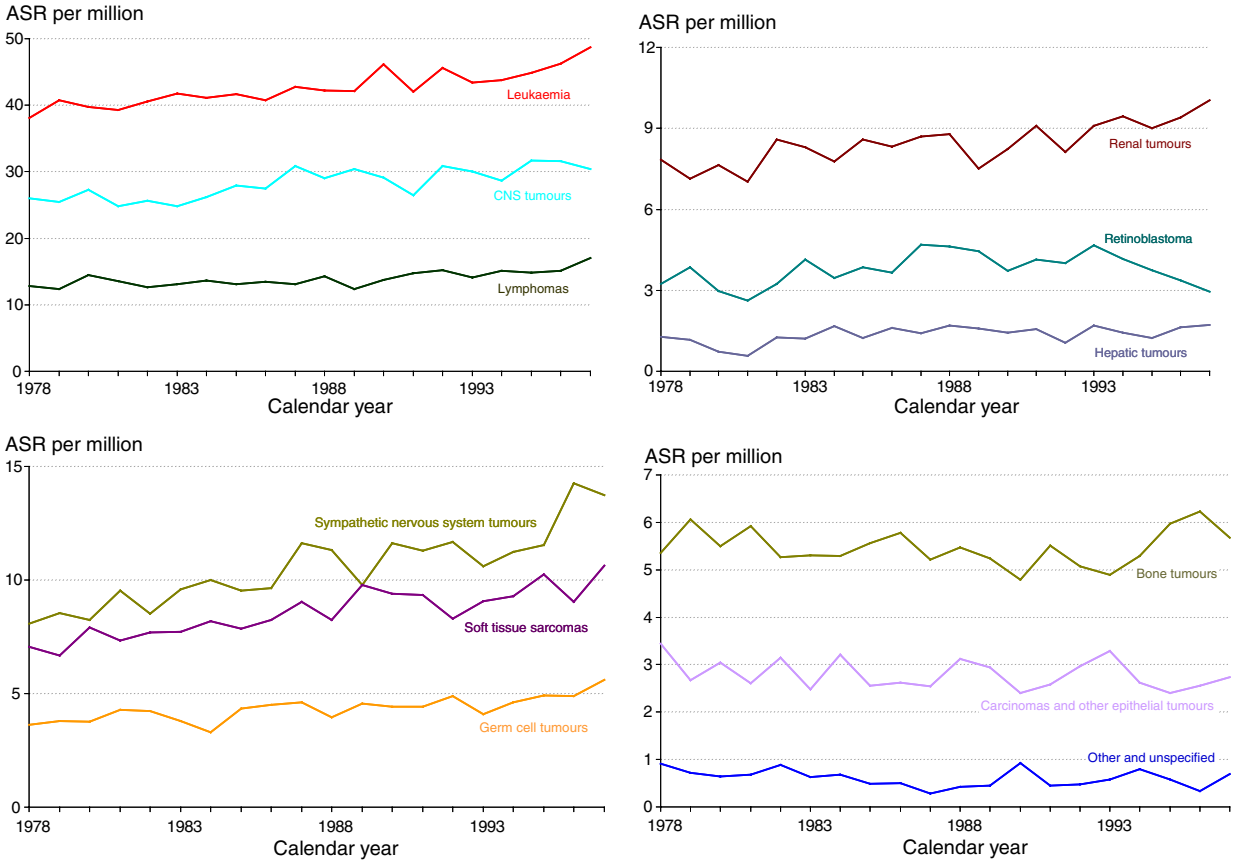

Fig. 3 – Age-standardised incidence rates (ASR, world standard) of all cancers in children aged 0–14 years registered in Europe in 1978–1997 and classified into the 12 ICCC main diagnostic groups (*n* = 77,111). Source: ACCIS.

other childhood age groups, the increase for these very young children is not significant and has the lowest AAPC when compared with other age groups. The highest increases were observed in the age group 10–14 years (AAPC 2.6%). Both sexes show significant increase in rates.

Germ-cell tumours increased overall (AAPC 1.6%, $P < 0.0001$). The rates did not increase in the British Isles and the East, while remarkable increases were seen for the other regions (AAPC for North: 3.2%, South: 5.9%, West: 2.3%). For Europe as a whole, the largest age-specific increases were seen in infants and in children in the age group 10–14 years, which corresponds to the bimodal age distribution of incidence rates. Increasing trend was more pronounced in girls than in boys, again reflecting the frequency distribution of these tumours by sex.

The overall increases in *carcinomas and other malignant epithelial neoplasms* can also be observed in the British Isles and in the South. The decrease seen in the West resulted from the exceptionally high ASR observed in the period 1978–1982, which was based on very few cases. For Europe as a whole, a significant trend was seen for thyroid carcinoma (439 cases, AAPC 3.0%, $P = 0.003$). This is mainly due to remarkably high ASR of 1.7 and 1.8 for the South in the periods 1988–1992 and 1992–1997.

The remaining heterogeneous and uncommon twelfth group of *other and unspecified malignant neoplasms* showed no marked trend overall nor for age group, sex or region. The only region with a significant increase was the British Isles, based on 106 cases.

Similarly, no trend was observed for the incidence of the specially defined NOS group of tumours, comprising 3655 cases. The change of ASR from 7.4 in 1978–1982 to 5.9, 5.4 and 5.8 in the following 5-year periods was accompanied by an entirely inconspicuous AAPC (0.6%) (data not shown in Tables).

4. Discussion

Over the study period 1978–1997 we have shown that there was a significant increase in childhood cancer incidence in Europe, rising by 1.1% per year on average. This result is based on a data-set of 77,111 cases. In total, cases were registered in 33 population-based cancer registries from 15 countries with comparable data of high quality. This increase is represented by a change in the ASR from about 120 per million children observed in 1978–1982 to 140 in 1993–1997. In each 5-year period, the incidence rate was higher than that in the preceding one. Overall incidence has increased in both sexes and in all four age groups. Similar results were obtained previously, using the data from the same cancer registries, for all years available during a longer time-period: 1970–1999.[14] In the current study, we have reduced the observation period by a third, accounting for a weaker coverage of the early 1970s and late 1990s in the participating cancer registries, and found concordant results.

As before,[14] this study confirms an increase in the majority of the tumour groups. Adamson and colleagues[15] considered this universal increase as a sign of a general improvement in the completeness of cancer registration. Although such improvement may play a role, our data do not support this reasoning. One example is provided by the observation that not all tumour groups show an increase. So the European incidence rates did not change either for retinoblastoma, hepatic tumours, bone tumours and the group of other and unspecified malignant neoplasms (group XII of ICCC).

The comparison of the incidence trends between the groups of specified and unspecified tumours lends further support to a limited role of the improvement in cancer registration in the overall increase. The constantly small numbers of cases in group XII over the study period indicate that any improvement in diagnosing childhood cancer was reflected only in the increases in the specific tumour types. The data from the cancer registries were thus fine enough to detect the changes in diagnostic methods, which have certainly occurred at least for tumours of the CNS system, with most universal increase (overall and across patients' subgroups). However, a general improvement in cancer registration would imply more cases in all tumour types and notably the unspecified, as a reflection of more complete ascertainment of all sources. At the same time, the proportion of cases diagnosed by various methods changed only very little over time (the proportion of DCO cases in the registries with access to this source of data was less than 1% in all time periods, that of MV was around 95%) [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. The absence of any time trends was also observed in the specially constituted group of unspecified cancers (NOS), which comprised the 'unspecified' morphologies from all ICCC categories. Our data show, that while the improvement in diagnosing childhood cancers may be reflected in the increase, there is lack of evidence for improvement in the ascertainment.

Having said that, improvement in the completeness of childhood cancer registration cannot be excluded and is indeed desirable. However, the extent of possible improvement in registration completeness, as evaluated from the data available, was insufficient to account for the extent and patterns of the increase, discussed in the following paragraphs. In the absence of a 'gold standard', other than a population-based cancer registry, no direct method of evaluation of completeness and its change over time exists. Evaluation of the completeness of registration and its changes over the time within the ACCIS database in the future is proposed elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

Incidence rates for all tumours combined had increased in all five regions of Europe. Considering the variable composition of each region, in terms of the type and number of the contributing registries as well as the length of their registration periods, the consistency of the increase across the regions argues in favour of the persistent rise of the background cancer incidence rates in childhood population.

At the same time, the variability in the rate of increase by tumour type across the regions is inconsistent with the assumption of registration improvement. A general improvement in registration would result in coherent increases, while only for the CNS tumours our data show an increase in all five regions. Undoubtedly, changes and improvements in tumour classification may have resulted in exchange of cases between some tumour groups over time, e.g. bone tumours versus soft tissue tumours or specified versus unspecified

groups. However, the potential existence of such exchanges would not explain the overall increase in the incidence rates.

Overall, and in some individual tumour groups (lymphomas, sympathetic nervous system tumours, renal tumours, carcinomas), the rate of temporal change by age group at diagnosis is roughly proportionate to the usual age-distribution for these tumour types. This observation would be consistent with the increase due to improving registration. However, for other tumour types (leukaemia, CNS tumours, soft tissue sarcomas, germ-cell tumours) the rate of increase was not proportional to the background age-specific incidence. Furthermore, the average increase was faster in girls than in boys, although the baseline cancer incidence was higher in boys, compared with girls. It is not conceivable in the populations and periods covered, that the baseline sex differences in childhood cancer incidence would reflect differential registration of boys and girls. The rate of increase disproportionate to the baseline rates is in contradiction with the hypothesis of a general improvement in registration, which is expected to affect all region-, age- and sex-specific patients' groups proportionately.

In general, the registration artefacts possibly influencing incidence time trends include changes in coding practice (e.g. benign tumours become malignant), diagnostic interdependency between different diagnostic groups (e.g. 'exchange' of cases between leukaemia and lymphomas), changing modes of operation (e.g. eligibility criteria for registration) or legislation (e.g. compulsory registration, confidentiality restriction), etc. However, our data do not provide sufficient information or evidence for such registration artefacts.

Advanced diagnostic procedures were partly reflected in the barely increasing proportion of microscopically verified cases (from 94% in 1978–1982 to 96% in 1993–1997), but mainly in the increase in the non-malignant tumours of the brain (about 3% over the 20 year study period) [Peris-Bonnet and colleagues, this issue]. The improvement in diagnostic techniques may inflate the incidence rates by diagnosing potentially latent tumours (e.g. some neuroblastomas), or advancing diagnosis to the childhood ages (e.g. brain tumours). This may be especially true for infants, in whom the tumours previously undetected may be diagnosed nowadays by non-invasive diagnostic techniques. Also, the screening for neuroblastoma, whether systematic or opportunistic (due to the larger use of ultrasound), carried out in some European regions, might have contributed to the increase in incidence rates of this tumour. However, screening cannot explain completely this effect, since the highest increase was seen in the East, the region where no screening programme was organised [Spix and colleagues, this issue].

In this paper, the time trends were analysed using relatively simple methodology, based on Poisson regression analysis of rate on calendar year, adjusted for possible confounders. This quite simple method is appropriate, given the descriptive aim of the paper. As it uses a summary statistic for describing the trend for the whole period it may not be able to detect variations in the trends within the period. More sophisticated trend models, such as step functions or piecewise linear functions (e.g. joint-point analysis) could possibly provide a more precise description of the data; they may not necessarily help to explain the causes of the increasing trend, unless an *a priori* hypothesis for the increase was available.

The registries included in this study do not have identical periods of activity, which may influence the observed time trend.[18] However, in the database used for the current analyses, the incidence rates were increasing irrespective of the choice of registries into the pool of data [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

It is also evident that the time trends observed in the large contributing registries will have influenced the overall results. For example, Piedmont and Slovenia registries contribute about half of all cases in the group of the 10 southern registries, just as the two registries of England & Wales and Germany do for the whole of Europe (Table 1). However, adding many smaller registries further increases the study size. The larger the pool of data, the smaller the changes in incidence may be discerned. The significant result, despite the heterogeneity of the database, gains in reliability. Furthermore, inclusion or exclusion of the two largest cancer registries did not seem to affect the incidence trends substantially [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

Incidence of several childhood cancer types has been reported to increase in several industrialised countries, although the tumour types involved and interpretation of the time trend differed. An increasing trend for all malignancies was observed both in Great Britain,[1–3] which go back to the 1950s, and in Sweden.[5] An increase for leukaemia was observed in Great Britain,[1,2] Italy[7] and Sweden,[5] but not in another study on the Nordic countries.[4] Incidence of CNS tumours was increasing mostly invariably, while the analyses of the incidence time trends for the remaining types of solid tumours were often difficult due to the low numbers of cases.

Results from SEER database (USA) for the period 1975–2001 are particularly relevant because of the size and the quality of the database[9]: they revealed a statistically significant increasing trend for total neoplasms as well as for leukaemia, CNS tumours, hepatoblastomas, osteosarcomas, soft tissue sarcomas, gonadal tumours, carcinomas and melanomas, while Hodgkin's disease showed a decreasing trend. Bunin and colleagues[10] presented a similar analysis for the Greater Delaware Valley Pediatric Tumor Registry (not included in SEER) which gave similar results for lymphomas, CNS tumours and all malignancies, however they did not observe any trend for leukaemias. A rising trend was found for neuroblastomas in the USA by Bunin and colleagues,[10] but not in the SEER data.[9] For Australia, significant increases were found for all malignancies and, among others, for acute non-lymphocytic leukaemias,[11] while in New Zealand there was an increase for lymphoid leukaemias, but not for acute non-lymphocytic leukaemias.[12] In Japan an increase in neuroblastomas was observed.[13]

While it is generally accepted that the increase in the tumours of nervous tissues is due to changes in diagnostic practices, this explanation of the trends is less evident for other tumour types. The increase in incidence rates of CNS tumours, observed in the mid-1980s in the USA, were explained by the jump model, whereby the increase coincided with the spread of magnetic resonance imaging in that period.[19] The

rising incidence of neuroblastoma in Japan was due to newly established screening programmes.[13] To explain the rising incidence of other tumours, some studies advance evidence for changes in the risk factors, rather than improvement in registration or other artefacts. For example, McNally and colleagues entitled their paper 'temporal increases ... are likely to be real'.[1]

Based on our data, we attribute the observed increase in incidence rates only marginally to the artefacts in cancer registration and selectively to improvement in diagnosis. Furthermore, we advance changes in risk factors as the explanation of the observed changes, at least to certain extent. Such risk factors are undoubtedly numerous and variable and they are not well understood. Some of them may be related to changes that had occurred in the studied populations, characterised by increasing mobility of humans and changing exposure to a variety of artificial and natural agents. Changes in lifestyle, familial aggregation, maternal diet and reproductive history, pregnancy and perinatal factors, responses of the immune system and the environmental exposures were also reportedly associated with risk of childhood cancer.[20,21] Changes in genetic factors cannot be excluded, due to improved medical care, which allows affected individuals reaching the reproductive age and possibly transferring predisposition to certain cancers. The risk factors were probably best studied for leukaemias, for which environmental factors may be responsible. But the factors challenging the immune system, such as infectious agents or atopic diseases, seem to play an increasing role in the development of leukaemia.[22–25] For CNS tumours, changes in environmental exposures or gene environment interactions, such as ionising radiation, pesticides or maternal diet have been suggested as being possibly responsible for the increase in incidence rates.[26] The possible risk factors are also discussed in the tumour-specific papers of this issue.

Childhood cancers are uncommon events, measured in numbers of cases per million. The European scale of this project is therefore a prerequisite for study of incidence time trends. Simultaneously, further efforts should be expended on the quality and comparability assurance, notably formal evaluation of completeness. The increase in incidence rates observed in this study reflects partly improvement in diagnostic techniques. Improvements in registration completeness cannot be excluded, although our data do not provide evidence for this. The nature and extent of the increases observed suggest changes in the background risk factors.

Conflict of interest statement

None declared.

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