Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study

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See Comment page 2074

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Summary

Background **Cancer is rare before age 20 years. We aimed to use the European database of childhood and adolescent cancer cases, within the Automated Childhood Cancer Information System project, to estimate patterns and trends of incidence and survival within Europe.**

Methods **Comparable, high-quality data from 63 European population-based cancer registries consisted of 113 000 tumours in children and 18 243 in adolescents diagnosed in 1970–99. Incidence rates and survival were compared by region (east *vs* west), period, and malignant disease.**

Findings **In the 1990s, age-standardised incidence rates were 140 per million for children (0–14 years) and 157 per million for ages 0–19 years. Over the three decades, overall incidence increased by 1·0% per year (p<0·0001) in children (increases for most tumour types), and by 1·5% (p<0·0001) in adolescents (15–19 years; notable increases were recorded for carcinomas, lymphomas, and germ-cell tumours). Overall 5-year survival for children in the 1990s was 64% in the east and 75% in the west, with differences between regions for virtually all tumour groups; 5-year survival was much the same in adolescents. Survival has improved dramatically since the 1970s in children and adolescents, more so in the west than in the east.**

Interpretation **Our results are clear evidence of an increase of cancer incidence in childhood and adolescence during the past decades, and of an acceleration of this trend. Geographical and temporal patterns suggest areas for further study into causes of these neoplasms, as well as providing an indicator of progress of public-health policy in Europe.**

Introduction

In European populations, about 1% of all malignant neoplasms arise in patients younger than 20 years.[1] This low frequency represents a major difficulty for studies of putative risk factors and clinical management, and is further accentuated by the many childhood tumour types that are uncommon in adults.

The Automated Childhood Cancer Information System (ACCIS) is a European Union funded project aiming at collection, presentation, and interpretation of data for cancer incidence and survival in children (aged 0–14 years) and adolescents (aged 15–19 years) in Europe. The ACCIS database contains data from 80 population-based cancer registries that cover about half the population aged 0–14 years and about a quarter aged 15–19 years living in the 35 participating countries.[1] It covers 1·3 billion person-years, giving rise to over 160 000 cases of childhood and adolescent cancer diagnosed from 1970 to 2001.

ACCIS provides a unique source of information for studies of causes of childhood cancer as well as for public-health purposes, by monitoring the patterns and trends of incidence and population-based survival in children and adolescents. We aimed to systematically analyse the ACCIS database with respect to aetiological research and public-health importance.

Methods

Procedures

Information was extracted from the ACCIS database about all malignant neoplasms, together with non-malignant tumours of the CNS, that were registered since the 1970s in patients younger than 20 years. A standard set of variables included basic demographic data (age, sex, and country or region of residence), information on the tumour (date of incidence, site, morphology, basis of diagnosis, grade, and laterality) and on follow-up (date of last contact and vital status). The underlying population-at-risk for each combination of registration area, calendar year, sex, and age (single year) was supplied from official national statistics, or was estimated by linear interpolation of available data. Details of registration practices and data coding were obtained for each registry.

Data were verified in the International Agency for Research on Cancer to reduce the number of errors.[2,3] The tumours, usually coded to ICD-O-2,[4] were grouped according to the International Classification of Childhood Cancer,[5] for presentation of the results. The duration of survival for every patient was calculated from the date of diagnosis and the date and status at last contact of every patient. The ACCIS Scientific Committee assessed quality and comparability of data using standard criteria.[6] Only datasets meeting defined

quality criteria for completeness, validity, and comparability were included in this study. The datasets excluded from the analyses consisted of 20% of available person-years in the age-group 0–14 years and 49% in the age-group 15–19 years for geographical analyses; 11% in the 0–14 years age-group and 29% in the 15–19 years age-group were excluded from analysis of time trends.

Consequently, data from 63 population-based cancer registries in 19 countries were included (figure 1), totalling 113 000 tumours in children and 18 243 in adolescents. There were 12 paediatric cancer registries and 14 with national coverage (including five paediatric registries). Registries were included in different types of analyses depending on their coverage of geographical area, period, and age-range (table). In case of overlap of two registration areas, the larger of two registries was included in a particular analysis.

Countries were classified as east or west (table). East included former socialist economy countries of central and eastern Europe; Turkey was included on geographical criteria. Data from East Germany, available for 1970–89, were used only for incidence analyses of Europe as a whole, because this part of the country belonged to the east during that period but to the west after the start of its coverage by the national German Childhood Cancer Registry in 1991. The ACCIS project was approved by the ethical committee of the International Agency for Research on Cancer.

Figure 1: **Coverage of populations of children or adolescents (%) in named countries in study**

Statistical methods

Incidence rates were calculated with standard methods[7] as the average annual number of cases per million person-years. Age-standardised incidence rates (ASRs) were calculated with 5-year age-specific incidence rates (for age-groups 0–4, 5–9, 10–14, and 15–19 years) and the weights of the world standard population.[8] 95% CIs for the incidence rates were calculated with the Poisson approximation;[7] those for the age-specific rates in the age-groups with fewer than 30 cases were calculated exactly.[9]

Pairs of age-specific incidence rates were compared by a normal test with a continuity correction.[9] Differences in incidence rates for geographical areas were measured with Poisson regression models and expressed as incidence rate ratio (IRR). These ratios were adjusted for sex and age-group, as long as these variables contributed significantly to the fit. The null hypothesis was IRR=1 (no difference between incidence rates in the two geographical areas). Change of these rates over time was calculated from a Poisson regression model, including year, sex, and age-group, as appropriate, and expressed as average annual percent change (AAPC). The null hypothesis here was that change (slope of the regression line of incidence rate) over time is zero. The study period covered three decades: 1970s, 1980s, and 1990s.

Population-based survival of cancer patients was analysed by the life-table method,[10] which is appropriate for survival analysis of aggregated data such as those obtained by population-based cancer registries. Patients with zero survival time were excluded from the analyses (notably those registered from death certificate only). The reported 5-year survival is the actuarial cumulative probability of surviving to the fifth anniversary of the date of incidence. Cumulative survival probability is plotted as a continuous line, joining the cumulative probabilities of survival for each year after diagnosis. To avoid nonsense values of confidence limits for small samples with the Greenwood formula, asymptotic 95% CIs of cumulative probability of survival were calculated.[11] Differences in survival of two or more groups of patients were compared for the entire survivorship curves by the log-rank χ^2 test.[9] STATA software (version 8.2) was used for most analyses.

Role of the funding source

The sponsors had no role in data collection, data analysis, data interpretation, writing of the report, or the decision to publish.

Results

The overall average annual ASR for cancer in children in Europe in the 1990s was 140 per million, based on 48 847 cases. The ASR for the age-range 0–19 years was

	Coverage			Average annual number of cases in 1990s	Region	Periods included in analyses		Follow-up	
	Registry	Age-range (years)	Notes			Geographical comparison	Time trends	End of follow-up	Notes
Belarus	National	0–14	P	353	E	1990–98		01 Sept, 200	
Denmark	National	0–19		143	W	1990–98	1978–98	31 Dec, 1997	
Estonia	National	0–19		42	E	1990–97	1970–97	31 Dec, 1998	
Finland	National	0–19		166	W	1990–98	1970–98	31 Dec, 1998	
France	Brittany	0–14	P	75	W	1991–97		01 Jan, 2000	
France	Lorraine	0–14	P	63	W	1990–97	1983–97	01 Jan, 1999	
France	PACA and Corse	0–14	P	115	W	1990–96	1984–96	31 March, 1998	
France	Rhone-Alpes	0–14	01, P	140	W	1990–99		01 June, 2000	
France	Doubs	0–19		12	W	1990–96	1978–96	01 June, 2001	
France	Herault	0–19		21	W	1990–98		NA	
France	Isere	0–19	01	39	W	1990–97	1979–97	NA	
France	Manche	0–19		13	W	1994–96		31 May, 2000	FY 1994–95
France	Bas-Rhin	0–19		29	W	1990–96	1975–96	31 Dec, 1997	
France	Haut-Rhin	0–19		19	W	1990–97		31 Dec, 1995	FY 1990–91
France	Somme	0–19		15	W	1990–96	1982–96	15 Aug, 2000	
France	Tarn	0–19		7	W	1990–97	1982–97	NA	
Germany	National	0–14	P	1737	W	1991–99	1991–99	31 Dec, 1998	
Germany	Former East	0–19		407	Europe		1970–89	31 Dec, 1987	FY 1970–87
Germany	Former West	0–14	P	1268	W	1990–90	1980–90	31 Dec, 1998	
Hungary	National	0–14	P	250	E	1990–99	1977–99	01 Jan, 2000	
Iceland	National	0–19		9	W	1990–99	1970–99	31 Dec, 2000	
Ireland	National	0–19		109	W	1994–97		31 Dec, 1998	
Italy	Piedmont, paediatric	0–14	02, P	92	W	1990–98	1976–98	31 Dec, 1999	
Italy	Marche	0–14	03, P	30	W	1990–98		30-Sept, 2000	
Italy	Ferrara	0–19		6	W	1991–95		31 Dec, 1998	
Italy	Latina	0–19		9	W	1990–97	1983–97	31 Dec, 1998	
Italy	Liguria	0–19		10	W	1990–95		15-April, 2000	
Italy	Lombardy	0–19		19	W	1990–97	1976–97	23 Sept, 1999	
Italy	Macerata	0–19	03	5	W	1991–98		30-Sept, 2000	
Italy	Parma	0–19		6	W	1990–95	1978–95	01 April, 1999	
Italy	Piedmont, general	0–19	02	19	W	1990–98		31 May, 2001	
Italy	Ragusa	0–19		8	W	1990–97	1981–97	30-March, 2000	
Italy	Sassari	0–19		10	W	1992–95		30-Dec, 1999	
Italy	Tuscany	0–19		23	W	1990–97		31 Dec, 1998	
Italy	Umbria	0–19		20	W	1994–96		31 Dec, 1999	
Italy	Veneto	0–19		41	W	1990–96		31 Dec, 1998	
Malta	National	0–19		10	W	1990–99		31 Dec, 1999	
Netherlands	National	0–19	04	379	W	1990–95		31 Dec, 1998	FA 0–14
Netherlands	Eindhoven	0–19	04	25	W		1978–97	01 July, 1999	
Netherlands	DCOG	0–14	04, L, P	115	W	1990–99	1973–99	01 Jan, 2000	
Norway	National	0–19		117	W	1990–97	1970–97	01 Jan, 2000	
Slovakia	National	0–19		156	E	1990–97	1978–97	31 Dec, 1997	
Slovenia	National	0–19		49	E	1990–97	1970–97	31 Dec, 1999	
Spain	National	0–14	05, P, Z	229	W	1990–95		31 Dec, 2000	
Spain	Albacete	0–19		8	W	1991–97		15-Sept, 2000	
Spain	Asturias	0–19		23	W	1990–97	1982–97	31 Dec, 1997	
Spain	Basque Country	0–19	05	40	W	1990–94		31 Dec, 2000	
Spain	Canaries	0–19		38	W	1993–96		NA	
Spain	Girona	0–19	05	10	W	1994–97		31 Dec, 1997	
Spain	Granada	0–14		20	W	1990–97		31 Dec, 1999	
Spain	Malorca	0–19	05	17	W	1990–95		31 Dec, 1998	
Spain	Navarra	0–19	05	8	W	1990–96	1973–96	31 Dec, 1997	
Spain	Tarragona	0–19	05	13	W	1990–97	1980–97	31 Dec, 1998	
Spain	Zaragoza	0–19	05	13	W	1990–96	1978–96	31 Dec, 1996	
Switzerland	Basel	0–19		10	W	1990–98	1981–98	30-June, 2000	
Switzerland	Geneva	0–19		10	W	1990–98	1970–98	31 Dec, 1999	
Switzerland	Graubunden and Glarus	0–19		6	W	1990–97		25-May, 2000	
Switzerland	St Gallen and Appenzel	0–19		13	W	1990–97	1983–97	01 Feb, 2001	
Switzerland	Valais	0–19		8	W	1990–97		01 Dec, 1998	FY 1990–93
Turkey	Izmir	0–19		83	E	1993–96		NA	
UK	England and Wales	0–14	P	1268	W	1990–95	1971–95	31 Jan, 2001	
UK	Northern Ireland	0–19		56	W	1993–96		31 Dec, 1999	
UK	Scotland	0–19		126	W	1990–97	1975–97	31 Dec, 1999	

DCOG=Dutch Childhood Oncology Group. E=included in analysis for east. Europe=included in incidence analysis for pooled European data only. FA=follow-up data only available for the patients of the specified age-range. FY=follow-up data only available for patients diagnosed in specified calendar period. L=national registry of paediatric leukaemias. NA=follow-up data not available. 01, 02, 03, 04, 05=part overlap of registration coverage. P=specialised paediatric cancer registry. PACA=Provence, Alpes, and Cote d'Azur. W=included in analysis for west. Z=complete for selected regions only.

Table: **Coverage by country of contributing registries and constitution of datasets for various analyses**

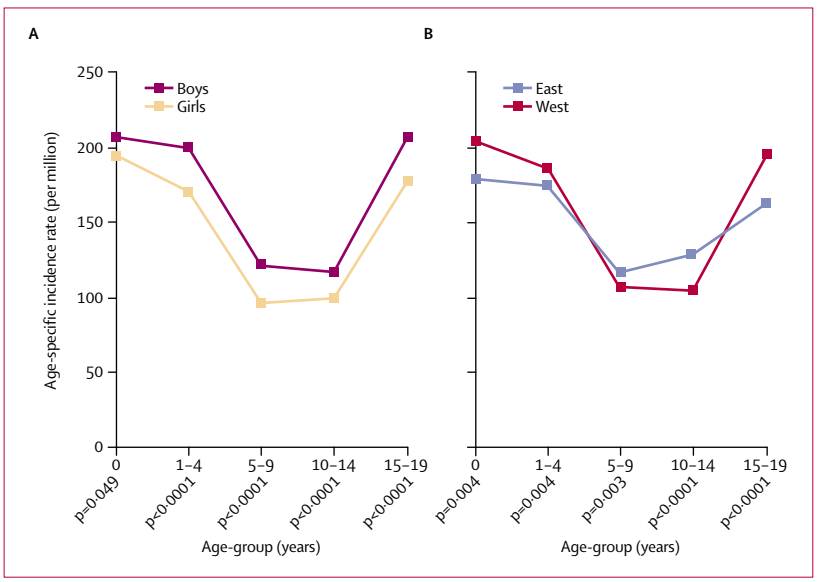

Figure 2: **Age-specific incidence rates of cancer in Europe for the 1990s by (A) sex and (B) geographical area**

157 per million, and the age-specific rate for adolescents was 193 per million (n=7109). In children, the overall cancer incidence in the east (ASR 143 per million, n=7650) was slightly higher than that in the west (ASR 140 per million, n=41197); the IRR adjusted for age and sex was 1·05, (95% CI 1·03–1·08, p<0·0001). In adolescents, the age-specific incidence rate in the east (166 per million, n=948) was significantly lower than that in the west (198 per million, n=6161; IRR=0·8 [0·8–0·9], p<0·0001). In all age-groups, incidence was significantly higher in boys than in girls (figure 2). The age-specific incidence rates for the two geographical areas differed significantly in all age-groups, although the direction of the difference varied (figure 2).

Figure 3 shows the proportions of tumour types, defined by the main diagnostic groups of the International Classification of Childhood Cancer,[5] for the five age-groups. The most common tumour type in infants was neuroblastoma (1260 [28%]). Leukaemias were most common in the age-group 1–4 years (7150 [41%]), and CNS tumours in the age-group 5–9 years (3748 [28%]). After age 10 years, embryonic tumours, such as retinoblastoma, nephroblastoma (most renal tumours), and hepatoblastoma (most hepatic tumours) almost disappeared, whereas other cancers became more frequent, notably lymphomas, carcinomas, germ-cell tumours, and bone tumours. In adolescents, lymphomas represented 25% (1745) and carcinomas 20% (1404) of the total. On the whole, the most common tumour types in children were leukaemias (ASR 44·8), CNS tumours (29·8), and lymphomas (15·5). In children, significant differences between the two geographical areas were recorded for leukaemias, carcinomas, CNS tumours, and lymphomas (p<0·0001). In the east, the ASR for leukaemias was 39·3 per million (n=2018), whereas in the west it was 45·7 per million (n=13 763; IRR 0·9 [95% CI 0·8–0·9]). The ASR for carcinomas was 11·8 per million (n=758) in the east and 2·7 per million in the west (n=925; IRR 4·4 [4·0–4·8], p<0·0001). CNS tumours were more common in the east (ASR 32·1, n=1741) than the west (ASR 29·4, n=8874; IRR 1·1 [1·0–1·2], p=0·0005). Lymphomas were more common in the east (ASR 17.4, n=1018) than in the west (ASR 15·2, n=4903; IRR 1·1 [1·1–1·2], p=0·0005). Smaller differences were recorded for retinoblastoma (east ASR 3·2, n=139 *vs* west ASR 4·0, n=1052; IRR 0·8 [0·7–1·0], p=0·058), hepatic tumours (east ASR 1·8, n=81 *vs* west ASR 1·4, n=377; IRR 1·3 [1·0–1·6], p=0·04), and germ-cell tumours (east ASR 3·9, n=206 *vs* west ASR 4·7, n=1396; IRR 0·8 [0·7–0·97], p=0·017).

The higher incidence of leukaemias in the west than in the east was mainly due to the peak in occurrence of lymphoid leukaemia at around age 2–3 years, which was more pronounced in the west than in the east. This difference seemed to be diminishing over time (figure 4), although in the 1990s, it was still significant for the age-group 1–4 years (p<0·0001).

In adolescents, the highest incidence rates were for lymphomas (European age-specific rate 47·4 per million), followed by carcinomas (38·1), CNS tumours (24·6), germ-cell tumours (24·5), and leukaemias (23·4). The largest difference between the two regions was for carcinomas (rate: east 27·4, n=156 *vs* west 40·1, n=1248; IRR 0·7 [0·6–0·8], p<0·0001), lymphomas (rate: east 40·2, n=229 *vs* west 48·7, n=1516; IRR 0·8 [0·7–0·9], p=0·007), leukaemias (rate: east 19·0, n=108 *vs* west 24·2, n=754; IRR 0·8 [0·6–0·96], p=0·018), soft-tissue tumours (rate: east 9·5, n=54 *vs* west 14·3, n=444;

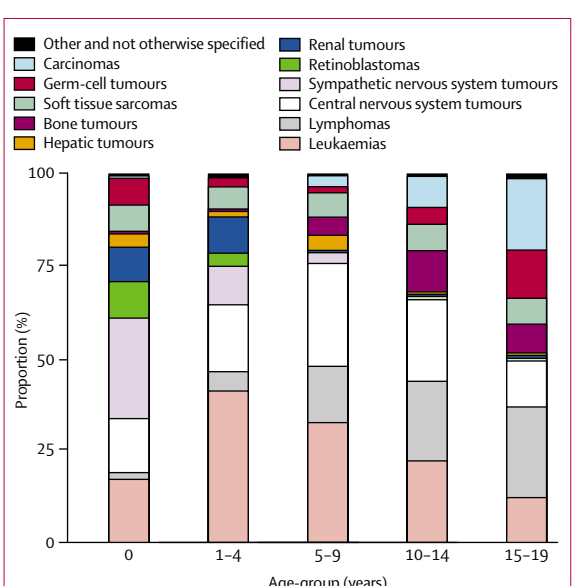

Figure 3: **Proportions of the 12 main tumour groups by age**

IRR 0·7 [0·5–0·9], p=0·005), and bone tumours (rate: east 12·6, n=72 *vs* west 16·1, n=501; IRR 0·8 [0·6–1·0], p=0·057).

The overall incidence rates of cancer have been increasing over time in all ages. The difference in age-specific rates between the first and the last decade was significant at all ages, and it was largest at the beginning and end of the age-range (figure 5). Based on 100 596 children with cancer, the average ASR per million was 118 in the 1970s, 124 in the 1980s, and 139 in the 1990s. The average annual change was 1·0% (p<0·0001): 0·8% (p<0·0001) between the 1970s and 1980s and 1·3% (p<0·0001) between the 1980s and 1990s. The rates increased slightly faster in the east than the west, but this difference was not sufficient for region to contribute significantly to the model.

In children, significant increases were evident for all leukaemias (AAPC 0·7%, p<0·0001), and the incidence of lymphoid leukaemia rose by an average of 1·4% per year (p<0·0001). The incidence of lymphomas increased by 1·3% per year (p<0·0001), with Hodgkin disease rising fastest (AAPC 1·5%, p<0·0001). The incidence of CNS tumours rose more rapidly in the east (AAPC 2·5%, p<0·0001) than the west (AAPC 0·8%, p<0·0001). A highly significant increase (p<0·0001) was also recorded for neuroblastoma (AAPC 2·0%), soft tissue sarcomas (AAPC 1·8%), and germ-cell tumours (AAPC 2·3%). Renal tumours rose by 1·1% per year (p=0·017), hepatic tumours by 1·0% (p=0·027), and bone tumours by 0·4% (p=0·023). Rates of retinoblastoma have been increasing only in the age-group 0, by 1·1% per year (p=0·018). There was no change in the incidences of carcinomas, and a significant decrease was evident for the other and unspecified tumours, at a rate of –4·1% per year (p<0·0001).

In adolescents, the age-specific rates per million were 147 in the 1970s, 165 in the 1980s, and 193 in the 1990s, on the basis of 15 460 cases. The AAPC was 1·5% (p<0·0001): about 1·3% between the 1970s and 1980s (p<0·0001), and 1·8% between the 1980s and the 1990s (p<0·0001). During the 30 years, the rates rose faster in the east (AAPC 2·0%, p<0·0001) than the west (AAPC 1·7%, p<0·0001). The steepest increase in the age-specific incidence rates in adolescents was for carcinomas (AAPC 3·9%, p<0·0001), then lymphomas (AAPC 2·4%, p<0·0001), germ-cell tumours (AAPC 1·7%, p<0·0001), soft-tissue sarcomas (AAPC 2·6%, p<0·0001), and CNS tumours (AAPC 1·4%, p<0·0001). Rates of lymphomas rose by 1·4% (p=0·02) in the east and by 3·0% (p<0·0001) in the west. No change was measured in the group of bone tumours. Retinoblastoma, renal tumours, and neuroblastoma are rare in adolescents, and no increase was detected during the study period. As in children, the incidence of other and unspecified tumours decreased by 9·7% per year (p<0·0001).

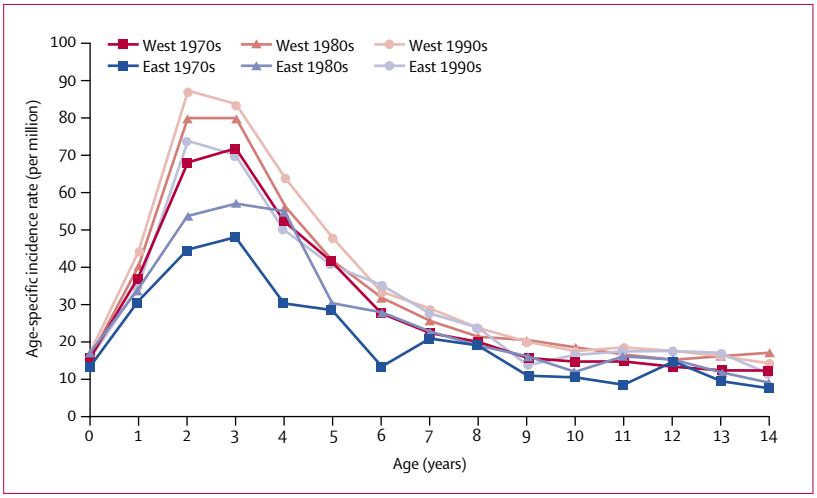

Figure 4: **Age-specific incidence rates of lymphoid leukaemia in children and adolescents**

Overall, 5-year survival of 44 438 children diagnosed in the 1990s in Europe was 73%. 5-year survival for 7512 children in the east was 64% (63–65%), and for 36 926 children in the west it was 75% (74–75%) (p<0·0001). Survival of children in the west was greater than that of children in the east for all tumour types except carcinomas. For these cancers, the 5-year observed survival was 86% (83–88%) in the west and 94% (92–95%) in the east (p<0·0001, figure 6). 5-year survival of the 5448 adolescents diagnosed in the 1990s was 73% (72–75%). In the east, of 912 adolescents, 63% (59–66%) survived for at least 5 years, compared with 75% (74–77%) of 4536 adolescents in the west (p<0·0001). The geographical differences were evident for most diagnostic groups, although they were slightly less clear-cut than those for children (figure 6).

Population-based actuarial survival has increased greatly over the past 30 years. Overall 5-year survival for 20 735 children diagnosed in the 1970s was 44% (44–45%); for 38 659 children diagnosed in the 1980s, it

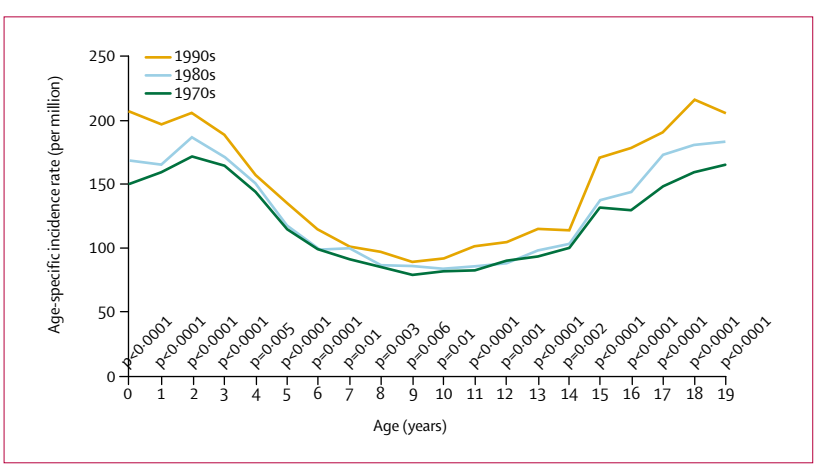

Figure 5: **Age-specific incidence rates of cancer in children and adolescents in Europe**
p values test difference between first and last decade.

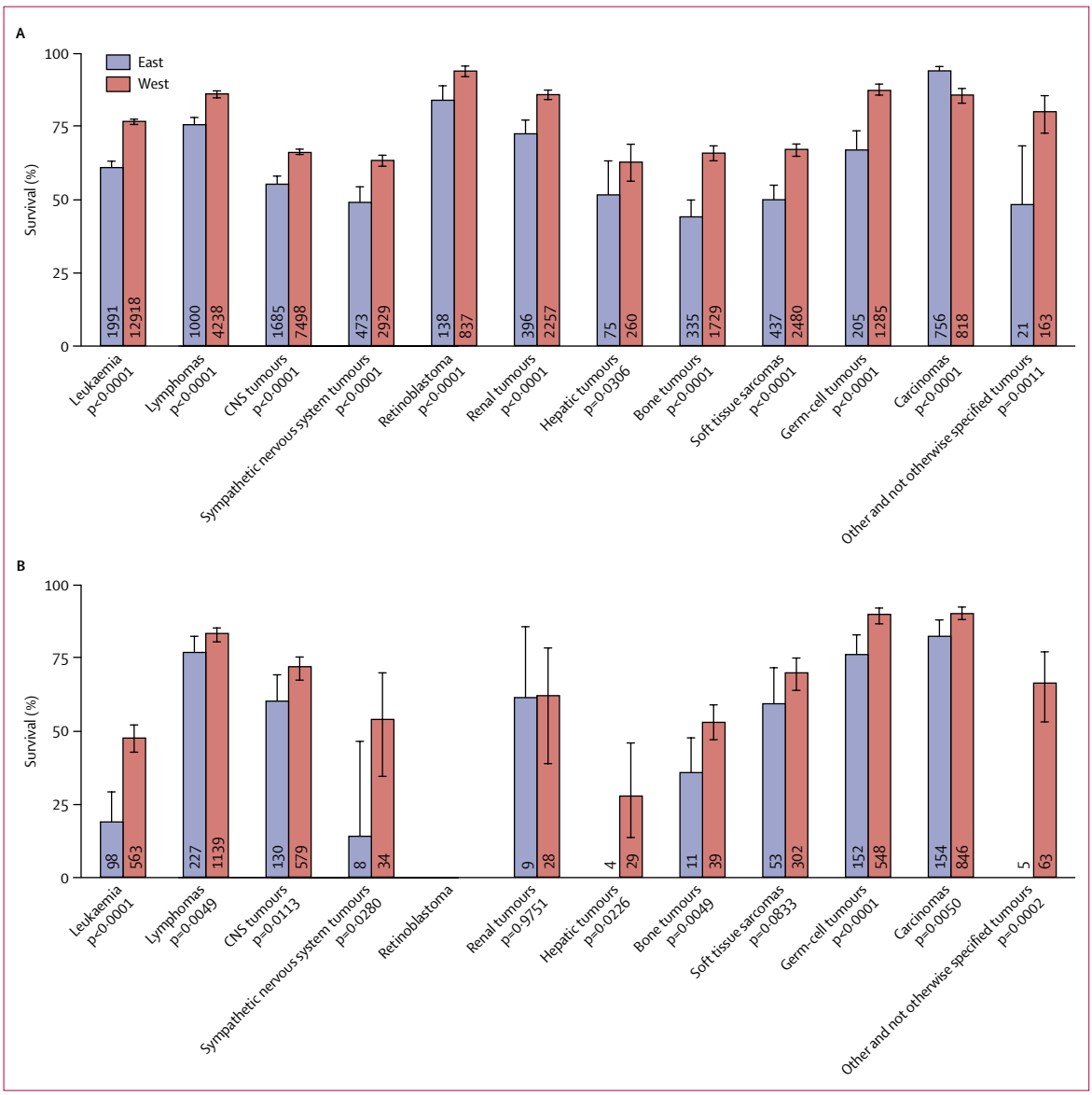

Figure 6: **5-year survival of (A) children and (B) adolescents diagnosed in the 1990s**
Vertical bars=95% CIs. Numbers=cases at risk tumour and region.

was 64% (64–65%), and for 34 319 children diagnosed in the 1990s, it was 74% (73–74%). The three survival curves differed significantly (p<0·0001). Figure 7 shows that this improvement in survival was in both regions of Europe, although to a lesser extent in the east. The survival curves for the three decades differed significantly in both: east (p<0·0001) and west (p<0·0001). 5-year survival of children rose significantly over the study period in all diagnostic groups, including carcinomas (p=0·0044, figure 8).

5-year actuarial survival for the 4004 adolescents diagnosed in the 1970s was 50% (48–51%); for the 6234 adolescents diagnosed in the 1980s, it was 63% (62–64%), and for those 4134 diagnosed in the 1990s, it was 74% (73–76%). The three survival curves differed significantly for all tumours combined (p<0·0001), as well as for leukaemias (p<0·0001), lymphomas (p<0·0001), CNS tumours (p<0·0001), bone tumours (p<0·0001), soft tissue sarcomas (p<0·0001), germ-cell tumours (p<0·0001), and carcinomas (p<0·0001, figure 8).

Discussion

Our data provide strong evidence for an increase in incidence rates over time for virtually all neoplasms, continued improvement in survival, and a difference in survival between eastern and western Europe in children and adolescents. The registries in this study are

members of European Network of Cancer Registries, and adhere to international standards of data collection and coding.[12] Data were subjected to uniform checks, expert assessment, and centralised analysis. These safeguards, in addition to the large size of the samples for different analyses, render the results highly reliable and unambiguous.

Nevertheless, a few points should be borne in mind when interpreting these findings. The patterns for a specific group of patients are not necessarily homogeneous within that group. Categorisation of countries into regions, calendar periods, tumour groups, and so on, is arbitrary, and more detailed analyses of other groupings are being undertaken within the ACCIS project. The indicators for large geographical areas discount the existing differences between countries and between cancer registries within the same country. Although such numerous comparisons could be a subject of other reports, they might also overlook possible underlying patterns that are discernible only in a large pool of data. Undoubtedly, both approaches need to be considered in aetiological research.[13] The results for children include data from several paediatric registries, four of them with national coverage (five for leukaemias), and thus are based on a larger reference population than are those for adolescents. More registries contributed to the geographical comparisons than to the time trends. Each type of analysis, however, was based on all available European data of standard quality.

In the 1990s, the overall incidence rates in children were slightly higher in the east than in the west of Europe, whereas the opposite was true in adolescents. This difference is partly due to the age distribution of lymphomas between the two regions: the high incidence in childhood is compensated by low rates in older ages in the east, whereas the low rates in children are followed by high rates in adolescents in the west. This pattern has been described earlier and might be related to a combination of genetic factors, socioeconomic status, infection, and climate.[14–18] The 1990s childhood cancer incidence in the east was also affected by high rates of thyroid cancer in Belarus. Discarding the 603 thyroid cancer cases would reduce the overall ASR for the east to 133, significantly lower than the rate for the west (140). Therefore, the excess rate in children in the east can probably be entirely attributed to the Chernobyl accident in 1986.[19]

Although the overall incidence rates are higher for boys than for girls in all age-groups, some tumours are more frequent in girls, notably germ-cell tumours in specific age-groups, and thyroid carcinomas.

Perhaps the most striking result is the clear evidence of an increase of cancer incidence in childhood and adolescence during past decades, and of the acceleration of this trend. The reduction in the incidence of the unspecified tumour group could indicate an improvement in diagnostic methods and coding of tumours, but it can explain only a small part of the overall increases for specific cancer. Another source of potential artifact could be an improvement in efficiency of registration of eligible cancer cases in Europe. We reduced a possible bias by selecting only the cancer registries gathering data over long periods for the analyses of the time trends. Although the increase was in all ages, this was true to a much larger extent for the youngest and the oldest age-groups. A large part of the increase is due to the rise in leukaemias (the peak of the lymphoid leukaemia in young ages) and lymphomas (peak in adolescents, especially for Hodgkin's disease). However, incidence rates were rising in almost all diagnostic groups, pointing to a true increase in the overall incidence rates of cancer in children and adolescents. Thus, our findings add convincing evidence to reports suggesting a rise in several childhood tumour types in Europe.[20–23] The increase was about 11 additional cases per million children per decade, and 23 additional cancer cases per million adolescents per decade. Considering all aetiological studies of childhood cancer, no single factor can be held responsible. Nevertheless, the changes in birthweight and exposure to infection might be good candidates.

To follow-up our important findings, it will be necessary to identify the tumour types and population groups that are specifically affected by these unfavourable trends, and to try to establish their reasons. The geographical variation in the available data will be especially useful in this process. The most obvious target for further research is the peak of lymphoid leukaemias in early childhood, which has been recorded in England and Wales and in the USA since the first half of the 20th century.[24] Geographical and temporal changes of this peak seem to be affected by both genetic and environmental determinants: the peak was more pronounced in populations of European

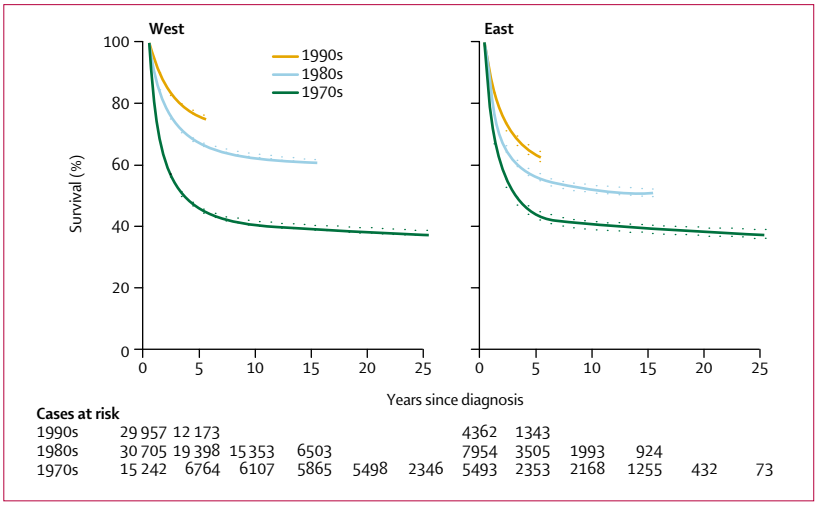

Figure 7: **Survival curves for children**
Dots=95% CIs.

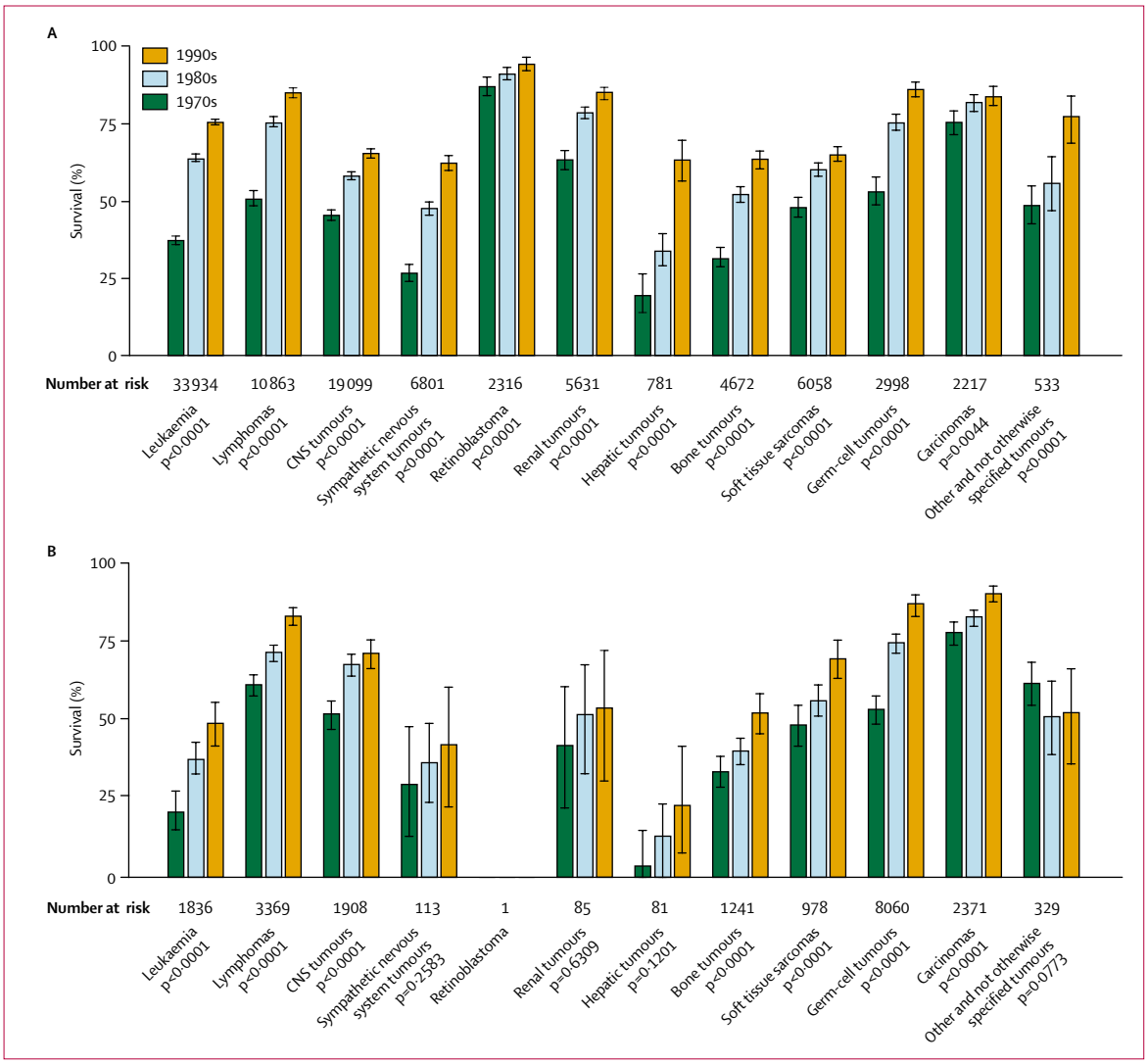

Figure 8: **5-year survival for (A) children and (B) adolescents in Europe**
Vertical bars=95% CIs. p values refer to log-rank test of equality of the entire survivorship curves for the three periods.

descent than in those of Asian or African descent; and within populations of similar ethnic origin it tended to be more pronounced in more affluent groups.[25–28] Additionally, the amplitude of the peak increases over time, which could be a surrogate for improvement of socioeconomic status, increased population mixing, or lack of exposure to certain viruses.[29–31]

The results with respect to survival confirm reports of improving survival of children with cancer.[32,33] Differences between the two regions of Europe are present for virtually all tumour types, and the rate of improvement in survival is slower in the east than in the west. The explanation could lie in earlier presentation, better referral, or greater availability of complex and expensive treatment regimens for childhood cancer cases in western Europe. These results provide a baseline against which improvements in policy and clinical care of children and adolescents with cancer can be monitored. Continuous updating of the ACCIS database is essential for this purpose.[34]

Contributors
F Berrino, J W Coebergh, P Kaatsch, B Lacour, M Parkin, and C Stiller are the members of the ACCIS Scientific Committee. They contributed to expert assessment of data quality and to writing of this report. E Steliarova-Foucher is the ACCIS coordinator, analysed data, and drafted the report.

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Conflict of interest statement

We declare that we have no conflict of interest.

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