available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Bone tumours in European children and adolescents, 1978–1997. Report from the Automated Childhood Cancer Information System project

C.A. Stiller[a,*], S.S. Bielack[b,c], G. Jundt[d], E. Steliarova-Foucher[e]

[a]Childhood Cancer Research Group, Department of Paediatrics, University of Oxford, 57 Woodstock Road, Oxford OX2 6HJ, UK
[b]Paediatrics 5 (Haematology, Oncology, Immunology), Olgahospital, Stuttgart, Germany
[c]University Children's Hospital Münster, Department of Paediatric Haematology and Oncology, Münster, Germany
[d]Basel Cancer Registry and Bone Tumour Reference Centre at the Institute of Pathology, University Hospital Basel, Basel, Switzerland
[e]Descriptive Epidemiology Group, International Agency for Research on Cancer, Lyon, France

ARTICLE INFO

Keywords:
Childhood cancer
Adolescent
Bone neoplasms
Osteosarcoma
Ewing's sarcoma
Europe
Epidemiology
Incidence
Survival
Registry

ABSTRACT

Data on 5572 children and adolescents diagnosed with malignant bone tumours (International Classification of Childhood Cancer, Group VIII) before the age of 20 years during 1978–1997 in Europe were extracted from the Automated Childhood Cancer Information System (ACCIS) database. Age-standardised incidence among children during the period 1988–1997 was similar for boys and girls aged 0–14 years (5.5–5.6 per million). Among adolescents aged 15–19 years, males had higher incidence (19.3 per million) than females (10.7 per million). Among children, osteosarcoma accounted for 51% of registrations and Ewing's sarcoma for 41%. Among adolescents, 55% of registrations were osteosarcoma and 28% Ewing's sarcoma. Both tumours had their highest incidence in late childhood or early adolescence. There were no significant time trends in incidence during 1978–1997. Five-year survival estimates for patients diagnosed during 1988–1997 were, respectively, 59% and 51% among children and adolescents with osteosarcoma and 62% and 30% among children and adolescents with Ewing's sarcoma. Between 1978–1982 and 1993–1997, survival increased for both children and adolescents with osteosarcoma, and for children with Ewing's sarcoma.

1. Introduction

Malignant bone tumours account for 3–5% of cancers diagnosed in children under 15 years of age[1] and 7–8% of those in adolescents aged 15–19 years in western populations.[2] Malignant bone tumours comprise more than 20 different entities, classified according to either the direct product of the tumour cells (e.g. osteoid in osteosarcomas) or the type of tissue they form (e.g. vascular channels in angiosarcoma of bone).[3] The great majority of malignant bone tumours occurring in young people under the age of 20 years are osteosarcoma and Ewing's sarcoma. Most malignant bone tumours, including both of these types, must be regarded as high-grade sarcomas that, at the time of diagnosis, are likely to have spread to distant sites, especially the lungs. In the pre-chemotherapeutic era, their prognosis was very poor, since treatment was focussed on local procedures.

Identified risk factors for osteosarcoma are limited to ionising radiation, e.g. radiotherapy for a previous cancer, and certain genetic conditions including familial retinoblastoma,

* *Corresponding author*: Tel.: +44 1865 315925; fax: +44 1865 315940.
E-mail addresses: charles.stiller@ccrg.ox.ac.uk, charles.stiller@ccrg.oxford.ac.uk (C.A. Stiller).
0959-8049/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2006.05.015

Li-Fraumeni syndrome and Rothmund-Thomson syndrome.[4,5] Ewing's sarcoma has long been known to have lower incidence among black and East Asian populations,[6] indicating that genetic factors may be important in its aetiology. Cytogenetic differences between Ewing's tumours from European and Japanese patients lend further support to this suggestion.[7] Analyses of combined data from several case-control studies in North America and Australia have confirmed earlier findings of a raised risk with a history of umbilical hernia, possibly with a common environmental cause,[8] and with parental occupation in farming, though with no indication of the relative importance of exposure to particular categories of chemicals or animals.[9]

This paper presents geographical patterns and time trends in the incidence and survival rates for malignant bone tumours among children and adolescents in Europe and identifies needs for further studies. The analyses are based on a large European database within the Automated Childhood Cancer Information System (ACCIS), which contains data from 80 population-based cancer registries in 35 participating countries.[10]

2. Material and methods

Malignant bone tumours were defined as all those neoplasms in group VIII of the International Classification of Childhood Cancer (ICCC).[11] All 5572 malignant bone tumours registered since 1978 in patients under 20 years of age in 59 participating cancer registries of 19 European countries were extracted from the ACCIS database (Table 1). This number included 2883 osteosarcomas (ICCC subgroup VIIIa), 231 chondrosarcomas (ICCC subgroup VIIIb), 2130 Ewing's sarcomas (ICCC subgroup VIIIc), 165 other specified malignant tumours (ICCC subgroup VIIId) and 163 unspecified tumours (ICCC subgroup VIIIe). Information available for each case included basic demographic data (age, sex, country or region of residence), information on the tumour (date of incidence, site, morphology, basis of diagnosis and laterality) and on follow-up (date of last contact and vital status). Detailed information on the database is given elsewhere [Steliarova-Foucher, Kaatsch, Lacour, and colleagues, this issue].

The selected cancer registries (Table 1) met defined quality criteria for completeness, validity and comparability [Steliarova-Foucher, Kaatsch, Lacour, and colleagues, this issue]. Table 1 shows the numbers of cases and indicators of data quality for each set of analyses. In nearly all the registries, more than 95% of cases were microscopically verified and, among those registries with access to mortality data, fewer than 1% were registered from death certificate only (DCO).

The contributing countries were grouped into five European regions according to geographical location, socioeconomic characteristics and data availability, as shown in Table 1. The underlying population at risk for each combination of registration area, calendar year, sex and single year of age was extracted, where available, from official statistics and otherwise was estimated by linear interpolation from available data [Steliarova-Foucher, Kaatsch, Lacour, and colleagues, this issue]. Only in the Northern region did all contributing registries provide data for the full age range 0–19 years. In all the other regions, substantial numbers of cases came from paediatric registries that did not cover adolescents aged 15–19 years.

For the analyses of time trends, the available time-span was divided into four periods of 5 years: 1978–1982, 1983–1987, 1988–1992 and 1993–1997. The registries contributing to the analyses of time trends were those covering at least three periods, as shown in Table 1. Quality indicators for the combined data included in the analyses of time trends are shown in Table 2, by time period and geographical region.

Incidence rates were calculated as the average annual number of cases per million person-years. Age-standardised rates (ASR) were calculated from the age-specific incidence rates for 5-year age groups weighted according to the World standard population. Variations in incidence between the five European regions were analysed by Poisson regression. Time trends in incidence were evaluated using Poisson regression, adjusted for sex, age and region as appropriate, and expressed as an average annual percentage change (AAPC).

The duration of survival for each case was calculated as the time elapsed between the date of diagnosis and the date of death (if the patient died) or closing date of the study for the given cancer registry. Survival rates were analysed using the life-table method. DCO cases and those without follow-up were excluded from the survival analyses. The extent of these exclusions can be evaluated from Tables 1 and 2. Variations in survival between groups of patients were tested by log-rank tests.[12] More details on the methods used can be found elsewhere [Steliarova-Foucher, Kaatsch, Lacour, and colleagues, this issue]. To assess differences in survival between children and adolescents we analysed data from the restricted set of registries covering the whole age range 0–19 years.

3. Results

Table 3 shows incidence of bone tumours during 1988–1997 by 5-year age group among males and females in Europe as a whole, and Fig. 1 shows incidence by single year of age. Osteosarcoma was the most frequent subgroup, accounting for 52% of all registrations. Ewing's sarcoma was second most frequent, accounting for 34%. Chondrosarcoma and other specified tumours accounted for 6% and 4%, respectively, and 4% of registrations were for tumours of unspecified type. All types of bone tumour were very rare before the age of 4 years (Fig. 1). For all bone tumours combined, and for osteosarcoma, Ewing's sarcoma and chondrosarcoma, incidence increased with age until a peak in late childhood or adolescence and then declined. Incidence rates for all subgroups were similar for boys and girls throughout childhood (Table 3, Fig. 1). Incidence of osteosarcoma reached a marked peak at age 15 years among males, however, and remained higher than among females thereafter. Incidence of Ewing's sarcoma among males was slightly higher at age 15–18 years than at 11–14 years, starting to decline only at age 19 years (Fig. 1), whereas among females the incidence was substantially lower than in late childhood (Table 3, Fig. 1). In consequence, incidence rates for all bone tumours combined were similar for males and females during childhood, whereas there was a pronounced male excess among adolescents (Fig. 1).

Table 1 – Data-sets contributed by the European cancer registries for the analyses of incidence and survival for bone tumours in children (age 0–14 years) and adolescents (age 15–19 years), with indicators of coverage, data quality and follow-up (Source: ACCIS)

Region	Registry	Coverage		Number of cases by age-range		Basis of diagnosis				Survival analysis				Notes
		Period	Time-trend	0–14	15–19	NOS (VIIIe)	MV	DCO	unknown	Included		Closing date	FU > 5y	
						%	%	%	%	*n*	%		%	
Britain & Ireland	IRELAND, National	1994–1997		25	23	4	96	0	0	47	98	31.12.1998	0	
	UNITED KINGDOM, England & Wales	1978–1995	+	992	–	2	96	<1	0	985	99	31.1.2001	99	P
	UNITED KINGDOM, Northern Ireland	1993–1996		8	12	15	90	0	0	20	100	31.12.1999	7	
	UNITED KINGDOM, Scotland	1978–1997	+	113	111	4	99	0	0	224	100	31.12.1999	83	
East	BELARUS, National	1989–1997		120	–	<1	100	0	0	120	100	1.9.2000	90	P
	ESTONIA, National	1978–1997	+	36	23	19	86	0	0	59	100	31.12.1998	44	
	HUNGARY, National	1978–1997	+	223	–	1	100	–	0	223	100	1.1.2000	78	P
	SLOVAKIA, National	1978–1997	+	134	104	5	96	3	0	227	95	31.12.1997	55	
	GERMANY, NCR (only former East)	1978–1989	+	263	236	5	100	0	0	450	90	31.12.1987	66	S
North	DENMARK, National	1978–1997	+	115	86	7	97	0	1	200	100	31.12.1997	68	
	FINLAND, National	1978–1997	+	104	94	4	99	0	<1	198	100	31.12.1998	73	
	ICELAND, National	1978–1997	+	9	7	13	100	0	0	16	100	31.12.2000	90	
	NORWAY, National	1978–1997	+	103	98	7	100	0	0	201	100	1.1.2000	70	
South	ITALY, Piedmont paediatric	1978–1997	+	114	–	0	98	0	0	114	100	31.12.1999	92	P o2
	ITALY, Marche	1990–1997		14	–	7	86	–	0	14	100	30.9.2000	33	P o3
	ITALY, Ferrara	1991–1995		1	2	33	67	0	0	3	100	31.12.1998	–	
	ITALY, Latina	1983–1997	+	10	2	8	92	0	0	12	100	31.12.1998	100	
	ITALY, Liguria	1988–1995		4	3	14	86	0	0	7	100	15.4.2000	100	
	ITALY, Lombardy	1978–1997	+	28	16	5	98	0	0	44	100	23.9.1999	52	
	ITALY, Macerata	1991–1997		2	1	33	100	–	0	3	100	30.9.2000	0	o3
	ITALY, Parma	1978–1995	+	7	6	0	100	0	0	13	100	1.4.1999	86	
	ITALY, Piedmont general	1988–1997		9	6	0	93	0	0	15	100	31.5.2001	86	o2
	ITALY, Ragusa	1983–1997	+	6	7	8	100	0	23	13	100	30.3.2000	100	
	ITALY, Sassari	1992–1995		4	3	0	100	0	0	7	100	30.12.1999	100	
	ITALY, Tuscany	1988–1997		10	16	0	58	0	0	26	100	31.12.1998	38	
	ITALY, Umbria	1994–1996		1	1	0	100	0	0	2	100	31.12.1999	100	
	ITALY, Veneto	1990–1996		16	6	14	82	5	0	21	95	31.12.1998	40	
	MALTA, National	1991–1997		2	2	0	100	0	0	4	100	31.12.1999	100	
	SLOVENIA, National	1978–1997	+	48	34	0	100	0	0	82	100	31.12.1999	72	
	SPAIN, National	1990–1995		100	–	3	99	0	0	99	99	31.12.2000	90	P o4 Z
	SPAIN, Albacete	1991–1997		6	5	0	73	0	0	11	100	15.9.2000	80	
	SPAIN, Asturias	1983–1997	+	31	21	6	96	2	0	51	98	31.12.1997	55	
	SPAIN, Basque Country	1988–1994		24	22	4	100	0	0	46	100	31.12.2000	100	o4
	SPAIN, Canary Islands	1993–1996		12	6	6	89	6	0	–	–	–	–	

	SPAIN, Girona	1994–1997		2	2	0	100	0	0	3	75	31.12.1997	0	o4
	SPAIN, Granada	1988–1997		20	–	5	95	0	0	20	100	31.12.1999	58	G
	SPAIN, Mallorca	1988–1995		8	6	7	100	0	0	14	100	31.12.1998	75	o4
	SPAIN, Navarra	1978–1996	+	18	11	3	97	3	0	28	97	31.12.1997	59	o4
	SPAIN, Tarragona	1983–1997	+	13	9	5	100	0	0	22	100	31.12.1998	36	o4
	SPAIN, Zaragoza	1978–1996	+	17	21	3	92	5	0	36	95	31.12.1996	62	o4
	TURKEY, Izmir	1993–1996		14	29	5	98	–	0	–	–	–	–	
West	FRANCE, Brittany	1991–1997		26	–	4	100	–	12	26	100	1.1.2000	76	P
	FRANCE, Lorraine	1983–1997	+	51	–	2	100	–	0	51	100	1.1.1999	62	P
	FRANCE, PACA	1984–1996	+	80	–	4	100	–	0	74	93	31.3.1998	45	P
	FRANCE, Rhone Alpes	1988–1997		77	–	3	100	–	0	74	96	1.6.2000	55	P o1
	FRANCE, Doubs	1978–1996	+	20	15	3	40	–	3	34	97	1.6.2001	21	
	FRANCE, Herault	1988–1997		12	9	0	100	–	0	–	–	–	–	
	FRANCE, Isere	1979–1997	+	27	25	2	100	–	0	–	–	–	–	o1
	FRANCE, Manche	1994–1996		5	2	0	100	–	0	4	57	31.5.2000	0	S
	FRANCE, Bas-Rhin	1978–1996	+	21	19	0	100	–	0	40	100	31.12.1997	81	
	FRANCE, Haut-Rhin	1988–1997		10	3	0	92	–	8	6	46	31.12.1995	100	S
	FRANCE, Somme	1983–1996	+	6	8	0	100	–	0	14	100	15.8.2000	75	
	FRANCE, Tarn	1983–1997	+	7	5	0	100	–	0	–	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	570	–	<1	100	–	0	546	96	31.12.1998	38	P
	GERMANY, GCCR (only former West)	1983–1990	+	471	–	<1	100	–	0	469	100	31.12.1998	94	P
	NETHERLANDS, National	1989–1995		108	135	<1	99	–	0	107	44	31.12.1998	55	S o5
	NETHERLANDS, Eindhoven	1978–1997	+	28	23	0	98	–	2	51	100	1.7.1999	58	o5
	SWITZERLAND, Basel	1983–1997	+	9	6	0	100	–	13	15	100	30.6.2000	89	
	SWITZERLAND, Geneva	1978–1997	+	9	11	0	100	0	0	20	100	31.12.1999	89	
	SWITZERLAND, Graubunden & Glarus	1989–1997		2	4	0	100	0	17	6	100	25.5.2000	80	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	9	13	0	100	0	0	22	100	1.2.2001	50	
	SWITZERLAND, Valais	1989–1997		2	1	0	100	0	0	–	–	–	–	S

n, number of cases registered in the given period; NCR, National Cancer Registry of the former German Democratic Republic. Data for 1978–1987 contributed only to analyses of time trends for Europe as a whole. Data on children for 1988–1989 were pooled with GCCR and included in West. For explanation, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue); GCCR, National German Childhood Cancer Registry (until 1990 only West, since 1991 for reunified Germany); PACA, Provence, Alps, Cote d'Azur; +, included in time trends; NOS (VIIIe) %, percentage of cases in ICCC subgroup VIIIe, Unspecified malignant bone tumours; MV %, percentage of microscopically verified cases; DCO %, percentage of registrations from death certificate only; Unknown %, percentage of registrations with unknown basis of diagnosis; FU > 5y %, percentage of cases followed up for at least 5 years among those not deceased by closing date; P, paediatric cancer registry, age-range of the patients is 0–14 years; G, general cancer registry, which has only contributed data for age-range 0–14 years; S, survival analyses were possible only for a restricted data-set [see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]; o1–o5, overlapping registration areas: for the overlapping years, data from the registry with larger coverage are included in each analysis, according to availability; Z, covers only selected areas, see Steliarova-Foucher, Kaatsch, Lacour et al. (this issue).

Table 2 – Numbers of cases and indicators of data quality and follow-up by region and age group for time trend analyses of incidence and survival for bone tumours in children (age 0–14 years) and adolescents (age 15–19 years) in Europe, 1978–1997 (Source: ACCIS)

Region	Period	Children (age 0–14 years)							Adolescents (age 15–19 years)						
		Cases	Histology NOS	Basis of diagnosis			Follow-up		Cases	Histology NOS	Basis of diagnosis			Follow-up	
				MV	DCO	Unknown	1+ days	5+ years			MV	DCO	Unknown	1+ days	5+ years
		n	%	%	%	%	%	%	*n*	%	%	%	%	%	%
		a	b	c	d	e	f	g	a	b	c	d	e	f	g
Europe	1978–1982	777	3	99	<1	<1	100	99	377	5	98	<1	0	100	100
	1983–1987	1032	3	98	<1	<1	99	89	341	9	96	<1	<1	99	74
	1988–1992	954	2	97	<1	2	98	91	206	4	96	<1	0	99	94
	1993–1997	929	2	99	<1	<1	97	31	241	5	98	0	<1	100	13
British Isles	1978–1982	363	2	100	0	<1	100	97	40	5	100	0	0	100	100
	1983–1987	280	3	97	<1	2	99	99	25	12	100	0	0	100	100
	1988–1992	280	3	91	1	6	99	99	26	8	100	0	0	100	100
	1993–1997	182	2	96	<1	3	99	90	22	0	100	0	0	100	27
East	1978–1982	86	6	98	1	0	99	100	37	11	95	3	0	97	100
	1983–1987	88	7	95	1	0	95	97	42	14	90	2	0	90	100
	1988–1992	112	4	97	<1	0	99	95	41	10	93	2	0	98	100
	1993–1997	107	2	99	0	0	100	27	50	2	98	0	0	100	4
North	1978–1982	101	5	99	0	0	100	100	101	5	99	0	0	100	100
	1983–1987	80	9	98	0	1	100	100	80	9	98	0	1	100	100
	1988–1992	63	0	100	0	0	100	100	63	0	100	0	0	100	100
	1993–1997	87	13	95	0	2	100	11	87	13	95	0	2	100	11
South	1978–1982	68	1	97	0	0	100	100	40	3	100	0	0	100	100
	1983–1987	87	1	99	0	0	100	100	51	2	98	0	0	100	100
	1988–1992	72	3	99	0	0	100	98	40	5	98	0	0	100	95
	1993–1997	65	2	100	0	0	100	23	47	2	100	0	0	100	3
West	1978–1982	30	0	83	0	0	100	100	30	0	83	0	0	100	100
	1983–1987	389	1	99	0	<1	100	92	35	0	89	0	3	100	71
	1988–1992	401	1	99	0	0	98	82	36	0	89	0	0	100	69
	1993–1997	488	1	100	0	0	95	19	35	0	100	0	0	96	40

Europe also includes data from the former GDR. *n*, number of cases registered in the given period; NOS, unspecified histology type; MV (%), percentage of microscopically verified cases; DCO (%), percentage of registrations from death certificate only; Unknown (%), percentage of registrations with unknown basis of diagnosis; 1+ days (%), percentage of cases included in survival analyses. Refers to the total registrations in the registries with follow-up; 5+ years (%), percentage of cases followed-up for at least 5 years among those included in survival analyses and not deceased by closing date.

Table 3 – Annual incidence rates per million of malignant bone tumours in Europe, 1988–1997 (Source: ACCIS)

Age	Numbers			Rates			
	0–14	15–19	0–4	5–9	10–14	0–14 (ASR)	15–19
Male							
Osteosarcoma	644	245	0.2	2.3	6.8	2.8	10.8
Chondrosarcoma	29	36	0.0	0.0	0.4	0.1	1.6
Ewing's sarcoma	522	124	0.9	2.2	4.4	2.4	5.5
Other specified	34	19	0.0	0.2	0.3	0.2	0.8
Unspecified	35	15	0.1	0.1	0.2	0.2	0.7
Total	1264	439	1.3	4.8	12.1	5.6	19.3
Female							
Osteosarcoma	626	127	0.3	2.5	6.7	2.9	5.8
Chondrosarcoma	32	21	0.0	0.1	0.3	0.1	1.0
Ewing's sarcoma	474	61	0.8	2.2	4.2	2.2	2.8
Other specified	31	14	0.1	0.1	0.3	0.1	0.6
Unspecified	21	10	0.1	0.1	0.1	0.1	0.5
Total	1184	233	1.3	5.0	11.6	5.5	10.7
Both sexes							
Osteosarcoma	1270	372	0.2	2.4	6.8	2.8	8.4
Chondrosarcoma	61	57	0.0	0.1	0.4	0.1	1.3
Ewing's sarcoma	584	185	0.9	2.2	4.3	2.3	4.2
Other specified	38	33	0.1	0.1	0.3	0.2	0.7
Unspecified	56	25	0.1	0.1	0.2	0.1	0.6
Total	2448	672	1.3	4.9	11.9	5.5	15.1

ASR, age-standardised rate (World standard).

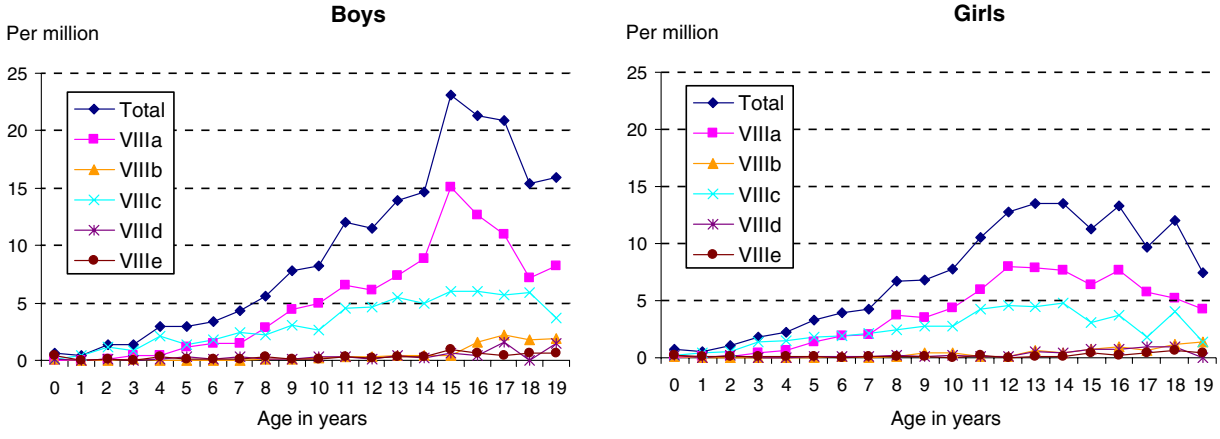

Fig. 1 – Age-specific incidence rates of malignant bone tumours in boys (n = 1703) and girls (n = 1417) in Europe, 1988–1997. Total, all malignant bone tumours; VIIIa, osteosarcoma; VIIIb, chondrosarcoma; VIIIc, Ewing's sarcoma of bone; VIIId, other specified bone tumours; VIIIe, unspecified bone tumours. Source: ACCIS.

Table 4 shows incidence rates in the five European regions. Within each region, incidence rates at age 0–14 years from registries that covered the age range 0–19 years were similar to those from the complete set of registries, indicating that ascertainment levels were similar in the paediatric and general cancer registries (results not shown). Total bone tumour incidence among both children and adolescents was higher in the South and West than in the other regions. For osteosarcoma, the most noticeable inter-regional variations were that in childhood the highest incidence was in the South, while in adolescence the lowest incidence was in the East. Ewing's sarcoma was markedly less frequent in Northern Europe than in other regions. There was a pattern of increasing incidence of Ewing's sarcoma from north to south for both age groups combined and among children, though it was less clear among adolescents.

The results of the analyses of time trends in bone tumour incidence during 1978–1997 are shown in Table 5 for Europe as a whole and in Fig. 2 for the five European regions. Among children in Europe as a whole there were no significant trends in incidence. In Eastern Europe there was a significant increase in total bone tumour ASR at age 0–14 years (AAPC

Table 4 – Numbers of cases (n) and annual incidence rates per million for malignant bone tumours in the five European regions, 1988–1997 (Source: ACCIS)

	Boys				Girls				Both sexes			
	0–14 years		15–19 years		0–14 years		15–19 years		0–14 years		15–19 years	
	n	ASR	*n*	Rate	*n*	ASR	*n*	Rate	*n*	ASR	*n*	Rate
Osteosarcoma												
British Isles	135	2.6	26	9.7	127	2.6	12	4.7	262	2.6	38	7.3
East	78	2.3	23	8.1	90	2.7	9	3.3	168	2.5	32	5.8
North	46	3.0	58	11.6	40	2.7	28	5.8	86	2.8	86	8.8
South	75	3.1	72	12.2	96	4.2	24	4.3	171	3.6	96	8.3
West	310	2.9	66	10.5	273	2.7	21	7.8	583	2.8	120	9.7
Ewing sarcoma												
British Isles	116	2.3	21	7.8	84	1.8	6	2.3	200	2.0	27	5.2
East	59	1.8	19	6.7	72	2.3	11	4.1	131	2.1	30	5.4
North	23	1.5	13	2.6	19	1.3	9	1.9	42	1.4	22	2.2
South	65	2.9	41	6.9	70	3.1	17	3.0	135	3.0	58	5.0
West	259	2.6	30	4.8	229	2.4	18	3.0	488	2.5	48	3.9
Total bone tumours												
British Isles	270	5.3	53	19.8	225	4.7	24	9.4	495	5.0	77	14.7
East	157	4.7	49	17.3	182	5.7	25	9.2	339	5.2	74	13.3
North	80	5.3	82	16.4	70	4.9	42	8.8	150	5.1	94	10.3
South	159	6.9	132	22.4	173	7.6	54	9.6	332	7.2	186	16.1
West	598	5.8	123	19.5	534	5.5	88	14.6	1132	5.6	211	17.1

ASR, age-standardised rate (World standard).

Table 5 – Trends in the incidence of malignant bone tumours among European children and adolescents, 1978–1997 (Source: ACCIS)

	Age 0–14 years			Age 15–19 years		
	n	AAPC	(95% CI)	*n*	AAPC	(95% CI)
Total	3429	−0.13	(−0.78–0.53)	775	0.31	(−0.95–1.59)
Osteosarcoma	1766	0.43	(−0.49–1.35)	437	0.51	(−1.16–2.21)
Chondrosarcoma	83	0.90	(−3.54–5.54)	63	0.34	(−4.40–5.32)
Ewing's sarcoma	1430	−1.01	(−2.02–0.01)	221	−0.07	(−2.50–2.42)
Other specified	68	−1.28	(−6.25–3.96)	41	–	–
Unspecified	82	0.63	(−3.49–4.93)	35	–	–

Numbers of cases (*n*) and average annual percentage change (AAPC) from models including sex, region and (for children) age group. Results not given for subgroups with fewer than 50 registrations.

2.9, $P = 0.002$). This was entirely due to an increase in osteosarcoma (AAPC 4.6, $P = 0.001$); no change was seen in the other subgroups. No changes were seen among adolescents in Europe as a whole, but rates were increasing in the South and West (Fig. 2).

Table 6 shows 5-year survival rates for children and adolescents diagnosed during 1988–1997. Adolescents had lower survival than children, with the difference being much more marked for Ewing's sarcoma than for osteosarcoma. In the restricted data-set from registries covering the whole age range 0–19 years, survival for all bone tumours combined was significantly higher ($P = 0.007$) among children ($n = 554$, 5-year survival 58%, 95% CI 53–62) than among adolescents ($n = 483$, 5-year survival 47%, 95% CI 43–52); differences in survival between children and adolescents were also significant for Ewing's sarcoma and unspecified bone tumours, but not for osteosarcoma. Inter-regional comparisons within each of these two age groups are based on the full data-set. Among children, the East had the lowest survival rates for all bone tumours combined. For osteosarcoma, survival was lowest in the East, intermediate in the British Isles, and higher in the other three regions (pooled estimate 65%, 95% CI 61–68). For Ewing's sarcoma, survival was again lowest in the East, while the other four regions had similar, higher survival rates (pooled estimate 66%, CI 63–70). Among adolescents, survival was low in the East for all bone tumours combined and for Ewing's sarcoma; otherwise no substantial interregional differences were observed.

Table 7 presents trends in survival during 1978–1997. In Europe as a whole, survival for all bone tumours combined increased significantly among both children and adolescents. Survival also increased in both age groups for osteosarcoma.

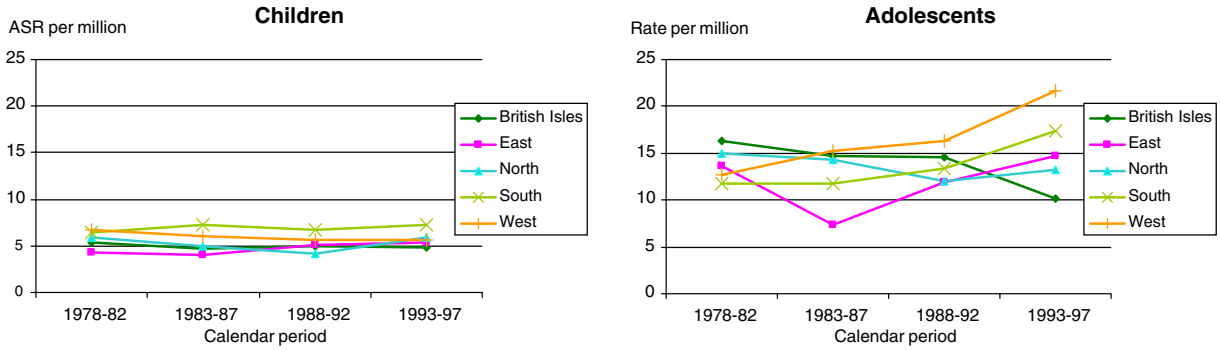

Fig. 2 – Time trends of incidence rates of malignant bone tumours in Europe. Age standardised rates (ASR) in children aged 0–14 years (*n* = 3692) and age-specific rates in adolescents aged 15–19 years (*n* = 1163). Source: ACCIS.

Table 6 – Five year survival (95% CI) of children and adolescents with malignant bone tumours diagnosed 1988–1997 (Source: ACCIS)

	Age 0-14		Age 15-19	
	n	Survival %	*n*	Survival %
Europe				
Osteosarcoma	1215	59 (56–62)	270	51 (44–57)
Chondrosarcoma	57	64 (49–75)	35	85 (67–93)
Ewing's	938	62 (58–65)	144	30 (22–38)
Other specified	62	79 (66–88)	16	–
Unspecified	50	71 (55–82)	18	–
Total	2322	61 (59–63)	483	47 (43–52)
British Isles				
Osteosarcoma	259	53 (47–59)	38	62 (42–77)
Ewing's	197	69 (62–75)	27	43 (23–61)
Total	489	61 (57–66)	77	57 (45–68)
East				
Osteosarcoma	168	43 (35–51)	32	33 (17–50)
Ewing's	131	35 (26–43)	30	10 (2–28)
Total	338	41 (36–47)	74	27 (17–38)
North				
Osteosarcoma	86	65 (53–74)	86	53 (41–64)
Ewing's	42	65 (45–79)	22	36 (17–55)
Total	150	66 (57–74)	124	52 (42–61)
South				
Osteosarcoma	159	65 (56–72)	80	53 (41–64)
Ewing's	122	61 (52–69)	47	30 (17–43)
Total	305	65 (59–70)	148	48 (39–56)
West				
Osteosarcoma	543	65 (61–69)	34	52 (35–68)
Ewing's	446	66 (61–71)	18	–
Other specified	23	75 (50–89)	1	–
Total	1040	66 (63–69)	60	55 (40–67)

Survival not shown for subgroups with fewer than 20 registrations.
n, number of patients with follow-up.

For Ewing's sarcoma, however, survival increased markedly for children, but not for adolescents. In contrast, for chondrosarcoma the survival rate increased for adolescents, but there was no evidence of an increase for children. Similar patterns of change in survival were mostly observed in the five European regions. The main exception was the absence of improvement for children with Ewing's sarcoma in the East.

4. Discussion

This is the largest ever population-based study of bone tumours in children and adolescents. There was some evidence of geographical variation in incidence within Europe, but no significant change in rates over time. Survival rates were generally higher for children than for adolescents, and were markedly lower in the East than in the other European regions. Survival increased substantially during the 20-year study period.

The total incidence of malignant bone tumours in childhood, the increasing incidence with age, the sex ratio close to unity and the predominance of osteosarcoma and, to a lesser extent, Ewing's sarcoma found in this study are typical of patterns observed among predominantly white populations worldwide.[1] There are few previous reports of incidence of bone tumours among adolescents, but the incidence patterns and rates observed in Europe in this study were broadly similar to those in the SEER Program registries of the United States of America (USA)[13] and in an independent analysis of cancer registration data for England.[14] The earlier age peak in females than in males is similar to that in the SEER data and is presumably related to the occurrence of maximum skeletal growth at an earlier age in girls.[13]

There was some variation in incidence between European regions. The higher incidence of childhood osteosarcoma in Southern Europe has not been previously noted, though Italy also had one of the highest incidence rates worldwide in the 1980s.[1] Similarly, the north-south gradient in the incidence of Ewing's sarcoma has not been reported previously, though this was also present in childhood data from the 1980s.[1] The higher incidence in the south may be consistent with parental employment in farming as a risk factor,[9] though it should be stressed that this has not been directly investigated in substantial numbers of patients from any European population.

There was little evidence of consistent changes in bone tumour incidence over the 20-year study period other than in Eastern Europe. Since the analysis of trends included many comparisons and there is no obvious explanation for

Table 7 – Five year survival (95% CI) of children and adolescents with malignant bone tumours diagnosed 1978–1997 (Source: ACCIS)

Age 0–14 years	1978–1982		1983–1987		1988–1992		1993–1997		p_{trend}
	n	Survival %	*n*	Survival %	*n*	Survival %	*n*	Survival %	
Europe									
Osteosarcoma	391	37 (32–41)	492	58 (53–62)	460	59 (55–64)	495	61 (55–65)	<0.0001
Chondrosarcoma	25	60 (38–76)	24	64 (40–80)	24	67 (44–82)	19	54 (26–76)	0.9
Ewing's	312	34 (29–40)	450	52 (47–56)	375	63 (58–68)	349	66 (60–72)	<0.0001
Unspecified	23	26 (11–45)	33	57 (38–73)	19	63 (38–80)	19	84 (59–95)	0.0004
Total	770	37 (33–40)	1017	56 (52–59)	904	62 (58–65)	895	63 (59–67)	<0.0001
British Isles									
Osteosarcoma	189	30 (24–37)	132	53 (44–61)	140	51 (43–59)	106	54 (44–63)	<0.0001
Ewing's	155	34 (26–41)	126	47 (38–55)	117	69 (60–77)	63	67 (54–77)	<0.0001
Total	363	32 (27–37)	278	51 (45–56)	276	61 (55–67)	182	59 (51–66)	<0.0001
East									
Osteosarcoma	36	22 (30–37)	30	53 (34–69)	49	47 (33–60)	58	51 (34–65)	0.002
Ewing's	39	31 (17–45)	42	33 (20–48)	50	36 (22–49)	40	34 (16–54)	0.2
Total	85	27 (18–37)	84	40 (29–50)	111	40 (31–50)	107	45 (33–56)	0.0006
North									
Osteosarcoma	58	40 (27–52)	41	59 (42–72)	37	70 (53–82)	49	54 (33–71)	0.009
Ewing's	34	35 (20–51)	28	39 (22–57)	18	61 (35–79)	24	78 (55–90)	0.008
Total	101	38 (28–47)	80	54 (42–64)	63	67 (54–77)	87	65 (50–77)	<0.0001
South									
Osteosarcoma	35	49 (31–64)	48	58 (43–71)	42	61 (45–74)	35	63 (41–79)	0.2
Ewing's	27	41 (23–58)	37	51 (34–66)	23	57 (34–74)	28	73 (49–87)	0.004
Total	68	44 (32–55)	87	54 (43–64)	72	62 (50–72)	65	67 (52–78)	0.002
West									
Osteosarcoma	9	44 (14–72)	195	65 (58–72)	192	66 (59–72)	247	66 (58–73)	0.2
Ewing's	15	47 (21–69)	173	63 (55–70)	167	68 (60–75)	194	68 (59–76)	0.07
Total	24	46 (26–64)	380	65 (59–69)	382	67 (62–71)	455	67 (61–72)	0.03
Age 15–19 years									
Europe									
Osteosarcoma	157	31 (24–38)	158	44 (36–51)	98	45 (35–55)	110	57 (46–67)	0.0001
Chondrosarcoma	29	48 (29–65)	27	49 (26–68)	13	85 (51–96)	17	88 (59–97)	0.006
Ewing's	75	23 (14–33)	92	34 (24–44)	57	34 (22–46)	50	29 (15–43)	0.2
Total	294	34 (28–39)	296	42 (36–47)	182	46 (38–53)	186	51 (43–59)	0.0002
British Isles									
Osteosarcoma	17	41 (19–63)	20	50 (27–69)	13	62 (31–82)	7	60 (13–88)	0.1
Total	37	35 (20–50)	32	41 (24–57)	26	65 (44–80)	16	65 (35–84)	0.004
East									
Osteosarcoma	16	23 (14–34)	7	43 (10–73)	13	23 (6–47)	19	41 (18–63)	0.009
Total	138	32 (24–40)	128	37 (27–46)	32	19 (8–34)	42	36 (20–51)	0.7
North									
Osteosarcoma	54	37 (24–50)	48	54 (39–67)	40	48 (32–62)	46	59 (41–74)	0.04
Ewing's	14	21 (5–41)	19	42 (20–62)	12	50 (21–74)	10	18 (2–47)	1
Total	83	38 (27–48)	78	49 (37–59)	61	51 (38–63)	63	53 (38–66)	0.048
South									
Osteosarcoma	11	27 (7– 54)	15	33 (12–56)	17	31 (11–54)	25	65 (32–85)	0.1
Total	20	33 (14–55)	31	37 (20–53)	35	42 (26–58)	41	56 (38–71)	0.3
West									
Osteosarcoma	11	26 (5–56)	14	53 (22–76)	15	60 (32–80)	13	45 (18–69)	0.5
Total	16	24 (6–48)	27	49 (28–67)	28	51 (31–68)	24	61 (36–79)	0.07

Survival reported only for cohorts with a minimum of 50 patients with follow-up. p_{trend} tests the hypothesis of no increase over the periods.

the findings, it seems likely that they were due to chance. They are unlikely to have been influenced by changes in the occurrence of bone tumours as second or later primaries, since these events accounted for only 1% of cases of osteosarcoma and less than 0.6% of other subgroups; the data for the East included only one case of osteosarcoma as a second primary neoplasm in a child. In the USA, incidence of both osteosarcoma and Ewing's sarcoma increased markedly during

the late 1970s but remained relatively constant thereafter,[13] again, there is no obvious explanation for this pattern.

Survival of adolescents with Ewing's sarcoma was substantially and significantly lower than that of children, whereas for osteosarcoma the difference was much smaller and non-significant. Lower survival among adolescents has also been observed in the USA, though the effect was less marked.[13] The comparisons of survival between children and adolescents in the present, population-based study broadly correspond with the findings from large multi-centre studies. In a series of 1702 patients aged under 40 years included in the German-Austrian-Swiss Cooperative Osteosarcoma Study Group (COSS) studies during 1980–1998 there was no significant effect of age on survival.[15] In a further analysis of 751 patients aged 0–14 years and 611 aged 15–19 years from the COSS studies, there was no significant survival difference between the groups ($P = 0.21$, log-rank). In a study of 975 patients diagnosed in 1978–1993 from the European Intergroup Cooperative Ewing's Sarcoma Study Group, survival was significantly higher for children than for older patients, a difference that was only partly attributable to the greater frequency of favourable primary site and absence of metastases at diagnosis among children.[16] Adolescents with Ewing's sarcoma diagnosed in Britain during 1980–1994 had significantly higher survival if they were included in a trial.[17] In the co-operative Ewing's sarcoma trials in the German-speaking countries, survival of patients aged over 15 years was higher in paediatric units than in other institutions.[18] These results together suggest that differences in survival between children and adolescents with Ewing's sarcoma would diminish if patterns of organisation of care were to become more similar for the two age groups.

Survival from both osteosarcoma and Ewing's sarcoma was lower in Eastern Europe than elsewhere, a continuation of the pattern reported in earlier years from the Eurocare studies.[19–21] The pattern of lower survival rates in countries of Eastern Europe for most cancers of children and adolescents is discussed elsewhere[20,21] [Sankila and colleagues, this issue; Stiller, Desandes, Danon and colleagues, this issue]. Financial constraints and lack of resources are presumably important, but lack of multi-institutional co-operation may also be a factor in some countries within the East. Some of the gap in survival of children with Ewing's sarcoma between regions or countries has been attributed to delayed diagnosis resulting in a higher proportion of metastatic cases (as seen in Hungary).[22] It should be borne in mind that within the East, as in most other regions, considerable heterogeneity of survival rates has been observed between individual countries [Pritchard-Jones and colleagues, this issue].

There was rather little variation in survival between the other four regions, except that, for osteosarcoma in the British Isles, survival was relatively low among children but unexpectedly high among adolescents compared both with the European average and with the results for children in the British Isles. Five-year survival of adolescents with osteosarcoma diagnosed in 1990–1994 in the whole of Great Britain was 48%, based on more than 100 cases.[17] This suggests that the 62% survival, based on only 38 cases, for the British Isles during 1988–1997 in the present study may be an overestimate, though the two results are compatible since the confidence interval includes the survival rate from the other study. Five-year survival for adolescents in Great Britain with Ewing's sarcoma diagnosed in 1990–1994 was 47%,[17] similar to the 43% in the present study.

Little progress was evident in outcome for osteosarcoma or Ewing's sarcoma since the mid-1980s. The late 1970s and early 1980s saw a dramatic change from local therapy alone (surgery for osteosarcoma, radiotherapy or surgery for Ewing's sarcoma) to local treatment plus systemic chemotherapy. Initial single institutional and early multi-centre trials in most parts of Europe gave way to widespread and sometimes population-based recruitment of patients into prospective therapy studies for both osteosarcoma and Ewing's sarcoma in Scandinavia,[23,24] the German speaking countries,[15,25] Italy,[26,27] the UK and elsewhere.[28–32] The drugs currently believed to be the most active against osteosarcoma, namely doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide, had all made their way into first-line protocols in the 1980s.[33] The same holds true for vincristine, actinomycin D, cyclophosphamide or ifosfamide, and doxorubicin against Ewing's sarcoma.[34] Basically, chemotherapy for bone tumours, in Europe as elsewhere, is very similar to that used in the mid 1980s, so that marked time trends in survival since then would not be expected. At the population level, however, there may be scope for further improvement in some areas through earlier diagnosis and referral and, just as importantly, inclusion of all patients into national or international collaborative trials, allowing them to benefit from centralised quality assurance systems.

Survival of children with Ewing's sarcoma diagnosed during 1988–1997 was identical in the West, for which Germany provided the majority of analysed cases, and the British Isles, with patients from the two areas registered into a common protocol (EICESS 92)[15,25] during much of the period. A similar comparison could not be made for adolescents because of the absence of data on patients aged 15–19 years from Germany. For osteosarcoma, by contrast, the two areas used different protocols and survival also differed between the two regions. The survival rates for osteosarcoma observed in the West and the British Isles as well as in the North and the South closely parallel the results reported from recent clinical trials within those regions,[15,23,26,30] and the numbers of patients in these trials are rather high, in accordance with the assumption that most children and many adolescents with bone tumours from these areas are now treated within these trials.

This study has revealed inter-regional differences in incidence and survival rates for bone tumours among children and adolescents in Europe. Extension of the ACCIS database will provide an opportunity for studying these variations based on larger numbers of registrations over a longer time period and in smaller geographical regions. It will also be important for monitoring the impact of changes in treatment protocols and in patterns of referral and care on population-based survival for this group of tumours, in which rather little progress was made during the period studied here.

Conflict of interest statement

None declared.

Acknowledgements

The ACCIS project was funded by the European Commission from the 'Europe Against Cancer' programme (1996–2002, contracts SI2.126875, SI2.321970 and SPC.2002303), jointly with the International Agency for Research on Cancer (IARC). Data analyses were partly funded by the French *Ligue Nationale contre le Cancer, Comité du Rhône*. The Childhood Cancer Research Group receives funding from the Department of Health and the Scottish Ministers. The views expressed in the publication are those of the authors and not necessarily those of the Department of Health and the Scottish Ministers.

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

The following collaborators from the cancer registries contributed actively to this study: S.V. Petrovich, O. Budanov (Belarus); H. Storm, N. Christensen (Denmark); T. Aareleid (Estonia); T. Hakulinen, R. Sankila, E. Pukkala (Finland); E. Le Gall, I. Tron (Brittany, France), B. Lacour, E. Desandes (Lorraine, France), J.L. Bernard, P. Pillon, J.C. Gentet (PACA and Corsica, France), F. Freycon, C. Berger (Rhone Alps, France), L. Remontet (Francim, France), A. Danzon, M. Mercier (Doubs, France), J.P. Daurès, B. Tretarre (Herault, France), F. Ménégoz (Isère, France), A.V. Guizard (Manche, France), M. Velten (Bas-Rhin, France), A. Buemi (Haut-Rhin, France), N. Raverdy (Somme, France), M. Sauvage, P. Grosclaude (Tarn, France); P. Kaatsch, B. Eisinger, R. Stabenow (Germany); D. Schuler, Z. Jakab, G. Borgulya (Hungary); L. Tryggvadottir, J.G. Jonasson, K. Bjarnadottir (Iceland); H. Comber, F. Dwane (Ireland); C. Magnani, G. Pastore (Piedmont, Italy), F. Pannelli, C. Pascucci (Marche, Macerata, Italy), S. Ferretti (Ferrara, Italy), E. Conti, V. Ramazzotti, M.C. Cercato (Latina Province, Italy), M. Vercelli, A. Puppo (Liguria, Italy), P. Crosignani, G. Tagliabue, A. Tittarelli (Lombardy, Italy), V. De Lisi, P. Sgargi (Parma, Italy), R. Zanetti, S. Patriarca (Piedmont, Italy), R. Tumino (Ragusa, Italy), M. Budroni, D. Piras (Sassari, Italy), E. Paci, E. Crocetti (Tuscany, Italy), F. La Rosa, F. Stracci (Umbria, Italy), P. Zambon, S. Guzzinati (Veneto, Italy); M. Dalmas (Malta); J.W.W. Coebergh, J. van Dijck, A. Wit (Netherlands); F. Langmark, A. Johansen, A. Andersen (Norway); I. Plesko (Slovakia); M. Primic Žakelj, V. Pompe-Kirn (Slovenia); R. Peris-Bonet, B. Giner (Spain), E. Almar Marques, A. Mateos Ramos (Albacete, Spain), J. Ramon Quiros Garcia, A. Cañada Martínez (Asturias, Spain), I. Izarzugaza (Basque, Spain), A. Alemán Herrera (Canary Islands, Spain), P. Viladiu, R. Marcos, A. Izquierdo (Girona, Spain), C. Martínez Garcia (Granada, Spain), A. Obrador, I. Garau (Mallorca, Spain), E. Ardanaz (Navarra, Spain), J. Borràs, J. Galceran (Tarragona, Spain), J. de la Bárcena Guallar, M.C. Martos Jiménez (Zaragoza, Spain); G. Jundt (Basel, Switzerland), C. Bouchardy, M. Usel (Geneva, Switzerland), J. Allemann, H. Frick (Graubünden and Glarus, Switzerland), T. Fisch, S. Ess (St Gallen Appenzell, Switzerland), F. Joris, D. de Weck (Valais, Switzerland); S. Yalcin Eser (Izmir, Turkey); C.A. Stiller, M.F.G. Murphy, G.J. Draper (England and Wales, UK), A. Gavin, C. Fox, W. Hamill, R. Middleton (Northern Ireland, UK), D. Brewster, L. Bhatti, A. McDonald (Scotland, UK). We also acknowledge the collaborators from the other registries participating in ACCIS, whose data were not included in this paper.

REFERENCES

1. Parkin DM, Kramárová E, Draper GJ, et al. *International incidence of childhood cancer: volume 2*. In: Parkin DM, Kramárová E, Draper GJ, et al., editors. Lyon: IARC; 1998.
2. Smith MA, Gurney JG, Gloeckler Ries LA. Cancer among adolescents 15–19 years old. In: Gloeckler Ries LA, Smith MA, Gurney JG, et al., editors. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995*. Bethesda,MD: NIH Pub No 99-4649; 1999, p. 157–164.
3. World Health Organization. *Pathology and genetics. tumours of soft tissue and bone*. Fletcher CDM, Unni KK, Mertens F, editors. Lyon: IARC Press; 2002.
4. Little J. *Epidemiology of childhood cancer*. Lyon: IARC; 1999.
5. Stiller CA. Epidemiology and genetics of childhood cancer. *Oncogene* 2004;**23**:6429–44.
6. Parkin DM, Stiller CA, Nectoux J. International variations in the incidence of childhood bone tumours. *Int J Cancer* 1993;**53**:371–6.
7. Ozaki T, Schaefer K-L, Wai D, et al. Population-based genetic alterations in Ewing's tumors from Japanese and European caucasian patients. *Ann Oncol* 2002;**13**:1656–64.
8. Valery PC, Holly EA, Sleigh AC, et al. Hernias and Ewing's sarcoma family of tumours: a pooled analysis and meta-analysis. *Lancet Oncol* 2005;**6**:485–90.
9. Valery PC, Williams G, Sleigh AC, et al. Parental occupation and Ewing's sarcoma: Pooled and meta-analysis. *Int J Cancer* 2005;**115**:799–806.
10. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *Lancet* 2004;**364**:2097–105.
11. Kramárová E, Stiller CA. The international classification of childhood cancer. *Int J Cancer* 1996;**68**:759–65.
12. Kirkwood BR, Sterne AC, editors. *Essential medical statistics*. Oxford: Blackwell Science Ltd; 2003.
13. Gurney JG, Swensen AR, Bulterys M. Malignant bone tumors. In: Gloeckler Ries LA, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, et al., editors. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995*. Bethesda,MD: NIH Pub No 99-4649; 1999, p. 99–110.
14. Birch JM, Alston RD, Quinn M, Kelsey AM. Incidence of malignant disease by morphological type, in young persons aged 12–24 years in England, 1979–1997. *Eur J Cancer* 2003;**39**:2622–31.
15. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol* 2002;**20**:776–90.
16. Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. *J Clin Oncol* 2000;**18**:3108–14.
17. Stiller CA, Passmore SJ, Kroll ME, et al. Patterns of care and survival for patients aged under 40 years with bone sarcoma in Britain, 1980–1994. *Br J Cancer* 2006;**94**:22–9.
18. Paulussen M, Ahrens S, Juergens HF. Cure rates in Ewing tumor patients aged over 15 years are better in pediatric oncology units. Results of GPOH CESS/EICESS studies. *Proc ASCO* 2003, Abstract No. 3279.

19. Stiller CA, Craft AW, Corazziari I. EUROCARE Working Group. Survival of children with bone sarcoma in Europe since 1978: results from the EUROCARE study. *Eur J Cancer* 2001;**37**:760–6.
20. Gatta G, Corazziari I, Magnani C, et al. Childhood cancer survival in Europe. *Ann Oncol* 2003;**14**:v119–27.
21. Gatta G, Capocaccia R, De Angelis R, et al. Cancer survival in European adolescents and young adults. *Eur J Cancer* 2003;**39**:2600–10.
22. Babosa M, Garami M, Hauser P, Schuler D, Szendroi M. Survival of Ewing's sarcoma patients in Hungary. *Hungarian Oncol* 2000;**44**:261–4.
23. Smeland S, Wiebe T, Bohling T, et al. Chemotherapy in osteosarcoma. The Scandinavian Sarcoma Group experience. *Acta Orthop Scand (Suppl)* 2004;**75**:92–8.
24. Nilbert M, Saeter G, Elomaa I, et al. Ewing's sarcoma treatment in Scandinavia 1984-1990: ten-year results of the Scandinavian Sarcoma Group Protocol SSGIV. *Acta Oncol* 1998;**37**:375–8.
25. Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. *Int J Radiol Oncol Biol Phys* 2003;**55**:168–77.
26. Bacci G, Longhi A, Fagioli F, et al. Adjuvant and neoadjuvant chemotherapy for osteosarcoma of the extremities: 27 year experience at Rizzoli Institute, Italy. *Eur J Cancer* 2005;**41**:2836–45.
27. Bacci G, Ferrari S, Bertoni F, et al. Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: analysis of 359 patients at the Istituto Ortopedico Rizzoli. *J Clin Oncol* 2000;**18**:4–11.
28. Medical Research Council working party on bone sarcoma. A trial of chemotherapy in patients with osteosarcoma. (A report to the Medical Research Council by theor Working Party on Bone Sarcoma). *Br J Cancer* 1986;**53**:513–18.
29. Bramwell VHC, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol* 1992;**10**:1579–91.
30. Souhami RL, Craft AW, van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997;**350**:911–7.
31. Craft AW, Cotterill SJ, Bullimore JA, Pearson D. Long-term results from the first UKCCSG Ewing's Tumour Study (ET-1). *Eur J Cancer* 1997;**33**:1061–9.
32. Craft A, Cotterill S, Malcolm A, et al. Ifosfamide-containing chemotherapy in Ewing's sarcoma: the second United Kingdom childrens's cancer study group and the medical research council Ewing's tumor study. *J Clin Oncol* 1998;**16**:3628–33.
33. Craft AW. Challenges in the management of bone tumors–1996. *Ann N Y Acad Sci* 1997;**824**:167–79.
34. Rodriguez-Galindo C, Spunt SL, Pappo AS. Treatment of Ewing sarcoma family of tumors: current status and outlook for the future. *Med Pediatr Oncol* 2003;**40**:276–87.