available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Liver cancer in European children: Incidence and survival, 1978–1997. Report from the Automated Childhood Cancer Information System project

C.A. Stiller[a,*], J. Pritchard[b], E. Steliarova-Foucher[c]

[a]Childhood Cancer Research Group, Department of Paediatrics, University of Oxford, 57 Woodstock Road, Oxford OX2 6HJ, UK
[b]Department of Paediatric Oncology and Haematology, Royal Hospital for Sick Children, Edinburgh, UK
[c]Descriptive Epidemiology Group, International Agency for Research on Cancer, Lyon, France

ARTICLE INFO

Keywords:
Childhood cancer
Liver neoplasms
Hepatoblastoma
Hepatocellular carcinoma
Europe
Epidemiology
Incidence
Survival
Registry

ABSTRACT

Data on 849 children diagnosed with malignant hepatic tumours (International Classification of Childhood Cancer, Group VII) before the age of 15 years during 1978–1997 in Europe were extracted from the ACCIS database. Age-standardised incidence during 1988–1997 was 1.5 per million overall, 1.2 per million for hepatoblastoma and 0.2 per million for hepatic carcinoma. Over 90% of cases of hepatoblastoma occurred before age 5 years, whereas hepatic carcinoma had a fairly flat age distribution. Both tumours had an incidence in boys of 1.5–1.6 times that in girls. There were no significant time trends in incidence during 1978–1997. Five-year survival from hepatoblastoma diagnosed during 1988–1997 was 63% overall, and ranged from 52% in Eastern Europe to 84% in the North. Survival from hepatic carcinoma was much lower (37%). Between 1978–1982 and 1993–1997, 5-year survival (95% confidence interval (95% CI)) increased from 28% (95% CI 18–39) to 66% (95% CI 55–74) for hepatoblastoma and from 17% (95% CI 6–33) to 50% (95% CI 26–70) for hepatic carcinoma. These increases reflect the impact of advances in treatment of childhood liver cancer at a population level.

1. Introduction

Primary liver cancer is rare in children, typically accounting for around 1% of all paediatric cancers.[1] The main types are hepatoblastoma and hepatocellular carcinoma (HCC), both of which are tumours of hepatocytes.[2] Predisposing genetic factors for hepatoblastoma include overgrowth syndromes, especially Beckwith–Wiedemann syndrome (BWS),[3] and inheritance of a mutated APC (adenomatous polyposis of colon) gene in the dominant disorder familial adenomatous polyposis (FAP).[4] An increased risk of hepatoblastoma in children with very low birth weight has been found in Japan, the United States of America (USA) and, most recently, the United Kingdom (UK).[5–7] By contrast, predisposing factors for HCC are those causing diffuse parenchymal liver disease in early life, including metabolic disorders such as tyrosinosis and glycogen storage disease, especially type 1.[2] Early infection with hepatitis B is certainly a cause of HCC in regions where it is endemic, and in Taiwan a national immunisation programme has already led to a sharply decreased incidence of HCC in childhood.[8] Hepatitis C infection is a known cause of HCC in adults[9] but data on its relation to HCC in children are not available.

Until the 1980s, survival from both types of childhood liver cancer was poor, but since then the outlook for children with hepatoblastoma has improved substantially.[10]

* *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
doi:10.1016/j.ejca.2006.05.011

In this paper we present geographical patterns and time trends in the incidence and survival rates for malignant liver tumours among European children. The analyses are based on a large European database within the Automated Childhood Cancer Information System (ACCIS) which contains information from 80 population-based cancer registries in 35 participating countries.[11]

2. Material and methods

Malignant hepatic tumours were defined as all those neoplasms in group VII of the International Classification of Childhood Cancer (ICCC).[12] All 849 malignant hepatic tumours registered since 1978 in patients aged under 15 years of age in 59 participating cancer registries of 19 European countries were extracted from the ACCIS database. This number included 640 hepatoblastomas (ICCC subgroup VIIa), 187 hepatic carcinomas (ICCC subgroup VIIb) and 22 unspecified hepatic tumours (ICCC subgroup VIIc). 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 and basis of diagnosis) 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, in the 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, socio-economic 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 in the participating countries and otherwise was estimated by linear interpolation from available data [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

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 these analyses 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. The 95% CIs for incidence rates were calculated using the Poisson approximation,[13] or exactly if fewer than 30 cases were observed.[13] Variations in incidence between the five European regions were analysed by Poisson regression. Time trends in incidence were modelled 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 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. Differences in survival between groups of patients were tested by log-rank tests.[13] More details on the methods used can be found elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

3. Results

Table 3 shows incidence rates for 1988–1997 by histological subgroup, age group, sex and region, and Fig. 1 shows incidence by histological subgroup and single year of age. Hepatoblastoma accounted for 80% of malignant hepatic tumours, hepatic carcinoma for 18% and unspecified tumours for 2%. Of the 92 cases in the subgroup of hepatic carcinoma, 89 (97%) were HCC not otherwise specified, 2 (2%) were fibrolamellar HCC and 1(1%) was mixed HCC and cholangiocarcinoma; there were no cases of pure cholangiocarcinoma. There was a male excess for hepatoblastoma, especially before age 5 years (Fig. 1). The sex ratio varied much less with age for hepatic carcinoma. Hepatoblastoma was predominantly a tumour of early childhood, with 42% of cases occurring in the first year of life and 91% by age 5 years. The age distribution showed slight differences by region (Fig. 2). Hepatic carcinoma, on the other hand, had a fairly flat age distribution. Incidence of hepatic tumours, and of hepatoblastoma in particular, was lower in the British Isles than elsewhere in Europe. The European regions with the highest rates were the North and East. Norway had the highest ASRs for all hepatic tumours (2.9 per million) and for hepatoblastoma (2.4 per million). Table 4 shows the results of analyses of time trends in incidence for Europe as a whole. There was no significant trend for hepatic tumours overall or for any diagnostic subgroup. No significant trends were found in any European region (results not shown).

Table 5 shows 5-year survival of children diagnosed during 1988–1997. For hepatoblastoma there was little sign of variation in survival with age group at diagnosis ($P = 0.6$). Survival rates were lowest in the East and highest in the North. Survival from hepatic carcinoma was much lower than for hepatoblastoma. Numbers of cases included in the analyses were very low in individual regions, but there was little sign of inter-regional variation ($P = 0.09$) other than the markedly higher survival in the North. Table 6 shows trends in survival during 1978–1997. There were impressive increases in survival during this period for children with hepatoblastoma in Europe as a whole and in all regions except the West. Survival also increased for hepatic carcinoma, though less markedly.

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

Region	Registry	Coverage				Basis of diagnosis			Survival analysis			Notes
		Period	Time-trend	*n*	NOS	MV	DCO	unknown	*n*	Closing date	FU > 5 years	
					%	%	%	%			%	
British Isles	IRELAND, National	1994–1997		3	0	100	0	0	3	31.12.1998	0	
	UNITED KINGDOM, England & Wales	1978–1995	+	181	0	91	1	3	173	31.1.2001	100	P
	UNITED KINGDOM, Northern Ireland	1993–1996		1	0	100	0	0	1	31.12.1999	–	
	UNITED KINGDOM, Scotland	1978–1997	+	21	0	95	0	0	21	31.12.1999	67	
East	BELARUS, National	1989–1997		29	21	100	0	0	29	1.9.2000	67	P
	ESTONIA, National	1978–1997	+	10	0	100	0	0	8	31.12.1998	50	
	HUNGARY, National	1978–1997	+	53	0	100	–	0	52	1.1.2000	82	P
	SLOVAKIA, National	1978–1997	+	42	14	86	0	0	32	31.12.1997	55	
	GERMANY, NCR (only former East)	1978–1989	+	23	0	100	0	0	17	31.12.1987	100	
North	DENMARK, National	1978–1997	+	30	3	93	3	3	26	31.12.1997	75	
	FINLAND, National	1978–1997	+	24	4	100	0	0	22	31.12.1998	79	
	ICELAND, National	1978–1997	+	1	0	100	0	0	1	31.12.2000	0	
	NORWAY, National	1978–1997	+	46	2	100	0	0	46	1.1.2000	78	
South	ITALY, Piedmont paediatric	1978–1997	+	21	5	95	0	0	21	31.12.1999	86	P o2
	ITALY, Marche	1990–1997		3	0	100	–	0	3	30.9.2000	100	P o3
	ITALY, Ferrara	1991–1995		0	–	–	–	–	–	–	–	
	ITALY, Latina	1983–1997	+	4	0	100	0	0	4	31.12.1998	100	
	ITALY, Liguria	1988–1995		1	100	0	100	0	–	15.4.2000	–	
	ITALY, Lombardy	1978–1997	+	3	0	100	0	0	3	23.9.1999	100	
	ITALY, Parma	1978–1995	+	3	0	100	0	0	3	1.4.1999	100	
	ITALY, Ragusa	1983–1997	+	0	–	–	–	–	–	–	–	
	ITALY, Sassari	1992–1995		1	0	100	0	0	1	30.12.1999	0	
	ITALY, Tuscany	1988–1997		1	0	100	0	0	1	31.12.1998	100	
	ITALY, Umbria	1994–1996		0	–	–	–	–	–	–	–	
	ITALY, Veneto	1990–1996		1	0	100	0	0	1	31.12.1998	0	
	MALTA, National	1991–1997		0	–	–	–	–	–	–	–	
	SLOVENIA, National	1978–1997	+	11	0	100	0	0	11	31.12.1999	80	
	SPAIN, National	1990–1995		13	0	92	0	8	12	31.12.2000	71	PZ o4
	SPAIN, Albacete	1991–1997		0	–	–	–	–	–	–	–	
	SPAIN, Asturias	1983–1997	+	2	0	100	0	0	2	31.12.1997	100	
	SPAIN, Basque Country	1988–1994		6	17	83	0	0	6	31.12.2000	100	o4
	SPAIN, Canary Islands	1993–1996		1	0	100	0	0	–	–	–	
	SPAIN, Girona	1994–1997		0	–	–	–	–	–	–	–	o4
	SPAIN, Granada	1988–1997		3	0	100	0	0	3	31.12.1999	50	P
	SPAIN, Mallorca	1988–1995		0	–	–	–	–	–	–	–	o4
	SPAIN, Navarra	1978–1996	+	3	0	100	0	0	3	31.12.1997	100	o4
	SPAIN, Tarragona	1983–1997	+	3	0	100	0	0	3	31.12.1998	100	o4
	SPAIN, Zaragoza	1978–1996	+	12	0	75	17	0	10	31.12.1996	67	o4
	TURKEY, Izmir	1993–1996		3	0	100	–	0	–	–	–	

(*continued on next page*)

Table 1 – *continued*

Region	Registry	Coverage				Basis of diagnosis			Survival analysis			Notes
		Period	Time-trend	*n*	NOS	MV	DCO	unknown	*n*	Closing date	FU > 5 years	
					%	%	%	%			%	
West	FRANCE, Brittany	1991–1997		8	0	100	–	0	8	1.1.2000	33	P
	FRANCE, Lorraine	1983–1997	+	14	0	57	–	0	14	1.1.1999	67	P
	FRANCE, PACA & Corsica	1984–1996	+	6	0	100	–	0	6	31.3.1998	25	P
	FRANCE, Rhone Alpes	1988–1997		13	0	92	–	0	13	1.6.2000	55	P o1
	FRANCE, Doubs	1978–1996	+	0	–	–	–	–	–	–	–	
	FRANCE, Herault	1988–1997		1	0	100	–	0	–	–	–	
	FRANCE, Isere	1979–1997	+	4	0	100	–	0	–	–	–	o1
	FRANCE, Manche	1994–1996		0	–	–	–	–	–	–	–	
	FRANCE, Bas-Rhin	1978–1996	+	6	0	100	–	0	6	31.12.1997	50	
	FRANCE, Haut-Rhin	1988–1997		1	0	100	–	0	–	–	–	
	FRANCE, Somme	1983–1996	+	3	33	67	–	0	3	15.8.2000	100	
	FRANCE, Tarn	1983–1997	+	2	0	100	–	0	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	106	0	100	–	0	26	31.12.1998	7	P
	GERMANY, GCCR (only former West)	1983–1990	+	106	2	100	–	0	100	31.12.1998	49	P
	NETHERLANDS, National	1989–1995		24	4	96	–	0	23	31.12.1998	38	o5
	NETHERLANDS, Eindhoven	1978–1997	+	5	20	60	–	20	5	1.7.1999	100	o5
	SWITZERLAND, Basel	1983–1997	+	2	0	100	–	0	2	30.6.2000	100	
	SWITZERLAND, Geneva	1978–1997	+	1	0	100	0	0	1	31.12.1999	–	
	SWITZERLAND, Graubunden & Glarus	1989–1997		1	0	100	0	0	1	25.5.2000	–	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	1	0	100	0	0	1	1.2.2001	0	
	SWITZERLAND, Valais	1989–1997		1	0	100	0	0	1	1.12.1998	100	

n, number of cases registered in the given period; PACA, Provence Alps Côte d'Azur; NCR, National Cancer Registry of the German Democratic Republic. Data for 1978–1987 contributed only to analyses of time trends for Europe as a whole. Data for 1988–1989 were pooled with GCCR and included in West. For explanation, see Steliarova-Foucher, Kaatsch, Lacour et al. (this issue); GCCR, National German Childhood Cancer Registry (until 1990 only West, since 1991 for reunified Germany); +, included in time trends; % 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 alive cases followed-up for at least 5 years as a percentage of those not deceased by the closing date P, paediatric cancer registry, age-range of the patients is 0–14 years; Z, covers only selected areas, see Steliarova-Foucher, Kaatsch, Lacour et al. (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.

Table 2 – Numbers of cases and indicators of data quality by region for time trend analyses of hepatic tumours in children (Source: ACCIS)

Region	Period	Cases	NOS	Basis of diagnosis			Follow-up	
				MV	DCO	Unknown	>0 days	5+ years
		n	%	%	%	%	%	%
		a	b	c	d	e	f	g
Europe	1978–1982	108	2	94	<1	2	92	100
	1983–1987	219	3	93	<1	<1	94	96
	1988–1992	225	1	96	<1	1	90	62
	1993–1997	197	2	96	<1	1	63	29
British Isles	1978–1982	47	0	94	0	4	96	100
	1983–1987	55	0	85	2	2	93	100
	1988–1992	58	0	91	2	3	97	100
	1993–1997	42	0	95	0	2	100	87
East	1978–1982	15	7	93	0	0	87	100
	1983–1987	33	6	94	0	0	88	100
	1988–1992	25	4	96	0	0	84	100
	1993–1997	32	6	94	0	0	91	33
North	1978–1982	24	0	100	0	0	83	100
	1983–1987	28	7	100	0	0	100	100
	1988–1992	23	0	100	0	0	100	100
	1993–1997	26	4	92	4	4	92	35
South	1978–1982	15	7	87	7	0	93	100
	1983–1987	21	0	90	5	0	95	100
	1988–1992	19	0	100	0	0	100	100
	1993–1997	7	0	100	0	0	100	40
West	1978–1982	1	0	100	0	0	100	–
	1983–1987	71	4	94	0	0	96	88
	1988–1992	94	1	97	0	1	83	21
	1993–1997	90	0	98	0	0	24	3

n, number of cases registered in the given period; MV, microscopically verified cases; DCO, registrations from death certificate only; unknown, registrations with unknown basis of diagnosis; f, total number of cases in the registries with follow-up data.
Totals for regions do not sum to total for Europe as the data from the former GDR are only included in the data for Europe as a whole.g, number of cases with follow-up >0 day and which have not deceased by closing date.

Table 3 – Numbers of registrations (*n*) and incidence rates per million for hepatic tumours among children in Europe, 1988–1997 (Source: ACCIS)

	n	0	1–4 years	5–9 years	10–14 years	ASR (95% CI)	Ratio of ASR M/F
Total							
British Isles	104	5.2	1.6	0.5	0.5	1.2 (1.0–1.4)	1.5
East	86	11.8	2.2	0.5	0.3	1.9 (1.5–2.3)	1.1
North	49	6.3	3.6	0.4	0.7	1.9 (1.4–2.5)	1.5
South	49	7.6	2.3	0.2	0.5	1.5 (1.1–2.0)	1.0
West	233	7.1	2.2	0.3	0.3	1.4 (1.2–1.6)	1.9
Total	521	7.2	2.2	0.4	0.4	1.5 (1.3–1.6)	1.5
Hepatoblastoma							
British Isles	82	5.0	1.5	0.2	0.2	1.0 (0.8–1.2)	1.5
East	65	10.6	1.6	0.3	0.1	1.4 (1.1–1.8)	1.0
North	38	6.3	3.3	–	0.1	1.5 (1.1–2.0)	1.8
South	35	7.1	1.8	0.1	0.1	1.2 (0.8–1.6)	1.0
West	196	6.7	2.1	0.1	0.1	1.2 (1.1–1.4)	1.9
Total	416	6.8	1.9	0.1	0.1	1.2 (1.1–1.3)	1.5
Carcinoma							
British Isles	22	0.2	0.1	0.3	0.3	0.2 (0.1–0.3)	1.7
East	12	0.3	0.3	0.2	0.1	0.2 (0.1–0.4)	3.7
North	10	–	0.1	0.4	0.5	0.3 (0.1–0.6)	0.7
South	13	0.4	0.3	0.2	0.5	0.3 (0.1–0.5)	0.8
West	35	0.3	0.2	0.2	0.2	0.2 (0.1–0.3)	1.9
Total	92	0.3	0.2	0.2	0.2	0.2 (0.2–0.3)	1.6
Unspecified							
Total	13	0.2	0.1	–	0.0	0.0 (0.0–0.1)	0.6

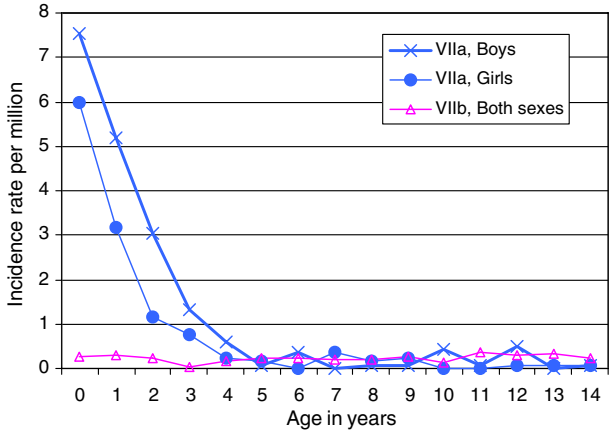

Fig. 1 – Age-specific incidence rates of hepatoblastoma (VIIa) and hepatic carcinoma (VIIb) in Europe, 1988–1997. Source: ACCIS.

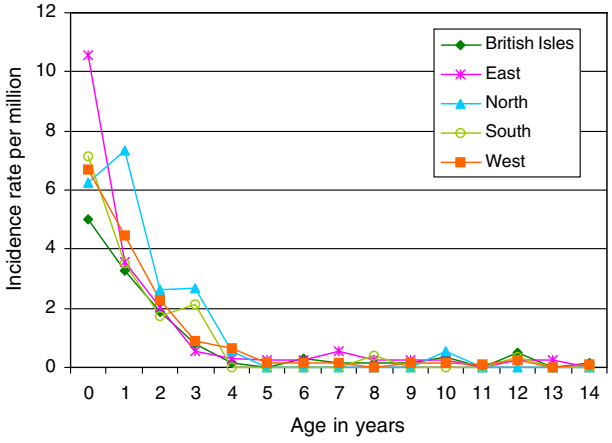

Fig. 2 – Age-specific incidence rates of hepatoblastoma (VIIa) in the European regions, 1988–1997. Source: ACCIS.

Table 4 – Trends in the incidence of malignant hepatic tumours among children in Europe, 1978–1997. Numbers of cases (*n*) and average annual percentage change (AAPC) in ASR from models including sex, region and age group (Source: ACCIS)

	n	AAPC	(95% CI)
Total	749	0.84	(−0.59–2.24)
Hepatoblastoma	567	1.00	(−0.63–2.70)
Carcinoma	168	−0.65	(−3.89–2.48)

Table 5 – Five-year % survival (95% CI) of children in Europe with malignant hepatic tumours diagnosed 1988–1997 (Source: ACCIS)

	Age (years)	Hepatoblastoma		Carcinoma	
		n	Survival	*n*	Survival
Europe	0	143	69 (60–76)	6	17 (1–52)
	1–4	157	57 (49–65)	15	47 (21–69)
	5–9	16	67 (38–85)	24	48 (27–66)
	10–14	13	56 (24–79)	29	27 (11–45)
	0–14	329	63 (57–68)	74	37 (26–48)
British Isles	0–14	82	62 (50–71)	20	34 (15–54)
East	0–14	61	52 (38–64)	12	25 (6–50)
North	0–14	37	84 (67–92)	9	78 (36–94)
South	0–14	32	72 (52–84)	11	31 (7–60)
West	0–14	117	57 (46–67)	22	35 (15–56)

4. Discussion

This is the largest ever population-based study of liver cancer in children. There is some evidence of geographical variation in incidence within Europe but no significant change in rates over time. The most striking findings relate to survival, namely the variation in survival rates between European regions and the increase in survival over the 20-year study period.

The incidence of childhood liver tumours was similar to that in earlier periods in Europe and other western countries.[1,14] As in the 1980s, Norway had the highest incidence of hepatoblastoma.[1] In common with most childhood cancers, little is known about the aetiology of hepatoblastoma. The most well-established risk factors are BWS, family history of FAP, low birth weight and smoking by either or both parents.[15,16] In a study of seven western European countries, five of which are represented in the present study, median birth weight was higher in Norway than in most other countries and there was no evidence of a Norwegian excess of low birth weight infants.[17] In a study of 12 western European countries, the prevalence of smoking among adults aged 20–44 years around 1990 was above average for women in Norway, though similar to that in Finland and West Germany and lower than in Denmark, but slightly below average for men.[18] We have no information on the prevalence of FAP in Norway. Information on congenital anomalies is collected by some contributing registries, but it is not currently included in the ACCIS database. It would be useful if these data could be incorporated in future so that, in particular, the frequency of BWS with hepatoblastoma across Europe could be investigated.

We found no significant trends in the incidence of childhood liver cancers, though a non-significant increase in hepatoblastoma was partly balanced by a decrease in carcinoma. In the USA a significant increase for hepatoblastoma was accompanied by a non-significant decrease for carcinoma.[19] These patterns may reflect improved coding of childhood liver cancers. Some clinical publications in the 1980s still used the generic term 'hepatoma' for hepatoblastoma and HCC.[20]

The impressive increases in survival rates for European children with hepatoblastoma in our study are similar to those observed in the EUROCARE studies for slightly earlier periods[10,21] and in the USA.[22] The less spectacular but still significant improvement in prognosis for childhood hepatic carcinoma has not been found previously in Europe.[10] A modest increase in survival for hepatic carcinoma was reported in the USA, but this was for the combined age group 0–19 years and results were not given separately for children.[22] The ser-

Table 6 – Five-year % survival (95% CI) of children in Europe with malignant hepatic tumours diagnosed 1978–1997 with P-values from a χ^2 (1df) test for trend (Source: ACCIS)

	1978–1982		1983–87		1988–92		1993–97		P
	n	Survival	*n*	Survival	*n*	Survival	*n*	Survival	
Europe									
Hepatoblastoma	68	28 (18–39)	141	41 (33–49)	154	61 (52–69)	104	66 (55–74)	<0.001
Carcinoma	29	17 (6–33)	60	18 (10–29)	40	39 (23–54)	18	50 (26–70)	0.0020
Total	99	24 (16–33)	206	34 (27–40)	194	56 (49–63)	123	63 (54–72)	<0.0001
British Isles									
Hepatoblastoma	34	29 (15–45)	35	40 (24–56)	43	56 (40–69)	36	72 (54–84)	<0.0001
Carcinoma	11	9 (1–33)	16	19 (5–40)	13	15 (2–39)	6	67 (19–90)	0.051
Total	45	24 (14–38)	51	33 (21–36)	56	46 (33–69)	42	71 (55–83)	<0.0001
East									
Hepatoblastoma	11	18 (3–44)	31	26 (12–42)	16	56 (30–76)	27	47 (26–65)	0.028
Total	19	16 (4–35)	40	23 (11–36)	21	52 (30–71)	29	47 (27–65)	0.0079
North									
Hepatoblastoma	13	15 (2–39)	17	53 (28–73)	17	82 (55–94)	20	85 (60–95)	<0.0001
Total	20	25 (9–45)	28	43 (25–60)	23	83 (60–93)	24	83 (61–93)	<0.0001
South									
Hepatoblastoma	9	44 (14–72)	14	29 (9–52)	14	64 (34–83)	5	80 (20–97)	0.030
Total	14	29 (9–52)	20	25 (9–45)	19	58 (33–76)	7	71 (26–92)	0.0017
West									
Hepatoblastoma	1	–	44	51 (36–65)	64	58 (42–71)	16	53 (25–74)	0.77
Total	1	–	67	39 (28–51)	75	57 (42–69)	21	44 (22–64)	0.33

ies of SIOPEL trials of treatment for paediatric liver cancer from 1990 onwards recruited patients from many European countries,[23,24] though during the period up to 1997 only the British Isles, Italy and Norway had truly national entry. The great advances in prognosis for hepatoblastoma and childhood HCC in these trials are reflected in the trends observed in survival rates at the population level, especially in the British Isles and Southern Europe. The most successful regimes for both tumour types are cisplatin-based, often with the addition of doxorubicin. Similar survival rates were observed in the national trials for hepatoblastoma in Germany,[25,26] albeit with more intensive chemotherapy including ifosfamide. Although Germany dominates the Western region in the present study, it is the only region with no suggestion of a trend in survival from hepatoblastoma between the 1980s and 1990s. This is probably because of the lack of follow-up data for many German patients, especially those diagnosed in the more recent periods. We found lower survival in the Eastern region of Europe, though there was a significant improvement over time. Of the East European countries represented in our study, only Hungary entered patients in the SIOPEL studies, and it seems likely that the poorer prognosis in the East was a consequence of lack of access to modern therapy in some countries of the region. 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]. Survival was especially high in the Northern European region. All countries in that region (except Iceland with a tiny number of cases) contributed to SIOPEL, but entry was only truly national in Norway. We have no information on other studies of hepatoblastoma treatment in the Nordic countries during this period.

Survival from hepatic carcinoma was much lower than from hepatoblastoma and comparable with the outcome in the SIOPEL trial for HCC.[27] The fibrolamellar subtype of HCC has traditionally had a relatively good prognosis.[28] Since only two patients were specified as having this subtype in our data, we were unable to assess their survival. The increased survival for childhood hepatic carcinoma in Europe contrasts with the absence of any improvement among adolescents [Stiller, Desandes, Danon and colleagues, this issue]. This may be linked to the fact that adolescents aged 16 years and over have not been eligible for the SIOPEL trials.[27]

In conclusion, the varying geographical pattern of incidence of hepatoblastoma may offer clues to aetiology, particularly in the regions with higher incidence, if artefacts could be excluded. The increased survival rates for hepatoblastoma and for hepatic carcinoma in children show the impact of clinical trials on outcome at the population level.

Conflict of interest statement

None declared.

Acknowledgements

The ACCIS project was funded by the European Commission from the 'Europe Against Cancer' action 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 ACCIS Scientific Committee and the 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, 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. 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., editors. *International incidence of childhood cancer: volume 2*. Lyon: IARC; 1998.
2. Hamilton SR, Aaltonen L, editors. *Pathology and genetics of tumours of the digestive system*. Lyon: IARC Press; 2000.
3. DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *J Pediatr* 1998;**132**:398–400.
4. Garber JE, Li FP, Kingston JE, et al. Hepatoblastoma and familial adenomatous polyposis. *J Natl Cancer Inst* 1988;**80**:1626–8.
5. Ikeda H, Matsuyama S, Tanimura M. Association between hepatoblastoma and very low birth weight: a trend or a chance. *J Pediatr* 1997;**130**:557–60.
6. Reynolds P, Urayama KY, Von Behren J, Feusner J. Birth characteristics and hepatoblastoma risk in young children. *Cancer* 2004;**100**:1070–6.
7. Ansell P, Mitchell CD, Roman E, et al. Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. *Eur J Cancer* 2005;**41**:741–8.
8. Chang M-H, Chen C-J, Lai M-S, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Eng J Med* 1997;**336**:1855–9.
9. Bosch FX, Ribes J, Díaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004;**127**:S5–S16.
10. Moller TR, Garwicz S, Corazziari I, Magnani C. Survival of children with liver tumours in Europe 1978–1989. *Eur J Cancer* 2001;**37**:744–9.
11. 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.
12. Kramárová E, Stiller CA. The international classification of childhood cancer. *Int J Cancer* 1996;**68**:759–65.
13. Kirkwood BR, Sterne AC, editors. *Essential medical statistics*. Oxford: Blackwell Science Ltd; 2003.
14. Parkin DM, Stiller CA, Draper GJ, et al., editors. *International incidence of childhood cancer (IARC scientific publications no. 87)*. Lyon: International Agency for Research on Cancer; 1988.
15. Pang D, McNally R, Birch JM on behalf of the UK Childhood Cancer Study Investigators. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. *Br J Cancer* 2003;**88**:373–81.
16. Sorahan T, Lancashire RJ. Parental cigarette smoking and childhood risks of hepatoblastoma: OSCC data. *Br J Cancer* 2004;**90**:1016–8.
17. Graafmans WC, Richardus JH, Borsboom GJJM, et al. Birth weight and perinatal mortality: a comparison of 'optimal' birth weight in seven Western European countries. *Epidemiology* 2002;**13**:569–74.
18. Cavelaars AE, Kunst AE, Geurts JJ, et al. Educational differences in smoking: international comparison. *BMJ (Clin Res Ed)* 2000;**320**:1102–7.
19. Darbari A, Sabin KM, Shapiro CN, Schwarz KB. Epidemiology of primary hepatic malignancies in U.S. children. *Hepatology* 2003;**38**:560–6.
20. Evans AE, Land VJ, Newton WA, et al. Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. *Cancer* 1982;**50**:821–6.
21. Gatta G, Capocaccia R, Stiller C, et al. Childhood cancer survival trends in Europe: a EUROCARE working group study. *J Clin Oncol* 2005;**23**:3742–51.
22. Bulterys M, Goodman MT, Smith MA, Buckley JD. Hepatic 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. 91–7.
23. Pritchard J, Brown J, Shafford E, et al. Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach —- results of the first prospective study

of the International Society of Pediatric Oncology. *J Clin Oncol* 2000;**18**:3819–28.
24. Perilongo G, Shafford E, Maibach R, et al. Risk-adapted treatment for childhood hepatoblastoma: final report of the second study of the International Society of Paediatric Oncology – SIOPEL 2. *Eur J Cancer* 2004;**40**:411–21.
25. von Schweinitz D, Byrd DJ, Hecker H, et al. Efficiency and toxicity of ifosfamide, cisplatin and doxorubicin in the treatment of childhood hepatoblastoma. *Eur J Cancer* 1997;**33**:1243–9.
26. Fuchs J, Rydzynski J, von Schweinitz D, et al. Pretreatment prognostic factors and treatment results in children with hepatoblastoma: a report from the German Cooperative Pediatric Liver Tumor Study HB 94. *Cancer* 2002;**95**:172–82.
27. Czauderna P, Mackinlay G, Perilongo G, et al. Hepatocellular carcinoma in children: Results of the first prospective study of the International Society of Pediatric Oncology Group. *J Clin Oncol* 2002;**20**:2798–804.
28. Farhi DC, Shikes RH, Murari PJ, Silverberg SG. Hepatocellular carcinoma in young people. *Cancer* 1983;**52**:1516–25.