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Malignant renal tumours incidence and survival in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

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ABSTRACT

More than 5000 cases of malignant renal tumour diagnosed in children under the age of 15 years during the period 1978–1997 in Europe, were extracted from the database of the Automated Childhood Cancer Information System (ACCIS). In 1988–1997 the age-standardised incidence rate of childhood renal tumours in Europe was 8.8 per million, with significant differences between regions. Wilms' tumour (WT, M-8960) accounted for 93% of renal tumours and about 7% were bilateral. The incidence rates of WT increased over the 20 years, by 0.7% per year. European 5-year survival for children diagnosed with WT in 1988–1997 was 85%, ranging from 73% in the East to 91% in the North. Patients in the age group 0–3 years at diagnosis had a more favourable prognosis (5-year survival 87%) than those diagnosed later (81%), $P < 0.0001$. Patients with unilateral WT ($n = 2085$) had better 5-year survival (85%) than 154 patients with bilateral tumours (76%), $P = 0.003$. Five-year survival for 64 patients with clear cell sarcoma of kidney was 68%, for 43 patients with rhabdoid tumour of kidney it was 23%, and for 56 patients with renal cell carcinoma it was 87%. For combined European data, 5-year survival for WT increased from 73% in 1978–1982 to 87% in 1993–1997 and the increase was significant in three out of five regions (East, North and West). Further development and exploitation of the ACCIS database will benefit clinical management and aetiological studies.

1. Introduction

Malignant renal tumours comprise 6% of all childhood cancers, with Wilms' tumour (WT) being the most frequent type (90%).[1] The majority of WT are solitary lesions, but approximately 12% of children develop multifocal tumours within a single kidney and almost 7% have bilateral involvement at diagnosis or later on.[2,3] Children with unilateral tumours

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are older than cases with bilateral ones, in accordance with Knudson's two hit hypothesis.[4]

WT occurs as part of several distinct congenital malformation syndromes. Overgrowth syndromes, in particular Beckwith–Wiedemann syndrome carry an approximately 5% risk of developing WT.[2] Syndromes involving genitourinary anomalies combined with aniridia and variable mental retardation, or with nephrotic syndrome are associated with mutations of the *WT1* gene on chromosome 11p13 and carry a greatly increased risk of developing WT.[2] Children with these congenital abnormalities are at risk of bilateral kidney involvement.[5] There is evidence for multiple WT predisposition genes. At least three susceptibility genes have been implicated in familial WT, which is found in 1–2% of cases.[6] Epidemiological studies suggest that ethnicity affects the incidence rates more than geographical region of residence.[1,7] These observations, in addition to inconsistent results from case-control studies, suggest that environmental factors play a marginal role in the aetiology of this tumour.[2,7]

Over the past 40 years, the prognosis of children with WT has improved due to risk-adapted use of an armamentarium of effective therapies. The development of treatment strategies for WT has been a paradigm for the contribution of randomised multicentre clinical trials to progress in paediatric oncology.[3,8–10]

Clear cell sarcoma of the kidney (CCSK) is a rare childhood renal cancer. The clinical course is characterised by a wider spread of metastases to bone, brain and lungs, by a longer period at risk of relapse and by historically poorer outcome than WT.[11]

Rhabdoid tumour of the kidney (RTK) occurs mostly in infants. It is a highly aggressive entity, often with brain metastasis at diagnosis: the survival is less than 1 year from diagnosis for the majority of cases. It is associated with mutation of the INI1 gene on chromosome 22q in both renal and non-renal rhabdoid tumours, a mutation that is often constitutional.[12]

Renal cell carcinoma (RCC), the most common renal tumour in adults, is rare in childhood. Children are at risk of RCC when affected by Von Hippel–Lindau disease or tuberous sclerosis. A specific translocation at Xp11.2, characteristic of alveolar soft part sarcoma, has also been reported in papillary RCC diagnosed in younger children.[13]

International studies published to date reported incidence rates[1,14] and survival[14–16] in Europe for the combined group of malignant renal tumours and for its three subgroups defined by the International Classification of Childhood Cancer.[17] We present data from 59 population-based registries in Europe participating in ACCIS.[18] In addition to a general overview of incidence and survival in Europe over the period 1978–1997 for the group of renal tumours, we also provide statistics for selected histological types; and compare data for unilateral versus bilateral Wilms' tumours. Finally, we discuss the geographical and temporal variations of incidence and survival observed and propose future priorities for study of renal tumours within ACCIS.

2. Material and methods

Children with malignant renal tumours diagnosed before the age of 15 years during the period 1978–1997 in 59 population-based cancer registries in 19 European countries were extracted from the ACCIS database and included in this study after a methodical evaluation of their quality and comparability.[18] Table 1 shows the list of datasets included in the report, their grouping into geographical regions, the numbers of cases and the quality indicators. The very small number of cases registered from death certificate only (less than 2%), the high proportion of patients with microscopically verified diagnosis (over 95%) and low proportion of unspecified types confirm the good quality of the data. Follow-up information was available in 53 registries. The closing date of the follow-up varied from 1995 to 2001. The European countries were grouped in five geographical regions: British Isles, East, North, South and West Europe, as shown in Table 1. The rationale for grouping of countries can be found elsewhere.[18]

Attending to the availability of data in the different geographical areas and registries, four sets of cases were used for different analyses: (i) incidence patterns in the most recent period 1988–1997, including all the registries listed in Table 1; (ii) incidence time trends for the period 1978–1997, including registries with long registration period; and for the registries with available follow-up information, (iii) survival for the period 1988–1997, and (iv) survival time trends for the period 1978–1997. Thirty registries were included in all types of analyses. Data quality and follow-up of the patients according to time period and region can be evaluated from Table 2. The indicators of methods of diagnosis were relatively stable. Inter-regional differences can be seen only in the indicators of follow-up in the last 5-year period, with virtually complete follow-up only in the British Isles.

The malignant renal tumours belong to group VI of the International Classification of Childhood Cancer (ICCC),[17] where they are classified into three categories: Wilms tumour, rhabdoid and clear cell sarcoma (VIa), renal carcinoma (VIb), and unspecified malignant renal tumours (VIc). The conversion table can be consulted in this issue [Steliarova-Foucher, Kaattsch, Lacour and colleagues, this issue]. In addition to these three subgroups, we present data for the individual histological types of the subgroup VIa, as defined in ICD-O-2:[18] Wilms' tumour (nephroblastoma, M-8960), clear cell sarcoma of kidney (M-8964) and rhabdoid tumour of kidney (M-8963). Separate analyses were conducted for WT (M-8960) according to laterality, using data from 31 registries, with known laterality for at least 90% of tumours (Table 1).

All incidence rates are expressed per million person-years of the relevant population at risk. Age-specific incidence rates were calculated for 'standard' age groups 0, 1–4, 5–9 and 10–14 years and for single years of age. The age-standardised rates (ASR) were calculated by the direct method, using the World standard population under 15 years of age.[19] Geographical differences between the European regions were formally evaluated from a Poisson model, including geographical region as the explanatory variable and gender and age-group as the confounders, and expressed as incidence rate ratios (IRR), with the British Isles as the reference region. Change in incidence rates over the period 1978–1997 was evaluated using Poisson regression models with year as a continuous explanatory variable, and adjusted for gender, age group and region. It is expressed as an average annual percent change (AAPC) of incidence rate. Incidence rate ratios for the 5-year periods

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

Region	Registry	Period	Time-trend	Renal tumours	NOS (VIc)	Basis of diagnosis			Wilms' tumour		Follow-up		Notes
						MV	DCO	Unknown	%	Laterality	Closing date	5+ years	
				n	%	%	%	%				%	
British Isles	IRELAND, National	1994–1997		18	0	100	0	0	94		31.12.1998	0	
	UNITED KINGDOM, England & Wales	1978–1995	+	1209	<1	97	<1	1	98	+	31.1.2001	99	P
	UNITED KINGDOM, Northern Ireland	1993–1996		11	9	73	0	0	91		31.12.1999	0	
	UNITED KINGDOM, Scotland	1978–1997	+	129	2	97	0	0	98		31.12.1999	85	
East	BELARUS, National	1989–1997		157	3	99	0	0	96	+	1.9.2000	76	P
	ESTONIA, National	1978–1997	+	78	13	88	0	0	87	+	31.12.1998	57	
	HUNGARY, National	1978–1997	+	281	0	100	0	0	97	+	1.1.2000	85	P
	SLOVAKIA, National	1978–1997	+	181	9	92	1	0	91	+	31.12.1997	66	
	GERMANY, NCR (only former East)	1978–1989	+	281	<1	99	0	0	98	+	31.12.1987	70	S
North	DENMARK, National	1978–1997	+	153	8	93	0	3	90	+	31.12.1997	80	
	FINLAND, National	1978–1997	+	182	<1	100	0	0	98	+	31.12.1998	80	
	ICELAND, National	1978–1997	+	7	0	100	0	0	100	+	31.12.2000	83	
	NORWAY, National	1978–1997	+	117	10	99	0	0	87		1.1.2000	81	
South	ITALY, Piedmont paediatric	1978–1997	+	90	0	97	1	0	97	+	31.12.1999	82	P
	ITALY, Marche	1990–1997		13	0	92	–	8	100		30.9.2000	40	P
	ITALY, Ferrara	1991–1995		0	–	–	–	–	–	–	–	–	
	ITALY, Latina	1983–1997	+	3	0	100	0	0	100		31.12.1998	100	
	ITALY, Liguria	1988–1995		5	0	100	0	0	100		15.4.2000	100	
	ITALY, Lombardy	1978–1997	+	19	5	74	0	0	95	+	23.9.1999	73	
	ITALY, Parma	1978–1995	+	3	0	100	0	0	100		1.4.1999	100	
	ITALY, Ragusa	1983–1997	+	12	0	100	0	0	92		30.3.2000	88	
	ITALY, Sassari	1992–1995		3	0	100	0	0	100	+	30.12.1999	100	
	ITALY, Tuscany	1988–1997		10	0	80	0	0	100		31.12.1998	60	
	ITALY, Umbria	1994–1996		2	0	100	0	0	100	+	31.12.1999	50	
	ITALY, Veneto	1990–1996		13	0	92	0	0	92	+	31.12.1998	50	
	MALTA, National	1991–1997		7	0	100	0	0	100		31.12.1999	50	
	SLOVENIA, National	1978–1997	+	54	2	98	0	0	98	+	31.12.1999	71	
	SPAIN, National	1990–1995		66	0	91	0	2	100	+	31.12.2000	93	P o1 Z
	SPAIN, Albacete	1991–1997		1	0	100	0	0	100	+	15.9.2000	0	
	SPAIN, Asturias	1983–1997	+	23	4	91	0	0	91		31.12.1997	60	
	SPAIN, Basque Country	1988–1994		8	0	100	0	0	88		31.12.2000	100	o1
	SPAIN, Canary Islands	1993–1996		3	0	100	0	0	100		–	–	
	SPAIN, Girona	1994–1997		2	0	100	0	0	50		31.12.1997	0	o1
	SPAIN, Granada	1988–1997		14	0	100	0	0	100	+	31.12.1999	77	G
	SPAIN, Mallorca	1988–1995		7	0	100	0	0	100		31.12.1998	40	o1
	SPAIN, Navarra	1978–1996	+	11	0	100	0	0	100		31.12.1997	70	o1
	SPAIN, Tarragona	1983–1997	+	8	13	88	13	0	75		31.12.1998	67	o1
	SPAIN, Zaragoza	1978–1996	+	23	0	96	0	0	100		31.12.1996	56	o1
	TURKEY, Izmir	1993–1996		16	0	100	–	0	100	+	–	–	

(*continued on next page*)

Table 1 – *continued*

Region	Registry	Period	Time-trend	Renal tumours	NOS (VIc)	Basis of diagnosis			Wilms' tumour		Follow-up		Notes
						MV	DCO	Unknown	%	Laterality	Closing date	5+ years	
				n	%	%	%	%				%	
West	FRANCE, Brittany	1991–1997		43	0	100	–	0	95	+	1.1.2000	41	P
	FRANCE, Lorraine	1983–1997	+	52	2	100	–	0	92	+	1.1.1999	64	P
	FRANCE, PACA	1984–1996	+	73	0	100	–	0	99	+	31.3.1998	68	P
	FRANCE, Rhone Alpes	1988–1997		91	0	99	–	0	97	+	1.6.2000	65	P o2
	FRANCE, Doubs	1978–1996	+	17	0	18	–	0	94	+	1.6.2001	21	
	FRANCE, Herault	1988–1997		11	0	100	–	0	100		–	–	
	FRANCE, Isere	1979–1997	+	46	0	100	–	0	100		–	–	o2
	FRANCE, Manche	1994–1996		1	0	100	–	0	100	+	–	–	S
	FRANCE, Bas-Rhin	1978–1996	+	41	5	95	–	0	93		31.12.1997	84	
	FRANCE, Haut-Rhin	1988–1997		14	0	100	–	0	100		31.12.1995	67	S
	FRANCE, Somme	1983–1996	+	21	0	100	–	0	95		15.8.2000	30	
	FRANCE, Tarn	1983–1997	+	7	0	100	–	0	100		–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	786	<1	99	–	0	99	+	31.12.1998	25	P
	GERMANY, WEST GCCR	1983–1990	+	592	0	100	–	0	98		31.12.1998	89	P
	NETHERLANDS, National	1989–1995		181	16	83	–	0	82	+	31.12.1998	63	S o3
	NETHERLANDS, Eindhoven	1978–1997	+	24	4	83	–	8	96	+	1.7.1999	67	o3
	SWITZERLAND, Basel	1983–1997	+	7	0	100	–	0	100		30.6.2000	71	
	SWITZERLAND, Geneva	1978–1997	+	6	0	100	0	0	83		31.12.1999	80	
	SWITZERLAND, Graubunden & Glarus	1989–1997		5	0	100	0	0	100	+	25.5.2000	50	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	13	0	100	0	0	100	+	1.2.2001	25	
	SWITZERLAND, Valais	1989–1997		2	0	100	0	0	100	+	1.12.1998	100	S

n, number of cases; NCR, National Cancer Registry of the former 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 geographical analyses of the period 1988–1997. 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); PACA, Provence, Alps, Cote d'Azur; +, registry included in the analyses; –, not applicable; MV, microscopically verified cases; DCO, registrations from death certificate only; Unknown, registrations with unknown basis of diagnosis; NOS, cases with unspecified histology code; 5+ years, 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; o1–o3: overlapping registration areas for the overlapping years, data from the registry with larger coverage are included in each analysis, according to availability; S, survival analyses were possible only for a restricted dataset [Steliarova-Foucher, Kaatsch, Lacour, and colleagues, this issue]; G, general cancer registry, which has only contributed data for age-range 0–14 years; Z, covers only selected area [see Steliarova-Foucher, Kaatsch, Lacour, and colleagues, this issue].

Table 2 – Numbers of cases and indicators of data quality by region for time trend analyses of renal tumours incidence and survival in children (age 0–14 years) in Europe, 1978–1997 (Source: ACCIS)

Region	Period	Cases	Basis of diagnosis				Follow-up	
		Renal	WT	MV	DCO	Unknown	0+ days[a]	5+ years[b]
		n	%	%	%	%	%	%
Europe*	1978–1982	796	95	96	<1	<1	98	99
	1983–1987	1250	97	98	<1	<1	99	90
	1988–1992	1268	97	98	<1	<1	98	87
	1993–1997	1235	97	98	<1	<1	97	32
British Isles	1978–1982	344	98	99	0	<1	98	100
	1983–1987	366	98	97	<1	<1	99	99
	1988–1992	380	98	97	<1	2	99	99
	1993–1997	248	96	96	<1	<1	98	90
East	1978–1982	146	92	95	<1	0	94	99
	1983–1987	136	92	96	0	0	97	99
	1988–1992	122	93	95	<1	0	94	95
	1993–1997	136	96	97	0	0	100	33
North	1978–1982	115	87	93	0	2	100	96
	1983–1987	116	93	99	0	0	100	100
	1988–1992	108	96	100	0	0	100	100
	1993–1997	120	93	98	0	2	100	34
South	1978–1982	51	98	98	0	0	100	98
	1983–1987	66	94	92	0	0	100	98
	1988–1992	52	98	96	2	0	98	94
	1993–1997	77	95	94	1	0	99	29
West	1978–1982	23	96	83	0	0	100	100
	1983–1987	450	98	98	0	<1	98	87
	1988–1992	558	97	98	0	0	97	74
	1993–1997	654	99	99	0	0	95	11

a Total number of cases in the registries with follow-up data, i.e. included in survival analyses.
b Number of cases with follow-up >0 days and which have not deceased by closing date.
* Europe includes the data of former German Democratic Republic for 1978–1987, not included in any other region; *n*, number of cases; WT (%), Wilms' tumour as a percentage of total renal tumours; MV, microscopically verified diagnosis; DCO, cases registered from death certificate only.

1978–1982, 1983–1987, 1988–1992 as compared with the reference period 1993–1997 were derived from a Poisson model, with period as the explanatory variable and adjusted for possible confounders.[19]

Survival analyses were carried out using actuarial life table method.[20] The duration of survival was calculated from the date of diagnosis to date of last contact. Cases with zero follow-up time were excluded from analyses. Survival rates were presented as cumulative actuarial probability of survival at 5-years after the diagnosis with 95% confidence interval (95% CI). The differences in survival between subgroups of patients were tested by a log-rank χ^2 test, evaluating the complete survival curves.[21] Survival probabilities are presented for standard age groups. In addition, we tried to determine the age limits at which prognosis changes, since survival of children with WT has been reported to differ according to age at diagnosis, not necessarily overlying the standard age groups.[3] This was done in four steps. First, life table was constructed for each single year of age: 0, 1, 2 up to 14. Second, the observed (O) versus expected (E) numbers of deaths were compared for each age, using O/E ratio. Third, two crude age groups were defined; the first one containing age zero and all successive years of age with the O/E < 1 (more deaths expected than observed) and the second containing the first lowest year of age with O/E > 1 and all the following years of age. Fourth, the survival for these two crude age groups was compared using life table method and log-rank test. This procedure was repeated for both sexes combined, as well as separately for boys and girls. A χ^2 test for trend was used to evaluate a presence of a time trend in survival over 1978–1997. Analyses were carried out using, SAS® and STATA® software.

3. Results

Data on 3134 newly diagnosed malignant renal tumours in children younger than 15 years of age during the period 1988–1997 were included in the incidence analysis. Table 3 presents the number of cases of renal tumour by histological subtype and age at diagnosis. The proportions of histological subtypes are shown in Fig. 1. WT (M-8960) was the most common type of renal tumour (93%). Over 77% were diagnosed in children before 5 years of age and 15% were diagnosed before the age of 1 year. The male to female ratio was 0.9. The incidence rates showed two peaks, at ages 1 and 3 years. This pattern was especially marked in females (Fig. 2). The median age at diagnosis was 3 years for females compared with 2 years for males.

The overall rates of renal tumours were strongly influenced by the rates of the largest subgroup, VIa, and within this subgroup by the nephroblastoma type (M-8960). Gender-specific rates did not differ in the standard age groups; the rates are therefore presented for both genders combined.

Table 3 – Numbers of children (age 0–14 years) with renal cancer registered in ACCIS database during 1988–1997 and proportion (%) of cases registered from death certificate only (DCO) and with microscopically verification of diagnosis (MV) (Source: ACCIS)

Histological type	*n* of cases	ASR (0–14 years)	Cum rate (0–14 years)	DCO %	MV %	Age-specific rates			
						0	1–4 years	5–9 years	10–14 years
VI. Renal tumours	3134	8.8	117.1	0.2	96.8	18.9	18.1	4.6	0.9
VIa. Wilms' tumour, rhabdoid and clear cell sarcoma	3018	8.5	114.4	0.1	98.1	18.6	17.7	4.4	0.6
Wilms' tumour (M-8960)	2905	8.2	110.0	0.1	98.0	17.0	17.1	4.3	0.6
Rhabdoid tumour of kidney (M-8963)	45	0.1	1.7	0.0	100	1.0	0.2	0.0	0.0
Clear cell sarcoma of kidney (M-8964)	68	0.2	2.6	0.0	100	0.5	0.4	0.1	0.0
VIb. Renal carcinoma	58	0.1	2.2	0.0	98.3	0.0	0.1	0.1	0.2
VIc. Unspecified malignant renal tumours	58	0.1	2.2	1.7	29.3	0.3	0.4	0.1	0.0

The incidence rates (ASR, age standardised to the World population and Cum, cumulative) are per million children per year. Both genders combined.

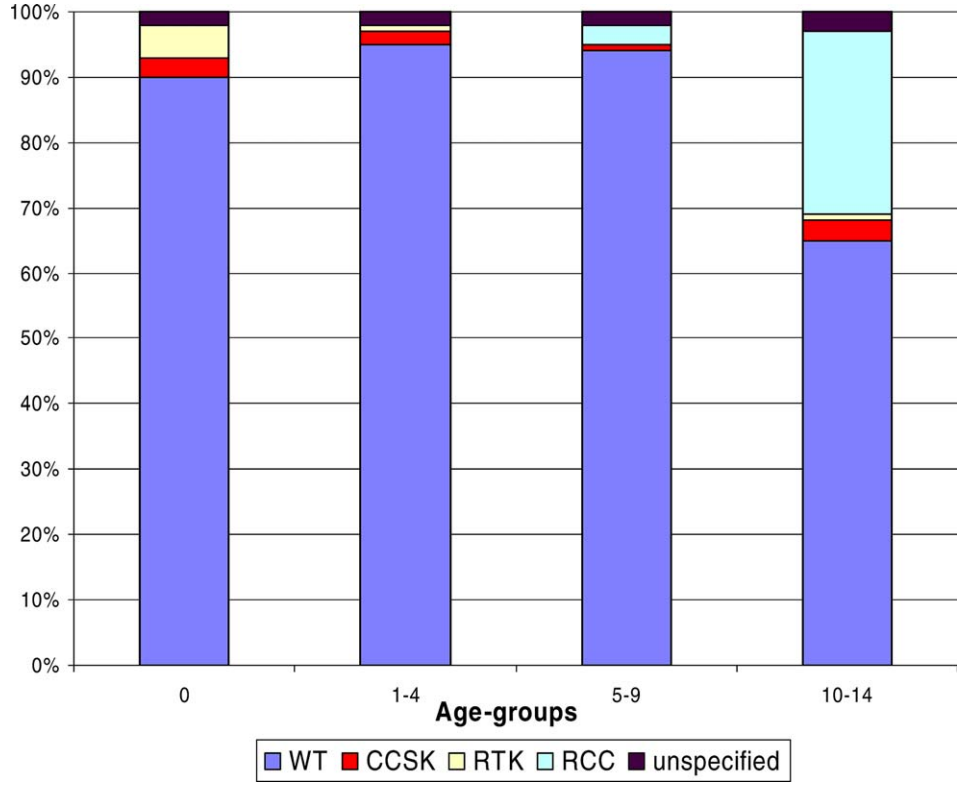

Fig. 1 – Distribution of childhood renal cancer (ICCC VI) cases (*n* = 3134) by histological type, 1988–1997. (WT, Wilms' tumour; CCSK, clear cell sarcoma of kidney; RTK, rhabdoid tumour of kidney; RCC, renal cell carcinoma). Source: ACCIS.

The ASR of childhood malignant renal tumours in Europe was 8.8 per million. The ASRs were 7.7 in British Isles, 8.3 in Southern Europe, 8.7 in Eastern Europe, 9.1 in Northern Europe and 9.5 in Western Europe. Adjusted for gender and age group, the relative risk for the North was 1.2 (95% CI 1.0–1.4) and for the West it was 1.2 (95% CI 1.1–1.3), while it was consistent with the European average in the other regions. The countries with the highest incidence rates were Estonia (12.7 per million) and Finland (11.6). The lowest observed rates were in Scotland (6.2), Norway (6.2) and Ireland (6.3).

Out of 2415 WT cases with reliable data on laterality, 2179 were unilateral (ASR = 7.4 per million), 167 (7.1%) bilateral (ASR = 0.6) and 69 with unknown laterality (ASR = 0.2). The distribution of the age at diagnosis differed according to tumour laterality and gender (Fig. 2). For the bilateral tumours, no difference in incidence rate was seen by gender.

During 1988–1997, 68 cases of CCSK were reported (ASR = 0.2 per million). The age-specific incidence peaked at age 1 (ASR = 0.8). RTK was diagnosed in 45 children (ASR = 0.1), affecting mostly infants with a rate of 1 per million. Renal carcinoma (VIb) was reported in 58 cases (ASR = 0.1). Incidence rate increased with age, reaching 0.2 per million in the age group 10–14 years. Unspecified malignant renal tumours were reported in 58 children (ASR = 0.2) (Fig. 3).

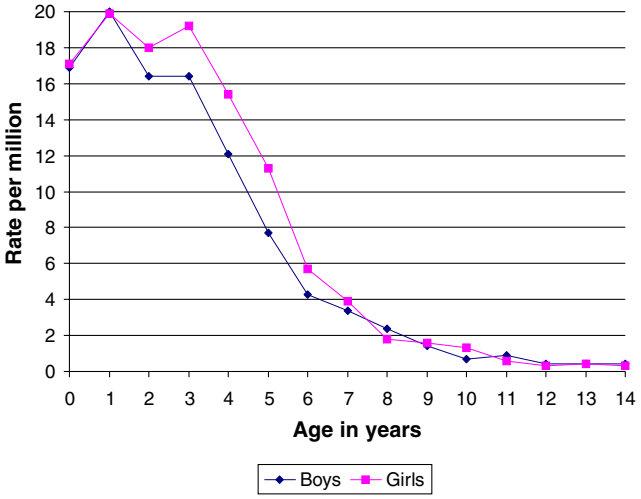

Fig. 2 – Incidence rates of Wilms' tumour (M-8960) (*n* = 2905) in Europe by age and gender, 1988–1997. Source: ACCIS.

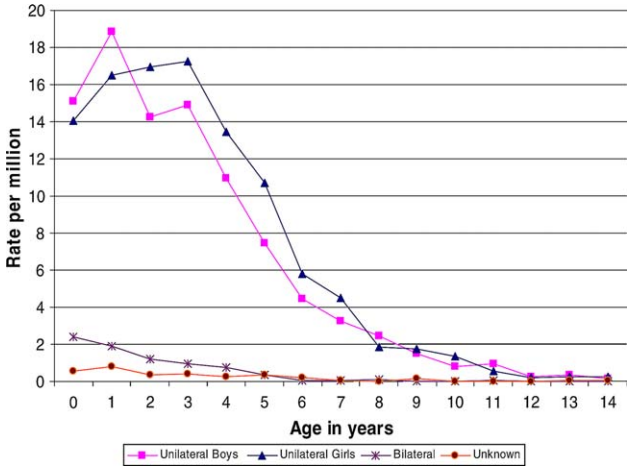

Fig. 3 – Incidence rates of Wilms' tumour (M-8960) in Europe, Registries with <10% of laterality unknown (*n* = 2415), 1988–1997. Source: ACCIS.

Analyses of incidence time trends based on 4549 cases were reported (Table 4). For all the geographical regions, the quality indicators were stable over time (Table 2) implying stable registration standards. The incidence rate of renal tumours increased by 0.8% per year ($P = 0.005$), adjusted for region, gender and age group. However, the increasing trends were by and large limited to the youngest age groups 0 (AAPC = 1.9%, $P = 0.016$, adjusted for region) and 1–4 years (AAPC = 0.8%, $P = 0.04$, adjusted for region and gender). Separate analyses by geographical regions (Fig. 4) showed a statistically significant increase in incidence only in the South (AAPC = 3.2%, $P = 0.006$, adjusted for age and gender) and the East regions (AAPC = 1.6%, $P = 0.036$, adjusted for age and gender). The overall incidence rate for the subgroup VIa increased by 0.9% ($P = 0.004$), while for the WT (M-8960) alone it increased by 0.7% per year ($P = 0.026$, adjusted for region, gender and age group). When analysed by age-groups, a significant increasing trend was observed only in age-group 1–4 (AAPC = 1.0%, $P = 0.005$, adjusted for region and gender).

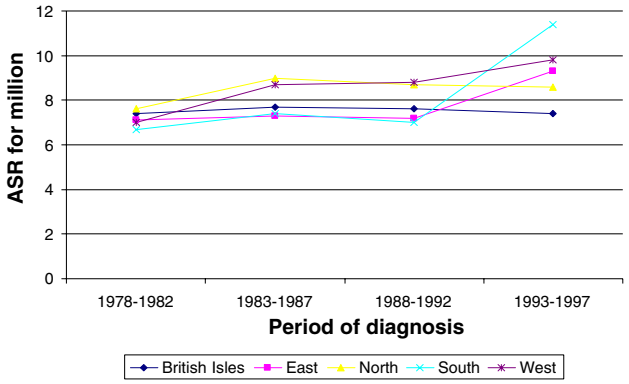

Fig. 4 – Age standardised rates (ASR) of Wilms' tumour, rhabdoid and clear cell sarcoma (VIa) by geographical regions and period, 1978–1997 per million children (*n* = 4402). Source: ACCIS.

Seventeen cancer registries with a sufficiently long study period provided information on laterality of WT (M-8960 only). Based on 2957 unilateral WT, the incidence rates increased by 0.9% per year ($P = 0.008$, adjusted for age group). The rates of bilateral WT were stable ($n = 205$, $P = 0.69$) and the incidence rates of WT with unknown laterality (116 cases) decreased by 6% per year ($P = 0.001$, adjusted for age group). This decreasing trend, reflecting an improvement of data quality, did not account entirely for the increase in unilateral WT: the incidence rate for the combined group of unilateral and unknown was increasing by 0.7% per year ($P = 0.04$, adjusted for age group).

Table 4 – Time trends incidence rate ratios (Source: ACCIS)

Period	VI. Renal tumours				VIa. Wilms' tumour, rhabdoid and clear cell sarcoma			
	n	ASR	IRR	95% CI	*n*	ASR	IRR	95% CI
1978–1982	796	7.6	0.88	0.80–0.97	755	7.3	0.86	0.78–0.95
1983–1987	1250	8.3	0.91	0.84–1.00	1212	8.1	0.91	0.84–0.99
1988–1992	1268	8.3	0.91	0.84–0.98	1232	8.1	0.91	0.84–0.98
1993–1997	1235	9.3	1	–	1203	9.1	1	–

Number (*n*) of children (age 0–14 years) with renal tumours (ICCC VI) and Wilms' tumour, rhabdoid and clear cell sarcoma (ICCC VIa), incidence rate ratio (IRR) and 95% confidence interval (95% CI), adjusted by region and by age-group, 1978–1997.
The incidence rates (ASR, age standardised to the World population) are per million children per year.

Table 5 – Number (*n*) of children with renal tumour and Wilms' tumour, rhabdoid and clear cell sarcoma and 5-year survival rates (5y%) and 95% confidence interval (95% CI) by age-group, 1988–1997 (Source: ACCIS)

Histological type	Age 0			Age 1–4 years			Age 5–9 years			Age 10–14 years			Age 0–14 years		
	n	5y%	95% CI	*n*	5y%	95% CI	*n*	5y%	95% CI	*n*	5y%	95% CI	*n*	5y%	95% CI
VI. Renal tumours	448	82	78–85	1817	85	83–87	591	81	77–84	110	75	66–83	2966	84	82–85
VIa. Wilms' tumour, rhabdoid and clear cell sarcoma	443	82	78–85	1774	86	84–87	563	81	77–84	74	71	59–80	2854	83	82–85
VIb. Renal carcinoma	0	–	–	5	100	100–100	19	88	61–97	32	84	66–93	56	87	74–94
VIc. Unspecified renal tumours	5	60	13–88	38	64	47–78	9	89	43–98	4	100	–	56	71	56–81

The incidence rates for CCSK, RTK and RCC and unspecified renal tumours were stable.

A total of 2966 children with renal tumours, diagnosed in the period 1988–1997 contributed to survival analyses (excluding 75 cases with zero follow-up time). Overall 5-year survival was 84% (95% CI 82–85). Data for both genders were combined, due to similar survival rates (Table 5).

Excluding 72 cases with no follow-up, 2854 cases of WT (M-8960) were analysed. For the pooled European data, the 5-year survival rate for children with WT was 85% (95% CI 84–86), ranging from 73% (95% CI 68–78) in the East to 91% (95% CI 86–95) in the North. Children diagnosed before age 4 years with WT experienced significantly better 5-year survival (87%) compared with the older children (81%), $P < 0.0001$ (Fig. 5). This pattern was modified slightly by gender: the favourable age at diagnosis was up to the fifth birthday in boys (5-year survival 88% versus 78%, $P < 0.0001$), and up to the third birthday in girls (89% versus 80%, $P = 0.0001$).

The 5-year survival was similar in the North and the West regions; the combined estimate was 89% (95% CI 88–91) and in the British Isles and the South Europe combined (83%, 95% CI 78–85). The poorest survival was seen for the East (72%, 95% CI 67–76). The three survival curves differed statistically ($P < 0.0001$).

Twenty-seven registries provided data on follow-up and laterality of WT (M-8960) for 2351 cases. The patients with unilateral WT had higher survival ($n = 2085$, 5-year survival 85%, 95% CI 84–87) than the patients with bilateral tumours ($n = 154$, 5-year survival 76%, 95% CI 68–83) and the difference between the survival curves was statistically significant ($P = 0.0028$).

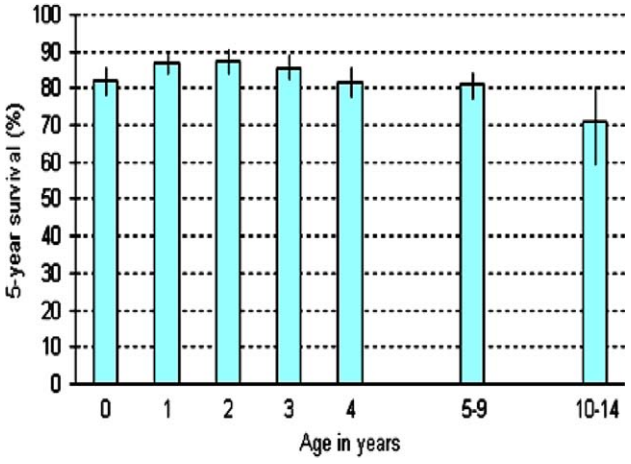

Fig. 5 – Five-year survival for 2854 children diagnosed with Wilms' tumour (VIa) in 1988–1997 and followed up by the contributing European registries. 95% CI are shown as line sections. Source: ACCIS.

The 5-year survival for CCSK (64 cases) was 68% (95% CI 52-79) and for RTK (43 cases) 23% (95% CI 12–37). Survival for patients with renal carcinoma (VIb) was more favourable than that for non-epithelial renal tumours (VIa). The prognosis for unspecified renal tumours (VIc) had a tendency to improve with increasing age at diagnosis (Table 5).

Table 6 presents survival of 4351 children with renal tumour diagnosed in the period 1978–1997 (excluding 97 cases with no follow-up). In Europe the 5 years survival rate for children with CCSK increased from 67% in 1983-87 to 88% in 1993–1997, the corresponding figures for the subgroup VIa were 80% and 87%.

Table 7 shows the survival data for 4094 patients with Wilms' tumour (M-8960). A significant increase in survival was observed, with overall 5-year survival of 73% for the first period increasing to 87% in the last one. This improvement

Table 6 – Time trend of survival of children (age 0–14 years) registered in Europe with renal tumour in the periods shown. Numbers of children (*n*), 5-year survival rates and 95% confidence interval (95% CI) by histological type, 1978–1997 (Source: ACCIS)

Histological type	*n*	5 y%	95% CI
VI. Renal tumours			
1978–1982	771	72	69–75
1983–1987	1219	79	77–81
1988–1992	1181	84	82–86
1993–1997	1180	86	84–88
Log-rank test for trend			$P < 0.0001$
VIa. Wilms' tumour, rhabdoid and clear cell sarcoma			
1978–1982	734	72	69–75
1983–1987	1184	79	77–82
1988–1992	1148	84	82–86
1993–1997	1150	86	84–88
Log-rank test for trend			$P < 0.0001$
Vib. Renal carcinoma			
1978–1982	18	67	40–83
1983–1987	19	68	43–84
1988–1992	22	91	68–98
1993–1997	19	83	55–94
Log-rank test for trend			$P = 0.11$
VIc. Unspecified malignant renal tumours			
1978–1982	19	58	33–76
1983–1987	16	69	40–86
1988–1992	11	64	30–85
1993–1997	11	70	33–89
Log-rank test for trend			$P < 0.72$

Table 7 – Survival of children registered in Europe with Wilms' tumours (M = 8960) in the periods shown. Number of cases (*n*), 5-year survival (5y%) and 95% confidence interval (95% CI) (Source: ACCIS)

	Age 0			Age 1–4 years			Age 5–9 years			Age 10–14 years			Age 0–14 years		
	n	5 y%	95% CI	*n*	5 y%	95% CI	*n*	5 y%	95% CI	*n*	5 y%	95% CI	*n*	5 y%	95% CI
1978–1982	94	80	70–87	437	73	69–77	165	68	61–75	27	63	42–78	723	73	69–76
1983–1987	163	81	74–86	729	83	80–85	230	72	66–78	33	76	57–87	1155	80	78–83
1988–1992	171	85	78–89	725	86	83–88	194	82	76–87	25	76	53–88	1115	85	82–87
1993–1997	162	88	81–93	669	89	86–91	242	82	76–87	28	77	55–89	1101	87	85–89
Log-rank test for trend			$P = 0.025$			$P < 0.0001$			$P < 0.0001$			$P = 0.22$			$P < 0.0001$

was influenced by the increases in survival of patients in the age group 1–4. In the East ($n = 492$), the North ($n = 422$) and the West ($n = 1493$) the increase was significant ($P < 0.0001$), while no improvement was detected in the British Isles ($n = 1230$, $P = 0.14$) and the South ($n = 234$, $P = 0.76$), Fig. 6. Considering Wilms' tumours (M-8960) from the 17 registries with follow-up and laterality information over a sufficiently long time (Table 1), the overall survival had improved significantly for unilateral ($n = 2920$, $P < 0.0001$), bilateral ($n = 201$, $P = 0.01$) and unknown ($n = 110$, $P = 0.0008$) cases (Fig. 7). The differences in survival between the patients with unilateral and those with bilateral tumours were significant in each study period.

All cases with CCSK diagnosed in the period 1978–1982 survived for more than 15 years. Excluding this first period from analysis, there was no change in survival for the following three periods ($P = 0.16$), with the combined 5-year survival of 81%, (95% CI 68–90, $n = 62$). There was an improvement in 5-year survival for children with RTK over the four periods of diagnosis: 17%, 18%, 22% and 30%, respectively. However, this trend was not significant ($P = 0.11$). No statistically significant improvement was seen for renal carcinoma (VIb, 78 cases) and for unspecified renal tumours (VIc, 57 cases) (Table 6).

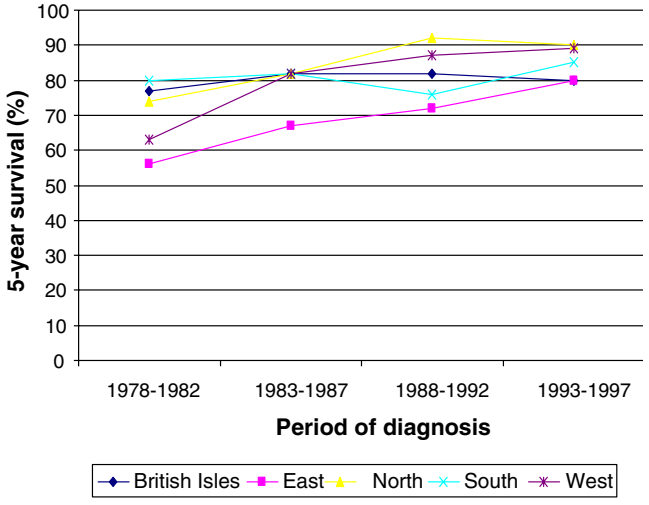

Fig. 6 – Five year survival for 3871 children with Wilms' tumours (M-8960) in Europe by regions and period, 1978–1997. Source: ACCIS.

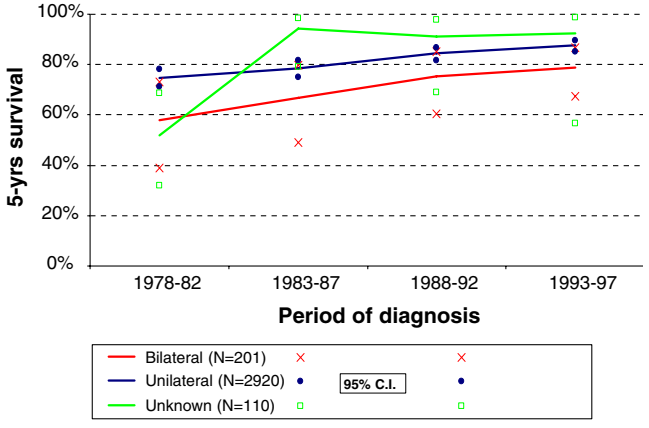

Fig. 7 – Five-year survival with 95% confidence intervals (95% CI) for children with Wilms' tumour (M-8960) by laterality in Europe, 1978–1997. Source: ACCIS.

4. Discussion

The present study is the largest report of childhood renal tumours in Europe (over 5000 childhood renal tumour cases), focusing on incidence and survival data in the period 1988–1997, as well as on incidence and survival temporal patterns over the years 1978–1997.

Heterogeneity of contributions underlined selection of data sets for different analyses. The aim was to include the majority of available data in each type of analysis, (rather than restrict analyses to a smaller number of cancer registries), and thus provide a reasonable representation of European patterns.

The patterns and incidence rates of WT, rhabdoid tumour of the kidney (RTK) and clear cell sarcoma of kidney (CCSK) are consistent with other studies from Europe and United States (US) Caucasian population.[1] The steady decline in incidence rates with age showed, in females, a bimodal distribution with a second peak in the fourth year of age to levels approaching those registered in infancy. On average, girls presented later than boys. A similar age distribution has been observed in the United States of America (USA).[11] This gender difference in age at onset may reflect gender-specific differences either in the persistence of the presumed WT precursor cells in the developing urogenital ridge or in the proportion of cases due to genetic predisposition.[2] Genetic predisposition may also explain the very few WT cases after the age of 10 years (less than 3% of cases).

The highest ASR for renal tumours among any of the five European regions was in the West. There was, however, considerable heterogeneity of rates between countries within

regions and the two highest national incidence rates were in Finland and Estonia, included in the North and East, respectively. The populations of these two neighbouring countries are genetically very similar, while differing from other European populations. This provides further support for the mainly genetic origin of WT or at least an interaction between genetic and environmental risk factors.[2,7,22] Over the period 1978–1997, incidence rates of WT remained stable in the British Isles, the North and the West, while it increased in the South and the East. Since the greatest increase in both regions occurred between the last two periods, it is important to continue monitoring of the rates for a possible change of the direction. Some cases of rarer tumour types (i.e. CCSK and RTK), at least in the early 1980s might have been grouped with WT (M-8960). However, such changes in the classification would cause a decrease, rather than increase in the incidence of WT (M-8960). In addition, changes in definition of WT alone would have to be compensated by a corresponding decrease in another diagnostic category, if the increase were just an artefact. Formal comparison of the completeness of registration, in general and with the focus on WT, in different cancer registries included in the ACCIS database would help to examine this assumption. Before this could be done, we have examined incidence trends in the dataset containing only the paediatric cancer registries and found an increase in the group of renal tumours ($n = 3083$, AAPC = 1.2%, $P = <0.0001$) and in the VIa subgroup ($n = 3021$, AAPC = 1.3%, $P = <0.0001$). Since WT is the childhood tumour 'par excellence', it is unlikely, that its registration would improve in paediatric cancer registries over time. This observation provides some evidence against the explanation of the incidence rise across Europe by the improved registration of these tumours. We have also observed that the increasing incidence was specific to the children under 5 years of age. This could reflect earlier diagnoses made by the increasingly widespread ultrasound examination during pregnancy and in the first months of life.[15,23] Earlier diagnosis would however not explain the overall increase in the incidence rates. Furthermore, we have considered the possibility of this increase being the result of the increased number of WT survivors in reproductive ages. However, the observed rise in incidence rates has probably occurred too soon to be explained by the increasing the pool of susceptibility genes. Unknown environmental factors may also be relevant.

Survival of children with WT has been increasing over the last three decades. Besides the advances in therapeutic options and supportive care, the development of prospective multi-centre randomised trials was the major step toward high cure rates and represents one of the best examples of success in paediatric oncology.[8–10,25] In Western Europe and some countries outside the continent, the International Society of Paediatric Oncology (SIOP) studies laid the cornerstone for treatment strategies.[9,25,26] For North America it was the National Wilms Tumour Study Group (NWTSG).[8,27] Other national groups, such as the United Kingdom Children's Cancer Study Group (UKCCSG) have contributed to the excellent results.[28] These groups, with different approaches (pre-operative chemotherapy versus immediate nephrectomy), have contributed to the definition of the current standards of therapy. Nowadays, in many Western countries more than 90% of patients with WT are treated according to these standards.[25,27] From the first to the fourth SIOP WT trial and study, the number of enrolled patients increased from 390 to 1029, and the 5-year survival rate from 64% to 84%.[24] In the SIOP 93–01 trial and study, enrolling 1940 children, attention was paid to analysing chemotherapy-induced changes as a new prognostic factor.[30] The higher recruitment as well as risk-adapted therapy is mirrored by increasing long-term survival. Today, specific objectives of clinical studies are to treat patients according to defined risk factors in order to achieve higher cure rates, to decrease the frequency of toxicity and to minimise the health-related cost of therapy.[3] A further goal of future trials will be to refine risk-grouping and treatment-intensity, based on results of histological and molecular studies of markers that may predict prognosis independently from traditional staging criteria.[29,30]

Reports of survival for CCSK and RTK are scanty in both population-based and clinical series due to the small number of such cases. Children with CCSK have a poorer outcome than children with WT, however their prognosis is improving in recent years, as also seen in this study. To date, no satisfactory treatment has been reported for children with RTK, which is also reflected in our findings. International collaboration is needed to collect epidemiological and clinical data and biological samples as well as to implement clinical trials for these rare renal tumours.[12]

The higher incidence rates of renal cell carcinoma (RCC) in girls (0.12) than in boys (0.07) aged 0–9 years observed in the present study is consistent with the results of both population- and hospital-based studies.[2,24] The improvement in survival observed for RCC is variable, perhaps reflecting the well-known low response rate of this tumour type to chemotherapy.[24] The 5 children diagnosed with RCC before 5 years of age over the period 1988–1997 in our study might represent a new entity related to alveolar soft part sarcoma.[13]

This study confirms that survival of children with WT in Europe continued to improve significantly during the entire period, in parallel with the results of clinical trials.[10] The lower survival observed in the East may be due to lower entry of children into clinical trials or other reasons. However, enhanced management strategies in some countries grouped within the East result in a more favourable outcome for children with cancer and continuation of the fast improvement in survival of children with renal tumours in this region [Magnani and colleagues, this issue] can therefore be expected.

ACCIS provides a unique source of data for purposes of public health, by monitoring the patterns and trends of incidence and survival of children with cancer at population level, as well as for analytical epidemiological research, by identifying a large cohort of childhood cancer patients to be followed-up for second cancers and possibly other diseases in order to provide further clues as to genetic basis of disease. Collection of further data items would be an asset: more complete laterality of WT, associated congenital malformations, extent of disease at diagnosis and types of treatment. With further extension of the ACCIS database follow-up data would presumably be completed. ACCIS should support studies focusing on external determinants of survival (i.e. unrelated

death, delay in diagnosis, availability of up-to-date treatment strategies).

Conflict of interest statement

None declared.

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