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Retinoblastoma incidence and survival in European children (1978–1997). Report from the Automated Childhood Cancer Information System project

A. MacCarthy[a,*], G.J. Draper[a], Eva Steliarova-Foucher[b], J.E. Kingston[c]

[a]Childhood Cancer Research Group, University of Oxford, 57 Woodstock Road, Oxford, OX2 6HJ, UK
[b]Descriptive Epidemiology Group, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France
[c]Retinoblastoma Service, Barts and the London NHS Trust, London, EC1A 7BE, UK

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ABSTRACT

Based on 2283 cases of retinoblastoma diagnosed in children aged 0–14 years, incidence and survival in Europe during the period 1978–1997 are described. Data were provided to the Automated Childhood Cancer Information System (ACCIS) from 60 paediatric and general cancer registries. During 1988–1997, the cumulative incidence of retinoblastoma in the ACCIS regions was found to be between 44.2 and 67.9 per million births. The highest incidence was seen in the first year of life. The age-standardised (World standard) incidence rate for the age-range 0–14 years was 4.1 per million. Approximately one-third of cases had bilateral tumours. Overall incidence increased over the period 1978–1997 by 1% per year, as derived from a model adjusted for sex, age group and type of registry (general or paediatric). The 5-year survival rate improved from 89% to 95% during the period covered by the study. This improvement was seen in both unilateral and bilateral cases but was significant only for the unilateral tumours. Survival was lower in the East region, although smaller differences were also observed between the other four regions (British Isles, North, South and West). Availability and quality of registration data on retinoblastoma need to be improved for effective evaluation of incidence and survival.

1. Introduction

In developed countries, retinoblastoma usually accounts for approximately 3–4% of all childhood cancers occurring during the age range 0–14 years.[1,2] Retinoblastoma is an embryonal tumour of the retina. More than 90% of cases are diagnosed during the first 5 years of life.[3] In approximately 60% of cases only one eye is affected.[3] There are two forms of the disease: heritable and non-heritable. Approximately 15% of the unilateral,[4] and all bilateral cases, have the heritable form. Only a minority of the heritable cases will have a previous family history and it appears that most of the heritable cases are the result of *de novo* mutations.[5] Heritable retinoblastoma behaves as an autosomal dominant condition with a variable, but usually high, degree of penetrance. The *RB1* gene acts as a tumour suppressor gene and loss or mutation of both alleles is necessary for a tumour to develop. There is a 50% chance that a parent with a germline mutation in the *RB1* gene will pass on the mutation to an offspring. There is then a very high probability that the offspring will develop a tumour following a further mutation or deletion leading to loss of function of the remaining *RB1* allele in one or more retinal cells.[6]

The survival rate for retinoblastoma has been high since the 1970s.[7–9] In the majority of children with unilateral

* *Corresponding author:* Tel.: +44 1865 315931.
E-mail address: angela.maccarthy@ccrg.oxford.ac.uk (A. MacCarthy).
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disease, excellent survival rates can be achieved by enucleation (removal of the eye) followed by adjuvant chemotherapy for those children found to have adverse histological features.[10] However, for children with bilateral disease, treatment is directed at saving vision as well as life. Depending on the size and location of tumours within each eye, preservation of the eye with useful vision can often be achieved by chemotherapy alone or by a combination of chemotherapy and focal therapies such as laser, cryotherapy or radioactive scleral plaque therapy.[10,11] External beam radiotherapy is reserved for children with bilateral retinoblastoma who develop recurrent disease after chemotherapy and can salvage vision in a good proportion of these children.[12]

As with all childhood cancers, it is essential that survivors of retinoblastoma should have long-term follow-up. In the case of heritable retinoblastoma this is particularly necessary because the mutant RB1 gene acts as a cancer susceptibility gene predisposing to the risk of a subsequent, histologically distinct cancer.[13] Clinicians are acutely aware of this increased risk and the possibility that certain treatments, such as radiotherapy and chemotherapy, may increase the risk. If possible, external beam radiotherapy should be avoided during the first year of life as this seems to be the period when radiation is most likely to increase the risk of second malignancies.[14] There is also a risk of leukaemias following certain chemotherapeutic agents, particularly alkylating agents and the epidopodophyllotoxins.[15]

This paper reports the incidence and survival rates of children with retinoblastoma in Europe, and the changes in these rates over the 20 year period 1978–1997. The results are based on the large European database of the Automated Childhood Cancer Information System (ACCIS).[16]

2. Methods

2.1. Data sources

All cases of retinoblastoma, as defined in group V of the International Classification of Childhood Cancer[17] were extracted from the ACCIS database. The 60 data-sets included are listed in Table 1, which gives the period of coverage, quality indicators and extent of follow-up for each. The populations-at-risk given for sex, calendar year and age group in each registration area originate from official national statistics and were supplied by the cancer registries. Any missing population figures were estimated by linear interpolation. Data were validated at the International Agency for Research on Cancer (IARC), in collaboration with the registries. More detail on the database composition and validation can be found in the paper by Steliarova-Foucher, Kaatsch, Lacour and colleagues [this issue].

For the purposes of comparison of incidence and survival, the contributing countries were grouped into five geographical regions (Table 1) and data for the period 1988–1997 were used. For the analyses of time trends, the total available time-span was divided into four periods of 5 years: 1978–1982, 1983–1987, 1988–1992 and 1993–1997. Registries were included in the analyses of time trends, if they provided data for at least three of these periods. Information on the quality of data for the analyses of time trends is given by region and period in Table 2.

For each case, the duration of survival was calculated as the time elapsed between the date of diagnosis and the closing date of the study (which varied according to the registry concerned, Table 1), or death if that occurred earlier. Cases with zero survival time were excluded from the analysis of survival; most of these were cases registered from death certificates only.

In many of the registries information on the laterality (unilateral or bilateral) of retinoblastoma was available, and for a sub-group of registries it was possible to conduct separate analyses for bilateral and unilateral cases. During the consolidation of the ACCIS database a specific check was conducted in collaboration with the registries to: (i) check the laterality of retinoblastoma, (ii) make sure that no bilateral retinoblastoma was recorded twice as unilateral, and (iii) to recode any case of 'multiple primary retinoblastoma' to 'bilateral retinoblastoma', if necessary. Laterality information was available for at least 90% of the cases in 27 registries. In two of them, however, the proportion of bilateral cases was so low that the information on laterality was assumed not to be reliable. The remaining 25 data-sets were pooled and used for calculating the incidence and survival rates for unilateral and bilateral cases (Table 1).

2.2. Statistical methods

Age-specific incidence rates were calculated as the number of cases per million person-years in the age-groups 0, 1–4, 5–9 and 10–14 years. The age-standardised incidence rates (ASR) were calculated as the average of the age-specific incidence rates for the age-groups 0, 1–4, 5–9, 10–14 years weighted by the World Standard Population.[2] To compare incidence rates between regions and by laterality we have also used the cumulative incidence rates, calculated as the sum of the age-specific rates each multiplied by the number of years in that age group. The cumulative incidence rate is an approximation to the risk of developing retinoblastoma before age 15 years. Differences in incidence rates for geographical areas or types of registry (paediatric or general) were evaluated using Poisson regression models, adjusted for sex and age group (as appropriate) and expressed as incidence rate ratios (IRR) with 95% confidence intervals (95% CI). Changes in incidence rates over time were analysed using a Poisson regression model, adjusted for sex, age group and region or type of registry and expressed as average annual percentage change (AAPC).

Actuarial life table methods were used for the survival analyses.[18] The reported 5-year survival rate is the estimated probability of surviving to the fifth anniversary of the date of incidence. Asymptotic 95% CIs were calculated using the method described by Kalbfleisch and Prentice.[19] The differences in survival between groups of patients were tested using the log-rank test; this tests for differences in the entire survivorship curve. Changes in survival over time were tested using log-rank test for trends.[20]

3. Results

3.1. Incidence

Table 3 shows numbers of cases, sex ratios and incidence rates for retinoblastoma in Europe for the period 1988–1997.

Table 1 – Datasets included in the analyses of retinoblastoma in children (age 0–14 years), with indicators of coverage and data quality (Source: ACCIS)

Region	Registry	Coverage		Cases		Basis of diagnosis			Survival analysis		Follow-up			Notes
		Period	Time-trend	*n*	Bilateral %	MV %	Clinical %	DCO %	*n*	%	5+ years %	Median Years	Closing date	
British Isles	IRELAND, National	1994–1997		8	–	63	38	0	8	100	0	3.6	31.12.1998	
	UNITED KINGDOM, England & Wales	1978–1995	+	616	34	78	17	<1	615	100	99	12.1	31.1.2001	P
	UNITED KINGDOM, Northern Ireland	1993–1996		5	–	80	20	0	5	100	0	<1	31.12.1999	
	UNITED KINGDOM, Scotland	1978–1997	+	75	–	95	5	0	75	100	90	12.2	31.12.1999	
East	BELARUS, National	1989–1997		53	–	94	6	0	53	100	78	7.4	1.9.2000	P
	ESTONIA, National	1978–1997	+	18	–	100	0	0	18	100	67	8.7	31.12.1998	
	HUNGARY, National	1978–1997	+	82	34	99	1	–	82	100	74	9.2	1.1.2000	P
	SLOVAKIA, National	1978–1997	+	92	21	100	0	0	90	98	76	10.1	31.12.1997	
	GERMANY, NCR (only former East)	1978–1989	+	125	27	100	0	0	96	77	66	6.3	31.12.1987	S
North	DENMARK, National	1978–1997	+	71	23	96	4	0	71	100	78	8.4	31.12.1997	
	FINLAND, National	1978–1997	+	76	–	95	5	0	76	100	82	10.5	31.12.1998	
	ICELAND, National	1978–1997	+	5	60	100	0	0	5	100	80	11.9	31.12.2000	
	NORWAY, National	1978–1997	+	78	–	90	10	0	78	100	89	10.9	1.1.2000	
South	ITALY, Piedmont paediatric	1978–1997	+	48	38	83	17	0	48	100	85	8.9	31.12.1999	P
	ITALY, Marche	1990–1997		4	–	25	0	–	4	100	75	9.0	30.9.2000	P
	ITALY, Ferrara	1991–1995		0	–	–	–	–	–	–	–	–	–	
	ITALY, Latina	1983–1997	+	1	0	100	0	0	1	100	100	6.3	31.12.1998	
	ITALY, Liguria	1988–1995		3	–	67	33	0	3	100	100	9.5	15.4.2000	
	ITALY, Lombardy	1978–1997	+	6	–	67	33	0	6	100	80	7.8	23.9.1999	
	ITALY, Parma	1978–1995	+	2	–	50	50	0	2	100	50	9.7	1.4.1999	
	ITALY, Ragusa	1983–1997	+	2	–	100	0	0	2	100	100	11.2	30.3.2000	
	ITALY, Sassari	1992–1995		1	0	100	0	0	1	100	100	5.5	30.12.1999	
	ITALY, Tuscany	1988–1997		2	–	100	0	0	2	100	0	3.9	31.12.1998	
	ITALY, Umbria	1994–1996		3	–	100	0	0	3	100	50	4.5	31.12.1999	
	ITALY, Veneto	1990–1996		3	33	100	0	0	3	100	33	3.7	31.12.1998	
	MALTA, National	1991–1997		2	100	100	0	0	2	100	50	5.7	31.12.1999	
	SLOVENIA, National	1978–1997	+	24	25	92	8	0	24	100	80	12.9	31.12.1999	
	SPAIN, National	1990–1995		29	31	83	17	0	29	100	83	5.8	31.12.2000	P Z o1
	SPAIN, Albacete	1991–1997		2	–	100	0	0	2	100	100	8.2	15.9.2000	
	SPAIN, Asturias	1983–1997	+	3	–	67	33	0	3	100	67	7.3	31.12.1997	
	SPAIN, Basque Country	1988–1994		3	–	67	33	0	3	100	100	7.6	31.12.2000	o1
	SPAIN, Canary Islands	1993–1996		3	–	100	0	0	–	–	–	–	–	
	SPAIN, Girona	1994–1997		2	–	100	0	0	2	100	0	2.4	31.12.1997	o1

	SPAIN, Granada	1988–1997		3	33	100	0	0	3	100	33	4.5	31.12.1999	G
	SPAIN, Mallorca	1988–1995		4	25	100	0	0	4	100	100	9.2	31.12.1998	o1
	SPAIN, Navarra	1978–1996	+	7	–	100	0	0	7	100	100	11.7	31.12.1997	o1
	SPAIN, Tarragona	1983–1997	+	8	–	100	0	0	8	100	71	9.7	31.12.1998	o1
	SPAIN, Zaragoza	1978–1996	+	7	–	100	0	0	7	100	100	10.4	31.12.1996	o1
	TURKEY, Izmir	1993–1996		8	0	100	0	–	–	–	–	–	–	
West	FRANCE, Brittany	1991–1997		13	38	92	0	–	13	100	58	5.5	1.1.2000	P
	FRANCE, Lorraine	1983–1997	+	21	24	81	19	–	21	100	63	6.2	1.1.1999	P
	FRANCE, PACA	1984–1996	+	42	29	95	5	–	41	98	63	7.5	31.3.1998	P
	FRANCE, Rhone Alpes	1988–1997		40	33	93	8	–	39	98	25	2.9	1.6.2000	P o2
	FRANCE, Doubs	1978–1996	+	8	–	50	50	–	6	75	17	1.3	1.6.2001	
	FRANCE, Herault	1988–1997		4	–	100	0	–	–	–	–	–	–	
	FRANCE, Isere	1979–1997	+	13	15	100	0	–	–	–	–	–	–	o2
	FRANCE, Manche	1994–1996		4	25	50	50	–	3	75	67	5.4	31.5.2000	S
	FRANCE, Bas–Rhin	1978–1996	+	20	–	90	10	–	20	100	78	11.5	31.12.1997	
	FRANCE, Haut–Rhin	1988–1997		4	–	75	25	–	2	50	100	8.6	31.12.1995	S
	FRANCE, Somme	1983–1996	+	7	–	100	0	–	7	100	33	4.5	15.8.2000	
	FRANCE, Tarn	1983–1997	+	2	50	100	0	–	–	–	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	240	33	100	0	–	114	48	4	0	31.12.1998	P
	GERMANY, GCCR (only former West)	1983–1990	+	261	–	100	0	–	236	90	65	6.0	31.12.1998	P
	NETHERLANDS, National	1989–1995		109	–	67	33	–	109	100	35	<1	31.12.1998	S o3
	NETHERLANDS, Eindhoven	1978–1997	+	18	–	56	17	–	18	100	67	7.5	1.7.1999	o3
	SWITZERLAND, Basel	1983–1997	+	6	–	83	17	–	6	100	83	8.3	30.6.2000	
	SWITZERLAND, Geneva	1978–1997	+	6	–	83	17	0	6	100	80	6.9	31.12.1999	
	SWITZERLAND, Graubunden & Glarus	1989–1997		0	–	–	–	–	–	–	–	–	–	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	5	0	100	0	0	5	100	25	2.5	1.2.2001	
	SWITZERLAND, Valais	1989–1997		1	–	100	0	0	–	–	–	–	–	S

+: Included in time trend analyses; –: Not applicable; 5+ years: Cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; Bilateral: Shown only for the registries with systematic (and assumed reliable) registration of laterality for retinoblastoma and having more than 90% of cases with known laterality; Clinical: Registrations based on clinical diagnosis; DCO: Registrations from death certificate only; G: General cancer registry, which has contributed data for age-range 0–14 years; GCCR: National German Childhood Cancer Registry (until 1990, only West; since 1991 for reunified Germany); MV: Microscopically verified cases; n: Number of cases; 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 for 1988–1989 were pooled with GCCR and included in West. For explanation, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue); o1–o3: Overlapping registration areas: for the overlapping years; data from the registry with larger coverage are included in the analyses; P: Paediatric cancer registry; age range is 0–14 years; PACA: Provence, Alps, Côte d'Azur; S: Survival analyses were possible only for a restricted dataset (see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue); Survival analyses:

Table 2 – Numbers of cases, indicators of data quality and extent of follow-up by region for time trend analyses of retinoblastoma in children (age 0–14 years) (Source: ACCIS)

Region	Period	Cases		Basis of diagnosis			Follow-up	
		n	Laterality %	MV %	Clinical %	DCO %	1+ days %	5+ years %
Europe[a]	1978–1982	315	77	90	8	0	100	96
	1983–1987	573	58	92	6	0	98	83
	1988–1992	621	65	92	7	0	95	73
	1993–1997	486	84	87	12	<1	77	40
British Isles	1978–1982	145	88	82	12	0	100	97
	1983–1987	190	88	83	13	0	100	99
	1988–1992	204	90	81	15	0	100	99
	1993–1997	152	91	73	24	<1	99	95
East	1978–1982	38	95	100	0	0	100	84
	1983–1987	55	91	100	0	0	98	93
	1988–1992	48	88	98	2	0	100	95
	1993-1997	51	90	100	0	0	98	30
North	1978–1982	52	29	100	0	0	100	100
	1983–1987	50	34	96	4	0	100	100
	1988–1992	72	35	96	4	0	100	100
	1993–1997	56	34	82	18	0	100	33
South	1978–1982	23	87	83	17	0	100	100
	1983–1987	31	52	94	6	0	100	96
	1988–1992	28	64	86	14	0	100	96
	1993–1997	26	73	85	15	0	100	43
West	1978–1982	15	13	87	13	0	100	90
	1983–1987	193	15	95	2	0	93	71
	1988–1992	240	45	99	1	0	86	37
	1993–1997	201	92	96	4	0	44	4

1+ days: Cases included in survival analyses, as a percentage of cases in the registries with follow-up data; 5+ years: Cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; Clinical: Registrations based on clinical diagnosis; DCO: Registrations from death certificate only; Laterality (%): Percentage of cases registered from registries having systematic information on laterality; MV: Microscopically verified cases; n: Number of cases.

a Europe includes the data of former GDR.

Cumulative incidence ranged from 44.2 to 67.9 per million. The age-specific rates are roughly three times as high in infants (children under 1 year of age) as in the age group 1–4, except in the East, where the corresponding ratio is approximately two. Less than 1 retinoblastoma per million person-years occurs in the age group 5–9 years, and after 10 years of age this tumour is exceedingly rare. There was virtually no difference between boys and girls (data not shown). The overall incidence rates are more than 15% higher in the North than in the other regions. The East has the lowest cumulative incidence of retinoblastoma, mainly due to the apparent lack of cases in infants.

The pool of 25 data-sets with information available on laterality was used to calculate the incidence of unilateral and bilateral retinoblastoma, as shown in Table 3. The incidence of retinoblastoma in this restricted data-set was virtually the same as in the total data-set; rates by laterality and region are shown in Fig. 1. The cumulative incidence of bilateral retinoblastoma was approximately half of that of the unilateral type; however, in infants (i.e. children in the first year of life) the incidence of bilateral cases was higher than that of unilateral cases (Table 3). Fig. 2 shows incidence by single year of age. Because of high incidence in the North (composed exclusively of general cancer registries) and lower incidence in the British Isles and West (composed predominantly of paediatric cancer registries), we have also compared the incidence rates according to the type of registry (Table 1). For the period 1988–1997, the average incidence rate reported from general cancer registries ($n = 492$, ASR = 4.7, 95% CI 4.3–5.1) was higher than that from paediatric cancer registries ($n = 925$, ASR = 3.8, 95% CI 3.6–4.1). Cumulative incidence rates for ages 0–14 years in general and paediatric cancer registries were 61 and 50 per million children, respectively. When adjusted for sex and age group, the risk of retinoblastoma was found to be 23% higher in the general compared with paediatric cancer registries (IRR = 1.23, 95% CI 1.10–1.37, $P < 0.0001$).

3.2. *Trends in incidence*

Based on the 1995 cases included in the analyses of time trends for the period 1978–1997 we did not detect any significant change in the incidence rates in a model adjusted for sex, age group and region (Table 4). The apparent increase in incidence shown for infants in Fig. 3 was not significant in a model adjusted for sex and region ($n = 770$, AAPC = 0.9%, $P = 0.2$).

Table 3 – Incidence of retinoblastoma in children (age 0–14 years) in Europe, 1988–1997 and comparison of rates by (a) regions of Europe and (b) laterality (Source: ACCIS)

Region	*n*	Sex ratio	ASR	95% CI	Age-specific rates				Cum inc rate 0–14	IRR	95% CI
					0	1–4	5–9	10–14			
EUROPE	1393	1.00	4.1	(3.9, 4.3)	20.4	7.5	0.5	0.1	53.3	–	–
(a) Region											
British Isles	369	1.01	4.4	(4.0, 4.9)	21.4	8.4	0.6	0.0	58.0	1.0	–
East	152	0.88	3.4	(2.9, 3.9)	13.7	7.1	0.5	–	44.2	0.8	(0.6, 0.9)
North	128	1.02	5.2	(4.3, 6.1)	25.5	9.6	0.8	–	67.9	1.2	(1.0, 1.4)
South	117	0.90	3.9	(3.2, 4.6)	18.3	7.4	0.6	0.1	50.9	0.9	(0.7, 1.1)
West	627	1.05	3.9	(3.6, 4.3)	21.3	6.8	0.5	0.1	51.6	0.9	(0.8, 1.0)
(b) Laterality (based on 25 datasets assumed to have reliable information on laterality: see Table 1)											
TOTAL	909	1.01	3.9	(3.4, 4.1)	19.6	7.0	0.5	0.1	50.7	–	–
Bilateral	288	1.06	1.3	(1.1, 1.4)	10.8	1.4	0.01	0.0	16.2	–	–
Unilateral	597	0.90	2.5	(2.3, 2.7)	8.5	5.4	0.5	0.1	33.2	–	–
Unknown	24	0.12	0.1	(0.1, 0.1)	0.3	0.2	0.02	0.0	1.3	–	–

n, number of cases. Sex ratio= ratio of ASR for boys to ASR for girls. ASR, age-standardised incidence rate per million, World standard. Age-specific rates, calculated per million person-years. Cumulative incidence rate, per million children. IRR, incidence rate ratio, derived from Poisson regression model of rate on region, adjusted for age group and sex (the reference category being region = British Isles, age group = 0, sex = boys).

Fig. 1 – Cumulative incidence rates of retinoblastoma in children aged 0–14 years, by laterality for the five regions of Europe, 1988–1997. Based on 25 datasets with information available on laterality (*n* = 909). Source: ACCIS.

Table 4 – Numbers of cases (n) and average annual percent change (AAPC) in incidence of retinoblastoma in children in Europe, 1978–1997, as estimated in various models (Source: ACCIS)

Type of registry	Terms included in regression model	*n*	AAPC	P
All registries	Year, Sex, Age group, Region	1995	0.5	0.27
All registries	Year, Sex, Age group, Type of registry	1995	1.0	0.02
Paediatric	Year, Sex, Age group	1310	0.8	0.14
General	Year, Sex, Age group	685	1.4	0.04

Data from 33 datasets were included in analysis of time-trends (see Table 1).

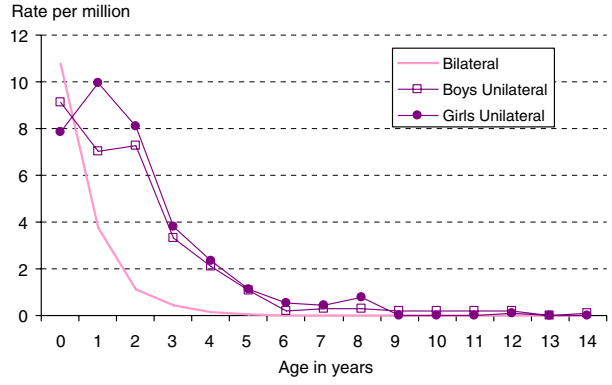

Fig. 2 – Age-specific incidence rates by laterality in Europe, 1988–1997. Based on 25 datasets with information available on laterality (*n* = 909). Source: ACCIS.

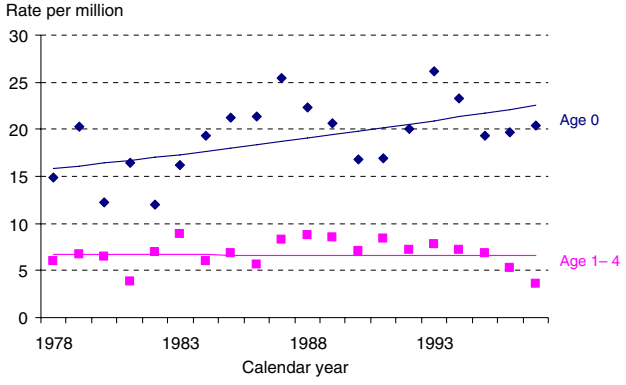

Fig. 3 – Time trends of incidence rates of retinoblastoma in children aged 0 and 1–4 years in Europe (*n* = 1882). Source: ACCIS.

Since the incidence rates for the period 1988–1997 differed between the paediatric and general cancer registries, the differences in incidence time trends (for period 1978–1997) according to the type of registry were also analysed. A significant increase of 1.4% per year was observed for the general cancer registries; for paediatric cancer registries there was a non-significant increase of 0.8% per year (Table 4). In a model containing adjustments for sex, age group and type of registry (general or paediatric), the overall incidence of retinoblastoma during the period 1978–1997 was found to have increased significantly by 1% per year ($P = 0.02$) (Table 4). This contrasts with the results from the model with adjustment for region rather than for type of registry.

3.3. *Survival*

It is clear from Table 1 that the percentage of patients for whom survival data were available varied between registries. In particular for Germany in the years 1991–1997 only 4% of cases were followed up for more than 5 years.

Five-year survival rates of children diagnosed in the period 1988–1997, for each of the five regions, are presented in Table 5(a). For age group 0–14 years the overall survival curves for the five regions differed significantly ($P < 0.0001$). The 5-year survival rate was lowest in the East. When individual age groups were considered, 5-year survival in the East was lower than in the other regions in both age groups 0 and 1–4.

For the registries with adequate information on laterality (Table 5(b)), there was no significant difference between the 5-year survival rates for patients with unilateral and bilateral tumours (95% and 93%, respectively; $P = 0.14$).

3.4. *Trends in survival*

A total of 1794 children with retinoblastoma were included in the analyses of time trends in survival. Overall 5-year survival has improved from 89% (95% CI 85–92) for children diagnosed in 1978–1982 to 95% (95% CI 91–97) for those diagnosed in 1993–1997 (Table 6(a)). The survival curves for children aged 0 and 1–4 years diagnosed in successive 5-year periods are shown in Fig. 4(a and b). However, the overall improvement was mostly due to a large effect in the age-group 1–4 (Table 6(a)).

The survival curves by laterality for children diagnosed in successive 5-year periods are shown in Fig. 5(a and b). The survival for the 803 patients with unilateral disease improved from 89% to 94% over the period ($P = 0.01$) (Table 6(c)). For the 379 children with bilateral tumours, there appeared to be a similar improvement in survival over the time periods, but this was not statistically significant.

4. Discussion

4.1. *Incidence*

From the data collected by ACCIS, there appears to be some variation in the incidence of retinoblastoma across European regions. The higher incidence of retinoblastoma for the North as compared with the rest of Europe is similar to the greater rate for all cancers in the North shown in Table 2 of the paper by Stiller, Marcos-Gragera, Ardanaz and colleagues [this issue] on the ACCIS data. Incidence showed an increase of 1% per year after adjustment for factors including type of registry but was not significant when including region rather than registry type. This may be a consequence of the differences in registration rates for the two types of registry. The (non-significant) increasing trend for infants reported in section 3.2 of the present paper was found to be significant for the period 1970–1999 for Europe as a whole in a previous study (AAPC = 1.1%; $P = 0.018$).[16]

The incidence rates of retinoblastoma found in the present study are similar to those reported for white populations in most developed countries. In the registries of Europe, North

Table 5 – Five-year actuarial observed survival for children with retinoblastoma diagnosed in Europe during 1988–1997 in each age-group shown, by (a) regions of Europe and (b) laterality (Source: ACCIS)

	Age 0–14 years			Age 0			Age 1–4 years			Age 5–9 years			Age 10–14 years		
	n	OS	95% CI	*n*	OS	95% CI	*n*	OS	95% CI	*n*	OS	95% CI	*n*	OS	95% CI
EUROPE	1,201	93	(91, 94)	452	92	(89, 94)	678	93	(91, 95)	63	94	(83, 98)	8	100	–
(a) Region															
British Isles	368	96	(93, 97)	136	96	(90, 98)	213	97	(93, 98)	18	89	(62, 97)	1	100	–
East	151	83	(75, 88)	43	82	(65, 91)	99	81	(72, 88)	9	100	–	0	–	–
North	128	97	(92, 99)	49	98	(86, 100)	72	97	(88, 99)	7	100	–	0	–	–
South	106	93	(86, 97)	40	87	(71, 94)	59	97	(87, 99)	6	100	–	1	100	–
West	448	92	(88, 95)	184	90	(83, 95)	235	94	(88, 96)	23	94	(63, 99)	6	100	–
(b) Laterality (based on 22 datasets assumed to have reliable information on laterality and follow-up shown in Table 1)															
TOTAL	741	94	(92, 96)	278	93	(89, 96)	416	95	(92, 97)	41	94	(77, 98)	6	–	–
Bilateral	235	93	(88, 96)	153	92	(86, 96)	81	95	(86, 98)	1	100	–	0	–	–
Unilateral	493	95	(92, 96)	123	94	(88, 97)	326	95	(92, 97)	38	93	(74, 98)	6	–	–
Unknown	13	100	–	2	100	–	9	100	–	2	100	–	0	–	–

n, number of cases included in survival analysis. OS, 5-year actuarial observed survival. Cl, confidence interval for the OS.

Table 6 – Five-year actuarial observed survival for quinquenia, by (a) age group, (b) region and (c) laterality (Source: ACCIS)

	n	OS	95% CI	*n*	OS	95% CI	*n*	OS	95% CI	*n*	OS	95% CI	*n*	OS	95% CI
(a) Age group	Age 0			Age 1–4 years			Age 5–9 years			Age 10–14 years			Age 0–14 years		
1978-82	115	91	(84, 95)	179	87	(81, 91)	15	100	–	4	50	(6, 84)	313	89	(85, 92)
1983-87	218	94	(89, 96)	310	91	(87, 93)	25	87	(65, 96)	2	100	–	555	92	(89, 94)
1988-92	202	96	(92, 98)	322	95	(92, 97)	30	89	(68, 96)	2	100	–	556	95	(93, 97)
1993-97	152	91	(84, 95)	194	97	(94, 99)	22	100	–	2	100	–	370	95	(91, 97)
p (trend)	*0.6142*			*<0. 0001*			*0.8572*			*0.1573*			*0.0001*		
(b) Region	British Isles			East			North			South			West		
1978-82	145	90	(84, 94)	38	86	(69, 94)	52	98	(87, 100)	23	70	(47, 84)	13	77	(44, 92)
1983-87	190	92	(87, 95)	54	81	(67, 89)	50	92	(80, 97)	31	90	(72, 97)	176	95	(91, 98)
1988-92	204	95	(91, 97)	48	85	(71, 92)	72	97	(89, 99)	28	96	(77, 99)	204	97	(93, 98)
1993-97	151	97	(92, 99)	50	84	(67, 93)	56	98	(88, 100)	26	87	(65, 96)	87	98	(88, 100)
p (trend)	*0.0031*			*0.6267*			*0.5108*			*0.0962*			*0.0195*		
(c) Laterality (based on 13 datasets assumed to have reliable information on laterality, follow-up and time trend shown in Table 1)	Bilateral			Unilateral			Unknown								
1978-82	69	88	(77, 94)	167	89	(83, 93)	4	100	–						
1983-87	107	87	(79, 92)	206	90	(85, 94)	14	93	(58, 99)						
1988-92	106	91	(83, 95)	241	95	(91, 97)	7	100	–						
1993-97	97	93	(84, 97)	189	94	(89, 97)	6	100	–						
p (trend)	*0.1841*			*0.0120*			*0.6090*								

n, number of cases included in survival analysis, OS, 5-year actuarial observed survival. CI, confidence interval for the OS.

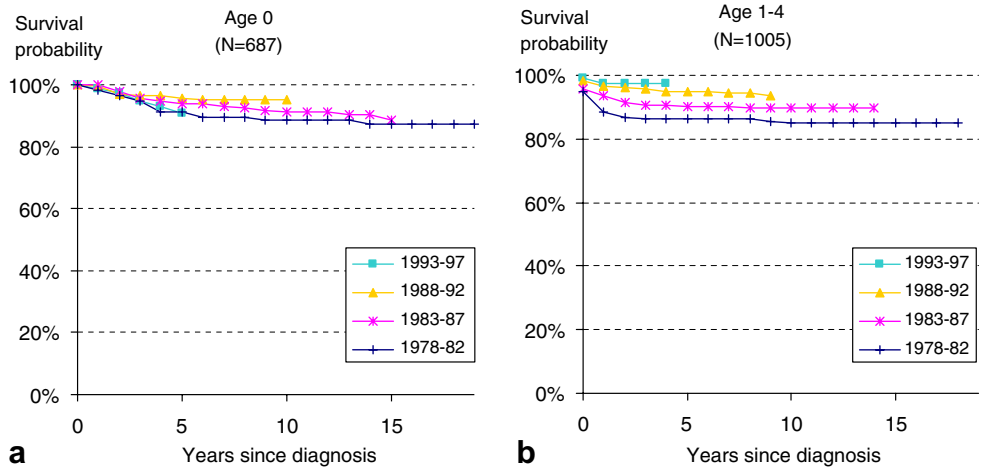

Fig. 4 – Survival curves for children with retinoblastoma diagnosed in Europe in the periods shown at (a) age 0 and (b) age 1–4 years. Source: ACCIS.

America and Oceania retinoblastoma accounts for approximately 3–4% of all childhood tumours. However, there are considerable world-wide variations.[1,2]

The analyses presented here are based on the work of a large number of cancer registries, many of them concerned mainly with cancers in adults; childhood cancer accounts for only approximately 1 in 200 cases included in European registries, and of these only approximately 3% are retinoblastoma.

The possibility that retinoblastoma was under-registered in some areas and periods covered by this study cannot be excluded. This idea is supported by the lower incidence rate found in paediatric, compared with general, cancer registries. Paediatric cancer registries often rely on paediatric oncology centres to register cases, and they may not get data from specialist ophthalmology hospitals, where children with retinoblastoma may be diagnosed and treated by ophthalmologists mainly concerned with the treatment of adults.

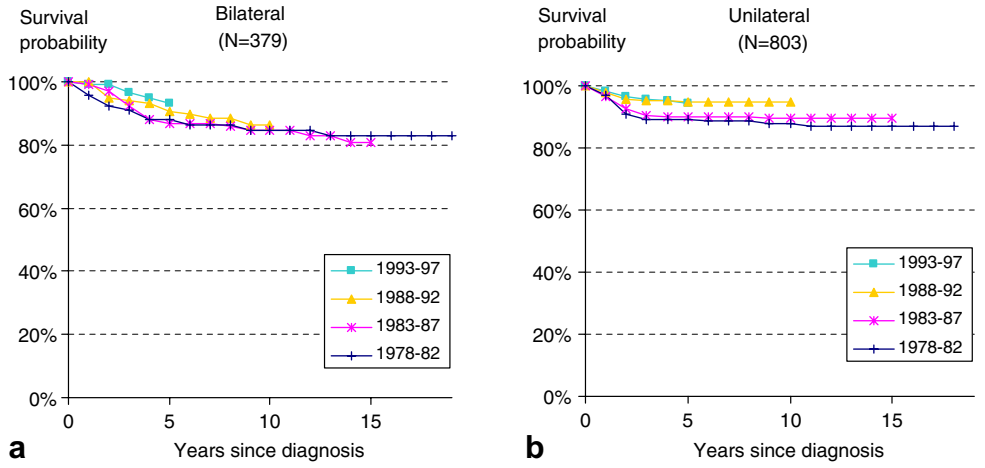

Fig. 5 – Survival curves for children with (a) bilateral and (b) unilateral retinoblastoma diagnosed in Europe in the periods shown. Based on the 13 datasets with information available on laterality and follow-up for at least three of the four periods of diagnosis. Source: ACCIS.

However, under-registration may also occur in general cancer registries. It is of course also possible that there may be over-registration of retinoblastoma in general cancer registries, either because of misclassification or through duplicate registration of cases where retinoblastoma occurs in two eyes at different dates. (Though this latter type of bias should have been excluded during specific checks of laterality of retinoblastoma cases in all contributing registries, prior to consolidation of the ACCIS database.) The possible systematic differences between paediatric and general cancer registries within ACCIS are described for all tumours combined [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue] and for thyroid tumours specifically [Steliarova-Foucher and colleagues, this issue]. It should be borne in mind that the overall incidence rates reported in this paper might be slightly underestimated, if there is indeed under-registration in paediatric cancer registries, since the paediatric cancer registries contributed the larger part of the data.

4.2. *Survival*

Survival rates have been very high throughout the period studied for both unilateral and bilateral cases in each region of Europe, though lower in the East than elsewhere. The improvement in survival mentioned in section 3.4 can probably be ascribed to the introduction of adjuvant chemotherapy following enucleation for patients with adverse histology, although it is not possible, with the data available, to definitely say which treatment modality was responsible.

Retinoblastoma is an eminently curable cancer and treatment is usually highly successful. Five-year survival rates for retinoblastoma have been in excess of 90% in the UK[7] and United States of America (USA)[8] and probably in other developed countries for some decades. In the EUROCARE study[9] overall 5-year survival for the period 1978–1989 was 93%. The results in Table 6(c) show that survival rates are similar for unilateral and bilateral cases. In Germany, in the 1990s there was a lack of follow-up for retinoblastoma (only 4% with follow-up from 5 years onwards, Table 1). This was due to the fact that approximately three-quarters of the German retinoblastoma cases are treated in only one centre, from which no follow-up data were reported to the national registry (Dr Peter Kaatsch, personal communication).

Incomplete follow-up here and elsewhere may, of course, lead to a biased estimate of survival rates.

One particular aspect of long-term survival needs to be considered: it is well known that patients with the heritable form of the disease are at a high risk of many forms of non-ocular cancer, and long-term surveillance is essential. High incidence of subsequent primary tumours following retinoblastoma was described, for example, in three large published series from the Netherlands,[21] the UK[22] and the USA.[23]

5. Conclusions and recommendations

From the data collected by ACCIS, there appears to be some variation in the incidence of retinoblastoma across European countries. The 5-year survival rate improved from 89% to 95% during the period covered by the study, an improvement being seen for both unilateral and bilateral cases. There were relatively small differences in survival between the five regions (British Isles, East, North, South, West) covered by the study though the 5-year survival rate appeared to be lower in the East region.

It is essential that all registries should try to get 100% ascertainment of cases and that retinoblastoma cases should be correctly classified as unilateral or bilateral. Registries should make particular efforts to determine whether a further eye tumour occurs in a patient initially recorded as having unilateral retinoblastoma. It seems likely that for the majority of bilateral cases both eyes will be affected at the time of registration.

For patients with heritable retinoblastoma, it is particularly important to ensure that they are monitored for the occurrence of subsequent, non-ocular, tumours. The incidence of such tumours is now fairly well documented, but it is essential to continue such studies particularly to assess the incidence of second malignancies following the recent

change from external beam radiotherapy to chemotherapy as the primary treatment for the majority of children with heritable retinoblastoma.

The ACCIS project should be continued and, in order to ensure complete ascertainment and follow-up, the organisers, in collaboration with cancer registries, should co-operate closely with paediatric oncology centres and specialist ophthalmological hospitals where many retinoblastoma cases are treated.

Conflict of interest statement

None declared.

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