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Geographical patterns of childhood cancer incidence in Europe, 1988–1997. Report from the Automated Childhood Cancer Information System project

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ABSTRACT

Data on more than 50,000 registrations in the Automated Childhood Cancer Information System (ACCIS) database were used to present an overview of regional patterns in childhood cancer incidence in Europe during 1988–1997, and to present additional detail on selected carcinomas whose occurrence in childhood is seldom described because of their rarity. Total age-standardised incidence was 138.5 per million for Europe overall, and varied between regions from 131.1 per million in the British Isles to 160.1 per million in Northern Europe. Incidence varied significantly between regions for nearly all diagnostic groups. The greatest range of regional incidence rates was for central nervous system (CNS) tumours, from 27.0 per million in the West to 43.8 per million in the North. Differences in registration practice for non-malignant tumours account for some of this variation. There was a marked excess of carcinoma in Eastern Europe, which was wholly attributable to the high incidence of thyroid carcinoma in Belarus, though there was also evidence of inter-regional variation attributable to differences in registration practice. The geographical heterogeneity of incidence rates for other diagnostic groups seems more likely to reflect variations in underlying risk.

1. Introduction

It is well known that there are substantial variations between regions of the world in the incidence of all childhood cancer combined and of the principal diagnostic groups,[1] though the differences tend to be less marked than in older adults. There is also evidence for considerable inter-regional and international variation within Europe.[2] Variations in the occurrence of cancer according to demographic variables (sex, age) and geographical area may provide clues to aetiol-

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ogy. The comparative rarity of childhood cancers, however, means that large databases can only be constituted by international collaboration.

The Automated Childhood Cancer Information System (ACCIS) is a collaborative project of the European cancer registries, aiming at collection, presentation and interpretation of data on cancer incidence and survival of children and adolescents in Europe. In this paper we use the ACCIS database to present an overview of geographical patterns in the incidence of cancer among children aged 0–14 years in Europe during 1988–1997. The main aim was to compare incidence rates for major diagnostic groups between European regions. This paper also contains additional detail on some carcinomas, whose occurrence in childhood is seldom described because of their rarity.

2. Material and methods

Detailed information on the ACCIS database is given elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. For this study, the analyses were based on data from the 58 population-based cancer registries in 19 countries, listed in Table 1, which met defined quality criteria for completeness, validity and comparability. All registrations for malignant neoplasms, together with non-malignant tumours of the central nervous system (CNS), registered during 1988–1997 in children aged under 15 years in the participating registries were extracted from the ACCIS database. A total of 53,717 children were included in the analyses of all tumour types. For leukaemia, the analyses were based on a larger population at risk, since the specialised leukaemia registry of the Netherlands (DCOG), which replaced the National registry of the Netherlands, provided data for a longer period. The 769 leukaemia cases registered in the National cancer registry were thus replaced by the 1095 cases registered by the DCOG (Table 1). Standard variables available for each case included basic demographic data (age, sex, country or region of residence) and information on the tumour (date of incidence, site, morphology, basis of diagnosis, grade and laterality). In nearly all the registries, more than 90% of cases were microscopically verified and, among those registries with access to mortality data, fewer than 1% were registered from death certificate only. Diagnoses were grouped according to the International Classification of Childhood Cancer (ICCC).[3]

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 and otherwise was estimated by linear interpolation from available data [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

Incidence rates were calculated as the average annual number of cases per million person-years. Age-standardised rates (ASR) were calculated by the direct method from the age-specific incidence rates for 5-year age groups using the weights of the World standard population. The 95% confidence intervals (95% CI) for the incidence rates were calculated using the Poisson approximation,[4] or exactly if less than 30 cases were observed.[4] Variations in incidence between the five European regions were analysed by Poisson regression [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

3. Results

Table 2 shows total numbers of cases and ASRs for boys and girls combined in each country and region represented in the study. The ASR was 139 per million for Europe as a whole, ranging from 131 to 160 between regions and from 116 to 173 between countries. Incidence rates were highest in the North of Europe and lowest in the British Isles. Within the North, South and East regions, there was substantial variation in ASRs between countries. The highest ASR in the North, and in all Europe, was observed in Finland. In the South, Italy had an ASR that exceeded those for each of the other countries by at least 15%, while that for Turkey was considerably lower. In the East, Belarus had an ASR that was much higher than those of other countries in the region.

Table 3 shows age-specific incidence rates and ASRs for boys and girls in the five European regions and Europe as a whole. Overall, incidence was highest among infants and slightly lower at age 1–4 years; incidence rates at ages 5–9 years and 10–14 years were similar to each other, but substantially lower than in the first 5 years of life. The difference in incidence between ages 0–4 years and 5–14 years was less marked in the East than in other regions. Fig. 1 shows total incidence in Europe as a whole by single year of age separately for boys and girls. Total incidence among boys was higher than among girls at all ages, but the male excess was highest at age 5–9 years (M/F = 1.27) and lowest for infants (M/F = 1.04). The sex ratio of ASRs ranged from M/F = 1.13 in the North to M/F = 1.19 in the South and the West. In the North, there was a slight female excess among infants (M/F = 0.97). Fig. 2 shows incidence in the five European regions by single year of age for boys and girls combined. Inter-regional variation was least at age 5–9 years and greatest in the first year of life.

Table 4 shows ASRs of the 12 ICCC groups for both sexes combined in the five regions and Europe as a whole. Incidence rates varied significantly between the five regions for all diagnostic groups except hepatic tumours, for which the variation was borderline non-significant. Leukaemia was the most common diagnostic group overall and in each region. It accounted for 32% of age-standardised incidence overall, but for only 28% in the East. Incidence varied widely, with ASRs significantly above average in the North and South and significantly below in the East. Brain and spinal neoplasms were the second most common group in all regions, accounting for 22% of total age-standardised incidence. Their incidence was significantly higher than the European average in the North, where they accounted for 27% of the total, and in the East, and significantly lower in the West. Lymphomas were the third most common group in all regions, with 11% of total incidence; their incidence rates were significantly higher than average in the South and the East and significantly lower in the British Isles. The East of Europe had the lowest leukaemia incidence and a significantly raised ASR for lymphomas but otherwise

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

Region	Registry	Calendar period	Cases	Non-malignant	NOS	Carcinoid	Basis of diagnosis			Notes
							MV	DCO	Unknown	
			n	%	%	*n*	%	%	%	
British Isles	IRELAND, National	1994–1997	434	2	6	0	95	0	<1	
	UNITED KINGDOM, England & Wales	1988–1995	9938	4	3	0	90	1	5	P
	UNITED KINGDOM, Northern Ireland	1993–1996	223	8	25	0	73	0	0	
	UNITED KINGDOM, Scotland	1988–1997	1242	–	4	0	95	<1	0	
East	BELARUS, National	1989–1997	3200	2	7	0	96	0	0	P
	ESTONIA, National	1988–1997	429	–	10	0	93	<1	0	
	HUNGARY, National	1988–1997	2475	4	1	1	96	–	0	P
	SLOVAKIA, National	1988–1997	1614	3	6	0	95	<1	0	
North	DENMARK, National	1988–1997	1403	10	10	3	90	<1	2	
	FINLAND, National	1988–1997	1608	2	9	28	98	0	<1	
	ICELAND, National	1988–1997	84	2	4	0	99	0	0	
	NORWAY, National	1988–1997	1188	2	10	0	97	<1	<1	
South	ITALY, Piedmont paediatric	1988–1997	926	4	3	0	96	<1	0	P
	ITALY, Marche	1990–1997	243	–	10	0	88	–	9	P
	ITALY, Ferrara	1991–1995	28	–	18	0	82	0	0	
	ITALY, Latina	1988–1997	103	–	17	0	90	0	3	
	ITALY, Liguria	1988–1995	90	2	7	0	77	1	0	
	ITALY, Lombardy	1988–1997	191	–	4	0	93	<1	0	
	ITALY, Parma	1988–1995	47	2	4	0	96	0	0	
	ITALY, Ragusa	1988–1997	72	–	6	0	96	0	0	
	ITALY, Sassari	1992–1995	41	–	5	0	93	0	5	
	ITALY, Tuscany	1988–1997	223	4	10	0	61	1	0	
	ITALY, Umbria	1994–1996	59	–	10	1	85	0	0	
	ITALY, Veneto	1990–1996	288	–	7	1	94	0	0	
	MALTA, National	1991–1997	78	6	3	0	96	0	1	
	SLOVENIA, National	1988–1997	485	1	3	0	98	0	0	
	SPAIN, National	1990–1995	1371	2	4	0	92	0	2	P o1 Z
	SPAIN, Albacete	1991–1997	57	–	9	0	89	2	0	
	SPAIN, Asturias	1988–1997	230	2	13	1	94	1	0	
	SPAIN, Basque Country	1988–1994	359	–	12	0	93	2	0	o1
	SPAIN, Canary Islands	1993–1996	150	–	4	0	87	4	3	
	SPAIN, Girona	1994–1997	49	–	6	0	96	0	2	o1
	SPAIN, Granada	1988–1997	208	–	2	0	98	0	<1	P
	SPAIN, Mallorca	1988–1995	132	–	5	0	97	0	0	o1
	SPAIN, Navarra	1988–1996	109	–	9	0	95	3	0	o1
	SPAIN, Tarragona	1988–1997	136	–	7	0	95	<1	0	o1
	SPAIN, Zaragoza	1988–1996	178	1	2	0	96	2	0	o1
	TURKEY, Izmir	1993–1996	332	–	3	0	96	–	<1	
West	FRANCE, Brittany	1991–1997	527	5	2	0	98	–	2	P
	FRANCE, Lorraine	1988–1997	641	3	2	0	92	–	<1	P
	FRANCE, PACA & Corsica	1988–1996	1060	3	2	4	98	–	0	P
	FRANCE, Rhone Alpes	1988–1997	1376	4	2	0	97	–	<1	P
	FRANCE, Doubs	1988–1996	118	–	8	1	64	–	2	
	FRANCE, Herault	1988–1997	211	–	3	1	92	–	0	
	FRANCE, Manche	1994–1996	40	–	0	0	90	–	0	
	FRANCE, Bas-Rhin	1988–1996	252	–	6	1	98	–	0	
	FRANCE, Haut-Rhin	1988–1997	190	–	4	0	95	–	<1	
	FRANCE, Somme	1988–1996	127	–	5	0	94	–	2	
	FRANCE, Tarn	1988–1997	79	–	4	1	96	–	0	
	GERMANY, NCR (only former East)	1988–1989	794	4	5	0	98	0	0	
	GERMANY, GCCR (East and West)	1991–1997	12,153	3	2	0	99	–	0	P
	GERMANY, GCCR (only former West)	1988–1990	3677	3	2	0	100	–	0	P
	NETHERLANDS, National	1989–1995	2665	–	5	44	95	–	0	o2
	NETHERLANDS, DCOG	1988–1997	1095	–	0	0	99	–	0	P o2
	SWITZERLAND, Basel	1988–1997	99	–	5	0	98	–	0	
	SWITZERLAND, Geneva	1988–1997	88	–	5	0	97	0	0	
	SWITZERLAND, Graubunden & Glarus	1989–1997	48	–	6	0	90	0	4	
	SWITZERLAND, St. Gallen Appenzell	1988–1997	133	2	6	0	97	0	0	
	SWITZERLAND, Valais	1989–1997	67	–	4	0	99	0	0	

Table 1 – *continued*

DCOG, Dutch Childhood Oncology Group; GCCR, National German Childhood Cancer Registry (until 1990, only West; since 1991 for reunified Germany); NCR, National Cancer Registry of the former German Democratic Republic. Data for 1988–1989 were pooled with GCCR and included in West. For explanation, see Steliarova-Foucher, Kaatsch, Lacour et al. (this issue); PACA, Provence, Alps, Côte d'Azur; Non-malig, non-malignant cases, only reported for registries with systematic registration of these cases; MV, microscopically verified cases; DCO, registrations from death certificate only; NOS, cases with unspecified histology, including the ICCC categories Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, the morphology codes M-8000 to M-8004 in Xe and topography codes C76 to C80 in XIf; Carcinoid, carcinoid tumour of appendix (C18.1, M-8240); P, paediatric cancer registry; age range for all registrations is 0–14 years; o1, overlapping registration areas in Spain; for overlapping years, only registrations from the National Paediatric Registry were included; o2, overlapping registration coverage in the Netherlands; National Cancer Registry data were used, except for leukaemias, for which DCOG was used; Z, covers only selected areas, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue).

there was little evidence of inverse correlation between incidence rates for these two diagnostic groups.

Sympathetic nervous system tumours, predominantly neuroblastoma, varied moderately in incidence between the regions; in the North, which had the highest incidence for all cancers combined, this diagnostic group had an ASR below the European average. Most regions had ASRs similar to the European average for retinoblastoma, renal tumours, hepatic tumours, bone tumours and soft tissue sarcomas. Incidence of bone tumours was especially high in the South, however, while the North had the highest rate for soft tissue sarcoma by a considerable margin.

There was more inter-regional variation for germ-cell and gonadal tumours, which had significantly high incidence in the North and significantly low rates in Britain and Ireland and the East. The proportion of cases in this group that were non-malignant intracranial and intraspinal germ-cell tumours ranged from 2.2% in the South to 10.5% in the North. When the group was restricted to malignant tumours, the ASR by region ranged from 3.4 per million in the East to 5.0 per million in the North, and the ranking of regions by ASR seen in Table 4 was unchanged.

Incidence of carcinoma and melanoma in the East was more than twice as high as in any other region; incidence for this group was also above average in the North and below average in the British Isles, the South and the West. The excess in the East was accounted for by a high incidence of thyroid carcinoma in Belarus [Steliarova-Foucher, Stiller, Pukkala and colleagues, this issue], while the North had a high incidence of carcinomas of other and unspecified sites.

Table 5 shows the results for miscellaneous carcinomas, namely those of the adrenal cortex (ICCC XIa), nasopharynx (ICCC XIc), and other and unspecified sites, except kidney, liver, gonads, thyroid and skin (ICCC XIf). Fig. 3 shows incidence rates by single year of age for the same three subgroups among boys and girls in Europe as a whole, but with carcinoid tumours of appendix removed from subgroup XIf. Adrenal cortical carcinoma was twice as common among girls as among boys. The highest incidence was in the second year of life. Nasopharyngeal carcinoma, by contrast, had a pronounced male excess and was usually diagnosed at age 10–14 years. For carcinomas of both these sites, the 95% CIs for the ASR in each region spanned the European average. Other and unspecified carcinomas were again registered predominantly among children aged 10–14 years. In Northern Europe the recorded incidence was over twice the rate in any other region and there was also a pronounced female excess (M/F = 0.6). Incidence rates were above average in all three Northern countries with substantial numbers of registrations, 1.4 in Norway, 1.8 in Denmark and 3.2 in Finland. The Netherlands also had a particularly high ASR of 3.0 per million. Table 6 shows incidence rates for this last subgroup further split by primary site. The most common site was the appendix, followed by the salivary glands. Incidence for both these sites was highest in the North, and incidence of tumours of the appendix was also relatively high in the West. There was a marked female excess for both of these sites.

Table 2 – Numbers of registrations and age-standardised annual incidence rates (ASR) per million with 95% confidence intervals (CI) for boys and girls combined in the five European regions and individual countries, 1988–1997 (Source: ACCIS)

	Registrations (*n*)	ASR	95% CI
British Isles	11,837	131.1	(128.8–133.5)
Ireland	434	132.9	(120.1–145.7)
UK	11,403	131.0	(128.6–133.5)
East	7718	140.9	(137.7–144.1)
Belarus	3200	155.0	(149.5–160.4)
Belarus[a]	2643	131.3	(126.3–136.4)
Estonia	429	137.1	(123.9–150.3)
Hungary	2475	130.8	(125.5–136.0)
Slovakia	1614	135.8	(129.0–142.5)
North	4283	160.1	(155.3–165.0)
Denmark	1403	160.4	(152.0–168.9)
Finland	1608	173.2	(164.7–181.7)
Iceland	84	133.0	(104.4–161.6)
Norway	1188	147.5	(139.1–155.9)
South	5534	148.5	(144.4–152.5)
Italy[b]	2311	167.4	(160.6–174.5)
Malta	78	143.5	(111.3–175.8)
Slovenia	485	133.5	(121.3–145.7)
Spain[b]	2328	141.7	(135.7–147.7)
Turkey[b]	332	115.6	(102.9–128.2)
West	24,345	135.9	(134.2–137.7)
France[b]	4621	137.5	(133.5–141.5)
Germany	16,624	134.7	(132.6–136.8)
Netherlands	2665	140.3	(134.9–145.6)
Switzerland[b]	435	145.2	(131.5–158.9)
Total	53,717	138.5	(137.3–139.7)

a Thyroid cancers excluded.
b Countries with subnational coverage.

Table 3 – Age-specific and age-standardised annual incidence rates per million for all cancers combined among boys and girls in the five European regions, 1988–1997 (Source: ACCIS)

	Registrations (*n*)	Boys					Girls				
		0 years	1–4 years	5–9 years	10–14 years	ASR	0 years	1–4 years	5–9 years	10–14 years	ASR
British Isles	11,837	173.2	193.8	110.1	110.5	141.0	165.6	164.9	91.9	93.7	120.7
East	7718	184.0	192.6	125.6	124.5	150.5	169.5	158.3	105.7	119.0	130.8
North	4283	223.7	232.2	131.9	130.1	169.6	230.8	208.5	106.1	115.8	150.3
South	5534	210.1	208.9	133.9	125.8	160.7	194.1	186.5	94.7	111.0	135.6
West	24,345	216.4	192.3	121.4	110.5	147.5	208.8	166.8	93.2	89.1	123.7
Total	53,717	201.7	197.1	121.3	115.7	149.3	193.5	169.8	95.6	98.8	127.1

ASR, age-standardised rates.

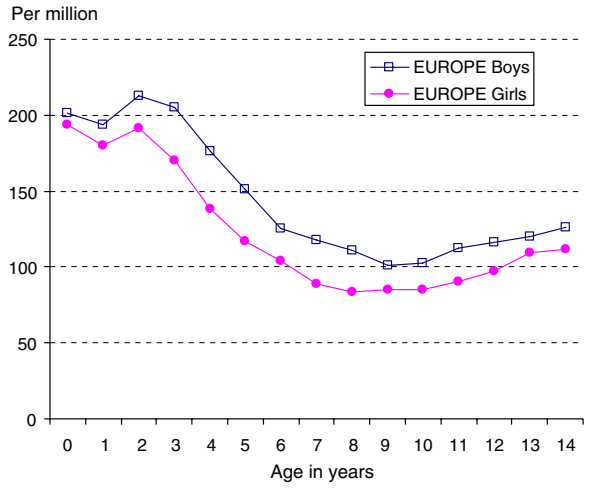

Fig. 1 – Age-specific cancer incidence among children in Europe as a whole by single year of age separately for boys and girls, 1988–1997. Source: ACCIS.

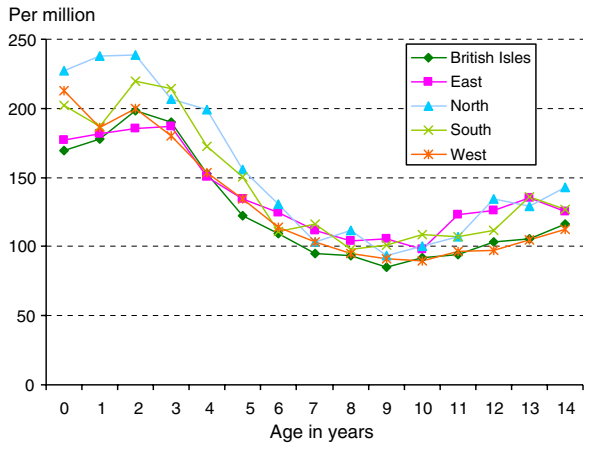

Fig. 2 – Age-specific cancer incidence among children in the five European regions by single year of age for boys and girls combined, 1988–1997. Source: ACCIS.

No other site had an ASR above 0.25 per million overall or in any European region. Carcinomas of the breast, uterus and cervix were especially infrequent.

4. Discussion

The incidence rates presented here are derived from the largest population-based series of childhood cancer cases ever assembled. Consequently, incidence rates even for relatively rare diagnostic groups and subgroups are based on unusually large numbers of cases, making it possible to detect moderate differences between regions and countries. In all the registries whose data were included in these analyses, there were high rates of microscopic verification and low percentages of cases registered from death certificate only, allowing correspondingly high reliance to be placed on the results. Nevertheless, it should be stressed that the results are based only on the data-sets included in Table 1. Data were only available for some countries in each region other than the British Isles, geographical coverage only extended to parts of some countries in the South and West European regions, and many of the data-sets did not cover the full 10-year study period.

In common with results from Europe for the 1980s and for industrialised countries in other world regions, total age-standardised incidence was between 100 and 200 per million and there was a moderate excess of boys. Incidence rates for all cancers combined and for individual diagnostic groups tended to be slightly higher than those reported for the 1980s in IICC-2. The extent to which this represents a true increase in risk rather than improved diagnosis and registration is discussed elsewhere [Kaatsch and colleagues, this issue].

Compared with the striking intercontinental differences in incidence for all childhood cancer and some diagnostic groups, the variation between European regions was modest. The ratio of largest to smallest regional ASR was 1.22 for all cancers combined and between 1.2 and 1.7 for all but two of the 12 diagnostic groups. The principal exception was Carcinoma and Melanoma, for which the region with the highest incidence, Eastern Europe, had an ASR 4.9 times that for the region with the lowest incidence, namely the West. The excess in the East was entirely due to the very high incidence of thyroid carcinoma in Belarus. The second highest ASR for Carcinoma and Melanoma was in the Northern region, and even this was 2.3 times the rate for the West. This diagnostic group is very heterogeneous, encompassing carcinomas of almost all sites in addition to melanomas; regional differences for individual sites are discussed in greater detail below and in other papers from this study [Steliarova-Foucher, Stiller, Pukkala and colleagues, this issue; de Vries and colleagues, this issue].

Table 4 – Age-standardised annual incidence rates per million children (95% CI) by ICCC groups in Europe as a whole and the five European regions, 1988–1997 (Source: ACCIS)

	Registrations (*n*)	Total	British Isles	East	North	South	West
Leukaemia[a]	17,065	44.0 (43.3–44.6)	43.1 (41.7–44.5)	39.1 (37.4–40.8)	48.0 (45.3–50.6)	47.0 (44.7–49.3)	44.5 (43.6–45.5)
Lymphoma	6384	15.2 (14.8–15.5)	11.6 (10.9–12.3)	17.1 (16.1–18.2)	13.9 (12.5–15.3)	19.3 (18.0–20.7)	15.6 (15.0–16.2)
CNS	11,829	29.9 (29.3–30.4)	30.3 (29.2–31.5)	31.8 (30.3–33.3)	43.8 (41.3–46.3)	29.3 (27.6–31.1)	27.0 (26.3–27.8)
Sympathetic	3890	11.2 (10.8–11.5)	9.5 (8.9–10.2)	10.2 (9.3–11.1)	9.9 (8.7–11.1)	12.9 (11.6–14.2)	12.2 (11.6–12.7)
Retinoblastoma	1393	4.1 (3.9–4.3)	4.5 (4.0–4.9)	3.4 (2.9–3.9)	5.2 (4.3–6.1)	3.9 (3.2–4.6)	4.0 (3.6–4.3)
Renal	3134	8.8 (8.5–9.1)	7.7 (7.1–8.3)	8.7 (7.8–9.5)	9.1 (7.9–10.2)	8.3 (7.3–9.3)	9.5 (9.0–9.9)
Hepatic	521	1.5 (1.3–1.6)	1.2 (1.0–1.4)	1.9 (1.5–2.3)	1.9 (1.4–2.5)	1.5 (1.1–2.0)	1.4 (1.2–1.6)
Bone	2448	5.5 (5.3–5.8)	5.0 (4.6–5.4)	5.2 (4.6–5.7)	5.1 (4.3–5.9)	7.2 (6.4–8.0)	5.6 (5.3–5.9)
Soft tissue sarcoma	3571	9.1 (8.8–9.4)	9.6 (9.0–10.3)	8.4 (7.6–9.2)	11.1 (9.8–12.3)	9.5 (8.5–10.5)	8.7 (8.3–9.2)
Germ cell and gonadal	1763	4.5 (4.3–4.7)	4.0 (3.6–4.4)	3.7 (3.2–4.2)	5.6 (4.7–6.5)	4.8 (4.0–5.5)	4.8 (4.5–5.1)
Carcinoma and melanoma	1821	4.1 (3.9–4.3)	3.5 (3.2–3.9)	10.7 (9.9–11.5)	5.1 (4.3–5.9)	3.7 (3.1–4.3)	2.2 (2.0–2.4)
Other and unspecified	224	0.6 (0.5–0.7)	1.0 (0.8–1.2)	0.7 (0.4–0.9)	1.5 (1.0–2.0)	1.0 (0.6–1.3)	0.2 (0.1–0.2)
Total	53,717	138.5 (137.3–139.7)	131.1 (128.8–133.5)	140.9 (137.7–144.1)	160.1 (155.3–165.0)	148.5 (144.4–152.5)	135.9 (134.2–137.7)

CNS, central nervous system.
a The results reported for leukaemia in Europe as a whole and in the West are based on a slightly larger data-set; the Netherlands was represented for leukaemia by data from the Dutch Childhood Oncology Group for 1988–1997, whereas for the other diagnostic groups and for the total it was represented by data from the National Cancer Registry for 1989–1995 (see also Table 1, note o2 and text).

Table 5 – Incidence rates per million children for miscellaneous carcinomas in the five European regions, 1988–1997 (Source: ACCIS)

		Registrations (*n*)	0 years	1–4 years	5–9 years	10–14 years	ASR (95% CI)	Ratio of ASR M/F
Adrenal cortex	British Isles	14	–	0.2	0.1	0.1	0.2 (0.1–0.2)	0.2
	East	16	0.9	0.3	0.1	0.3	0.3 (0.1–0.4)	0.8
	North	8	0.5	0.3	0.1	0.4	0.3 (0.1–0.5)	0.4
	South	10	0.9	0.1	0.4	0.1	0.3 (0.1–0.4)	0.3
	West	22	0.3	0.3	0.0	0.0	0.1 (0.1–0.2)	1.0
	Total	70	0.4	0.3	0.1	0.1	0.2 (0.1–0.2)	0.5
Nasopharynx	British Isles	20	–	–	0.1	0.6	0.2 (0.1–0.3)	2.9
	East	20	–	0.1	0.1	0.8	0.3 (0.2–0.4)	2.7
	North	4	–	–	0.1	0.3	0.1 (0.0–0.3)	0.3
	South	17	–	–	0.2	1.0	0.3 (0.2–0.5)	2.4
	West	47	–	–	0.0	0.7	0.2 (0.2–0.3)	2.5
	Total	108	–	0.0	0.1	0.7	0.2 (0.2–0.3)	2.4
Other and unspecified[a]	British Isles	74	–	0.1	0.5	1.9	0.7 (0.6–0.9)	1.0
	East	43	–	0.2	0.5	1.5	0.7 (0.5–0.9)	1.8
	North	66	0.5	0.5	1.3	5.4	2.2 (1.7–2.7)	0.6
	South	45	–	0.3	0.6	2.3	0.9 (0.7–1.2)	1.0
	West	140	0.3	0.0	0.4	1.8	0.7 (0.6–0.8)	1.0
	Total	368	0.2	0.1	0.5	2.1	0.8 (0.7–0.9)	0.9

CI-Confidence interval; ASR, age-standardised rates; M/F, males/females.
a All sites except kidney, liver, gonadal, adrenal cortex, thyroid, nasopharynx and skin.

Incidence of haematological malignancies, both leukaemias and lymphomas, was higher in the South than in other regions. While the East had significantly low incidence of leukaemia and significantly high incidence of lymphomas, there was little evidence elsewhere for inverse correlation between the incidence rates for these two diagnostic groups. The distinctive patterns of occurrence for leukaemias and lymphomas in Southern and Eastern Europe have been observed previously[2,5] and the possible reasons are also discussed in other articles [Coebergh, Reedijk, de Vries and colleagues, this issue; Clavel and colleagues, this issue; Izarzugaza and colleagues, this issue]. Large-scale misclassification between the two groups in any region seems unlikely.

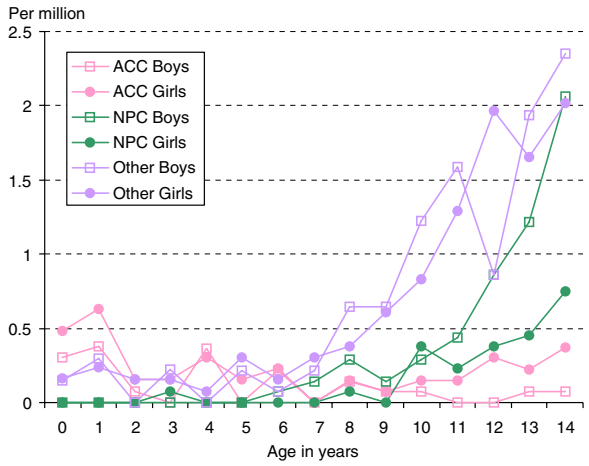

Fig. 3 – Age-specific incidence of Adrenal cortical carcinoma (ACC, XIa), Nasopharyngeal carcinoma (NPC, XIb) and Other and unspecified carcinomas (Other, XIf) among boys and girls in Europe, 1988–1997. The 'Other' group excludes carcinoid tumours of the appendix (C18.1, M-8240). Source: ACCIS.

In absolute terms CNS tumours had the greatest range of regional registration rates for any diagnostic group, with a difference of 16.8 per million between the highest and lowest. The highest incidence was in Northern Europe, as had been found previously in the 1980s. Some of the variation could be attributed to marked differences in registration rates for non-malignant tumours. The North had the highest incidence for malignant CNS tumours, however [Peris-Bonet and colleagues, this issue], and therefore geographical differences in underlying risk factors cannot be excluded.

Among the diagnostic groups that include the main embryonal tumours of childhood, there was relatively little variation between regions for sympathetic nervous system tumours (mostly neuroblastoma) or renal tumours (mostly Wilms' tumour). Formal mass screening for neuroblastoma affected only a small proportion of the study population, but some of the variation in incidence of sympathetic nervous system tumours might be accounted for by varying rates of detection of asymptomatic tumours under different systems of health checks in early childhood [Spix and colleagues, this issue]. Retinoblastoma, by contrast, was 1.5 times as frequent in the region with the highest incidence (North) as in that with the lowest rate (East). There was a similar range of variation for hepatic tumours (principally hepatoblastoma), but these tumours were rare in all regions.

The highest incidence of bone tumours by far was in the South, while rates in the other four regions were quite similar. The highest rate for soft tissue sarcoma was in the North. The combined incidence of bone and soft tissue tumours still varied substantially between regions, however, from 13.6 per million in the East to 16.7 in the South.

Some, but not all, of the variation in the incidence of germ cell and gonadal tumours was attributable to differences in rates for non-malignant intracranial and intraspinal germ cell tumours. Therefore, as with CNS tumours discussed above, inter-regional variations in underlying risk factors cannot be ruled out.

Incidence of carcinomas of the adrenal cortex and nasopharynx varied rather little, but numbers of registrations were very low. The highest recorded incidence of miscellaneous carcinomas was in countries that also had high rates in the 1980s.[1] As in that earlier period, the especially high incidence in Finland and the Netherlands was attributable to large numbers of tumours of the appendix. This is an artefact resulting from the frequent coding of carcinoid tumours of the appendix as malignant in some cancer registries. The relatively high rate for miscellaneous carcinomas in the North also included a substantial contribution from tumours of the salivary glands. Incidence of carcinoma of the salivary glands in children does vary between populations, one example being the higher rates among African-American children compared with white children in the United States of America (USA).[6] Therefore, the higher incidence in Northern Europe may represent a higher underlying risk. Epithelial salivary gland tumours occur in a spectrum from benign to malig-

Table 6 – Age-standardised incidence rates per million children aged 0–14 years of Other and Unspecified Carcinomas (ICCC XIf), by primary site and European region, 1988–1997 (Source: ACCIS)

	Registrations (*n*)	British Isles	East	North	South	West	Total	M/F
Salivary	55	0.2	0.1	0.3	0.1	0.1	0.1	0.7
Other head and neck	30	0.1	0.1	0.2	0.1	<0.1	0.1	1.3
Stomach	10	<0.1	<0.1	0.0	0.0	<0.1	<0.1	2.1
Appendix	90	0.0	<0.1	1.1	0.1	0.3	0.2	0.6
Large bowel	28	0.1	0.1	0.1	0.1	<0.1	0.1	1.8
Pancreas	12	<0.1	<0.1	0.1	0.0	<0.1	<0.1	0.7
Lung	29	0.1	<0.1	0.1	<0.1	0.1	0.1	1.4
Thymus	15	<0.1	<0.1	0.0	<0.1	<0.1	<0.1	2.7
Breast	2	0.0	0.0	0.0	0.0	<0.1	<0.1	1.0
Cervix and uterus	2	<0.1	0.0	0.0	0.0	<0.1	<0.1	–
Bladder	13	0.1	<0.1	<0.1	0.1	0.0	<0.1	2.0
Eye	6	<0.1	<0.1	0.1	0.0	<0.1	<0.1	0.4
Other specified	39	0.1	0.2	0.1	0.2	<0.1	0.1	1.2
Unspecified	37	0.1	0.1	0.2	0.2	<0.1	0.1	0.5

M/F, males/females.

nant,[7] however, and variations in registration and coding practice for less aggressive lesions cannot be ruled out.

Among the European regions, the North had the highest incidence rates, with markedly elevated incidence in seven main diagnostic groups. Further investigation should address the effect of coding practices in the Nordic countries, where various obsolete classification systems were used until recently and may have contributed to the observed differences. The North had by far the highest incidence of soft tissue sarcomas, but one of the lowest rates for sympathetic nervous system tumours (mainly neuroblastoma). This raises the possibility of exchange of cases between these two groups, especially since the ICD up to and including ICD-9, as well as ICD-O-1, did not distinguish site codes for peripheral nerves from those for connective tissue. In addition, different diagnostic criteria may at least partly explain the high incidence rates in the North for CNS tumours and possibly also for soft tissue sarcomas and germ cell tumours, should the definition of malignancy include lower grade tumours than in the rest of Europe. On the other hand, the North was the only region covered exclusively by national, general cancer registries, which would favour complete registration of tumours with good prognosis such as carcinomas. These tumours are more common in later childhood and readily referred to clinicians outside paediatric oncology networks, which might explain their low incidence rates in the West, dominated by the national childhood cancer registry of Germany. This is less likely to explain the relatively low incidence rates of several diagnostic groups in the British Isles, mostly represented by the national childhood cancer registry in England and Wales, since that registry includes regional and national general cancer registries among its sources of ascertainment. More careful quality control in the paediatric cancer registries could have led to more efficient exclusion of misclassified cases in the relevant diagnostic groups with low incidence in the British Isles and the West [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. Errors in the date of birth for a tiny proportion of adult cases in general cancer registries, leading to miscalculation of their ages as under 15 years, would have a disproportionate effect on the recorded incidence rates for children, in whom cancer is much less frequent. The high rates recorded in the East for some diagnostic groups, notably lymphomas, CNS tumours and carcinomas, are unlikely to have arisen from artefacts, since the overall incidence in this region is relatively low and assumptions of different risks are plausible, as described above. This is probably also the case for the high incidence of lymphomas observed in the South, though the excesses of sympathetic nervous system tumours and malignant bone tumours in this region need further exploration.

In this study, we have concentrated on comparisons of incidence between the five European regions. This has the advantage of providing large numbers of registrations and correspondingly stable incidence estimates even for relatively rare diagnostic groups. The implicit assumption that the rates calculated for a region are representative of those for all countries within the region should not, however, be taken too uncritically. Total incidence rates for individual countries that provided data within each region were fairly homogeneous in the British Isles and the West. In the East, Belarus had markedly higher incidence than the other three countries only because of the exceptionally high rate for thyroid carcinoma. There was a wide spread of incidence rates in the North and South regions, implying heterogeneity of registration or underlying risk. Furthermore, in some countries the data refer to only part of the national population and/or only part of the 10-year study period. The most extreme example is Turkey, for which only 4% of the national person-years at risk were covered, but the data for Italy, Switzerland, Spain and France also covered well under half of the respective national person-years. For yet other countries, notably some in the East with large populations, no data were available for analysis.

In conclusion, while differences in completeness and accuracy of registration cannot be excluded as an explanation for some of the inter-regional and international variations in childhood cancer incidence across Europe, the geographical heterogeneity of higher and lower rates for several diagnostic groups seems more likely to be due to variations in underlying risk. Childhood cancer is a heterogeneous group of diseases whose causes are largely unknown. The complex patterns of variation in incidence may indicate correspondingly complex patterns of geographical variation in genetic susceptibility and the prevalence of risk factors for specific cancers. Furthermore, geographical differences in the occurrence of and mortality from other childhood diseases, notably infectious ones, may influence childhood cancer incidence rates to various extents, and such associations warrant formal examination. More complete delineation of patterns of childhood cancer incidence in Europe must await the availability of high-quality registration data from a larger proportion of countries and areas within countries.

Conflict of interest statement

None declared.

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