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Thyroid cancer incidence and survival among European children and adolescents (1978–1997): Report from the Automated Childhood Cancer Information System project

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ABSTRACT

Data on 1690 childhood and adolescent cases of thyroid cancer registered in 61 European cancer registries were extracted from the database of the Automated Childhood Cancer Information System (ACCIS) and included in analyses of incidence and survival. In 1988–1997, the age-standardised incidence rates (ASR) for children aged 0–14 years varied in European regions from 0.5 to 1.2 per million and the age-specific incidence in adolescents aged 15–19 years ranged from 4.4 to 11.0 per million. Over the age-span 0–19 years, the female to male ratio increased from 1 to around 3. Papillary thyroid cancer accounted for almost 65% of cases in children and 77% in adolescents. In the childhood population of Belarus, the ASR for 1989–1997 was 23.6 per million and the proportion of papillary tumours was 87%. No association was found between thyroid cancer risk and national dietary iodine status across 16 countries. Incidence of thyroid carcinoma among children and adolescents in Europe (excluding Belarus) increased during 1978–1997 by 3% per year, largely due to papillary carcinoma. Survival of children and adolescents was high over the entire study period and in all regions of Europe. Children with medullary carcinoma had slightly lower 5-year survival (95%, 95% CI 81–99), than those with papillary carcinoma (99%, 95% CI 95–100). More than 90% of patients survived 20 years after diagnosis. Further standardisation of diagnostic, classification and registration criteria will be fundamental for future studies of thyroid carcinomas in young people.

1. Introduction

Thyroid cancer is rare in children, especially before the age of 10 years.[1] In European populations, the incidence rate increases steadily over the lifetime from around 1–2 cases per million in the age group 10–14 years[1] to some 70 per million at around 50 years of age, and then plateaus.[2] Cancer affecting the thyroid gland is one of few that are more frequent

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in females than in males, with a ratio of almost 3,[2] already seen in later childhood,[1] which may suggest the importance of hormonal factors in its aetiology.

Morphologically, four main types of thyroid carcinoma are distinguished, with different aetiology and prognosis: papillary and follicular (differentiated) carcinomas are derived from follicular cells, while medullary cancers arise from embryologically distinct C-cells. The anaplastic (undifferentiated) type is uncommon at young ages.[3]

The best known cause of thyroid carcinoma is ionising radiation, recently demonstrated by the spectacular increase in thyroid cancer incidence in the vicinity of the Chernobyl accident of 1986, especially in the childhood population.[4] At first, the increase was suspected to be largely related to opportunistic screening for these tumours and registration of non-malignant tumours. The extent of the geographical differences, however, in conjunction with the histological types of the tumours reported, removed any doubts about the reality of the association,[5] although some of the increase may still have resulted from early diagnosis of tumours that would otherwise have presented at later ages.

Exposure to radiation gives rise to differentiated types, notably to the papillary type, although a causal association for the other types cannot be excluded.[5] Medullary carcinomas are linked to hereditary factors in 25% of cases. They occur in families with multiple endocrine neoplasia (MEN) syndromes and are caused by germline mutations in the RET proto-oncogene with an autosomal dominant inheritance.[3] However, some cases of non-medullary thyroid carcinomas are also found in association with familial syndromes (e.g. adenomatous polyposis, multiple hamartomas), and their presence confers a more aggressive behaviour to these tumours.[6]

The incidence of thyroid carcinoma may also be influenced by the presence of dietary iodine (drinking water, iodised salt). Iodine deficiency has been linked with follicular carcinoma,[7] while adequate or high iodine intake may be related to higher relative frequency of papillary carcinoma.[8] Lack of dietary iodine is also associated with endemic goitre, a non-malignant disease of the thyroid gland, which may lead to the development of follicular carcinoma if specific genetic conditions are met.[9] The risk factors described above are not specific to young patients.

With the exception of the anaplastic type, thyroid carcinomas have a good prognosis. Survival of children diagnosed with thyroid cancer cases in 1978–1989 and included in the EUROCARE study was 97%[10] and similar results were also reported from the United States of America (USA).[11] These favourable figures may be partly counterbalanced by the late effects, which were reported to be more common in patients diagnosed at a young age than in adulthood.[12]

The database of the Automated Childhood Cancer Information System (ACCIS) contains records from 78 European population-based cancer registries that cover about 50% of the population aged 0–14 years and about 25% of the population aged 15–19 years living in the 35 participating countries.[13] Over the last 30 years, 1300 million person-years of observation gave rise to over 160,000 cases of childhood and adolescent cancer. The ACCIS database is particularly useful for study of rare neoplasms of children and adolescents, such as thyroid cancer. In this paper we use the ACCIS data to describe the burden of thyroid cancer in the young population of Europe in terms of incidence and survival, and propose topics for further studies.

2. Material and methods

All malignant neoplasms of the thyroid gland, registered between 1978 and 1997 in 61 European cancer registries were included in this study. The contribution of each registry, in terms of the number of cases, geographical region, calendar period, age-range of cases, method of diagnosis and follow-up for vital status is shown in Table 1. These data-sets were evaluated as 'comparable' and included in the presented analyses. Selected data quality indicators shown in Table 1 permit evaluation of each contribution. A total of 1690 cases extracted from the common ACCIS database were included in different types of analysis, as described below. Seventeen of them were second primary tumours (the second and higher primary tumours were supplied incompletely to the ACCIS database). A full account of the data collection, content of the ACCIS database and methods of its exploration is given elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

For each case, the information available included basic demographic data (age, sex, country or region of residence), information on the tumour (date of incidence, site, morphology and basis of diagnosis) and on follow-up (date of last contact and vital status). Details of registration practices and data coding were provided by each registry. The population-at-risk for each registration area was supplied from official national statistics, for each sex, calendar year and age unit. Any missing population figures for combinations of calendar year, sex and age were estimated by linear interpolation of available data.

The registries were grouped into five geographical regions (British Isles, East, North, South and West). The attribution of the registries to different regions is shown in Table 1 and it was based on geographical location, combined with data availability. Because of huge differences in incidence rates of thyroid carcinoma between Belarus and the rest of Europe, the data from Belarus were excluded from the European total and presented separately. Geographical patterns of occurrence and survival were described for the period 1988–1997, which was covered by all participating registries. For the time trends analyses, the available time-span was divided into four periods of 5 years: 1978–1982, 1983–1987, 1988–1992 and 1993–1997. The registries contributing to the analyses of time trends were those contributing to at least three periods, as shown in Table 1. Table 2 shows the distribution of cases and acceptable values of the selected data quality indicators for the data-sets used in the analyses of time trends.

In this paper, the thyroid cancer is defined as in the subgroup XIb of the International Classification of Childhood Cancer (ICCC).[14] In the process of database consolidation, all tumours localised in the thyroid gland were verified in collaboration with the registries, if their original code was contained in the range M-8000 to M-8004 of the International Classification of Diseases for Oncology, second edition.[15] If applicable, such cases have received consequently more specific codes. This re-coding contributed to validity of

Table 1 – Data-sets contributed by the European cancer registries to the analyses of thyroid cancer incidence and survival in children and adolescents (age 0–19 years) in Europe, 1978–1997 (Source: ACCIS)

Region	Registry	Coverage		Registrations				Basis of diagnosis			Follow-up				Notes
		Period	Time-trend	*n*	(age 0–14 years)	M/F	NOS %	MV %	DCO %	Unknown %	*n*	Closing date	5 + years %	Median Years	
British Isles	IRELAND, National	1994–1997		5	(0)	0.3	0	100	0	0	5	31.12.1998	0	2.6	
	UNITED KINGDOM, England & Wales	1978–1995	+	94	(94)	0.5	1	95	0	5	94	31.1.2001	100	14.4	P
	UNITED KINGDOM, Northern Ireland	1993–1996		4	(2)	0.0	0	100	0	0	4	31.12.1999	25	1.9	
	UNITED KINGDOM, Scotland	1978–1997	+	49	(12)	0.3	4	98	0	0	49	31.12.1999	78	11.7	
East	BELARUS, National	1989–1997		557	(557)	0.6	21	100	0	0	557	1.9.2000	74	6.6	P
	ESTONIA, National	1978–1997	+	9	(1)	0.3	0	100	0	0	9	31.12.1998	67	7.2	
	HUNGARY, National	1978–1997	+	14	(14)	0.6	0	100	–	0	14	1.1.2000	77	9.2	P
	SLOVAKIA, National	1978–1997	+	61	(24)	0.5	2	98	2	0	60	31.12.1997	62	6.4	
	GERMANY, NCR (only former East)	1978–1989	+	149	(53)	0.4	4	100	0	0	124	31.12.1987	72	6.9	S
North	DENMARK, National	1978–1997	+	56	(20)	0.5	0	98	0	0	56	31.12.1997	82	12.3	
	FINLAND, National	1978–1997	+	127	(30)	0.2	10	100	0	0	127	31.12.1998	75	10.1	
	ICELAND, National	1978–1997	+	5	(1)	0.0	0	100	0	0	5	31.12.2000	80	7.8	
	NORWAY, National	1978–1997	+	71	(19)	0.2	1	100	0	0	71	1.1.2000	83	11.4	
South	ITALY, Piedmont paediatric	1978–1997	+	12	(12)	0.3	0	100	0	0	12	31.12.1999	83	8.0	P o2
	ITALY, Marche	1990–1997		0	(0)	–	–	–	–	–	–	–	–	–	P o3
	ITALY, Ferrara	1991–1995		3	(2)	0.5	0	100	0	0	3	31.12.1998	100	6.1	
	ITALY, Latina	1983–1997	+	4	(1)	0.0	0	100	0	0	4	31.12.1998	75	8.5	
	ITALY, Liguria	1988–1995		2	(1)	1.0	0	100	0	0	2	15.4.2000	100	10.3	
	ITALY, Lombardy	1978–1997	+	14	(5)	0.6	0	100	0	0	14	23.9.1999	71	9.0	
	ITALY, Macerata	1991–1997		1	(0)	0.0	0	100	–	0	1	30.9.2000	0	3.0	o3
	ITALY, Parma	1978–1995	+	8	(3)	0.0	0	88	0	0	8	1.4.1999	75	11.2	
	ITALY, Piedmont general	1988–1997		15	(5)	0.3	7	100	0	0	15	31.5.2001	80	9.0	o2
	ITALY, Ragusa	1983–1997	+	7	(2)	0.8	0	86	0	14	7	30.3.2000	100	10.8	
	ITALY, Sassari	1992–1995		5	(0)	0.0	0	100	0	0	5	30.12.1999	60	5.3	
	ITALY, Tuscany	1988–1997		13	(4)	1.2	0	100	0	0	13	31.12.1998	77	6.4	
	ITALY, Umbria	1994–1996		4	(0)	0.0	0	100	0	0	4	31.12.1999	75	5.2	
	ITALY, Veneto	1990–1996		14	(1)	0.4	0	100	0	0	14	31.12.1998	64	5.9	
	MALTA, National	1991–1997		1	(0)	–	0	100	0	0	1	31.12.1999	0	3.2	
	SLOVENIA, National	1978–1997	+	30	(11)	0.4	3	100	0	0	30	31.12.1999	67	9.7	

	SPAIN, National	1990–1995		11	(11)	1.2	9	100	0	0	11	31.12.2000	91	6.1	P Z o4
	SPAIN, Albacete	1991–1997		1	(1)	0.0	0	100	0	0	1	15.9.2000	100	7.4	
	SPAIN, Asturias	1983–1997	+	12	(4)	0.3	0	100	0	0	12	31.12.1997	67	7.2	
	SPAIN, Basque Country	1988–1994		18	(3)	0.5	0	100	0	0	18	31.12.2000	100	9.6	o4
	SPAIN, Canary Islands	1993–1996		7	(2)	0.4	0	100	0	0	–	–	–	–	
	SPAIN, Girona	1994–1997		1	(1)	0.0	0	100	0	0	1	31.12.1997	0	2.2	o4
	SPAIN, Granada	1988–1997		3	(3)	0.0	0	100	0	0	3	31.12.1999	33	4.5	G
	SPAIN, Mallorca	1988–1995		5	(1)	0.3	0	100	0	0	5	31.12.1998	80	9.9	o4
	SPAIN, Navarra	1978–1996	+	22	(7)	0.4	0	100	0	0	22	31.12.1997	73	8.2	o4
	SPAIN, Tarragona	1983–1997	+	10	(2)	0.1	0	100	0	0	10	31.12.1998	80	10.2	o4
	SPAIN, Zaragoza	1978–1996	+	12	(4)	0.3	0	100	0	0	12	31.12.1996	64	9.9	o4
	TURKEY, Izmir	1993–1996		10	(2)	0.3	0	100	–	0	–	–	–	–	
West	FRANCE, Brittany	1991–1997		2	(2)	1.0	0	100	–	0	2	1.1.2000	0	2.6	P
	FRANCE, Lorraine	1983–1997	+	7	(7)	0.8	0	100	–	0	7	1.1.1999	71	7.5	P
	FRANCE, PACA	1984–1996	+	25	(25)	0.8	8	68	–	0	24	31.3.1998	50	2.9	P
	FRANCE, Rhone Alpes	1988–1997		6	(6)	1.0	33	100	–	0	6	1.6.2000	50	5.3	P o1
	FRANCE, Doubs	1978–1996	+	8	(4)	0.3	0	50	–	0	4	1.6.2001	0	0.0	
	FRANCE, Herault	1988–1997		8	(0)	1.0	0	100	–	0	–	–	–	–	
	FRANCE, Isere	1979–1997	+	16	(3)	0.3	6	100	–	0	–	–	–	–	o1
	FRANCE, Manche	1994–1996		1	(0)	0.0	0	100	–	0	–	–	–	–	S
	FRANCE, Bas-Rhin	1978–1996	+	7	(2)	0.2	0	100	–	0	7	31.12.1997	80	6.4	
	FRANCE, Haut-Rhin	1988–1997		3	(1)	0.0	0	100	–	0	1	31.12.1995	100	6.2	S
	FRANCE, Somme	1983–1996	+	2	(0)	0.0	0	100	–	0	2	15.8.2000	50	4.5	
	FRANCE, Tarn	1983–1997	+	2	(1)	0.0	0	100	–	0	–	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	44	(44)	0.6	7	100	–	0	26	31.12.1998	16	0.5	P
	GERMANY, GCCR (only former West)	1983–1990	+	23	(23)	1.1	17	100	–	0	22	31.12.1998	95	9.0	P
	NETHERLANDS, National	1989–1995		82	(29)	0.5	4	99	–	0	29	31.12.1998	38	4.4	S o5
	NETHERLANDS, Eindhoven	1978–1997	+	8	(4)	0.3	0	100	–	0	8	1.7.1999	50	5.5	o5
	SWITZERLAND, Basel	1983–1997	+	7	(4)	0.2	0	100	–	0	7	30.6.2000	71	7.9	
	SWITZERLAND, Geneva	1978–1997	+	3	(1)	0.0	0	100	0	0	3	31.12.1999	67	7.3	
	SWITZERLAND, Graubunden & Glarus	1989–1997		2	(1)	1.0	0	100	0	0	2	25.5.2000	100	6.3	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	6	(2)	0.5	0	100	0	0	6	1.2.2001	40	2.5	
	SWITZERLAND, Valais	1989–1997		2	(0)	0.0	0	100	0	0	1	1.12.1998	0	4.9	S

Percentages were rounded to the nearest integer. –, not applicable; +, included in time trend analyses; 5+ years, cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; DCO, registrations from death certificate only; G, general cancer registry, which has only contributed data for age-range 0–14 years; GCCR, National German Childhood Cancer Registry (until 1990 covering only West and since 1991 the 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 on children for 1988–1989 were pooled with GCCR and included in West for geographical analyses of the period 1988–1997 (see Steliarova-Foucher, Kaatsch, Lacour and colleagues this issue); NOS, cases with unspecified histology, comprising the following morphology codes of the ICD-O-215: 8010, 8070, 8140, 8211 and 8230; o1–o5, overlapping registration areas: for overlapping years, data from the registry with larger coverage were included in each analysis, according to availability (see text); P, paediatric cancer registry: age range for all registrations is 0–14 years; PACA, Provence, Alpes, Côte d'Azur; S, survival analyses were possible only for a restricted data-set (see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue); Unknown, registrations with unknown basis of diagnosis; Z, covers only selected areas (see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue).

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

Region	Period	Children (age 0–14 years), combined data-set								Adolescents (age 15–19 years), general cancer registries							
		Cases	M/F	NOS	Basis of diagnosis			Follow-up		Cases	M/F	NOS	Basis of diagnosis			Follow-up	
		n		%	MV %	DCO %	Unknown %	1 + days %	5 + years %	*n*		%	MV %	DCO %	Unknown %	1 + days %	5 + years %
Europe[a]	1978–1982	72	0.5	4	97	0	1	99	99	115	0.3	6	98	<1	0	98	99
	1983–1987	127	0.4	4	98	0	<1	99	85	132	0.3	3	98	0	0	100	84
	1988–1992	119	0.5	4	96	0	2	96	87	100	0.3	1	97	0	0	99	95
	1993–1997	121	0.6	4	96	0	<1	86	25	119	0.2	3	99	0	<1	100	20
British Isles	1978–1982	27	0.4	4	96	0	4	100	100	9	0.1	11	100	0	0	100	100
	1983–1987	35	0.5	0	97	0	3	100	100	12	0.7	8	92	0	0	100	100
	1988–1992	26	0.6	0	92	0	8	100	100	5	0.3	0	100	0	0	100	100
	1993–1997	18	0.6	0	94	0	6	100	78	11	0.2	0	100	0	0	100	45
East	1978–1982	4	3.0	0	100	0	0	100	100	6	0.5	17	83	17	0	83	100
	1983–1987	10	0.7	0	100	0	0	100	100	6	0.0	0	100	0	0	100	100
	1988–1992	12	0.5	0	100	0	0	100	100	13	0.3	0	100	0	0	100	100
	1993–1997	13	0.4	0	100	0	0	100	25	20	0.4	0	100	0	0	100	5
North	1978–1982	10	0.4	0	100	0	0	100	100	46	0.4	7	100	0	0	100	100
	1983–1987	26	0.4	0	100	0	0	100	100	44	0.2	5	98	0	0	100	100
	1988–1992	13	0.3	8	100	0	0	100	100	48	0.2	2	100	0	0	100	96
	1993–1997	21	0.3	14	100	0	0	100	33	51	0.2	8	100	0	0	100	22
South	1978–1982	5	0.7	0	100	0	0	100	100	13	0.0	0	92	0	0	100	100
	1983–1987	8	0.6	0	100	0	0	100	100	17	0.4	0	100	0	0	100	100
	1988–1992	21	0.4	0	100	0	0	100	100	25	0.5	0	100	0	0	100	100
	1993–1997	17	0.5	6	100	0	0	100	18	25	0.1	0	96	0	4	100	16
West	1978–1982	2	1.0	0	50	0	0	0	0	4	0.0	0	100	0	0	100	50
	1983–1987	24	0.5	17	96	0	0	96	87	13	0.3	8	100	0	0	100	71
	1988–1992	42	0.7	10	93	0	0	90	64	9	0.1	0	67	0	0	88	57
	1993–1997	52	0.8	2	92	0	0	67	6	12	0.2	0	100	0	0	100	20

Percentages were rounded to the nearest integer. 1 + days, cases followed-up for 1 or more days, as a percentage of all cases in the registries with follow-up ; 5 + years, cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; DCO, cases registered from death certificate only; MV, microscopically verified diagnosis; *n*, number of cases; NOS, cases with unspecified histology, comprising the following morphology codes of the ICD-O-215: 8010, 8070, 8140, 8211 and 8230.

a Europe includes the data of the former German Democratic Republic, which were not included in any of the regions.

Table 3 – Definition of histological groups of thyroid carcinomas and their numerical representation in this study (Source: ACCIS)

Histology group[16]	*n*	ICD-O-2 histology code[15]		*n*
Papillary carcinoma	1261	8050	Papillary carcinoma, NOS	772
		8260	Papillary adenocarcinoma, NOS	335
		8340	Papillary carcinoma, follicular variant	150
		8350	Nonencapsulated sclerosing carcinoma	4
Follicular carcinoma	224	8290	Oxyphilic adenocarcinoma	9
		8330	Follicular adenocarcinoma, NOS	199
		8331	- - well differentiated	12
		8332	- - trabecular	4
Medullary carcinoma	139	8510	Medullary carcinoma, NOS	132
		8511	- - with amyloid stroma	7
Anaplastic (undifferentiated) carcinoma	6	8020	Carcinoma, undifferentiated, NOS	2
		8021	Carcinoma, anaplastic, NOS	4
Other and unspecified carcinomas	60	8010	Carcinoma, NOS	16
		8070	Squamous cell carcinoma, NOS	2
		8140	Adenocarcinoma, NOS	42
Total	1690			1690

n = number of cases in children and adolescents (age 0–19 years) within the complete database composed of the data-sets listed in Table 1 and excluding overlapping area-years.

comparisons according to histology type. Five histological groups were considered,[16] as shown in Table 3. The large majority of the thyroid cancers were papillary (75%), the remainder was composed of follicular (13%), medullary (8%), 'other' carcinomas (3.6%) and of anaplastic type (0.4%).

The records contained in the ACCIS database come from both paediatric and general cancer registries. The paediatric cancer registries only registered cases of cancer occurring in children aged 0–14 years, while the general cancer registries recorded cancer cases occurring in all ages, including children

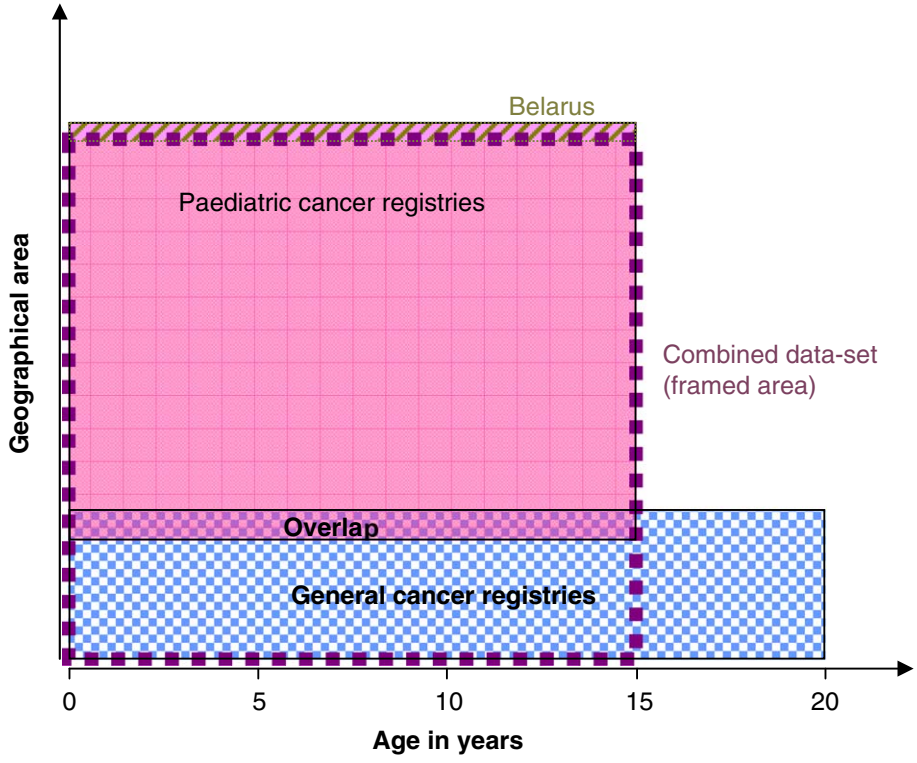

Fig. 1 – Graphical representation of data-sets used for analyses. The areas are proportional to the person-years contributed by the registries for the total study period. Some areas are covered by both the general and paediatric registries (Overlap). Contribution from various sources varied with time (Table 1, not illustrated). Source: ACCIS.

(age 0–14 years) and adolescents (age 15–19 years). As can be seen in Table 1, a small proportion of the available childhood population was covered by both a paediatric and a general cancer registry. Fig. 1 illustrates the way the childhood and adolescent population was covered in this study. Paediatric cancer registries were the only source of information on childhood cancer in the whole of Germany, Hungary, England and Wales and some large regions of France, Italy and Spain. They are represented by the pink rectangle in Fig. 1, which also includes the paediatric cancer registry of Belarus, treated separately in this paper. Data from all paediatric cancer registries except Belarus, together with the data from general cancer registries for the age-range 0–14 years were included in the 'combined' data-set, represented by the area of the rectan-

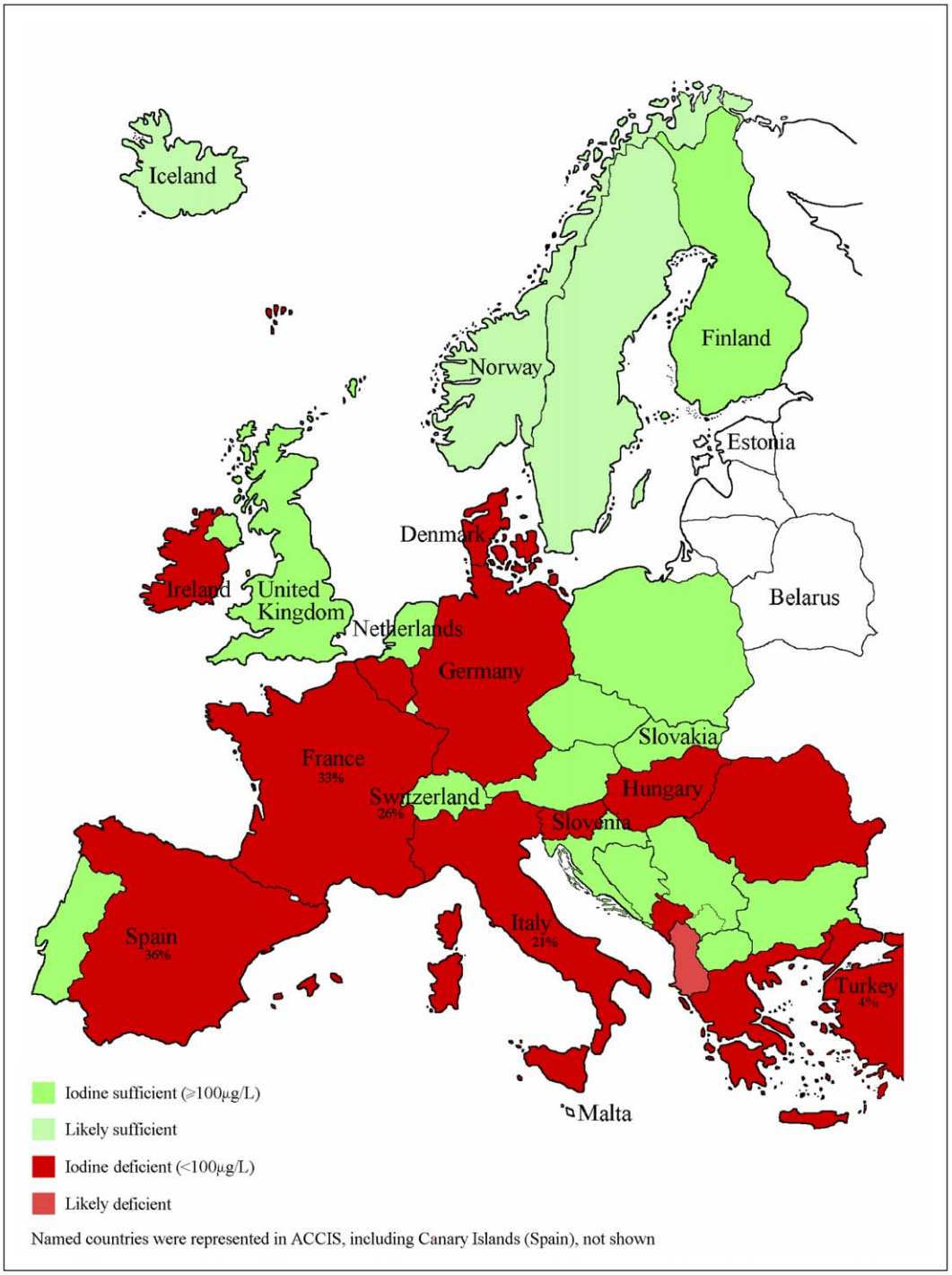

Fig. 2 – Iodine status in some European countries, based on urinary iodine excretion (μg/l) as estimated by the West and Central European Region of the International Council for Control of Iodine Deficiency Disorders.[17] Iodine status in Cyprus (not shown) was categorised as 'sufficient'. Data for Belarus, Estonia and Malta (included in ACCIS) were not available. The percentages show the population coverage within ACCIS, if less than 100%. Source: ACCIS.

gle delimited by the dotted violet line in Fig. 1. For the populations covered both by paediatric and general cancer registries, (the 'Overlap' in Fig. 1), only the paediatric registries were included in the 'combined' data-set. The 'combined' data-set overlapped partially with the data-set composed exclusively of general cancer registries, the latter represented by the blue chequered rectangle in Fig. 1. Data from general cancer registries were used alternatively: (i) as a part of the 'combined data-set' within the age-range 0–14 years, (ii) on their own for the age-range 0–14 years, and (iii) for adolescents aged 15–19 years.

Since the incidence of thyroid carcinoma may be related to the presence of iodine in the environment,[6,8] we also calculated incidence rates for groups of countries classified according to their iodine status. Dietary iodine status was based on measurements of urinary iodine excretion, whereby areas with excretion levels of 100 μg/l or more were classified as 'sufficient' and those with lower levels were 'deficient',[17] as shown in Fig. 2. We have thus classified the majority of the countries included in the ACCIS database, considering the 'likely sufficient' status of Iceland and Norway as 'sufficient'.

2.1. *Statistical methods*

Incidence rates were calculated as the average annual number of cases per million person-years.[18] Age-standardised incidence rate (ASR) for the age-range 0–14 years reported throughout this paper are equivalent to truncated standardised rate for age-range 0–14 years and were calculated as the average of the age-specific incidence rates weighted by the World standard population,[19] specific for 5-year age-groups. The weights were 12, 10 and 9 at ages 0–4, 5–9 and 10–14 years, respectively. Cumulative incidence rates were calculated as the sum of age-specific incidence rates for the age-groups 0–4, 5–9, 10–14 years (and 15–19), each multiplied by 5, the number of years within each age-group. Differences in incidence rates for geographical areas were evaluated using Poisson regression models, adjusted for sex and age group (as appropriate) and expressed as incidence rate ratios (IRR) and their 95% confidence intervals (CI). Change of incidence rates over time was evaluated from Poisson regression model, adjusted for region, sex and age group (as appropriate) and expressed as average annual percent change (AAPC). The *P*-values indicate the probability of observing the estimated rate of change by chance.

The actuarial life-table method was used for survival analyses.[20] The duration of survival was calculated for each patient as the time elapsed between the date of diagnosis and the earlier of the two dates: date of death or closing date of the study for the given cancer registry (Table 1). Cases with zero survival time were excluded from the analysis of survival (most of them were the cases registered from death certificate only, DCO). The 5-year observed survival is the actuarial cumulative probability of surviving to the fifth anniversary of the date of incidence. The 95% CIs of the cumulative survival were calculated according to Kalbfleisch and Prentice.[21] Differences in survival of two or more groups of patients were compared for the entire survivorship curves using the log-rank χ^2 test.[20] The *P*-values indicate the probability of observed differences in survival during the entire follow-up period being due to chance. A log-rank test for trend was used to tests a monotonic change in survival for the cohorts of cases diagnosed in the successive time periods, 1978–1982, 1983–1987, 1988–1992, 1993–1997.[22]

Most of the statistical analyses were conducted using STATA© software.[23]

3. Results

3.1. *Incidence*

Incidence rates of thyroid cancer in children (age 0–14 years) were examined in several data-sets, because of the considerable variation according to the selection of the population at risk (Fig. 3), despite similar distribution of person-years over calendar years and age groups in the compared data-sets. During the period 1988–1997, incidence rate in the general cancer registries was up to double of that estimated from the combined data-set (comprising paediatric and general cancer registries), depending on sex, region and age group (Table 4). The difference was especially remarkable in the West, whereas ASRs differed very little between the two data-sets for the British Isles. The incidence rates from the combined data-set were necessarily identical to those from general cancer registries for the North, since all the data for this region were provided by general cancer registries.

Overall, the ASR for children was 1.2 per million in the general cancer registries, while it was 0.7 per million in the combined data-set (Table 4). Depending on sex and region, the

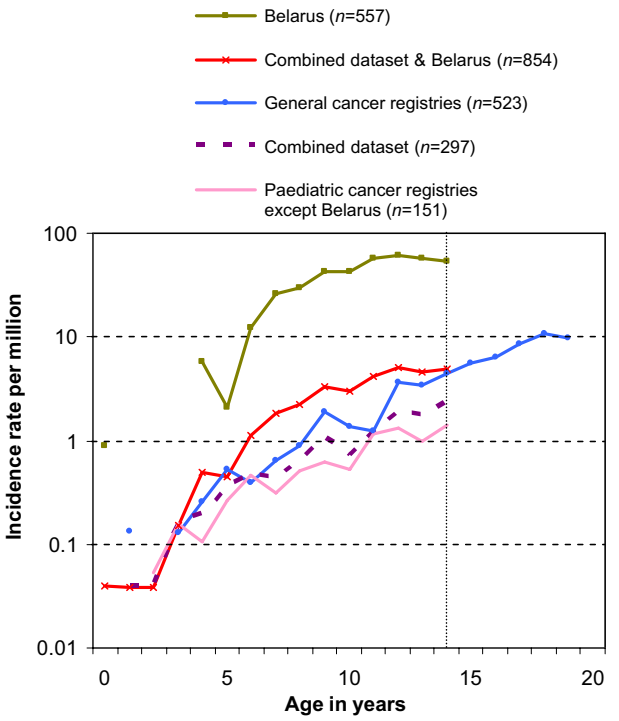

Fig. 3 – Age-specific incidence rates of thyroid cancer observed in Europe in 1988–1997 in various data-sets; both sexes combined. *n*, number of cases included in analysis. In general cancer registries there were 155 incident cases of thyroid cancer in children aged 0–14 years. Source: ACCIS.

Table 4 – Numbers of cases (n) and incidence rates of thyroid cancer per million person-years in children (age 0–14 years) and adolescents (age 15–19 years) registered in Europe (excluding Belarus), 1988–1997 (Source: ACCIS)

	Combined data-set					General cancer registries					
	Rate by age group			Age 0–14 years		Age 0–14 years		Age 15–19 years		Age 0–19 years	
	0–4	5–9	10–14 years	*n*	ASR	*n*	ASR	*n*	Rate	*n*	Cum
Both sexes											
EUROPE	0.1	0.6	1.6	297	0.7	155	1.2	368	8.3	523	60.5
British Isles	0.1	0.4	1.1	46	0.5	9	0.5	23	4.4	32	31.0
East	0.2	0.7	1.1	25	0.6	17	0.9	33	6.0	50	45.1
North	0.1	0.6	3.1	34	1.1	34	1.1	99	10.1	133	69.1
South	0.0	0.6	3.5	60	1.2	51	1.5	127	11.0	178	81.0
West	0.1	0.7	1.3	132	0.7	44	1.2	86	7.0	130	54.5
Boys											
EUROPE	0.1	0.6	1.0	110	0.5	50	0.7	84	3.7	134	30.6
British Isles	0.1	0.4	0.6	17	0.3	2	0.2	4	1.5	6	11.4
East	0.0	0.5	0.7	8	0.4	5	0.5	9	3.2	14	24.6
North	0.2	0.2	1.3	8	0.5	8	0.5	18	3.6	26	26.5
South	0.0	0.5	2.4	22	0.9	19	1.1	29	4.9	48	43.5
West	0.1	0.7	1.0	55	0.5	16	0.9	24	3.8	40	33.0
Girls											
EUROPE	0.1	0.7	2.2	187	0.9	105	1.6	284	13.1	389	91.9
British Isles	0.1	0.3	1.7	29	0.6	7	0.9	19	7.4	26	51.6
East	0.4	0.9	1.6	17	0.9	12	1.4	24	8.8	36	66.4
North	0.0	0.9	4.9	26	1.7	26	1.7	81	16.9	107	113.7
South	0.0	0.6	4.6	38	1.5	32	2.0	98	17.4	130	120.4
West	0.1	0.8	1.7	77	0.8	28	1.6	62	10.3	90	76.9

ASR, age-standardised rate (World standard) per million; Cum, cumulative rate per million.

ASR for children varied between 0.3 and 2.0 per million. For all paediatric registries (excluding Belarus), the ASR of thyroid carcinoma for the period 1988–1997 was 0.5 per million (based on 151 cases). Of all tumours, thyroid carcinomas represented between 0.6% (in the combined data-set) and 0.9% (in general cancer registries) in children and 4.4% in adolescents. These percentages refer to the respective total numbers of cases: 53,160 in the combined data-set [Stiller, Marcos-Gragera, Ardanaz and colleagues, this issue]; 17,640 in children of general cancer registries [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]; and 8272 in adolescents [Stiller, Desandes, Danon and colleagues, this issue].

Despite the differences in the incidence rates between the two overlapping data-sets, the ranking of the regions was similar in the two data-sets in children and adolescents (Table 4). The regions with low incidence were the British Isles and the East (excluding Belarus), while the incidence in the other three regions was elevated (compared with the reference British Isles), with the highest rates in the South, closely followed by the North (Table 5).

In adolescents (age 15–19 years) incidence rates were much higher than in children (Table 4). The steep increase in incidence with age was especially pronounced in girls (Fig. 4), so that, while before the age 15 there were 2 girls diagnosed for each boy, in the adolescents, this ratio increased to 3.5. By the age of 20 years, the cumulative incidence of thyroid cancer in girls was about triple that in boys (Table 4).

By far the most common histological type was papillary carcinoma, comprising almost 65% of cases in children and about 77% in adolescents (Table 6). Medullary carcinoma represented about 22% of cases in children and 9% in adolescents. The persistent differences in incidence rates for children between the two data-sets (the combined versus general cancer registries) did not affect the histology- and sex-specific ranks. For the age-range 0–19 years, papillary car-

Table 5 – Numbers of cases (n) included in the analysis of geographical differences of incidence of thyroid carcinoma in children and adolescents in Europe (excluding Belarus), 1988–1997 (Source: ACCIS)

Region	*n*	IRR	(95% CI)
Children (age 0–14 years), combined data-set			
British Isles	46	1	
East	25	1.3	(0.8–2.1)
North	34	2.5	(1.6–3.9)
South	60	2.9	(1.9–4.2)
West	132	1.4	(1.0–2.0)
Children and adolescents (age 0–19 years), general cancer registries			
British Isles	32	1	
East	50	1.4	(0.9–2.2)
North	133	2.2	(1.5–3.3)
South	178	2.6	(1.8–3.8)
West	130	1.7	(1.2–2.5)

IRR, incidence rate ratio and its 95% confidence interval, estimated from Poisson regression model adjusted for sex and age group, with the British Isles as the reference.

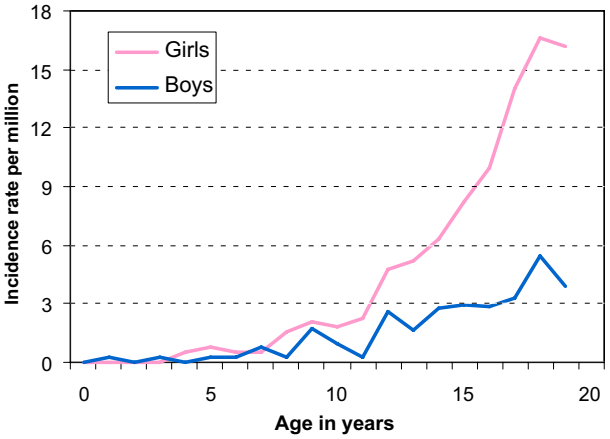

Fig. 4 – Age-specific incidence rates of thyroid cancer observed in Europe in 1988–1997. General cancer registries, *n* = 523. Source: ACCIS.

cinoma was the most common type in boys and girls, while the second most common was follicular type in girls and medullary type in boys. Whereas papillary and follicular types were much more frequent in girls than in boys, the incidence of medullary and other types was comparable between the two sexes (Table 6). There were only two cases of anaplastic carcinoma reported in children and none in adolescents during 1988–1997. Incidence of all tumour types was increasing with age with variable gradients (Fig. 5).

The spectrum of histological types of thyroid carcinomas differed somewhat between the five European regions (Fig. 6), with a higher proportion of papillary carcinomas in the South and North, the regions with the highest overall incidence. In a Poisson regression model adjusted for sex and age group, with the British Isles as the reference region, the incidence rate ratio (IRR) for papillary carcinoma for the South was 3.7 (95% CI 2.3–6.0) in the age range 0–14 years of the combined data-set and 3.0 (95% CI 1.9–4.7) in the age-range 0–19 years in the data-set constituted of the general cancer registries. The respective figures for the North were IRR = 3.1, 95% CI 1.8–5.4, and IRR = 2.6, 95% CI 1.6–4.2. A slightly elevated rate of papillary carcinoma was also observed in the West for age-range 0–19 years in the general cancer registries (IRR = 1.6, 95% CI 1.0–2.5, $P = 0.07$). In the North an increased rate ratio (IRR = 3.2, 95% CI 0.9–11.3, $P = 0.07$) was observed for the group of other and unspecified carcinomas in the combined data-set for children. No other significant region-specific IRRs were seen for any other histology group.

Extremely high incidence rates were observed in the paediatric cancer registry of Belarus (ASR = 24 per million, Table 7). The incidence rates were strikingly higher in all ages, compared with the rest of data (Fig. 3), with the cumulative rate attaining almost 400 per million children by the age of 15 years (Table 7). Most tumours were papillary (87%), 9% were follicular, 3% were classified as 'other and unspecified' and only 1 case was of medullary type. Of note is the peak in incidence of papillary carcinoma at age 12 and 13 years in boys and girls, respectively in Belarus, in contrast to the other European data (compare Figs. 5 and 7).

Table 8 shows that there was no difference in incidence of thyroid cancer between two groups of countries, classified according to dietary iodine status.[17] For the age-range 0–19 years (based on data from general cancer registries) the incidence rate of papillary carcinoma was slightly higher in the iodine-deficient than in the iodine-sufficient countries (IRR = 1.2, 95% CI 1.0–1.5, $P = 0.08$).

The incidence time trends for the period 1978–1997 were examined using two data-sets (combined and general registries), since there were differences in the incidence between

Table 6 – Numbers of cases (n) and incidence rates of different histological types of thyroid carcinoma per million person-years in children (age 0–14 years) and adolescents (age 15–19 years) in Europe (excluding Belarus), 1988–1997 (Source: ACCIS)

	Combined data-set					General cancer registries					
	Rate by age group			Age 0–14 years		Age 0–14 years		Age 15–19 years		Age 0–19 years	
	0–4 years	5–9 years	10–14 years	*n*	ASR	*n*	ASR	*n*	Rate	*n*	Cum
Both sexes											
Papillary	0.02	0.33	1.13	191	0.44	99	0.72	283	6.4	382	44.0
Follicular	0.02	0.03	0.16	27	0.06	13	0.10	46	1.0	59	6.8
Medullary	0.05	0.20	0.24	62	0.15	36	0.28	32	0.7	68	8.1
All other	0.00	0.05	0.07	15	0.04	7	0.05	7	0.2	14	1.7
Boys											
Papillary	0.03	0.31	0.71	68	0.31	27	0.39	59	2.6	86	19.5
Follicular	0.00	0.03	0.05	5	0.02	1	0.01	9	0.4	10	2.2
Medullary	0.10	0.18	0.21	30	0.14	18	0.28	14	0.6	32	7.5
All other	0.00	0.03	0.06	6	0.03	4	0.06	2	0.1	6	1.4
Girls											
Papillary	0.05	0.35	1.58	123	0.59	72	1.07	224	10.3	296	69.6
Follicular	0.05	0.03	0.29	22	0.11	12	0.18	37	1.7	49	11.5
Medullary	0.05	0.21	0.27	32	0.16	18	0.29	18	0.8	36	8.8
All other	0.00	0.06	0.08	9	0.04	3	0.05	5	0.2	8	1.9

ASR, age-standardised rate (World standard) per million; Cum, cumulative rate per million.

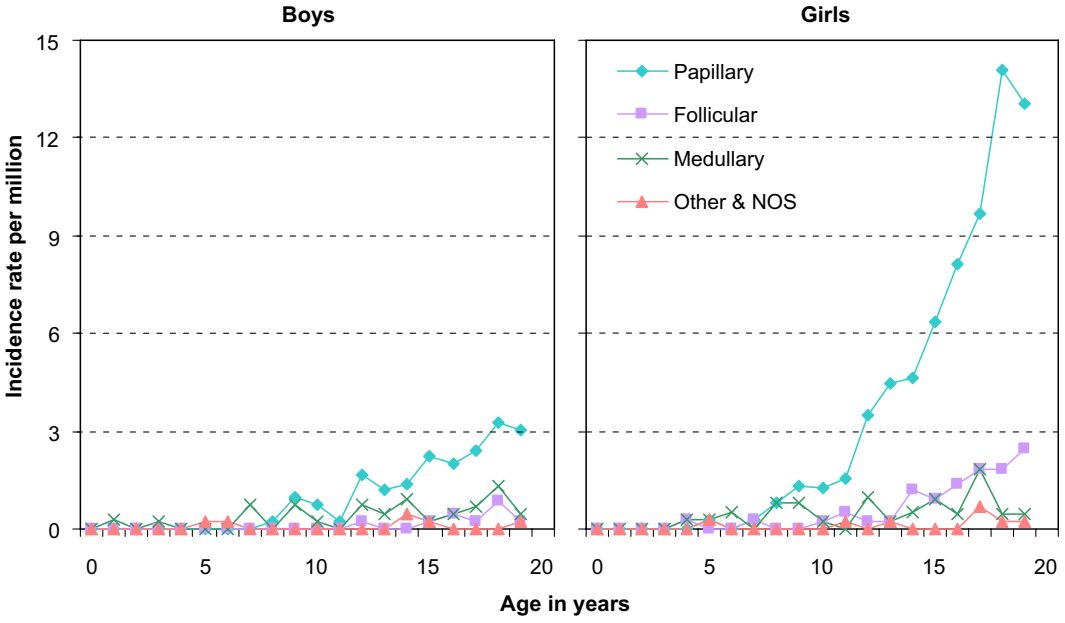

Fig. 5 – Age-specific incidence rates of different histological types of thyroid cancer observed in Europe in 1988–1997 in general cancer registries (n = 523). Source: ACCIS.

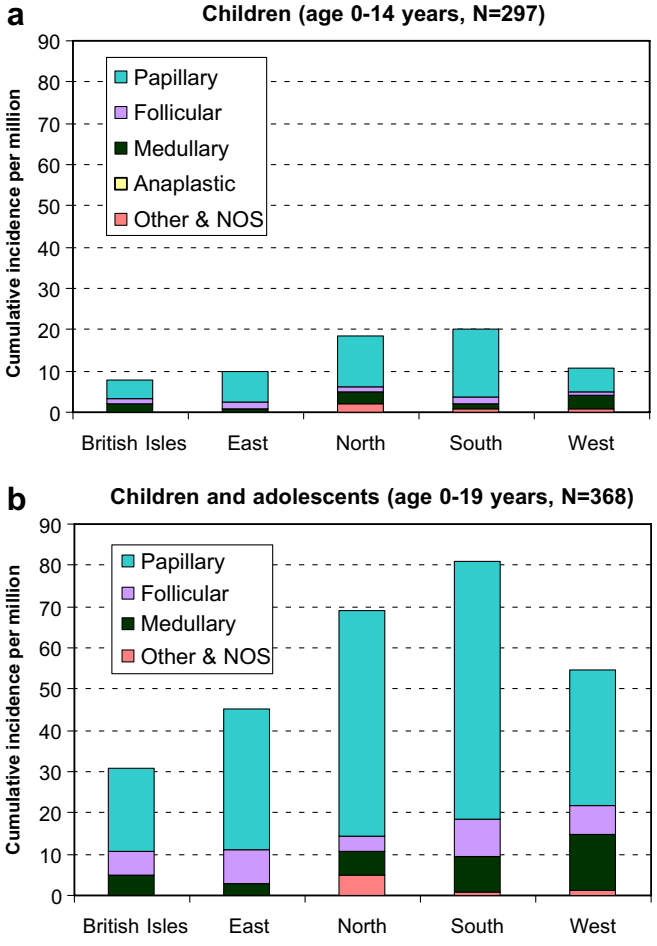

Fig. 6 – Cumulative incidence rates of different histological types of thyroid carcinomas in children and adolescents of Europe (excluding Belarus) for 1988–1997, both sexes combined. (a) Children aged 0–14 years, combined data-set; (b) children and adolescents aged 0–19 years, general cancer registries. Source: ACCIS.

Table 7 – Numbers of cases (n) and incidence rates of thyroid cancer per million person-years in children (age 0–14 years) registered in Belarus, 1988–1997 (Source: ACCIS)

	n	Rate by age group			Age 0–14 years	
		0–4 years	5–9 years	10–14 years	ASR	Cum
Both sexes	557	1.4	22.7	54.3	23.6	391.8
Boys	217	0.3	17.2	42.6	18.0	300.3
Girls	340	2.6	102.0	230.0	29.4	486.1
Histology type						
Papillary	487	0.6	19.0	48.9	20.6	342.4
Follicular	51	0.6	2.5	4.1	2.2	36.0
Medullary	1	0.0	0.1	0.0	0.04	0.7
All other	18	0.2	1.1	1.3	0.8	12.6

ASR, age-standardised rate (World standard) per million; Cum, cumulative rate per million.

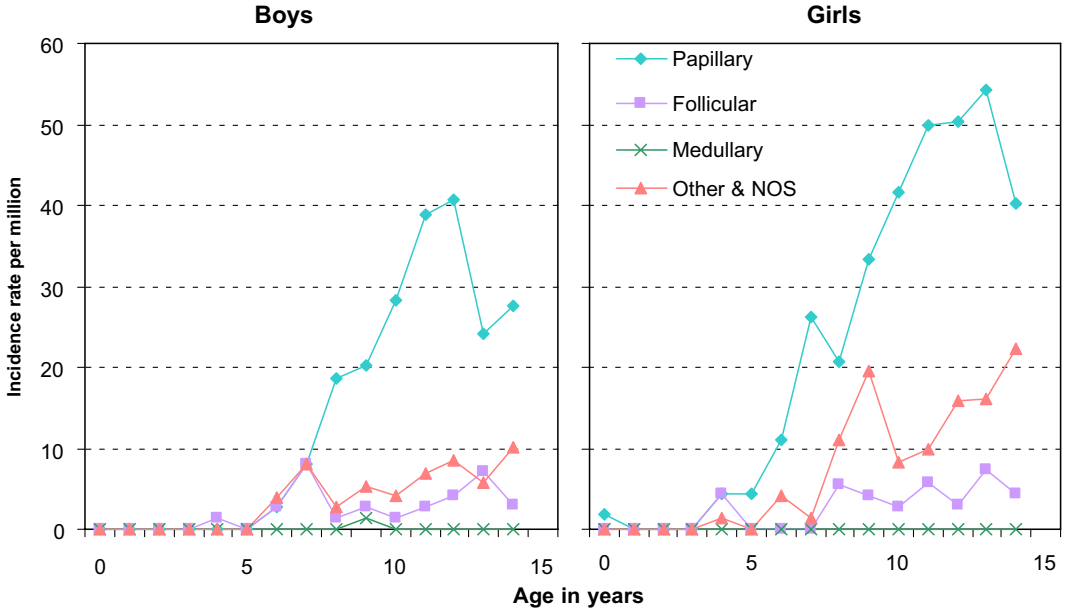

Fig. 7 – Age-specific incidence rates of different histological types of thyroid cancer observed in the national paediatric registry of Belarus in 1988–1997 (*n* = 557). Source: ACCIS.

these two partially overlapping data-sets over the whole study period (Fig. 8). Notwithstanding, the incidence rates were shown to increase in Europe over the period 1978–1997 by about 3% per year in children and adolescents in both data-sets (Table 9). A general tendency of an increase across the time periods can be observed for the majority of population groups in Table 10. Fig. 9 illustrates the differences in the incidence time trends of papillary carcinoma in girls compared with boys, in children aged 10–14 years compared with adolescents and in the two data-sets.

3.2. *Survival*

The 5-year survival of patients diagnosed with thyroid carcinoma in 1988–1997 was 98% in children and 99% in adolescents (Table 11). No significant differences in survival were observed between boys and girls or between the regions. The 5-year survival was lowest in the age group 1–4 years: 76%, based on 10 cases. Children with papillary carcinoma had significantly better survival than those with medullary carcinoma ($P = 0.04$), although the difference in 5-year survival was not large (Table 12). No differences in survival were observed for other groups of patients according to the histological type of the tumour. One of the two patients with the anaplastic type died before 5 years of follow-up.

Larger data-sets were available for analyses of time trends in survival of the patients diagnosed during the period 1978–1997 (Table 11). There was no temporal change in survival for any patient group or tumour type (Table 12), as documented by the *P*-values linked to the log-rank test for trend. Somewhat increased risk of dying was observed after the 5 follow-up years, although on average, over 93% of children or adolescents with thyroid cancer survived 10, 15 or 20 years after diagnosis.

Table 8 – Numbers of cases (n) included in analysis and cumulative incidence rate (Cum) of thyroid carcinoma per million person-years in children and adolescents in Europe (1988–1997) according to the urinary iodine excretion status[17] (Source: ACCIS)

	n	Cum	IRR	(95% CI)
Children (age 0–14 years), combined data-set[a]				
Thyroid carcinoma				
All 16 countries[b,c]	296	11.7		
Sufficient[b] (>100 μg/l)	124	13.2	1	
Deficient[c] (<100 μg/l)	172	10.7	0.8	(0.6–1.0)
Papillary				
All 16 countries[b,c]	190	7.5		
Sufficient[b] (>100 μg/l)	68	7.3	1	
Deficient[c] (<100 μg/l)	122	7.6	1.0	(0.8–1.4)
Follicular				
All 16 countries[b,c]	27	1.1		
Sufficient[b] (>100 μg/l)	12	1.3	1	
Deficient[c] (<100 μg/l)	15	0.9	0.7	(0.3–1.6)
Children and adolescents (age 0–19 years), general cancer registries[a]				
Thyroid carcinoma				
All 14 countries[b,d]	517	61.7		
Sufficient[b] (>100 μg/l)	279	60.4	1	
Deficient[d] (<100 μg/l)	238	62.9	1.1	(0.9–1.3)
Papillary				
All 14 countries[b,d]	378	44.9		
Sufficient[b] (>100 μg/l)	191	41.2	1	
Deficient[d] (<100 μg/l)	187	49.4	1.2	(1.0–1.5)
Follicular				
All 14 countries[b,d]	57	6.7		
Sufficient[b] (>100 μg/l)	29	6.3	1	
Deficient[d] (<100 μg/l)	28	7.3	1.2	(0.7–2.0)

IRR, incidence risk ratio derived from a Poisson regression model adjusted for sex and age-group, with the 'sufficient' as the reference.
a Excludes Estonia and Malta, for which the iodine status was not specified.
b Comprises Finland, Iceland, Netherlands, Norway, Slovakia, Switzerland and United Kingdom.
c Comprises Denmark, France, Germany, Hungary, Ireland, Italy, Slovenia, Spain and Turkey.
d Comprises Denmark, France, Ireland, Italy, Slovenia, Spain and Turkey.

4. Discussion

We described the pattern of occurrence of thyroid cancer in Europe over the period 1978–1997, using the largest ever-assembled database on childhood and adolescent cancer. Overall, this study confirms female predominance in thyroid cancer occurrence in children and adolescents, its increasing frequency with age, high proportion of papillary tumour type, growing incidence over time and low fatality from this cancer. In our crude analysis a relationship between dietary iodine status and risk of thyroid carcinoma in the young population was not confirmed.

Based on data collected by the national paediatric cancer registry of Belarus since 1989 (3 years after the Chernobyl accident), we observed about a 20-fold higher incidence, compared with the rest of Europe. Belarussian data in the ACCIS database comprised fewer papillary tumours (87%) than the 98% reported previously.[24,25] The high proportion of papillary carcinomas, their early onset with the peak at 12–14 years of age and a small proportion of medullary carcinomas are concordant with the theory of the preferential development of papillary carcinomas following irradiation.[5] The high incidence of thyroid cancer in the most contaminated regions, such as Belarus, is the only measurable consequence on cancer rates that can clearly be attributed to date to radiation from the Chernobyl accident.[26] This conclusion is also supported by at least two other findings from the routine descriptive data collected by cancer registries; notably the observations that the increase in incidence rates had already started before the Chernobyl incident,[27–32] as discussed below, and the increase was also apparent in the southern hemisphere among some populations of 0–19-year-olds (females in New South Wales, Australia, males in South Australia[33]), which were not exposed to radioactive fallout from Chernobyl.

For other regions of Europe, we have reported the results based on the 'combined' data-set, because it comprised the maximum of records and may be thus considered as providing the most likely estimate of overall thyroid cancer occurrence in the European childhood population. Since this estimate differed from the one generated by general cancer registries, we also reported data for the latter data-set, to correctly study the evolution of incidence rates over the four age groups in populations of identical geographical areas.

In the age-range 0–14 years occurrence reported by some childhood cancer registries was less than a half that reported from general cancer registries. The lower incidence rates in some paediatric cancer registries may be due to lack of access to certain data sources, which are available to the general cancer registries (e.g. endocrinology units). For example in France, 63% of children with thyroid cancer were reported from nuclear medicine units, while only 13% from paediatric oncologist.[34] Information on data sources used to register each case was not collected within the ACCIS project. However, some registries do record the (number of) institutions supplying data on each case patient. Collecting these data from all collaborating registries would help to evaluate systematic differences between paediatric and general cancer registries. It should also be remembered that the paediatric and general cancer registries did not cover the same geographical areas; true geographical differences cannot be therefore excluded. The difference in the estimates of the incidence rates from the two data-sets was largest in the West, where the national childhood cancer registry of Germany was the principal source of information in childhood age-range, while Germany was not represented among the general cancer registries for the period 1988–1997. It would imply that the incidence rates in German children are about half of those in the combined data for France, Netherlands and Switzerland (grouped within the West in this study). Indeed, the age-standardised rate for the period 1988–1997 was 0.2 per million in Germany and 0.5 for the combined population of children covered by the four paediatric cancer registries in France. In the age range 0–75 years, shown in the latest volume of Cancer Incidence in Five Continents,[35] the cumulative incidence rates of thyroid carcinomas did not

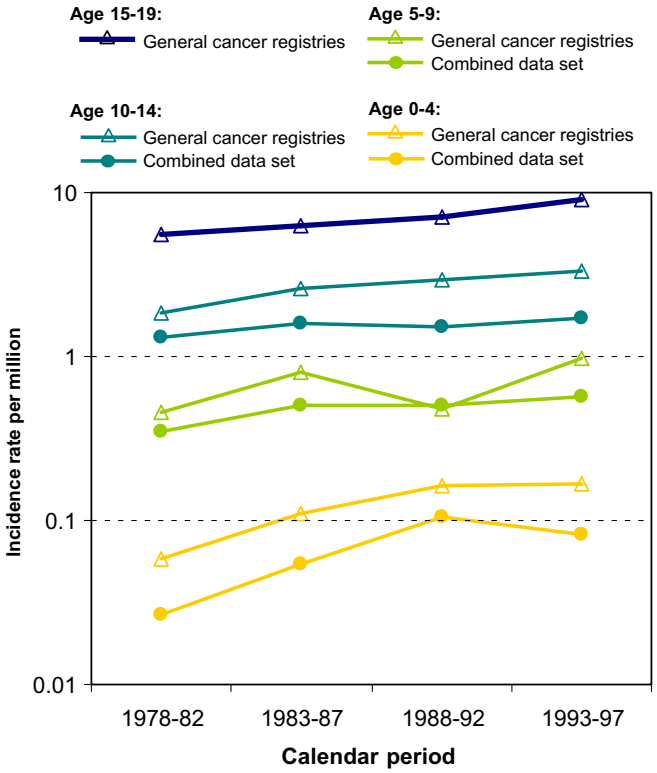

Fig. 8 – Time trends of age-specific incidence rates of thyroid carcinoma in Europe (excluding Belarus), 1978–1997, both sexes. Source: ACCIS.

Table 9 – Numbers of cases (n) included in the analysis of incidence time trends of thyroid carcinoma in Europe, 1978–1997 and the change in rates expressed as average annual percent change (AAPC) (Source: ACCIS)

	n	AAPC	P
Children (age 0–14 years), combined data-set			
Thyroid carcinoma	439	3.0	0.003
Papillary	286	3.4	0.007
Follicular	60	1.0	0.7
Medullary	71	–1.0	0.7
Anaplastic	4	–	–
All other	18	–4.0	0.6
Children and adolescents (age 0–19 years), general cancer registries			
Thyroid carcinoma	681	2.9	<0.0001
Papillary	482	2.6	0.003
Follicular	111	0.5	0.8
Medullary	62	–0.2	0.9
Anaplastic	2	–	–
All other	24	4.9	0.3

AAPC was derived from Poisson regression of rate on calendar year, adjusted for sex, age group and region, with the British Isles as the reference.

seem to differ much between the general cancer registry of Saarland in Germany and those reported by the cancer registries of the other three countries. Obviously, Saarland represents only a small proportion of the German population on the western edge of Germany, while large differences in incidence of thyroid cancer were observed within each of the countries cited above.[35] In the presence of such contradictory arguments, it is difficult to deduce which of the two partially overlapping data-sets presented in this paper for the West region provides a more valid estimate of the incidence rate. There was hardly any difference between the two data-sets (combined compared with general registries) representing the British Isles. Here the largest participant, the paediatric cancer registry of England and Wales, links their records routinely with the general cancer registries covering the same population at risk,[36] so resemblance of estimates from the two data-sets was expected. In spite of the variability of the estimate of the overall incidence rate of thyroid cancer in childhood population of Europe, the ranking of regions, sex, age groups and histological types was relatively consistent irrespective of the data-set used.

The increase in the age-specific incidence of thyroid carcinoma seen in this study is the beginning of the general age pattern. In males the age-specific incidence rate increases throughout the life span up to around 40 per million. In females a much steeper increase is observed, which may stabilise in some populations at around age 50 years and beyond with 70–100 cases per million.[2] The sex difference in the level of incidence rates (most marked in the ages of ample secretion of sex-specific hormones) observed in this and many other reports may imply a specific susceptibility gene with sex hormone receptor in the pathogenesis of thyroid carcinomas.[3]

Table 10 – Numbers of cases (n) included in analysis and incidence rates of thyroid carcinoma per million person-years in children (age 0–14 years) and adolescents (age 15–19 years) in Europe (1978–1997) (Source: ACCIS)

	Combined data-set					General cancer registries								
	n	ASR (age 0–14 years)				*n*	ASR (age 0–14 years)				*n*	Rate (age 15–19 years)			
		1978–82	1983–87	1988–92	1993–97		1978–82	1983–87	1988–92	1993–97		1978–82	1983–87	1988–92	1993–97
EUROPE[a]	439	0.5	0.7	0.6	0.7	215	0.7	1.1	1.1	1.4	466	5.6	6.2	7.0	9.0
Boys	150	0.3	0.4	0.4	0.5	66	0.5	0.6	0.5	0.9	101	2.3	3.1	3.0	3.1
Girls	289	0.7	0.9	0.9	0.9	149	0.9	1.5	1.6	1.9	365	9.0	9.5	11.2	15.1
British Isles	106	0.4	0.6	0.5	0.5	12	0.3	0.5	0.4	0.9	37	4.0	5.5	2.8	7.0
East	39	0.2	0.4	0.6	0.7	25	0.2	0.7	1.1	0.8	45	2.3	2.5	4.8	7.0
North	70	0.5	1.6	0.9	1.4	70	0.5	1.6	0.9	1.4	189	8.3	8.0	9.5	10.7
South	51	0.5	0.6	1.7	1.8	39	0.9	0.7	1.7	2.2	80	7.6	6.5	9.5	10.6
West	120	0.4	0.4	0.6	0.6	21	0.4	0.3	1.3	1.7	38	2.7	5.7	4.3	7.0
Papillary	286	0.3	0.4	0.4	0.5	148	0.5	0.7	0.8	0.9	334	3.6	4.0	5.4	7.4
Follicular	60	0.1	0.1	0.06	0.07	31	0.1	0.2	0.1	0.1	80	1.2	1.5	0.9	0.8
Medullary	71	0.04	0.08	0.1	0.2	27	0.03	0.1	0.2	0.3	35	0.4	0.5	0.6	0.5
Anaplastic	4	0.01	0.01	0.01	0.0	1	0.0	0.02	0.0	0.0	1	0.0	0.05	0.0	0.0
Other & NOS	18	0.03	0.03	0.03	0.03	8	0.04	0.02	0.02	0.1	16	0.3	0.2	0.07	0.3

ASR, age-standardised incidence rates, World standard.

a Includes former GDR, which is not included in any of the regions.

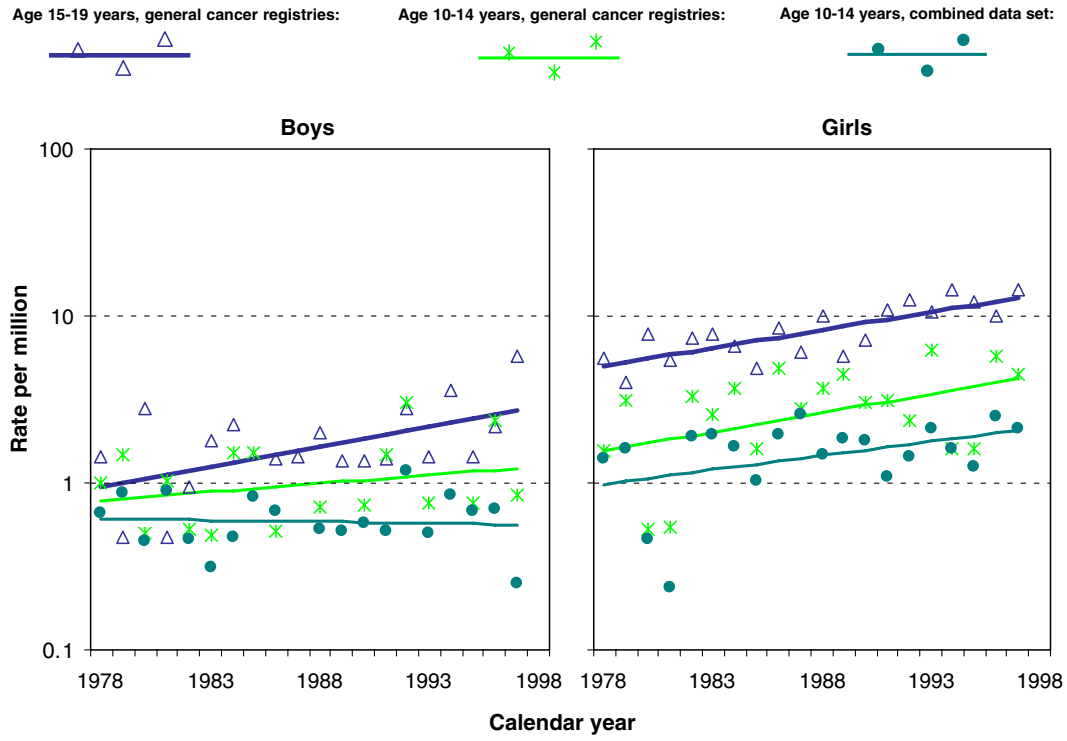

Fig. 9 – Time trends of age-specific incidence rates of papillary thyroid carcinoma in Europe (excluding Belarus), 1978–1997, estimated from two partially overlapping data-sets. The point markers represent the observed age-sex-year-specific observed incidence rate. The trend lines were calculated from linear regression of the logarithm of the age-sex-year-specific incidence rate on calendar year. Source: ACCIS.

Regional differences and temporal trends of occurrence of thyroid carcinoma may be explained, at least partly, by variability between regions and development over time of diagnostic practices and classification rules. In particular, the behaviour of these tumours may be difficult to establish in the continuum of the progression from benign forms (adenomas). Papillary microcarcinomas are remarkably prevalent in thyroid glands examined for other reasons.[3] The detection methods have been changing, from nodule examination by palpation to nodule identification by ultrasound and fine needle aspiration biopsy. This trend results in the microcarcinomas representing an increasing proportion of thyroid cancers and also translates into changes in the staging of papillary microcarcinomas in most recent tumour-node-metastases (TNM) classification.[3] In a Swiss study, the proportion of microcarcinomas or silent carcinomas among papillary type increased insignificantly from 17% in 1970–1979 to 24% in 1990–1998 (based on 436 thyroid cancer cases of all ages),[37] suggesting that improved diagnostic methods may be responsible for some part of the increase in incidence. Registry-based data may be analysed for space-time clustering in order to detect regions with intensive diagnostic activity.[38] However, in childhood and adolescent patients, the notion of microcarcinomas is virtually non-existent,[39] which reduces the role of misdiagnosis of benign tumours as malignant in the geographical and temporal pattern of incidence in this study.

While the different histological types of thyroid carcinoma have been relatively well defined,[3] there was a change in classification recommended by WHO in 1988,[40] whereby tumours with any papillary element were to be classified as papillary tumour type. This recommendation has the potential to produce artificial geographical and temporal differences in the incidence of thyroid tumour types. The Swiss study mentioned earlier found that papillary carcinomas were more commonly classified as follicular at the beginning than the end of the study period. A review and subsequent reclassification of cases have reduced slightly the rate of papillary carcinoma in 1990–1998, but it was still 30% higher than in the period 1970–1980.[37] The change in classification might also have been reflected in the current study, whereby the increase in papillary carcinomas was accompanied by stable rates or even a decrease in incidence of the follicular type. The lack of geographical differences or temporal changes in the incidence of other histological types of thyroid carcinoma may result from small proportions of such cases, which does not allow discovery of small differences, although detection rate were related to diagnostic diligence also for medullary thyroid cancer.[41] Simultaneous evaluation of all histological groups (including unspecified) is therefore important. In this study, the overall rate for all thyroid cancers was increasing irrespectively of possible misclassification between histology groups.

The increasing incidence trends of papillary carcinomas were seen in adolescents of both sexes. Increasing incidence of thyroid cancer among some European populations has been reported previously,[27,28] though the increase among

Table 11 – Numbers of cases (n) included in analyses of survival and 5-year observed survival of children and adolescents diagnosed with thyroid carcinoma in Europe in the periods shown (Source: ACCIS)

	1988–1997			1978–1997					
	n	Survival (%)	(95% CI)	Survival (%)					
				n	1978–1982	1983–1987	1988–1992	1993–1997	*P* (trend)[b]
Children (age 0–14 years), combined data-set									
EUROPE[a]	265	98	(94–99)	407	98	100	96	97	0.08
Boys	99	97	(89–99)	139	100	100	97	97	0.12
Girls	166	98	(94–99)	268	98	100	96	98	0.27
Age group 1–4	10	76	(33–94)	13	100	100	80	100	0.30
Age group 5–9	67	100	–	89	100	100	100	100	–
Age group 10–14	188	98	(94–99)	305	98	100	96	98	0.19
British Isles	46	95	(82–99)	106	96	97	92	100	0.70
East	25	91	(69–98)	39	100	100	92	89	0.33
North	34	100	–	70	100	96	100	100	0.89
South	56	100	–	51	100	100	95	100	0.91
West	104	99	(91–100)	93	–	100	100	96	0.14
Belarus	557	99	(97–99)	–	–	–	–	–	–
Adolescents (age 15–19 years), general cancer registries									
EUROPE[a]	284	99	(97–100)	449	98	98	99	99	0.44
Boys	61	98	(89–100)	99	100	97	100	95	0.35
Girls	223	100	(97–100)	350	98	99	99	100	0.44
British Isles	23	100	–	37	100	92	100	100	0.63
East	33	97	(79–100)	44	100	100	92	100	1.00
North	99	99	(93–100)	189	100	100	100	98	0.20
South	114	100	–	80	100	100	100	100	–
West	15	100	–	23	100	100	100	100	0.29

Only selected registries (Table 1) contributed to analyses of time trends for the period 1978–1997. Survival is not shown for very small groups of patients. Percentages were rounded to the nearest integer. –, not applicable.

a Includes former GDR, which is not included in any of the regions.

b Significance of change over time in survival of patients diagnosed in the four successive periods (log-rank test).

adolescent girls apparently did not continue in the most recently observed birth cohorts.[29] A study in Scotland covering the years 1961–2000[29] suggested that the rapid increase in incidence of papillary carcinomas in adolescent girls was in part a simple shift of the diagnoses to earlier ages. A part of the sex difference (or the shift of diagnosis to younger age) may also reflect a more health-conscious behaviour in young women than in men. In a French study, the increasing relative risk of papillary carcinoma was found in successive birth cohorts of women from 1900 through 1980 (with reference to the birth cohort 1928),[31] which may also reflect improvements in medical care and possibly increasing awareness in general population.

In the large data-set of the SEER Program in the USA, higher incidence rates of thyroid cancer were reported[11] than in this study. In the USA, the rates were higher in children by 25%, and in adolescents by 75%. The difference was most pronounced in girls. Applying the World standard population to the SEER data, the ASR for girls aged 0–14 years was 2.2 per million (compared with 1.6 per million in the ACCIS data-set of general cancer registries) and the age-specific rate for adolescent girls in the SEER data was 24.4 per million, compared with 13.1 per million in our study. In the black population of children and adolescents the incidence rates were less than half of those in the whites. The high incidence rates among whites in the SEER data may possibly reflect intensive diagnostic activity, which has been suggested as contributing to the increase in incidence over time in the USA.[32] Further increase in the incidence rates may therefore be expected in Europe, unless different environmental risk factors play a role on the two sides of the Atlantic.

Although the incidence patterns in Europe (elsewhere than Belarus) were determined predominantly by sex, age and calendar time, we did observe also consistent regional differences, with higher rates in the South and North than elsewhere. This pattern may be related to variable diagnostic, classification or registration practices (as mentioned earlier), but also to variation in possible risk factors, although the extent of the contribution of these are difficult to establish based on current knowledge. The radiation from Chernobyl does not seem to play an important role, since the estimated doses to thyroid were slightly elevated (11–49 mSv) in children under 5 years of age in only two of the countries included in this study (Slovakia and Slovenia).[26] Dietary iodine may also play a role, but this was not demonstrated. Based on urinary excretion levels of iodine, we did not find different incidence rates of thyroid cancer in iodine-deficient compared with iodine-sufficient countries. Among the two regions with the highest incidence rates, the North was mainly composed of iodine-sufficient countries, while the countries in the South were mostly iodine deficient. Our observation cannot be considered conclusive though, because of the heterogeneity of io-

Table 12 – Numbers of cases (n) included in analyses of survival and 5-year observed survival of children and adolescents diagnosed with different histological types of thyroid carcinoma in Europe in the periods shown (Source: ACCIS)

Histology type	1988–1997			1978–1997					
	n	Survival (%)	(95% CI)	Survival (%)					
				n	1978–1982	1983–1987	1988–1992	1993–1997	*P* (trend)[a]
Children (age 0–14 years), combined data-set									
EUROPE									
Papillary	171	99	(95–100)	267	100	100	99	98	0.14
Follicular	23	100	–	56	100	100	100	100	–
Medullary	55	95	(81–99)	64	83	100	91	94	0.89
Anaplastic	2	–	–	4	–	–	–	–	–
Other & NOS	14	100	–	16	100	100	100	100	–
Belarus									
Papillary	388	99	(97–100)	–	–	–	–	–	–
Follicular	51	100	–	–	–	–	–	–	–
Medullary	1	–	–	–	–	–	–	–	–
Anaplastic	0	–	–	–	–	–	–	–	–
Other & NOS	117	98	(93–100)	–	–	–	–	–	–
Adolescents (age 15–19 years), general cancer registries									
EUROPE									
Papillary	224	99	(96–100)	323	99	100	99	99	0.64
Follicular	33	100	–	78	96	100	100	100	0.27
Medullary	21	100	–	33	100	89	100	100	0.99
Anaplastic	0	–	–	1	–	–	–	–	–
Other & NOS	6	–	–	14	100	100	100	100	–

Only selected registries (Table 1) contributed to analyses of time trends for the period 1978–1997. Survival is not shown for very small groups of patients. Percentages were rounded to the nearest integer. –, not applicable.
a Significance of change over time in survival of patients diagnosed in the four successive periods (log-rank test).

dine status within countries and on an individual level.[42] Furthermore, the geographical areas defined for this study may not correspond with the areas of predilection of factors modulating incidence levels. In Belarus, the spectacular increase in thyroid carcinomas might have been reinforced by the moderate iodine deficiency around Chernobyl, shown to increase the odds of developing thyroid cancer after a 1-Gy exposure in the most deficient areas to 3.2 (95% CI 1.9–5.5).[43] This observation cannot be compared directly with our results, since in the Chernobyl study, the iodine status was estimated from soil levels, which does not take into account dietary intake and the association might have been modified by the higher doses of radioactive iodine.

Survival of children with thyroid carcinoma has been excellent since the late 1970s. Similar results were shown in the earlier EUROCARE study[10] and the SEER programme in the USA,[11] while the 5-year survival was shown to decrease with age over the lifetime.[44]

From clinical point of view, papillary and follicular thyroid cancers in childhood and adolescence differ from those occurring in adults: they are more advanced upon presentation (higher frequency of extra-thyroidal spread), the recurrence rate is higher while the prognosis is better.[12,39] Primary treatment comprises a combination of surgery (including total thyroidectomy), radioiodine (^{131}I) ablation, and thyroid hormone therapy applied at varying levels of intensity.[39] Medullary thyroid cancer in children and adolescents often occurs as part of the MEN2 syndrome. Early detection of mutation of the *RET* proto-oncogene (the cause of familial medullary thyroid carcinoma) by direct DNA analysis in these kindreds, followed by a prophylactic thyroidectomy, may result in a normal life expectancy.[45,46] Long-term consequences of treatment of thyroid cancer relate to complications of thyroid surgery, ^{131}I treatment and thyroid-stimulating hormone (TSH)-suppression, and may result in unfavourable reproductive outcomes, pulmonary fibrosis or another cancer.[39]

Despite the huge number of person-years gathered within the ACCIS database, we were able to make a range of estimates (rather than a single estimate) of the incidence of thyroid cancer in European childhood population. The difficulties arise probably from the low rate of occurrence of these cancers, whereby few cases markedly affect incidence rates. For this rare tumour, definition of standard criteria of diagnosis, classification and registration as well as compliance with them is particularly important. To monitor successfully the rising incidence of thyroid cancer, sensitive both to risk factors and public concern, evaluation of data completeness, quality and comparability are as important as the further extension of the ACCIS database.

Conflict of interest statement

None declared.

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REFERENCES

1. Parkin DM, Kramárová E, Draper GJ, et al., editors. *International incidence of childhood cancer*: **volume 2**. IARC scientific publications no. 144. Lyon: IARC; 1998.
2. Ferlay J, Bray F, Pisani P, Parkin DM, GLOBOCAN 2000. *Cancer incidence, mortality and prevalence worldwide, version 1.0. IARC CancerBase No.* 5. Lyon: IARC Press; 2001.
3. DeLellis RA, Williams ED. Thyroid and parathyroid tumours: introduction. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, editors. *World Health Organization Classification of Tumours. Pathology and genetics of tumours of endocrine organs*. Lyon: IARC Press; 2004. p. 51–6.
4. Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl. *Nature* 1992;**359**:21.
5. Williams D. Cancer after nuclear fallout: lessons from the Chernobyl accident. *Nature Reviews Cancer* 2002;**2**: 543–9.
6. Loh KC. Familial nonmedullary thyroid carcinoma: a meta-review of case series. *Thyroid* 1997;**7**:107–13.
7. Williams ED, Doniach I, Bjarnason O, Michie W. Thyroid cancer in an iodide rich area: a histopathological study. *Cancer* 1977;**39**:215–22.
8. Harach HR, Escalante DA, Day ES. Thyroid cancer and thyroiditis in salta, Argentina: a 40-yr study in relation to iodine prophylaxis. *Endocr Pathol* 2002;**13**:175–81.
9. Ron E, Kleinerman RA, Boice Jr JD, LiVolsi VA, Flannery JT, Fraumeni Jr JF. A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* 1987;**79**:1–12.
10. Storm HH, Plesko I. Survival of children with thyroid cancer in Europe 1978–1989. *Eur J Cancer* 2001;**37**:775–9.
11. Bernstein L, Gurney JG. Carcinomas and other malignant epithelial neoplasms. In: Ries LAG, Smith MA, Gurney JG, et al., editors. Cancer incidence and survival among children and adolescents: United States. SEER Program 1975–1995. National Cancer Institute, SEER Program. Bethesda, MD: NIH Pub. No. 99-4649; 1999, p. 139–148.
12. Grigsby PW, Gal-or A, Michalski JM, Doherty GM. Childhood and adolescent thyroid carcinoma. *Cancer* 2002;**95**: 724–9.
13. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since 1970s: the ACCIS project. *Lancet* 2004;**364**:2097–105.
14. Kramárová E, Stiller CA. The International Classification of Childhood Cancer. *Int J Cancer* 1996;**68**:759–65.
15. Percy C, Van Holten V, Muir CS, editors. *International Classification of diseases for oncology*. 2nd ed. Geneva: World Health Organisation; 1992.
16. Parkin DM, Shanmugaratnam K, Sobin L, et al. Histological groups for comparative studies. IARC technical report no. 31. Lyon: International Agency for Research of Cancer; 1998.
17. Vitti P, Delange F, Pinchera A, Zimmermann M. Europe is iodine deficient. *Lancet* 2003;**361**:1226.
18. Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet R, editors. Cancer registration: principles and methods. IARC scientific publications no. 95. Lyon: International Agency for Research on Cancer; 1991.

19. Doll R, Payne P, Waterhouse JAH. *Cancer incidence in five continents*, vol. I. Geneva: UICC; Berlin: Springer; 1966.
20. Berkson J, Gage RP. Calculations of survival rates for cancer. *Proc Staff Meet Mayo Clin* 1950;**5**:270–86.
21. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980.
22. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient, II, analysis and examples. *Br J Cancer* 1977;**35**:1–39.
23. Intercooled Stata 8.2 for Windows.
24. Furmanchuk AW, Averkin JI, Egloff B, et al. Pathomorphological findings in thyroid cancers of children from the Republic of Belarus. *Histopathology* 1992;**21**:401–8.
25. Nikiforov Y, Gnepp DR. Pediatric thyroid cancer after the Chernobyl disaster. *Cancer* 1994;**74**:748–66.
26. Cardis E, Krewski D, Boniol M, et al. Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. Int J Cancer (early view published online on 20 April 2006).
27. Sprogel P, Storm HH. Thyroid cancer: incidence, mortality and histological pattern in Denmark. *Int J Epidemiol* 1989;**4**:990–2.
28. Plesko I, Macfarlane GJ, Obsitnikova A, Vlasak V, Kramarova E. Thyroid cancer in Slovakia, 1968–1990: incidence, mortality and histological types. *Eur J Cancer Prev* 1994;**4**:345–9.
29. van der Horst M, Winther JF, Olsen JH. Cancer incidence in the age range 0–34 years: Historical and actual status in Denmark. Int J Cancer 2005. *Int J Cancer* 2006;**118**:2816–26.
30. Reynolds RM, Weir J, Stockton DL, Brewster DH, Sandeep TC, Strachan MW. Changing trends in incidence and mortality of thyroid cancer in Scotland. *Clin Endocrinol (Oxf)* 2005;**62**:156–62.
31. Colonna M, Grosclaude P, Remontet L, et al. Incidence of thyroid cancer in adults recorded by French cancer registries (1978–1997). *Eur J Cancer* 2002;**38**:1762–8.
32. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 2006;**295**:2164–7.
33. Parkin DM, Whelan S, Ferlay J, Storm H. Cancer incidence in five continents, **Vol. I to VIII**. Lyon: IARC CancerBase No. 7; 2005.
34. Lacour B. FRANCIM. Renforcement de la surveillance des cancers thyroïdiens chez l'enfant et l'adolescent sur le plan national: etude de faisabilité. *Bulletin épidemiologique hebdomadaire. Institut de veille sanitaire* 2006;**7**:55–7.
35. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. *Cancer Incidence in five continents*, volume VIII. Lyon: International Agency for Research on Cancer, IARC Press; 2002.
36. Stiller CA, Allen M, Bayne A et al., National Registry of Childhood Tumours, England and Wales, 1981–1990. In: Parkin DM, Kramárová E, Draper GJ, et al., editors. International Incidence of Childhood Cancer: **volume 2**. IARC scientific publications No. 144. Lyon: IARC; 1998, p. 365-367.
37. Verkooijen HM, Fioretta G, Pache JC, et al. Diagnostic changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland. *Cancer Causes Control* 2003;**14**:13–7.
38. Finnish cancer registry. Thyroid gland cancer in women in Finland, 1954–2003. 3 May 2006. Available from: www.cancerregistry.fi/flash/fin2_wom_thyroid.swf.
39. Jarzab B, Handkiewicz-Junak D, Wloch J. Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. *Endocrine-Related Cancer* 2005;**12**:773–803.
40. Hedinger C, Williams ED, Sobin LH. *World Health Organization International Histological Classification of Tumours*. 2nd ed. *Histological typing of thyroid tumours*. Berlin: Springer; 1988.
41. Harach HR, Williams ED. Childhood thyroid cancer in England and Wales. *Br J Cancer* 1995;**72**:777–83.
42. Fonzo D, Germano L, Gallone G, Migliardi M. Spot urinary iodine concentration as a measure of dietary iodine, evaluated in over 3800 young male subjects undergoing medical check-up preliminary to military enrolment in Piemonte and Aosta Valley (Italy). *J Endocrinol Invest* 2003;**26**:1186–91.
43. Cardis E, Kesminiene A, Ivanov V, et al. Risk of thyroid cancer after exposure to 131I in childhood. *J Natl Cancer Inst* 2005;**97**:724–32.
44. Berrino F, Capocaccia R, Estève J et al., Survival of cancer patients in Europe: the EUROCARE-2 study. IARC scientific publications no. 151. Lyon: International Agency for Research on Cancer; 1999.
45. Pacini F, Vorontsova T, Demidchik EP, et al. Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. *J Clin Endocrinol Metabol* 1997;**82**:3563–9.
46. Wiersinga WM. Thyroid cancer in children and adolescents – consequences in later life. *J Pediatr Endocrinol Metab* 2001;**14**(suppl 5):1289–96.