German Childhood Cancer Registry
Head: Dr. P. Kaatsch

Incidence, time trends and regional variations of childhood leukaemia

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(Director: Professor Dr. Maria Blettner)

International Workshop on Risk Factors for Childhood Leukaemia
Berlin, 5-7 May, 2008

Structure of presentation

Incidence, time trends and regional variations of childhood leukaemia

1. German data

   based on the German Childhood Cancer Registry (GCCR)

2. European data

   based on Automated Childhood Cancer Information System (ACCIS)

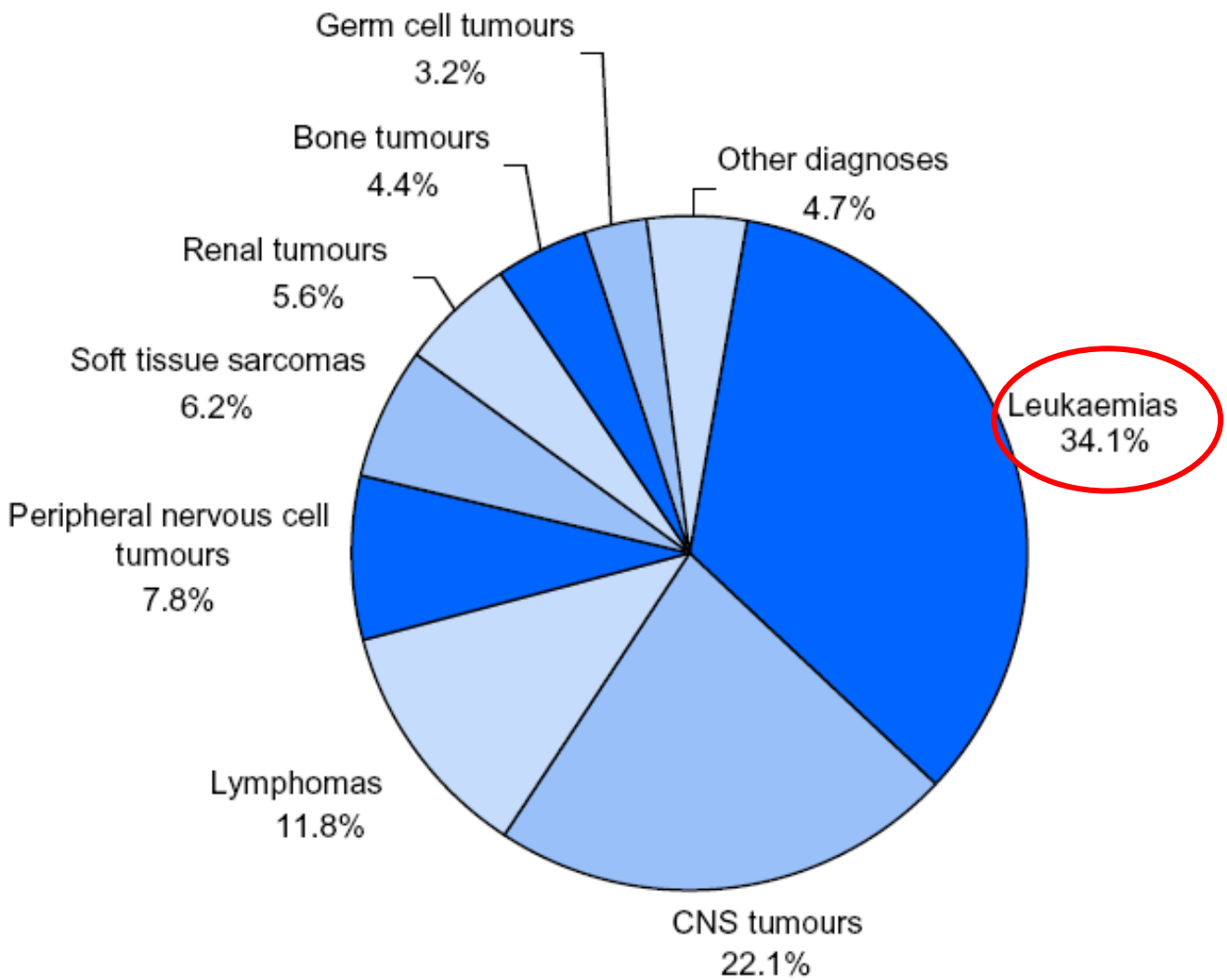
The German Childhood Cancer Registry (GCCR)

- population-based -

◆ Begin of registration	1980
◆ Population base	13.0 million children*)
◆ Completeness of registration	ca. 95 %
◆ Number of cases annually	1,700-1,800
◆ Since 1991 inclusion of former GDR	
◆ Number of reported cases (1980-2007)	42.885 *)

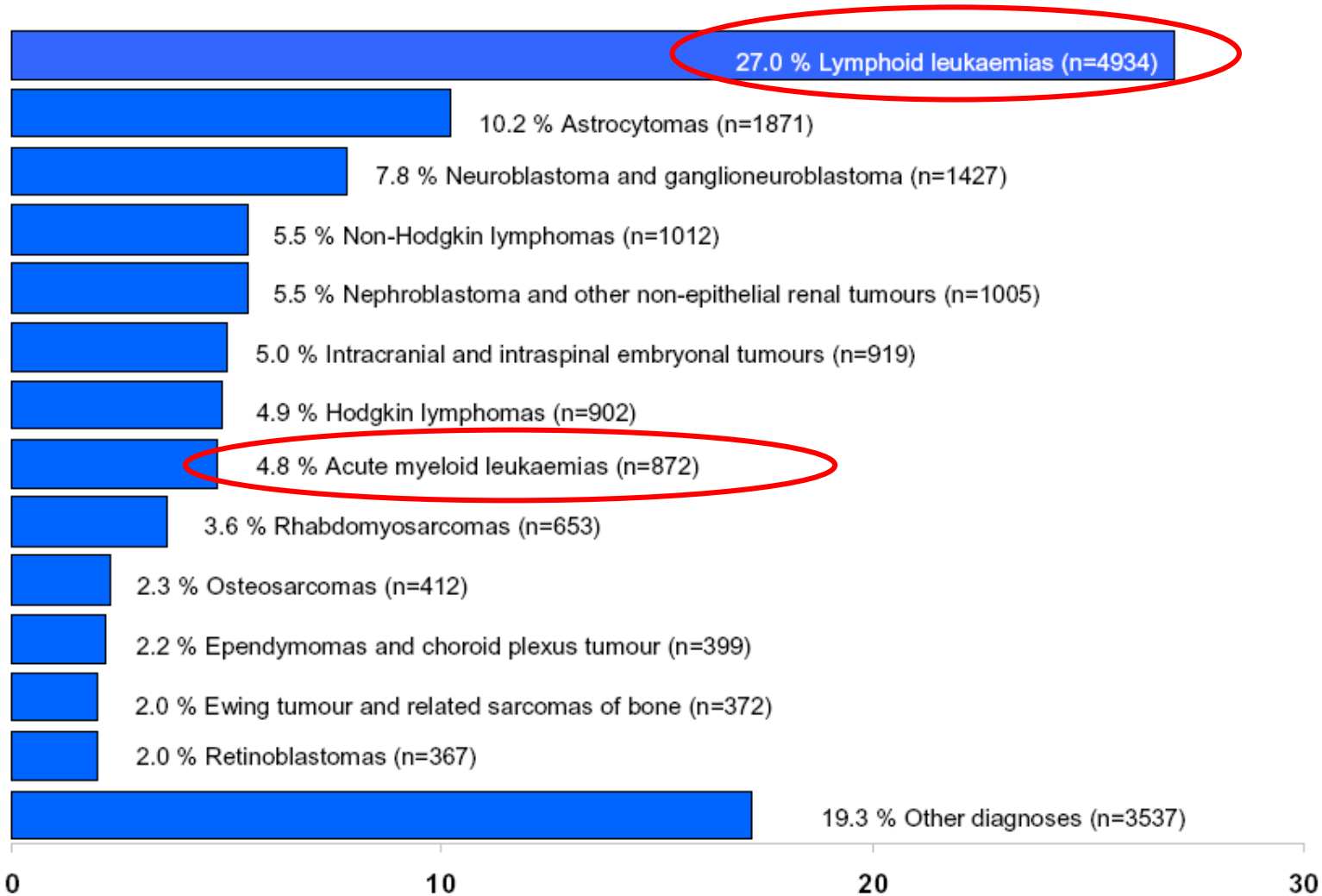
*) below 15 years

Relative frequency of main diagnostic groups (1997-2006) (n=18,283)



Source: P. Kaatsch et al., Annual Report 2006/07 GCCR

Relative frequency of the most common diagnoses (1997-2006) (n=18,283)



Source: P. Kaatsch et al., Annual Report 2006/07 GCCR

All cases are classified by:

International Classification of Childhood Cancer, Third Edition *)

Table 1: Main ICCC-3

Diagnostic group		ICD-O-3 codes	
		Morphology	Topography
I	**LEUKAEMIAS, MYELOPROLIFERATIVE AND MYELODYSPLASTIC DISEASES**		
(a)	Lymphoid leukaemias	9820, 9823, 9826, 9827, 9831-9837, 9940, 9948	
(b)	Acute myeloid leukaemias	9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931	
(c)	Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960-9964	
(d)	Myelodysplastic syndrome and other myeloproliferative diseases	9945, 9946, 9975, 9980, 9982-9987, 9989	
(e)	Unspecified and other specified leukaemias	9800, 9801, 9805, 9860, 9930	

continued

✸ *Tumours with non-malignant behaviour are included*

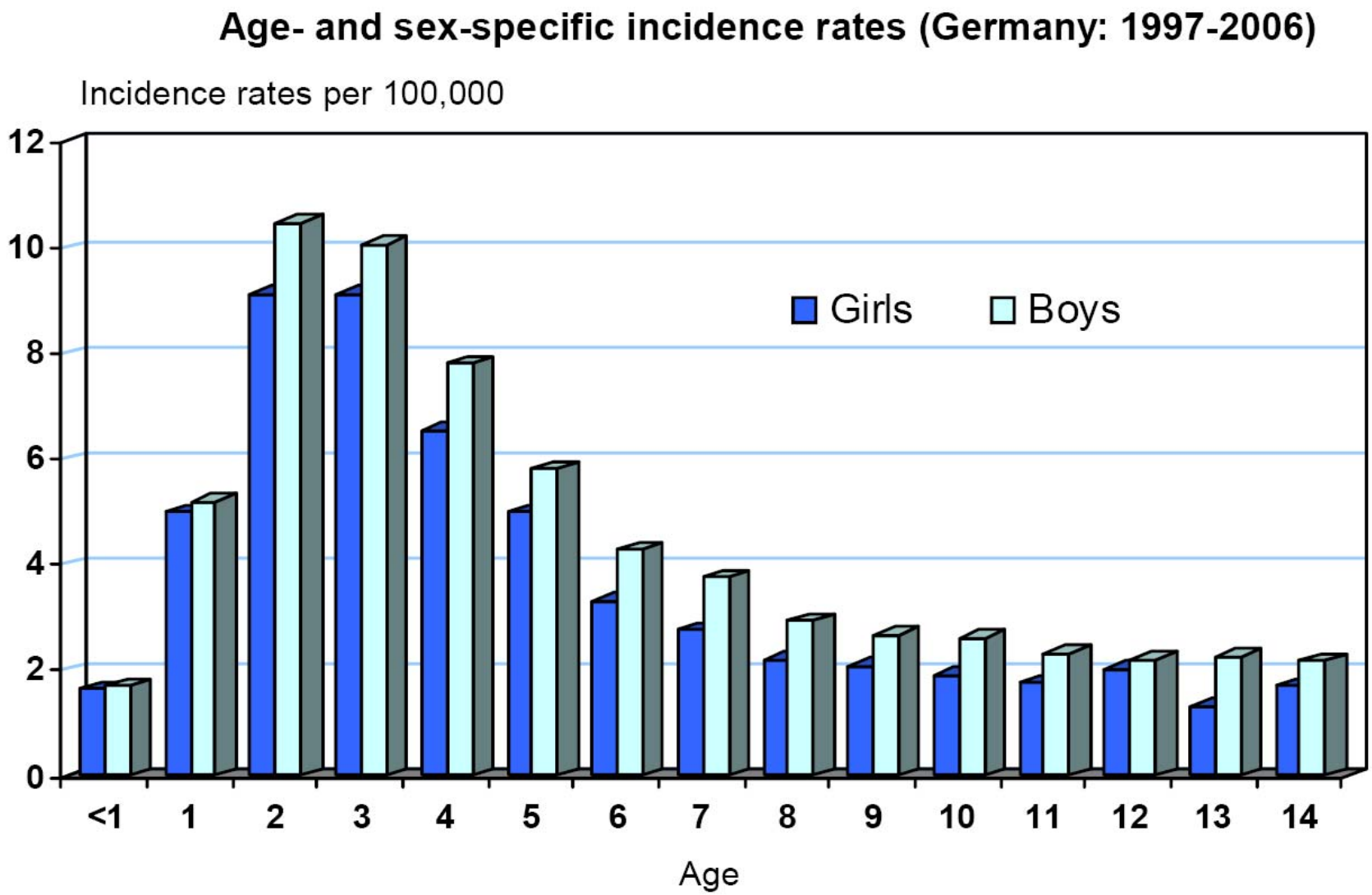
*) *Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P.* Cancer 103, 1457-1467, 2005.

Number of cases under 15 years of age in Germany, sex ratio, age median, relative frequency of patients of participating at clinical trials by diagnostic groups (1997-2006)

Diagnoses	Number of cases			Sex ratio boys to girls	Age median (year month)	Trial participants (%)
	N	Relative (%)	Group (%)			
All malignancies	**18283**	**100.0**	**100.0**	**1.2**	**5y 10m**	**91.7**
Leukaemias, myeloproliferative and myelodysplastic diseases	6237	34.1	100.0	1.2	5y 0m	99.2
Lymphoid leukaemias	4934	27.0	79.1	1.3	4y 9m	99.7
Acute myeloid leukaemias	872	4.8	14.0	1.1	6y 3m	98.5
Chronic myeloproliferative diseases	84	0.5	1.3	0.7	11y 5m	92.9
Myelodysplastic syndrome and other myeloproliferative diseases	291	1.6	4.7	1.5	5y 9m	93.8
Unspecified and other specified leukaemias	56	0.3	0.9	1.9	5y 4m	100.0
Lymphomas and reticuloendothelial neoplasms	2154	11.8	100.0	1.9	10y 7m	97.4
Hodgkin lymphomas	902	4.9	41.9	1.4	12y 6m	97.9
Non-Hodgkin lymphomas	1012	5.5	47.0	2.3	9y 3m	96.9
Burkitt lymphoma	223	1.2	10.4	4.1	8y 3m	97.8
Miscellaneous lymphoreticular neoplasms	12	0.1	0.6	1.0	0y 11m	83.3
Unspecified lymphomas	5	0.0	0.2	-	13y 3m	100.0
CNS and miscellaneous intracranial and intraspinal neoplasms	4049	22.1	100.0	1.2	6y 11m	80.6
Ependymomas and choroid plexus tumour	399	2.2	9.9	1.3	3y 9m	78.9
Astrocytomas	1871	10.2	46.2	1.1	7y 3m	82.8
Intracranial and intraspinal embryonal tumours	919	5.0	22.7	1.7	6y 1m	83.4
Other gliomas	306	1.7	7.6	1.1	7y 8m	81.0
Other specified intracranial and intraspinal neoplasms	494	2.7	12.2	1.1	9y 2m	71.7
Unspecified intracranial and intraspinal neoplasms	60	0.3	1.5	1.3	6y 4m	51.7

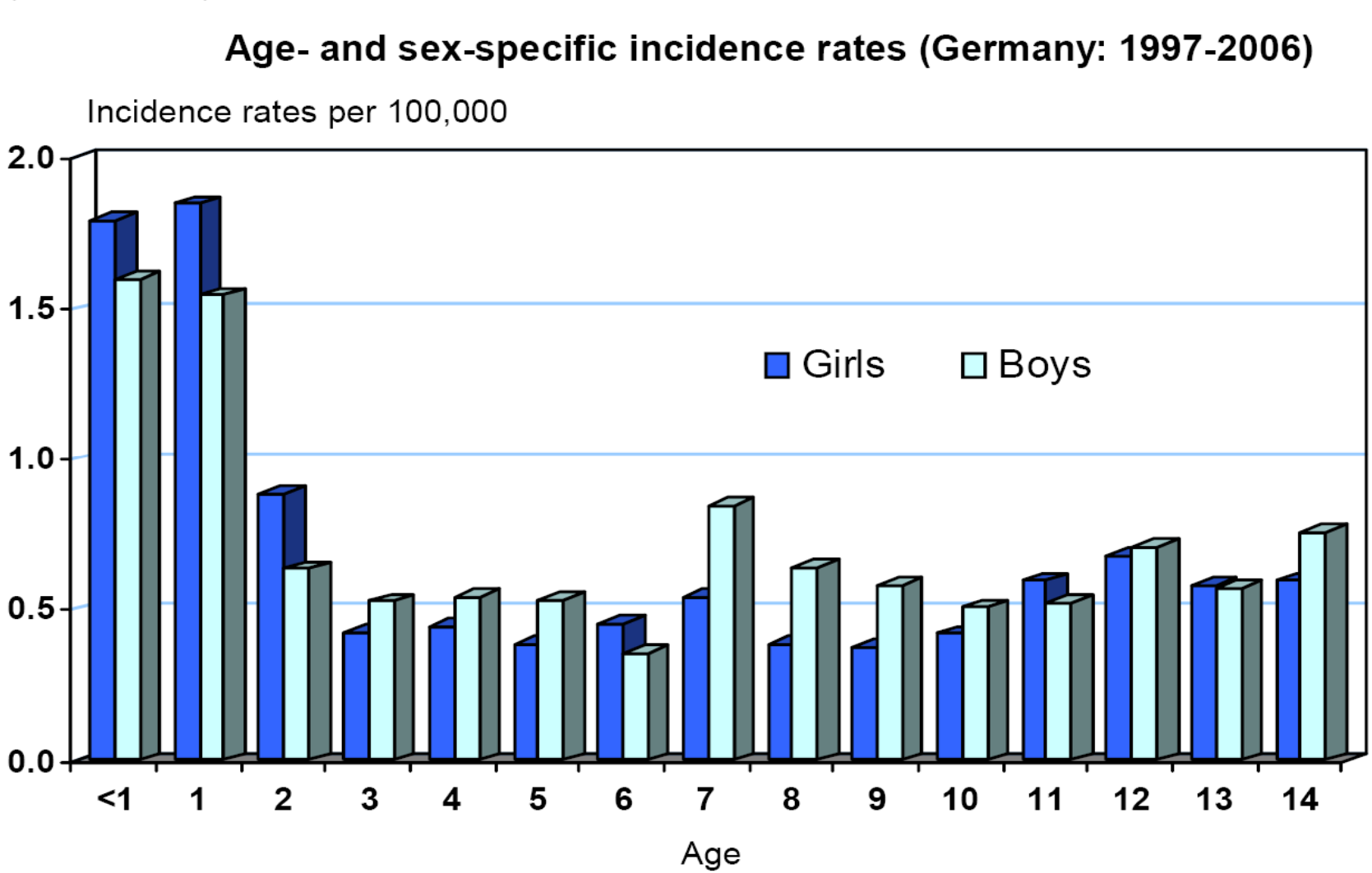
Source: P. Kaatsch et al., Annual Report 2006/07 GCCR

Lymphoid leukaemias



Source: P. Kaatsch et al., Annual Report 2006/07 GCCR

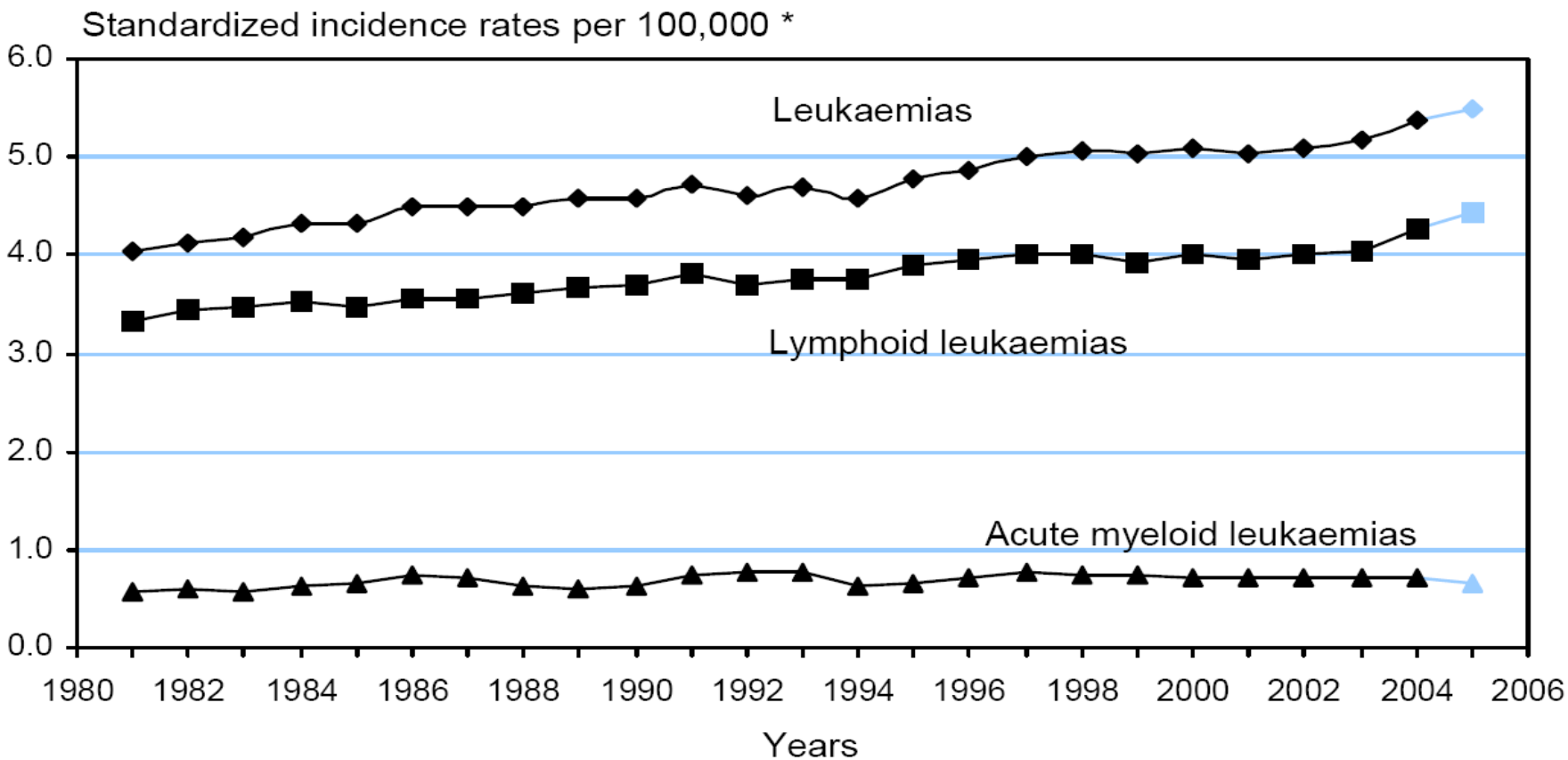
Acute myeloid leukaemias



Source: P. Kaatsch et al., Annual Report 2006/07 GCCR

Time Trends in Germany

Age-standardized incidence rates for leukaemias, lymphoid leukaemias and acute myeloid leukaemias of patients under 15 in West Germany without Berlin by year of diagnosis



* Standard: West Germany in 1987 (census)

Source: P. Kaatsch et al., Annual Report 2006/07 GCCR

German Childhood
Cancer Registry

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Int. J. Cancer: **122,** 1859–1867 (2008)

Temporal trends in the incidence rate of childhood cancer in Germany 1987–2004

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The German Childhood Cancer Registry regularly presents graphs of childhood cancer incidence rates by period, but no systematic analysis. The Automated Childhood Cancer Information System-project found an increasing trend in Europe. Against this background we present the first detailed trend analysis of childhood (aged under 15) malignancies in Germany. We examined incidence rates separately in western Germany 1987–2004 and eastern Germany 1991–2004. We analyzed all malignancies, all main diagnostic groups and relevant subsets using an age-period-cohort model. Additionally we fitted fractional polynomials to assess the linearity of the drift. All malignancies combined (excluding Central Nervous System-tumors and neuroblastoma) show a significant trend: +0.7% in western and +1.1% per year in eastern Germany. The overall trend in Germany is mostly due

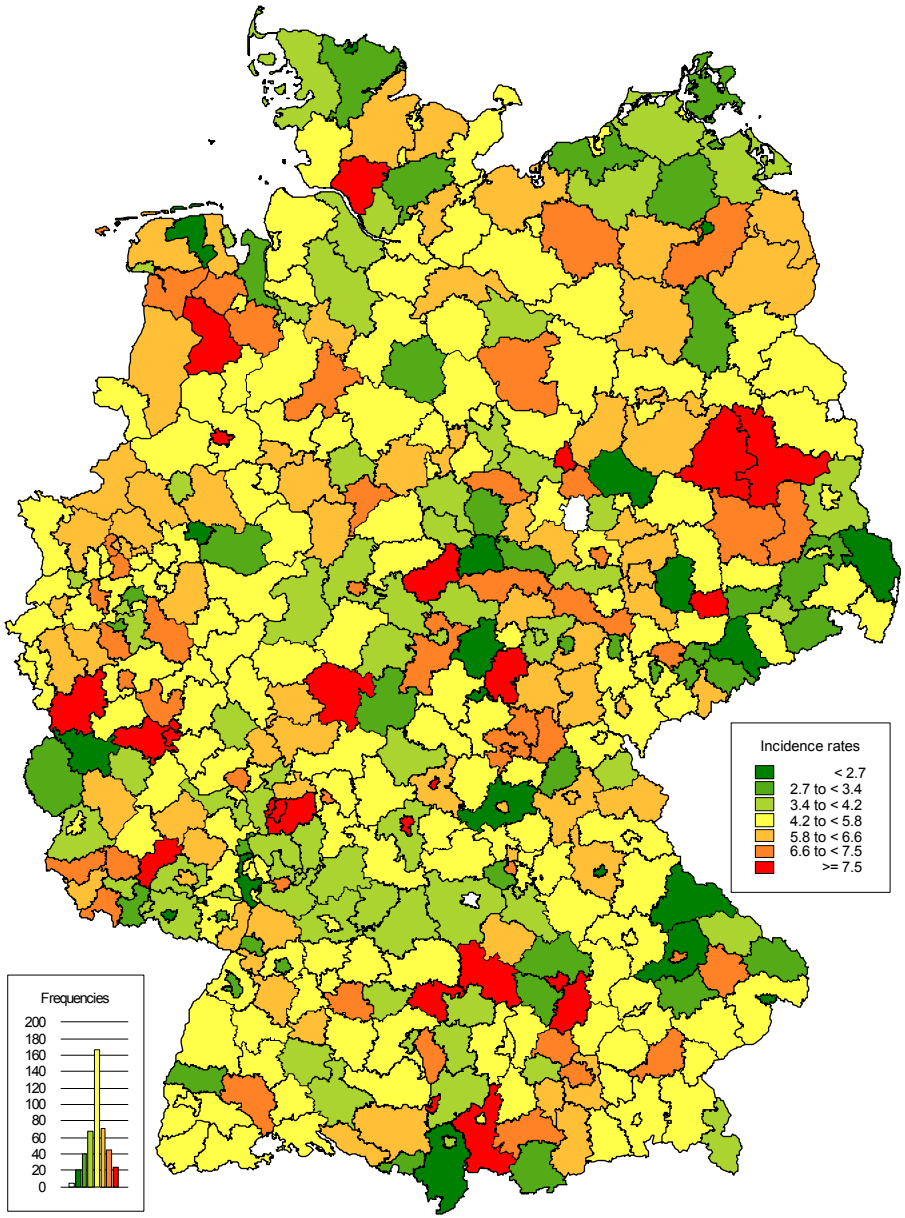
this case we would expect similar increases for all diagnoses. On the other hand, if the change were due to underlying causes, the changes in life style in eastern Germany through unification would be expected to show a diagnosis specific effect. The notion of an effect beyond completeness issues was supported by the observation of age-specific changes in the incidence rates for all malignancies in eastern Germany: Incidence rates almost doubled from 1993 (11.7 per 100,000) to 1994 (19.4 per 100,000) for children below 1 year of age. Three years later, from 1996 to 1997, the rate increased for children between 1 and 4 years (from 14.0 to 23.0 per 100,000). This temporal delay in the increase of the incidence rates between the different age groups could be due to a cohort effect. However, a corresponding increase in the incidence rates of

TABLE II – SUMMARY OF RESULTS FROM THE APC MODEL FITTING PROCESS

ICCC-diagnosis groups as used in ACCIS[27]	Selected subgroups and specific diagnoses	Western Germany 1987–2004			Eastern Germany 1991–2004		
		Best model	Average annual change in percent	95%-CI	Best model	Average annual change in percent	95%-CI
All malignancies (I–XII)		Drift	+0.8%	[0.6%;1.1%]	Drift	+2.1%	[1.2%;2.9%]
	All malignancies (excluding CNS (III) and neuroblastoma (IVa))	Drift	+0.7%	[0.4%;1.0%]	Drift	+1.1%	[0.1%;2.1%]
Leukemia (I)		Drift	+0.6%	[0.2%;1.1%]	Drift	+2.1%	[0.7%;3.5%]
	Lymphoid leukemia (ALL) (Ia)	Drift	+0.7%	[0.2%;1.2%]	Drift	+2.1%	[0.6%;3.7%]
	ALL+NHL (Ia+IIb)	Drift	+0.6%	[0.2%;1.0%]	Drift	+1.7%	[0.3%;3.1%]
	Acute non-lymphocytic leukemia (Ib)	Age	+0.3%	[−0.8%;1.4%]	Age	+1.3%	[−2.2%;5.0%]
Lymphomas and reticuloendothelial neoplasms (II)		Drift	+0.9%	[0.2%;1.6%]	Age	−0.9%	[−3.0%;1.2%]
	Hodgkin's disease (IIa)	AC	+1.6%	[−4.5%;8.0%]	Age	−2.0%	[−5.1%;1.1%]
	Non-Hodgkin lymphoma (NHL) (IIb)	Age	+0.1%	[−0.9%;1.2%]	Age	+0.2%	[−2.8%;3.4%]
CNS and miscellaneous intracranial and intraspinal neoplasms (CNS) (III)		Drift	+1.1%	[0.6%;1.6%]	Drift	+5.5%	[4.6%;7.4%]
	All other solid tumors (IV–XI, excluding IVa)	Age	+0.5%	[−0.0%;1.0%]	Age	+0.7%	[−1.0%;2.4%]
Sympathetic nervous system tumors (IV)		AP	+0.1%	[−1.6%;1.8%]	Age	+2.3%	[−0.8%;5.5%]
	Neuroblastoma and ganglioneuroblastoma (IVa)	AP	+0.1%	[−1.5%;1.8%]	Age	+2.3%	[−0.8%;5.5%]

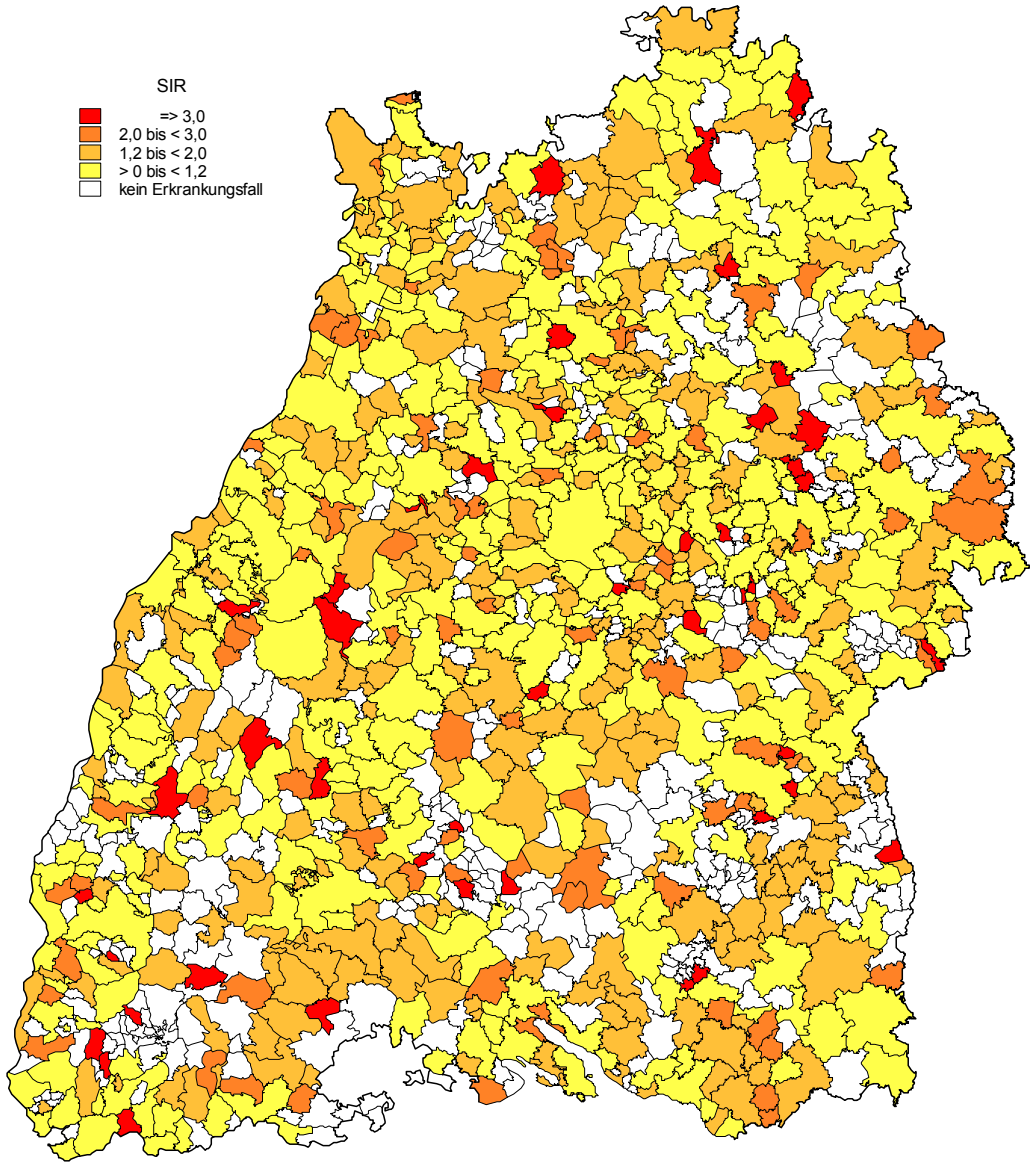
The drift parameter, expressed as average annual change in percent, is taken from the drift model, whenever "drift" or "age" was the best fitting model (in the latter case the drift is always not significant) and otherwise taken from the respective AP- or AC-model as indicated. The numerals (I–XII) refer to the ICCC-classification.[17] ALL, Acute lymphocytic leukemia; CNS, Central nervous system; NHL, Non-Hodgkin lymphoma.

Regional variation in Germany



Incidence rates of childhood leukaemia in Germany

by counties (1996-2005)



Regional distribution of standardized incidence rates (SIR) for all childhood malignancies in Baden-Württemberg (SIR: observed / expected cases of childhood cancer)

by communities (1997-2006)

Selected epidemiological studies at the GCCR

Selected epidemiological studies at the GCCR (1)

- Evaluation of Neuroblastoma-Screening
- Second cancer after childhood cancer

  (Case-control on therapy-related risk factors)
- German case-control-study on etiology of childhood cancer

German case-control-study on etiology of childhood cancer

- Interview of
  - 2,358 parents with diseased children (cases) and
  - 2,588 parents with non-diseased children (controls)
- Questions related to
  - maternal factors, pregnancy and birth
  - Factors regarding the immune system
  - Exposure to ionizing radiation
  - Parental occupation and environmental factors
- First publication: 1997, last publication: 2003

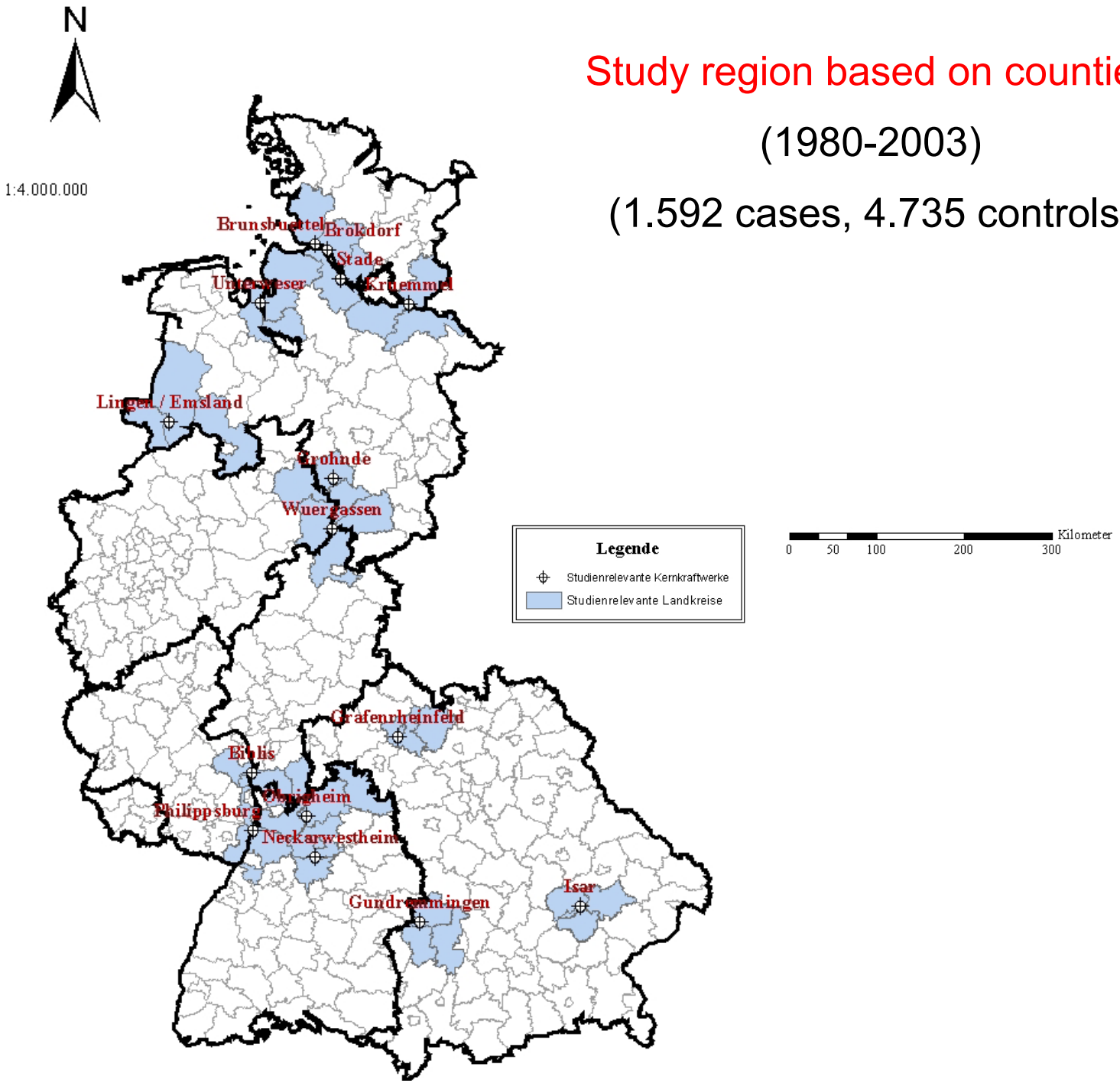
Selected epidemiological studies at the GCCR (2)

- Childhood leukaemia in the vicinity of radio and television transmitters (KISS-study)
- Cohort study for estimating risk of childhood cancer by diagnostic radiation exposure (RICC-study)
- Case-control-study on nuclear power plants and childhood cancer (KiKK-study)

Study region based on counties

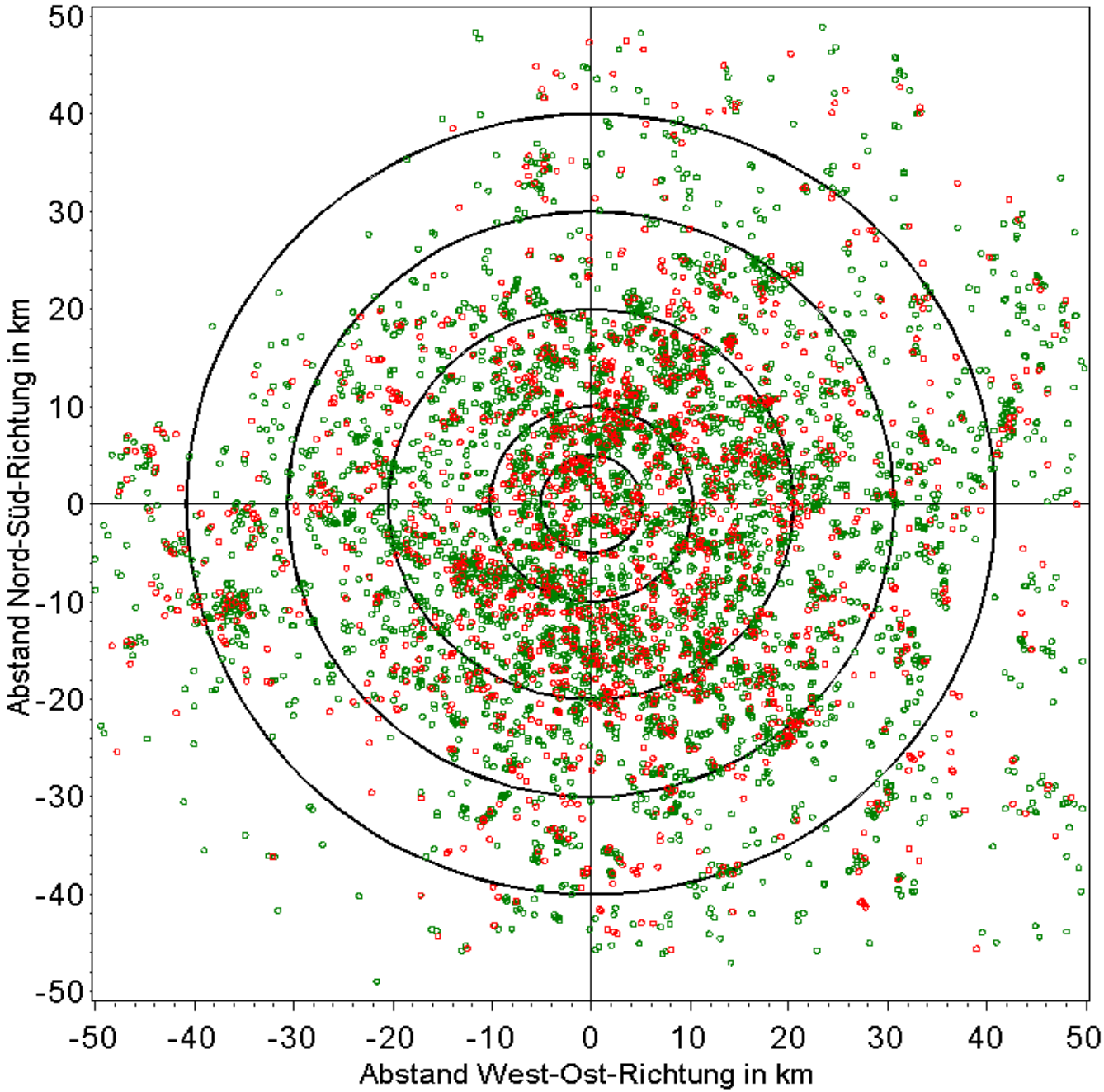
(1980-2003)

(1.592 cases, 4.735 controls)



Spatial position of cases and controls in relation to the chimney of the individually closest nclear power plant

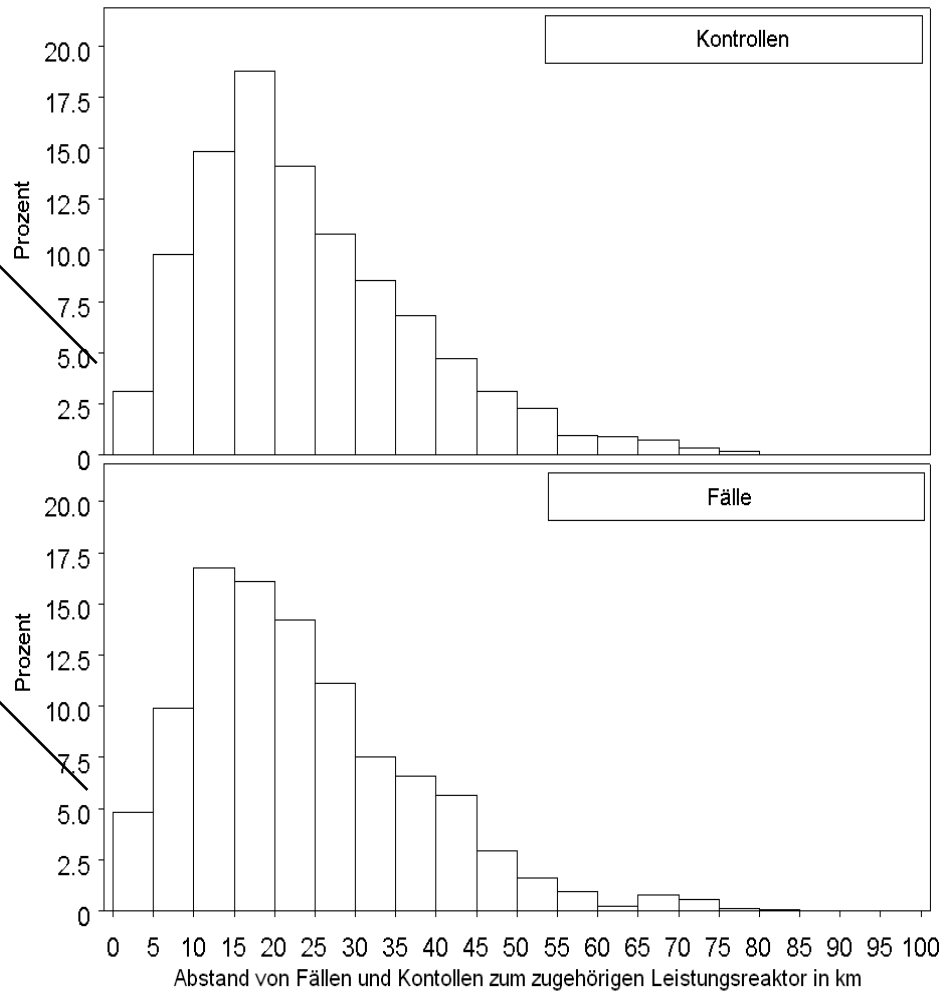
(All npp regions pooled, graph restricted to distances up to 50 km)



Distribution of distance between plant and residence

3,1 %

4,8 %



Controls

(n= 4.735)

Cases

(n= 1.592)

Structure of presentation

Incidence, time trends and regional variations of childhood leukaemia

1. German data

   based on the German Childhood Cancer Registry (GCCR)

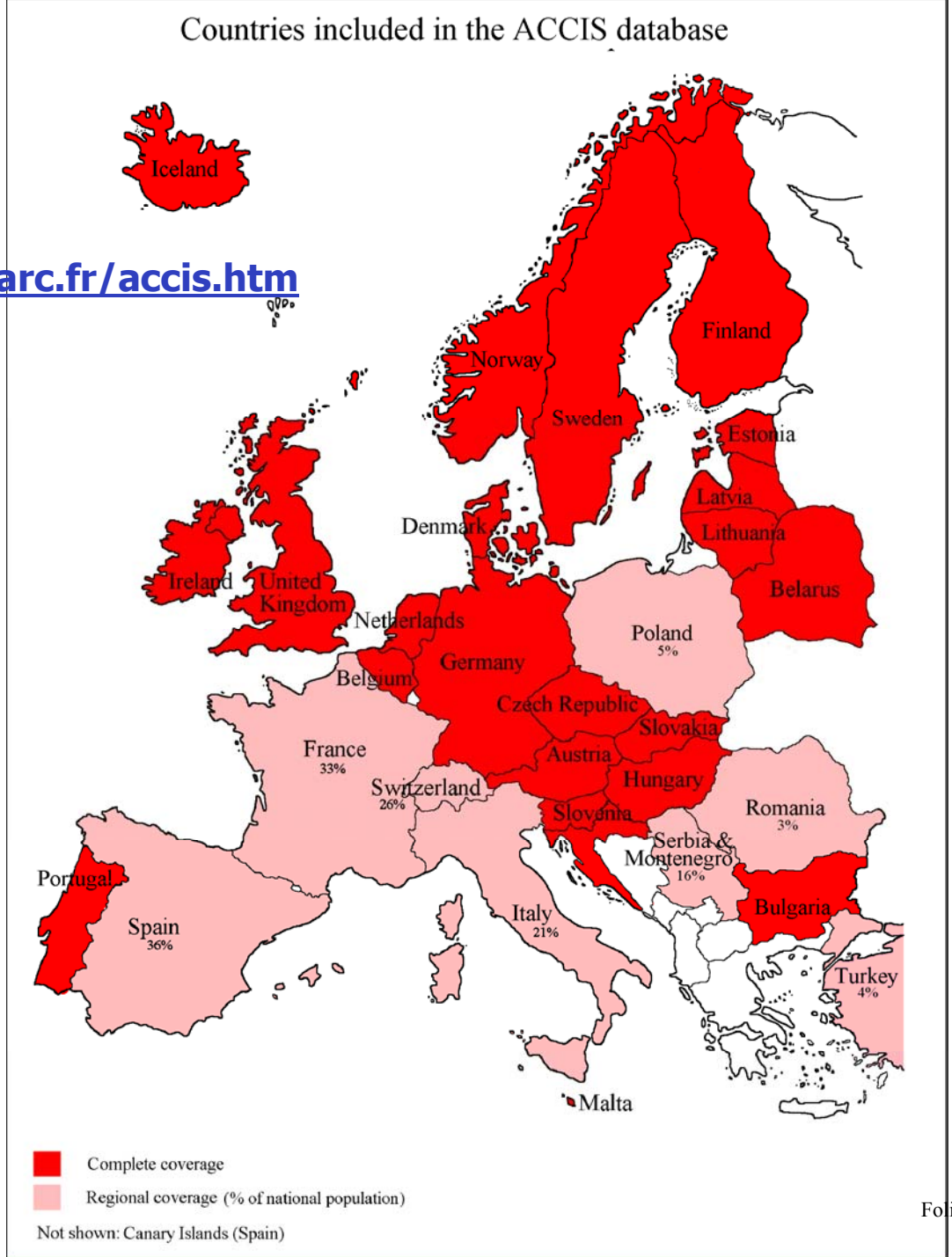
2. European data

   based on Automated Childhood Cancer Information System (ACCIS)

Automated Childhood Cancer Information System (ACCIS)

- A web-based automated information system on European incidence rates and survival probabilities in childhood cancer
  http://www-dep.iarc.fr/accis.htm
- Central coordination: International Agency for Research on Cancer (IARC) (Dr Eva Steliarova-Foucher)
- over 160.000 patients diseased in 1970-2000 (children and adolescents)
- data of 186 registries from 57 countries

http://www-dep.iarc.fr/accis.htm



Folie erstellt von Eva Steliarova-Foucher

Special issue:

Cancer in children and adolescents in Europe.

Steliarova-Foucher E, Coebergh JW, Kaatsch P, Pritchard-Jones K, Stiller C (editors).

Eur J Cancer 42 (13), 1913-2190, 2006.

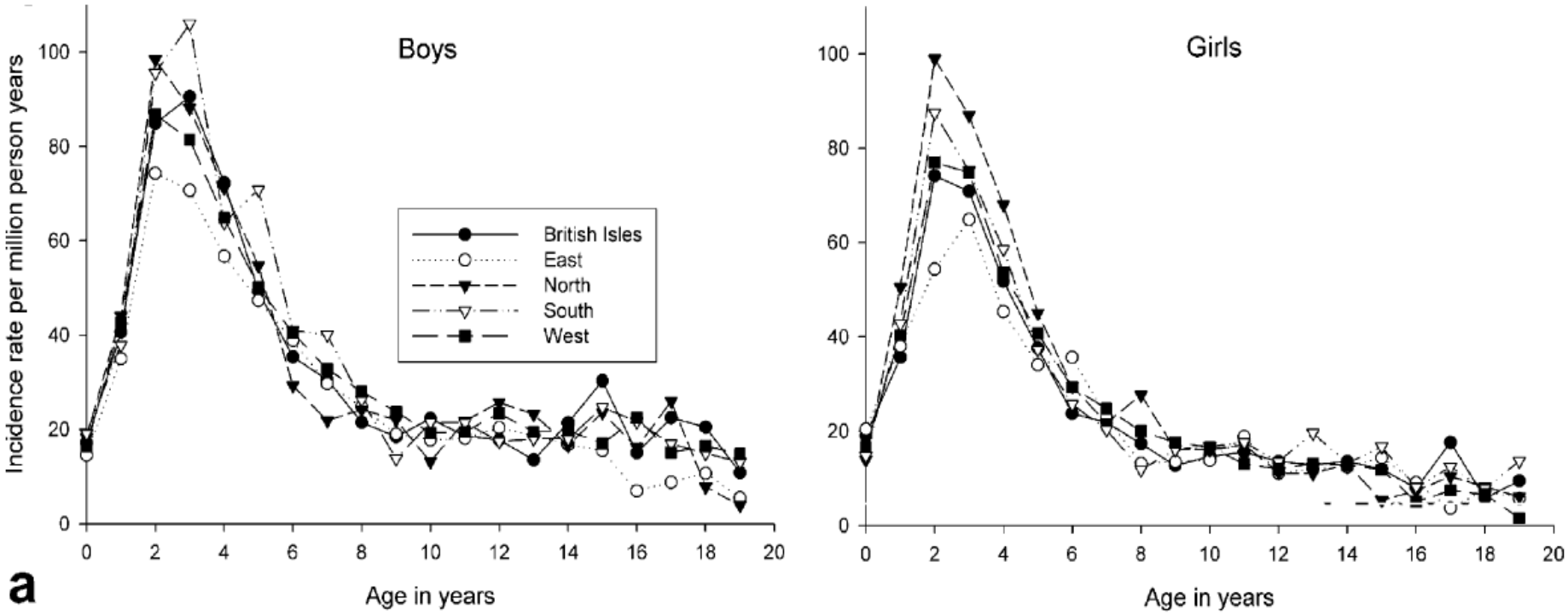
References from ACCIS

- *Coebergh JWW, Reedijk AMJ, de Vries E, Martos C, Jakab Z, Steliarova-Foucher E, Kamps WA.*
  Leukaemia incidence and survival in children and adolescents in Europe during 1978-1997. p. 2019-2036.

- *Stiller CA, Marcos-Gragera R, Ardanaz E, Pannelli F, Almar Marqués E, Cañada, Martinez A, Steliarova-Foucher E.*
  Geographical patterns of childhood cancer incidence in Europe, 1988-1997. p. 1952-1960.

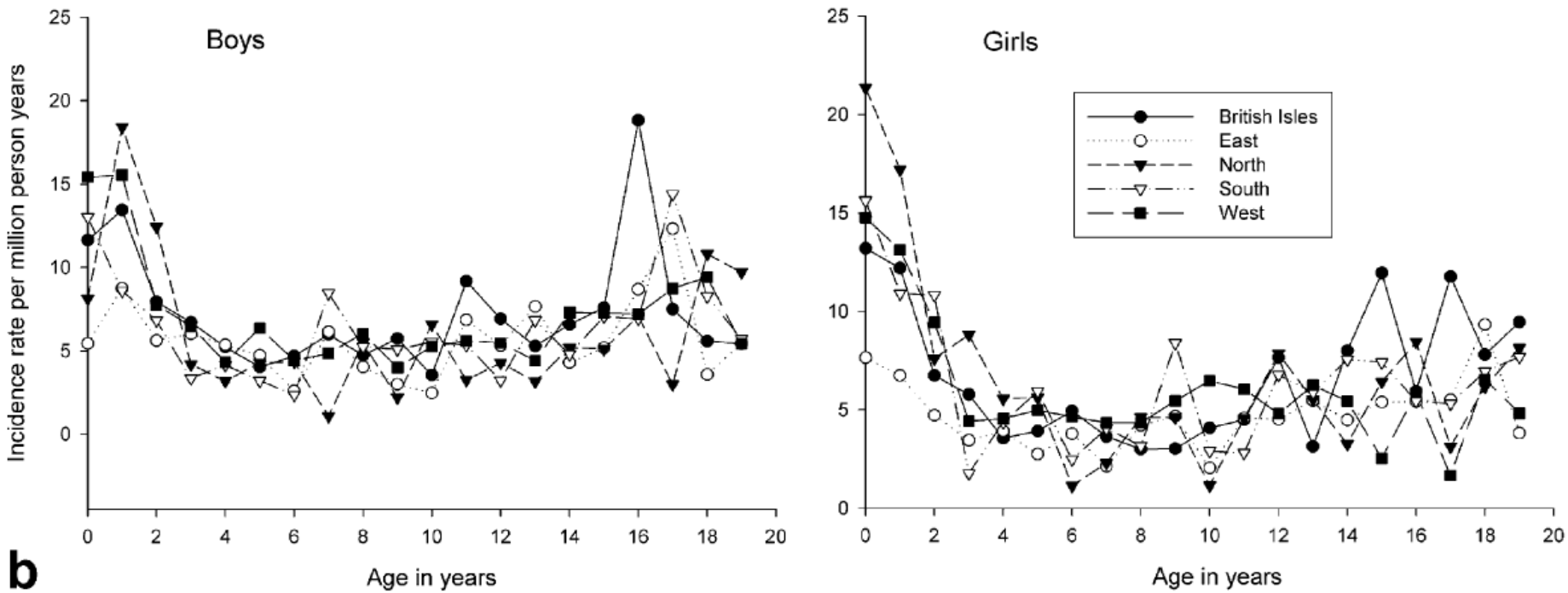
- *Kaatsch P, Steliarova-Foucher E, Crocetti E, Magnani C, Spix C, Zambon P.*
  Time trends of cancer incidence in European children (1978-1997). p. 1961-1971.

Age-specific incidence rates (per million person-years) of lymphoid leukaemia among children (0-14 years) and adolescents (15-19 years).



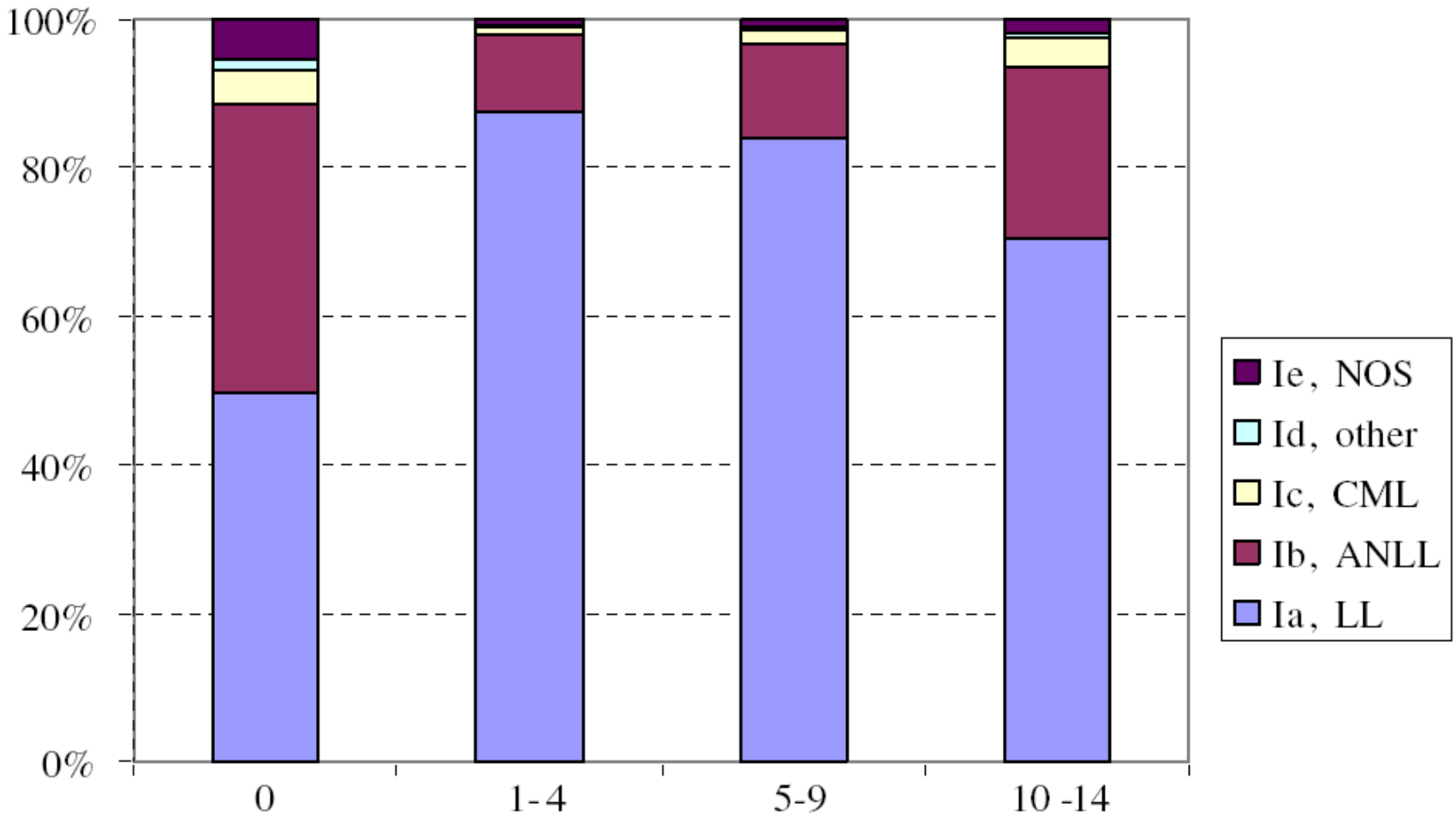
Source: J.W.W. Coebergh et al., EJC 42, 2006; ACCIS

Age-specific incidence rates (per million person-years) of acute non-lymphocytic leukaemia among children (0-14 years) and adolescents (15-19 years).



Source: J.W.W. Coebergh et al., EJC 42, 2006; ACCIS

Distribution of leukaemia subgroups in Europe, 1988-1997
- by age groups -



Source: J.W.W. Coebergh et al., EJC 42, 2006; ACCIS

Time Trends in Europe

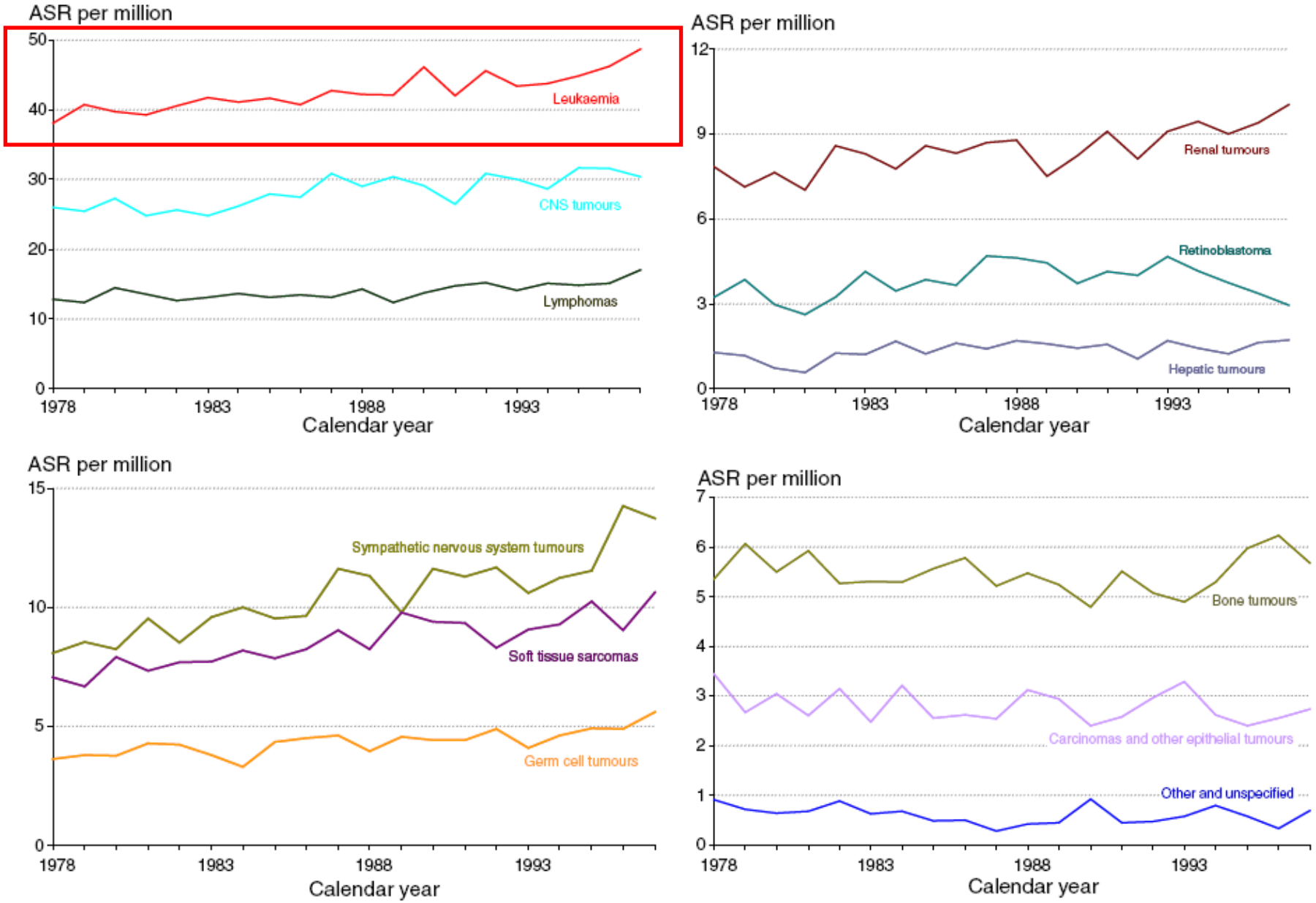


Fig. 3 – Age-standardised incidence rates (ASR, world standard) of all cancers in children aged 0–14 years registered in Europe in 1978–1997 and classified into the 12 ICCC main diagnostic groups (n = 77,111). Source: ACCIS.

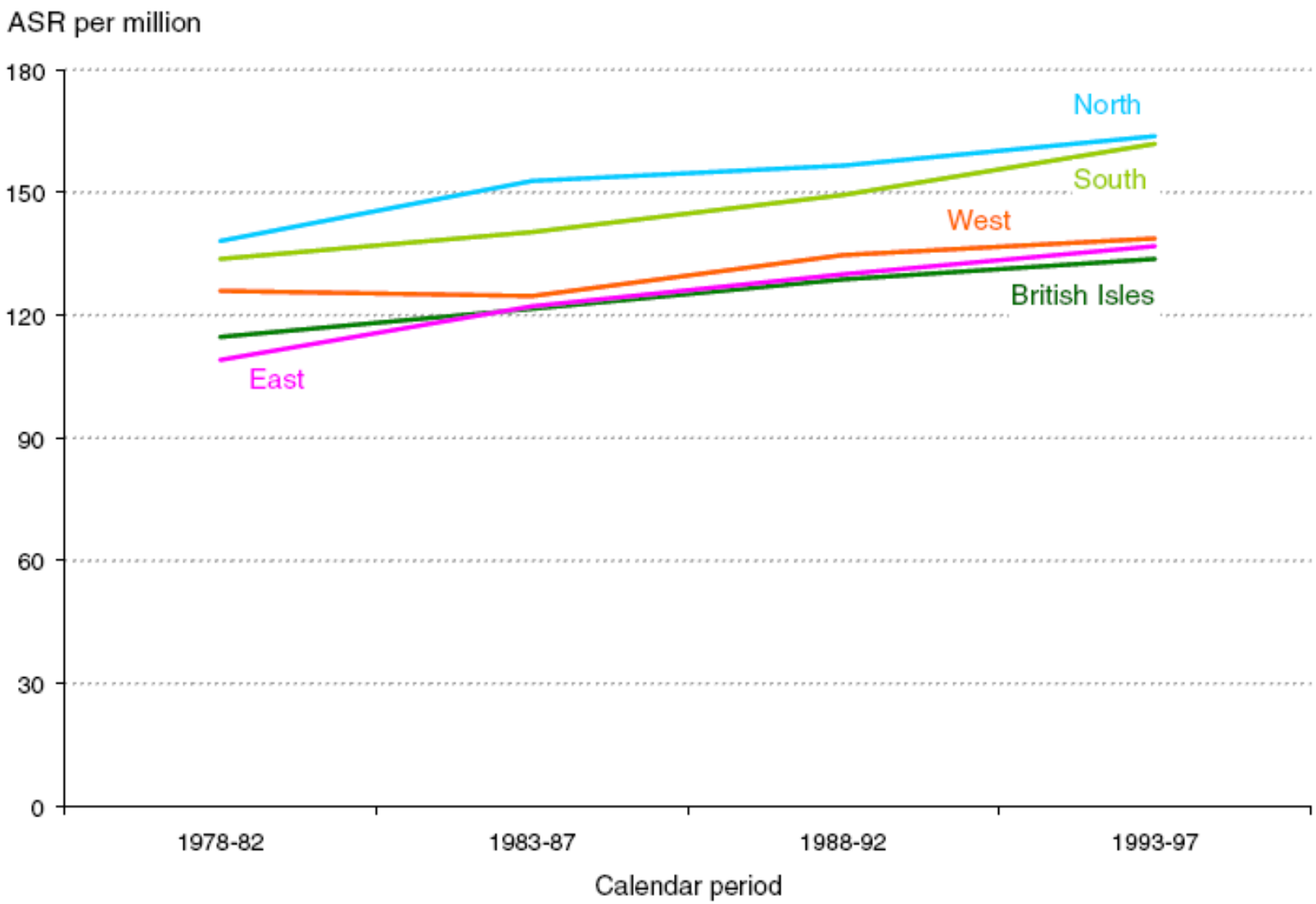


Fig. 1 – Age-standardised incidence rates (ASR, world standard) of all cancers in children aged 0–14 years, registered in the European regions in 1978–1997(n=72,280). Source: ACCIS.

Table 3 – Age-standardised incidence rates (ASR) for childhood cancer (age 0-14 years) in Europe by time period and main diagnostic groups added by number of cases (1978-1997), average annual percent of change (AAPC) and result of trend test (*P<0.0001) (Source: ACCIS)**

Region	Time period	ASR for diagnostic groups (per million)		
		Leu	Ly	CNS
Europe	1978-1982	39.7	13.1	25.9
	1983-1987	41.6	13.3	27.4
	1988-1992	43.6	14.1	29.2
	1993-1997	45.1	15.1	30.4
	No. of cases	26,690	8971	17,057
	AAPC	0.6%***	0.9%***	1.7%***

Source: P. Kaatsch et al., EJC 42, 2006

Table 4 – Average annual percent of change (AAPC) and result of trend test for childhood cancer (age 0–14 years) in Europe by age groups and sex for total cancer and main diagnostic groups (*P < 0.05; ** P < 0.01; *** P < 0.0001) (1978–1997) (Source: ACCIS)

	AAPC for diagnostic groups											AAPC for total (%)
	Leu (%)	Ly (%)	CNS (%)	Symp (%)	Ret (%)	Ren (%)	Hep (%)	Bone (%)	Soft (%)	Germ (%)	Ca (%)	Oth (%)	
Age 0	0.6	−1.6	2.4***	2.2***	0.9	1.9*	1.5	−7.4	1.3	3.9**	−0.4	3.2	2.1***
Age 1–4 years	0.7***	0.6	1.8***	1.7***	0.4	0.8*	1.2	−0.5	1.9***	−0.1	0.6	−0.2	1.1***
Age 5–9 years	0.5*	0.7	1.6***	0.1	−0.6	0.5	−1.8	−1.2	1.3*	0.90	−0.9	1.0	0.8***
Age 10–14 years	0.5*	1.3***	1.7***	1.9	−6.0	0.5	0.3	0.2	2.6***	2.5**	2.2***	1.7	1.3***
Male	0.7***	0.5*	1.5***	1.5***	0.3	0.4	0.9	−0.3	1.7***	1.2*	1.2	0.2	0.9***
Female	0.6**	1.7***	2.0***	2.0***	0.7	1.3**	0.6	−0.2	2.0***	2.0**	1.3*	2.0	1.4***

Leu, leukaemias; Ly, lymphomas; CNS, CNS tumours; Symp, tumours of the sympathic nervous system; Ret, retinoblastoma; Ren, renal tumours; Hep, hepatic tumours; Bone, malignant bone tumours; Soft, soft tissue sarcomas; Germ, germ-cell tumours; Ca, carcinomas; Oth, other and unspecified malignant neoplasms.

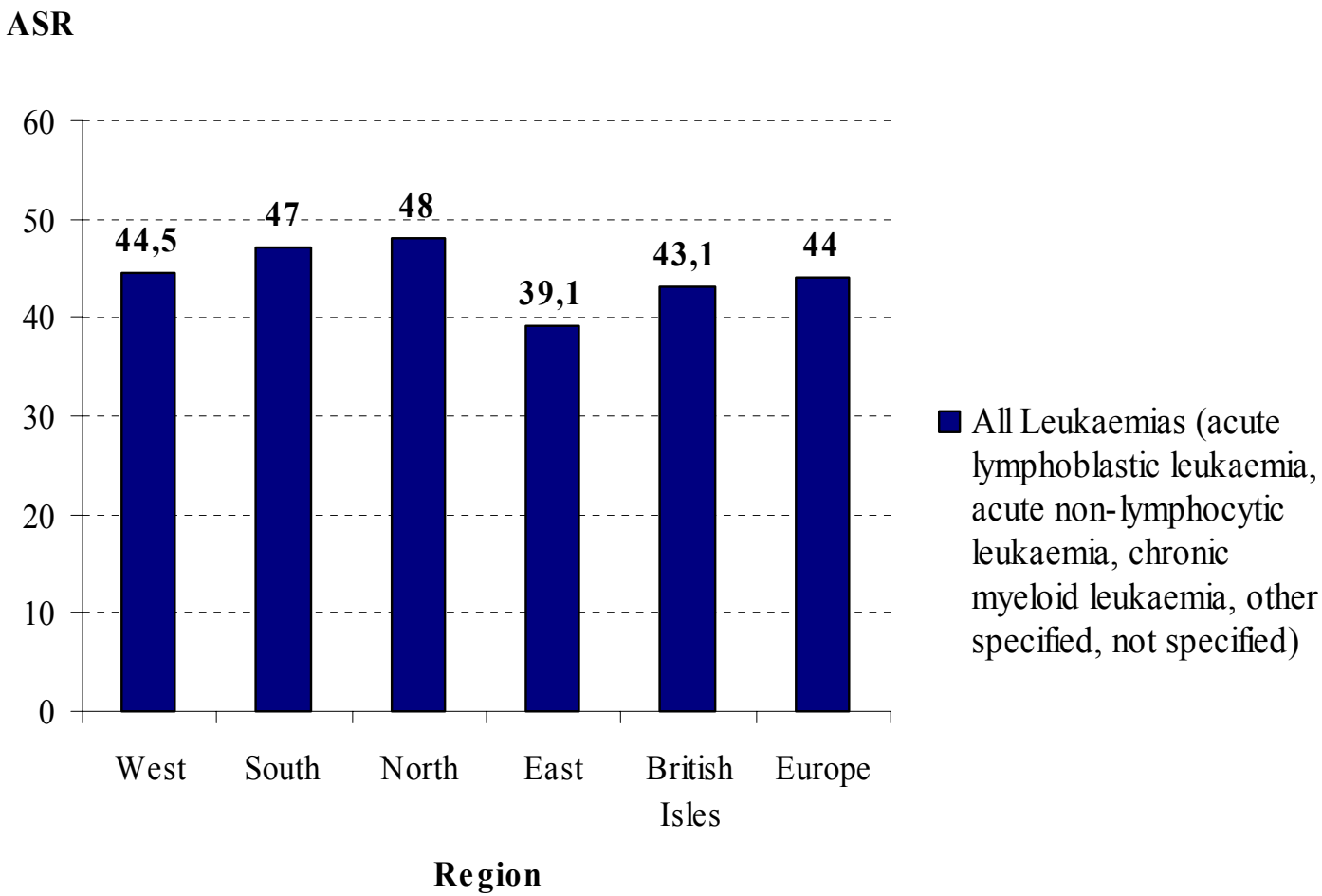
Table 6 – Numbers of cases (*n*) and incidence rates (per million person-years) of leukaemias in children (0–14 years) and adolescents (15–19 years) across Europe, 1978–1997 (Source: ACCIS)

Region	Period	Children		Rate by age group				Adolescents	
		n	ASR	0	1–4 years	5–9 years	10–14 years	*n*	Rate
(a) Lymphoid leukaemia (mostly acute lymphoblastic leukaemia)									
Europe	1978–82	3948	31.8	17.5	57.0	26.2	14.9	175	8.5
	1983–87	5799	33.8	16.6	61.2	28.1	15.6	226	10.7
	1988–92	6078	35.4	16.0	64.9	29.0	16.1	184	12.9
	1993–97	5727	37.2	17.6	67.6	30.3	17.5	163	12.3
(b) Acute non-lymphocytic leukaemia									
Europe	1978—1982	769	5.8	9.7	6.6	4.7	5.2	166	8.0
	1983—1987	1112	6.2	10.8	7.6	4.3	5.7	138	6.5
	1988—1992	1185	6.7	13.8	8.3	4.6	5.6	91	6.4
	1993—1997	1030	6.5	13.4	7.7	4.5	5.6	99	7.5
(c) Chronic myeloid leukaemia									
Europe	1978–1982	125	0.97	1.2	1.5	0.49	0.90	47	2.3
	1983–1987	145	0.80	1.1	1.0	0.55	0.82	27	1.3
	1988–1992	147	0.84	1.6	1.1	0.55	0.65	30	2.1
	1993–1997	135	0.84	1.8	0.8	0.48	1.0	21	1.6

Source: J.W.W. Coebergh et al., EJC 42, 2006

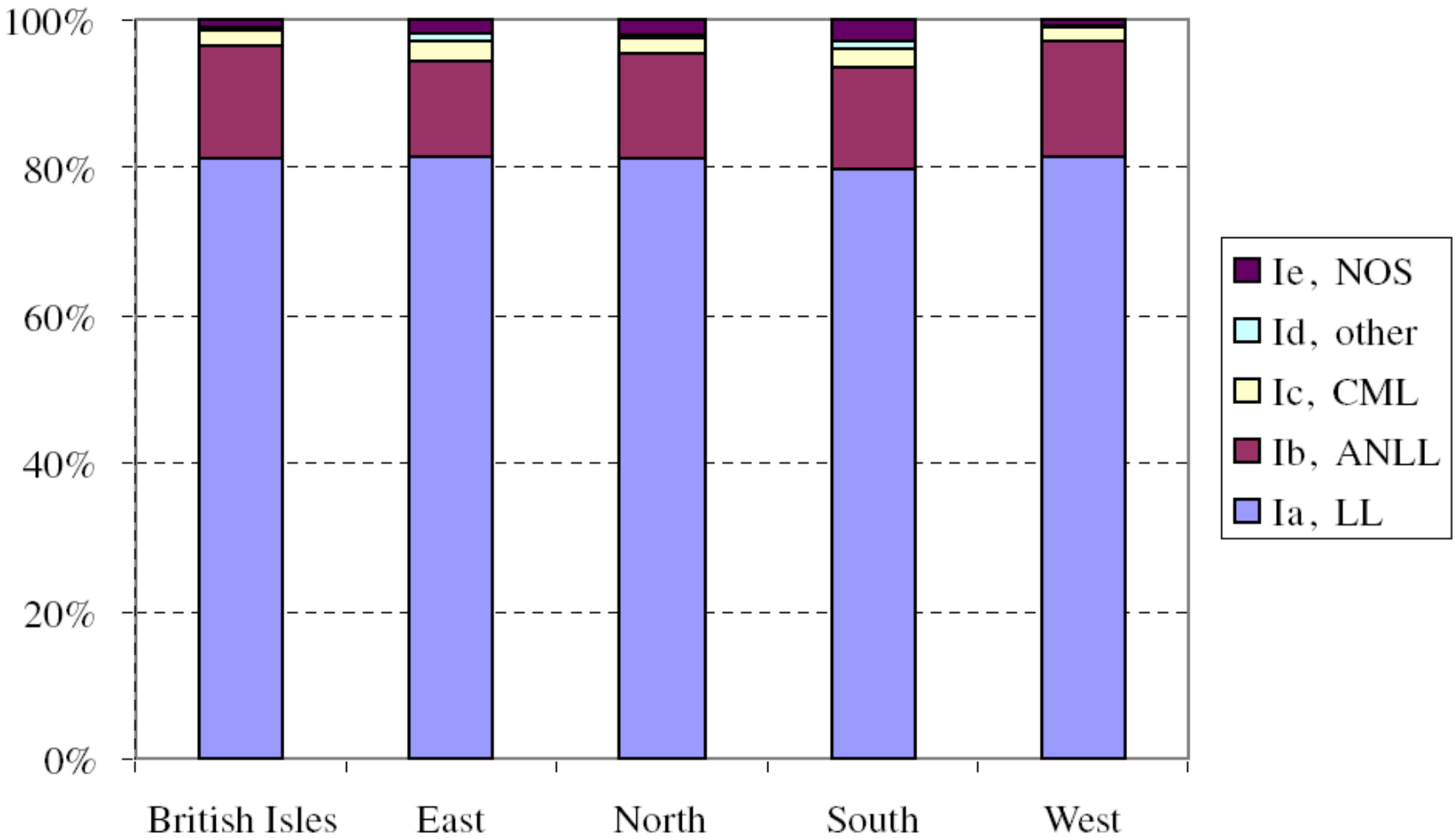
Regional variation in Europe

Regional variation of incidence rates of leukaemia in children (age 0-14 years, both sexes) across Europe during 1988-1997, per million children. ASR, age-standardised rate



from: Stiller et al. 2006, p. 1957; ACCIS)

Distribution of leukaemia subgroups in Europe, 1988-1997
- by regions -



Source: J.W.W. Coebergh et al., EJC 42, 2006; ACCIS

Table 3 – Age-standardised incidence rates (ASR) for childhood cancer (age 0-14 years) in Europe by time period and main diagnostic groups added by number of cases (1978-1997), average annual percent of change (AAPC) and result of trend test (*P<0.0001) (Source: ACCIS)**

Time period	ASR for Leukaemias (per million)				
	British Isles	East	North	South	West
1978-1982	39.3	37.3	44.4	45.6	41.9
1983-1987	40.2	35.0	52.2	44.2	43.7
1988-1992	42.8	38.9	47.4	51.1	44.4
1993-1997	43.5	37.6	48.5	48.7	46.2
No. of cases	7650	2666	2546	1569	10949
AAPC	0.7%**	0.3%	0.3%	0.5%	0.8%***

Source: P. Kaatsch et al., EJC 42, 2006

General remarks

and

Summary

Summary (1)

- In Europe 11 childhood cancer registries (5 of them are nationwide)
- German Childhood Cancer Registry (1980-2006)
  - 14,312 leukaemias
    - » 11,489 lymphoid leukaemias
    - » 2,080 acute myeloid leukaemias
- Automated Childhood Cancer Information System (1978-1997)*)
  - 26,690 leukaemias
    - » 21,552 lymphoid leukaemias
    - » 4, 096 acute myeloid leukaemias

*) including data from GCCR

Summary (2):
source: ACCIS (C.A. Stiller et al. EJC 2006)

Incidence rates*) of leukaemia in Europe (1988-1997)

- Age-standardized incidence rates: 44.0
- Highest in Northern Europe: 48.0
- Lowest in Eastern Europe: 39.1
- Significant increase: 0.6 % average annual percent change (1978-1997)

*) rates per million children below 15 years

Summary (3)

- In Europe, an increase of incidences rates for childhood leukaemia is observed (as well as for childhood cancer generally).
- Improvements in diagnostic procedures and registration artefacts account for only part of the increase.
- So an actual increase of the rates exists.
- Increase possibly is due to variations in risk factors in the last decades.

Thank you for your attention !

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