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Incidence and time trends of soft tissue sarcomas in German children 1985–2004 – A report from the population-based German Childhood Cancer Registry

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ABSTRACT

The incidence of soft tissue sarcoma (STS) in Europe is increasing, but it is unclear whether this increase can also be seen in Germany. We analysed the heterogeneous group of STS recorded to the German Childhood Cancer Registry (GCCR) between 1985 and 2004 with respect to incidence data. Age-specific, age-standardised and cumulative incidence rates were calculated. Additionally, the average annual percent change (AAPC), derived from a Poisson regression model, was estimated, using time in years as the explanatory, continuous variable. Two thousand sixty-one children were diagnosed at a median age of 72 months. Most common are rhabdomyosarcomas (RMS) ($n = 1202$) and fibrosarcomas ($n = 174$). The age-standardised incidence rate (ASR) is 0.9 per 100,000/year for all STS, 0.70 for rhabdomyosarcoma-like ($n = 1588$) and 0.18 for non-rhabdomyosarcoma-like ($n = 411$) STS. AAPC is +0.4% (95%-confidence interval [–0.4;+1.2%]) for STS. In Germany, the increase in incidence rate is less evident than in other European countries.

1. Introduction

Soft tissue sarcomas (STS) in childhood are a heterogeneous group of malignant tumours: they originate from connective tissue,[1] are primarily of mesenchymal origin and develop at various sites in the body.[2,3] These tumours are characterised by a broad diversity of morphological entities. Childhood STS can be subdivided into two pathology-derived groups, i.e. the rhabdomyosarcomatous (RMS) and the non-rhabdomyosarcomatous STS (NRSTS), and, applying clinical criteria, into RMS-like and non-RMS-like STS. STS in children and adolescents differ from the STS of adults with respect to incidence rate, the distribution of histological subtypes, biological behaviour and prognosis.[4]

STS represent 6.6% of all childhood malignancies in Germany and thus rank fifth amongst the malignancies registered during the last decade[5] behind leukaemias (33.1%), brain tumours (21.4%), lymphomas (12.2%) and sympathetic

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nervous system tumours (8.3%). Amongst the extracranial solid tumours of childhood, RMS are the third most common neoplasm after neuroblastoma and Wilms tumour.[3] According to data from several cancer registries, STS account for about 8% of all childhood cancers, i.e. 3571 cases under the age of 15 years, reported to European cancer registries between 1978 and 1997.[6] This is documented in the Automated Childhood Cancer Information System project (ACCIS) which collected data from 59 cancer registries in 19 European countries. It is based on the International Classification of Childhood Cancer (ICCC)[7] and estimates age-standardised annual incidence rates (ASR, world standard, and per 100,000 patients below the age of 15) of 0.91 for all STS, 0.54 for RMS, 0.11 for fibrosarcomas, 0.20 for 'other' STS and 0.06 for 'unspecified' STS.[6] The incidence rate of RMS is about 50% of STS, all forms combined.[2,6] The incidence rate of specific STS subtypes and the distribution of histological NRSTS subtypes is age-dependent.[8] Two thirds of the cases of RMS are diagnosed in children aged 6 years or younger.[2,6]

An analysis based on ACCIS data were published in 2006[6,9]: a significant, increasing trend was shown for STS with an average annual percent change (AAPC) of 1.8% for Europe between 1978 and 1997. The largest increase was observed in the British Isles (AAPC +2.8%), the smallest in Western Europe (+0.4%).[9] The 5-year survival for children with STS was 65%, which was mainly determined by the survival rate in the RMS subgroup (63%).[6] In Western Europe, the 5-year survival was estimated to be 66% for all STS and 67% for RMS.[6] The German cohort, which was part of the ACCIS database (Western European region), comprised data from former East Germany (1978–1989), former West Germany (1983–1990) and post-unification East and West Germany combined (1991–1997). The German Childhood Cancer Registry (GCCR) is one of the largest population-based registries for childhood cancer worldwide and can claim a high degree of completeness. The following report presents a detailed analysis of German STS data for the years 1985–2004.

2. Patients and methods

The analysis is based on the data of the GCCR and covers the years 1985 through 2004. Children diagnosed prior to this time were excluded from the analysis because of potential underreporting in the early years of registration and the intended limitation to a 20 year time period. The methods of the registry as a whole have been described in more detail elsewhere.[10] Briefly, the GCCR was established at the Johannes Gutenberg University of Mainz in 1980. It cooperates with the German Society of Paediatric Oncology and Haematology (GPOH). All of the German departments of paediatric oncology (currently about 80) report their cases to the GCCR. The GPOH-associated multi-centre clinical trials are consultation partners for validation and fill in missing information. The GCCR records all forms of malignancies as well as benign tumours of the brain diagnosed in children up to age 15 years at diagnosis. Since 1991, patients from the area of the former German Democratic Republic have been included as well. The underlying population base consists of 12.5 million children resident in Germany (averaged 2000–2004). The level of completeness has been estimated to exceed 95% from about 1987 onward.[11]

The data presentation in this paper follows ICCC-3[12] which refers to the International Classification of Disease for Oncology, 3rd ed. (ICD-O-3).[13] Additionally, the group of RMS has been subdivided according to ICD-O-3 criteria, distinguishing embryonal (M-8910/3, M-8991/3) from alveolar (M-8920/3) and other RMS (M-8900/3, M-8901/3 and M-8902/3). This distinction is important with a view to clinical behaviour and prognosis.[14,15] In keeping with common practice when looking at childhood cancers, the analysis considered four different age groups, i.e. 0, 1–4, 5–9 and 10–14 years, for reasons of comparability.

For classification of tumour site, we refer to the ICD-O-3 topography code[13] as follows: head and neck (C00.0–C14.8, C30.0–C32.9, C41.0–C41.1, C44.0, C44.2–C44.4, C47.0, C49.0, C76.0), orbit (C69.0–C69.9, C44.1), pelvis (C41.4, C47.5, C49.5, C76.3), genito-urinary subdivided in 'genito-urinary (not bladder/prostate)' (C51.0–C57.9, C60.0–C60.9, C62.0–63.9, C64.9–C66.9,C68.0–C68.9), and 'bladder/prostate' (C61.9, C67.0–C67.9), limbs (C40.0–C40.9, C44.6, C44.7, C47.1, C47.2, C49.1, C49.2, C76.4 and C76.5), thorax (C49.3, C76.1), not otherwise specified (C76.2, C76.7, C76.8, C80.9 and C49.9) and 'others' including all codes not listed in another category.

There was only one patient with a generalised Kaposi sarcoma. 93.5% of all STS patients and 97.3% of the RMS patients were registered to clinical CWS-trials and treated accordingly. Consecutive trials of the Cooperative Soft Tissue Sarcoma Study group (Cooperative Weichteilsarkom-Studie, CWS) have been conducted in Germany since 1981.[15,16] Inclusion in a clinical trial is an indicator for good quality in that the diagnosis is peer reviewed (i.e. confirmed by a reference pathologist), treatment is highly standardised and compliance with the protocol is controlled. The centralisation of pathological review[4] and the associated improvements in diagnostic accuracy owing to advances in molecular pathology have gradually developed during the consecutive CWS trials as has the centralisation of radiological review.

With respect to clinical behaviour and treatment the CWS study protocol distinguish mainly two subgroups of STS, i.e. RMS-like STS and non-RMS-like STS. We applied the same criteria in consideration of the impact for clinicians. Whilst 62 STS cases could not be allocated because of lack of information 1999 patients were classified in this manner. The exact ICD-O-3 based definition of the two groups is given in the footnotes of Tables 3 and 6. The four most common RMS-like STS are RMS, extraosseous tumours of the Ewing family (i.e. EES/pPNET) and synovial sarcoma.

ASR were adjusted to world standard population as recommended by the IARC.[17] Cumulative incidence reflects the overall risk up to the age of 15 and is calculated by summing up fifteen 1-year age specific incidence rates.

The change of an incidence rate over time is expressed as the average annual percent change (AAPC). The AAPC was derived from a Poisson regression model with year as the explanatory continuous variable coded naturally (year 1985 is year 1). Indicators for the four age groups were always included, so that the trend is corrected for possible shifts in the age distribution. Annual age group specific population data were included as an offset in the regression model, thus

Table 1 – Absolute number, percentage, incidence rate (per 100,000), median age, sex ratio of children (0–14 years) with soft tissue sarcomas by ICCC-3[a] subgroups (n = 2061); Germany 1985–2004

ICCC-3	Diagnostic group	ICCC-3 division	Number of patients			Incidence rates, ASR[b]	Median age, month (years)	Sex ratio, male/female
			Absolute (*n*)	Relative (%)	Group (%)			
IX	All STS[c]		**2061**	**100**		**0.90**	**72 (6.0)**	**1.2**
IXa	Rhabdomyosarcomas		**1202**	**58.3**	**100**	**0.54**	**59 (4.9)**	**1.4**
		Embryonal	831	40.3	69.1	0.38	54 (4.5)	1.4
		Alveolar	258	12.5	21.5	0.11	79 (6.6)	1.1
		Others	113	5.5	9.4	0.05	59.5 (5.0)	1.5
IXb	Fibrosarcomas, peripheral nerve sheath tumours, and other fibrous neoplasms		**174**	**8.4**	**100**	**0.08**	**97.5 (8.1)**	**0.8**
		Fibroblastic and myofibroblastic tumours	73	3.5	42.0	0.03	9 (0.8)	1.1
		Nerve sheath tumours	101	4.9	58.1	0.04	126 (10.5)	0.7
		Other fibrous neoplasms	0	0.0	0.0	0.00	–	–
IXc	Kaposi sarcoma		**1**	**<0.1**	**100**	**<0.01**	**58 (4.8)**	–
IXd	Other specified STS[c]		**563**	**27.3**	**100**	**0.23**	**116 (9.7)**	**1.1**
		Ewing tumour and Askin tumour of soft tissue	102	5.0	18.1	0.04	99.5 (8.3)	0.9
		pPNET[d] of soft tissue	142	6.9	25.2	0.06	117 (9.8)	1.0
		Extrarenal rhabdoid tumour	33	1.6	5.9	0.02	21 (1.8)	1.8
		Liposarcomas	14	0.7	2.5	0.01	77 (6.4)	2.5
		Fibrohistiocytic tumours	39	1.9	6.9	0.02	109 (9.1)	1.3
		Leiomyosarcomas	36	1.8	6.4	0.02	100.5 (8.4)	1.1
		Synovial sarcomas	127	6.2	22.6	0.05	138 (11.5)	1.1
		Blood vessel tumours	10	0.5	1.8	<0.01	80 (6.7)	0.4
		Osseous and chondromatous neoplasms of soft tissue	7	0.3	1.2	<0.01	88 (7.3)	0.8
		Alveolar soft part sarcoma	21	1.0	3.7	0.01	152 (12.7)	0.6
		Miscellaneous soft tissue sarcomas	32	1.6	5.7	0.01	76 (6.3)	1.3
IXe	Unspecified STS[c]		**121**	**5.9**	**100**	**0.05**	**92 (7.7)**	**1.4**

a International Classification of Childhood Cancer, 3rd ed.[12]
b Age standardised incidence rate, world standard.
c STS, soft tissue sarcomas.
d pPNET, peripheral primitive neuroectodermal tumour.

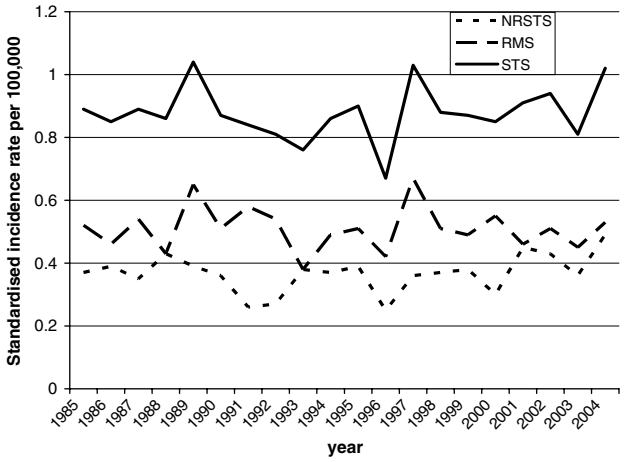

Fig. 1 – Age standardised annual incidence rates of children (0–14 age) with all soft tissue sarcomas (STS, *n* = 2061) according to rhabdomyosarcomas (RMS, *n* = 1202) and non-rhabdomyosarcomas (NRSTS, *n* = 859) from 1985 to 2004 in Germany (0–14 years).

fully accounting for secular trends in the population base and the population age distribution.[9]

3. Results

Between 1985 and 2004, a total of 2061 STS patients below 15 years of age resident in Germany were reported to the GCCR. This represents 6.5% of the total number of 32,043 malignancies registered. Most of the STS are RMS (58.3%). The median age at diagnosis for all STS is 6.0 years (first quartile = 2.8; third quartile = 11.1), for RMS it is 4.9 years (first quartile = 2.6; third quartile = 8.8). Table 1 provides information on the absolute and the relative number of patients, ASR, median age at diagnosis and sex ratio according to ICCC-3. ASRs for STS, RMS and NRSTS by calendar year are shown in Fig. 1. The age and sex-specific incidence rates are given in Table 2 and Fig. 2. The highest incidence rate for all STS combined and for most of the subgroups is observed in the first year of life. For RMS-like and non-RMS-like STS some information is provided in Table 3.

Table 4 presents both the frequency and distribution of STS and RMS, respectively, by site and ICCC-3 group. Most of the RMS are located in the head and neck, the second most common site is the pelvis. This distribution is mostly attributable to the proportion of embryonal RMS in the group; the site distribution is clearly different when looking at alveolar RMS: most of those can be found at the limbs in contrast to embry-

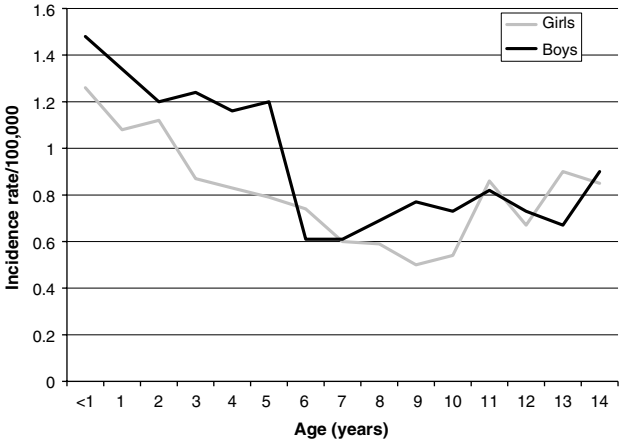

Fig. 2 – Age and sex specific incidence rates of 2061 children (0–14 age) with soft tissue sarcoma in Germany (1985–2004).

Table 2 – Absolute number of cases, age and sex specific incidence rates (per 100,000), ASR[a] and cumulative incidence (per 100,000) of soft tissue sarcomas by ICCC-3[b] in 2061 children (0–14 years) diagnosed between 1985 and 2004 in Germany

	N	Incidence rates					
		Age specific				ASR[a]	Cumulative incidence
		0	1–4	5–9	10–14		
IX Soft tissue sarcomas	2061	1.37	1.11	0.71	0.77	0.90	13.20
Girls	929	1.25	0.97	0.64	0.77	0.83	12.20
Boys	1132	1.48	1.23	0.78	0.77	0.97	14.14
IXa Rhabdomyosarcomas	1202	0.62	0.85	0.46	0.29	0.54	7.74
Girls	510	0.57	0.72	0.39	0.27	0.47	6.75
Boys	692	0.67	0.97	0.53	0.31	0.61	8.69
IXb Fibrous neoplasms	174	0.32	0.03	0.04	0.09	0.08	1.11
Girls	95	0.32	0.03	0.05	0.11	0.08	1.24
Boys	79	0.32	0.04	0.03	0.07	0.07	0.99
IXd Other specified STS[c]	563	0.32	0.18	0.17	0.33	0.23	3.56
Girls	273	0.32	0.18	0.16	0.34	0.23	3.54
Boys	290	0.32	0.18	0.18	0.33	0.23	3.57
IXd Unspecified STS[c]	121	0.11	0.04	0.04	0.06	0.05	0.77
Girls	51	0.04	0.04	0.04	0.06	0.04	0.66
Boys	70	0.17	0.04	0.04	0.06	0.06	0.87

a ASR, Age standardised incidence rate, world standard per 100,000.
b International Classification of Childhood Cancer, 3rd ed.[12]
c STS, soft tissue sarcomas.

Table 3 – Absolute number, percentage, incidence rate (per 100,000), median age, sex ratio and AAPC[a] of children (0–14 years) by RMS-like[b] and non-RMS-like[c] soft tissue sarcomas (STS) 1985–2004, n = 1999, in Germany

STS	Number of patients	Incidence rates, ASR[d]	Median age, month (years)	Sex ratio, male/female	AAPC(%)[a]	95% confidence interval
RMS-like STS[b]	1588	0.70	68 (5.8)	1.3	0.6	–0.3 – +1.5
Non-RMS-like STS[c]	411	0.18	97 (8.1)	1.1	–0.3	–2.0 – +1.5

a AAPC, average annual percent change derived from a Poisson regression model adjusted for age group.
b Rhabdomyosarcoma-like STS: IDC-O-3 (M-codes, only '/3') 8805/3, 8900/3 to 8920/3, 9040/3 to 9043/3, 9260/3, 9364/3 to 9365/3.
c Non-rhabdomyosarcoma-like STS: ICD-O-3 (M-codes, only '/3') 8804/3, 8806/3 to 8811/3, 8814/3, 8830/3, 8832/3, 8850/3 to 8852/3, 8890/3, 8891/3, 8895/3, 8921/3, 8963/3, 8990/3, 8991/3, 9044/3, 9120/3, 9130/3 to 9150/3, 9220/3, 9240/3, 9540/3 to 9561/3, 9581/3.
d Age standardised incidence rate, world standard.

Table 4 – Frequency and percentage of soft tissue sarcomas by site and ICCC-3[a] subgroups; Germany 1985–2004, patients 0–14 years

Site of tumour	Rhabdomyosarcomas IXa[b]				IXb[b] (%)	IXd[b] (%)	IXe[b] (%)	All STS[b] (%)	M/F[c]
	Embryonal (%)	Alveolar (%)	Other (%)	All IXa[b] (%)					
Head and neck	230 (27.7)	49 (19.0)	22 (19.5)	301 (25.0)	28 (16.1)	83 (14.7)	24 (19.8)	436 (21.2)	1.3
Orbit	116 (14.0)	11 (4.3)	7 (6.2)	134 (11.2)	0 (0.0)	7 (1.2)	4 (3.3)	145 (7.0)	1.0
Pelvis	134 (16.1)	43 (16.7)	23 (20.4)	200 (16.6)	13 (7.5)	46 (8.2)	14 (11.6)	273 (13.3)	2.4
Genito-urinary (not bladder/ prostate)	66 (7.9)	0 (0.0)	5 (4.4)	71 (5.9)	1 (0.6)	3 (0.5)	1 (0.8)	76 (3.7)	1.3
Bladder/prostate	108 (13.0)	2 (0.8)	5 (4.4)	115 (9.6)	0 (0.0)	3 (0.5)	1 (0.8)	119 (5.8)	2.4
Limbs	38 (4.6)	93 (36.1)	13 (11.5)	144 (12.0)	67 (38.5)	206 (36.6)	19 (15.7)	436 (21.2)	1.0
Thorax	23 (2.8)	14 (5.4)	4 (3.5)	41 (3.4)	12 (6.9)	72 (12.8)	6 (5.0)	131 (6.4)	0.9
Not otherwise specified	10 (1.2)	11 (4.3)	11 (9.7)	32 (2.7)	2 (1.2)	33 (5.9)	2 (1.7)	70 (3.4)	1.1
Other	106 (12.8)	35 (13.6)	23 (20.4)	164 (13.6)	51 (29.3)	110 (19.5)	50 (41.3)	375 (18.2)	1.1
Total	831 (100.0)	258 (100.0)	113 (100.0)	1202 (100.0)	174 (100.0)	563 (100.0)	121 (100.0)	2061 (100.0)	1.2

a International Classification of Childhood Cancer, 3rd ed.[12]
b IXa: rhabdomyosarcoma, IXb: fibrosarcoma, IXd: other specified soft tissue sarcomas, IXe: unspecified soft tissue sarcomas, STS: soft tissue sarcoma.
c m/f, male/female.

Table 5 – Frequency of RMS-like[a] and non-RMS-like[b] soft tissue sarcomas (STS) by site subgroups; Germany 1985–2004, patients 0–14 years (n = 1999)

Site	RMS-like STS		Non-RMS-like STS	
	Absolute (*n*)	Relative (%)	Absolute (*n*)	Relative (%)
Head and neck	362	22.8	60	14.6
Orbit	138	8.7	5	1.2
Pelvis	237	14.9	32	7.8
Genito-urinary (not bladder/prostate)	72	4.5	4	1.0
Bladder/prostate	117	7.4	1	0.2
Limbs	271	17.1	155	37.7
Thorax	99	6.2	29	7.1
Not otherwise specified	53	3.3	16	3.9
Other	239	16.1	109	26.5
Total	1588	100	411	100

a Rhabdomyosarcoma-like STS: IDC-O-3 (M-codes, only '/3') 8805/3, 8900/3 to 8920/3, 9040/3 to 9043/3, 9260/3, 9364/3 to 9365/3.
b Non-Rhabdomyosarcoma-like STS: ICD-O-3 (M-codes, only '/3') 8804/3, 8806/3 to 8811/3, 8814/3, 8830/3, 8832/3, 8850/3 to 8852/3, 8890/3, 8891/3, 8895/3, 8921/3, 8963/3, 8990/3, 8991/3, 9044/3, 9120/3, 9130/3 to 9150/3, 9220/3, 9240/3, 9540/3 to 9561/3, 9581/3.

onal RMS. Regarding genito-urinary sites and pelvis there is a clear preponderance of boys. Overall, the majority of STS are located at the limbs and the head and neck (21.2% each). Tables 5 and 6 provide frequencies by site of RMS-like (predominantly head and neck) and non-RMS-like STS (predominantly limbs).

Table 6 – Incidence rate and incidence trend in children aged 0–14 with soft tissue sarcoma (ICCG-3[a] IX) and for the rhabdomyosarcoma subgroup (ICCG-3[a] IXa), according to site of tumour; Germany 1985–2004

STS[b] (*n* = 2061)	Incidence							
	Number	Age specific incidence rates				ASR[c]	AAPC(%)[d]	95%-confidence interval
		0 years	1–4 years	5–9 years	10–14 years	0–14 years		
Site								
Head and neck	436	0.23	0.25	0.19	0.12	0.19	–0.8	–2.5 – +0.9
Orbit	145	0.07	0.08	0.07	0.04	0.06	–0.1	–3.0 – +2.9
Pelvis	273	0.12	0.16	0.12	0.08	0.12	0.8	–1.4 – +3.0
Genito-urinary (not bladder/prostate)	76	0.05	0.05	0.02	0.03	0.03	0.7	–3.4 – +4.9
Bladder/prostate	119	0.12	0.12	0.02	0.02	0.06	0.0	–3.2 – +3.3
Limbs	436	0.31	0.14	0.12	0.25	0.18	0.4	–1.3 – +2.1
Thorax	131	0.14	0.07	0.03	0.05	0.06	4.3	1.0 – +7.7
Not otherwise specified	70	0.04	0.03	0.02	0.04	0.03	–2.4	–6.4– +1.8
Other	375	0.31	0.20	0.12	0.14	0.17	1.0	–0.8 – +2.9
Total	2061						0.4	–0.4 – +1.2
Rhabdomyosarcoma (n = 1202)								
Head and Neck	301	0.12	0.20	0.15	0.06	0.13	–2.0	–3.9 – +0.1
Orbit	134	0.05	0.07	0.07	0.04	0.06	–0.5	–3.5 – +2.6
Pelvis	200	0.07	0.14	0.09	0.05	0.09	0.5	–2.0 – +3.1
Genito-urinary (not bladder/prostate)	71	0.05	0.05	0.02	0.02	0.03	0.8	–3.3 – +5.2
Bladder/prostate	115	0.12	0.12	0.02	0.01	0.06	–0.5	–3.7 – +2.9
Limbs	144	0.08	0.09	0.05	0.05	0.06	–0.4	–3.3 – +2.6
Thorax	41	0.04	0.03	0.01	0.01	0.02	3.4	–2.3 – +9.4
Not otherwise specified	32	0.01	0.02	0.01	0.01	0.01	–6.3	–12.1 – –0.1
Other	164	0.08	0.13	0.05	0.04	0.08	5.1	2.1 – +8.2
Total	1202						0.1	–0.9 – +1.1

a International Classification of Childhood Cancer, 3rd ed.[12]
b STS, soft tissue sarcomas.
c ASR, age standardised incidence rate, world standard per 100,000.
d AAPC, average annual percent change derived from a Poisson regression model adjusted for age group.

Table 7 – Age standardised incidence rates per 100,000 (world standard) and incidence trend of soft tissue sarcomas diagnosed in children aged 0–14 according to ICCG-3[a]; Germany 1985–2004

	N	ASR[b]				AAPC(%)[d]	95%-confidence interval
		1985–1989	1990–1994[c]	1995–1999	2000–2004		
IX Soft tissue sarcomas	2061	0.92	0.84	0.91	0.94	0.4	–0.4 – +1.2
IXa Rhabdomyosarcoma	1202	0.55	0.51	0.57	0.54	0.1	–0.9 – +1.1
Embryonal	831	0.41	0.36	0.38	0.38	–0.3	–1.5 – +1.0
Alveolar	258	0.10	0.12	0.12	0.11	0.7	–1.5 – +2.9
Other	113	0.04	0.04	0.07	0.05	1.4	–2.0 – +4.8
IXb Fibrosarcoma	174	0.08	0.07	0.07	0.08	1.1	–1.6 – +3.9
IXc Kaposi sarcoma	1	–	–	–	–	–	–
IXd Other specified	563	0.25	0.23	0.22	0.24	0.3	–1.2 – +1.8
IXe Unspecified	121	0.05	0.03	0.05	0.07	2.8	–0.5 – +6.3

a International Classification of Childhood Cancer, 3rd ed.[12]
b ASR, Age standardised incidence rate, world standard per 100,000.
c Since 1991 East Germany, the former German Democratic Republic, is included.
d AAPC, average annual percent change derived from a Poisson regression model adjusted for age group.

There is a non-significant increase in the incidence rates of STS (AAPC = +0.4%, 95%-confidence interval [–0.4; +1.2%]). Variations in the secular trend of incidence rates are associated to a lesser extent with the differences in histological appearance and more clearly with tumour site (Tables 6 and 7). Overall, we find a significant increase of STS of the thorax (AAPC = 4.3, 95%-confidence interval [+1.0; +7.7%]). For RMS, there is a significant decreasing trend regarding the 'not otherwise specified' site and a significant increasing trend for 'other' sites. However, there are only 32 cases in the 'not

otherwise specified' group. Remarkably, a borderline trend of –2.0% per year is seen for RMS of the head and neck. 'Unspecified' STS (ICCC-3 IXe) seem to increase (Table 7), but based on merely 121 cases. Whilst there is no significant trend all indicators point to an increasing trend for incidence in the other main ICCC-3 groups. It has to be noted that there is a dip of ASR in the early 1990s (Table 7). The subgroup analysis of genito-urinary STS shows a decreasing incidence rate of RMS of the bladder and the prostate and an increase regarding all other sites. RMS-like STS seem to increase and non-RMS-like STS seem to decrease (Table 3).

4. Discussion

The incidence rates described here are comparable with those described elsewhere for Europe[6] and the USA.[2,3] We could not confirm the significant increases of STS incidence found in a pan-European analysis[6,9]; whereas a positive trend can in fact be stated there are several distinctions to the trend reported elsewhere.[6,18] Some interesting findings concern the analysis by site. Thoracic STS are increasing significantly and so are RMS at 'other' locations, however not those at 'not otherwise specified' sites which show a significant decrease.

The GCCR is one of the largest population based registries for childhood cancer worldwide. At present, the time period covered exceeds 25 years. It is well accepted that the data of the GCCR are of excellent quality.[19,20] It is a strong point of any analysis done at the GCCR that the registry comprises complete in depth data from 20 consecutive years, using the same methods as comparable reports, and can place those data in context with the European data. Malignancies are registered based on the new ICCC-3 classification and for the first time are reported according to this schema.[12] Moreover, excellent cooperation with the clinicians allows for the interpretation of the data in the light of specific clinical circumstances influencing the data. The vast majority of children registered in the GCCR are treated in clinical trials and, as mentioned earlier, inclusion in a clinical trial is associated with high quality documentation. Because there are no other clinical trials for children with STS in Germany apart from CWS it is likely that the vast majority of paediatric STS patients have been treated according to CWS-protocols. This holds particulary true for RMS-like STS patients treated in paediatric oncology departments, as chemotherapy (and not only surgery/radiation) is considered a standard of care in these tumours.

We confirm the drop in ASR of STS in the years 1990–1994 earlier described in the USA.[2] The reasons for this decrease are still not clear. One has to be aware that this was the time when the registration of malignancies from East Germany (the area of the former German Democratic Republic) to the GCCR started. There might be some impact on the German data from possible initial under-reporting or differences in diagnostic procedures.

Pastore and colleagues described a significant increase in trend for all STS mainly based on embryonal and alveolar RMS.[6] This is not seen in the German data. A modifying factor may be the difference in time period as the ACCIS data cover the years 1978–1997 and the data reported here refer to 1985–2004. The increase observed by Pastore and colleagues reflects a lower rate in the first ten years followed by a higher rate in the later years.[6]

Looking at time trends in the ACCIS data Kaatsch and colleagues described a non-significant AAPC of +0.4% for STS in the Western countries (France, Germany, Netherlands and Switzerland) and a significant increase for the British Isles, Northern and Eastern Europe (+2.8%, +2.4% and +2.1%, respectively).[9] In West Germany, the incidence rate of STS increased significantly by +1.3% per year (95% confidence interval [+0.3%;+2.3%]) between 1987 and 2004,[18] with the most intense increase in the birth cohort since the year 2000, whilst no comparable increase has been observed in East Germany (AAPC –0.6% per year since 1991, 95% confidence interval [–2.9;+4.3%]). The present analysis has gone on to consider data from unified Germany as a whole.

5.9% of all STS are classified as 'unspecified' soft tissue sarcomas (ICCC-3 IXe) in our data. In principle, the 'unspecified' fraction ought to be small in a high quality register. However, this quality indicator may be regarded as inappropriate in STS, because STS are a very heterogeneous group of diseases and not every STS subgroup is covered by groups IXa to IXd. On the other hand, it is not always possible to clearly assign a disease to a subgroup even in a setting providing for quality controlled peer review as it exists in Germany. About 7% of all STS in the European registries selected for the ACCIS project are 'unspecified'.[6] However, high standard peer reviewed diagnosis has not been or is still not the rule in other European countries.

In our dataset the largest increase of ASR over time is observed in the group of 'unspecified' STS (IXe). The fairly high but non-significant AAPC (+2.8%) in this group is mainly explained by the data from the time period between 2000 and 2004. As mentioned before, 'unspecified' STS are suspected to be the most heterogeneous group. However, the last 20 years have brought about a change in diagnostic patterns and STS classification which enabled better characterisation of STS.[6] It is thus unclear why the IXe group in particular is growing. The development of diagnostic procedures during the last years reflects new approaches in studying the molecular behaviour of the tumour, which may signal changes in pathological assessment.

In the 1980s, it was shown that for prognostic reasons small focal evidence of alveolar histology in a tumour required the diagnosis of alveolar RMS, which prompted a change in the interpretation of pathologists' classification criteria.[21] The increasing incidence of alveolar RMS has been observed in the CWS study group as well as other cooperative clinical study groups investigating paediatric RMS.[22] The sex specific incidence rates in the study population show a preponderance of boys. This is in agreement with the literature[2,6] and is most apparent in the RMS group.

An increase in genito-urinary STS (+1.8% per year) was seen in Europe between 1978 and 1997[6] whereas in Germany it was the thoracic sites which showed a significant AAPC from 1985 to 2004. The reasons remain unclear. However, thoracic STS represent only a comparatively small subset. The decrease of 'not otherwise specified' RMS might be explained by better ascertainment and a shift in favour of the group of 'other' RMS.

Eight to nine percent of childhood STS seem to be inherited. This is especially apparent in patients with Li-Fraumeni

syndrome, which is associated with p53 mutations and retinoblastoma gene abnormality.[23] These are rare diseases and changes in this pattern should not have too much of an impact on the overall incidence of STS. However, the GCCR is not complete concerning this kind of information and there is no Li-Fraumeni syndrome documented in this study population. Whilst known risk factors for RMS have changed little over time, e.g. recreational drug abuse of the parents,[24] immunosuppression might also play a role. This has been shown in other cancers, for example malignant lymphoma. One well-known risk factor that interferes with T-cell immunology is HIV, probably in combination with HHV-8.[25] The risk of the associated Kaposi sarcoma amongst American AIDS patients of all ages in the pre-HAART era has been between 700 and 900 times as high as in the general population.[26] Kaposi sarcoma was reported only once in the entire study period. This is consistent with data from other registries. Only about 20 children per year are reported to be infected with HIV in Germany,[27] and only 500 children have been known to be infected with HIV in the entire study period.

Some older studies proposed a relationship between STS and the use of phenoxy herbicides.[23] As the use of phenoxy herbicides has decreased over the last decades, this should be reflected by a negative trend in STS incidence.

In summary, it can be said that contrary to the European data investigated in the ACCIS project (1978–1997) the incidence rate of STS in Germany was stable over the 1985–2004 period. The observed changes might be attributable to changes in pathological ascertainment and classification. Our data demonstrate clearly the relevance and possibilities of a comprehensive, high quality cancer registry.

Conflict of interest statement

The authors disclose no financial or personal relationship with people or organisations that could inappropriately influence or bias our work.

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