4 Cancer in children

Since taking up its work in 1980, the German Childhood Cancer Registry (GCCR), Department of Childhood Cancer Epidemiology, has been located at the Institute of Medical Biometry, Epidemiology and Informatics of the University Medical Centre of the Johannes Gutenberg University Mainz. Close cooperation with the Society for Paediatric Oncology and Haematology (GPOH) and its associated clinics was already intended in the conception of the GCCR. As a result, the registry has a characteristic that is not easily transferable to adult oncology. A comprehensive, nationwide epidemiological cancer registry was created for the entire Federal Republic of Germany with high data quality and a completeness of

Figure 4.1
Most frequent tumour sites as percent of all incident cancer cases in children under 18 years (determined for the period 2010–2019)

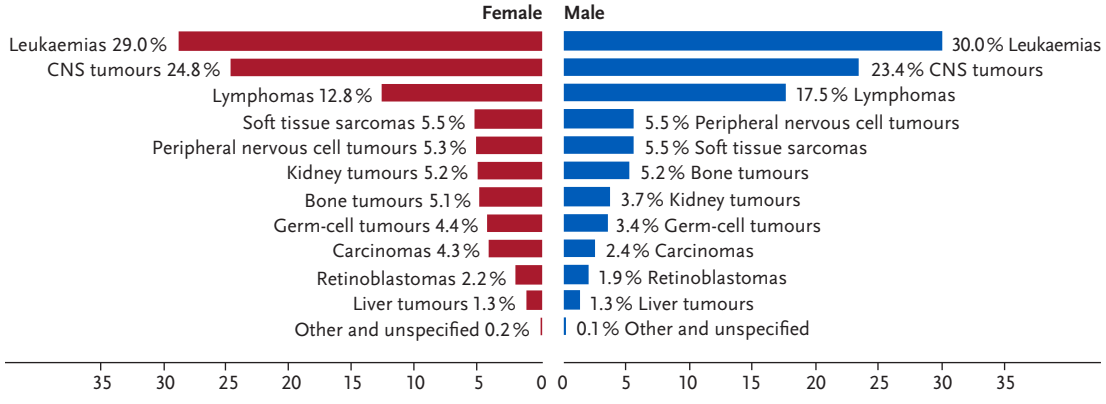


Table 4.1
Incidence* and survival rates for the most frequent diagnoses in childhood (under 18 years), by sex**

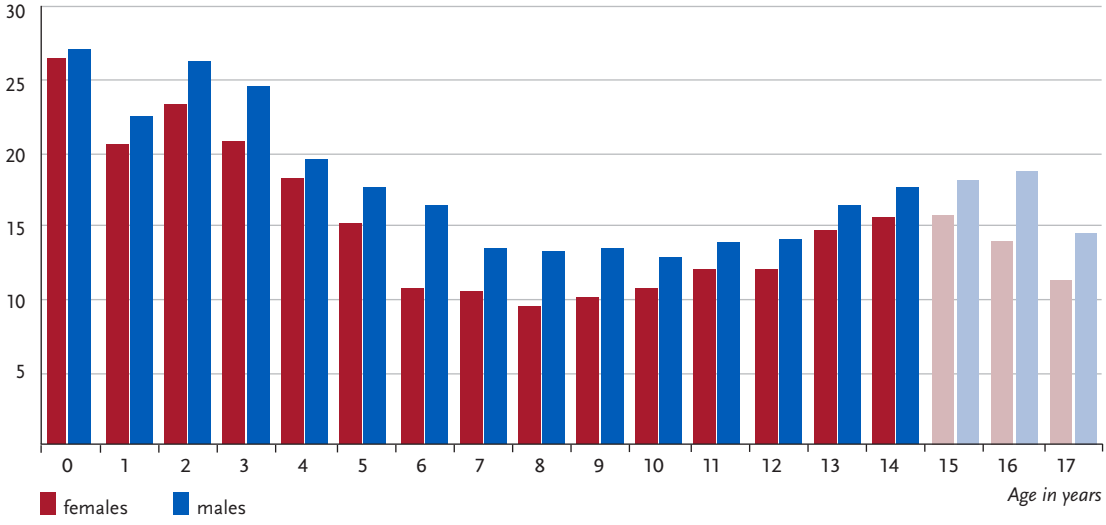
	Incidence*		survival rate in %**					
			after 5 years		after 10 years		after 15 years	
Cancer sites	females	males	females	males	females	males	females	males
Lymphoid leukaemias	3.5	4.3	92	92	91	91	90	90
Acute myeloid leukaemias	0.7	0.7	76	76	74	75	74	75
Hodgkin lymphomas	1.0	1.2	98	98	98	97	97	97
Non-Hodgkin lymphomas	0.4	1.1	88	91	87	90	86	88
Astrocytomas	1.8	1.9	86	83	84	82	83	80
Intracranial and intraspinal embryonal tumours	0.6	0.9	68	68	64	61	61	58
Neuroblastomas and ganglioneuroblastomas	1.0	1.3	85	79	84	77	83	77
Retinoblastomas	0.4	0.4	98	98	98	98	98	98
Nephroblastomas	0.9	0.8	94	93	93	92	92	92
Osteosarcomas	0.4	0.4	81	75	78	69	76	68
Rhabdomyosarcomas	0.4	0.6	70	72	68	70	68	69
Germ-cell tumours	0.7	0.6	97	91	95	91	95	90
All malignancies	15.7	18.4	87	86	85	84	84	83

* Cases per 100,000 children under age 18, age-standardised, standard: Segi world population, diagnosis years 2010–2019
** For children diagnosed between 2009 and 2018, predicted according to: Brenner H, Spix C. Combining cohort and period methods for retrospective time trend analyses of long-term cancer patient survival rates. Br J Cancer 89, 1260–1265, 2003

over 95% (since about 1987). The GCCR thus meets the international requirements for an epidemiological cancer registry. Another characteristic of the GCCR is the active open-end long-term follow-up well into adulthood. Thus, the registry also provides the basis for research into late sequelae, second tumours and generally for studies with long-term survivors.

Since 1980, the registry population included children who were diagnosed with a malignant disease or a histologically benign brain tumour before their fifteenth birthday and who belonged to the resident population of the Federal Republic of Germany at the time of diagnosis. Since about 1987, it can be assumed that the data are largely complete. Since 1991, cases in the new federal states have also been recorded.

Figure 4.2
Incidence rate by age and sex, all childhood malignancies
Number of cases per 100,000 by age group, determined for the period 2010–2019



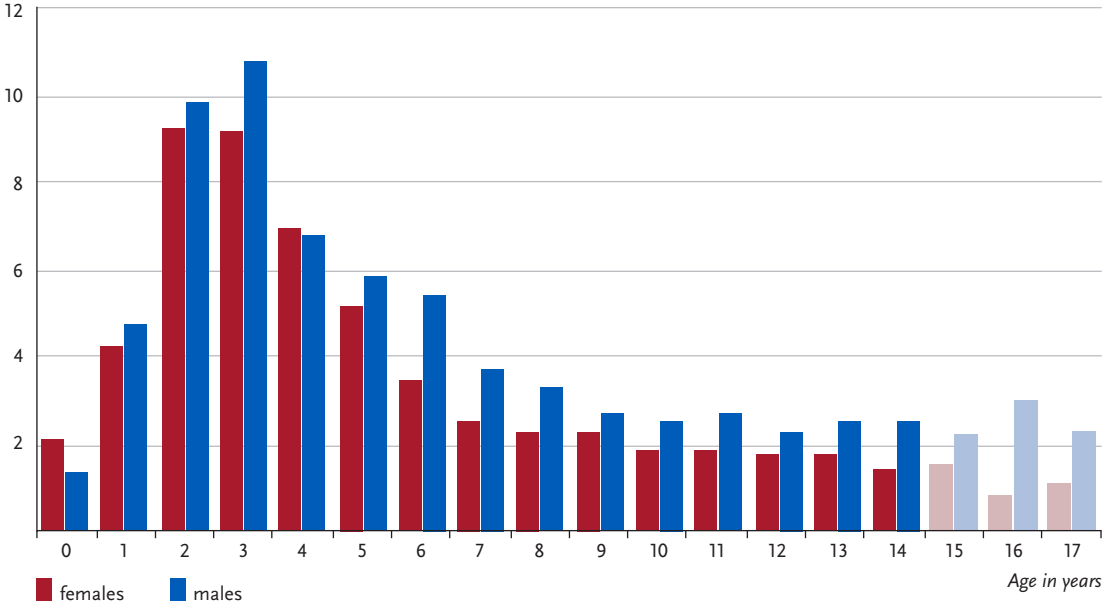
Suspected under-reporting among adolescents 15 years and older

Table 4.2
Number of incident cancer cases, incidence rates* and survival rates among children under 18 years for each of the 4 most frequent diagnoses in childhood and adulthood according to ICD-10, by sex**

		No. of incident cases		Incidence rate*		survival rate** in %					
						after 5 years		after 10 years		after 15 years	
Cancer sites	ICD-10	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
Leukaemia	C91–C95	2,590	3,368	4.3	5.2	89.8	89.9	88.8	88.7	88.1	88.1
Central nervous system	C70–C72	1,414	1,771	2.3	2.7	69.6	68.2	65.4	62.9	63.0	60.1
Hodgkin lymphoma	C81	741	873	1.0	1.1	97.9	98.3	97.6	97.5	97.4	96.6
Soft tissue without mesothelioma	C46–C49	731	750	1.3	1.2	79.5	74.4	77.0	71.9	76.3	71.3
Lung	C33–C34	39	45	0.1	0.1	69.7	81.0	69.7	78.5	69.7	76.3
Prostate	C61		7		0.0						
Breast	C50	3	2	0.0	0.0						
Colon and rectum	C18–C21	155	91	0.2	0.1						

* Cases per 100,000 persons under the age of 18, age-standardised according to the Segi world population, 2010–2019
** For children diagnosed between 2009 and 2018
♀female, ♂male

Figure 4.3
Incidence rate by age and sex, childhood lymphoid leukaemia (LL)
Number of cases per 100,000 by age group, determined for the period 2010–2019



Since 2009, the GCCR recorded all children and adolescents up to the age of 17 (= diagnosed before their eighteenth birthday) based on the »Guideline of the Joint Federal Committee on Quality Assurance Measures for the Inpatient Care of Children and Adolescents with Haematological Diseases«. This allows to meet the requirements of the cooperating hospitals, which had already included paediatric and adolescent medicine for several years and thus also treat adolescents above the age of 14 with corresponding diagnoses. The currently available data set is based on a total of approx. 70,000 cases.

Incidence of childhood cancers

In Germany, there are about 2,200 newly diagnosed cases under the age of 18 every year. With a population of about 13 million under 18-year-olds, this results in annual incidence rates for girls of 15.7 per 100,000 children and for boys of 18.4 per 100,000 children in this age group. The probability for a newborn child to suffer a malignant disease within the first 18 years of life is 0.3%. Thus, one in every 330 children will be diagnosed with a malignant cancer by the age of 18. Within the first 30 years after the initial diagnosis, at least one subsequent cancer (second neoplasia) was reported in currently 1,661 patients, which represents 6.1% of those affected (cumulative incidence).

In a European comparison, Germany is roughly in the middle of the field in terms of incidence rates. The most important reasons for differences in incidence rates are generally differences in recording, as well as random effects in countries with a very small data base, e.g. if there is no national coverage.

Range of diagnoses

In general, the distribution of diagnoses in children is completely different from adults. The most appropriate classification of entities for children therefore also focuses on morphology. The largest diagnostic groups are leukaemias (30%), tumours of the central nervous system (CNS; 23 to 25%) and lymphomas (13 to 17%), especially Hodgkin lymphomas. Embryonal tumours (neuroblastomas, retinoblastomas, nephroblastomas, medulloblastomas, embryonal rhabdomyosarcomas or germ cell tumours) are also frequent in childhood, but almost never observed in adulthood. Carcinomas, on the other hand, are extremely rare (about 2 to 4% of all malignancies). The median age at diagnosis for children and adolescents under 18 years of age is seven years and seven months. Boys are diagnosed 1.2 times more frequently than girls.

Analogous to the usual recording and presentation according to the ICD in adulthood (predominantly localisation-based), the fourth most frequent diagnosis group after leukaemias, lymphomas and malignant CNS tumours is »tumours in soft tissue without mesotheliomas«, which includes a number of different morphologies. In contrast, the organs most commonly affected in adulthood – lung, prostate,

breast and colon – are markedly rarely affected in childhood and adolescence. Most childhood tumours in these locations are not carcinomas comparable to the disease in adults; for example, the tumours reported in childhood in the colon are predominantly appendix carcinoids, and the lung tumours are mostly pulmonary carcinoids.

Survival

Less than 1% of all cancer patients are children under 18 years of age. However, malignant neoplasms are the second most common cause of death in children. Fortunately, the survival probability has improved considerably in the last 40 years thanks to more differentiated diagnostics and the use of multimodal therapy concepts. While the probability of survival five years after diagnosis was 67% for children diagnosed in the early 1980s, this value is now 87% for girls and 86% for boys among patients belonging to the registry population and been diagnosed between 2009 and 2018. Survival probabilities vary relatively strongly depending on the entity.

Long-term follow-up of former paediatric cancer patients is increasingly coming into focus with the encouraging increase in long-term survival. The GCCR provides an ideal data basis for conducting studies with long-term survivors. As can be seen from the figures above, estimates of the long-term probability of survival (after 15 years and more) or the long-term risk of developing a second neoplasia after childhood cancer are available. Investigations of the occurrence of other late effects, such as possible consequences of therapy on fertility, offspring or cardiovascular late effects are examples of further research fields. About 44,000 of the more than 54,000 patients currently known to the registry to be alive have been under observation for at least five years. The majority of these former patients are now 18 years or older.

Leukaemias

Leukaemias account for almost one third of all cancers in patients under the age of 18. With 22.1%, lymphoid leukaemia (LL) is the most frequent single diagnosis overall. It is almost twice as frequent in the under-five-year olds as in the other age groups. 4.1% of all malignancies in childhood are acute myeloid leukaemias (AML). AML is most common in the under-two-year olds. The survival probability of AML is significantly lower than for LL. 10.5% of all second neoplasms are AML, they occur predominantly in the first 10 years after initial diagnosis.

Until the early 2000s, a slight steadily increasing trend was observed for leukaemias, which was also observed in Europe as a whole. Since then, incidence rates have remained largely constant.

The causes of childhood leukaemias still remain largely unclear. Environmental influences have long been suspected of causing childhood leukaemias. Meanwhile, it has been shown that the proportion of cases caused by most environmental factors (ionising radiation in the low-dose range as well as non-ionising radiation or pesticides) is rather small, even if a weak association with the occurrence of a childhood leukaemia cannot be ruled out. There is mounting evidence for hypotheses assigning a key role to infectious pathogens and the immune system in the development of childhood lymphoid leukaemias in particular. Genetic causes continue to be increasingly investigated and discussed for all childhood neoplasms.

Lymphomas

The most common lymphomas are non-Hodgkin lymphoma (NHL) including Burkitt's lymphoma (6.4% overall) and Hodgkin's disease (7.3%). Survival rates for Hodgkin's disease are among the highest in paediatric oncology (97 to 98% after 15 years). Unfortunately, the risk of a second neoplasia is also particularly high after Hodgkin's disease, at more than 13% (within 30 years of initial diagnosis), with a particular risk for breast cancer in young women.

Regarding lymphomas, the incidence rate was largely constant, but since lymphomas occur much more frequently in older children and adolescents, significantly more cases have been recorded since the additional registration of 15- to 17-year-olds, and a higher incidence rate is observed than in those under 15 years of age.

Children with congenital or acquired immunodeficiency and after immunosuppressive therapy are at an increased risk of developing NHL.

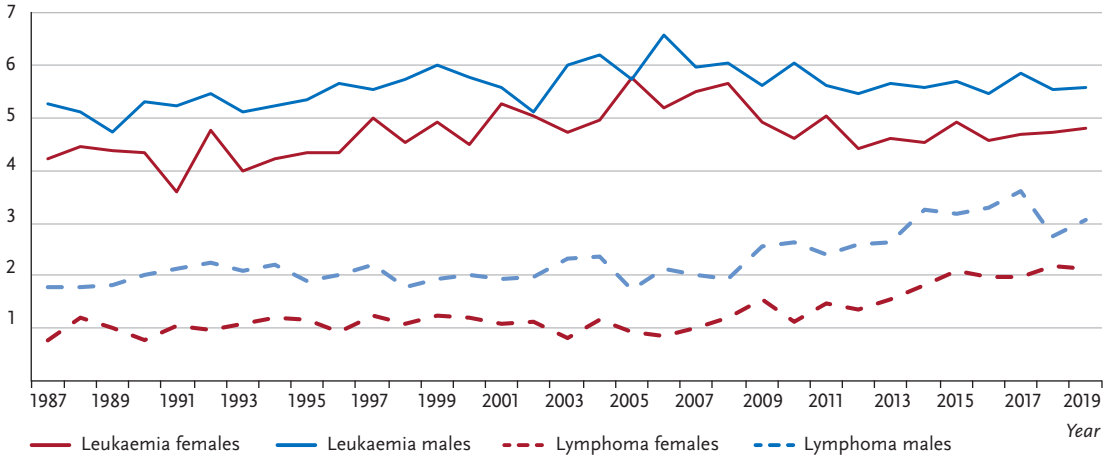
CNS tumours

The most commonly diagnosed CNS tumours in children are astrocytomas (10.6% overall), intracranial and intraspinal embryonal tumours (4.0%) and ependymomas (1.6%). 22% of all second neoplasms are CNS tumours. The increase in incidence of CNS tumours in childhood observed in Germany in recent decades, but also in a number of western countries, is probably primarily related to better recording. General changes in environmental factors and the resulting exposures are also discussed. For example, a number of epidemiological studies investigated the potential influence of ionising radiation, electromagnetic fields or pesticides, as well as genetic aspects, but no consistent correlations have been found so far.

Other common malignant diseases

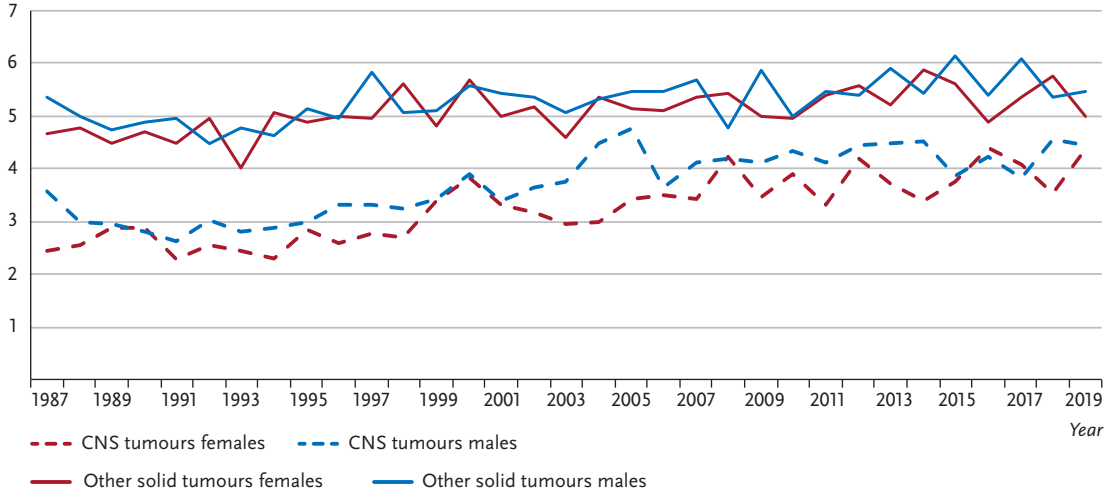
Other common malignant diseases in childhood are neuroblastoma (nerve cell tumour), nephroblastoma (kidney tumour), germ cell tumours, bone tumours

Figure 4.4
Trends in incidence of childhood leukaemia and lymphoma (under 15 years until 2008, under 18 years from 2009), by sex, 1987–2019
Number of cases per 100,000 (age-standardised according to Segi), including eastern Germany since 1991



In the last decade, further neoplasms of the lymphatic system have been newly classified as malignant (Langerhans cell histiocytosis).

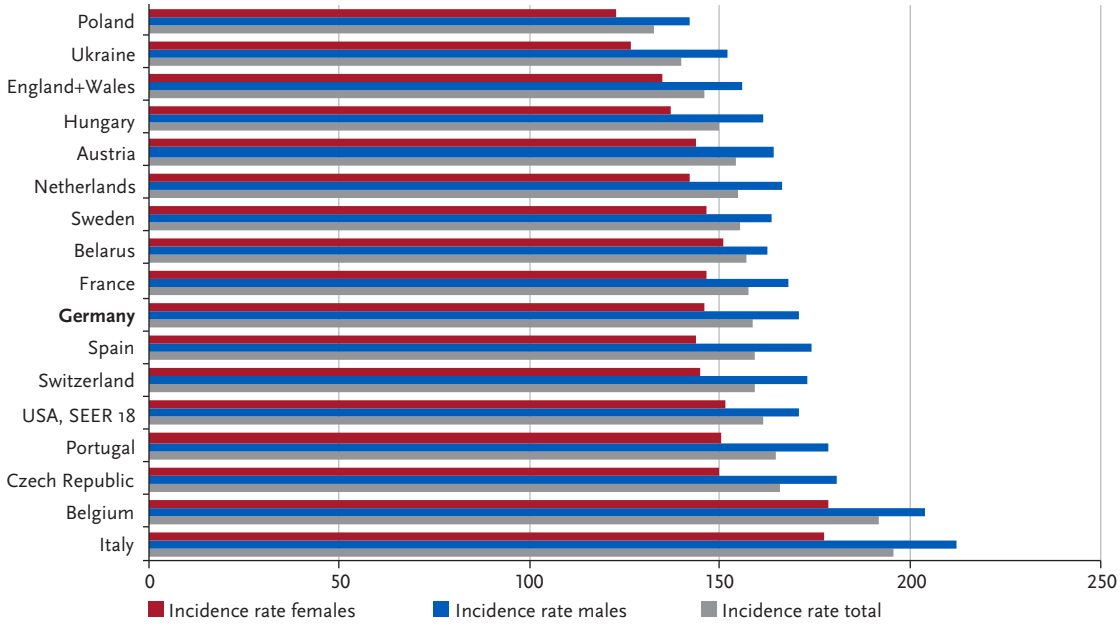
Figure 4.5
Trends in incidence of childhood CNS tumours and other solid tumours (under 15 years until 2008, under 18 years from 2009), by sex, 1987–2019
Number of cases per 100,000 (age-standardised according to Segi), including eastern Germany since 1991



and rhabdomyosarcoma (tumour of the skeletal muscles). The prognosis for children with nephroblastoma or germ cell tumour is much more favourable than for other tumours. Leukaemias and CNS tumours are particularly frequent secondary neoplasms, as already described. Others are skin tumours, thyroid carcinomas and breast cancer in young women.

There tends to be no real trend in incidence rates for solid tumours outside the CNS. Over the years, additional diagnoses were recategorized as malignant and registered from then on. Certain solid tumours in older children, some of which are not primarily treated in paediatric oncology, such as gynaecological and urological carcinomas and skin tumours, are under-registered, but this is slowly improving. Overall, this led to a slight increase in the number of reported cases.

Figure 4.6
International comparison of age-standardised cancer incidence rates for children under 15 years, by sex
Number of cases per 100,000 children (age-standardised according to Segi world population), different periods between 1990 and 2014



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