

Childhood Cancer

1. Incidence and types of cancer (listed more or less alphabetically)

The most common form of childhood cancer globally is **leukaemia** (between 25% and 30% of childhood cancers). **Brain tumours** are usually the second most common type of cancer (23% to 25%), and **lymphomas** generally come third. There is quite a lot of variation between countries, possibly due to inadequate data recording (Counsell [1997](#), Gurney [1999](#), Pobereskin [2000](#), [2001](#), Missaoui [2011](#)) particular ethnic mixes, or different environmental conditions (Glazer [1999](#), Datta [2010](#), González-García [2010](#), Kaatsch [2010](#), Marcos-Gragera [2010](#), Rosychuk [2010](#), Bodkyn & Lalchandani [2010](#)), with the incidence rate increasing over time for most types of cancer (Kaatsch [2006](#)) and in most countries (Peris-Bonet [2010](#)), though not all (Baba [2010](#)). Kaatsch suggested that *“the patterns and magnitude of the increases suggest that other factors, e.g. changes in lifestyle and in exposure to a variety of agents, have contributed to the increase in childhood cancer in the recent decades.”* For example, there was a high incidence of thyroid carcinoma in Belarus, following the Chernobyl nuclear power station accident, and a 12-fold increase in childhood cancer in Iraq, possibly due to the use of novel weapons, some containing depleted uranium (Busby [2010](#)).

As well as differences between countries, there are also age, sex, socioeconomic (Pan [2010](#), de Camargo [2011](#)) and other differences in incidence (Stiller [2006](#), Mousavi [2010](#)). Some countries have apparently unique cancer profiles, such as the relatively high incidence of nephroblastoma in girls under 5 in Trinidad and Tobago (Bodkyn & Lalchandani [2010](#)).

The survival rate for children with cancer has greatly improved in recent years due to better treatment, though it does depend on the type of cancer (Johnston [2010](#)), the stage it had reached before diagnosis, and the country (Trigg [2008](#), Linabery [2008](#), Baade [2010](#), Couto [2010](#), Kulkarni & Marwaha [2011](#)). From the United Kingdom Childhood Cancer Study (UKCCS), the 5-year survival was 72.7% for all childhood cancers, dropping to 67.9% at 15 years from diagnosis.

It is now almost universally agreed that the development of most forms of cancer, with a few exceptions, seems to be largely a multi-factorial process, with several factors being implicated, no one factor being ‘necessary’ or ‘sufficient’ to cause cancer in children. The first factor, or event, is regarded as an initiation process, whilst subsequent events are ‘promotional’. Promotional factors may not coincide with each other in terms of timing, and the exposures may occur at different stages in a child's life. These factors need to be taken into account as the time-window of exposure for childhood cancer is not known (Urayama [2009](#)).

Unfortunately, the treatment itself can cause fatal consequences (Molgaard-Hansen [2010](#), Oskarsson [2010](#)). It can result in problems for the ongoing wellbeing of the child (see section 9), as well as the devastation caused within the family.

Bone cancer (including Ewing's sarcoma)

Between 1988 and 1997 the incidence in the UK of bone tumours in boys and girls aged 0-14 years was about 5.5 per million, with the rate increasing with age to 10.7 for females and 19.3 for males by age 19.

Among children, osteosarcoma accounted for 51% and Ewing's sarcoma for 41% of tumour registrations; among adolescents these were, respectively, 55% and 28% (Stiller [2006](#)). The

incidence of osteosarcoma increased at an annual rate of 2.5% between 1981-2002 (Eyre [2010](#)) with no change in incidence of Ewing's sarcoma or chondrosarcoma.

Brain and central nervous system (CNS) tumours

Figures released in April 2009 show that the number of children dying from a brain tumour in 2007 was 33% higher than in 2001. The reason for the increase in CNS cancer rates in the past two decades is unknown. Changes in environmental exposures may be responsible for the increasing incidence rates, or it could be improvements in diagnostic technology.

Statistics from the UK and other countries include:-

- Brain tumours affect approximately 350 children (and their families) in the UK each year (CancerBackup 2005, now Macmillan Cancer Support). 40% of all cancer deaths in children are from a brain tumour. In 2007 there were 47% more deaths from brain tumours among under-15s than from leukaemia. Whilst on average 75% of all childhood cancer patients in Britain survive five years, for brain tumour patients, five year survival remains at 12% for males and 15% for females.
- The incidence of childhood brain tumours in the UK is rising by almost 3% a year, mostly occurring in 1-2 year-olds. The Observer reported in April 2009, that Kevin O'Neill, a consultant neurosurgeon at Imperial College London said *"In my unit we have seen the number of cases of child brain tumours nearly double in the last year."* Yang ([2006](#)) reported an 11.7% growth in incidence of infant brain tumour in Taiwan between 1995 and 2004.
- Smith MA ([1998](#)) found a 'step change' in childhood brain tumour incidence in the US in the mid 1980s. The authors concluded that the change *"somehow resulted from changes in detection and/or reporting of childhood primary malignant brain tumors."*
- CNS malignancies represent 16% of all childhood malignancies; astrocytomas accounting for 52% of CNS malignancies, Primitive Neuroectodermal Tumours (PNETs) 21%, other gliomas 15% and ependymomas 9%. The incidence of CNS tumours tends to be higher in boys than girls and higher among white children than black, although brain tumours in African children are now becoming more common (Idowu [2008](#)). The incidence of CNS tumours in Europe between 1988-1997 was 29.9 per million, with the highest rates in the North. The incidence increased significantly during 1978-1997 on average by 1.7% per year. Astrocytoma incidence was 11.8 per million; PNET 6.5 per million; ependymoma 3.4 per million (Peris-Bonet [2006](#)).
- Some brain and CNS tumour types are more common at different ages, and may cluster for reasons that are not yet clear (Ortega-García [2011](#)). Young children have a relatively high occurrence of malignancies in the cerebellum and the brain stem, and older children have higher rates in the cerebrum. In children between the ages of 5 and 9, brain stem malignancies are nearly as common as cerebral malignancies, and cerebellum malignancies are far more common than cerebral malignancies. The pattern shifts among children between the ages of 10-19, when brain stem and cerebellar cancer incidence decrease and cerebral malignancies increase slightly.

There are several different types of brain and central nervous system tumour:

- **Primitive Neuroectodermal Tumours (PNETs)** are a type of small round cell tumour developing from migrating embryonal cells of the neural crest. PNET incidence is fairly steady from infancy to age 3, then gradually declines. **Medulloblastoma**, a form of PNET, is a highly malignant brain tumour comprising 14.5% of newly diagnosed cases in young

people aged 20 or less. The incidence of childhood medulloblastoma is higher in males (62%) than females (38%). 40% of medulloblastoma patients are diagnosed before the age of 5, 31% are between the ages of 5 and 9, 18.3% are between the ages of 10 and 14, and 12.7% are between the ages of 15 and 19.

- **Gliomas** within the brainstem comprise 10-20% of all paediatric CNS tumours. They can occur at any age, although they generally present in childhood with the mean age of diagnosis at 7-9 years (Jallo [2006](#)). **Astrocytomas** are cancers of the brain that originate in star-shaped brain cells called astrocytes. They are graded according to their aggressiveness from 1 (least aggressive) to 4 (most aggressive), 4 being more common in adults than children. The incidence of astrocytomas peaks at age 5 with a second peak at 13. Up to 10% of childhood tumours of the central nervous system are **ependymomas**, which are usually intracranial. The occurrence of ependymomas seems to peak at age 5 years and then again in adulthood. Among children aged 5-14, ependymomas are very rare.
- **Meningiomas** are primary tumours of the central nervous system, usually benign, but they can be malignant. They constitute less than 5% of CNS tumours (Kotecha [2011](#)).
- **Glioblastomas** are aggressive brain tumours, more common in adults than children.

Hodgkin's disease (HL)

The European incidence rates in 1988-1997 were 5.8 per million in children and 29.7 per million in adolescents, with higher rates in the East and South. Incidence rates increased steeply with age, while the male predominance, marked for the youngest children, vanished in the highest age groups. The incidence increased in age groups 10-14 years (+1% per year) and 15-19 years (+3.5% per year) mainly due to the nodular sclerosis subtype (Clavel [2006](#)). The nodular sclerosis subtype is significantly more common in children and adolescents compared with adults, with a better survival rate. The mixed cellularity subtype was more prevalent in children under 10, less likely in older children (Bazzeh [2010](#)).

Non-Hodgkin's lymphoma (NHL)

The incidence rate for European children between 1988-1997 aged under 15 was 9.4 per million and has been increasing over 20 years by 0.9% per year. In adolescents aged 15-19 years, the incidence rate was 15.9 per million, increasing annually by 1.7% (Izarzugaza [2006](#)). NHL is the most common of all head and neck cancers in children. Chemotherapy and/or radiation therapy is able to achieve remission in about two-thirds of the patients, however prognosis remains poor with cumulative 5-year survival rates at about 30% for all types of sino-nasal NHLs (Zagolski [2010](#)).

Kidney tumours

Wilms tumour (WT) accounts for 93% of renal tumours and about 7% are bilateral. The incidence of WT has increased over 20 years by 0.7% per year. In the first year of life **mesoblastic nephroma** and **rhabdoid tumour** are the most common in the UK. There are significant differences between different European countries and the incidence of renal tumours.

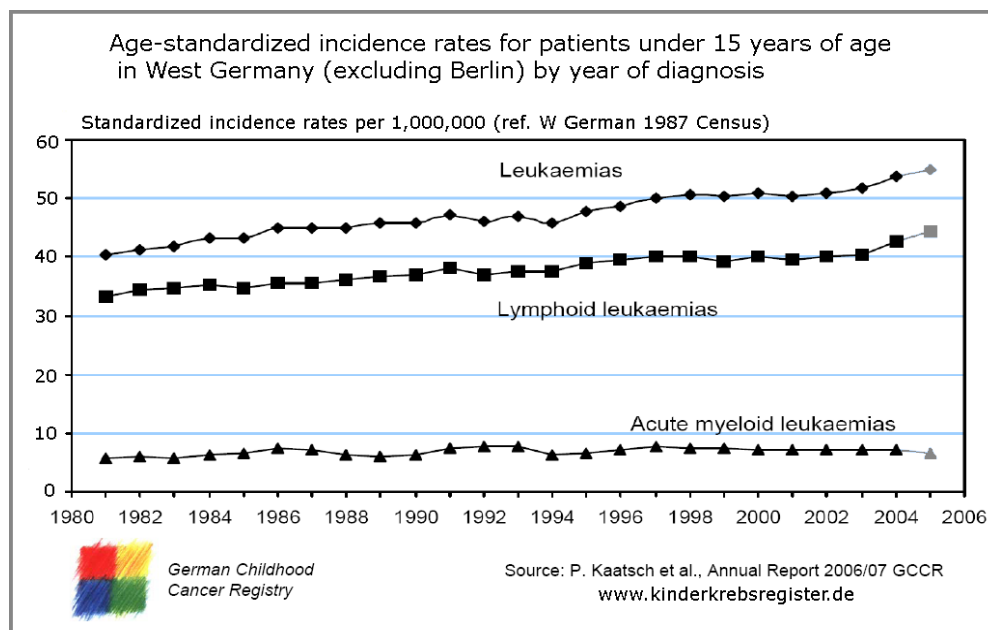
In children aged 10-16 nearly 75% of renal tumours are WT (Popov [2010](#)). Patients in the age group 0-3 years at diagnosis had a more favourable prognosis, and those patients with unilateral WT had a better prognosis than those with bilateral tumours. Survival rates for those with **renal**

cell carcinoma was about 87%, but for those with a **clear cell carcinoma**, or rhabdoid tumour of the kidney, the prognosis was less good (Pastore [2006](#)).

Leukaemia

Each year about 500 children in the UK develop leukaemia, the most common type of childhood cancer, accounting for about 30% of all cancers diagnosed in children younger than 15 years, and 10% of adolescent leukaemias (15-19 years). **Acute lymphoblastic (lymphoid) leukaemia (ALL)** accounts for more than 80% of all cases of childhood leukaemia. **Acute myeloid leukaemia (AML)** and **chronic myeloid leukaemias** make up most of the others.

The incidence of childhood leukaemia has been rising fairly steadily over the last 30 years (Hosny & Elkaffas [2002](#), Coleman [2004](#), Steliarova-Foucher [2004](#), Yang [2006](#), Coebergh [2006](#), Kaatsch & Mergenthaler [2008](#), Hagopian [2010](#)), with slightly different rates according to age, gender (Forsythe [2010](#)), and country, or particular environmental circumstances. Schmeidel ([2011](#)) found spatial clustering at the time of diagnosis for children aged 2-6 with ALL in Denmark. The authors suggested an environmental risk factor, possibly infection, or geographically localised exposure to something that compromised the development or response of the immune system, or even may have been due to chance.



The rise can be seen in the data above from Germany (this is used because UK data is unavailable for the most recent years, though up to 2000 is very similar to the German data).

An Australian study (Baade [2010](#)) reported a plateau in cancer incidence rates for boys and older children. This may be difficult to interpret as it suggests perhaps different causes overall or for different subtypes of leukaemia that are not yet understood.

Infant leukaemia

Leukaemias diagnosed in the first 12 months of life account for 2.5 to 5% of ALLs and 6 to 14% of AMLs (Pui [1995](#)). There are slightly more girls than boys with infant leukaemia, the reverse of that found in older age groups (Chessells [1992](#), Birch & Blair [1992](#)).

Liver Cancer

Between 1978 and 1997, liver cancer incidence in children 15 years old or less was 1.2 per million for **hepatoblastoma** and 0.2 per million for **hepatic carcinoma**. Over 90% of cases of hepatoblastoma occurred before age 5 years, whereas hepatic carcinoma had a fairly flat age distribution. Both tumours had an incidence in boys of 1.5-1.6 times that in girls (Stiller [2006](#)).

Neuroblastoma

Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy. 75% of neuroblastoma arise in the abdomen and pelvis, 20% in the thorax and 5% in the neck. The incidence of neuroblastoma in Europe in 1988-1997 was 10.9 cases per million children and 52.6 cases per million infants (Spix [2006](#)). Close to 50 percent of neuroblastoma cases occur in children younger than two years old, and 75% of them present in children less than 4 years old, 95% by the age of 10. Woods ([1997](#), [2002](#)) found that despite being able to screen infants for neuroblastoma, this screening did not seem to be able to reduce the mortality rate from the disease, and there was no long-term effect on diagnosis rates (Barrette [2007](#)). Approximately 50% of children will have metastasis at presentation (Al-Shammari ([2009](#)).

A low incidence of neuroblastoma was found among Mexican children (Juárez-Ocaña [2009](#), Palma-Padilla [2010](#)), but the authors believed this may have been due to the difficulty in early diagnosis, as the majority of the cases were diagnosed in the advanced stages.

Black and Native American patients with neuroblastoma have a higher prevalence of high-risk disease, accounting for their worse event-free survival when compared with whites. The higher prevalence of late-occurring events among blacks with high-risk disease suggests that this population may be more resistant to chemotherapy (Henderson [2011](#)).

Neuroendocrine tumours (NETs)

The most common NET sites were lung, breast and appendix. They remain an unrecognised cancer threat to children, comparable to neuroblastoma, in both number of those affected and severity (Navalkele [2011](#)).

Retinoblastoma (Rb)

Retinoblastoma is a rapidly developing cancer which develops in the cells of the retina. In the developed world, Rb has one of the best cure rates of all childhood cancers (95-98%). The highest incidence is seen in the first year of life, and about a third have bilateral tumours. Between 1978-1997, the incidence increased by 1% per year (MacCarthy [2006](#)). There are two forms of the disease; a genetic, heritable form and a non-genetic, non-heritable form. Approximately 55% of children with Rb have the non-genetic form. Mutations in both alleles of the RB1 gene are a prerequisite for the genetic form to develop (Lohmann [2010](#)).

Rhabdomyosarcoma (RMS)

Rhabdomyosarcoma is the most frequent soft tissue sarcoma in children. Children diagnosed between the ages of 1 and 9 have the best 5-year survival rate (Company [2011](#)).

Salivary gland tumours

These are rare in children, being responsible for 8-10% of head and neck paediatric tumours. In children, 50% of salivary gland tumours are malignant, a higher figure than that for adults.

Epithelial tumours are the most common, mucoepidermoid carcinomas of the parotid in particular (Thariat [2011](#)).

Skin cancer

The UK has the highest incidence of skin cancers in children and adolescents. In Europe, **melanomas** are more common in adolescents in the North and West and **skin carcinomas** in the South and East. Between 1978 and 1997 the annual increase in incidence for adolescent cancers has been 4.1% for melanoma and 2.5% for skin carcinoma (de Vries [2006](#)). The number of children affected was significantly smaller than the number of adolescents. The study authors suggest that the aetiology between childhood and adolescent skin cancers may be different, or it may also be that parental care with respect to skin screening is more influential for children than for adolescents.

Soft Tissue Sarcoma (STS)

Soft tissue sarcomas are cancers of connective tissues, in which the cancer cells are thought to arise from skeletal muscle progenitors. STS represent almost 8% of neoplasms in children, almost half of whom are less than 5 years at diagnosis. The most common are **rhabdomyosarcomas** (RMS)(50%) and **fibrosarcomas**. During 1988-1997 the incidence in Europe was 9.1 per million increasing at almost 2% per year in Europe, though not uniformly, and Weihkopf ([2008](#)) did not find evidence of an increase in Germany. The increase was mostly due to an increase in genitourinary rhabdomyosarcoma. Incidence is lowest in the West and East of Europe and highest in the North (Pastore [2006](#)).

There are two types of rhabdomyosarcoma, **embryonal (ERMS)** and **alveolar (ARMS)**. A study by Ognjanovic ([2009](#)) found that between 1975 and 2005, the incidence of ERMS was stable, whereas there was a significant increase in the incidence in ARMS, though the study team were unsure whether this may have been due to shifts in diagnosis. The five year survival rate is higher for ERMS than for ARMS. These variations suggest that the causes of the two types of RMS may be different. This was supported by a further study by Ognjanovic in [2010](#), showing a positive association between accelerated *in utero* growth and embryonal RMS, but not alveolar RMS.

Thymic epithelial tumours

Thymic epithelial tumours, both thymoma and carcinoma, are exceptionally rare in children. The prognosis is poor (Carretto [2011](#)).

Thyroid Cancer

Between 1988-1997, the incidence of thyroid cancer in children aged 0-14 varied between countries from 0.5 to 1.2 per million; the incidence for adolescents aged 15-19 was from 4.4 to 11.0 per million. Over the age range 0-19 years, the female to male ratio increased from 1 to around 3. No association was found between thyroid cancer risk and national dietary iodine status across 16 countries. The incidence of thyroid carcinoma increased during 1978-1997 by 3% per year, largely due to **papillary carcinoma**. More than 90% of patients survived 20 years after diagnosis, though slightly less for children with **medullary carcinoma** (Steliarova-Foucher [2006](#)).

Papillary thyroid cancer accounted for almost 65% of cases in children and 77% in adolescents. In Belarus, the incidence was 23.6 per million and the proportion of papillary tumours was 87%. The increase in thyroid cancer that resulted from the Chernobyl accident had a strong relationship with a young age at exposure (Williams [2008](#)). Radiation causes typical double-strand DNA

breaks, and Williams suggests that oncogenic rearrangements may commonly involve both a tumour-suppressor gene (or a DNA repair gene) as well as an oncogene.

Modern research has revealed that many children are born with a genetic susceptibility to cancer, either inherited or occurring in the womb (Wiemels [1999](#), Greaves & Wiemels [2003](#)) and possibly due to maternal environmental exposure (Cocco [1996](#), Guo [2009](#)). We briefly mention some of what is known about genetic susceptibility in Section 2. DNA changes and mutations that can be passed on to succeeding generations can occur after parental exposure to environmental hazards, causing preconceptual damage to either eggs or sperm. After conception, the first 6 months of pregnancy, and especially the first two months, is a critical time for foetal development.

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