

## **Powerwatch Childhood Cancer Articles**

The Powerwatch Childhood Cancer set of articles article is separated into 11 sections, each of which can be individually downloaded, or you can download it as one document.

It is a 'work in progress' incorporating new information whenever time permits.

### **Section 1**

## **Childhood Cancer Incidence**

The complete set:

1. Childhood cancer incidence and types of cancer
2. Genetics and parental exposure
3. Ionising radiation
4. Non-ionising radiation – electromagnetic fields (EMFs)
5. Chemical and infections
6. Other possible causative factors
7. Types of childhood cancer – Astrocytoma to kidney cancer
8. Types of childhood cancer – Leukaemia to thyroid cancer
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<http://www.powerwatch.org.uk/library/index.asp>

# Childhood Cancer

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

The most common form of childhood cancer globally is **leukaemia** (generally between 25% and 30% of childhood cancers). **Brain tumours** are usually the second most common type of cancer (23% to 25%) (Aurelie Pujol [2014](#)), and **lymphomas** are third. There is quite a lot of variation between countries, or even different areas of one country (Fajardo-Gutiérrez [2007](#), Howard [2008](#), Harmon [2011](#), Supriyadi [2011](#), Roy [2012](#), Togo [2014](#)) possibly due to inadequate, or different, data recording (Ducore [2004](#), Counsell [1997](#), Gurney [1999](#), Pobereskin [2000](#), [2001](#), Missaoui [2011](#), Al-Mulla [2014](#)), particular ethnic mixes, or different environmental conditions (Glazer [1999](#), Datta [2010](#), González-García [2010](#), Kaatsch [2010](#), Marcos-Gragera [2010](#), Rosychuk [2010](#), Bodkyn & Lalchandani [2010](#), Rajalekshmy [2011](#), Alrudainy [2011](#), Stefan [2014](#)) 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](#)). Linet ([1999](#)) suggested that there was no substantial change in incidence for the major paediatric cancers in the United States, rates having remained stable since the mid-1980s, including childhood brain tumours (McKean-Cowdin [2013](#)). The modest increases observed for brain/CNS cancers, leukaemia and infant neuroblastoma were confined to the mid-1980s.

In Jamaica, the 3 commonest groups are the same, but there are differences in frequency and gender distribution of neuroblastoma and brain and spinal neoplasms (Bishop [2013](#)). In India, the frequency of retinoblastoma, renal tumours, neuroblastoma and hepatic tumours were higher in children less than 5 years whereas lymphoma, leukaemia, bone tumours and CNS tumours were found more in children over 5 years (Roy [2012](#)). In Shanghai, the incidence rate of paediatric malignant solid tumours among males was higher than females and it differed among different age groups with the highest in the first 5 years of life. CNS tumours were the most common type of solid tumours in children (Bao [2013](#)). Turkish rare tumour rates (3.7%) are lower than rare tumour rates of western countries (15%) probably due to difficulties of diagnosis and referral problems (Tacyildiz [2013](#)).

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](#)), during the recent wars that have taken place there.

As well as differences between countries, there are also age (Juárez-Ocaña [2008](#)), sex, socioeconomic (Pan [2010](#), de Camargo [2011](#)) and other differences in incidence (Stiller [2006](#), Mousavi [2010](#), Wiangnon [2011](#)), though there are also many similarities, especially with regard to leukaemia incidence, age peak and subtype (Fajardo-Gutiérrez [2007](#), Bernaldez-Rios [2008](#)).

Socioeconomic differences within one country reveal different incidences of cancer. Alston ([2007](#)) found lymphomas, central nervous system tumours and gonadal germ cell tumours had a higher incidence in *less* deprived census wards in the UK. Chronic myeloid leukaemia and carcinoma of the cervix had a higher incidence in *more* deprived wards. In the least deprived wards, melanoma incidence was nearly twice that in the most deprived. This study looked at teenagers aged 13 + and young adults, and the incidences are different from those seen in younger children.

Some countries have apparently unique cancer profiles, such as the relatively high incidence of neuroblastoma in girls under 5 in Trinidad and Tobago (Bodkyn & Lalchandani [2010](#)).

Diagnosis times can be quite varied from country to country. Araz & Guler (2014) found that delayed diagnosis was associated with age, type/localisation and stage of tumour, the first doctor consulted and area of residence.

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, often prenatal, 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).

The incidence of childhood cancer in Pennsylvania was evaluated before and after hydraulic fracturing (Fryzek 2013), following concern about a potential association. No increase was found except for a small excess for central nervous system tumours in counties with the fewest number of wells.

In the UK, the incidence of teenage and young adult cancer (those aged between 15 and 24) can be seen in this chart:



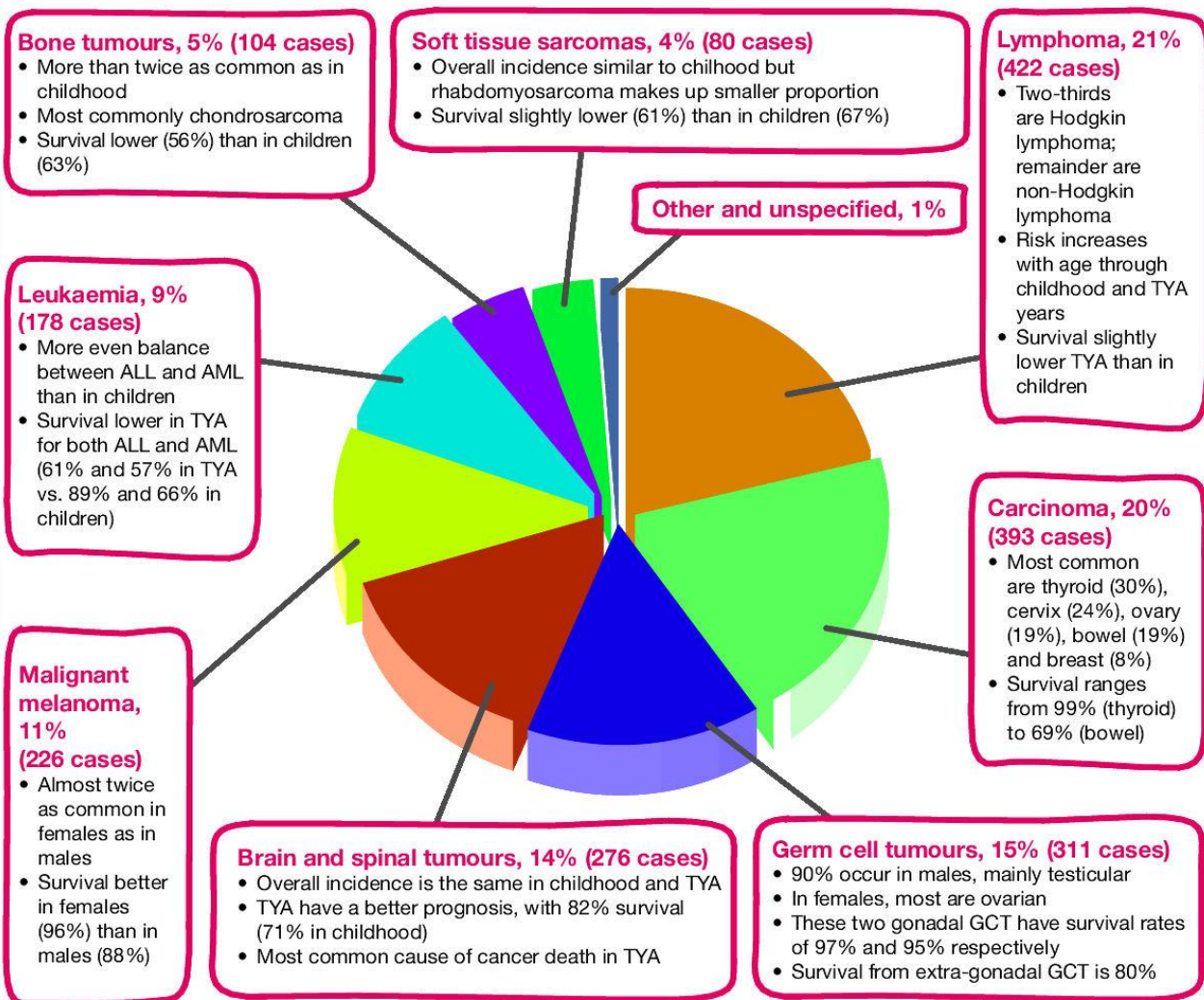
## Teenage and young adult cancer

TYA cancers are quite different from childhood cancers. They bridge the gap between paediatric and adult oncology: many of the childhood cancers no longer feature and adult cancers begin to make up a significant proportion of the overall cancer burden.

Around 2,000 15 to 24 year olds (referred to as teenagers and young adults, or TYA) are diagnosed with cancer every year in the UK.

Although more than 80% of TYA with cancer survive at least five years from diagnosis, cancer is still the leading cause of death from disease in TYA in the UK.

**Relative contributions of main diagnostic groups of teenage and young adult cancers to overall incidence among teenagers and young adults aged 15 to 24 years, UK, 2000 to 2009. (Figures in brackets are the average annual number of new cases).**



Data source: Cancer Research UK (2013). Teenage and Young Adult Cancer Incidence, UK, 2000-2009.

## Survival

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, ethnicity (Goggins & Lo 2012) and the country (Trigg 2008, Linabery 2008, Baade 2010, Couto 2010, Kulkarni & Marwaha 2011, Kulkarni 2011, Bravo 2013, Gatta 2014, Gupta 2014). In Australia, there was a difference in survival time between indigenous and non-indigenous children, partially explained by place of residence, socio-economic disadvantage

cancer diagnostic group, and possibly differences in treatment (Valery [2013](#)). 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.

Unfortunately, the different treatments for cancer itself can cause fatal consequences (Molgaard-Hansen [2010](#), Oskarsson [2010](#)). There have been major developments in treatment, reducing fatalities and improving survival rates. However, the treatments can often result in problems for the ongoing wellbeing of the child (see section 9), physically, emotionally and neurologically, with accompanying societal costs and a financial burden on the stretched resource of the health care system. The family themselves are often on the receiving end of many of these side effects which are often not discussed (see also section 10). The reason may be given as 'not looking at the problems which may never occur'. It does not help if they do occur and the family is left with inadequate support.

## **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.

During childhood, the percentage of malignant bone tumours amounts to 6% of all infant malignancies. Only leukaemia and lymphoma show a higher incidence in adolescence. The peak incidence of all bone tumours occurs between 15 and 19 years. The most common primary malignant bone tumours are osteosarcoma (35%), chondrosarcoma (25%), and Ewing's sarcoma (16%). Less frequently occurring tumours are chordoma, malignant fibrous histiocytoma of bone and fibrosarcoma of bone. Vascular primary malignant tumours of bone and adamantinoma are very rare (von Eisenhart-Rothe [2011](#)).

## **Brain and central nervous system (CNS) tumours**

Primary central nervous system (CNS) tumours include tumours of the brain, cranial nerves, cerebral meninges, spinal chord, and spinal meninges (Filippini [2012](#)).

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. Von Hoff ([2011](#)) reported that between 1988 and 2004 the incidence of children less than 1 year old with atypical teratoid rhabdoid tumours (AT/RT) of the CNS had increased. Changes in environmental exposures may be responsible for the increasing incidence rates.

Each week in the UK, 10 children and young people are diagnosed with a brain tumour. An average GP sees a new childhood cancer every 6 years; a quarter of these will be brain tumours (Wilne 2013). Statistics from the UK and other countries include:-

- CancerBackup, now Macmillan Cancer Support, in 2005 reported that brain tumours affected approximately 350 children (and their families) in the UK each year. 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, and the long-term effects of treatment can be very debilitating (see Section 9). Central nervous system (CNS) neoplasms are a major cause of ill-health and death among children with cancer. A genetic basis for brain tumours is relatively common in children.

- 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 tumours 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 20 to 25% of all childhood malignancies (Mueller & Chang 2009). 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. A child harbouring a germline mutation in a cancer-related gene will be predisposed to develop CNS tumours.
- 57% of pediatric CNS tumours in France were gliomas, especially astrocytomas. PNETs and ependymomas mainly occurred in children under 5. Survival was 84.8% at 1 year and 72.9% at 5 years (Desandes 2014).
- In youngsters aged 0-19, glioma was the most common form of primary brain tumours in China (Jiang 2011).

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, the most common form of embryonal tumour in childhood (Packer 2012), 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 of Europe. 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](#)). This 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

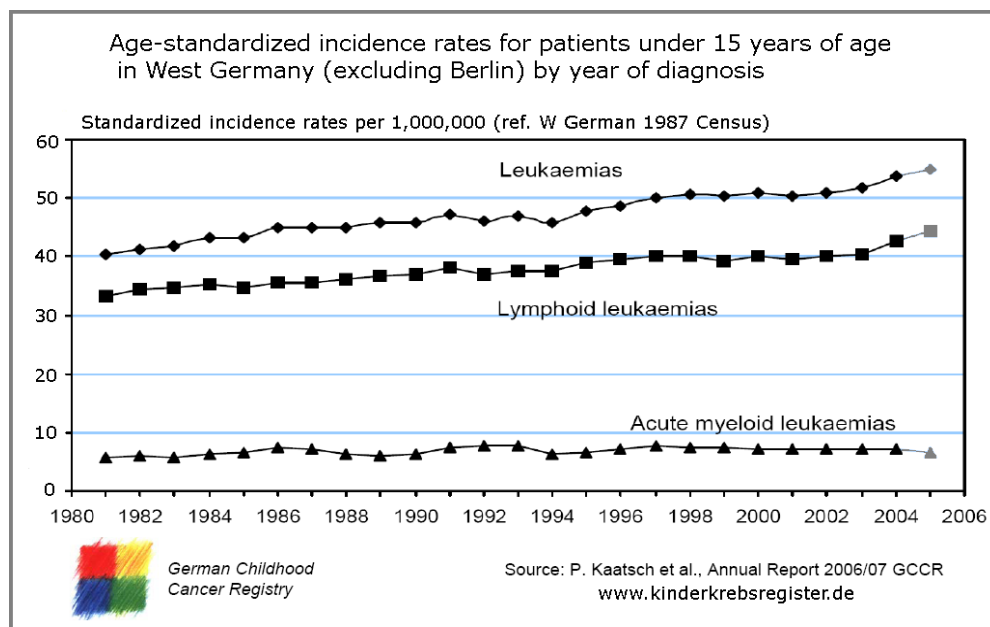
Wilms tumour (WT) accounts for 93% of renal tumours and about 7% are bilateral. The incidence of WT has increased over 20 years by 0.7% per year. In the first year of life mesoblastic nephroma and rhabdoid tumour are the most common in the UK. There are significant differences between different European 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](#), Török [2001](#), [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 (Ducore [2004](#), Arora [2009](#), de Camargo [2010](#), Perez-Saldivar [2011](#)), 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.



## 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. Some of the genetic characteristics are being identified (Hajjari [2014](#)). Mutations in both alleles of the RB1 gene are a prerequisite for the genetic form to develop (Lohmann [2010](#)).

## Salivary gland tumours & epithelial 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](#)).

Epithelial solid tumours are responsible for about 9% of all childhood cancers. Differentiated thyroid carcinomas (DTCs) are the most common of the endocrine neoplasia in all childhood malignancies (Ozkan [2011](#)). Thymic epithelial tumours, both thymoma and carcinoma, are exceptionally rare in children. The prognosis is poor (Carretto [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 about 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. Children diagnosed with Rhabdomyosarcomas between the ages of 1 and 9 have the best 5-year survival rate (Company [2011](#)). 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 genito-urinary 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 ERMS, but not ARMS.

## 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. 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](#)).

The incidence of thyroid cancer is increasing (Hogan [2009](#)). Females have a higher incidence than males, but enjoy longer survival. Papillary thyroid cancer has overall excellent survival.

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](#)). 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.