Cancer in Children and Young People

The Cancer in Children and Young People set of articles is separated into 12 sections, each of which can be individually downloaded. It is a 'work in progress' incorporating new information whenever time permits.

Section 8

Leukaemia to thyroid cancer

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 contributory factors

7. Types of childhood cancer – Astrocytoma to kidney cancer

8. Types of childhood cancer – Leukaemia to thyroid cancer

9. Challenges affecting survivors of childhood cancer

10. The needs of parents, family, GPs of childhood cancer survivors and things which may help

11. Precaution, prevention and protection

12. References

Types of childhood cancer

The specific cancers covered in Section 8 are:
Leukaemia; liver cancer; medulloblastoma; meningioma; neuroblastoma; oesophageal cancer; oral squamous cell carcinoma; pituitary adenoma; primitive neuroectodermal tumours (PNETs); retinoblastoma; rhabdomyosarcoma (RMS); skin cancer; testicular tumours; thyroid cancer

The specific cancers covered in Section 7 are:
Anal canal carcinoma; astrocytoma; astroglial tumour; bone cancer (including Ewing's sarcoma); brain tumours; CNS tumours; colon cancer; ependymoma; germ cell tumours; gliomas; Hodgkin's disease (HL); Non-Hodgkin's lymphoma (NHL); infant leukaemia; kidney tumour.

Leukaemia

General

Eden's summary of the aetiology of childhood leukaemia (2010) said *"For some leukaemias (e.g. infant MLL positive ALL) the first (genetic) event appears adequate to create a malignant clone but for the majority of ALL and AML further 'genetic' changes are required, probably postnatal. Many environmental factors have been proposed as causative for leukaemia but only ionising irradiation and certain chemicals have been confirmed and then principally for AML. It appears increasingly likely that delayed, dysregulated responses to 'common' infectious agents play a major part in the conversion of pre-leukaemic clones into overt precursor B cell ALL."* He continued *"There is little evidence to support any role of viral transformation in causation. Other environmental factors for which some evidence exists include non-ionising electromagnetic radiation and electric fields."* The recommendations were *"To date few clear preventative measures have emerged, except the complete avoidance of first trimester X-rays in pregnancy; a healthy diet with adequate oral folic acid intake both preconception and early in pregnancy; and the early exposure of children to other children outside the home to facilitate stimulation and maturation of the natural immune system."*

Rossig and Juergens' review (2008) acknowledged the necessity for the postnatal 'hits' described by Eden. They reported that the higher incidence of the most common leukaemia subtype in affluent societies, as well as the age peak between 2-5 years, suggest a contributory role of socioeconomic factors. An abnormal immune response during delayed exposure to common infections provides a plausible mechanism for malignant progression of preleukaemic clones in a subgroup of children. They concluded that a common cause for all types and subtypes of childhood leukaemia is highly unlikely. Creutzig (2016) found the frequencies of cytogenetic subgroups were age-dependent. Favourable subtypes decreased in general from the paediatric age group to the oldest groups; unfavourable cytogenetics were frequent in infants less than 2 years, had a low frequency in children and young adults, and increased in frequency up to 36% in patients older than 85 years.

Mathonnet (2003) suggested an association between ALL susceptibility and a DNA repair problem, pointing to the effect of environmental exposure.

Ou (2002) found that the risk of pre-B-cell ALL increased with advanced paternal age, younger and advanced maternal age and high birth order, and T-cell ALL was associated with high birth weight and a history of induced abortion. The author concluded that *"the association of ALL with birth characteristics and maternal reproductive factors varies with the immunophenotype of the ALL."*

Murray (2002) found that the risk of ALL increased with high paternal age, and high birth weight, but decreased with previous miscarriage, more than 40 weeks gestation, and more crowded households, including those with 3 adults. J Zhang (2016) found that sex, history of abortion, catching a cold, father's occupational exposure to petroleum products and home decoration during pregnancy were risk factors for childhood ALL.

However, most studies have not looked at specific phenotypes, not always differentiating between ALL and AML (often because of the small numbers of children involved), and so it is difficult to gain a clear idea of what other factors may be important in the development of specific leukaemia subtypes. Some genetic changes influence both susceptibility to ALL, and also other subtypes (Pastorczak 2011). The ataxia telangiectasia mutated (ATM) gene plays a major role in repairing the double-strand breaks and maintaining the genome stability. A study by Wang (2011) suggested that the ATM polymorphism may be indirectly associated with childhood leukaemia.

The increase in incidence of childhood leukaemia during the 20th century suggests that changes in environmental factors, including lifestyle, are at least partly responsible. There is no single factor that is either 'necessary or sufficient' for the development of leukaemia. There are multiple pathways involved. Buffler's study (2005) estimated that the aetiology is unclear in 90% of the cases of childhood leukaemia. The authors believe that a wide range of factors, including environmental, sociological and lifestyle influences are implicated as well as genetic susceptibility.

Wiemels (2012) says that the causes of childhood acute leukaemia in the majority of cases are not known. About 80% are precursor-B cell in origin (CD19+, CD10+), and this immunophenotype has increased in incidence over the past several decades in the Western world. Part of this increase may be due to the introduction of new chemical exposures into the child's environment including parental smoking, pesticides, traffic fumes, paint and household chemicals. However, much of the increase in leukaemia rates is likely linked to altered patterns of infection during early childhood development, mirroring causal pathways responsible for a similarly increased incidence of other childhood-diagnosed immune-related illnesses including allergy, asthma, and type 1 diabetes. Factors linked to childhood leukaemia that are likely surrogates for immune stimulation include exposure to childcare settings, parity status and birth order, vaccination history, and population mixing. In case-control studies, acute lymphoblastic leukaemia (ALL) is consistently inversely associated with greater exposure to infections, via daycare and later birth order. New evidence suggests also that children who contract leukaemia may have a congenital defect in immune responder status. This may help explain the appearance of leukaemia clusters which tend to appear as a leukaemia "outbreak" among populations with low herd immunity to a new infection.

75% of children with ALL have biologically and therapeutically relevant genetic abnormalities especially trisomy 21, or Down syndrome (Malinge 2012). The most consistent associations with childhood AML are parental exposures during gestation and child exposure prenatally and perinatally in the first 5 years of life (Ross 1998). These associations probably reflect the extreme vulnerability of the foetus to leukaemogenic agents. Chang (2011) found that children with ALL may have a dysregulated immune function present at birth, as measured by the deficit of IL10. Han (2010) suggested that genetic polymorphisms in innate immunity genes might play a role in the genesis of childhood leukaemia.

Non-genetic causes of AML (smoking, ionising radiation and cancer chemotherapy) only explain about 20% of AML incidence, leaving 80% unexplained (Smith 2011). So, although the stage for developing the illness is set in the womb, *something else is needed* for the disease to develop, the

two (or more)-hit (or multi-factor) hypothesis. The risk of developing AML *increases* with increasing birth order. It may be also that more than one environmental factor has to happen at the same time, rather than sequentially (Anderson 2006). Metayer (2016) found increased risks for pre- and postnatal smoking with higher risks reported for heavy smokers. Associations with paternal smoking varied by histological type. The authors' analyses suggest an association between paternal smoking and childhood AML. The association with maternal smoking appears limited to Hispanic children, raising questions about ethnic differences in tobacco-related exposures and biological mechanisms.

In both B- and T-ALL settings, the prognosis was negatively correlated to age (Mi 2012). For childhood T-ALL, it was also discovered that the HOX11 expression represented a favourable prognostic factor.

Parental

Most studies have observed an increased risk for childhood leukaemia with advanced maternal age (Schüz 1999, Reynolds 2002, Johnson 2009, Feller 2010), advanced paternal age (Ou 2002), or advanced parental age for leukaemia (Dockerty 2001), especially under the age of 5 (Yip 2006), although Ou (2002) reported a risk association in ALL with young maternal age.

In a meta-analysis of 77 studies, Sergentanis (2015) concluded that older maternal and paternal age were associated with increased risk for childhood ALL. The association between maternal age and risk of childhood AML showed a U-shaped pattern, with symmetrically associated increased risk in the oldest and the youngest, whereas only younger fathers were at increased risk of having a child with AML.

There was an increased risk of AML in children with Down syndrome for parents who had tried for a year or more to become pregnant (Puumala 2007). Hormone treatment for infertility (Schüz 1999) or oral contraceptive use during the index pregnancy (Ou 2002) was also found to increase the risk of acute leukaemia. IVF has been associated with an increased risk of early onset ALL (Petridou 2012).

A significantly higher risk was found for childhood ALL from reported parental occupational exposures to organic solvents or pesticides (Abadi-Korek 2006).

Shi (2013) found that chemical exposure to parents may increase the risk of acute leukaemia in their children. These included, 1) maternal: diesel oil, gasoline, paints, insecticides, pesticides, herbicides, and chemical fertilizers from 3 months before pregnancy to the end of pregnancy; working experiences in agriculture and forestry, spinning, leather processing, decoration, and vehicle repair before and during pregnancy 2) paternal: insecticides and chemical fertilizers within 3 months before pregnancy; working experiences in agriculture and forestry and in spinning, leather processing, decoration, and vehicle repair.

Paternal

Paternal abdominal X-ray (especially more than one) or intravenous pyelogram was associated with an increased risk of ALL if administered before the child was conceived. Maternal procedures did not seem to add to the risk (Bailey 2010b). Heavier paternal smoking around the time of conception was found to be a risk factor for ALL (Milne 2011).

Paternal smoking (R Liu 2011) and father's high risk job were related to the risk of childhood leukaemia (Hashemizadeh 2013).

Paternal occupational exposures to chlorinated hydrocarbons, combustion exhaust, metals, and possibly asbestos and the risk of ALL in the children of Latino fathers increased the risk of ALL in subsequent children (Metayer 2016).

Maternal

Archer (2016) found that 3 maternal genetic signatures were identified that may play a modest role in ALL susceptibility.

A maternal history of previous miscarriages is a frequently reported risk factor for development of ALL – and in some cases AML – in a subsequent child (Perrillat 2002, Dorak 2007 - especially boys, Hernández-Morales 2009). Ou (2002) found that an induced abortion prior to the index pregnancy increased the risk of a leukaemia diagnosis for children under 2.

Ajrouche (2014) found that maternal histories of stillbirth and miscarriage may be more frequent among mothers of children with leukaemia.

Ezzat (2016) reported that older maternal age, use of medications for ovulation induction and Caesarian section were all associated with an increased risk of the child developing ALL.

Maule (2009) states *"Childhood leukaemia risk increased with maternal age for mothers born in the past, whereas maternal age had no effect on this risk for mothers born more recently. This finding may explain the inconsistency of previous studies and suggests that leukaemia risk may be related to an environmental factor to which women's exposure has changed over time."*

Molar pregnancy has been associated with ALL in the large UKCCS study though the numbers were small (Roman 2006).

Girls born to mothers with multiple sclerosis (MS) have an increased risk of ALL (Morrison 2010).

Metayer (2011) looked at the role of maternal folate with respect to risk of ALL. The researchers found that maternal folate intake modified some genetic variations, but these were variable both ethnically and individually. Some maternal genetic combinations that increase foetal iron exposure was associated with a higher ALL risk, particularly in females (Dorak 2009).

Kumar (2014) found that mother's education, occupation and pesticides exposure during pregnancy were significantly associated with the risk of childhood leukaemia.

Family factors

A review of the literature by Poole (2006) found a consistent inverse association between incidence of childhood leukaemia and family income, mother's and father's education.

Pregnancy

Ognjanovic suggested that some maternal health conditions during pregnancy may be relevant in childhood leukemogenesis, when the child also has Down syndrome. Her 2009 study reported that vaginal bleeding was associated with a reduced risk of leukaemia, whilst amniocentesis was associated with an increased risk of AML.

ALL and AML have both been associated with maternal antibiotic use (Kaatsch 2010). The authors of the study were uncertain as to whether this link may have been to the underlying infection rather than the treatment.

Different genetic polymorphisms may create hostile pregnancy conditions leading either to foetal loss or the development of specific leukaemia subtypes in subsequent offspring, notably distinct associations of maternal miscarriage history confined to AML and stillbirth history confined to ALL (specifically B-ALL) (Karalexi 2015).

Diet

Increased risk of childhood leukaemia has been associated with DNA topoisomerase inhibitors. This includes some drugs used in chemotherapy, benzene metabolites (from air pollution and cigarette smoke), certain fruits, tea, coffee, wine, soy and cocoa and many other substances (Gilliland 2004). Menegaux (2005) and Milne (2011) found that maternal coffee drinking during pregnancy increased the risk of ALL, the risk increasing with increased consumption (Arab 2010). Tea-drinking may be protective, depending on the leukaemia subtype.

Orsi (2015) found that maternal alcohol drinking, more than 2 cups of coffee daily and paternal smoking were associated with leukaemia.

Children with chromosomal translocations seemed to have increased risk if mothers drank high levels of coffee or tea. Topoisomerase inhibitors inhibit DNA repair and are strongly associated with one of the chromosome rearrangements common in AML (Spector 2005). Petridou (2005) reported that ALL risk was higher for children born to mothers who ate more sugars and syrups, and meat and meat products. Consumption of cured/smoked meat and fish more than once a week has been associated with an increased risk of acute leukaemia (Liu 2009).

Birth

Marcotte (2016) found an increased risk of childhood ALL after pre-labour caesarean delivery, but not emergency caesarean delivery for ALL. They suggested that if this association is causal, maladaptive immune activation due to an absence of stress response before birth in children born by pre-labour caesarean delivery could be considered as a potential mechanism.

Birth weight

Birthweight of 3,000 grammes or more (Ou 2002, Paltiel 2004, Podvin 2006, Johnson 2008, Spix 2009, Rangel 2010) is associated with an increased risk of ALL in children diagnosed before the age of 2 especially girls (Smith 2009), and AML (McLaughlin 2006, Caughey & Michels 2009), possibly due to an association with a specific chromosomal abnormality (O'Neill 2011). Weighing 4,000 g at birth increases leukaemia risk by as much as 100% (Ross 2006) in children diagnosed under 2 years of age. Dorak (2007) found that in boys with ALL, there was a nonlinear association with birth weight, but not for girls, suggesting possible differences in aetiology between boys and girls.

Ross speculated that levels of insulin-like growth factor-I are positively correlated with birthweight and may be important to consider in childhood leukaemia. Circulating IGF levels are highly correlated with foetal growth, and IGFs are believed to play an important role in carcinogenesis. However, the exact mechanism by which these two factors may be linked has not been clearly established (Callan 2009). Serum levels of IGF-1 and IGFBP-3 are reduced in children with ALL, but increase significantly after complete remission (Zhao 2011).

McLaughlin (2006) found that high birth weight was associated with ALL only when the mother was not overweight, whilst heavier maternal weight was associated with ALL only when the infant was not high birth weight. Increased pregnancy-related weight gain was associated with ALL. For AML, birth weight under 3,000 grammes and higher pre-pregnancy weight were both associated with increased risk. These findings suggest that childhood leukaemia may be related to factors influencing abnormal foetal growth patterns.

Schüz (1999) found an increased risk of acute leukaemia with weights above 4,000 g *and* below 2,500g.Westergaard suggested that "*a plausible explanation may be that increasing birth weight is associated with a higher rate of cell proliferation and/or a larger number of precursor cells being at risk of malignant transformation.*" Caughey & Michels (2009) found low and high birthweight was associated with AML, suggesting that the risk is elevated at both extremes, a U-shaped association.

Hjalgrim's meta-analysis of 18 studies (2003) concluded that for each 1 kg increase in birthweight, the risk of ALL increases by 14% and AML risk increases by 29%.

L Milne reported (2008) "*Most studies of the association between birth weight and risk of childhood ALL have reported positive associations, while results have been less consistent for AML. Few studies have taken account of gestational age in the analysis of birth weight. As birth weight is a function of both intrauterine growth and length of gestation, it is not possible to differentiate between an association with high birth weight per se and an association with accelerated intrauterine growth, without accounting for gestational age.*" It seems to be accelerated growth, rather than high birth weight (Milne 2007, 2009, Sprehe 2009) that is involved in the causal pathway for ALL. This did not seem to be true of AML. Foetal growth is determined by a mixture of genetic, nutritional and hormonal factors, possibly with a role for insulin-like growth factor in the causal pathway.

Neonatal jaundice was found to carry an increased risk of leukaemia (Hernández-Morales 2009).

Naumberg (2002) suggested that resuscitation with 100% oxygen with a face mask and bag directly postpartum was associated with increased risk of childhood lymphatic leukaemia and Spector (2005) found a 3-fold increase in risk in childhood cancer if oxygen was administered for 3 minutes or more.

1-minute Apgar scores of less than 7 increased risk of ALL and AML (Johnson 2008).

Gender

That the incidence of ALL in boys and girls is different is well established, with boys being more likely to develop ALL than girls (Pearce & Parker 2001, Johnson 2008), although the incidence of girls is often higher among young children. Males tend to have a worse prognosis (Eden 2000). Adelman (2007) found that boys (but not girls) had an elevated risk of developing ALL in areas of relatively high re-location rates.

Birth order

Being the first born child has been associated with increased risk of leukaemia (Dockerty 2001), especially between the ages of 1 and 5, although the opposite has also been reported (Ou 2002). Jourdain-Da Silva (2004) found that having many siblings increased the risk of ALL.

Infante-Rivard (2000) found that having a school age sibling at the time of diagnosis significantly increased the risk in all children, but most markedly in those diagnosed before 4 years of age.

Birth order is used as a proxy for infection as it is assumed that children in larger families – especially those lower down the birth order – are exposed to more infections in early childhood. A number of studies have reported results but there is little consensus. Of 13 recent case-control studies, five showed an increased risk of childhood leukaemia in larger families, seven found no effect and two showed a protective effect. The different results of the studies may reflect some impact of changing social conditions in the countries studied, and over time.

Ethnicity

Incidence of ALL is significantly lower among black children in the US (Reynolds 2002, Adelman 2007, Johnson 2008) and Africa. During the first few years of life, the incidence rate of AML among African American children is approximately ⅓ the rate of Caucasian children; however, African American children ≥ 3 years of age have higher rates than Caucasians. Hispanics had a higher incidence of ALL, particularly in childhood, in a study by Yamamoto (2008), but there were differences in incidence, depending on the subtype (Aldrich 2006).

Hicks (2013) found four genes which have been implicated in paediatric B-ALL differentially expressed between Whites, Blacks, Hispanics and Asians in the USA. B-ALL is the most prevalent childhood haematological malignancy as well as the leading cause of childhood cancer-related mortality (Woo 2014).

However, for many adult cancers, ethnicity seems less important than the country you are living in and the adopted lifestyle, as the incidence levels in immigrants generally begins to resemble that of the indigenous population in the country they are living in – certainly in subsequent generations. A study by Spallek (2008) found that children born in Germany into a family of Turkish descent (as determined by name) had no increased risk of developing leukaemia compared with children of German descent.

Seasonal variation

Higgins (2001) found significant links between leukaemia and month of birth, for those born before 1960, and month of diagnosis for those diagnosed before 1962. Seasonal variations at diagnosis have also been found (Westerbeek 1998, Ross 1999, Karimi & Yarmohammadi 2003). Feltbower (2001) found variations according to birth area; and HT Sørensen (2001) found an April birth peak for leukaemia diagnosis in the under 4s. Other studies found no variation (Kajtár 2003). The variations may be proxies for infections which can have seasonal peaks of occurrence. Yaniv (2010) found that children who develop ALL and AML have a different month of birth pattern from the general population, which depended on the leukaemia subtype.

Childhood

Diet

The introduction of artificial formula within 14 days of birth was positively associated with ALL, as was exclusive formula feeding to 6 months (Greenop 2015). Longer duration of formula feeding and later age at the introduction of solid foods were independently associated with increased risk of ALL (Schraw 2014).

It has been suggested (Lachenmeier 2010) that infant carrot juice contains substances that may act as precursors for benzene formation during food processing. Benzene exposure has been linked to childhood leukaemia. The authors concluded that the risk was very low, though care should be taken to reduce contaminants to as low levels as reasonably achievable.

A study of Mexican children with ALL looked at whether malnutrition was a predictor of early mortality during the first year of treatment. Early mortality was high (12.1%) and malnutrition by different indicators was not associated with mortality at induction phase and at 6th month; a high risk of dying was observed in the group of malnourished children with a high-risk ALL (Martín-Trejo 2017).

Environment

Röösli (2013) suggests that, if causal, 1-4% of all childhood leukaemia cases could be attributed to low-frequency magnetic fields.

In a study by Carlos-Wallace (2016) looking at parental, in utero and early life occupational and household use of benzenes and solvents, and traffic density, and traffic-related air pollution, the risks for AML more than doubled, and for ALL was 1½ times more likely especially with maternal exposure. The authors concluded that benzene exposure was a factor that increased the risk of leukaemia.

Of the 111 potential water contaminants and 29 potential air pollutants evaluated by IARC in a study of unconventional oil and gas (UO&G) development (including fracking) (119 unique compounds), 49 water and 20 air pollutants were known, probable, or possible human carcinogens (55 unique compounds). A total of 17 water and 11 air pollutants (20 unique compounds) had evidence of increased risk for leukaemia/lymphoma, including benzene, 1,3-butadiene, cadmium, diesel exhaust, and several polycyclic aromatic hydrocarbons. The authors concluded that their findings supported the need for investigation into the relationship between UO&G development and risk of cancer in general and childhood leukaemia in particular (Elliott 2017).

Residential status

There may be differences in spatial clustering as to urban, semi-urban or rural places where children live. Children younger than 10 years old, living in an urban environment had an increased risk of developing leukaemia, and localised environmental exposures could contribute to the aetiology of childhood leukaemia. This may have relevance to a theory of infection or pollution, and there may be other factors at work as well.

Socioeconomic status

Incidence of ALL is higher in areas of high social class (Dockerty 1999, Borugian 2005, Draper 2005), though A. Smith (2006), analysing the large UKCCS study found no effect. Adam (2008), in a literature study, suggests any such link is likely to be weak, possibly more significant at the birth of the child, than later. Smith suggested that previous studies varied because of the statistics used to analyse the result. This is always a problem with the small number of children concerned.

Evidence from developing countries suggests that incidence of ALL in children aged 1-4 years is rising with improved socioeconomic conditions (Hrusák 2002).

Chemicals

An increased risk of ALL was found for professional pest control treatments carried out during the index pregnancy and possibly the child's early years (Bailey 2011).

Chemical exposure during childhood (OR = 4.7), maternal exposure to chemicals (OR = 4.5), household insecticides use during 0-3 years of child (OR = 2.9), and renovating after their

children's birth (OR = 3.1) were associated with an increased risk of childhood acute leukaemia (Chen 2015).

Childhood leukaemia has been associated with residential traffic exposure during the postnatal period (Boothe 2014).

Liver cancer (PHM – pediatric hepatic malignancies)

81% of hepatic tumours in children are malignant. Hepatoblastoma is the most common liver tumour (69%) diagnosed usually during the first three years of life (Shirazi 2016), followed by hepatocellular carcinoma (15%). The spectrum of hepatic tumours in children is different from that found in the older age group. Males are twice as vulnerable as females (Zaman 2011).

The main constitutional risk factors for PHMs are 1) Beckwith-Wiedemann (BW) syndrome; 2) isolated hemihyperplasia syndrome (IHS); 3) adenomatous polyps of the colon 4) hemachromatosis 5) Hereditary Tyrosinemia Type 1; 6) a-1-antitrypsin deficiency; 7) porphyrias 8) cirrhosis 9) nonalcoholic steatosis; and 10) primary sclerosing cholangitis. The main environmental risk factors are a) hepatitus B virus (HBV) and C virus (HCV); b) B1 aflatoxin (B1AF); c) ionizing radiation; d) alcohol; e) hormonal treatments; f) occupational exposure to pesticides, solvents, vinyl chloride and metals; g) smoking; h) arsenic; I) prematurity and very low birth weight; and j) trematodes.

There is an increased risk of hepatoblastoma in children with very low birth weight which suggests that the aetiology may differ between children with very low birth weight and children with normal birth weight (Reynolds 2004).

HBV universal vaccination of newborns provides the biggest opportunity to prevent a substantial proportion of PHMs (Ferris i Tortajada 2008).

Medulloblastoma

Medulloblastoma is the most common paediatric brain tumour arising in the cerebellum and can disseminate through the cerebrospinal fluid. It is a highly malignant paediatric brain tumour, often inflicting devastating consequences on the developing child (Lin CY 2016). Dissemination is found in up to 40% of children at diagnosis and in most children at the time of recurrence (Wu 2012).

Family and genetic factors

A 5-year-old boy diagnosed with medulloblastoma was found to have 12 times the amount of L-2-hydroxyglutaric aciduria in his urine. There were other inherited characteristics that suggested a potential aetiologic factor (Yazici 2009). The incidence of medulloblastoma in males is higher than in females.

The most common chromosomal abnormality in medulloblastoma is the location of the tumour suppression gene p53 (Philipova 2011).

Pre-conceptional, pregnancy and birth factors

The peak month of birth for a risk of developing medulloblastoma is October, according to findings by Hoffman (2007), especially females aged 5-19. The authors suggest an environmental

exposure may be responsible. Harder (2008) found that medulloblastoma was associated with high birth weight.

Maternal use of a sauna close to conception or in the first trimester, and paternal use in the 3 months before the pregnancy, use of an electric blanket, or any heat source have been linked to an increased risk of medulloblastoma. Heat and magnetic field exposure would both have been involved (Bunin 2006), and both may have contributed.

Cured meats combined with low vitamin C intake Bunin (2006), or oil products (Pogoda 2009), or french fries, chilli peppers and non-chocolate candy (Bunin 2005) consumed in pregnancy have been associated with an increased risk of medulloblastoma.

An increased risk of medulloblastoma was associated with paternal lawn care using pesticides and a weak association with stripping paint, both during pregnancy and after the birth of the index child (Rosso 2008).

Infections

Harding (2009) concluded that an early exposure to infections is not strongly implicated in the aetiology of CNS tumours, but the effect for social contact outside the home, particularly for medulloblastoma warrants further investigation.

Meningioma

Neurofibromatosis type 2 and ionising radiation (including cranial radiotherapy) are two known risk factors. There have been associations made with Rubinstein-Taybi and with Golin syndromes.

Neuroblastoma

Neuroblastoma is the most common cancer in infancy (Heck 2013), and accounts for 10% of childhood cancers (Wang 2014).

Family and genetic factors

The anaplastic lymphoma kinase (ALK) gene increases the risk for familial neuroblastoma (Mossé 2008, Devoto 2011).

Menegaux (2005) found an association between neuroblastoma and congenital, especially urogenital, and cardiac, anomalies. Munzer (2008) found a strong link between neuroblastoma and congenital malformations in children aged less than 1 year, but not those older.

Pre-conceptional, pregnancy and birth factors

McLaughlin (2009) looked at neuroblastoma incidence in 3 age groups; 1-6 months; 7-18 months and older than 18 months. She found that no factors were identified to be consistently associated with risk across all three age groups. More risk factors were identified as associated with neuroblastoma among the youngest age group (1-6 months) relative to older ages, including high birth weight, heavier maternal gestational weight gain, maternal hypertension, older maternal age, ultrasound and respiratory distress. Among older infants (7-18 months), low birth weight was associated with increased risk while heavier maternal gestational weight gain was protective.

In the oldest age group, first born status, primary caesarian delivery, prolonged labour and premature rupture of the membranes were associated with increased risk.

A history of infertility and the use of infertility medication, specifically, the use of clomiphene, has been associated with an increased risk of neuroblastoma, especially in male children (Olshan 1999). Brassesco (2009) found a genetic abnormality in a 13-month-old boy with neuroblastoma, born after infertility treatment. The authors were unsure whether the abnormality may have been associated with the assisted reproductive technologies and felt further investigation should be carried out.

Children of women who suffered from pre-eclampsia during pregnancy were at a higher risk of developing neuroblastoma (Bjørge 2008). Hamrick (2001) found associations between neuroblastoma in the child and a large number of prior pregnancies, a history of previous miscarriages, induced abortions, hypertension during pregnancy, threatened miscarriage, anaesthetic during labour (specifically epidural), and Caesarean and premature delivery.

Maternal anaemia has been associated with an increased risk of neuroblastoma diagnosed within the first year (Bluhm 2008).

Use of any hair dye, especially temporary hair dye, in the month before and/or during pregnancy has been associated with an increased risk of neuroblastoma (McCall 2005). The authors felt that more investigation was needed with respect to application methods, colour, and chemical composition. Parodi (2014) found neuroblastoma risk increased with exposure during pregnancy to chemical products for domestic work, hair dye (especially in children 0-17 months), including the use of solvents at work, particularly aromatic hydrocarbons. Neuroblastoma risk was increased with higher maternal exposure to carbon tetrachloride and polycyclic aromatic hydrocarbons, particularly indeno(1,2,3-cd)pyrene and dibenz(a,h)anthracene (Heck 2013).

Mothers who took opioid agonists, such as medication containing codeine while pregnant or nursing (Cook 2004), or used diuretics (Schüz 2007, Heck 2009) or hypertensives, and vitamin, folate or iron supplements Schüz (2007) had an increased risk of neuroblastoma in the child. Maternal use of any illicit or recreational drug, especially the use of marijuana, was associated with an increased risk of neuroblastoma (Bluhm 2006) in their offspring. Bluhm found that the effect was strongest in children diagnosed before the age of one.

Respiratory distress at birth has been associated with neuroblastoma (Bluhm 2008).

Parental occupational factors

De Roos (2001) concluded that maternal exposure to most chemicals was not associated with neuroblastoma; however, paternal exposure to hydrocarbons, such as diesel fuel, lacquer thinner, and turpentine, or pesticides (Van Wijngaarden 2003), wood dust and solders were associated with an increased incidence of neuroblastoma.

In a large study (2920 cases of neuroblastoma) paternal occupational exposure to leather was the only exposure out of the 32 looked at, that was associated with an increased risk of neuroblastoma. Inferred exposure rather than actual exposure was used and the range of time 1962 to 1999, may mean that the results may be more difficult to interpret (Maccarthy 2010). Van Wijngaarden (2003) showed neuroblastoma was linked to paternal occupational exposure to herbicides.

Olshan (1999) found increased risk of neuroblastoma for fathers employed as broadcast, telephone and dispatch operators, electrical power installers and power plant operators, landscapers and groundskeepers and painters. Increased risks were associated with mothers

employed as farmers and farmworkers, florists and garden store workers, hairdressers and barbers, electric power installers and power plant operators and sailors, fishers and railroad workers.

Parental lifestyle factors

Some papers have linked brain tumours (including neuroblastoma) with parental alcohol consumption (Heck 2009). Foetal alcohol spectrum disorders were associated with neuroblastoma in 46% of the children in a study by Burd (2014); neuroblastomas comprise only about 10% of childhood cancers, so this is quite significant.

An increase in risk of neuroblastoma was found with pesticide use in the home and garden Daniels (2001), and stronger links when the diagnosis was later than 1 year of age.

Oesophageal cancer

Environmental factors (unspecified) were considered to be important for oesophageal cancers. However, there was also a high familial risk, so Hemminki & Jiang (2002) felt that there are also heritable factors contributing to their observed familial clustering.

Oral Cancer

Oral cancer associated with the human papilloma virus (HPV) is on the increase. Girls are routinely vaccinated against HPV, to help prevent cervical cancer. HPV can infect tonsils and lead to tumours in the throat and mouth, and is becoming more common affecting males as well as females. The strongest link to oral HPV infection is the number of sexual partners someone has had, particularly if a high number have been engaged in oral sex.

Oral Squamous Cell Carcinoma (OSCC)

Paediatric OSCC, though uncommon, is not rare. This review has strongly highlighted the need to carry out an objective, thorough and standardised examination of the child's oral cavity, especially when systemic predisposing diseases, such as Epidermolysis bullosa, Xeroderma pigmentosum, Juvenile papillomatosis and Fanconi's anaemia, are present (Tettamanti 2012).

Pituitary adenoma

Inherited mutations in the ARYL hydrocarbon receptor interacting protein (AIP) gene may be involved in the predisposition to pituitary adenoma formation, as this was discovered in one patient, and 5 relatives who did not have tumours (Naves 2010).

Primitive Neuroectodermal Tumours (PNETs)

Pre-conceptional, pregnancy and birth factors

Stålberg (2007) found an increased risk of PNET with prenatal abdominal X-ray exposure.

French fries, chilli peppers and non-chocolate candy eaten in pregnancy were associated with an increased risk of PNET (Bunin 2005).

McNally ([2012](#)) found some evidence for a transient environmental component to the aetiology of PNETs in Yorkshire, without hypothesising about a potential cause.

Parental occupational and lifestyle factors

Paternal exposure to polycyclic aromatic hydrocarbons (PAHs) increased the risk for PNETs (Cordier [2004](#)). An increased risk of PNET was associated with paternal lawn care using pesticides and a weak association with stripping paint, both during pregnancy and after the birth of the index child (Rosso [2008](#)).

PNETs (Yeni-Komshian & Holly [2000](#)) have been associated with both maternal and child exposure to pigs, poultry, dogs and cats. Children who were on a farm for more than a year and were first on a farm when they were less than 6 months of age (Holly [1998](#)) had an increased risk for PNETs, as did the children of mothers who ever had worked on livestock farms (Efird [2003](#)).

Infections

Harding ([2009](#)) concluded that an early exposure to infections is not strongly implicated in the aetiology of CNS tumours, but the effect for social contact outside the home, particularly for PNET warrants further investigation.

Retinoblastoma (Rb)

As retinoblastoma has both heritable and non-heritable forms, genetic screening is advisable. Parental knowledge of retinoblastoma nature and heritability is crucial to good patient outcomes, but translating this knowledge into appropriate action (i.e. screening of at-risk children) is still deficient (Soliman [2016](#)). Screening is crucial for assessing short-term (risk of additional tumours in the same eye and other eye) and long-term (risk of nonocular malignant tumours) prognosis and offering cost-effective surveillance strategies (Mallipatna [2016](#)).

Second cancers remain a major concern in heritable retinoblastoma survivors. Consistent with previous reports, radiotherapy increased second cancer incidence and influenced type and localization. However, chemotherapy was the strongest risk factor for second malignancies outside the periorbital region (Temming [2017](#)).

Spector ([2009](#)) suggested there may be an association with very low birth weight (1500-1999 g).

Paternal occupational exposure to oil mists in metal working at the birth of the child concerned is associated with a higher risk of retinoblastoma, both the heritable and non-heritable form (MacCarthy [2009](#)). Proximity to industries involved in glass and mineral fibres and organic chemical industries in Spain were associated with a risk of retinoblastoma in a study by García-Pérez ([2016](#)).

Where parents lived, whether the mother fed pets before pregnancy and paternal exposure to harmful chemicals preconceptually were risk factors identified by Yang ([2016](#)).

Maternal smoking in pregnancy has been associated with an increased risk of retinoblastoma (Stavrou [2009](#)).

Retinoblastoma (particularly bilateral retinoblastoma in children younger than 6) were associated with traffic density during pregnancy or the child's residence at birth (Heck [2013](#)).

Abdolahi ([2013](#)) suggested a potential role of paternal occupational exposures to non-welding metals and perhaps pesticides in the aetiology of childhood retinoblastoma.

Rhabdomyosarcoma (RMS)

Childhood rhabdomyosarcoma (RMS) accounts for approximately 3.5% of cancer cases among children 0 to 14 years of age. Genetic conditions associated with high risk of childhood RMS include Li-Fraumeni syndrome, pleuropulmonary blastoma, Beckwith-Wiedemann syndrome, and some RASopathies, such as neurofibromatosis type 1, Costello syndrome (CS), and Noonan syndrome (NS). Salem (2016) hypothesized that the inciting event for tumour development in this case is due to the germline mosaic duplication of SOS1, which was duplicated in all cells of the tumour, and the ultimate development of the tumour was further driven by multiple chromosomal aberrations in the tumour itself.

In a study of Chinese children with rhabdomyosarcoma, the primary sites were found in the head and neck, and the 2-year survival rate was 63% in patients who received a combination of surgery, chemotherapy and radiotherapy (Zhao 2011).

Ognjanovic (2010) found a positive association between accelerated *in utero* growth and embryonal RMS (the more common form of RMS), but not alveolar RMS

Skin cancer

Melanoma

Paediatric melanoma is rare, but increasing in incidence. Some risk factors for melanoma include xeroderma pigmentosum, giant congenital melanocytic naevi, dysplastic naevus syndrome, atypical naevi, many acquired melanocytic naevi, family history of melanoma (Tripp 2016) and immunosuppression (Jen 2009).

Solar and artificial (sunbed) UV-exposure is the main risk factor for the development of epithelial skin cancer as well as for malignant melanoma. UV exposure in childhood and adolescence is especially important (Greinert & Boniol 2011).

Around 40-50% of total UV to age 60 occurs before the age of 20. High numbers of naevi and freckles, red hair, blue eyes, inability to tan, as well as a family history are the primary determinants of melanoma among adolescents (AC Green 2011).

Testicular tumours

Nogueira Neto (2012) found that the main histological types were germ cell tumours (53%), and rhabdomyosarcomas (RMS) 38.3%. Adolescents present a higher incidence of rhabdomyosarcomas, lymph node metastases and distant metastases. Survival in RMS cases is longer for children.

Stephansson (2011) found an association between testicular germ-cell cancer and birth weights at both the low and the high ends.

Trabert (2012) concluded that testicular germ cell tumours are not associated with common childhood infections, including mumps.

Thyroid cancer

Normal thyroid gland function is critical for early neurocognitive development, as well as for growth and development throughout childhood and adolescence.

Living in an area of relative iodine deficiency, having one or both parents from a similar region, with a family history of thyroid disease, older age and higher body weight are all risk factors for thyroid cancer in children (Bandurska-Stankiewicz 2010).

Medullary thyroid carcinoma (MTC) is a rare cancer during childhood. MTC is sporadic in approximately 80% of cases and hereditary in 20% (Segura 2016).