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 7

Astrocytoma to kidney cancer

Types of childhood 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.

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

Anal canal carcinoma

Squamous cell carcinoma of the anal canal in children is rare. To date, the aetiology and outcome of this condition have been not fully understood. Human papillomavirus infection was considered as a causative factor in the carcinogenesis (Watanabe 2016).

Astrocytoma

Family and genetic factors

In a study by Toledano (2009) two siblings developed astrocytoma aged 13 and 14. Genomic DNA testing in the family demonstrated a high degree of microsatellite instability.

Pre-conceptional, pregnancy

Maternal consumption of cured meat (Pogoda 2009) has been associated with a doubling of risk for astrocytomas.

Birth factors

High birth weight (>4,000g) was associated with astrocytoma (Harder 2008, Ross 2006) and the higher the weight the greater the risk.

Environmental factors

Mothers' occupational exposures to insecticides, herbicides and non-agricultural fungicides were associated with a slight increase in astrocytoma (van Wijngaarden 2003). A significant risk of astrocytoma was associated with exposures to herbicides from residential and occupational use (Shim 2009).

Wood preservative exposure was linked to astrocytoma risk (Schüz 2001).

Mueller suggested (2004) that the risk of astrocytoma may be associated with the levels of nitrite found in drinking water, and recommended a closer evaluation of well water content. Thompson (2010) found an increased risk in astrocytoma in the children whose mothers lived in an American watershed at the time of birth. The authors considered the possibility that the foetus was exposed to environmental toxins through maternal consumption of contaminated water.

Astroglial tumour

Birth factors

The use of anaesthetic 'gas' has been associated with an increased risk of astroglial tumours (McCredie 1999).

Parental occupational and lifestyle factors

Li (2009) suggests a possible association between maternal occupational ELF-EMF exposure shortly before and during pregnancy (including among sewing machine operators), and astroglial tumours in their children. Maternal exposure to solvents or kerosene at a high level also increased the risk (Cordier 1997).

Paternal exposure to polycyclic aromatic hydrocarbons (PAHs) increased the risk for astroglial tumours (Cordier 2004).

Bone cancer (including Ewing sarcoma)

Predisposing medical conditions

A study of bone sarcomas (Chowdhry 2009), which included some children (as well as adults), found that they were 8 times more likely to develop in people who were already suffering from neurofibromatosis type 1.

Height & birth weight

Mirabello (2011) believes that rapid bone growth during puberty and *in utero* contributes to the development of osteosarcoma.

The average height of young people with osteosarcoma, but not Ewing sarcoma, was significantly above the average height of the reference population by 2-3 centimetres in 5 studies reviewed by Arora (2011). The authors felt that the observed differences indicated the involvement of pubertal longitudinal bone growth in osteosarcoma development while different biological pathways could be relevant for Ewing sarcoma.

Other

Eyre (2009) found associations between hernias and Ewing sarcoma, high fluoride exposure and osteosarcoma and parental farming (also Valery 2005) and residence on a farm, younger age at puberty and family history of cancer for all bone tumours, especially osteosarcoma. The risk doubled for those whose mothers handled pesticides and insecticides, or fathers who handled solvents and glues, and oils and greases (Valery 2002). The authors suggested that it is likely that studies of gene-environment interactions may prove to be the most fruitful of future research. Levy & Leclerc (2011) found that water fluoridation status has no influence on osteosarcoma incidence rate during childhood and adolescence.

Bone sarcoma as a second malignancy is rare but highly fatal (Schwartz 2014).

Brain tumours

Brain tumours are the most common paediatric solid tumour and the leading cause of death by in children (Russell 2013). The risk factors are not well established and Johnson (2014) reviewed studies that examined potential genetic, immune system, developmental and birth characteristics and environmental risk factors.

The multifactorial causation of brain tumours, the inaccuracies of recall of past exposures, and the study of all paediatric brain tumours as a single aetiologic entity may be contributing to the difficulty in identifying risk factors (Bunin 2000).

In a study by Feltbower (2014) of children, teenagers and young adults with brain tumours, the prevalence of breastfeeding was lower in cases than controls, whilst cases were more likely to be delivered by caesarean section. Cases were significantly more likely to have a birthweight of more than 3.5 kg compared to controls and were also more likely to come from a family with 3 or more siblings than controls.

High birth weight, pesticide exposure (childhood exposure, and parental occupational exposure) and maternal consumption of cured meat during pregnancy may also increase the risk of onset of childhood brain tumours. Conversely, maternal intake of pre-natal supplements (folic acid) appeared to decrease risk (Quach 2016).

Catechol-O-methyltransferase (COMT) may indicate a potential resiliency factor against neurocognitive effects of cancer and its treatment (Howarth 2014).

The HeadSmart campaign has led to a reduction in the total diagnostic interval for brain tumours in children to 7 weeks, and the ultimate aim is to reduce it further to 5 weeks which will be on a par with the time taken in other developed countries (Fry 2014).

As many as 50% of children with brain tumours are detected at diagnosis with cognitive difficulties; 6% of patients present with true-diagnosed mental retardation. The location of the tumour is the principal determinant of cognitive deficits, with major impairment in children with cortical tumours (Iuvone 2011).

Pineal calcification was detected in patients (23.5%) with a primary brain tumour, while only 11 patients (8.5%) without a tumour had pineal calcification. Adjusted for patients' ages and genders, pineal calcification was associated with an increase in primary brain tumour of 2.82-fold (Tuntapakul 2016). As melatonin is produced in the pineal gland and has been associated with inhibiting the growth of brain tumour cells, this may be significant. Melatonin supplementation may help increase the availability of melatonin.

Family factors

No relationship between childhood brain tumour occurrence and cancers in family members was found by Searles Nielsen (2008).

Parental occupational and lifestyle factors

Peters (2014) found that parental occupational exposures to solvents may be related to an increased risk of brain tumours, with maternal occupational exposures to chlorinated solvents; and paternal exposure to solvents in the year before conception, mainly attributable to exposure to aromatic solvents for benzene and for other aromatics.

Pregnancy

In the UK, cases among children are increasing by almost 3% a year, with most childhood brain tumours occurring in one to two-year-olds (Mail 2009). Epidemiologists from McGill University in Montreal revealed that women who worked in low-frequency magnetic environments when pregnant, such as machinists, hairdressers, nurses and dry-cleaners, were twice as likely to have babies that developed brain tumours. These occupations also include exposures to chemicals which may have had a synergistic effect, or may have been responsible.

Holly (2002) found a nearly twofold increase in risk was associated with a single use of hair colourant in the month before pregnancy, and the same risk for the use of semi-permanent dye in the month before or during pregnancy, especially the first 3 months.

Maternal consumption of cured meat (Bunin 2004, 2008, Searles Nielsen 2011) has been associated with up to a doubling of risk for brain tumours. The authors suggest a possible adverse effect of dietary nitrites and nitrosamines. A further study by Pogoda and Preston-Martin (2001) suggested that higher doses of nitrite consumption increased the risk factor, but that in general nitrite levels in cured meat is decreasing. It is tempting to assume a chemical role with respect to maternal consumption in the causation of childhood cancers, however eggs and dairy produce are also associated with an increased risk of brain tumour (Pogoda 2009). Perhaps a comparison between organic and non-organic food may be helpful in determining what role chemicals may have.

Greenop (2014) found a positive association between coffee intake of 2 or more cups per day and risk of brain tumours in children younger than 5.

A study by McKean-Cowdin (2003) found no association between childhood brain tumours in general and maternal nitrosatable drug (such as antihistamines, aspirin, antibiotics, etc,) taken during pregnancy. However, they did find an increased risk for 'other glial' tumours.

Maternal exposure to pigs, horses or poultry during the index pregnancy has been associated with childhood brain tumours (Holly 1998, Bunin 2004) and for the children of mothers who ever had worked on livestock farms (Efird 2003).

Child at birth

Head circumference has been linked with brain tumours (Samuelsen 2006) *"suggesting that brain pathology originates during foetal life."*

The use of anaesthetic 'gas' has been associated with an increased risk of brain tumours (McCredie 1999), especially for children aged 0-4 years.

A low 1-minute apgar score was linked to an increased risk of developing a brain neoplasm by Fear (2001) and Bluhm (2008). This may indicate concerns of a wider nature, and is likely to be an effect rather than a cause.

An increased risk for developing a brain tumour with non-cephalic birth presentation was found by Fear (2001). Why this should be is unclear.

Birth weight

Michaelis in an analysis of the German Childhood Cancer Registry (2000) and Hamrick (2001) found an increased risk with *low* birth weight.

Birth defects and congenital anomalies

Children with malformations in the nervous system have been found to be at increased risk of developing cancer in the brain or nervous system (Bjørge 2008).

Ethnicity

Generally, children of mixed-race parentage inherited a higher risk of developing brain tumours (Chow 2010).

Environment

Water

Water sources may play some role in the risk of childhood brain tumours, but the link is unclear. Mueller (2001), overall, observed no increased risk associated with wells as the source of residential water, though the risk was increased in western Washington among offspring of women who relied exclusively on well water, but a decreased risk was observed in Los Angeles, suggesting possibly, a local contaminant that was responsible. Nitrates in drinking water was associated with a higher risk of childhood brain tumour development in Taiwan (Weng 2011).

Animal exposure

An increased brain tumour risk continues for 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, especially when exposed to pigs and poultry. If cats were added to the combination of pigs and horses, children living on a farm had a threefold elevated risk for brain tumours (Efird 2003). However, Christensen (2012) found an inverse association between the mother during pregnancy or the child living on a farm and brain tumour risk. This suggests, they said, that a potential protective effect of farm residence is mediated by some other factor than animal contact.

It is unclear what aspects of animal care on the farm is responsible for the increased risk. No comparison has been made (as far as we know) between an organic farm, a non-organic farm and a biodynamic farm to determine whether the hazard may be a direct or an indirect chemical one.

CNS tumours

Maternal age

Older maternal, but not paternal, age is associated with an increased risk of CNS tumours (Johnson 2009). The authors did not hypothesise about why this should be.

Family factors

Better survival was seen with parents living together (Simony 2016).

Pregnancy

There have been some investigations into the link between maternal diet during pregnancy and the risk of brain tumour in the offspring. The varied results suggest that particular foods may only be associated with specific tumour subtypes, and that broad food groups should also be narrowed down.

There was a strong association found between CNS tumours and high maternal consumption of both tea and coffee (Plichart 2008). This may be a response to a chemical, or some other unspecified lifestyle risk, which is a part of the life of women who drink a lot of tea or coffee.

Mallol-Mesnard (2008) found that one miscarriage increased the risk of a malignant CNS tumour. It is not clear whether this may indicate a general germline problem, that manifests in different ways, including the non-viability of a foetus. Partap (2011) also found that offspring from mothers who had had 2 or more foetal losses after 20 weeks' gestation had a 3-fold risk for CNS tumours, and a 14-fold increased risk for high-grade gliomas. Birth defects increased the risk for CNS cancers ; nearly doubled for medulloblastoma, nearly quadrupled for PNETs, and rose by more than 6 times for germ cell tumours. The authors suggested that previous pregnancy losses and birth defects may be surrogate markers for gene defects in developmental pathways that lead to CNS tumours developing.

Birth weight, birth order, delivery other than term and multiple births

Schüz (2001) and Spix (2009) found an increased risk for CNS tumours with *low* birth weight. Heck (2013) found links for rhabdoid sarcomas and atypical teratoid/rhabdoid tumours and low birthweight and multiple births. Preterm and late term delivery increased the risk of rhabdoid sarcomas.

Breast feeding

No significant effect on risk for CNS was detected in the study by Harding (2007).

Colon cancer

High parental age at birth and exposure to smoke prenatally increase the risk of colon cancer (Ozdemir 2011).

Ependymoma

Pre-conceptional, pregnancy and birth factors

Maternal consumption of cured meat (Pogoda 2009) and maternal smoking (Schüz 2001) have been linked to an increased risk of ependymoma.

Schmidt (2009) found no seasonality for CNS tumours in general, but ependymoma showed a seasonal variation.

Germ Cell Tumour (GCT)

Germ cell tumours can be cancerous or non-cancerous tumours. Germ cells normally occur inside the gonads (ovary or testis). Germ cell tumours that originate outside the gonads may be birth defects resulting from errors during the development of the embryo.

The incidence rate of GCTs was slightly higher in girls. In children aged less than 1 year, the highest incidence rates were seen for girls with GCTs in the pelvis and for boys with GCTs in the testis. For 10- to 14-year-old boys, the tumours occurred most often in the central nervous system; for girls, the most common site was in the ovaries. Only the incidence rate for ovarian GCTs increased statistically significantly (Kaatsch 2015).

The mediastinum is among the most frequent anatomic region in which germ cell tumors (GCT) arise, second only to the gonads. Mediastinal GCT (mGCT) account for 16% of all mediastinal neoplasms (Bremmer & Ströbel 2016). In pre-pubertal children of both sexes, mGCT consist exclusively of teratomas and yolk sac tumours. In post-pubertal adults, virtually all patients with malignant mGCT are males.

In a study by Johnson (2009) investigating any links between congenital abnormalities and germ cell tumours, the authors found a significant association with cryptorchidism (absence of one or more testes from the scrotum). About 3% of full-term and 30% of premature infant boys are born with at least one undescended testis.

A family history of cancer under the age of 40 has been associated with a reduced risk of GCT among females, especially ovarian or uterine cancer; and an increased risk among males, especially melanoma. The authors of the study which reported these findings (Poynter 2010) concluded that the sex and cancer site specific associations might provide clues to the aetiology of paediatric GCT.

A diet rich in fruit and vegetables was associated with a decreased risk of GCTs in males but not females (Musselman 2011).

Gliomas

Birth weight

Spector (2009) found that gliomas other than astrocytomas and ependymomas were possibly associated with very low birth weight (1500 – 1999 g). Low birth weight was associated with an increased risk of low-grade gliomas and high birth weight with an increased risk of high-grade gliomas. High birth order (fourth or higher) was associated with a decreased risk of low-grade gliomas and increased risk of high-grade gliomas. MacLean (2010) concluded that the factors that drive growth *in utero* may increase the risk of low-grade gliomas.

Hodgkin's disease (HL) and Non-Hodgkin's lymphoma (NHL)

Childhood Hodgkin lymphoma counts for about 30% of all paediatric lymphomas in Sweden. The median age at diagnosis was around 14 years, and more boys were affected than girls (Englund 2014).

Bener (2008) found that low age and low education of mother increased the risk of HL and NHL.

The risk of NHL was higher in children with higher birth weight, and there was an inverse relationship between NHL risk and sun exposure (Petridou 2007). A significant association was found between risk of NHL and increased frequency of reported pesticide use in the home, professional exterminations within the home, postnatal exposure and maternal occupational exposure to pesticides (Buckley 2000).

Rudant (2011) reported that an abnormal maturation of the immune system might play a role in childhood HL or NHL. Children and adolescents with pre-existing conditions such as DNA repair defects or other primary immunodeficiencies have an increased risk of non-Hodgkin's lymphoma (Attarbaschi 2016). These pre-existing conditions included: a) cancer predisposition syndromes (58%), b) primary immunodeficiencies not further specified (13%), c) genetic diseases with no increased cancer risk (19%), and d) non-classifiable conditions (10%). 64% cancer predispositions were reported in groups with more than 20 patients: ataxia telangiectasia (32), Nijmegen breakage syndrome (26), and constitutional mismatch repair deficiency (21).

Infant leukaemia

One of the less common forms of leukaemia is infant leukaemia, primarily AML, which is diagnosed usually within the first year after birth, but can be up to 18 months. This is different from leukaemias developed later, as the cause seems to be primarily genetic, due to DNA changes *in utero*, or inherited from either parent. There seems to be little opportunity, or evidence for any environmental factor to be of significance before diagnosis.

Parents of 13.9% of infants with cancer, including leukaemia, in Iran, had consanguinity relationships (Bahoush-Mehdiabadi 2014), which could support the genetic causal possibility.

Slater (2011) found that gestational exposure to petroleum products was associated with infant leukemia, particularly AML, and MLL. Benzene is implicated as a potential carcinogen within this exposure category, but a clear biological mechanism has yet to be identified.

A study (Puumala 2009) that looked at how similar the groups of children with infant leukaemia were to the comparison control groups, showed that the two ways of obtaining control families (random digit dialling and birth certificate) resulted in control families that were similar to each other, but that were different from the families of children with infant leukaemia, and so not always directly comparable.

Maternal

Ross (1997) found that infant AML was associated with increased maternal age. No association was found between infant leukaemia risk and prenatal vitamin or iron supplementation (Linabery 2010).

Pregnancy

Ma (2005) found a link between multiple miscarriages and an increased rate of infant leukaemia.

Pombo de Oliveira (2006) found a strongly significant association between maternal use of hormones during pregnancy and infant acute leukaemia. They suggested that oestrogen exposure could be investigated with respect to its role in intrauterine leukaemogenesis.

Puumala (2010) found no link between infertility treatment and infant leukaemia.

Loss of imprinting of the IGF-II gene occurs in malignant lymphoblasts of more than 50% of children with ALL (Vorwerk 2003). Wiemels (1999) suggested that transplacental exposure to topoisomerase-II may induce MLL gene changes (Strick 2000). An increased maternal consumption of DNA topoisomerase-II-inhibitor-containing foods in pregnancy, such as specific fruits and vegetables that contain quercetin; soybeans (genistein); tea, cocoa, and wine (catechins); and caffeine have all been related to an increased risk of infant leukaemia (Alexander 2001, Greaves & Wiemels 2003), especially AML (1998, Greaves 1997, Spector 2005). Infantile leukaemia is nearly twice as common in several large Asian cities where soy intake is 2-5 times as high as in the USA.

Birth

Being heavier at birth has been associated with infant leukaemia diagnosed between 6 months and 1 year (Ross 1997),

Most studies have shown that an increased incidence of high birth weights and a low incidence of low birth weights correlate with higher rates of infant ALL and AML (Ross 1997, Westergaard 1997, Hjalgrim 2004, Koifman 2008). It has been suggested that high levels of insulin-like growth factor-1 might produce large babies and contribute to leukaemogenesis, an interesting theory that remains to be proved (Petridou 2000).

No evidence was found to support an association between infant leukaemia and congenital abnormalities (Johnson 2010).

Kidney tumour

Renal tumours contribute about 7% of childhood cancers. Improved rates of survival have led to the appearance and identification of late effects, especially secondary malignant neoplasms and cardiac dysfunction. A few children have genetic abnormalities predisposing to Wilms tumour development, which result in renal dysfunction in the long term and may be exacerbated by cancer treatment regimes (Levitt (2011).

Children who were multiples had a reduced risk of Wilms tumour, especially diagnosed before the age of 2. The study (Puumala 2009) authors suggested that mechanisms other than birth weight and gestational age may influence the lower risk of Wilms tumour in multiple births.

There was an increased incidence of renal cancer in children whose mothers lived in two American watersheds (Thompson 2010) The authors were concerned about the possibility of waterborne toxins being responsible.

Wilms tumour

Wilms tumour is the most common renal malignancy of childhood. Genetic predispositions were identified by Turnbull (2012).

A moderately increased risk of developing Wilms tumour has been associated with labour induction, prenatal vaginal infection and upper respiratory infection. Low (less than 2,500g) and high (more than 4,500g) birth weight and preterm delivery also carried a higher risk, as did neonatal respiratory problems (Daniels 2008). The association for high birth weight was present only among children with perilobar nephrogenic rests, possibly distinguishing a specific association among a biologically distinct subgroup of Wilms tumour cases.

Chu (2010) found increased risk of Wilms tumour with maternal exposure to pesticides before the child's birth, maternal hypertension, high birthweight and preterm birth. Being a second or later birth was associated with a decreased risk.