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 6

Other possible causative factors

The complete set:

1. Childhood cancer incidence and types of cancer
2. Genetics and parental exposure
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These are freely downloadable from:

http://www.powerwatch.org.uk/library/index.asp

Childhood Cancer
6. Other possible causative factors, ones which have been largely discounted and protective factors

We include in this first section other factors that have been linked to the development of childhood cancer in general, or more than one type of cancer. When ***specific*** cancers are associated with a particular factor, this is included in Sections 7 'Astro to Kidney' and 8 'Leuk to Thyroid cancer'. We include, in this article, factors which were thought to be implicated in increasing the risk for developing childhood cancer, but increasing research has, by and large, excluded them. At the end we include factors which are thought to decrease the risk of childhood cancer.

Smulevich (1999) found significantly higher risk for children who have cancer in close relatives, with maternal pathology associated with pregnancy, including threatened miscarriage, toxaemia and hormone treatment during pregnancy. Pre-term births were significantly associated with brain-cancer risk. They also found links to low birth weight equal to, or less than, 2500 g in children born from full-term pregnancy, for all cancers combined and for leukaemias specifically. There was a slightly higher risk for those whose birth weight equalled or exceeded 4000 g. Risk of nephroblastoma was also significantly related to this factor. A medical history of dermatitis or viral hepatitis in the child increased the risk.

Younger maternal age, maternal smoking, delivery by caesarean section and low Apgar score at 5 minutes were independently associated with increased risk of childhood cancer (Bhattacharya 2014).

Maternal factors

Maternal age

Slight increases in risk for leukaemia, lymphoma, central nervous system tumours, neuroblastoma, Wilms tumour, bone tumours and soft tissue sarcomas were found with increased ***maternal*** age (Johnson 2009).

Maternal health

Maternal diabetes may be a risk factor for childhood cancer (Westbom 2002).

Birth

Some birth characteristics including older parental age and low gestational age may be related to childhood carcinoma aetiology (Johnson 2011).

Birthmarks & birth defects

Mertens (1998) found a higher reported frequency of birthmarks in both those with acute lymphoblastic leukaemia (ALL) and those with acute myeloid leukaemia (AML), or childhood cancer in general (Johnson 2007). Children with cancer were more likely to have birth defects (Savitz & Ananth 1994). Children with chromosomal birth defects were 30 times more likely to develop leukaemia; children with nonchromosomal birth defects were one and a half times more

likely to develop childhood cancer, particularly brain tumours, lymphomas, neuroblastoma and germ cell tumours (Fisher 2012).

Children with neonatal tumours were more often associated with congenital malformations than other paediatric cancers (Berbel Tornero 2008).

An association has been found with rib anomalies and childhood cancer, specifically AML, renal tumours and hepatoblastoma (Zierhut 2011).

Multiple births

Twins were more common among siblings of children with cancer (Savitz 1994), maybe implying a genetic tendency for increased cell growth.

Birth weight

Unusual weight at birth seems to be implicated in many types of childhood cancer (Savitz 1994) and may be suggestive of factors that underlie cell growth and division that are less than optimal. Skalkidou (2002) suggested that elevations of insulin-like growth factor (IGF-I) in early life might explain the increased risk of cancer in individuals born with a higher birth weight.

A study that looked at children aged 0-14 years newly diagnosed between 1991-1996, found that children with cancer were, on average, 30g heavier at birth than controls. Children with hepatic tumours weighed on average 500g *less* than controls at birth and those with leukaemia were 50g heavier. Girls had a higher risk of ALL with birth weights over 4,000g (A Smith 2009).

The estimated risk for all cancers has been found to be statistically and significantly higher in children with a birth weight of more than 4,000g (Rangel 2010); specifically leukaemia, non-Hodgkin lymphoma and Wilms tumour. A moderate increased risk of both leukaemia and non-Hodgkin lymphoma was also associated with birth weight between 3,000 and 3,999 g. High birth weight was associated with all cancers also when adjusted by gestational age, length at birth, and gender. An increase in hazard rate with a 1 kg increase in birth weight was found for leukaemia, CNS cancers and other cancer diagnoses (Samuelsen 2009). Papadopoulou (2012) says *"Current evidence suggests that birth weight might be a too crude indicator to reveal a genuine association of fetal growth with specific lymphoma categories; hence, there is an emerging need for use of more elaborate proxies, at least those accounting for gestational week."*

Birth and diagnosis month

Basta (2010) found that there was a birth peak in March for ALL aged 1-6; in September for boys aged 0-14 for acute non-lymphocytic leukaemia; October for astrocytoma. A diagnostic peak was found in March for lymphomas in girls; January for Hodgkin lymphoma; and October for boys with osteosarcoma. The authors suggest that their results are consistent with a role for environmental factors in the aetiology of these diagnostic groups.

Birth order

A decreasing risk with increasing birth order was seen in the central nervous system tumors, neuroblastoma, bilateral retinoblastoma, Wilms tumor and rhabdomyosarcoma. We observed increased risks with increasing birth order for acute myeloid leukemia but a slight decrease in risk for acute lymphoid leukemia (Von Behren 2010).

Birth injury

there was a 2.6 fold increase in risk of brain tumours for children who received a head injury, or were delivered by forceps at birth ***and*** had a subsequent head injury (Gurney 1996). It is unclear what role the original injury had in brain tumour development, as a head injury on its own was associated with a small increased risk, which was larger if the child lost consciousness, or received an overnight admission to hospital.

Ethnicity

The incidence of Hodgkin and non-Hodgkin lymphoma and lymphoid leukaemia were higher in Florida's Hispanic children compared with whites and the incidence in black and mixed-race children was significantly lower than whites. The incidence of lymphoma in Florida's Hispanic children (primarily Cuban and Central American origin) differed from similar reports from Texas and California, where Hispanics are primarily of Mexican origin (Wilkinson 2001).

Socioeconomic status

In Korea there was found to be an inverse relationship between childhood cancer mortality and parental socioeconomic position (Son 2010), as in parts of Brazil (de Camargo 2011).

Childhood environment

Childhood cancer is a complex illness and is likely to be due to more than one factor acting together in the developing child's biological systems. If the child has already developed a susceptibility due to genetic changes of some sort, then their homes and lifestyles will bring them into contact with many experiences that may result in a changed cell developing into a cancer.

Diet

We have seen in section 5, that childhood cancer risk is increased by pesticide exposure. Many pesticide residues have been measured on vegetables and fruit, the most contaminated being apples, lettuce, potatoes, grapes and some carrots, many containing the residue of more than one pesticide. One lettuce sample was found to contain inorganic bromide at a level 22 times above that considered safe for children. It may be worth thinking about ensuring a supply of organic food for your child, especially if there are concerns about his or her health.

Geopathic stress

Geopathic stress may be a factor in undermining biological systems within the body (Freshwater 1997, Saunders 2003). Sleeping on lines of geopathic (earth) stress is recognised in many countries as being a significant factor in the development of cancer. Geopathic stress lines are not recognised by most main-stream scientists, as it has not been determined what physical attributes they have. They are usually detected by dowsing. However, peer-reviewed papers are available that show that good dowsers are better at finding drinkable water than scientists using the latest geophysical surveying tools, although it is not known why this is so.

Residential status

There was a statistically significant increase in the rate of leukaemia and brain / CNS tumours reported in South and North east Florida (Amin 2010). The authors concluded *"This evidence is suggestive of the presence of possible predisposing factors in these cluster regions."*

Sunlight

Musselman & Spector (2011) found a link between sunlight exposure and risk of childhood cancer, possibly due to the role of vitamin D as a regulator of cell growth and differentiation.

Factors which have been largely discounted as causes of childhood cancer. These include the following:-

Human Growth Hormone (GH)

After more than 20 years since an association was first suggested, the link between leukaemia, and GH, has not been confirmed (Bell 2010).

Ultrasound scans

Concerns arose in the early 1980s about potential links between ultrasound scans in pregnancy and an increased risk of childhood leukaemia.

There has been little evidence that i*n utero* diagnostic ultrasound tests are linked with an increased risk of childhood leukaemia (Petridou 1997), either ALL (Petridou 1997, Naumburg 2000, Shu XO 1994, 2002), or Acute Non-lymphocytic Leukaemia, ANLL (Van Duijn 1994), although Naumburg found a small increase in risk for ultrasound scans carried out in the second trimester of pregnancy. Dr Razum in Germany did a re-analysis of the Naumburg results and suggested that her data was consistent with the probability that a small proportion of cases of childhood leukaemia might be attributable to prenatal ultrasound exposure. It is also possible that ultrasound was used selectively, when abnormal pregnancies were suspected, or being investigated.

Some studies have shown an association between ultrasound exposure and left-handedness in boys (Kieler 1998, Salvesen 1999, 2002), which could show that foetal development can be affected, possibly in ways that have not been looked at.

Although the risk levels are small and contested, ultrasound scans as a form of "baby TV" should not be routine, but should be used for diagnostic or therapeutic use only. There is concerning evidence of links between ultrasound scans and autism. The Health Protection Agency (HPA) states that there have been some reports suggesting possible neurological effects on the unborn child. The concern is that with souvenir scans the beam of ultrasound stays static over the baby's head for longer in order to get a sharp mug shot.

Ziskin & Morrissey (2011) comment that some higher power Doppler ultrasound devices under some conditions are capable of raising foetal temperature several degrees and their use in examinations of the foetus should be minimised.

Vitamin K injections

Since the 1960's vitamin K has been used widely in the UK, throughout Europe and the US, being given as a single injection just after birth. This is a cheap and effective way of avoiding vitamin K deficiency, a rare but serious condition, with no recorded treatment failures, even in babies with liver disease, who are at most risk.

Research carried out by Parker (1998) found a very slight increase in risk for children developing ALL with intra-muscular vitamin K injections.

A review by Roman (2002) found no evidence to support these findings, and a joint UK Medicines Control Agency, Committee on the Safety of Medicines and Department of Health expert group has concluded that overall, the available data do not support an increased risk of cancer, including leukaemia, caused by vitamin K.

Protective factors

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.

Atopic dysfunction (allergies)

The raised immunosurveillance in atopic individuals might protect against the development of some diseases, including brain tumours (Harding (2008). Children who suffered from asthma and eczema, amongst other atopic conditions, showed a reduction in risk for medulloblastoma and PNET (Harding 2008).

A history of allergies (including asthma, eczema hay fever, food or drug allergies, or hives) has been found (Petridou 1997, Schüz 1999, 2003, Wen 2000, Jourdain-Da Silva 2004, Rosenbaum 2005, Hughes 2007) to have a protective effect against leukaemia, even amongst siblings (Wen 2000). Heck (2009) found a link between allergies and a reduced risk of developing neuroblastoma.

As always, the research is not unanimous and a late history of asthma (Spector 2004) was found to increase the risk of leukaemia, or allergies in general were linked to a specific type of leukaemia (Buckley 1994). A review by Linabery (2010) of 10 case-control studies concluded that both ALL and AML were associated with atopy/allergies, and inverse associations with asthma, eczema and hay fever and ALL.

Miedema (2012) found that in children with atopic eczema, specific genotypes were found more often than in control subjects and less often in children with ALL than in control subjects, supporting the immune surveillance hypothesis.

Protective associations were observed between HL and day care attendance and repeated early common infections among non-breastfed children. Protective associations were seen between NHL and birth order 3 or more, prolonged breastfeeding, regular contact with farm animals, frequent farm visits in early life and history of asthma. The authors felt that the results partly supported the hypothesis that an abnormal maturation of the immune system might play a role in childhood HL or NHL (Rudant 2011).

Birth order & multiple births

Birth order can be used as a proxy for prenatal and postnatal exposures, such as infections and in utero hormone exposure.

Von Behren (2010, 2011) found an inverse relationship between childhood cancer risk and birth order, specifically for CNS tumours, neuroblastoma, bilateral retinoblastoma, Wilms tumour and rhabdomyosarcoma, and a slight decrease for acute lymphoid leukaemia. Altieri (2006) found a decreased risk for Hodgkin's lymphoma for children with 5 or more older siblings.

Being one of twins may reduce the risk of leukaemia (Murphy 2008), though not necessarily so (Cnattingius 1995). The reason for any possible risk reduction is unclear. Children who were multiples had a reduced risk of neuroblastoma (Puumala 2009). The authors suggested that mechanisms other than birth weight and gestational age may influence the lower risk of neuroblastoma in multiple births.

Infante-Rivard (2000) found that having a school age sibling during the first year of life was significantly protective for those older than 4 years at the time of diagnosis. Altieri 2006) found that having many siblings increased the risk of ALL, but if they were older, the risk was significantly decreased. Westergaard (1997) found that the risk of ALL went down with increasing birth order.

Breast-feeding

There is a fairly substantial body of evidence pointing towards a protective effect against cancer of even short-term breast feeding (Smulevich 1999, Shu 1999a, Perrillat 2002, McNally & Parker 2006, Shaw 2006, MacArthur 2008, Flores-Lujano 2009), including brain tumour and neuroblastoma (Daniels 2002), and Wilms tumour (Saddlemire 2006) risk. A meta-analysis reported a relative risk of 0.76 (Kwan 2004). Shu (1999a) & Ortega-García (2008) found that the reduction in risk was stronger with a longer duration of breast-feeding, and Bener (2001, 2008) concluded that long-term (longer than 6 months) was protective, especially for ALL, Hodgkin's lymphoma, and non-Hodgkin's lymphoma but short-term was associated with an increased risk of all cancers. Waly (2011) did not find any link between breastfeeding and risk of leukaemia in Oman.

A study looking at the relationship of breast feeding with Hib infection (Silfverdal 1997) suggested that breast feeding acts in a manner similar to vaccination, stimulating the immune system. It could therefore provide a protective effect against childhood cancer.

Diet

Evidence from one study suggests that there is a strong protective effect of consumption of oranges and bananas in early life (Kwan 2004). Other studies (Jensen 2004, Petridou 2005, McNally & Parker 2006) have suggested that consumption of fresh fruit and vegetables generally have a protective effect up to age 2 years (Kwan 2009). Consumption of yellow-orange vegetables and grains during pregnancy were associated with a reduced risk of brain tumours, including cruciferous vegetables (e.g. cabbage, brussels sprouts, broccoli, cauliflower) being associated with a decreased risk of astrocytoma (Pogoda 2009). The consumption of many vegetables and fruit is associated with a decreased risk of cancer. This is at least partly due to the antioxidant elements of these foods. As some processed foods are linked to cancers, non-processed, organic (to avoid chemical contamination) vegetables and fruit should be included as main ingredients in a diet to reduce the risk of cancer. Vegetables and bean-curd were both found to be protective against acute leukaemia (Liu 2009).

Petridou (2005) also found a decreased risk with maternal consumption of fish and seafood. Maternal consumption of fresh fish is associated with a decreased risk of astroglial tumours (Pogoda 2009). Jensen thought that dietary carotenoids and glutathione appeared to be important.

Curcumin and turmeric have been shown to inhibit cancer (Alaikov 2007) (including childhood leukaemia) at initiation, promotional and progression stages of development (Nagabhushan 2004) in different ways (Blasius 2007). A mechanism for the ant-cancer effect of curcumin has been proposed by Langone (2012) who suggests that it suppresses NF-kB, inhibiting tumour-promoting proteins. A study by Banderali (2011) proposed that the inhibition of Kv11.1 activity by curcumin may lead to interference with leukaemic cell physiology and consequently the suppression of survival and proliferation of AML cells. Curcumin is one of the ingredients of the spice turmeric.

Ethnicity

Ma (2005) found that parentally reported ear infection during infancy was associated with a significantly reduced risk of ALL in non Hispanic white children. They highlight an important ethnic difference but it is not clear whether this may be due to cultural/environmental factors or biological characteristics.

Asian and mixed-race children were at lower risk of developing brain tumours (Chow 2010), and Hispanic and mixed-race children had a lower risk of developing neuroblastoma.

Many of the factors discussed above shed some insight, perhaps, on the sort of environmental exposures that could be avoided, in order to prevent an increased likelihood of developing cancer and the potential for relapse in children recovering after treatment. The most important factor for survival is the interval between first remission and occurrence of the first relapse (van den Berg 2011).

Gestational age

A reduced risk of germ cell tumours was found for children born at term rather than earlier (Shu 1995).

Infection

Children attending day care (often used as a surrogate for infectious exposure) are less likely to develop leukaemia (Perrillat 2002, Jourdan-Da Silva 2004, Gilham 2005, Ma 2005, Kamper-Jørgensen 2007, Urayama 2010), particularly common B-cell precursor ALL (c-ALL) (Urayama 2008), and neuroblastoma (Menegaux 2004). Shaw (2006) found that the risk of a childhood brain tumour was reduced by day care attendance for more than a year.

It was assumed that attendance increased their exposure to infections, strengthening the immune system. In fact any social activity outside the family in the first year of life significantly reduced the risk of ALL (Gilham 2005), and CNS tumours (Spix 2009). Spix found this protective effect continued until the 5th year. Perrillat found that day-care without developing infections, did not offer a protective effect; neither did infections without the day-care, although Canfield (2004) did find an effect. Older siblings (Infante-Rivard 2000, Jourdan-Da Silva 2004), or the number of infectious episodes (Neglia 2000, Perrillat 2002) had a protective effect. However, several studies have reported no protective effect (Roman 1994, Petridou 1997, Rosenbaum 2000, Chan 2002).

The different conclusions may indicate that there are important confounders that have not been adequately considered, or we need to question whether day care attendance is a reliable proxy for infectious exposure.

Rudant (2010) found a number of factors which seemed to be protective against the risk of leukaemia, that implicated early infections, as factors involved. These included birth order, attendance at a day-care centre before the age of 1, prolonged breastfeeding, repeated early common infections, regular contact with farm animals, frequent farm visits in early life, and a history of asthma or eczema.

The evidence suggests that early childhood infections in general, within the first two years of life, are protective, whereas infections in later life may not be.

Lifestyle

The results of a study by Bellizzi (2011) support the hypothesis that early-life exposure to pets, birds and particularly with chickens might be associated with a reduced risk of lymphoma.

Medication use

Some medications were found to be negatively associated with infant leukaemia (Ross 2003). These were prescribed for a variety of reasons and the mechanism of protection therefore is unclear. Actual medical records were used, so recall bias would have played no part in the findings, except for 'over the counter' medication.

MacArthur (2008) found that the use of immunosuppressant medication by children decreased leukaemia risk.

Miscarriage or still birth

A history of miscarriage or stillbirth halved the risk of astrocytoma (Bunin 1994). A history of spontaneous abortions was negatively associated with neuroblastoma risk by Munzer (2008).

Vaccinations

Pagaoa (2011) found that some common childhood vaccines (hepatitis B, the inactivated poliovirus vaccine) appeared to be protective against ALL at the population level. Whether this is linked to the issue of infections is unclear, but possible.

Vitamins and minerals

Maternal vitamin supplementation during pregnancy reduced the risk of brain tumours in children under the age of 5. The longer in the pregnancy the supplements were taken, the greater the degree of protection (Preston-Martin 1998). This may partially make up for what is not available in the diet, but supplementation is not always as usable by the body as vitamins and minerals from natural sources. Any maternal vitamin use during the 6 months before conception through the nursing period, was associated with a reduced risk of GCTs (Johnson 2009).

Maternal use of vitamins, cod liver oil, folate and iron supplements have been associated (Wen 2002, Schüz 2007) with a decreased risk of ALL, medulloblastoma (Bunin 2006), and neuroblastoma (Olshan 2002, Heck 2009) although children's vitamin intake was found to increase the risk of leukaemia (MacArthur 2008), especially AML, if multivitamins were taken

during the first year of life or for an extended period of time (Blair 2008). The timing seems to be particularly critical as Ross (2005) found that vitamin use before the index pregnancy reduced risk for ALL, as did Milne (2009), but not for AML, and increased the risk of both if taken during pregnancy. It is believed that inadequate folate may cause the first 'hit' in the leukaemia pathway, or prevent the child repairing the first or subsequent hits.

Folic acid supplementation before the 21st and 36th days of gestation resulted in significantly lower nervous system tumours (NST), especially central nervous system tumours. Preconceptional intakes of folic acid were also lower in NST (Ortega-García 2010).

Folate metabolism is thought to be important in the development of leukaemia. There is some evidence to suggest that maternal folate supplementation during pregnancy may protect against childhood leukaemia (Thompson 2001), though Dockerty (2007) both in the team's own New Zealand study, and in their meta analysis, including results from Australia and Canada did not find evidence to support Thompson's hypothesis. There are differences in the way that individuals metabolise folate and this may be important (Wiemels 2001). Koppen (2010) concluded that *"susceptibility to (childhood) ALL is partly related to constitutional differences in folate gene polymorphisms*" (supported by Lightfoot 2010) and that some polymorphisms in the MTHFR gene were associated with a decreased susceptibility to childhood ALL in non-Asian populations.