

# Childhood Cancer

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

We include in this 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'. We also include 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.

### 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

#### Birth marks & 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 neonatal tumours were more often associated with congenital malformations than other paediatric cancers (Berbel Tornero [2008](#)).

#### Birth order

Birth order can be used as a proxy for prenatal and postnatal exposures, such as infections and *in utero* hormone exposure. Von Behren ([2011](#)) found an inverse relationship between overall childhood **cancer** risk (**ALL, CNS tumours, neuroblastoma, bilateral retinoblastoma, Wilms tumour** and **rhabdomyosarcoma**) and birth order.

#### 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.

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 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, including 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.

### 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, **leukaemia**, a major safety issue initially believed associated with 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 *in 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.

## 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.

Golding ([1992](#)) suggested that intra-muscular vitamin K injections significantly increase children's chances of developing childhood **leukaemia**. Research carried out by Parker ([1998](#)) found a very slight increase in risk for children developing **ALL**.

Follow-up international studies, including Klebanoff (1993) who found no significant effect on any childhood cancer, and 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

### 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](#)).

### 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.

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 21<sup>st</sup> and 36<sup>th</sup> 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.

## 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.

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

## Birth order & multiple births

Behren ([2010](#)) 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.

## Gestational age

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

## Breast-feeding

There is a fairly substantial body of evidence pointing towards a protective effect against **cancer** of even short-term breast feeding (Shu [1999a](#), Perrillat [2002](#), McNally & Parker [2006](#), Shaw [2006](#), MacArthur [2008](#), Flores-Lujano [2009](#)), including **brain tumour** and neuroblastoma (Daniels [2002](#)), 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.

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.

## 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.

## Atopic dysfunction

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**.

## 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, independent of the child's diet 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.

Petridou 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, promotion and progression stages of development (Nagabhushan & Bhide [1992](#), 2004) in different ways (Blasius [2007](#)).

## Infection

Children attending day care (often used as a surrogate for infectious exposure) are less likely to develop **leukaemia** (Petridou [1993](#), 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 5<sup>th</sup> 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. However, several studies have reported no protective effect (Roman [1994](#), Petridou [1997](#), Rosenbaum [2000](#), Chan [2002](#)). Older siblings (Infante-Rivard [2000](#), Jourdan-Da Silva [2004](#)), or the number of infectious episodes (Neglia [2000](#), Perrillat [2002](#)) had a protective effect.

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.

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.

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.

## Ethnicity

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](#)).

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