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 11

Precaution, prevention and protection

1. Childhood incidence and types of cancer

2. Genetics and parental exposure

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7. Types of childhood cancer – Astrocytoma to kidney cancer

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The quality of life for cancer survivors may be improved by behaviours that promote health and well-being. These include a healthy diet, exercise, a healthy weight and regular medical and dental checkups. Avoiding behaviours that are damaging to health is also important. Getting vaccinations for hepatitis A & B may help protect the liver. Smoking, excess alcohol use, illegal drug use, being exposed to sunlight, or not being physically active may worsen organ damage related to treatment and may increase the risk of second cancers.

S Wu (2016) concluded that cancer risk is heavily influenced by extrinsic factors. These results are important for strategizing cancer prevention, research and public health. Not only is the information essential for the prevention of cancer, but also for continuing health and wellbeing for survivors of cancer.

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 (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.

A late history of asthma (Spector 2004) was found to increase the risk of leukaemia. 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). 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.

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, Greenop 2015) 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) and Amitay (2015, 2016) 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.

Breast feeding may act in a manner similar to vaccination, stimulating the immune system. It could therefore provide a protective effect against childhood cancer.

Complementary and alternative medicine (CAM)

Many parents use one or more CAM for their child in the context of cancer. The most used type of CAM is homeopathy, dietary supplements and aromatherapy. The most frequent goal for CAM use is to limit the side effects of conventional treatment. In a study by Philibert (2015) in 87.5% of the users the CAM was effective. However, some CAM such as herbal supplements could potentially cause interactions with cancer treatments, so more information about interactions would be useful for both parents and practitioners.

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 (and protein sources Abiri 2016) 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 anti-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. Park (2013) summarised research that has found that vitamin C at high concentrations induced a dose- and time-dependent inhibition of proliferation in acute myeloid leukaemia (AML) cell lines and in leukemic cells from peripheral blood specimens obtained from patients with AML. Inhibition of leukemic cells was also observed after administration of high concentrations of L-ascorbic acid (Kawada 2013).

Studies suggest carcinogens from a mother's diet can cross the placenta into an unborn baby's bloodstream, and Henshaw, says some of the carcinogens could come from processed meats and burned barbecue meats eaten by pregnant women.

Eating a healthy diet full of fruit and vegetables is important for all the family, including pregnant women and children, says Henshaw.

In addition, an Australian study found mothers who took folate and iron supplements during pregnancy had more than a 60% reduced risk of their children developing leukaemia (Irish Examiner September 2016).

Singer (2016b) found that higher maternal diet quality score was associated with reduced risk of ALL and possibly AML. No single component appeared to account for the association. The association of maternal diet quality with risk of ALL was stronger in children diagnosed under the age of 5 years and in children of women who did not report using vitamin supplements before pregnancy. These findings suggest that the joint effects of many dietary components may be important in influencing childhood leukaemia risk. Singer adds *"There were 470 cases of childhood leukaemia (0-14 years of age) in 2014. If we could prevent 20% of them, that would save 94 children from developing childhood leukaemia per year."* A previous study by Singer (2016) showed that higher maternal intake of one-carbon metabolism nutrients (folate, vitamins B12 and B6, riboflavin, and methionine) may reduce risk of childhood leukaemia.

The higher diet quality for women who are pregnant or lactating comprises 12 nutritional components: 9 'adequacy' components (total fruit, whole fruit (excluding fruit juice), total vegetables, greens and beans, whole grains, dairy products, total protein foods, seafood and plant proteins, fatty acids) and 3 'moderation' components (refined grains, Na, and empty calories).

Zhou (2017) identified and characterized intestinal bacteria that exhibited potent anti-malignancy activities on a broad range of solid cancers and leukaemia. The bacteria mostly belonged to Actinobacteria but also included lineages of other phyla such as Proteobacteria and Firmicutes. In animal cancer models, sterile culture supernatant from the bacteria highly effectively inhibited tumour growth. Remarkably, intra-tumour administration of the bacterial products prevented metastasis and even cleared cancer cells at remote locations from the tumour site.

Electromagnetic fields (EMFs)

Luukkonen (2014) found persistently elevated levels of micronuclei in the progeny of MF-exposed cells, indicating induction of genomic instability.

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).

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, other studies have reported no protective effect (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.

Frequent contact with other children when 0-3 years old and ventilation during sleeping in summer were associated with a decreased risk of childhood acute leukaemia (Chen 2015).

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.

Meditation and Yoga

Meditation and yoga practice showed a significant decline in levels of oxidative damage to sperm DNA, the adverse effect of tobacco on the paternal genome, after 6 months (Kumar 2015). This effect could be responsible for non-familial sporadic heritable retinoblastoma.

Miscarriage or still birth

A history of spontaneous abortions was negatively associated with neuroblastoma risk by Munzer (2008).

Sun protection

Children of melanoma survivors are at higher risk than other children of developing melanoma. Melanoma survivors may have a heightened awareness of the importance of their children's sun protection, but their children are not routinely protected. It is suggested that subgroups of survivors could be targeted with interventions to improve sun protection (Tripp 2016).

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.

Sankaran (2016) found a possible protective effect of immunisations against the development of childhood rhabdomyosarcoma (RMS), as long as the immunisation schedule was completed. However, infections did not appear to be associated with childhood RMS. It is unclear what aspects of immunisation were protective.

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, Metayer 2014) 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.

Pineal calcification was detected in a quarter of patients with primary brain tumours. Adjusted for patients' ages and genders, pineal calcification was associated with a 3-fold increase in primary brain tumour (Tuntapakul 2016). As the pineal gland is a major source of melatonin, the body's natural anti-cancer hormone, melatonin supplementation may be very useful in strengthening the body's immune system.

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). Folic acid supplementation during preconception may reduce the risk of childhood leukaemia (Ajrouche 2014).

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.

In the home

In a study by Bailey (2015) the authors concluded after pooling 12 case-control studies, that 'it would appear prudent to limit the use of home pesticides before and during pregnancy, and during childhood'. They had found links with ALL and AML.

Greenop (2013) found that preconception pesticide exposure, and possibly exposure during pregnancy, both professional pesticide treatment and paternal occupational exposure, is associated with an increased brain tumour risk, especially for low- and high-grade gliomas. The authors suggested that 'it may be advisable for both parents to avoid pesticide exposure during this time'.

Bailey (2015) found that home paint exposure shortly before conception, during pregnancy, and/or after birth appeared to increase the risk of childhood ALL. The authors suggested it may be prudent to limit exposure during these periods.

The cancer risk of DEHP (the plasticizer di(2-ethylhexyl) phthalate) via inhalation in children was lower than that in adolescents and adults, but the risk in children via dermal and oral exposure to indoor dust and soft PVC toys should be considered (Miao 2017).