Childhood brain and central nervous system (CNS) tumours (general)

The incidence rate of childhood brain tumours is rising, some oncologists say rising rapidly. It is difficult to know exactly how many cases of brain tumours there are, as Brain Tumour UK believes that under-recording of tumours, both primary and secondary, malignant and non-malignant, is distorting the information we have.

This is important, as the more data we have, the greater the likelihood that possible causes can be detected and better treatments can be given. Only about 50% of primary brain tumours were recorded in Scotland (Counsell 1997) and Devon and Cornwall (Pobereskin 2000, 2001). Let us hope that statistical information about brain tumours and childhood brain tumours has improved since these reports were published. Gurney in 1999 summed up the situation thus "*Because of the potentially profound adverse health effects on children who experience CNS tumors, the systematic collection of both malignancies and nonmalignancies is consistent with the mission of public health surveillance. Without such population-based data, analytic epidemiologic studies to evaluate disease etiology and assess disease consequences are greatly hindered.*"

Research into the causes of childhood brain tumours is underfunded, receiving less than 1% of the national spend on cancer research in the UK.

More effective treatment protocols have increased cure and survival rates for leukaemia, which used to be responsible for the highest mortality rate in children, but this is not yet as true for brain and CNS tumours. Figures released in April 2009 show that the number of children dying from a brain tumour in 2007 was 33% higher than in 2001, whilst child deaths from leukaemia were 39% lower than in 2001. The reason for the increase in CNS cancer rates in the past two decades is unknown. Changes in environmental exposures may be responsible for the increasing incidence rates, or it could be improvements in diagnostic technology.

Statistics from the UK and other countries include:-

- Brain tumours affect approximately 350 children (and their families) in the UK each year (CancerBackup 2005).
- CNS malignancies represent 16% of all childhood malignancies; astrocytomas accounting for 52% of CNS malignancies, Primitive neuroectodermal tumours (PNETs) 21%, other gliomas 15% and ependymomas 9%. The incidence of CNS tumours tends to be higher in boys than girls and higher among white children than black. The incidence of CNS tumours in Europe between 1988-1997 was 29.9 per million, with the highest rates in the North. The incidence increased significantly during 1978-1997 on average by 1.7% per year. Astrocytoma incidence was 11.8 per million; PNET 6.5 per million; ependymoma 3.4 per million (Peris-Bonet 2006).
- The Observer reported in April 2009, that Kevin O'Neill, a consultant neurosurgeon at Imperial College London said "In my unit we have seen the number of cases of child brain tumours nearly double in the last year." Yang (2006) reported an 11.7% growth in incidence of infant brain tumour in Taiwan between 1995 and 2004.
- 40% of all cancer deaths in children are from a brain tumour. In 2007 there were 47% more deaths from brain tumours among under-15s than from leukaemia.

- Whilst on average 75% of all childhood cancer patients in Britain survive five years, for brain tumour patients, five year survival remains at 12% for males and 15% for females.
- On average it takes longer to diagnose a child with a brain tumour in the UK than in North America and a number of European countries. The principal cause of delay in diagnosis is the failure by front-line health professionals to include brain tumours in the differential diagnosis.
- Brain tumours in African children are now becoming more common (Idowu 2008).
- Some brain and CNS tumour types are more common at different ages. Young children have a relatively high occurrence of malignancies in the cerebellum and the brain stem, and older children have higher rates in the cerebrum. In children between the ages of 5 and 9, brain stem malignancies are nearly as common as cerebral malignancies, and cerebellum malignancies are far more common than cerebral malignancies. The pattern shifts among children between the ages of 10-19, when brain stem and cerebellar cancer incidence decrease and cerebral malignancies increase slightly.

The cure rates for brain tumours are not as high as for leukaemia, and finding the causes of these cancers should be a matter of urgency, to avoid children and their families going through the immediate physical trauma of treatment, and also the longer-term physical and psychological effects of the treatments on health and wellbeing. Often the more complex the treatment needed e.g. radiotherapy and chemotherapy as well as surgery, the more likely that some adverse health effects will follow later. Radiation treatment always carries an increased risk of developing other cancers later in life (Neglia 2006), though whether it does so, or not, may also depend on genetic susceptibility (Flint-Richter 2007).

Strokes are more likely in survivors of brain tumours (Bowers 2006, Gurney 2003). Late complications occur in many CNS tumour survivors. These complications include as well as hearing loss, blindness, cataracts, double vision, hypothyroidism, seizure disorders, growth hormone deficiency, need for medical induction of puberty, osteoporosis, cardiovascular conditions, angina-like symptoms, ovarian failure and musculoskeletal (including co-ordination and motor control) problems and pulmonary abnormalities (Laverdière 2005, Packer 2003, Gurney 2003). The majority of these are of mild-moderate severity, with only 4% being life-threatening (Laverdière 2005).

Hudson (2003) found that adult survivors of childhood CNS tumours were likely to report problems with adverse general health, mental health, activity limitations and functional impairment.

Adult short stature and obesity in female brain cancer survivors was reported, especially where the cancer was diagnosed at an early age and where the treatment involved the hypothalamic-pituitary axis (HPA) (Gurney 2003).

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).

The risk factors for childhood brain & CNS tumours in general are listed below, with the relevant references. Research linking risk factors to specific tumours, again with references, are listed in section 2. The references themselves are listed in Section 3.

Risk factors for childhood brain and CNS tumours, without specified subtypes

- **General** – chemical exposure; ELF magnetic field exposure
- **Parental and wider family –** genetics; occupational exposure; smoking and alcohol consumption.
- **Maternal –** animal exposure; caffeine; diet; infection; prescription drugs; pregnancy complications; X-rays & ultrasound.
- **Child at birth** - apgar score; birth defects and congenital anomalies; birth weight; non-cephalic birth presentation.
- **Childhood environment** – animal exposure; infections; powerfrequency radiation exposure; radiofrequency radiation exposure; radon.
- **Protective factors –** atopic dysfunction; breast-feeding; diet; infection; vitamins and minerals.

General

Chemical exposure

Zahm and Ward's extensive review of 26 studies on pesticide exposures and risk of brain tumour (1998) concluded that there were risks and they depended upon the time of exposure, whether this was preconceptual, pre- or postnatal. They suggested that children were more susceptible than adults and the risk factors were greater. Infante-Rivard and Weichenthal (2007) brought the subject up to date with the 21 studies published since the Zahm & Ward review. 15 of these studies showed significantly increased risk between pesticide exposure to parents or child and childhood cancer.

ELF (powerfrequency) magnetic field exposure

There is quite a difference of opinion as to the involvement of electromagnetic fields in the causation of childhood tumours. This may be because the research has not included differences in genetic susceptibility and type of tumour that makes the risk (if any) difficult to quantify with any degree of certainty.

In a meta-analysis of 13 studies (Mezei 2008), there was a very slightly elevated risk of brain tumours with exposure to magnetic field levels in the home over 0.2 microtesla (μT), with a greater risk at levels of 0.3 or 0.4μT.

Preston-Martin (1996) found no association, but she concluded that the prevalence of high fields in Los Angeles homes was too low to detect a moderate effect. Gurney (1999) concluded that electromagnetic fields (EMFs) played no causal role in brain cancer development.

Parental & wider family

Genetics

Genetic susceptibility to brain & CNS cancers could be due to a number of circumstances. How important each of these factors is, may well depend on the different subtypes of cancer. Kuijten' studies (1990, 1993) led the authors to conclude*"Childhood brain tumors may result from a genetic susceptibility and that some risk factors may affect childhood astrocytoma and PNET differently."*

- Family history of cancer. The review by Dearlove (2008) of 16 studies looking at the family history of cancer among children with brain tumours, found limited evidence of a link which was not significant.

- Specific (inherited) germline mutations can also increase the risk of brain tumours and other cancers (Krüger 2008).

- Certain genetic conditions, such as neurofibromatosis, tuberous sclerosis and Weaver (Coulter 2008) and Li-Fraumeni (Bunin 2000) syndromes carry an increased risk of brain tumours, though these conditions account for no more than 5% of all brain tumours.

As the knowledge of the human genome increases, risk factors due to inheritable mutations may well become better understood.

Parental occupational exposure

Some parental occupations seem to increase the risk of children developing cancer. There may be 'windows' of exposure that mean that paternal germ cell exposure, or maternal exposure preconception, or during pregnancy may have different implications for cancer development in their offspring. Sometimes, chemicals may be brought home on clothing which also could be involved. Occupational exposure is not always particularly well-defined, can be calculated retrospectively and may be used differently in different studies. This can make direct comparisons not very meaningful.

Children of parents who worked in the chemical industry, agriculture or motor-vehicle related occupations (Cordier 1997) or electrical workers (McKean-Cowdin 1998) had an increased risk of developing brain tumours. Paternal welding in the one-year preconception period was associated quite strongly with an increased brain tumour risk (Wilkins 1996) in the child. However, the authors felt that welders were exposed to a wide range of toxic agents and it was not clear what exposure may be significant. Paternal exposure to paints has been associated with an increased risk of nervous system cancers in their children (Colt & Blair 1998).

Children under 5 also had an increased risk of cancer if their mothers, were employed as electrical workers (Cordier 2001). Maternal work in the textile industry, or electronic parts and components manufacturing also carried a higher risk (Ali 2004), as did working in the health services.

Children of mothers who had preconception/prenatal farm- or agriculture-related employment involving potential contact with animals had increased risk of brain tumours. During the 5 years preceding the index child's birth, maternal exposures to fertilisers, pesticides, animal manure and unprocessed wool were associated with risk (Efird 2003).

Parental occupational creosote exposure has been strongly linked to childhood brain cancers (Feingold 1992)

Smoking and alcohol consumption

Smoking and alcohol consumption is included in the chemical exposure section, as it is assumed that any link to child cancer is likely to be due to toxic chemical ingestion, causing the relvant changes. There may also be other lifestyle confounders that are not included, which may explain some of the different conclusions come to in the studies.

Paternal smoking has been associated with brain tumours (Plichart 2008), and some papers have linked brain tumours with parental alcohol consumption (Heck 2009). Maternal smoking during pregnancy has also been associated with CNS tumours (Michaelis 2000). Yang (2000) found no such link and the findings in a review of 33 studies by Infante-Rivard and El-Zein (2007) were inconclusive. The authors suggested that subtypes of tumours should be considered, and genetic susceptibility, to determine what role alcohol may have in the subsequent development of brain tumours.

Maternal

Included here are factors which relate specifically to the mother of the child rather than the father specifically, or both parents, where these factors have not been considered above.

Age

Older maternal age, 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.

Animal exposure

Maternal exposure to pigs or horses during the index pregnancy has been associated with childhood brain tumours (Bunin 2004).

Children who were on a farm for more than a year and were first on a farm when they were less than 6 months of age (Holly 1998) had an increased risk for brain tumours, as did the children of mothers who ever had worked on livestock farms (Efird 2003).

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

Caffeine

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.

Diet

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. This also holds true for the protective effects of dietary factors (see section 2).

Maternal consumption of hotdogs (Sarasua 1994), or cured meat (Bunin 2004, 2008, Preston-Martin 1996, Kuijten 1990) has been associated with a doubling of risk for brain tumours. The authors suggest a possible adverse affect 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 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 may be helpful in determining what role chemicals may have.

Infection

Fear (2001) found that children whose mothers had documented evidence of a clinically diagnosed viral infection during pregnancy had an approximately 11-fold increase in risk of developing a malignant neoplasm of the brain or other part of the nervous system. It may not just be the infection, but also the treatment which has a role, as Shaw (2006) concluded that childhood brain tumours may be associated with exposure to infective agents, particularly the use of antibiotics during pregnancy.

Prescription drugs

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,) taking during pregnancy. However, they did find an increased risk for 'other glial' tumours.

Pregnancy complications

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.

X-rays & ultrasound

X-rays have been associated in the past with an increased risk of cancer. Due to the pioneering work of the late Alice Stewart, X-rays as a matter of course during pregnancy were discontinued and they are rarely done now. In a review of 25 studies published between 1990 and 2006, there was no association found between pre- and postnatal X-rays and brain tumours (Schulze-Rath 2008).

X-rays were superseded by ultrasound scans as a means of checking on the developmental progress of foetuses. Ultrasound exposure has not been found to be a risk for brain tumours (Stålberg 2008), but there are other concerns about ultrasound exposure leading to neurological changes, which suggest that they should be used where there are concerns about the child's wellbeing, rather than an automatic procedure.

Child at birth

Having looked at some of the factors in the wider family and in the parents that may be implicated in the development of a cancer, we now look at the newborn child. Premature birth has been linked with brain tumours (Savitz & Ananth 1994).

Apgar score

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.

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).

Birth weight

Michaelis in an analysis of the German Childhood Cancer Registry (2000) and Hamrick (2001) found an increased risk with *low* birth weight, as did Schüz (2001) and Spix (2009) for CNS tumours. Spector (2009) found that gliomas other than astrocytomas and ependymomas were possibly associated with very low birth weight (1500 – 1999 g at birth).

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.

Non-cephalic birth presentation

An increased risk for developing a brain tumour was found by Fear (2001). Why this should be is unclear.

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. Here are some of the factors associated with a general risk of developing a brain or CNS tumour. Specific subtypes and some of the relevant study findings are included in Section 2.

Animal exposure

Children of mothers who were exposed to pigs, horses or poultry during the index pregnancy had an increased risk of childhood brain tumours (Holly 1998), and children who were exposed to pigs and poultry also had elevated risks. 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).

Infections

Infections as a cause of childhood cancer (especially leukaemia) have been well-researched. Sometimes day-care, or social contact has been used as a surrogate for infections, as it is assumed that children in day care, with older siblings, or having a lot of social contact are likely to be exposed to more bacterial and viral infections than children without these lifestyle experiences. As stated above, there may also be a role for medication etc. used in the treatment of such infections in the development of cancer.

Harding (2009) looked at the relationship between infectious exposure in the first year of life and the likelihood of developing a CNS tumour. The studies they looked at had findings that were inconsistent with respect to tumour subtype, and Harding's team concluded that an early exposure to infections is not strongly implicated in the aetiology of CNS tumours, but the effect for social contact outside the home warrants further investigation.

Shaw (2006) concluded that childhood brain tumours may be associated with exposure to infective agents, particularly the use of antibiotics, removal of tonsils, adenoids or appendix, being at least second in the family and having siblings.

Bunin (2004) in a review of non-genetic causes of childhood brain tumours concluded that polyomaviruses may have an aetiologic role.

Power-frequency radiation exposure

It has been accepted internationally that childhood leukaemia is associated with exposure to power-frequency electromagnetic fields or distance to powerlines. There has been less investigation into any link between such exposures and childhood brain and CNS tumours. One such study found a positive association between exposure to residential magnetic fields above 0.4 microtesla and the risk of brain tumours (Saito 2010).

Radio-frequency radiation exposure

People have expressed concern about the use of mobile phones and brain tumours, but this is a relatively new technology, children have only just begun to use them extensively and brain & CNS tumours can take some time to develop and be diagnosed. Meanwhile, this uncertainty may influence whether we discourage our young people from exposing themselves to such a potential hazard.

As well as the risk from phones, people have wondered whether the radio-frequency emissions from the mobile phone network of masts and other sources may also result in an increased risk of tumours in children who live nearby. We wait for the research findings.

No link was found between the radiation from AM radio transmitters and the incidence of brain tumours (Ha 2007).

Radon

Radon is a naturally occurring gas, found in many areas of the UK. In some cases, remedial work is necessary to prevent the radon contaminating a house, especially the lower floors. A report by Kaletsch (1999) found a link between residential radon exposure and CNS tumours, though the number of children affected was small, and in general the authors said *"there is little support for an association with CNS tumours in the literature."*

Some factors have been associated with negative risk for brain tumours; that is, they may offer a degree of protection, though why this should be so in some cases, is unclear.

Protective factors

Atopic dysfunction

The raised immunosurveillance in atopic individuals might protect against the development of some diseases, including brain tumours (Harding (2008).

Breast-feeding

Breast-feeding has been inversely associated with the risk of brain tumours (Shaw 2006). This again, suggests an immune system strengthening.

Diet

Consumption of yellow-orange vegetables and grains during pregnancy were associated with a reduced risk of brain tumours (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.

Infection

Shaw (2006) found that the risk of a childhood brain tumour was reduced by day care attendance for more than a year. This was used as a surrogate for infection (see above). Spix (2009) found that social contact had a significant protective effect against CNS tumours.

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.