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 2

Genetics and parental exposure

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Childhood Cancer
2. Genetics & parental exposure

Genetic predisposition to childhood cancer varies according to the site and type of cancer. Some families have an inheritable DNA which is associated with an increased risk of children developing cancer, e.g. the inheritable form of retinoblastoma. In retinoblastoma, RB1 mutations are found in 92% of bilateral and familial patients with retinoblastoma and in 10% of non-familial patients (Dommering 2014). In other cases, the parents of a child may be exposed, either at home or at work to substances which create the DNA changes that make a child conceived afterwards more likely to be susceptible to cancer (Xu 2012). Diagnosis of a childhood cancer associated with early-onset or multiple lesions, or a malformation syndrome, or a positive family history of cancer should raise an alarm of a cancer predisposition syndrome (Gauthier-Villars & Stoppa-Lyonnet 2011).

As some types of cancer occur in children with a genetic susceptibility the inclusion of a genetic evaluation is recommended for both survivors and other family members (Knapke 2012). There are other considerations, too. Children whose families have hospital insurance at the time of their diagnosis had a significantly lower chance of abandoning treatment and a higher chance of survival (Mostert 2013).

This section is separated into two. The first part looks at a very little of the genetics. If you are very interested in the genetics of carcinogenesis in childhood, we suggest you look at more detailed publications, as we have neither the information nor the understanding needed to explain the complexity of the genetics involved.

The second part looks at parental exposure, at work and elsewhere, that may be implicated in the DNA mutations that lead to cancer in the children.

As the knowledge of the human genome increases, risk factors due to heritable mutations are becoming better understood.

Most of the environmental and lifestyle factors which may be implicated in the causes of childhood cancer are extremely difficult to investigate in an epidemiological study with a case-control design. The problems are two-fold.

- Firstly, the rarity of most forms of childhood cancer is such that too few cases may have a sufficiently wide range of exposures to environmental agents to allow an effect on cancer risk to be detected with statistical confidence. The factors responsible for different forms of cancer may be quite different and therefore an amalgamation of cases may lose any information of significance.

- Secondly, many such exposures are ubiquitous, meaning that in a case-control study both cases and controls could be equally exposed and an effect on cancer risk would be undetectable. Air pollution and background radiation in particular fall into these categories. It has been suggested that about 5% of cases of leukaemia are induced by background radiation, and up to 15% in people under the age of 25 (Kendall 2011).

The result could be that factors which may have a major bearing on childhood cancer risk lie undetected, even undetectable, by conventional epidemiology. It is this situation which has really limited progress in understanding the *causes* of childhood cancer.

Against this background of uncertainty, any description of our current understanding of the causal factors leading to childhood cancer needs to take account of the totality of the available genetic, cancer subtype, laboratory and epidemiological evidence.

There have been considerable advances in understanding the biology of childhood cancer, for example, in the identification of gene rearrangements many of which appear to occur *in utero* and mark the first step in what is at least a two-stage process. While some aspects of the biological aetiology or the mechanics of how cancer develops, are known, the reasons why gene mutations occur are poorly understood.

Excessive exposure to chemicals; radiation, both ionising and non-ionising; and biological agents have been linked to an increased risk of developing the illness. Environmental agents, which may not be genotoxic or carcinogenic themselves, can contribute to cancer by increasing the genotoxic potential of other agents, interfering with the DNA repair processes, or by allowing a cell with DNA damage to survive and stimulating the cell division, resulting in alteration of the normal functions of the cell. For example, leukaemic cells show chromosome rearrangements that occur in around one per cent of newborn babies, but less than one per cent of these will go on to develop leukaemia. So, although the stage for developing the illness is set in the womb, *something else is needed* for the disease to become manifest.

Some animal experimentation using chemicals to promote cancer in rats, has shown that the differences in study outcome could be accounted for by different susceptibilities in the strain of rats used. It may be that humans have the same variation in susceptibility as the specially bred rats, whose sensitivities are variable enough to reduce replicability in the experiments.

Tumour predisposition in children is rare, accounting for approximately 10% of all cancers in childhood. It is now almost universally agreed that the development of most forms of cancer, with a few exceptions, seems to be largely a multi-factorial process, with several factors being implicated, no one factor being 'necessary' or 'sufficient' to cause cancer in children. The first factor, or event, often prenatal, is regarded as an initiation process, whilst subsequent events are 'promotional'. Promotional factors may not coincide with each other in terms of timing, and the exposures may occur at different stages in a child's life. These factors need to be taken into account as the time-window of exposure for childhood cancer is not known (Urayama 2009).

What causes childhood cancer?

There are several factors that are involved in cancer susceptibility and initiation. These can be grouped into broad categories (Sinnett 2007), including:

- Cellular growth and differentiation
- DNA replication and repair
- Metabolism of carcinogens
- Apoptosis (programmed cell death)
- Oxidative stress response
- Failure of immune system recognition of transformed cells

Most childhood cancers arise from the abnormal transformation of a single cell. Stem cells, the precursors of cells, divide frequently. There are probably about 100,000,000,000 cell divisions a day in an adult and even more *in utero* when the embryo is growing rapidly. These cells undergo DNA re-arrangement to create the large number of different types of cells needed by the immune system. This process is intrinsically prone to DNA errors – which may occur either spontaneously or as a result of exposure to external carcinogens (Lightfoot & Roman 2004, Galetzka 2012). When cell DNA is damaged by some factor, the cells usually either die or the DNA is repaired. Any un-

repaired or mis-repaired damage will lead to changes in chromosomes, or mutations, some of which may lead to the development of cancer.

Given the extraordinary number of cell divisions that occur each day and the lack of complete fidelity of DNA replication and repair, it is likely that mutations in most, if not all, genes occur all the time. Why we do not all have cancer does require an explanation.

Most mutations happen either in irrelevant cells (e.g. dying cells) or they are functionally neutral for the cell, or they kill the cell. Usually, an initiating mutation must be functionally complemented by other independent mutations in order to produce disease, before the affected cell is exterminated by differentiation or other control mechanisms. Such mutations may have to arise in a particular sequence or occur in particular pairings (Buffler 2008, Mullighan 2009).

Precisely how many sequential co-operating mutations are required to produce overt, clinical cancer is not entirely clear, but the relatively short latency, especially in infancy and childhood suggests that only a few are needed in comparison with most adult carcinomas that are thought to evolve over decades and that demonstrably can have an accumulated set of 5 to 15 mutations (Vogelstein & Kinzler 1998). In adult tumours, the minimum number of genetic events seems to be 3 or 4 (Hahn 1999), but leukaemia may require fewer as it is not dependent on tissue structure (Greaves 1999).

The inheritance of certain genes (Thol 2011), or higher numbers of genes such as activating KIR genes, can reduce the risk of childhood leukaemia (Almalte 2011).

Lee (2012) suggests that changes in chromatin structure and epigenetic regulation can increase the chance of cancer formation. Their results demonstrate that high mutation rates are not necessary for the initiation of cancers by mutation of a chromatin remodelling complex. Consequently, he concludes that cancer (particularly highly malignant rhabdoid cancers) can be a remarkably genetically simple disease.

Some pre-cancerous cells show chromosome rearrangements that occur in a lot of newborn babies (Mori 2002), but very few of them will go on to develop cancer. The study by Lausten-Thomsen into leukaemia (2010) supports the theory that the pre-leukaemic cells peak at term or early childhood and they suggest that, as yet unknown factors are necessary to clear them of potential carcinogenicity.

Studies into the causation of childhood cancer can be difficult to conduct (Schulz & Grimes 2002). Bias can be present for a number of reasons, e.g. exposure may be measured indirectly, may be self-reported, and may be differentially recalled by parents of a well, rather than a sick, child (Infante-Rivard & Jacques 2000) and specific subsections of the population may not respond to the study survey (Mezei 2008). Small numbers of children may distort the statistical validity that can be drawn, and the variable latency of the disease can make results hard to interpret. There are also difficulties in looking at exposures when there can be a time lapse between these and diagnosis. The incidence rates of childhood and adult cancer vary, which may imply different causes, or may be related to maturation, as in some of the hormonally-mediated cancers.

With identical twins, if one develops ALL in ***infancy***, the chances are 50:50 that the other will also develop the illness. An identical twin is twice as likely as the general population to develop leukaemia if his or her twin developed the illness before the age of 7 (Zipf 2000), but by the age of 15, the risk becomes the same.

A high degree of concordance for childhood leukaemia has been observed for identical twins or triplets (Buckley 1996, Zipf 2000), but it has been suggested that this may be more to do with shared placental circulation than to an inherited genetic mutation (Ford 1998, Wiemels 1999b,

Maia 2001, 2003, Zuna 2003). Kempski's study on identical twins (2003), suggested that initial cell changes occurred *in utero*, which imposed the chromosomal instability which then could lead on to the development of leukaemia.

It is clear that as people get older, life-time environmental factors play a more important role in determining whether they develop leukaemia or not. For instance, people with both the GSTM1 and GSTT1 null polymorphisms may not develop melanoma. But if they suffer from sunburn in childhood, they have an extremely high risk of melanoma (Fortes 2011).

The factors which have been linked to childhood cancer can be divided into 3 categories:

- Exposure to ***causative*** factors which ***increase*** the risk of a child developing the disease;
- Exposure to ***protective*** factors which ***reduce*** the risk of a child developing the disease;
- Factors which are linked to the incidence of cancer but are not directly causative or protective, more likely they reflect the likelihood of exposure to another causative or protective factor.

While enormous progress has been made in understanding the biology of the disease, much research remains to be done to understand the underlying ***causes*** of the disease. It is also important to remember that children who survive childhood leukaemia due to the fantastic advances in treatment, have consequences affecting their lives, the lives of their families, and there are repercussions on the larger society that they are a part of, that make finding and removing the causes even more important (for more details of these survivorship effects, see section 9).

Against this background of uncertainty, any description of our current understanding of the causal factors leading to childhood cancer will always be incomplete.

We present below an incomplete version of some of the information known about the cellular basis for childhood cancers

There have been considerable advances in understanding the biology of childhood leukaemia, for example, in the identification of gene rearrangements some of which may be passed on by parents (Biondi 1998), and many of which appear to occur *in utero* and mark the first step in what is at least a two-stage process (Taub & Ge 2004). In a study by Gruhn (2008) preleukemic cells were detected on neonatal Guthrie cards in 63% of B-precursor ALL patients. MT Smith (2005) found specific chromosome re-arrangements in neonatal Guthrie cards, suggesting that maternal and perinatal exposures such as chemical and infectious agents are likely to be critical. C-ALL susceptibility may be triggered by exposure to infectious agents (GM Taylor 2002).

While some aspects of the biological aetiology or the mechanics of how leukaemia develops are known, the reasons why gene mutations occur are poorly understood. Identifying subgroups of children, in which the similarities are sufficient to allow for comparison, and defining time windows (Anderson 2000) when mutations are likely to arise because of specific exposures, is quite a challenge especially when different cellular and molecular mechanisms may be implicated according to the kind of exposure.

In utero chromosomal translocations, re-arrangements or other gene fusion sequences can be very early or initiating events (Gale 1997, Mahgoub 1998, Fasching 2000, Yagi 2000, Taub 2002, Panzer-Grümayer 2002, Greaves & Wiemels 2003, Bateman 2010, Braoudaki 2010) for both ALL and AML. It is likely that one or more additional postnatal genetic changes are required (S Yamamoto 1998, Kim-Rouille 1999, Ross 2008, Chang 2010). Reichel (1998) suggested that the cellular DNA damage-repair machinery is likely to be involved. Lilljebjörn (2010) found an average number of

3.5 recurrent changes for ALL. The frequency was 7 times higher in children aged up to 2 years of age, and twice as high in those up to 5 (Andreeva 2010).

There is a postnatal latency which is variable but often protracted (Wiemels 2002, Maia 2004) ~ 1-14 years. Particular chromosomal abnormalities may be found more frequently in certain types of leukaemia or at less predictable times. For example, children with infant ALL have arrangements more similar to those aged 3 or more years, suggesting that the particular genetic change is initiated later in foetal development than most, and have a shorter latency period *in utero* (Fasching 2001).

Bener (2001) found that a family history of cancer was found more often in children with acute lymphoblastic leukaemia (ALL), suggesting a genetic predisposition. There is a difference in opinion as to whether cancer in the family predisposes children to leukaemia. Infante-Rivard & Guiguet (2004) suggested that only familial malignancies involving blood-forming cells increases ALL risk to children, whereas Ripert (2007) reported that such a familial history increases the risk of AML by over 4 times; a family history of solid tumours, genital cancers and brain tumours can increase the risk of childhood leukaemia significantly. The risk doubles if more than 2 relatives are affected. Hemminki & Jiang (2002) reported that parental leukaemia has not been associated with childhood ALL but leukaemia in a sibling has been a risk factor for leukaemia in other siblings.

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 did not achieve statistical significance. Specific (inherited) germline mutations can also increase the risk of brain tumours and other cancers (Krüger 2008), such as ALL (Ellinghaus 2011). Germline TP53 mutations, impairment or functional inactivation of this pathway by other means contribute to childhood cancer (Pinto 2011, Barone 2014).

Certain genetic conditions, such as neurofibromatosis, tuberous sclerosis, 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 cases.

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.

The list of chromosome changes and gene mutations in leukaemia is now very extensive, involving more than 100 identified genes and including changes that are leukaemia, and sometimes subtype specific (Rubnitz 1994, Sorensen 1994, Megonigal 1998, Wiemels 1999, Garte 2000, Emerenciano 2006, Mullighan 2007, Spector 2007, Eguchi-Ishimae 2008, Papaemmanuil 2009, Taylor 2009, Han 2010, Healy 2010, Oh 2010, de Jesus Marques-Salles 2010, Vijayakrishnan & Houlston 2010,Wang 2010, Xue 2010, Canalle 2011, Huang 2011, Tumer 2011, Zanrosso 2011, Zhao 2011, Tong 2011, Silveira 2012), gender specific (Chan 2010), country-specific (Vijayakrishnan 2010), or ethnic group specific (Daniel-Cravioto 2009, Chang 2010, Miladpour 2010, Siddiqui 2010, Piwkham 2011, Rahimi 2011, Tumer 2011).

The majority of mutations in leukaemia are acquired (Wiemels 2000, Bernardin 2002, Hattori 2007, Fischer 2007, Hong 2008, Wiemels 2008, Zhou 2010), but in themselves, they are not necessarily sufficient to induce leukaemia (Andreasson 2001, Ayton & Cleary 2001, Yuan 2001). In rare cases (1-5% of acute leukaemias) inherited mutant genes may be involved. Wu (2010) suggested that a specific allele of XRCC4, in combination with the deletion of intron 3 may be responsible for childhood leukaemia. XRCC4 is a DNA repair gene, important in maintaining the overall genome stability, and is thought to play a key role in human carcinogenesis. Schuler (2014) found significant differences in double-strand break repair capacity in children with cancer, compared with healthy children. Some variations of the FAS promoter regions are

associated with a decreased risk of childhood ALL (Tong 2012). Górniak (2014) found a link between rs4132601 site and age at diagnosis of childhood ALL. The authors concluded that their data were further evidence of a biological role of gene variants in ALL development. Chang found that leukaemia risk was also dependent on day care attendance, which implies that the immune system also plays a part in genetic susceptibility. Han (2011) suggests that genetic changes in immune response genes might play a role in childhood leukaemia development.

Ferguson (2011) found that the HLXB9 gene may have a dual role in leukaemia, as an oncogene in infant AML but as a tumour suppressor in childhood ALL. DP2 supertype is associated with susceptibility to ALL and DP1 is associated with protection (Taylor 2011), and there seems to be maternal undertransmission of the infrequent supertypes DP11 and DP15, which may be protective.

In mice experiments, some mutations result in embryonic death, due to an absence of normal haematopoiesis (Higuchi 2002). Hunger (1998) described a child's foetal death at 36 weeks gestation from widely disseminated AML, demonstrating that the initiator was clearly *in utero.*

AML accounts for 15 to 25% of childhood acute leukaemias. A small number of genes were implicated (Damm 2011) revealing a deregulated tryptophan metabolism. Tryptophan is a precursor of melatonin. Some genetic abnormalities impact on disease prognosis positively (Kömür 2010), though some are cancer-promoting (Zhang 2011).

It has been suggested (Dekeyser 2011) that the development of neonatal AML indicates a chromosomal rearrangement, possibly the MLL gene. Children with compromised DNA repair mechanisms may be susceptible to MLL re-arrangements produced by maternal consumption of flavonoids (Vanhees 2011).

Sinnett (2006, 2007) suggested that the combination of genotypes were more predictive of risk than when each was considered independently. The authors concluded that their *"results indicate that the genetic investigation of several enzymes (or metabolic pathways) is needed to explain the physiopathology of childhood leukemia because of the complexity of the environment and that of inter-individual variability in cancer susceptibility"*. Earlier studies (Krajinovic 1999, Sinnett 2000) had suggested that gender-specific effect of DNA variants may explain why ALL is more prevalent among boys, although Tumer (2010) found particular genotypes increased the risk for females. They also found that carriers of more than one of the risk-elevating genotypes increased the risk by up to 3 times.

Children born with inherited diseases, such as Down syndrome (DS), Fanconi's anaemia, ataxia telangiectasia, neurofibromatosis 1, Bloom syndrome, certain types of hereditary immunodeficiency and conditions that include bone marrow failure (Prasad 2008), an abnormal number of chromosomes or genetic instability are much more susceptible to leukaemia, especially AML (Reynolds 2002, Hemminki & Jiang (2002), Ross 2005). Children with DS are 30 times more likely to develop leukaemia (Malkin 2000), especially acute megakaryoblastic leukemia (AMKL)(Khan 2011). Further investigation of the leukaemias of DS are likely to contribute to the general understanding of the chromosome changes common in cancer (Izraeli 2007). Linabery (2008) concluded that congenital malformations did not confer additional risk of leukaemia beyond the risk attributable to trisomy 21 found in children with DS. Chromosome 21 instability was the only anomaly common to all patients with a specific subgroup of childhood B-cell precursor ALL (Rand 2011), suggesting that the initiating event is in the complex rearrangements of this chromosome.

Several of the genes involved in these syndromes have been identified, which all regulate the integrity of DNA or its repair after damage. Over 200 genetic alterations have been linked to leukaemia, though it has been suggested that there may be significant differences according to

birth continent (Liang 2010). High hyperdiploidy is common in ALL, occurring in 25-30% of cases. Near triploidy and tetraploidy are found in less than 1% of ALL (Mkrtchyan 2010). Wiemels (2010) suggests *"a natural history for hyperdiploid leukaemia in which prenatal mitotic catastrophe is followed by a postnatal RAS mutation to produce the leukemic cell phenotype."*

The occurrence of chromosomal abnormalities varies, as a number of aberrations have been observed more frequently than others, while some aberrations are related to particular subtypes (Papafthymiou 2008), especially when other factors such as maternal age and paternal preconception smoking are also included (Wiemels 2005). Some gene variants predispose children to leukaemia due to a reduced ability to deal with toxins (Canalle 2004, Infante-Rivard 1999, Krajinovic 2002).

A study by Shalapour (2010) indicated a relationship between stem cells and leukaemia cells, suggesting their involvement in the pathophysiology of ALL.

Evidence has been accumulating that AML is initiated and propagated by leukaemic stem cells. Witte (2011) suggests these most immature leukaemia cells are more resistant to therapy and subsequently initiate relapse.

Goldin (2005) found susceptibilities for Hodgkin Lymphoma on chromosomes 2, 4 and 11. They said their results were consistent with recessive inheritance.

Huang (2010) found that children who had hepatitis B virus, and also had a pre-S deletion were more likely to develop hepatocellular carcinoma.

Parental occupational exposure

There have been suggestions about the biological mechanisms whereby parental occupational exposures may affect their children's risk for cancer. These include genetic alteration of the father's sperm, which may transmit cancer susceptibility to the child, or transplacental foetal exposure after the parent brings a toxic exposure into the home, such as bringing chemicals home on clothing. 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. Occupational exposure is not always particularly well-defined, it mat be difficult to calculate 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, and ALL (Castro-Jiménez & Orozco-Vargas 2011). 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.

Reid (2011) found a small increase in risk of ALL with either maternal or paternal exposure any time before the birth, to extremely low frequency electromagnetic fields (ELF EMFs).

Parental exposures prior to conception, including exposures to petroleum products, organic solvents, unspecified chemicals, soldering aerosols, ionising radiation, electromagnetic fields (EMFs), visual display units (VDUs, or computer monitors) and high temperature in the workplace were significantly more frequent amongst parents of children with cancer, including leukaemia, non-Hodgkin's lymphoma and neuroblastoma (Smulevich 1999).

Specific biological pointers suggest that the classic form of infant ALL originates in a stem cell that has not fully committed to lymphoid differentiation (Biondi 2000). These changes can arise due to exposures to specific cancer-causing agents in the mother during pregnancy, and in both parents before the child's conception.

Maternal factors

Children under 5 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 an increased risk (Efird 2003). We have not found studies that compared farming practices such as organic or biodynamic farming techniques, which may shed some light on whether chemical exposure may underlie the genetic changes responsible for the increased childhood cancer risk.

Childhood leukaemia was associated with maternal occupational exposure to aromatic and aliphatic hydrocarbons, particularly in the preconception period (Miligi 2013).

Paternal factors

A study using an occupational exposure index by Perez-Saldivar (2008) reported that children whose fathers had been exposed to a high level of carcinogenic agents had a greater risk of developing acute leukaemia. Paternal exposure to diesel exhaust fumes, mineral oils and lead was associated with childhood leukaemia. The risk of NHL appeared to be related to paternal exposure to oxygenated solvent and petrol exhausts (Miligi 2013).

Paternal employment in the manufacture of iron and metal structures, in machine workshops, as machinists and as smiths also carried significantly increased risks.

Paternal exposure to paints has been associated with an increased risk of nervous system cancers in their children (Colt & Blair 1998).

Men with an academic degree were also associated with their children having an increased risk, though the reason for this is unclear.

In a study investigating the amount of paternal occupational contact with others in rural Sweden. There was an association between childhood leukaemia at ages 0-4 years, and high levels of contact (Kinlen 2002).