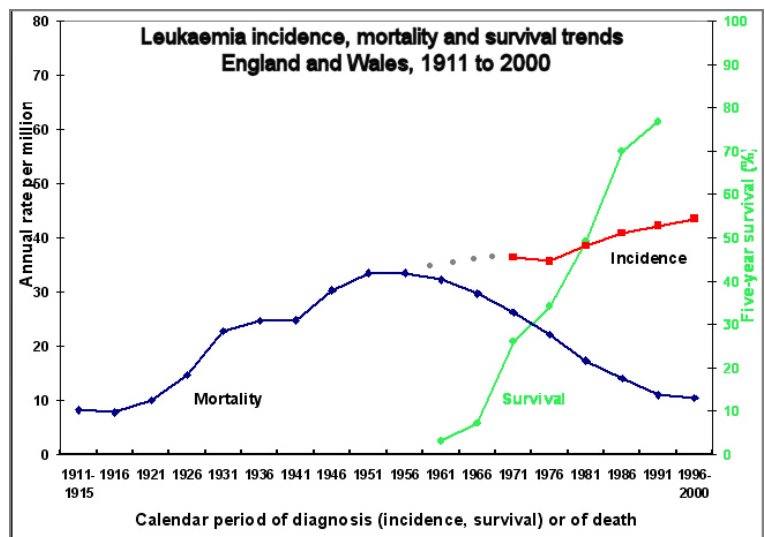


Childhood leukaemia

Each year about 500 children in the UK develop leukaemia, the most common type of childhood cancer, accounting for about 30% of all cancers diagnosed in children younger than 15 years. Around 100 children die of it. The lifetime risk (0-15 years old) of a child developing childhood leukaemia is about 1 in 1600. Acute lymphoblastic (lymphoid) leukaemia (ALL) accounts for more than 80 per cent of all cases of childhood leukaemia. ALL occurs approximately 5 times more frequently than acute myeloid leukaemia (AML) and accounts for approximately three quarters of all childhood leukaemia diagnoses. Chronic myeloid leukaemias make up most of the other childhood leukaemia cases.

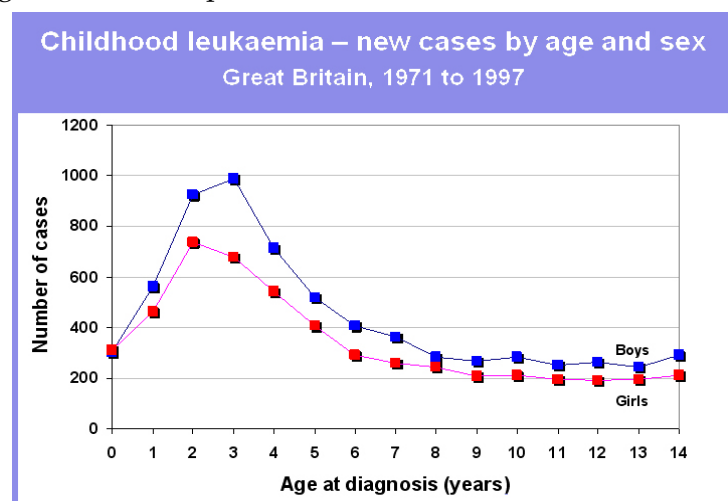
The incidence of childhood leukaemia has increased fairly steadily over the last century and was almost unknown pre-1900, though that may well have been because the children died of other causes before leukaemia developed. However, it was well recognised by the early 1900s and was almost always fatal within a short time, so mortality data give a good indication of incidence.

The mortality rate for children with leukaemia has greatly reduced in recent years due to better treatment. The overall 5-year survival rate (often called the cure rate) for childhood ALL is now approximately 85%, for AML approximately 68%, and for infant leukaemia 45%. A report looking at data from the USA (Trigg 2008), showed a 10-year event-free survival for children with ALL of 62%, and 11% of children with initial relapses survived without second events, bringing the cure rate to 73%.



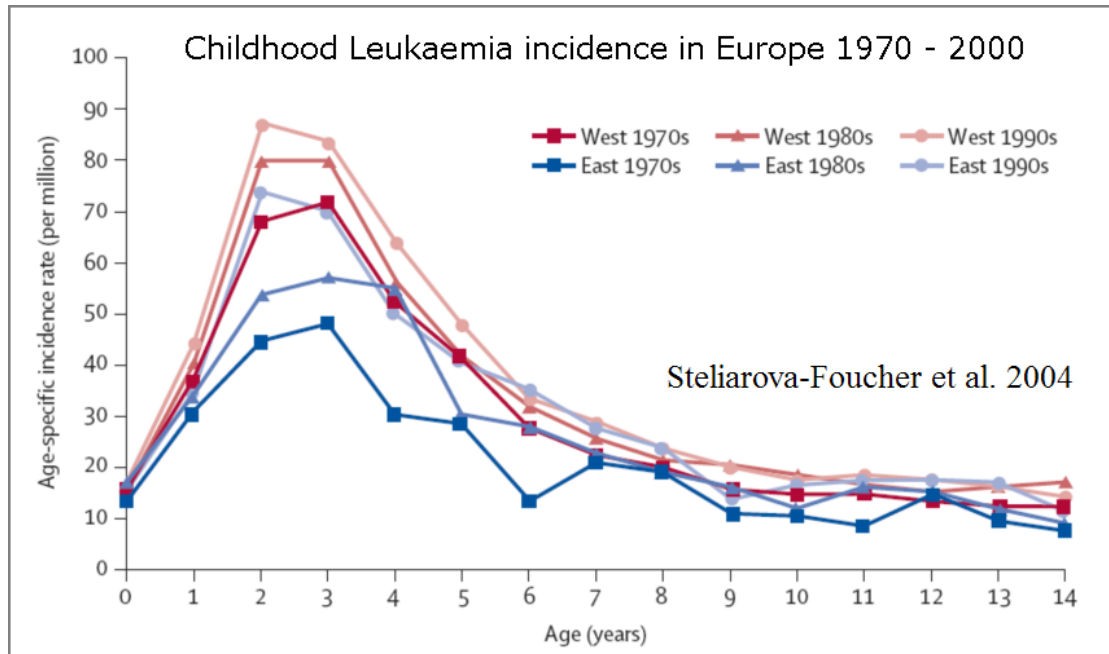
The graph showing information from the UK is from Shah & Coleman (2007). Before 1950, childhood leukaemia was nearly always fatal and so the mortality data will be almost identical to the incidence data, maybe with a lag of year or two. Other countries have shown similar increases (Linabery 2008).

Most of the increased incidence occurs in a characteristic 2 to 4 year-old incidence peak in acute lymphoblastic leukaemia (ALL) emerged in developed countries (Spix 2008) in line with industrialisation – it was not seen before the 1920's and the peak has gradually increased since then. These incidence trends suggest that environmental factors and lifestyle play an important part in the causation of leukaemia, as our genetic make-up does not change significantly over such a short time scale. Within developed countries themselves, research has shown that higher socio-economic status carries a higher risk for childhood leukaemia. Because of this, it seems that lifestyle factors are likely to play a significant

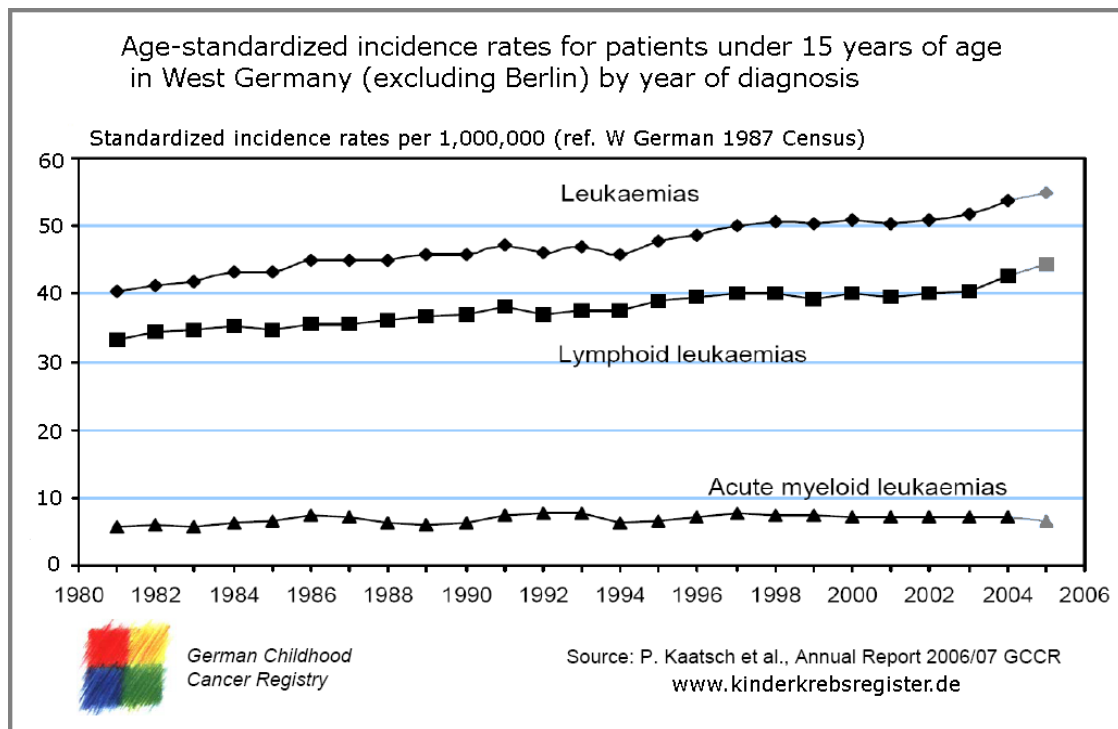


role.

However, the number of children diagnosed with leukaemia is still steadily increasing (Hosny 2002, Coleman 2004, Steliarova-Foucher 2004, Yang 2006), mainly in the 2 to 5 year old age range. This can be seen in the following graph, with Eastern-bloc countries catching up with modern western lifestyles and environments.



Over the last 30 years, the incidence of all child leukaemias has been rising fairly steadily by about 0.7% per annum. This can be seen in the data from Germany (this is used because UK data is unavailable for the most recent years, though up to 2000 is very similar to the German data).



Modern genetic research has revealed that many children are born with a genetic susceptibility to leukaemia, either inherited or occurring in the womb, possibly due to maternal environmental exposure.

It is now almost universally agreed that development of leukaemia seems to be largely a multi-factorial process, with several factors being implicated, no one factor being 'necessary' or 'sufficient' to cause leukaemia in children. A possible exception to this may be infant leukaemia, when genetic changes may be adequate to induce the illness without further factors being necessary.

The first factor, or event, is regarded as an initiation process, whilst subsequent events are 'promotional'. Promotional factors may not coincide with each other in terms of timing, and indeed it is considered probable that the exposures may occur at different stages in a child's life. Variations in leukaemia occurrence by subtype suggest that risk factors may not be identical for the different forms of leukaemia.

At present, most of the research money spent on leukaemia each year is spent on curing and treating those with the disease. CHILDREN with LEUKAEMIA believe that it is just as important to prevent the disease from happening in the first place.

Recently there have been many promising advances in our knowledge of the health sciences, from genetics to environmental factors, and our understanding of what is behind the development of childhood leukaemia is improving. It is now clear that 80 to 90% of childhood leukaemia cases have genetic changes that originated at conception or in the womb (Wiemels et al 1999, Greaves & Wiemels 2003). This means that environmental factors affecting the mother and / or the father are likely to have been involved. The first 6 months, and especially the first two months, of pregnancy is a critical time for foetal development.

This report mentions many of the factors being investigated by epidemiological and laboratory studies. Some, if not all, may play their part in childhood leukaemia development.

What causes childhood leukaemia?

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

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

Leukaemia arises from the abnormal transformation of a single cell. Stem cells, the precursors of blood 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. The cells that go on to become white blood 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). Leukaemic cells show chromosome rearrangements that occur in around one per cent of

newborn babies (Mori 2002), but less than one per cent of these will go on to develop leukaemia. 75% of children with ALL have biologically and therapeutically relevant genetic abnormalities (Pui 1997).

The most consistent associations with childhood AML are parental exposures during gestation and child exposure prenatally and perinatally in the first 5 years of life (Buckley 1989, Severson 1993, van Duijn 1994, Robison 1995, Ross 1996, 1998, Shu 1996). These associations probably reflect the extreme vulnerability of the foetus to leukaemogenic agents.

So, although the stage for developing the illness is set in the womb, *something else is needed* for the disease to develop, the two-hit (or multi-factor) hypothesis. The exception to this is infant leukaemia, i.e. diagnosis at less than one year of age, more or less, in which it is thought that all necessary changes take place at conception or *in utero*.

Childhood leukaemia is luckily, a rare illness, though its rarity does mean that studies into causation can be difficult to conduct (Schulz and 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), specific subsections of the population may not respond to the study survey (Mezei 2008). The small number of children may distort the statistical validity that can be drawn, and, due to the latency of the disease. There are also difficulties in looking at exposures when there can be a time lapse between these and diagnosis.

When cell DNA is damaged by some factor, the cells usually either die or the DNA is repaired. Any unrepaired or misrepaired damage will lead to changes in chromosomes, or mutations, some of which may lead to the development of cancer.

One recent report (Buffler 2005) estimates that in 90% of the cases of childhood leukaemia, the aetiology is unclear. They believe that a wide range of factors, including environmental, sociological and lifestyle influences are implicated as well as genetic susceptibility.

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, allowing a cell with DNA damage to survive and sometimes stimulating cell division resulting in alteration of the normal functions of the cell.

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. 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.

The increase in incidence of childhood leukaemia during the 20th century suggests that changes in environmental factors, including lifestyle, are at least partly responsible. There is no single factor to which a child must be exposed if they are to develop leukaemia; and there is no single factor, exposure to which is guaranteed to result in the development of leukaemia. There are multiple pathways involved.

The factors which have been linked to childhood leukaemia 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 leukaemia but are not directly causative or protective, more likely they reflect the likelihood of exposure to another causative or protective factor.

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

- Firstly, the rarity of childhood leukaemia is such that too few cases may have a sufficiently wide range of exposures to environmental agents to allow an effect on leukaemia risk to be detected with statistical confidence.
- 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 leukaemia risk would be undetectable. Air pollution and background radiation in particular fall into these categories.

The result could be that factors which may have a major bearing on childhood leukaemia risk lie undetected, or even undetectable, by conventional epidemiology.

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, due to these limiting factors.

Against this background of uncertainty, any description of our current understanding of the causal factors leading to childhood leukaemia needs to take account of the totality of the available laboratory and epidemiological evidence, and will be incomplete.

The biological aetiology of childhood leukaemia - basic biological mechanisms, *in utero* markers – full blown leukaemia

There have been considerable advances in understanding the biology of childhood leukaemia, 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 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 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.

Childhood leukaemia is a collective term for a group of subtypes.

Infant leukaemia

One of the less common forms is infant leukaemia, primarily AML (Gurney 1995), which is diagnosed usually within the first year after birth, but can be up to 18 months. This is different from leukaemias developed later, as the cause seems to be primarily genetic, due to DNA changes *in utero*, or inherited from either parent. There seems to be little opportunity, or evidence for any environmental factor to be of significance before diagnosis. Among the parents of infants with leukemias lacking *ALL1/MLL/HRX* gene rearrangements, the frequencies of single and double GST genes (class M-GSTM; class T-GSTT) deletions were significantly higher than expected (Biondi 1998).

Leukaemias diagnosed in the first 12 months of life account for 2.5 to 5% of acute lymphoblastic leukaemias (ALLs) and 6 to 14% of acute myeloid leukaemias (AMLs) of childhood (Pui 1995). There

are slightly more girls than boys with infant leukaemia, the reverse of that found in older age groups (Chessells 1992, Birch 1992).

Leukaemias that develop within the first year of life have distinctive biologic and clinical features. Up to 80% of infant leukaemias have abnormalities of the 11q23 chromosome (Rubnitz 1994, Wiemels 1999), and changes in the MLL gene on this chromosome are present in nearly 60% of cases of AML and 70-80% of ALL cases. It was suggested by Chen (1993) that the presence of germline 11q23 DNA may have a different aetiology to other ALL. For instance, in one study, increasing birth weight showed a slight increase in risk for infants with MLL+, but not MLL-; and a significant inverse risk with birth order for MLL+, but not MLL- (Spector 2007).

Some changes occur more frequently during foetal development, accounting for the high incidence of this genetic abnormality in infants with leukaemia, and if the change occurs in a susceptible cell subtype, it is sufficient to induce leukaemia. Megonigal (1998) identified a region of chromosome band 22q11.2 involved in both leukaemia and a constitutional disorder. 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.

Some studies (Eguchi-Ishimae 2005, Money Penny 2006) have found when pregnant women are exposed to particular chemicals, especially solvents, these can cross the placental barrier and produce the MLL fusion genes that are responsible for infant ALL. Other MLL translocations have been associated with the development of infant leukaemia (Smith 2002).

Ross (2008) suggested that the MLL gene rearrangements found in the majority of infants with leukaemia arose in utero, and that there is increasing evidence that environmental and genetic factors contributing to the risk of MLL-defined infant leukaemias. The presence of *ALL1/MLL/HRX* fusion in a susceptible cell type appears sufficient to induce leukaemia, whereas with other genetic alterations, additional postnatal mutations are required. It is also likely that *ALL1/MLL/HRX* fusion occurs more frequently during foetal development, accounting for the high incidence of this genetic abnormality in infants with leukaemia.

Kim-Rouille (1999) suggested that the MLL-AF4 fusion gene, and its instability (Yamamoto 1998) may be necessary but insufficient for the clinical development of infant leukaemia. RAS mutations played a limited role in ALL with similar translocations (Mahgoub 1998).

Specific gene markers other than MLL fusion in the child, or the parent, (Garte 2000) are also associated with infant leukaemia (Emerenciano 2006). Often these studies are instigated with a view to improving treatment rather than establishing causation.

Potential causative factors in infant leukaemia

Pombo de Oliveira (2006) found a strongly significant association between maternal use of hormones during pregnancy and infant acute leukaemia. They suggested that oestrogen exposure could be investigated with respect to its role in intrauterine leukaemogenesis.

Maternal alcohol consumption, but not smoking, during pregnancy has been correlated with an increased risk of infant leukaemia, especially AML (Severson 1993, Van Duijn 1994, Shu 1996). Most studies have shown that an increased incidence of high birth weights and a low incidence of low birth weights correlate with higher rates of infant ALL and AML (Kaye 1991, Cnattingius 1995, Ross 1996, 1997, Westergaard 1997, Hjalgrim 2004, Koifman 2008). It has been suggested that high levels of insulin-like growth

factor-1 might produce large babies and contribute to leukaemogenesis, an interesting theory that remains to be proved (Ross 1996, Petridou 2000). Loss of imprinting of the IGF-II gene occurs in malignant lymphoblasts of more than 50% of children with ALL (Vorwerk 2003). Wiemels (1999) suggested that transplacental exposure to topoisomerase-II may induce MLL gene changes (Strick 2000). An increased maternal consumption of DNA topoisomerase-II-inhibitor-containing foods in pregnancy, such as specific fruits and vegetables that contain quercetin; soybeans (genistein); tea, cocoa, and wine (catechins); and caffeine have all been related to an increased risk of infant leukaemia, especially AML (Ross 1994, 1996, 1998, Greaves 1997). Infantile leukaemia is nearly twice as common in several large Asian cities where soy intake is 2-5 times as high as in the USA.

In infant ALL/AML, research involving identical twins suggests that any required environmental exposures are likely to be confined to the prenatal period during pregnancy (Ford 1993). It also seems that parental genetic susceptibility may be responsible for the variability in effects seen.

Whether parental preconceptual or *in utero* exposure to radiation increases the risk of infant leukaemia remains controversial. One report suggests that there might have been a transient increase in infant leukaemia in northern Greece in association with radioactive fallout from the Chernobyl accident (Petridou 1996). However, the European Childhood Leukaemia-Lymphoma Incidence Study failed to show any increase in the incidence of childhood leukaemia as a consequence of this event (Parkin 1996). Likewise, in a subsequent study, German investigations were not able to correlate an increased incidence of infant leukaemia with ionizing radiation from the accident (Michaelis 1997).

Most children who develop leukaemia do so after the age of 1, with a childhood peak in ALL at 2-5 years of age.

The following sections look at potential causative factors which may be involved in the development of childhood leukaemia, beginning with genetic susceptibility, and moving on to environmental exposures that may provide the second or more 'hits' that results in the disease becoming manifest.

Possible causative factors in childhood leukaemia

1. Genetics
2. Ionising radiation, such as X-rays - where the electromagnetic energy is sufficient to break chemical bonds
3. Non-ionising radiation - where the energy is too weak to break chemical bonds, though biological effects can still be produced
4. Chemical exposure
5. Infectious exposure

1. Genetics

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 subtype specific (Mullighan 2007).

The majority of mutations in leukaemia, especially TEL-AML1 translocations, are acquired (Bernardin 2002, Hattori 2007, Fischer 2007, Hong 2008), but in themselves, they are not necessarily sufficient to induce leukaemia (Andreasson 2001, Ayton 2001, Yuan 2001). Wiemels (2000) suggested that TEL-AML1

breakpoints may be distributed into microclusters because of specific DNA sequences in susceptible cells. In rare cases (1-5% of acute leukaemias) inherited mutant genes or constitutive trisomy 21 (Down's) may be involved.

In mice experiments, AML1-ETO fusion results in embryonic death, due to an absence of normal haematopoiesis (Higuchi 2002). Hunger (1998) described a foetal death at 36 weeks gestation from widely disseminated AML, demonstrating that the initiator was clearly *in utero*.

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. They also found that carriers of more than one of the risk-elevating genotypes increased the risk by up to 3 times.

Given the extraordinary number of blood cell divisions that occur each day (about 10^{11}) 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 leukaemia 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 (Buffer 2008).

Precisely how many sequential co-operating mutations are required to produce overt, clinical leukaemia 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 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).

In utero chromosomal translocations, re-arrangements or other gene fusion sequences can be very early or initiating events (Wasserman 1992, Gale 1997, Fasching 2000, Yagi 2000, Taub 2002, Panzer-Grümayer 2002, Greaves 2003) for both ALL and AML. It is likely that one or more additional postnatal genetic changes are required. Reichel (1998) suggested that the cellular DNA damage-repair machinery is likely to be involved.

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 for t(4;11)+, infant ALL is initiated later in foetal development than most B-cell precursor ALL, and have a shorter latency period *in utero* (Fasching 2001). C-ALL susceptibility may be triggered by exposure to infectious agents (Taylor 2002).

There is a difference in opinion as to whether cancer in the family predisposes children to leukaemia. Infante-Rivard (2004) suggested that only familial malignancies involving blood-forming cells (hematopoietic cells) increases ALL risk to children, whereas Ripert (2007) reported that a familial history of hematopoietic malignancies increases the risk of AML by over 4 times;

solid tumours increase the risk of ALL by 1.6 times; genital cancers triples the risk, and brain tumours increases the risk of childhood acute leukaemia by nearly 11 times. The risk doubles if more than 2 relatives are affected. Hemminki (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.

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, an abnormal number of chromosomes (chromosome aneuploidy) or genetic instability are much more susceptible to leukaemia (Willis & Lindahl 1987, Reynolds 2002, Hemminki 2002, Ross 2005). AML is more common than ALL in the neonatal period for children with these syndromes. Children with DS are 30 times more likely to develop leukaemia (Malkin 2000) and higher than this for some variants. Extra copies of chromosome 21 are often found in sporadic leukaemias. As there is a constitutional trisomy 21 in DS, which is associated with a markedly increased risk of developing leukaemia, a further investigation of the leukaemias of DS are likely to contribute to the general understanding of the chromosome changes common in cancer (Israeli 2007).

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, including point mutations, gene deletions, and inversions, have been linked to leukaemia, resulting in chromosome changes such as hyperdiploidy and translocations. 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 morphologic or phenotypic subtypes (Papafthymiou 2008). Some gene variants predispose children to leukaemia due to a reduced ability to deal with toxins (Canalle 2004, Infante-Rivard 1999, Krajcinovic 2002).

There have been suggestions about the biological mechanisms whereby parental occupational exposures may affect their children's risk for leukaemia. 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. A study using a validated occupational exposure index (OEI) 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. Many studies have suffered from problems of evaluating exposure or have used different exposure metrics, which can make comparisons difficult.

A high degree of concordance for childhood leukaemia has been observed for monozygotic twins or triplets (Inskip 1991, 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 1993, 1998, Wiemels 1999b, Maia 2001, 2003, Zuna 2003). Kempski's study on monozygotic 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.

2. Ionising radiation

It is estimated that background ionising radiation is implicated in around 34% of cases of childhood leukaemia, particularly AML, with exposure during preconception, *in utero* and in the postnatal period being important (COMARE 4th Report, Doll & Wakeford 1997). The magnitude of the risk depends on the dose of radiation, the duration of exposure, and the age and susceptibility of the individual at the time of exposure.

Ionising radiation is relatively ineffective at inducing mutations in DNA, but is effective at inducing DNA strand breaks. Most single stranded breaks are rapidly repaired, but double-stranded breaks can result in chromosome re-arrangements. Such aberrations, if they are not lethal, or if they are mis-repaired, can lead to cancer.

The explosion of research into radiation induced genomic instability (both direct and transgenerational (Vorobtsova 2008)) and the bystander effect has brought into sharp debate the risks of exposure to radiation at low doses (see Day 2 of www.leukaemiaconference.org, CHILDREN with LEUKAEMIA conference 2004).

A review of research into the genetic damage done to children by accidental exposure to ionising radiation (Fucic 2008) concluded that *“the evidence from the studies conducted following the Chernobyl accident, nuclear tests, environmental radiation pollution and indoor accidental contamination reveals consistently increased chromosome aberration and micronuclei frequency in exposed children.”* They suggested that further research should be carried out with regard to the combined effects of low doses of radiation and chemical agents from food, water and air.

Information about the effect of ionising radiation on leukaemia rates comes primarily from atomic bomb survivors; *in utero* irradiation of the foetus by obstetric X-rays; occupational exposure to radiation in, and residential proximity to, nuclear facilities; nuclear fallout from power station accidents, such as Chernobyl; bomb testing; and natural sources of ionising radiation, such as radon.

Japanese Atomic Bomb survivors

The Atomic Bomb survivors' risk factors for leukaemia were based on radiation doses of much higher levels (from 0.1 to 10 Sieverts (Sv) than the average UK natural background level of 2.2 millisieverts (mSv) per year). It is likely that using Atomic Bomb survivors as subjects for research could distort the effect of ionising radiation, as it is certain that those susceptible to varying (even small) amounts will have died as a result of their exposure, leaving a more resistant (i.e. not necessarily random) group of survivors.`

Diagnostic X-rays

Alice Stewart as long ago as 1958 (Stewart 1958) raised the question about the safety of prenatal X-rays. She was ostracised by many of her peer-group, including Richard Doll. Sir Richard later produced a paper (Doll 1997) showing a 40% increase in risk to the child of a radiographic examination. Other studies found that obstetric X-rays of the foetus produce an increased risk of leukaemia later in childhood (Mole 1990, Boice 1999, Shu 1994, 2002).

Excess cancer deaths decreased suddenly for births in and after 1958. A major factor was concerted action initiated in 1956 to reduce radiation exposure of foetal gonads for fear of genetic hazards. In 1957 and early 1958 obstetric radiography began to be used much less frequently, and the use of pelvic X-rays was virtually abandoned. In the 1970s the rate of X-raying increased again and so did cancer risk but not significantly. X-rays are now used much more cautiously and more recent studies (Meinert 1999, Naumberg 2001) have failed to find an increased risk of leukaemia, probably as a result of this. X-rays have been superseded in most cases by ultrasound scans, which have not been associated with the same level of risk. There is still some uncertainty about using ultra sound scans unless there is a medical need, as there have been questions asked about the increased risk of the scanned child developing autism as a result of these examinations.

It may be that, in some cases, the medical reasons that women receive prenatal X-rays might be responsible for the increased leukaemia risk and not the X-ray exposures themselves.

Different types of leukaemias may be more likely to result from X ray exposure. Shu (2002) noted a significantly increased risk for children with pre-B cell All, especially if they had 3 or more X-rays, and they were more than 5 years old.

Diagnostic X-rays are the largest man-made source of radiation exposure to the general population, contributing about 14% of the total annual exposure worldwide from all sources. It is accepted that about 0.6 per cent of UK cancers in general are due to medical X-ray procedures (Berrington de González 2004), rising to a figure as high as 3% in Japan.

Computed Tomography (CT) Scans

CT scans are increasingly used to diagnose medical problems. A single CT scan exposes the patient, on average, to a 7 times higher dose than a normal x-ray. A chest CT scan is the equivalent dose of 60 normal chest x-rays. Although the risk from a single CT scan to an individual is small, there are concerns about the build-up of risk over time, especially for children, who are more susceptible to radiation. Obese people require more radiation to get the same amount of physiological information. Many CT centres are set up for adults, and are therefore not suitable for children, who need adjustments to limit dose and radiation risk, without appropriate changes in exposure.

Occupational exposure in, and residential proximity to, nuclear facilities

Many studies have investigated the possibility of paternal exposure to ionising radiation being a potential risk factor in the development of leukaemia in their children.

Gardner (1990, 1991) found that the risk of leukaemia was higher in children born near Sellafield, and for children of fathers employed at the plant at their conception, and that the higher the dosage they were exposed to (particularly the testicles), the higher the risk (Roman 1999). Other studies did not find the increased risk in children whose fathers worked at Sellafield, but who lived further away from the installation (Doll 1994). It could be that there was a synergistic effect of paternal exposure and something else nearer the child's home before the leukaemia was initiated.

Dickinson & Parker (2002) extended Gardner's 1990 work by including all children born to mothers who lived in Cumbria between 1950 and 1991. They found that the children of radiation workers had an increased risk of developing leukaemia and non-Hodgkin's lymphoma. Gathering data about occupational exposure is further complicated by the fact that external radiation exposure does not necessarily correlate with potential internal contamination of workers, which was not measured.

Some studies looking at different types of parental occupational environments found increased risks of leukaemia with radiation (McKinney 1991) whilst other studies found no correlation (Watson 1991, Kinlen 1993, McLaughlin 1993). Maternal exposure was also included by Meinert (1991) who found that there was an association with radiation and some forms of childhood cancer, but not necessarily leukaemia and was also dependent on the age of the child.

Urquhart (1991) did not find a link to childhood leukaemia and parental occupational exposure, but they did find one for use of beaches within 25 kilometres of the Dounreay nuclear facility. It has been suggested that other nuclear power facilities (Sellafield, La Hague, etc.) have cancer clusters in the residential areas around them and that merely living nearby could increase the likelihood of a child developing cancer (Spix 2008). Some study authors have acknowledged that the number

of children suffering from leukaemia in Cumbria (Draper 1993), Berkshire (Barton 2001), Hampshire (Roman 1993) and Germany (Hoffmann 2007, Kaatsch 2008) was higher than would be expected, but they were unsure of the cause.

A large meta analysis was carried out by Baker & Hoel (2007) on studies that included 136 nuclear facilities, and found that the majority of these found elevated levels of childhood leukaemia in nearby residents.

Nuclear accidents and bomb testing

There have been various investigations into the after effects of the Chernobyl accident. Noshchenko (2001) found that *in utero* exposure caused the rates of ALL to be dramatically elevated for males and to a lesser extent for females. A study by Peterka (2007) found that a significantly decreased number of male babies were born in the areas most affected by Chernobyl fallout. This may reflect a greater susceptibility to radiation for males rather than females, especially prenatally. For both genders combined, the risk for ALL was more than three times greater in the exposed compared to the unexposed region. Petridou (1996) found an increased risk for infant leukaemia, Hjalmar (1994) found an increase in cancer in children aged under 5, Steiner (1998) was ambivalent and Sali (1996) did not find significantly increased leukaemia risks, although the latter did not rule out the possibility of a small increased risk.

It is difficult to compare many of the studies due to difficulties of getting information because of the breakup of the Soviet Union into its constituent countries; differences in cancer registration systems; means of case ascertainment; and very real differences in Chernobyl-related exposures across regions within countries (Hjalmar 1994, Parkin 1996).

It is important that not just *in utero* exposure is considered, as Mangano, looking at the Three Mile Island as well as the Chernobyl accidents (Mangano 2006) documents that there is a short latency of cancer onset in young children who are especially susceptible to adverse effects of radiation exposure, even at relatively low doses.

Stevens (1990) reported an association between leukaemia rates and amounts of fallout in South Western Utah from nuclear tests (1952 to 1958). The greatest excess risk was found in those individuals in the high-dose group with acute leukaemia who were less than 20 years old at the time of exposure.

Yamamoto (2007) investigated patterns of leukaemia incidence in the United States and reported that Asian-Pacific Islanders had the highest rates of AML. A possible explanation for this may be that DNA damage due to bomb testing was passed on to successive generations.

Natural radiation

Measurements in children's teeth show that even in children living near to the British Nuclear Fuels Sellafield plant in Cumbria, the level of man-made plutonium in the body is around one thousand times lower than for naturally occurring ^{210}Po . Environmental uptake by man of ^{239}Pu is low.

A body of geographical or ecological studies have been consistent in showing an association between radon and childhood leukaemia (Henshaw & Allen 2002), similar to the radiation risk estimates in the more recent work by Evrard (2005) at 10 mSv, which is comparable with the natural background radiation in areas of Cornwall where there is a high level of exposure to radon. Due to the relatively ubiquitous exposure to background natural radiation, any childhood leukaemia

excess would be undetectable in a case-control study. Kaletsch's German study (1999) did not find an association. Levels of radon vary significantly in different countries.

All journeys by air expose plane travellers to cosmic ionising radiation which is less shielded by the atmosphere at the high altitude.

3. Non-ionising radiation

Some animal experimentation, using chemicals to promote cancer in rats, has shown that difference in study outcome could be accounted for by different susceptibilities in the strain of rats used. It is recognised that 100% of the chemicals that are known to cause leukaemia in humans cause some sort of cancer when tested on rats and mice. In 73% of these, the chemical exposure results in leukaemia or lymphoma in rodents. 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. The fact that EMFs do have an effect in some laboratories cannot be ignored despite the problems of reproducibility.

How could non-ionising radiation, such as electromagnetic fields (EMFs), be involved in the development of leukaemia?

The evidence is mixed as to whether EMFs can be responsible for direct DNA damage. It is possible that the way EMF exposure has been measured may be responsible for the mixed results. Binhi (2008) suggested that magnetic nanoparticles in the human body may be one of the avenues by which EMFs may be implicated in the development of childhood leukaemia. Changes in levels of cellular proteins or ions can affect cell function (such as removing unnecessary or damaged cells) and cause cancer cells to develop. Some experiments have shown that EMFs affect these functions, though they have been difficult to reproduce and therefore remain controversial. Calcium ions play a critical role in determining the rate of cell division. Changes in B lymphocytes can also change cellular division rates. These findings may prove particularly important with regard to B-lineage ALL. However, the original results have not yet been replicated, perhaps pointing to the need to tighten experimental protocols. The overall evidence is that magnetic fields induce changes in apoptosis (cell death), according to a review by Santini (2005). A series of studies (Uckun et al, 1995; Dibirdik et al, 1998; Kristupaitis et al, 1998) demonstrated EMF effects that made cells more likely to become cancerous.

However, cells are not autonomous units responding to damage as independent entities. Recently, there have been many reports of effects arising in non-irradiated cells as a consequence of inter-cellular communication. These non-targeted effects have been demonstrated in the descendants of irradiated cells (radiation-induced genomic instability) and in cells that have received signals produced by neighbouring irradiated cells (radiation-induced bystander effects) but the expression of such effects is significantly influenced by genetic factors (Wright 2008).

Evidence for indirect effects as a result of the 'bystander effect' has been shown by Wright and Mair (2008). Mair suggested that *"EMF carcinogenesis involves the transport by macrophages of toxins (possibly including free radicals) to sites of infection or tumour localisation. This could increase mutation rates at these sites, perhaps promoting malignancy by introducing mutations, or by increasing the DNA instability of small early tumours, thereby engendering a more aggressive phenotype."* Mair also suggested that EMFs could be mutagenic on their own, or could potentiate ionizing radiation mutations.

Some of the other ways that EMFs could act indirectly to cause effects that result in leukaemia, are:

- By directly increasing the level of harmful free radicals within the body
- By affecting exposure to airborne pollutants, making them more harmful
- By decreasing the level of the protective hormone melatonin

Free radical effects

In body tissue free radicals are dangerous high-energy particles that damage cells and can both cause and accelerate the progression of cancer. Timmel & Henbest (2004) were the first to show that exposure to EMFs can increase the yield of free radicals by more than 60%. The premise was reviewed by Simko & Mattson (2004) who concluded that EMFs cause a general increase in the levels of free radicals, which could explain the diverse and often inconsistent nature of observed effects of EMFs, free radicals being intermediates in many natural processes. DNA damage could arise as a result of persistently elevated free radical concentrations, caused by long-term EMF exposure, or via the radical pair mechanism, by which magnetic fields increase the lifetime of free radicals, allowing more DNA damage to occur (Rollwitz 2004, Henshaw 2008).

Airborne pollutant effects

Airborne pollutant particles are known to have a significant effect on health and a number of studies have reported an association between childhood leukaemia and exposure to traffic pollution (see section 4 on chemical exposure). The strong electric fields associated with high voltage power lines may affect the charge on the chemicals found in traffic pollution, making them more likely to be absorbed by the body. This effect can be observed up to 7 kilometres downwind of a high voltage powerline (Fews 1999a). The older the cable and the wetter the weather the more charged ions are emitted (Fews 1999b). Very small particles are particularly hazardous because of their ability to penetrate deeply into the lung and pass into the bloodstream (Seaton 1995). These small particles are in the size range where electrical charging can significantly increase lung deposition when inhaled. The report by Draper (2005) found increased risk of leukaemia in children born within 600 metres of National Grid 400 and 275 kilovolt power lines.

Melatonin effects

The hormone, melatonin is thought to protect the body from cancer (a) by neutralising free radicals, (b) by inhibiting the uptake of growth factors by cancer cells, (c) by increasing the likelihood of cancer cells undergoing apoptosis (cell death), and (d) by inhibiting the growth of blood vessels in tumours. Stevens (1987) proposed that the production of melatonin at night (when the majority of melatonin is produced by the body's pineal gland) was reduced significantly by light at night and magnetic fields associated with the electricity supply (Henshaw & Reiter, 2005, Erren 2005). Vijayalaxmi (1995,1996,1999) and Badr (1999) found that melatonin protects cells from genetic damage.

A variety of bone marrow cells have been shown to produce melatonin (Tan 1999, Conti 2000, Carrillo-Vico 2004). Whilst the specific function of melatonin in these cells remains unknown, its suppression could have clear implications for leukaemia initiation and / or progression. A reduction in melatonin in the leukocyte precursor cells would be expected to enhance free radical-mediated DNA damage, thereby increasing the likelihood of these cells becoming carcinogenic.

Melatonin reduces the growth of HL-60 myeloid leukaemia cells *in vitro* (Henshaw 2008).

Light at Night

Evidence suggests that increasing exposure to light at night (LAN) and the consequent disruption of circadian rhythms, especially nocturnal pineal melatonin is a significant factor in the increasing incidence of breast cancer in recent decades in industrialised countries (Blask 2005).

Whether LAN features in childhood leukaemia risk is not known, however melatonin has been shown to be highly protective of oxidative damage to the human haemopoietic system (Vijayalaxmi 1996) and protects from oxidative damage in animal foetus' (Wakatsuki 1999, Okatani 2001). Melatonin levels are particularly high during pregnancy (Nakamura 2001).

Powerfrequency (ELF) EMFs

Powerlines

Since the first paper by Wertheimer and Leeper (1979), in the USA, more than 25 epidemiological studies around the world have investigated the association between childhood leukaemia and EMF exposure (inc Olsen 1993). Other papers which followed this initial finding found an increased risk of childhood leukaemia from powerlines or substations (Coleman 1989) and some as much as a 2-3 fold increase with residential proximity to powerlines (Savitz 1988, London 1991, Feychting 1993). Yang (2008) found genetic markers that showed those carrying this gene variant were four times more likely to develop childhood leukaemia if they also live within 100 metres of power lines or transformers, compared to those with a fully functioning version of the gene. This groundbreaking piece of research indicates a potential for identifying individual susceptibility.

About 11% of childhood leukaemia cases may be linked to magnetic fields (Henshaw 2008). Not all studies have found an association (Verkasalo 1993, Tynes 1997, Fulton 1980, Kleinerman 2000), and possibly the use of wire codes and calculated fields in some of these studies rather than measured fields from specific sources of EMFs, may explain some of the different results.

Individual studies are often limited because of the relative rarity of childhood leukaemia and the relatively low number of children exposed to high levels of EMFs.

Three reports which pooled the data from individual studies found an increase in risk with exposure to magnetic fields of 0.3 – 0.4 microtesla (Ahlbom 2000, Greenland 2000, Wartenberg 2001). The 0.3 - 0.4 microtesla level was confirmed by Japanese (Kabuto 2006) and Iranian (Feizi 2007) studies. Other papers have found increased risk of leukaemia with proximity to high voltage powerlines or high residential magnetic fields (Fajard-Gutierrez 1993, Lin & Lee 1994, Theriault 1997, Linet 1997, Michaelis 1997, 1998, Dockerty 1998, Li 1998, McBride 1999, UKCCS 1999, Bianchi 2000). A study by Lowenthal (2007) found that living within 300 metres of a high voltage powerlines within the first 15 years of life tripled the risk of developing a lymphoproliferative or myeloproliferative disorder in later life. The risk was increased 5-fold if it was in the first 5 years of life.

The Ahlbom study, above led the International Agency for Research on Cancer (IARC) to classify magnetic fields as a possible carcinogen.

Another study, published in the BMJ (Draper 2005), the largest single study of childhood cancer and powerlines, reported an increased risk in the children whose birth address was within 600 metres of a high voltage power line, which may also involve electric field exposure (see about airborne pollutant particles, above).

The Stakeholder Advisory Group on ELF EMF (SAGE), the official Department of Health working group which was set up to recommend policy about powerlines to government,

produced its First Interim Assessment in April 2007. They concluded that banning the building of new homes and schools within 60 metres of power lines is the best available option for reducing deaths from childhood leukaemia and possibly other diseases. The report fell short of recommending this as government policy because of fierce disagreements within the group. It said that such a policy, if implemented by the government would have a dramatic effect on property prices within power line corridors. It put the cost of restricting development at £1bn. Michael Jayne of the Royal Institution of Chartered Surveyors (RICS) called on the Government to take precautionary measures in order to ensure that the health risk is minimised by preventing the building of residential properties within specified distances of power lines.

Residential exposure

The California EMF Programme report (2002) produced by Neutra et al, has been recognised as one of the more definitive documents of recent times. They concluded that EMFs increased the risk of childhood leukaemia. The International Agency for research on Cancer (IARC) classified magnetic fields as a “possible human carcinogen”, though this was not sufficient to influence public health policy according to Kheifets (2006). The results of one Canadian study by Green (1999), based on personal measured fields rather than spot measurements found a significant increase in risk of childhood leukaemia at 0.14 microtesla, though there was no association with living near high voltage powerlines.

For those already genetically susceptible (children with some congenital syndromes), exposure to magnetic fields seemed to increase the risk of developing leukaemia (Mejia-Arangure 2007).

Schüz (2001) suggested that night-time levels were of particular importance, though when he made a further analysis of his findings (2007) his conclusions were less clear. Schüz also looked at residential exposure to magnetic fields at 16.7 Hz from the electrified railway system in Germany, and found a moderate but statistically non-significant association with childhood leukaemia (2001).

Exposure to various electrical appliances, both during pregnancy and in childhood were looked at by Hatch (1998) who found a link with childhood ALL and some appliances.

Occupational exposure

Children whose mothers were occupationally exposed to low levels of powerfrequency magnetic fields during pregnancy, have a slightly increased risk of developing ALL between 0-9 years (Infante-Rivard 2003).

The hypothesis that paternal exposure prior to the child’s conception may be a factor in the development of childhood leukaemia was recently supported by Pearce (2007). In this study they found that paternal occupational exposure to EMFs resulted in a significant increased risk of ALL for male children.

Other EMF exposure

Changes in magnetic field level above 1.6 microtesla, such as can be found when travelling in electric trains, have been linked with an increased risk of miscarriage (Li 2002). It is possible that the magnetic fields may also change DNA in ways that may not be destructive enough to result in a miscarriage.

Söderberg (2002) found a slightly elevated risk for AML, but not ALL in children who had been exposed to high magnetic fields from infant incubators.

Although there is disagreement as to whether this is a direct causal relationship between leukaemia risk and elevated magnetic fields, or whether there is a coincidental association with some other, as yet undiscovered, factor, the relative risk is surprisingly consistent, despite the different methods used for assessing residential magnetic field exposures. Epidemiology is a bit of a blunt instrument to detect causal factors in a multi-factorial illness.

It seems unlikely that there is a straightforward answer to whether EMFs *cause* cancer. We believe there is increasing evidence that they may play a definite role in affecting the body's ability to cope with pre-cancerous cell damage. There almost certainly will be other factors involved in the final outcome of a diagnosis of leukaemia.

Effect of EMFs on survival after treatment

Exposure to magnetic fields appeared to decrease the survival time of children in remission from leukaemia, at over 0.3 microtesla (Foliart 2006), or over 0.1 microtesla (Svendson 2007). However, the numbers involved were small, so general conclusions should be treated with caution.

An influential report (www.bioinitiative.org) published in 2008 (Hardell & Sage) concluded that in view of the association between electromagnetic fields and childhood leukaemia, a new lower public safety limit for habitable space adjacent to all new or upgraded power lines should be applied. A new lower limit should also be used for existing habitable space for children and/or women who are pregnant.

Static fields

Very little has been done to identify whether exposure to static fields may be related to the risk of leukaemia. Bowman (1995) suggested that childhood leukaemia may be related to the combined effects of the earth's static magnetic fields and low levels of ELF magnetic fields resulting in various molecular ion resonances.

Radio frequency (RF) EMFs

Radiofrequency radiation has been part of our environment since the 1920s. It has been assumed that these signals are benign and without health consequences. However, there have been some studies that have found increases in leukaemia risk as a result of living in proximity to radio or TV transmitters (Maskarinec 1994, Hocking 1996, Dolk 1997a, 1997b, Michelozzi 2002), that mean we cannot be complacent about the effects of RF signals. The study authors concluded that there was a small increased risk in adult and childhood leukaemia (within 2 kilometres (Ha 2007)), but the confidence levels were low due to the small number of cases involved. Another study showed no such increase in risk (Merzenich 2008).

Hocking (2003) also found an association between living near to the transmitters and decreased length of survival after leukaemia diagnosis.

These masts transmitted analogue signals. The situation has now changed with the arrival of digital radio and TV and the omnipresent telecommunications (mobile phone) masts. There are also other sources of digital signal transmission (WiFi, etc) that are being increasingly situated within houses, schools, offices, leisure facilities, etc. that is increasing the general public's exposure to radiofrequency radiation significantly.

It has been suggested by many scientists that digital signals may well have a greater biological impact on living systems; this includes not only people, but also animals and plants. If this is so,

we would expect to see increasing evidence of health problems associated with exposure, though this may not include an increase in childhood leukaemia risk.

Navarro (2003) and Santini (2002, 2003) found evidence of ill-health as a result of living near to mobile phone masts, but they were not looking at leukaemia incidence. Two studies on cancer incidence near masts found significant increases (Wolf & Wolf 2004, Eger 2004) and one (Wolf & Wolf) found a ten-fold increase in female cancer. Neither looked at childhood leukaemia incidence.

4. Chemical exposure

Pollution in air, food and water, etc.

Air pollution

The majority of exposure to air pollution arises from vehicle exhausts, especially from the polycyclic aromatic hydrocarbons (PAHs), such as benzo[*a*]pyrene (Reynolds 2003). Modern cars with catalytic converters emit particles mainly in the form of ultra-fine or nano-aerosols. Such very small particles can travel considerable distances from their source, and can go deeply into the bloodstream. As such the exposure of children to air pollution in the UK is essentially ubiquitous and therefore how it may influence the risk of leukaemia is extremely difficult to determine. It has been suggested that 30-80% of childhood leukaemia and other cancers in the UK could be linked to traffic pollution *in utero* and in early infancy.

Other epidemiological evidence supports the suggestion that air pollution may feature in the causes of childhood leukaemia and other cancers (Knox 2005a, 2005b). Knox (2006) found the risk of childhood cancer doubled if the mother (during pregnancy) or the newly born child, lived within 100 metres of bus or railway stations, ferries, railways and A or B roads. A UKCCS study by McKinney (2003) found that paternal exposure to vehicle related exhaust fumes and/or inhaled hydrocarbons, just before or just after his partner became pregnant, was associated with a small increase in risk. The association that Knox found with birth address suggests the importance of early and *in utero* exposure through inhalation by the mother and transplacental transfer.

Children whose homes were exposed to significant amounts of road traffic emissions (Crosignani 2004) using nitrogen dioxide as an indicator of exposure (Weng 2008, 2008) were more likely to develop leukaemia.

Some intriguing experiments on the heritable effects of exposure to ambient air pollution levels have been carried out in Ontario. Yauk & Quinn (1996) found 2-3 times the rate of heritable genetic mutations in herring gulls nesting in an urban industrialised site compared with a rural site 30 kilometres away. Somers (2002) exposed mice 1 km downwind of two steel mills in Ontario. 1.5 to 2.0-fold increased heritable mutations via the paternal germline were found compared with control mice placed 30 km away in a rural location. Somers (2004) further exposed mice 1 km downwind from the above steel mills, alongside control mice who breathed air filtered from particulates down to 0.1 mm. A 2.8-fold increased rate of heritable mutations in "exposed" mice was observed.

Other chemical exposure (including hydrocarbons)

The incidence of AML has been linked to chemical, especially petrochemical exposure, of both parents and children (Buckley 1989). European White Spirit can contain up to 10 parts per million of benzene which is known to cause myeloid leukaemia. White spirit can be detected in the bloodstream for up to 3 days after physical exposure (e.g. by inhalation or by skin contamination)

and will pass into the foetus – albeit at very low concentration levels. There is no published direct link between white spirit exposure and childhood leukaemia, though there are with a variety of other serious birth defects. There are published papers showing a statistical association between maternal exposure to solvent chemicals, especially petrol, with about a 50% increase in leukaemia incidence.

In studies on occupational exposure, including a review of 7 different papers on parental exposure by Savitz and Chen (1990), maternal or parental exposure (van Steensel-Moll 1985, Lowengart 1987, Shu 1999, 2004, Schütz 2000, Sung 2008) to solvents, thinners, and paint, during the pre-conception period and during pregnancy, were related to an increased risk of ALL and AML. It has been suggested that the chemicals may have been brought into the house on the clothing worn by the parent in question. The authors concluded that the effect of parental occupational exposure to hydrocarbons on offspring may depend on the type of hydrocarbon, the timing of the exposure, and the age of onset of the disease. Freedman (2001) found that exposure to solvents through hobbies or frequent internal house painting increased the risk of ALL, although how much participation there was by the children was not clear. Shu (2004) also found that paternal exposure to plastic materials before, and maternal exposure during and after pregnancy were related to ras mutations found in children who develop ALL. Exposures to oil and coal products and other hydrocarbons were also linked to such changes. Buffler (2008) suggested that some genetic translocations were more vulnerable to paint and petroleum products.

Pesticides

Children are exposed to pesticides from a number of sources, including residential and agricultural applications. Parental exposure is also of concern, due to possible germline effects for fathers and exposure of foetuses due to cross placental transfer from mother to baby during pregnancy. As more is known about genetic predisposition to DNA changes, it is clear that these will become an important confounder in future studies and may well change associations made between cancer and pesticide exposures in previous studies when this knowledge was not available (Infante-Rivard 2007). Windows of vulnerability have not always been examined in studies especially where the authors believed that parental recall bias could render data unreliable.

Despite these caveats, associations have been reported between childhood leukaemia (ALL or AML) and exposure to pesticides for either parent (Lowengart 1987, Buckley 1989, Daniels 1997, Infante-Rivard 1999, Meinert 2000,) Ma (2002, Zahm & Ward 1998 Monge 2007, Lafiura 2007, Rudani 2007) found that insecticide and pesticide exposures early in life appear to be more significant than later exposures, and the highest risk was observed for exposure during pregnancy. Additionally, more frequent exposure to insecticides was associated with a higher risk. The study by Emerenciano (2007) found that infant acute leukaemia specifically was linked with maternal exposure to pesticides.

Exposure to home pesticides and insecticides, used outdoors or indoors (Grossman 1995, Menegaux 2006) has been associated with an increased risk. Children exposed to professional pest control services at any time 1 year before birth to 3 years after, were found to have an increased risk of leukaemia (Ma 2002). However, Urayama (2007) found that certain specific genetic subtypes seemed to be less susceptible to the leukemogenic effects of indoor insecticide exposures. Alderton (2006) found positive associations between pesticides, professional pest exterminations and any chemical in children with Down syndrome with ALL.

Childhood leukaemia (Meinert, 2000, Reynolds 2002, 2005) especially AML (Carozza 2008) has been associated with the use of agricultural pesticides.

Chemicals found in head-lice treatments can be quite toxic, and small quantities are absorbed through the skin. Menegaux (2006) found an association between childhood leukaemia and

pyrethroid-based shampoos. It may be worth looking for natural remedies that do not contain organophosphates.

Lu (2008) looked at the exposure of young children to organophosphorus pesticides in their diet and discovered by switching them to an organic diet for a brief period of time and measuring urinary metabolites, that a standard (non-organic) diet was the chief contributor to pesticide exposure. It seems that eating a largely organic diet, when possible, may help to eliminate children's exposure to these potential carcinogens.

Jurewicz concluded after a literature review (2006) that *"In the light of existing, although still limited evidence of adverse effects of pesticide exposure, it is necessary to reduce exposure to pesticides. The literature review suggests a great need to increase awareness among people occupationally or environmentally exposed to pesticides about their potential negative influence on health of their children."*

Smoking

Epidemiological evidence to support a link between parental smoking and childhood leukaemia is inconsistent, possibly because of genetic susceptibilities.

One study (John 1991) found an increased risk for ALL. Rudant (2008) found that paternal, but not maternal, smoking was associated with an increased risk of ALL and AML. The risk increased with the number of cigarettes smoked.

Maternal smoking

Maternal smoking, especially 10 or more cigarettes per day was associated with an increased risk of AML (Cnattingius 1995, Mucci 2004), but not ALL (Mucci 2004), and De la Chica (2005) found chromosomal abnormalities in foetuses of smoking mothers. No association has been found between maternal smoking and ALL. Clavel (2005) suggested that maternal smoking may be a risk factor for leukaemia in children who carry CYP1A1 or GSTM1 genotypes.

Paternal smoking

There does seem to be some evidence for paternal preconception smoking and subsequent childhood leukaemia (Sorahan, 1995, 1997, Ji 1997).

Prescription drugs (pre-natal exposure)

One study has reported an association between childhood ALL and maternal use of antihistamines and allergy remedies (Wen 2002). Robison (1989) reported a link between maternal use of anti-emetic medication and AML.

Other drugs (pre-natal exposure)

Parental use of amphetamines or diet pills and mind-altering drugs before and during the pregnancy was related to an increased risk of childhood ALL (Wen 2002, Shu 2004), particularly among children where both parents reported using these drugs. If the mother used both mind-altering drugs, and antihistamines or allergy remedies the risk for infant ALL was strongly increased.

Parental alcohol consumption

Metabolites of alcohol are likely carcinogens, which is why this has been the subject of several papers looking at potential links to childhood leukaemia of parental alcohol consumption. A review of 33 studies by Infante-Rivard & El-Zein (2007) found mixed results, with maternal alcohol

consumption being linked most frequently, though there was some evidence of modest consumption having a protective effect. A small number reported a link to paternal alcohol consumption. The authors suggested that genetic susceptibility and cancer subtypes may be responsible for the different findings. Individual studies have found some evidence for a possible link between maternal alcohol consumption and AML (van Duijn 1994) especially in very young children (Severson 1993, Shu 1996) though the evidence for ALL risk is uncertain. Some studies have found such a risk (Menegaux 2005, 2007, Macarthur 2008) whilst others did not (Little 1999). Paternal alcohol consumption before conception did not appear to increase risk (Shu 1996, Macarthur 2008).

Recreational drugs (pre-natal and pre-conceptual exposure)

Maternal use of marijuana has been reported to increase the risk of childhood ALL (Wen 2002), and in one study was associated with a 10-fold increased risk of AML when used just before or during pregnancy (Robison 1989). However, Trivers (2006) found an inverse relationship between maternal marijuana use just before and during pregnancy and AML risk. There is evidence that the risk may be higher when both parents use the drug.

Fluoridated water

An American study found an increase in osteosarcoma in young boys (not girls) drinking water which contained fluoride (Bassin 2006). Ramesh (2001) had found a correlation between high fluoride content in the bone and osteosarcoma. Half of all fluoride ingested is stored in the body, accumulating in calcifying tissue such as teeth and bones (more than 90%). Although no research has looked at leukaemia, the fact that the risk increase is age-specific and that fluoride changes bone chemistry may be important.

Paternal military exposure

A study by Wen et al (2000) showed a small but significant increase in the risk for AML (not ALL) among the children of personnel who had served in Vietnam or Cambodia, especially with a diagnosis under the age of 2. It may be that it has to do with chemical exposure. A study on Gulf War veterans might be useful to see if the same effect was found.

5. Infectious exposure

Our ability to fight infections is determined, in part, by our genes. There is a group of genes that code for molecules on our lymphocytes (known as HLA molecules) and determine how they respond to foreign invaders. Different people have different HLA molecules and will therefore respond in varying ways to infections. Dorak (1999) found that one particular type of HLA molecule was increased in his childhood leukaemic patients, especially males, and another was decreased, suggesting that particular HLA molecular changes are genetic risk factors for childhood ALL. Taylor (2008) and Yari (2008) found the same results.

Speculations concerning a link between infections and childhood leukaemia were first published as long ago as the 1920s (Poynton 1922), based on the observations that the age distribution of the disease was similar to that of common childhood infectious diseases and that many patients had a record of infections around the time of diagnosis.

There are now three main hypotheses concerning the possible role played by infection in childhood leukaemia:

1. infectious exposure *in utero* or around the time of birth increases the risk of childhood leukaemia

2. delayed exposure beyond the first year of life to common infections increases the risk of childhood leukaemia
3. unusual population mixing introduces new infections to previously unexposed populations and childhood leukaemia may be an unusual result of such an infection

Infectious exposure *in utero* or around the time of birth

There is some evidence to suggest that some maternal infections may increase the risk of childhood leukaemia (Fine 1985, Canfield 2004). A model proposed by Smith (1997) suggests that an infectious agent causes a primary infection in the mother which is subsequently passed on to the foetus, and as a result of this infection the child is more likely to develop leukaemia in the next few years, perhaps because of stress and genetic instability caused by the infection.

McNally and Eden (2004) linked maternal infections during pregnancy with an increased risk of childhood leukaemia, especially ALL. Adenovirus DNA was detected in 13 of 49 children who developed ALL and only in 3 of 47 who did not (Gustafsson 2007). It is interesting to note that 3 control children showed the change without developing leukaemia and 36 children developed leukaemia without the change, again demonstrating the complexity of causation in childhood cancer.

There are several good studies showing an increased risk with infections (Roman 1997) and some which looked at specific infections:

- a history of sexually transmitted disease (Kwan 2007)
- maternal lower genital tract infection, especially for infant leukaemia and those diagnosed after the age of four (Naumburg 2002)
- Epstein-Barr virus (EBV) reactivation (Lehtinen 2003, 2005, Tedeschi 2007)
- Helicobacter Pylori (Lehtinen 2005)
- possibly neonatal adenovirus-C infection (Gustafsson 2007)

but there are also good studies which show no such association, with respect to influenza (Nyari 2003), EBV (Bogdanovic 2004), and parvovirus B19 (Isa 2004).

Many of the studies are generally reliant on small numbers of cases, and it may not be one particular infection but infections in general which impact on risk, so it is difficult to draw firm conclusions.

Delayed exposure beyond the first year of life, or a rare response to common infections

This theory is, in part, based on the hygiene hypothesis first proposed by Strachan (1989) which suggests that infections and unhygienic contact with older siblings or through other exposures may confer protection against the development of allergic illnesses. This protection may come from either overt or unapparent infections with viruses and bacteria, non-invasive microbial exposures in the environment, or some combination of the two (von Mutius, 2007).

Greaves (1997) has suggested that one factor in susceptibility is that in early childhood children are less exposed to common infections, including influenza, (Dockerty 1999, Ma 2002, Perrillat 2002) than they used to be in the past. In fact many chronic infections have been eliminated entirely. This may result in a less developed, or dysregulated (Roman 2006) immune system and an increased risk of leukaemia later in childhood, i.e. delayed infection (Chan 2002).

It has been suggested that clinically diagnosed leukaemia occurs as a result of a rare response to common infections (Greaves & Alexander 1993, Petridou 2001, 11th COMARE report 2006). This is both plausible and logical in view of the biology of how leukaemia appears, but it of course does not address the underlying environmental factors linked to the disease.

That the final stage of leukaemia is triggered while the immune system is otherwise occupied (fighting a common infection) is plausible. There is also the possibility of 'inverse causality' that pre-leukaemic children are themselves prone to contract common infections. McKinney (1987, 1999), Hartley (1988) Simpson (2007) and Roman (2007) all found a link with leukaemia and increasing numbers of illnesses before the age of 1 year.

As ALL is more common in developed, more affluent societies, Greaves suggests that not only hygiene (Smith 1998), but also other lifestyle influences such as childrearing, social and breastfeeding practices may be involved in immune system inadequacy.

Vaccinations

The situation with respect to vaccinations seems more mixed, with some work finding a positive association with childhood leukaemia (Buckley 1994) whilst others found the opposite, that some vaccines seemed to have a protective effect (Hartley 1988, McKinney 1987, Nishi & Miyake 1989, Schuz 1999b, Auvinen 2000, Groves 1999, 2001, 2002, Ma 2005b, 2005) and yet others found it seemed to make little, if any, difference. (Dockerty 1999, Petridou 1997, von Kries 2000, Mallo-Mesnard 2007) Whether there is a link or not may depend on the particular type of vaccine.

Unusual population mixing leading to a rare response to infection

The most recent Committee on Medical Aspects of Radiation in the Environment (COMARE) 11th report concluded "*there is some good evidence for a weak case aggregation of acute lymphoblastic leukaemia. The term weak is used because the average numbers of cases in each ward is low, but the results reinforce the concepts that case occurrence is not entirely random.*" What is not clear is what is causing this clustering.

Kinlen (1988, 1990, 1993, 1993, 1994, 1995, 1997, 2001) proposed that childhood leukaemia was a rare response to infection, possibly occurring *in utero* or postnatally, arising from an influx of population into a small, otherwise relatively isolated community. Whereas this hypothesis may have some validity in some of the examples examined, they certainly cannot explain most of the incidences, which don't conform to this picture. 'Extreme' population mixing was looked at with regard to new towns, commuter belts, major construction sites and country areas used for wartime evacuation or for military camps. There seem to be other possible factors which may be common to these places, such as chemicals, building materials, etc. that might be as important as the infection hypothesis.

Clearly, studies designed to assess the infection hypothesis need to take the critical time windows into account – the first year of life and the period 3 to 12 months prior to diagnosis. The situation remains unclear whilst there is an inadequate definition of what is meant by 'population mixing' which means that many of the studies are looking at different mixtures in different settings. Feltbower (2005) found that population mixing was significantly associated with ALL in Yorkshire, and commented that the association found for large regions was weaker for small areas. Alexander (1997) found clustering for cALL in the childhood peak (age 2-7) in Hong Kong, but not for other age groups, or for leukaemia subsets that did not have peak times of diagnosis.

On balance, it appears that population mixing in areas that were originally very isolated results in an increasing rate of childhood leukaemia, especially during the childhood 2-5 year old peak

(Bellec 2008, Stiller 2008), when children are least likely to possess sophisticated immune systems. By comparison, population mixing in urban areas where there is a consistently high level of mixing results in a decreased rate of leukaemia, though Alexander (1998, 1999) and Ross (1999) found an increased risk of ALL, and some evidence of clustering, in areas of higher population density. When parental social contact at work was investigated, as a surrogate for a child's risk of infection, Chang (2007) found that there was an increased risk for leukaemia in children where the parents' job was of sufficient duration, though Fear (1999) did not. There was also a link with living in a rural area. Research into population density and the risk of childhood leukaemia seems to be equally inconclusive, and may depend on the type of leukaemia and the age of diagnosis as much as the actual level of population.

Some of the studies that have found associations between infection (or its proxies) and childhood leukaemia, have found them most strongly for the cALL sub-type. If infection is involved in the aetiology of childhood leukaemia then it may be specific to cALL.

Other factors linked with childhood leukaemia

Ou (2002) found that the risk of pre-B-cell ALL increased with advanced paternal age, younger and advanced maternal age and high birth order, and T-cell ALL was associated with high birth weight and a history of induced abortion. The author concluded that *"the association of ALL with birth characteristics and maternal reproductive factors varies with the immunophenotype of the ALL."*

However, most studies have not looked at specific phenotypes, not always differentiating between ALL and AML (often because of the small numbers of children involved), and so it is difficult to gain a clear idea of what other factors may be important in the development of specific leukaemia subtypes.

Parental age

Most studies have observed an increased risk for childhood leukaemia with advanced maternal age (Schüz 1999; Reynolds 2002), advanced paternal age (Ou 2002), or advanced parental age for leukaemia (Dockerty 2001), especially under the age of 5 (Yip 2006), although two studies have reported a risk association in ALL with young maternal age (Shu 2002; Ou 2002). Ross (1997) found that infant AML was associated with increased maternal age.

Reproductive history

A maternal history of previous miscarriages is a frequently reported risk factor for development of ALL - and in some cases AML - in a subsequent child (Perrillat 2002). Yeazel (1995) found that a previous history of foetal loss was associated with leukaemia diagnosed before the age of 4 and especially before the age of 2. One previous foetal loss increased the risk for ALL and AML by 5 times and 2 or more losses increased the risk for ALL by 25 times and AML by 12 times. The authors concluded *"Childhood acute leukemia occurring at younger ages may be associated with an underlying genetic abnormality or chronic environmental exposure, which can be either lethal to the developing fetus or mutagenic and result in the development of acute leukemia."* Ma (2005) found a link between multiple miscarriages and an increased rate of infant leukaemia. Ou (2002) found that an induced abortion prior to the index pregnancy increased the risk of a leukaemia diagnosis for children under 2.

Molar pregnancy has been associated with ALL, in the large UKCCS study though the numbers were small (Roman 2006).

There was an increased risk of AML in children with Down syndrome for parents who had tried for a year or more to become pregnant (Puumala 2007). Hormone treatment for infertility (Schüz 1999) or oral contraceptive use during the index pregnancy (Ou 2002) was also found to increase the risk of acute leukaemia.

Hypertension

Hypertension has been linked with AML in one study (Cnattingius 1995).

Caesarian section

In one study that looked at potential links with leukaemia, Cnattingius (1995) found an association with AML.

Resuscitation

Very little mention has been made of this as a risk factor. However, Naumberg (2002) suggested that resuscitation with 100% oxygen with a facemask and bag directly postpartum was associated with increased risk of childhood lymphatic leukemia and Spector (2005) found a 3-fold increase in risk in childhood cancer if oxygen was administered for 3 minutes or more.

Head size

Though rarely assessed, children with leukaemia have been found to have a significantly smaller head circumference than control children (Méhés 1985).

Apgar score

1-minute Apgar scores of less than 7 increased risk of ALL and AML (Johnson 2008).

Birth marks

Mertens (1998) found a higher reported frequency of birthmarks in both those with ALL and those with AML, or childhood cancer in general (Johnson 2007).

Birth order

Being the first born child has been associated with increased risk of leukaemia (Kaye 1991, Dockerty 2001), especially between the ages of 1 and 5, although the opposite has also been reported (Shu 2002, Ou 2002). Kaye's team had found that not just firstborns, but those with the next oldest sibling more than 5 years older had an increased risk. Jourdain-Da Silva (2004, Altieri 2006) found that having many siblings increased the risk of ALL, but Altieri found if they were older, the risk was significantly decreased. Westergaard (1997) found that the risk of ALL went down with increasing birth order, whilst the risk for AML went up, especially for a diagnosis at 2 or 3 years of age.

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, whereas having a school age sibling at the time of diagnosis significantly increased the risk in all children, but most markedly in those diagnosed before 4 years of age.

Birth order is used as a proxy for infection as it is assumed that children in larger families – especially those lower down the birth order – are exposed to more infections in early childhood. A number of studies have reported results but there is little consensus. Of 13 recent case-control studies, five showed an increased risk of childhood leukaemia in larger families, seven found no

effect and two showed a protective effect. The different results of the studies may reflect some impact of changing social conditions in the countries studied, and over time.

Birth weight

High birthweight (Ou 2002) of 3,000 grammes (Paltiel 2004) or 4,000 grammes or more (Westergaard 1997, Podvin 2006, Johnson 2008) is associated with an increased risk of ALL and AML. Hjalgrim's meta-analysis of 18 studies (2003) concluded that for each 1 kg increase in birthweight, the risk of ALL increases by 14% and AML risk increases by 29%. Being heavier at birth has been associated with infant leukaemia diagnosed between 6 months and 1 year (Ross 1997), before the age of 2 (Yeazel 1997), especially for children with AML, and Robison (1987) found that weight over 3800 gms significantly increased the risk of ALL for children diagnosed before the age of 4, but not later. Schüz (1999) found an increased risk of acute leukaemia with weights above 4,000 g and below 2,500g. Westergaard suggested that *"a plausible explanation may be that increasing birth weight is associated with a higher rate of cell proliferation and/or a larger number of precursor cells being at risk of malignant transformation."*

Milne reported (2008) *"Most studies of the association between birth weight and risk of childhood ALL have reported positive associations, while results have been less consistent for AML. Few studies have taken account of gestational age in the analysis of birth weight. As birth weight is a function of both intrauterine growth and length of gestation, it is not possible to differentiate between an association with high birth weight per se and an association with accelerated intrauterine growth, without accounting for gestational age."* In a recent analysis she found that it is accelerated growth, rather than high birth weight that is involved in the causal pathway for ALL. This did not seem to be true of AML. Foetal growth she sees as determined by a mixture of genetic, nutritional and hormonal factors.

Diet

Increased risk of childhood leukaemia has been associated with DNA topoisomerase inhibitors. This includes some drugs used in chemotherapy, benzene metabolites (from air pollution and cigarette smoke), certain fruits, tea, coffee, wine, soy and cocoa and many other substances (Greaves 1997, Gilliland 2004). Menegaux (2005) found that maternal coffee drinking during pregnancy increased the risk of ALL, the risk increasing with increased consumption. Topoisomerase inhibitors inhibit DNA repair and are strongly associated with one of the chromosome rearrangements common in infant leukaemia (Alexander 2001, Greaves 2003) or AML (Ross 1996, Spector 2005). Petridou (2005) reported that ALL risk was higher for children born to mothers who ate more sugars and syrups, and meat and meat products. N-nitroso compounds (found in cured meats and hot dogs) have been linked with childhood leukaemia in at least one study (Peters 1994). Hamburgers eaten once a week or more doubled the risk of ALL (Sarasua 1994), and was greater if the child did not take vitamin supplements. The author believed *"there was a possible adverse effect of dietary nitrites and nitrosamines"*.

Residential status

The Petridou study (1997) found differences in spatial clustering as to urban, semi-urban or rural places where children live. Children younger than 10 years old, living in an urban environment had an increased risk of developing leukaemia, and Petridou concluded that localised environmental exposures could contribute to the aetiology of childhood leukaemia. This may have relevance to a theory of infection, and there may be other factors at work as well.

Socioeconomic status

Incidence of ALL is higher in areas of high social class (Alexander 1991; Stiller & Parkin 1996; Dockerty 1999, Borugian 2005, Draper 2005), though Smith (2006), analysing the large UKCCS study found no effect, and neither did Swensen (1997). Smith suggested that previous studies varied because of the statistics used to analyse the result. This is always a problem with the small number of children concerned.

However, evidence from developing countries suggests that incidence of ALL in children aged 1-4 years is rising with improved socioeconomic conditions (Hrusak 2002).

Seasonal variation

Higgins (2001) found significant links between leukaemia and month of birth, for those born before 1960, and month of diagnosis for those diagnosed before 1962. Seasonal variations at diagnosis have also been found (Westerbbek 1998, Ross 1999 Karimi & Yarmohammadi 2003). Feltbower (2001) found variations according to birth area; and Sorensen (2001) found an April birth peak for leukaemia diagnosis in the under 4s. Other studies found no variation (Kajtar 2003). The variations may be proxies for infections which can have seasonal peaks of occurrence.

Gender

That the incidence of ALL in boys and girls is different is well established, with boys being more likely to develop ALL than girls (Zahm and Devesa 1995, Pearce and Parker 2001, Johnson 2008), although the incidence of girls is often higher among young children (Gurney 1995, Ross 1997). Males tend to have a worse prognosis (Eden 2000). Adelman (2007) found that boys (but not girls) had an elevated risk of developing ALL in areas of relatively high re-location rates.

Ethnicity

Incidence of ALL is significantly lower among black children in the US (Gurney 1995, Reynolds 2002, Adelman 2007, Johnson 2008) and Africa, and mixed race children in South Africa and Chile (Greaves 1993). During the first few years of life, the incidence rate of AML among African American children is approximately $\frac{1}{3}$ the rate of Caucasian children; however, African American children ≥ 3 years of age have higher rates than Caucasians. Hispanics had a higher incidence of ALL, particularly in childhood, in a study by Yamamoto (2007).

However, for many adult cancers, ethnicity seems less important than the country you are living in and the adopted lifestyle, as the incidence levels in immigrants generally begins to resemble that of the indigenous population in the country they are living in – certainly in subsequent generations.

Geopathic stress

This is recognised in many countries as being a significant factor in the development of cancer, which is likely to include childhood leukaemia. 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. There are also papers linking geopathic stress lines with various cancers. (referenced in Bachler 1976).

Possible protective factors in childhood leukaemia

Multiple births

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.

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. Petridou also found a decreased risk with maternal consumption of fish and seafood. 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 1992, 2004, see also www.leukaemiaconference.org day 4), in different ways (Blasius 2007).

Supplements

Maternal use of vitamins, cod liver oil, folate and iron supplements have been associated (Shu 1988, Wen 2002, Schüz 2007) with a decreased risk of ALL, 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, but not 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.

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).

Infectious exposure

Children attending day care are slightly less likely to develop leukaemia (Petridou 1993; Perrillat 2002; Jourdan-Da Silva 2004; Gilham 2005; Ma 2005; Kamper-Jorgensen 2007). It was assumed that attendance increased their exposure to infections, strengthening the immune system. In fact Gilham (2005) found that any social activity outside the family in the first year of life significantly reduced the risk of ALL. 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.

If an abnormal immune response to an infection is a key step in the development of childhood leukaemia then there may be associations to be found with other abnormal immune responses, for example allergy or atopy. A history of allergies (including asthma, eczema hay fever, food or drug allergies, or hives) has been found (Nishi & Miyake 1989, Petridou 1997, Schuz 1999, 2003, Wen 2000, Jourdain-Da Silva 2004, Rosenbaum 2005, Hughes 2007) to have a protective effect against leukaemia, even amongst siblings (Wen 2000). 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).

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.

Prescription 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.

Breast feeding

There is a fairly substantial body of evidence pointing towards a protective effect of even short-term breast feeding (Shu 1999a, Perrillat 2002, McNally & Parker 2006, MacArthur 2008). A meta-analysis reported a relative risk of 0.76 (Kwan 2004). Shu found that the reduction in risk was stronger with a longer duration of breast-feeding.

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 leukaemia. MacArthur (2008) also suggested this possibility as the use of immunosuppressant medication by children decreased leukaemia risk.

There have been concerns about various practices in the past that have largely been cleared as leukaemia risks. These include the following:-

Ultrasound scans

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

There has been little evidence that even repeated in utero diagnostic ultrasound tests are linked with an increased risk of childhood leukaemia (Petridou), either ALL (Cartwright 1984, 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.

Kinnier Wilson (1984) found no evidence of an increased risk and suggested that *“the observed difference between cases and controls exposed during the earlier years of ultrasound use may be due to the selective application of this technique to abnormal pregnancies at that time”*.

Ultrasound exposure, in vitro, has been shown to cause membrane changes (Dinno 1989), and some studies have shown an association between ultrasound exposure and left-handedness (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 be used for diagnostic or therapeutic use. There is concerning evidence of links between ultrasound scans and autism.

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.

In the 1990s 2 papers were published in the medical literature, suggested that intra-muscular vitamin K injections significantly increase children's chances of developing childhood leukaemia (Golding 1990, 1992). Research carried out by Parker (1998) found a very slight increase in risk for children developing ALL.

Follow-up international studies, reviewed 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.

Discussion

With the increase in knowledge about the subtypes of childhood leukaemia and the genetic changes that characterise them, it would seem that it may become easier to determine what factors will add to or decrease the risk of developing particular types of leukaemia. However, due to the fortunate rarity of the illness, the numbers of children with specific phenotypes is going to make this information difficult to obtain, without significant international co-operation, extensive funding for such studies and shared protocols, to ensure that the same things were being investigated. Even then, important factors or, indeed co-factors, could easily and accidentally be omitted from studies.

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 leukaemia and the potential for relapse in children recovering after treatment.

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