

Childhood leukaemia

Genetics and Ionising Radiation

All the references (Author year) in this article are listed alphabetically by author in "Childhood Leukaemia Section 6: References". Where the [year](#) is in blue, and underlined, it is a hyperlink to the pubmed entry.

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. See section 3: "EMFs and Childhood Leukaemia".
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](#), Han [2010](#), Oh [2010](#), de Jesus Marques-Salles [2010](#)), or country -specific. Siddiqui found ([2010](#)) that a particular fusion gene was found in Pakistan, Myanmar and Sudan, at a much lower rate than reported from Western populations.

B cell precursor ALL (BCP ALL) is associated with one in seven of the DPB DP6 supertypes. DPB1(*)0601 is significantly over-transmitted (76.9%) from parents to children with BCP ALL (Taylor [2009](#)). NOTCH1 may be an early or initiating event in T-ALL arising prenatally (Eguchi-Ishimae [2008](#)). Healy ([2010](#)) identified fetomaternal genetic subtypes that modulate the risk of childhood ALL. They suggested that the mother's genotype plays an important role in the susceptibility to early-onset diseases.

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 & Cleary [2001](#), Yuan [2001](#)). Wiemels ([2000](#)) suggested that TEL-AML1 breakpoints may be distributed into microclusters because of specific DNA sequences in susceptible cells, del(12p) being one such point (Wiemels [2008](#)). 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, although Tumer (2010) found particular genotypes increased the risk for females. They also found that carriers of more than one of the risk-elevating genotypes increased the risk by up to 3 times.

Xue (2010) found a specific polymorphism is involved in the aetiology of childhood ALL and is a potential candidate gene for determining cancer susceptibility, though it may be ethnically variable (Miladpour 2010).

Vijayakrishnan & Houlston (2010), in a meta-analysis of published studies, found significant associations between ALL and 8 of the polymorphic variants studied.

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 (Buffler 2008, Mullighan 2009).

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 & Kinzler 1998). In adult tumours, the minimum number of genetic events seems to be 3 or 4 (Hahn 1999), but leukaemia may require fewer as it is not dependent on tissue structure (Greaves 1999).

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 & Wiemels 2003, Bateman 2010) 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. Lilljebjörn (2010) found an average number of 3.5 recurrent changes for ALL, up to 26% being the same recurrent changes and 74% showing a unique pattern of changes. In children diagnosed with AML 42.3% had clonal chromosome abnormalities, especially in chromosomes 8,9 and 21. The basic mechanisms were trisomy, deletion and monosomy. The frequency was 7 times higher in children aged up to 2 years of age, and twice as high in those up to 5 (Ukraine 2010).

There is a postnatal latency which is variable but often protracted (Wiemels 2002, Maia 2004) ~ 1-14 years. Particular chromosomal abnormalities may be found more frequently in certain types of leukaemia or at less predictable times. For example, children with infant ALL have arrangements more similar to those aged 3 or more years, suggesting that 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 (GM Taylor 2002).

There is a difference in opinion as to whether cancer in the family predisposes children to leukaemia. Infante-Rivard & Guiguet (2004) suggested that only familial malignancies involving blood-forming cells (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 & Jiang (2002) reported that parental leukaemia has not been associated with childhood ALL but leukaemia in a sibling has been a risk factor for leukaemia in other siblings.

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 & Jiang (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 (Izraeli 2007). Linabery (2008) concluded that congenital malformations did not confer additional risk of leukaemia beyond the risk attributable to trisomy 21.

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

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

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

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

A paediatrician in Germany explained in very clear terms why children may be more at risk than adults when exposed to radiation, even low grade (Eisenberg [2009](#)).

She said that the reasons that children are extremely sensitive to radiation is:-

- Growth means a high rate of cell division in all organ systems. Cell division is the risky phase for radiation damage; an embryo grows at an almost explosive rate. Its cells are constantly dividing, which is why even tiny amounts of radiation are extremely hazardous.
- The repair mechanisms that our organism uses to identify and eliminate mutated cells are not yet effective in children, especially in unborn children.
- Children have a positive substance balance - in order to thrive they have to consume more than they excrete, in contrast to adults who merely have to maintain their fully grown bodies. The positive balance in children leads to a prolonged biological half life in incorporated radioactive isotopes.
- Malignancies have a long latency period; in pathologies caused by radioactivity, decades may lie between exposure and detectable onset of illness. Children have their lives ahead of them; in contrast to older people, they may have the misfortune of experiencing the end of the latency period.

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). In the UK, the percentage of cases of childhood leukaemia attributable to natural background radiation is suggested to be about 20% (Wakeford [2009](#)), though this has been revised downwards to 15-20% by Little ([2009](#)). 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.

Red bone marrow, the tissue in which leukaemia is considered to originate, can be affected by natural radiation. Doses *in utero* include contributions resulting from the ingestion of radionuclides by the mother and placental transfer to the foetus. Postnatal doses include those from radionuclides in breast-milk and those ingested in other food (Kendall [2009](#)).

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.

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 & Wakeford [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 & Miller [1999](#), Shu [1994](#), [2002](#)). Wakeford ([2008](#)) found an increase in risk of leukaemia for prenatal X-ray exposure, but not postnatal, however, he expressed uncertainty about the safety of paediatric CT scans.

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 ultrasound 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. No increase in general risk as a result of postnatal diagnostic X-rays was found by a German study (Hammer [2009](#)).

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 & Darby [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 ([1999](#)) 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](#), [2008](#), Nussbaum [2009](#)) was higher than would be expected, but they were unsure of the cause. Nussbaum found a doubling in risk in children under 5 living within 5 km of plant exhaust stacks. Laurier ([2008](#)) found no such link in children below the age of 5 years with French nuclear power plants, neither did Heinävaara find an increase in childhood leukaemia near Finnish nuclear power plants ([2010](#)), though they acknowledged that the small sample size limited the strength of the conclusions.

Dr Körblein commented on the leukaemia cancer clusters ([2009](#)) saying "*ecological studies are much less able to detect regional clusters than more elaborate case-control studies. When the authors refer to the results of a recent study from England that, in contrast with the German study, has not shown a leukaemia*

increase in the vicinity of nuclear power stations, it has to be borne in mind that this study, again, is an ecological study." Bithell (2008) commented "this apparent discrepancy (in study findings) could be accounted for by a number of differences in approach, especially those relating to the distances from the power stations and the ages of the children studied." Laurier (2008) in a review of 198 nuclear sites throughout 10 countries concluded "A large variability was noticed in the quality of the data as well as in the definition of the study population and in the methods of analysis" although the review also confirmed that "some clusters of childhood leukaemia cases exist locally."

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 & Goodman (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, Evrard 2006), even if a weak

one (Raaschou-Nielsen [2008](#)), similar to the radiation risk estimates in another study 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.