Childhood leukaemia – incidence and causation, Infant leukaemia

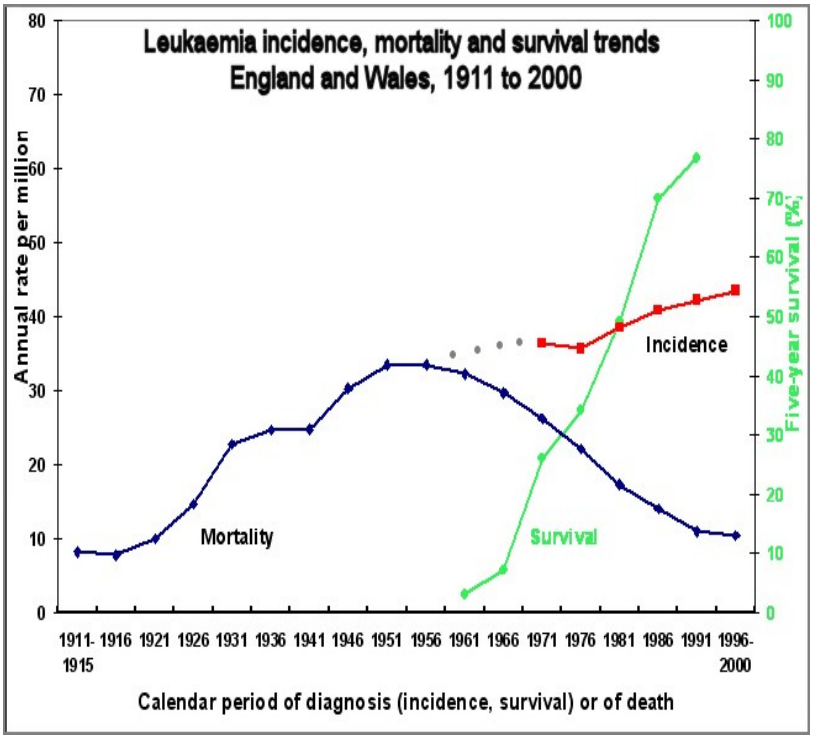
All the references in this article are listed alphabetically by author and year in "Childhood Leukaemia, Section 6: References". Where the year is blue and underlined, it is a hyperlink to the pubmed abstract.

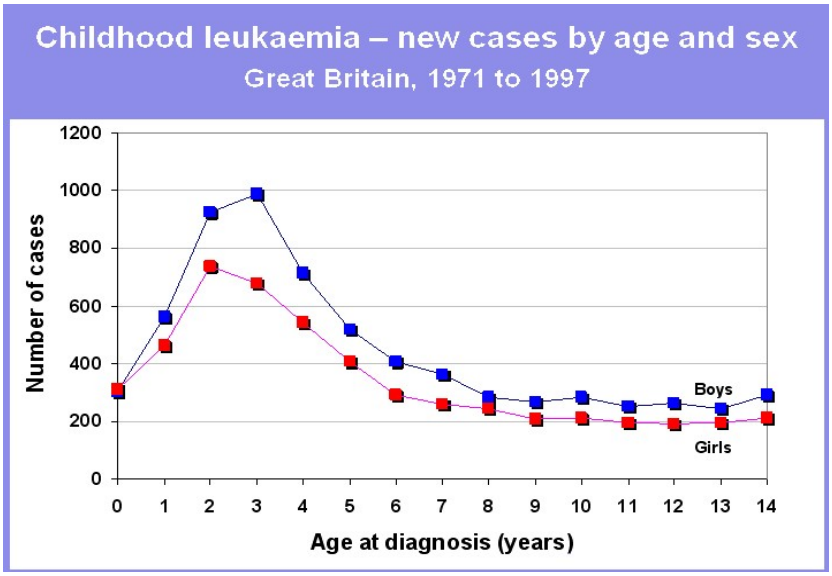
Each year about 500 children in the UK develop leukaemia, the most common type of childhood cancer, accounting for about 30% of all cancers diagnosed in children younger than 15 years, and 10% of adolescent leukaemias (15-19 years). Around 100 children die of it. The lifetime risk (0-15 years old) of 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 incidence of lymphoid leukaemia rose in European children between 1988-1997, in children by 0.6% per year and adolescents by 1.9% per year (Coebergh 2006, Kaatsch & Mergenthaler 2008). Kaatsch & Mergenthaler found that the highest rates were in Northern Europe and the lowest in Eastern Europe. An Australian study (Baade 2010) reported a plateau in cancer incidence rates for boys and older children. This may be difficult to interpret as it suggests perhaps different aetiologies that are not yet understood. Forsythe (2010) found that the gender incidences in Mississippi were comparable with the national average for ALL overall, but that boys were 4 times more likely than girls to present with high-risk B-precursor ALL. Childhood leukaemia rates in Basrah, Iraq, more then doubled between 1993 and 2007 (Hagopian 2010). There may be a number of environmental factors responsible for this.

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, brining the cure rate to 73%.

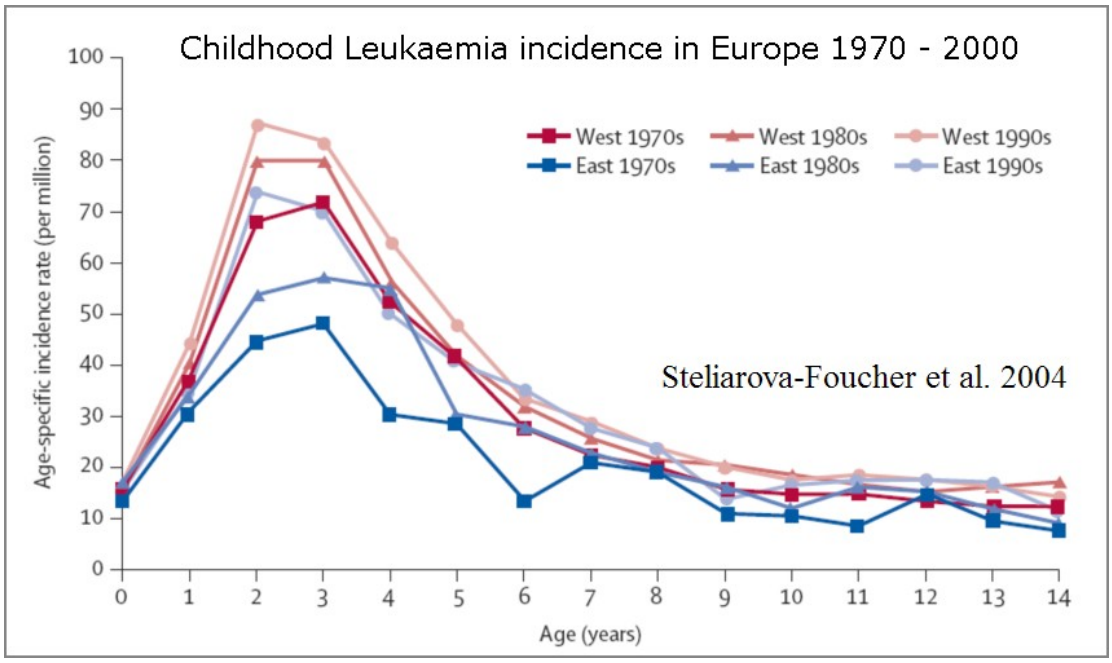




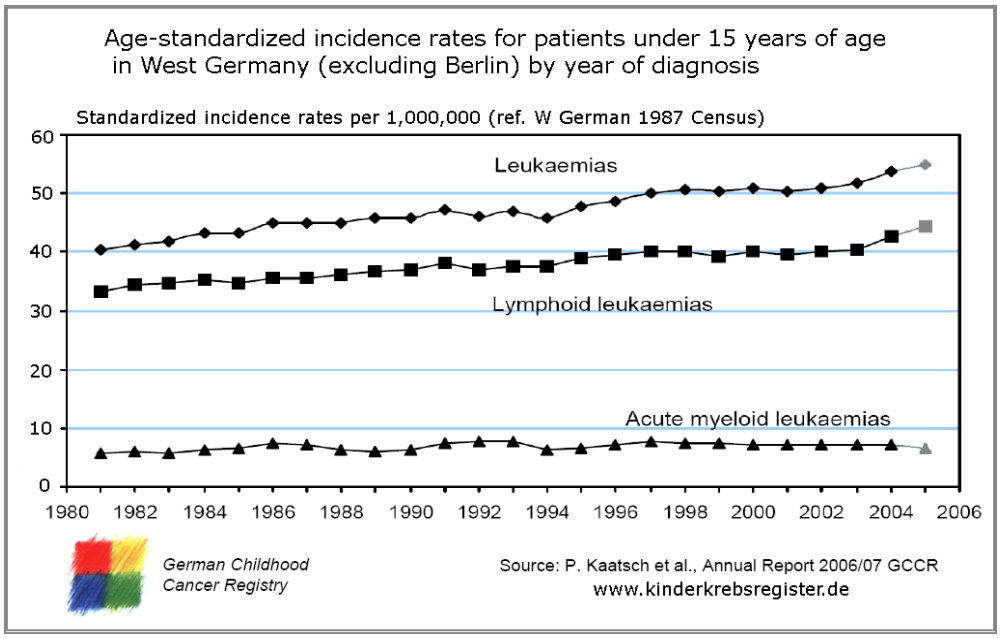
The graph above, showing information from the UK is from Shah & Coleman (2007). Before 1950, childhood leukaemia was nearly always fatal and so the mortality data will be almost identical to the incidence data, maybe with a lag of year or two. Other countries have shown similar increases (Linabery 2008).

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. It may be likely that childhood acute leukaemia incidence is similar in developing countries, but there is a significant under reporting of cases (Azevedo-Silva 2009).

However, the number of children diagnosed with leukaemia is still steadily increasing (Hosny & Elkaffas 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. A study of children in China diagnosed with leukaemia between October 2003 and June 2006 found differences between the Northern region of China and other regions and races, which point to differences in genetics and environmental exposure that may be responsible for leukemogenesis (Guo 2009). Cocco (1996) found a family history of cancer predisposed children to develop ALL.

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. One of the complications of investigating environmental causes of any illness is population mobility; greater residential mobility is associated with an older age of diagnosis for the child, younger age of the mother at the child's birth and lower household income. These factors need to be taken into account as the time-window of exposure for childhood leukaemia is not known (Urayama 2009). Several 'clusters' of cases have been investigated, to see if there is a common environmental cause, but the results are inconclusive.

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 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 article 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 (Sinnett 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. The study by Lausten-Thomsen (2010) supports the theory that the preleukaemic cells peak at term or early childhood and they suggest that factors are necessary to clear them. 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 & Ross 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. It may be also that more than one environmental factor has to happen at the same time, rather than sequentially (Anderson 2006). 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 & 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 (Taub & Ge 2004). In a study by Gruhn (2008) preleukemic cells were detected on neonatal Guthrie cards in 63% of B-precursor ALL patients. MT Smith (2005) found specific chromosome re-arrangements in neonatal Guthrie cards, suggesting that maternal and perinatal exposures such as chemical and infectious agents are likely to be critical. While some aspects of the biological aetiology or the mechanics of how leukaemia develops are known, the reasons why gene mutations occur are poorly understood. Identifying subgroups of children, in which the similarities are sufficient to allow for comparison, and defining time windows (Anderson 2000) when mutations are likely to arise because of specific exposures is quite a challenge especially when different cellular and molecular mechanisms may be implicated according to the kind of exposure.

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.

A study (Puumala 2009) that looked at how similar the groups of children with infant leukaemia were to the comparison control groups, showed that the two ways of obtaining control families (random digit dialling and birth certificate) resulted in control families that were similar to each other, but that were different from the families of children with infant leukaemia, and so not always directly comparable.

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 & Blair 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, Sorensen 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, Moneypenny 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. Eguchi (2006) also suggested that such fusion genes may be more vulnerable to further DNA damage and mutation in the presence of chronic exposure to the agent(s) that induced the MLL fusion itself. Other MLL translocations have been associated with the development of infant leukaemia (MT 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 (S 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. Puumala (2010) found no link between infertility treatment and infant leukaemia.

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.

Paternal occupation in petrol stations, car or truck repair and aircraft maintenance increases the risk of infant leukaemia, especially in girls (Vianna 1984).

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. Busby (2009) looked at the records of 15,466,845 children born in the UK, Greece, and Germany between 1980 and 1990. He found an excess of infant leukaemia reported from 5 different countries; Scotland, Greece, Germany, Belarus and Wales and Scotland combined. The excess risks showed a biphasic response to exposure. Busby concludes "*Since the cohort is chosen specifically on the basis of exposure to internal radionuclides, the result can be expressed as evidence for a significant error in the conventional modelling for such internal fetal exposures.*" Fairlie (2009) looked at studies of leukaemia near nuclear installations and suggested that "*the observed high rates of infant leukaemias may be a teratogenic effect from incorporated radionuclides. Doses from environmental emissions from nuclear reactors to embryos and foetuses in pregnant women near nuclear power stations may be larger than suspected. Hematopoietic tissues appear to be considerably more radiosensitive in embryos / foetuses than in newborn babies.*"

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 and other factors that may provide the second or more 'hits' that results in the disease becoming manifest.

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