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REVIEW

Risk factors for childhood leukemia: a comprehensive literature review

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ABSTRACT

Background: Although overall incidence is rare, leukemia is the most common type of childhood cancer. It accounts for 30% of all cancers diagnosed in children younger than 15 years. Child leukaemia has been related to external factors to which children are exposed during their lives as well as internal factors.

Aim: The aim of the present study was to explore the risk factors for childhood leukemia.

Method and Material: An electronic search of CINAHL and PubMed was undertaken, along with citation searches. Studies were selected if risk factors for childhood leukaemia were described in the title or abstract and original data were included. Study quality was taken into consideration.

Results: The search produced 1726 articles from which 26 articles met the inclusion criteria. Several internal and external risk factors for childhood leukaemia were identified in this review. These factors included the magnetic fields and high voltage transmission lines, parental occupational exposure (to chemicals), nuclear power plants and ionising radiation, intramuscular vitamin K, population mixing and endogenous factors including baby weight.

Conclusions: Most risk factors have been found to be weakly and inconsistently associated with either form of acute childhood leukemia. Only one environmental risk factor (ionizing radiation) has been significantly linked to acute lymphocytic leukaemia or acute myelogenous leukaemia. Knowledge of these particular risk factors can be used to support measures to reduce potentially harmful exposures and decrease the risk of disease.

Key words: Children, leukemia, risk factors, environment.

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INTRODUCTION

Childhood leukaemia is the most common cause of malignancy under the age of 15, representing an annual incidence rate of 43 cases per million in the United States.[1] Within this population, acute lymphocytic leukaemia (ALL) occurs approximately five times more frequently than acute

myelogenous leukaemia (AML) and accounts for approximately 78% of all childhood leukaemia diagnoses.[2] Epidemiologic studies of acute leukaemias in children have examined possible risk factors, including genetic, infectious, and environmental, in an attempt to determine aetiology.

According to the International Commission of Non-Ionizing Radiation Protection there is increasing evidence that a first damaging event to the haematopoietic stem cells (1st hit) occurs during the prenatal phase and one or more postnatal hits are needed to transform the pre-leukaemic clones into leukaemia cells.[3] In parallel to research investigating the different indicators of molecular damage, therapeutic procedures have been continually developed in the past. Today individually optimized therapeutic plans for childhood ALL patients are available which result in a survival rate of more than 80%.[3]

In spite of the many available epidemiological studies, the exact causes of most of the leukaemia cases are still unknown. The aim of this paper is to draw on the current knowledge about the role of genetic and environmental risk factors in childhood leukaemia. However it became clear that the puzzles connected with leukaemia are still rather incomplete and that no simple way to explain the whole processes involved in leukaemia is likely to become available in the near future.

Material and Method

We identified studies of the association between external (environmental) and internal (endogenous) risk factors for developing childhood leukaemia, listed in CINAHL and PubMed between January 1987, up to January 2003. Specifically, we performed a literature search using the index terms child, leukaemia, cancer, risk factor, environmental factors and birth weight, in various combinations. The electronic search yielded 1726 articles from which 26 articles met the inclusion criteria. Analytically 1 meta-analyses, 1 pooled analysis and 24 case-control studies were included in the review (tables 1-3). Studies were selected if risk factors for childhood leukaemia were described in the title or abstract and original data were included. A second independent reviewer selected studies from a random 10% of the references to ensure that selection of studies was reliable. Where differences of opinion occurred, these were resolved by discussion.

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The quality of the articles was assessed by using two methods, namely a 'hierarchy of evidence' and a 13-item checklist. The latter was based on a checklist developed by Walburn et al.,[4] and it was based on a number of sources.[5,6] The checklist focused upon those variables most often highlighted in critical appraisal, namely, justification of sample size, sampling, response/drop-out rates, validity of measures and the generalisability of the results.[3] The former method was based in the hierarchy of bias which increases downwards (from RCT to Case studies). The categorisation for each study was carried out by the researchers independently and any disagreements were resolved by discussion.

Identified risk factors for childhood leukaemia

The data collected for the purposes of this review varied into the different risk factors for childhood leukaemia. The majority of articles were related to electromagnetic fields (EMF), parental occupational exposure to chemicals and nuclear power plants. According to Soderberg et al.,[6] power lines and electrical installations close to the children's homes are the most studied source of exposure. The findings from the research articles identified for the purposes of this review were conflicting but after their examination and evaluation and always in relation with the aims and objectives of this study it was possible to specify some risks for childhood leukaemia that were related to magnetic fields and high voltage transmission lines, parental occupational exposure to chemicals, nuclear power plants and ionising radiation, intramuscular vitamin K, and population mixing.

Magnetic fields and high voltage transmission lines

Numerous epidemiologic studies have reported associations between measures of power-line electric or magnetic fields (EMFs) and childhood leukemia. The basis for such associations remains unexplained. The possibility that these associations are caused by bias or confounders, however, cannot be ruled out. In addition, extensive investigations in animals at much higher levels of EMFs have not demonstrated adverse effects.[7]

London et al.,[8] conducted a case control study in order to address the hypothesis that childhood leukaemia is related to increased exposure to electric and magnetic fields in Los Angeles, USA. They indicated a no clear association between childhood leukaemia and magnetic or electric fields. But an association between the Denver

Wertheimer-Leeper wiring configuration and childhood leukaemia was observed with (OR=2.15, CI=1.08-4.28 and *p* for trend= 0.008). Furthermore cases reported more frequent use of appliances that produce high electric and magnetic fields than controls. The results of this study supported an association between childhood leukaemia and wiring configuration.

Feychting and Ahlbom[9] conducted a case control study in Sweden in order to test the hypotheses that exposure to magnetic fields of the type generated by high-voltage power lines increases cancer incidence in children. They observed a high risk for childhood leukaemia when the historical calculations were used as exposure assessment for childhood leukaemia with a cut-off point at 0.1 and 0.2 microtesla (μT), and an estimated relative risk increased over the two exposure levels estimated at 2.7(CI=1.0-6.3) for 0.2 μT and over; *p* for trend =0.02. When the upper cut-off point was shifted to 0.3 μT, the relative risk was 3.8 (CI=1.4-9.3) *p* for trend =0.005. These results also persisted when adjustments were made for other confounding factors.

Michaelis et al.,[10] conducted a population-based case-control study in Germany in order to explore the potential health hazards and possible causes of childhood leukaemia due to the electromagnetic fields in Germany. Contrary to the previous studies, they concluded that there was no increased risk of childhood leukaemia associated with any residential electromagnetic field and for children that were exposed to more than 0.2μT an elevated odds ratio was observed which was not significant (OR=3.2, CI=0.7-14.9) and these findings were related to only 4 leukaemia cases and 3 controls as only 1.5 percent of the study population was classified as highly exposed.

Li et al.,[11] conducted a study in order to examine the risk of leukaemia in children living near High-Voltage Transmission Lines (HVTL) in three districts of northern Taiwan. They reported that children living outside of 100m of HVTL when compared with children living within 100 m of HVTL showed a slightly significant increase of SIR for leukaemia (standardised incidence ratio, SIR=2.43, CI=0.98-5.01). The SIR was higher in all of the three ages, with an increase among the 5-9-year-old group. When compared with all children in Taiwan, children within 100m of HVTL in the study districts had again showed a significantly elevated SIR and again the risk among children of 5-9

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years was higher than the other ones (SIR=2.69, CI=1.08-5.55). On the contrary the children in households outside 100m of HVTL when compared with all the children in Taiwan did not show any significantly elevated risk of childhood leukaemia.

McBride et al.,[12] conducted a case control study of childhood leukaemia in relation to power-frequency electric and magnetic fields (EMF), in Canada. They indicated that the results pointed to a no related risk of leukaemia and personal magnetic fields (OR=0.95, *p* for trend = 0.73) or acute lymphatic leukaemia (OR=0.93, *p* for trend = 0.64) with no clear association for the predicted magnetic field exposure two years before the diagnosis date or over the subject's lifetime or with any personal exposure to electric fields. A furthermore statistically no significant elevated risk of acute lymphatic leukaemia was observed with the very high wiring configurations among residents and subjects 2 years before the diagnosis (OR= 1.72 compared with underground wiring (CI = 0.54-5.45).[12]

Thomas et al.,[13] reanalysed the Los Angeles case-control study conducted by London et al.,[8] in order to predict long-term magnetic field exposure using the wiring configuration model. They argued that their findings strengthened the hypothesis that magnetic fields from electrical distribution and transmission lines, plus the associated ground currents, are a risk factor for childhood leukaemia. They concluded that although the measured fields had no association with childhood leukaemia (*P* for trend= .88), the risks were significant for predicted magnetic fields above 1.25mG (OR=2.00, CI=1.03-3.89), and a significant dose response was seen (*P* for trend = .02). When exposures were determined by a combination of predictions and measurements that corrects for errors, the odds ratio (OR= 2.19, CI=1.12-4.31) and the trend (*p*=. 007) showed somewhat greater significance.[13]

Soderberg et al.,[6] conducted a population-based study with the purpose to determine whether exposure to magnetic fields in infant incubators was related to any risk towards childhood leukaemia. They concluded that for acute lymphoblastic leukaemia, the risk estimates were close to unity for all exposure definitions. For acute myeloid leukaemia, the findings were indicating a slightly high risk, but with wide confidence intervals and with no indication of dose response. Overall results gave little evidence that exposure to magnetic fields inside infant

incubators is associated with an increased risk of childhood leukaemia.

Parental occupational exposure

Two case-control studies[14,15] tried to identify a number of different risk factors related to childhood leukaemia. This was an opportunity to group them together with six other case control studies[15-20] that were on their own as each one was examining a different risk factor that was also examined in the above two studies presenting the possibility for better comparison and evaluation. Only the results of these studies will be presented here as more details about the purpose and methods of the studies can be seen in Table 3.

Shu et al.,[14] observed an association of ANLL with younger maternal age at menarche (OR=4.3, CI=1.3-13.9) and a protective effect for long-term use of cod liver oil for both ALL (OR=0.4, CI=0.2-0.9) and ANLL (OR=0.3, CI=0.1-1.0). They reported an increased risk for ANLL for children whose mothers were employed in metal refining and processing (OR=4.6, CI=1.3-17.2). Furthermore they reported that prenatal X-ray exposure was associated with a slightly increased risk of leukaemia (OR=1.4, CI=0.9-2.3) and paternal preconception X-ray exposure was again noticeably related to an elevated risk for ALL (OR=2.6, CI=1.5-4.6) and ANLL (OR=3.7, CI=2.0-7.0) with exposure to ten or more X-rays.

In another study Shu et al.,[20] failed to report an association between in uterus pelvimetric diagnostic X-Rays and the risk of childhood ALL (OR=1.2, CI=0.8-1.7). Even when all the types of childhood ALL were combined there was not a link with postnatal diagnostic X-Rays (OR=1.1, CI=0.9-1.2). Neither maternal (OR=0.9, CI=0.8-1.2) nor parental (OR=1.1, CI=0.8-1.4) lower abdominal preconception diagnostic X-Rays were associated with the risk of childhood ALL. Among the multiple comparisons for age-sex and subtype-specific sub grounds, researchers indicated an increase risk of ALL among children at the ages 11-14 at diagnosis (OR=2.4, CI=1.1-5.0) in relation to in uterus pelvimetric diagnostic X-Ray exposures and a small increase of in pre-B ALL for all ages combined (OR=1.7, CI=1.1-2.7) in relation to postnatal diagnostic X-Rays.

Shu et al[14]., had also reported an increased risk of ALL when the mothers of children were occupationally exposed to pesticides (OR=3.5, CI=1.1-11.2). This relationship came to refute Meinert et al.,[18] who found that the use of

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pesticides on farms was weakly related to childhood leukaemia (OR=1.5, CI=1.0-2.2) while their use in gardens was not associated with childhood leukaemia (OR=1.0, CI=0.8-1.2). Again the positive results of Shu et al.,[14] had wide confidence intervals resulting to a no confident reliability that pesticides are a risk for childhood leukaemia.

Cocco et al.,[15] reported that none of the risk factors analysed in their study were significantly associated with childhood acute lymphoblastic leukaemia. But an increased risk for childhood acute lymphoblastic leukaemia was related to parents born outside of Carbonia (OR=4.1, CI=0.8-21.4), family history of cancer (OR= 2.7, CI=0.4-15.9), fathers' exposure to solvents at their workplaces (OR=1.5, CI=0.3-8.0), the use of medication during pregnancy (OR=4.0, CI=0.6-26.3). In relation to maternal smoking and ALL, they indicated that there was an increased risk (OR=1.8, CI=0.4-9.5) something that Brondum et al.,[16] failed to observe. In fact they reported a no risk for ALL with the father having ever smoked (OR=1.04, CI=0.90-1.20) or the mother having ever smoked (OR=1.04, CI=0.91-1.19). Similarly no significant risk for AML and paternal (OR=0.88, CI=0.67-1.16) or maternal smoking (OR=0.95, CI=0.74-1.22) was observed. The results of Cocco et al.,[15] had wide confidence intervals (CI) and that may explain their findings.

The results reported by Costas et al.,[17] in relation to leukaemia and potential exposure to contaminated water during the mothers' pregnancy found a non-significant association (OR= 8.33, CI= 0.73-94.67). Still a significant dose-response relationship was identified for this exposure period ($P< 0.05$). The child's potential for exposure to contaminated water from the date of birth till diagnosis showed no association with childhood leukaemia. The authors indicate that the wide confidence intervals suggest cautious explanation of association magnitudes. On the other hand Cocco et al.,[15] reported an increased risk for leukaemia and the presence of a well in the backyard (OR=4.0, CI=0.6-28.6) of the house. Both studies reported wide confidence intervals something that makes it very difficult to rely on their findings.

Naumberg et al.,[21] indicated that a history of maternal infection was not significantly associated with childhood leukaemia (OR=1.25, CI=1.95-1.65). However, maternal lower genital track infection was increased (OR=1.78, CI=1.17-2.72) and especially when children were over the age of 4 at the date of diagnosis (OR=2.01, CI=1.12-3.80). Supporting to the above results

Shu et al.,[14] reported that a history of dysentery was related to an increased risk for ALL (OR=3.9, CI=1.0-15.5).

In relation to parental alcohol consumption on one hand Infante-Rivard et al.,[19] suggest a protective effect to childhood leukaemia when mothers were drinking alcohol during pregnancy (OR=0.7, CI=0.5-0.9) and the interaction odds ratios for the GSTM1 null genotype during third pregnancy trimester were 2.4 (CI=1.1-5.4) and for CYP2E1 variant G-1295C during the nursing period were (OR=4.9, CI=1.5-16.7). On the other hand Cocco et al.,[15] reported that fathers' alcohol consumption exceeding 60g/d (OR=1.8, CI=0.2-19.5) was related to an increased risk of childhood leukaemia.

Since the case-control studies above varied in relation to their chosen risk factor examined it was more appropriate to use the two case-control studies conducted by Shu et al.,[14] and Cocco et al.,[15] who examined a number of different factors within their studies to compare them with. The overall results from the analysis of the above studies pointed out that none of the above discussed factors could pose as risk for childhood leukaemia as studies observing an increase risk in their results were not reliable due to the wide confidence intervals they were presenting.

Parental occupational exposure to chemicals

The results from the following studies[21,22] revealed that parental occupational exposure to chlorinated solvents, paints or thinners and plastic materials could cause leukaemia in children. Parental occupational exposure to some certain chemicals like benzene can trigger the development of leukaemia in their offspring as well as to themselves.[23]

Lowengart, et al.,[22] conducted a matched case-control study in Los Angeles and investigated the possible etiologic factors for childhood leukaemia related to parents occupational and home exposures. The results indicated an increased risk of leukaemia for children whose father had an occupational exposure after the birth of the child to chlorinated solvents (OR=3.5, P=.01), spray paint (OR=2.0, P=.02), dyes or pigments (OR=3.0, P=.05), methyl ethyl ketone (CAS: 78-93-3; OR=3.0, P=.05), and cutting oil (OR=1.7, P=.05). An increased risk was also found for fathers that were exposed during the mother's pregnancy with the child to spray paint (OR=2.2, P=.03). The risk for childhood

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leukaemia was also increased when the father worked in industries manufacturing transportation equipment (OR=2.5, P=.03) or machinery (OR=3.0, P= .02). Increased risk was also found for children's when the parents used pesticides at home (OR=3.8, P=.004), or garden (OR=2.7, P=.007). Risk for leukaemia was also related to the mothers' employment in personal service industries (OR=2.7, P=.04).

Draper, et al.,[24] conducted a study in Great Britain in order to test the 'Gardner hypothesis' that childhood leukaemia and non-Hodgkin's lymphoma can be caused by fathers' exposure to ionising radiation before the conception of the child. They found an increased risk for childhood leukaemia and non-Hodgkin's lymphoma among children of radiation workers (relative risk 1.77, CI=1.05 to 3.03) but that result was not related to the ionising dose exposure. Additionally mothers' radiation work was associated with an increase of childhood cancers (relative risk 5.00, CI=1.42-26.94) based only on the mothers of 15 cases and 3 controls.

Meinert et al.,[25] conducted a case-control study in Germany with the main purpose to investigate the associations between sources of exposure to ionising radiation and childhood cancer in Germany. The results did not provide any convincing evidence that exposure to ionising radiation plays a noticeable role in the development of childhood cancer with results of maternal occupational exposure during pregnancy and lymphomas (OR=3.87, CI=1.54-9.75), parental occupation in the nuclear industry and childhood leukaemia (OR=1.80, CI=0.71-4.58) and prenatal X-ray examinations of the father and childhood leukaemia (OR=1.33, CI=1.10-1.61).

Shu et al.,[23] conducted a case-control study in Minnesota by using the recently completed study by the Children's Cancer Group in order to conduct an in-depth evaluation of association between parental occupational exposure and the risk of childhood leukaemia in their offspring. Increased risk of childhood acute lymphoblastic leukaemia was also observed when the mother of child was exposed to solvents (OR=1.8, 95% CI=1.3-2.5) and to paints or thinners (OR=1.6, 95% CI=1.2-2.2) during the preconception period, and during pregnancy (OR=1.7, 95% CI=1.2-2.3) and to plastic materials during postnatal period (OR=2.2, 95% CI=1.0-4.7). Parental exposure to plastic materials during the preconception period also increased the risk (OR=1.4, 95% CI=1.0-1.9). Similarly, a large-scale United States study by Schuz et al.,[26] reported an

association between parental exposure to hydrocarbons at work and the risk of childhood leukemia. Parental occupational exposure to different chemicals and industrial dusts or fumes also was assessed in three German case-control studies that were conducted from 1992–1997. The design and methods of exposure assessment were similar for these studies; therefore, they were pooled for this analysis. In total, these three studies involved 1138 cases of acute lymphocytic leukemia (ALL) and 2962 controls. We found that maternal exposure to paints or lacquers during the preconception period (odds ratio, 1.6; 95% confidence interval, 1.1–2.4) and during the index pregnancy (odds ratio, 2.0; 95% confidence interval, 1.2–3.3) was related to an increased risk of childhood ALL.

Nuclear power plants and ionising radiation

The results of this review after the analysis of the research articles gathered pointed to a small risk between nuclear power plants, ionising radiation and childhood leukaemia. One of the research articles examined suggested an association between the incidence of leukaemia and exposure to weak doses of radiation.[27]

Hjalmars et al.,[28] conducted a case control study in Sweden in order to evaluate the risk of acute childhood leukaemia in areas of Sweden contaminated after the Chernobyl reactor accident in April 1986. The results show that one in ten children lived in high contaminated areas Cs-137 activity >10 kBq/m^2 and 52 of them were diagnosed with acute leukaemia during period one (January 1980 to May 1986), and 47 diagnosed with acute leukaemia during period two (June 1986 to December 1992). From these cases 17 and 27 respectively were cases of acute lymphoblastic leukaemia among children under the age of five. Therefore after the analysis there was no significant evidence showing an increase of childhood leukaemia in the areas of Sweden with high ground levels of Cs-137 activity >10 kBq/m^2.

Pobel and Veil[27] conducted a case control study in order to investigate the association between childhood leukaemia and risk factors related to the La Hague nuclear waste reprocessing plant, in France. Both studies used case-control methodology but were conducted in a different way. Pobel and Veil[27] were more precise in their findings as they pointed to an increased risk for childhood leukaemia when mothers and

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children were using the local beaches (P≤0.01); relative risks 2.87 (CI= 1.05-8.72) and 4.49 (1.52-15.23) when categories were aggregated in two levels (more or less than once a month). An additional increased risk was related to the consumption of local fish and selfish (P0.01); relative risk 2.66 (0.91-9.51) when categories were grouped in two levels (more or less than once a week). A risk of 1.18 a year (1.03-1.42) was also observed for the length of residence in a granite-built house or in a granite area. Association with parental occupational radiation exposure and the risk for childhood leukaemia was not observed.

Intramuscular vitamin K

The findings of this review in relation to intramuscular vitamin K and childhood leukaemia revealed that a small risk does exist and research up to date had failed to eliminate totally the risk of childhood leukaemia.

McKinney et al.,[29] conducted a population case-control study with the purpose to test the postulation of a link between neonatal intramuscular vitamin K and childhood leukaemia and other cancers in the population of Scotland. Data was gathered from hospital medical records. The results showed no significant positive association with leukaemia (OR=1.30, CI=0.83-2.03). For ALL the results were (OR=1.21, CI=0.74-1.97). The results for lymphomas were (OR=1.06, CI=0.46-2.42), for central nervous system tumours were (OR=0.74, CI=0.40-1.34) and other solid tumours (OR=0.59, CI=0.37-0.96). The odds ratio for 'recorded' ALL in ages 1 to 6 years was (OR=1.16, CI=0.62-2.15) and for the 'imputed' data it was (OR=1.33, CI=0.70-2.53).

Passmore, et al.,[30] undertook a matched case-control study aiming to investigate whether there was a possible link between neonatal vitamin K administration and childhood cancer in England and Wales. The results for intramuscularly vitamin K and all the cancers were not significant (OR=1.44, P=0.05). For childhood leukaemia the association was stronger (OR=1.53, P=0.17) as it was for ALL in children 1-5 years (OR=1.03). They asserted that most of the studies did not show a significant risk of the association between intramuscular vitamin K and childhood leukaemia but were also incapable to exclude the possibility that its use raise the risk of childhood cancer by up to a 10%.

Population mixing

In regard to population mixing two studies were identified and included in

this review. Both studies evaluated[31,32] pointed towards an association between an infection agent and childhood leukaemia.

Kinlen et al.,[32] conducted a geographical study in Britain with the main objective to determine whether population mixing produced by large, non-nuclear construction projects in rural areas is associated with an increase in childhood leukaemia and non-Hodgkin's lymphoma. The results pointed to a 37% excess of leukaemia and non-Hodgkin's lymphoma at the age of 0-14 years old at the time of construction as well as and the following year. When construction workers and operating staff overlapped in areas of high social class then the excess was greater (72%). The overall findings supported the infection hypothesis meaning that children are more likely to develop leukaemia when they come into contact with a large number of people or when there is a population mixing.

Boutou et al.,[31] also conducted a geographical study in Nord Cotentin, France, aiming to investigate the association between population mixing and the occurrence of leukaemia in young people under the age of 25-years. The overall results reported an Incidence Rate Ratio of 2.7 in rural 'communes' that belonged to the highest tertile of population mixing (95% Bayesian credible interval, 95% BCI=1.2-5.9). Furthermore a positive trend was also observed in the rural strata with increasing population mixing (IRR for trend=1.4, 95% BCI=1.1-1.8). Finally the risk became even stronger for acute lymphoblastic leukaemia in children at the age 1-6 years old that where in the highest tertile of population mixing (IRR=5.5, 95% BCI=1.4-23.3). Therefore researchers indicated that their findings were more supporting towards the hypothesis of the infective cause of childhood leukaemia.

Supporting to the above findings was Greaves[24] who argued that children usually linked to the 'infection hypothesis' and population mixing are children who had not gone through any infections in infancy, children that were not socially related to other people in infancy and more probably were first born children.

Endogenous risk factors in childhood leukaemia

Petridou et al.,[33] conducted a nationwide case control study in Greece with the main aim to explore the role of sociodemographic, medical and environmental risk factors, as well as of

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the IGF-1 and IGFBP-3 in the aetiology of childhood leukaemia. The IGF is the Insulin-like Growth Factor-1 hormone and the IGFBP-3 is the IGF principal Binding Protein-3 that are associated with the mediation of the growth hormone. The results indicated that through the three risk factors (gender, birth weight and maternal anaemia) for childhood leukaemia examined in the study the IGF-1 was positively associated with birth weight (p=0.0001), whereas girls had higher levels of IGFBP-3 (p=0.01).

In a meta–analysis of 18 epidemiologic studies of the association between birth weight and childhood leukaemia risk by Hjalgrim et al.,[34] it was found that children weighing 4,000g or more at birth were at higher risk of acute lymphoblastic leukaemia than children weighing less (odds ratio (OR) = 1.26, 95% confidence interval (CI): 1.17, 1.37). The studies included information on more than 10,000 children with leukaemia. The analyses demonstrated a significantly increased risk of ALL in children with high birth weights (>=4,000 g vs. <4,000 g). Importantly, most studies, although not all, demonstrated a clear dose-response relation between birth weight and leukaemia risk, with ALL risk increasing approximately 14 percent per 1,000-g increase in birth weight. The association between birth weight and leukaemia risk was observed consistently in studies conducted over a period of more than 40 years.[34]

Discussion

ALL and AML are the most common malignancies of childhood. Despite many advances in the treatment of childhood leukaemia, the causative factors remain unclear. Identifying risk factors for childhood leukaemia is an important step in the reduction of the overall burden of the disease. Even though several risk factors have been identified in the literature, these remain controversial and only a few of these can be strongly associated with the development of childhood AML or ALL.

This review indicated that parental exposure to chemicals, parental occupational exposure, EMF, intramuscular vitamin K, population mixing (infections), nuclear power plants and ionising radiation and endogenous factors (body weight, IGF-1, IGFBP-3) can all be considered as risk factors for the development of childhood leukaemia. Some factors were found to be strongly associated with childhood leukaemia (EMF, benzene and ionizing radiation) and others weakly associated

(intramuscular vitamin K, endogenous factors).

Exposure to electromagnetic fields has been shown to induce chromosomal breaks and lymphoblastic transformation in experimental studies. However, the results of clinical studies are conflicting. Measurement of exposure is difficult, given that electromagnetic field not only exists near high voltage powerlines, but is also generated by several equipments including computers, television monitors and cellular phones.

The effects of paternal occupation and exposure to some chemicals including pesticides on the development of childhood cancers have also received attention by the literature. Contaminations in drinking water, food additives, pesticides in environment can expose children particularly living in rural area.

The association of higher birthweight and the risk of the development of ALL is an area of controversy as well. Studies show that accelerated fetal growth may be a risk factor for childhood ALL, a tenet supported by evidence that both are related to increased levels of IGF-I. Support is also provided by a recent study in which McLaughlin et al.,[35] reported an increased risk of ALL among children with birth weights greater than 3,500 g, but only if the mothers weighed less than 80 kg--that is, when fetal growth was greater than expected.

Large epidemiological studies have documented that ionizing radiation under certain conditions of exposure induces human cancers including leukemia. In a study by the American National Academy of Science[36] prenatal exposure to ionizing irradiation during the first trimester was found to be associated with five fold increased risk of childhood cancers and when the exposure occurred beyond the first trimester, the risk has been shown to be increased 1.5 folds.

The role of viral infections in the pathogenesis of leukemia has frequently been brought to the attention. Although it has not been confirmed in humans, many viruses have been shown to induce leukemogenesis in animals. In immunocompromised individuals the Ebstein Barr virus (EBV) has been shown to cause lymphoproliferative disorders, and in its most aggressive form, EBV infections can result in chromosomal breaks, translocation and malignant transformation to a monoclonal proliferation.

Considering the great number of different risk factors identified from the research articles it will be wise to say

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that as long as the real cause of childhood leukaemia remains unknown then researchers, scientists and medical professionals will always be investigating anything and everything in order to find the real cause. Some risk factors can trigger the development of the disease and therefore the respective public should not be kept in the dark.

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ANNEX

Table 1. Systematic Reviews, meta-analysis

REFERENCE	INCLUDED STUDIES	SEARCH STRATEGY	JOURNAL
Hjalgrim et al 2003	18 Epidemiologic Studies	Medline or Embase database	Am J Epidemiol

Table 2. Pooled analysis studies

REFERENCE	COUNTRY	AIM	DATA DESCRIPTION AND METHODS	METHODS	TOOL FOR ANALYSIS	JOURNAL
Schuz et al 2000	Germany	To test the hypotheses that parental occupational exposure to hydrocarbons at work might pose a risk for childhood leukaemia.	3 large scale population based case-control studies: • Cases: children diagnosed with cancer before the age of 15-years. Total number of cases was 1138. • Controls: in all studies matched for gender and date of birth within 1-year except one study that controls were also matched for community. Total number of controls was 2962.	• Self-administered questionnaire, which listed a number of chemicals to which parents might have been occupationally exposed. • Telephone interviews with both parents	• Logistic Regression model • Conditional Logistic Regression model	Cancer Epidemiology, Biomarkers & Prevention

Table 3. Case-control studies

Reference	Country	Aim of study	Cases	Controls	Data collection	Tool for analysis	Journal
Brondum et al. 1999	Minnesota USA	To report the relation of parental smoking to the risk of childhood acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML)	• Identified by the CCG • Newly diagnosed with leukaemia between January 1989 and March 1993 for AML and June 1993 for ALL. • Younger than 15 years old at the date of diagnosis for ALL and; • Younger than 18 years for AML. • Have a telephone at home and an English-speaking mother available for an interview	• Random digit dialling • Matched to age, race and telephone area code and exchange • Matched case-control sets were 1842 for ALL and 517 for AML • 1842 case-control mothers interviewed • 1618 case-control fathers interviewed	• Telephone interviews by using a structured questionnaire	• Conditional Logistic Regression model	Cancer
Cocco et al. 1996	Carbonia Italy	To investigate the aetiology of a	• Identified from hospital units • Diagnosed	• Selected from the birth register of municipality of	• Interviews with the parents of cases and controls at their	• Unconditional logistic regres	Archives of Environmental

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		childhood acute lymphoblastic leukaemia cluster in Carbonia, in Italy	between 1974 and 1989 • 9 cases	Sardonia • Matched to gender and date of birth • 36 controls	residences • Questionnaires	sion model	Health
Costas et al. 2001	USA	To identify factors potentially responsible for the cluster of 1981 in Woburn for childhood leukaemia	• Identified by the MCG • Diagnosed with leukaemia prior to their 19th birthday and within January 1969 and August 1989 • Residents of Woburn at the time of diagnosis. • The number of cases were 19	• Selected by random from the WPSR • Matched on race, sex and date of birth • Residents of Woburn at the time of diagnosis of cases • The number of controls were 37	• All parents interviewed in person and; • Mothers and fathers were administered with a different questionnaire	• ANALYSIS • STATCALC • Conditional Logistic Regression model	The Science of the Total Environmen
Draper et al. 1997	Great Britain	To test the 'Gardner hypothesis' that childhood leukaemia and non-Hodgkin's lymphoma can be caused by fathers'	• Identified by the NRCT, the OSCT and the Scottish study (Kinlen at al., 1993) • Diagnosed before the age of 15 y • Born and	• Identified by OPCS • Matched on same area of birth, sex and date of birth within 6 months • Some of the controls already available from the two	• Information about parents of cases-controls obtained from the previews studies and from the Office of Population Censuses	• Conditional Logistic Regression model by means of the PECAN statistical	British Medical Journal

		exposure to ionising radiation before the conception of the child	diagnosed with cancer in Britain between 1952-1986, for Scotland diagnosed with leukaemia and non-Hodgkin's lymphoma between 1987-1990	previous studies • Total number of cases-controls sets was 35,949	and Surveys • Also information from the NRRW	package	
Feychting and Ahlbom 1993	Sweden	To test the hypotheses that exposure to magnetic fields of the type generated by high-voltage power lines increases cancer incidence in children	• Identified through a record linkage to the SCR • Under the age of 16 years old and were diagnosed with cancer (39 leukaemia, 33 central nervous system tumour) • Lived in a property located within 300 meters of any of the 220 and 400 kV power lines	• Controls selected at random from the study base • 4 controls per case • Matched on year of birth, sex and lived in the same parish during the year of case diagnosis and had to live near the same power line as the case • A total number of 558 controls	• Exposure assessment performed by spot measurements and calculations of magnetic fields that were generated by power lines, taking distance, line configuration, and load into account. • Information gathered for historical loads on the power lines were	• Spearman rank correlations used for comparison of calculated and measured magnetic fields • Conditional Logistic Regression model	American Journal of Epidemiology

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			during the years 1960 to 1985. • A total number of 142 cases		used in order to calculate the magnetic fields for the year closest to the date of diagnosis		
Hjalmars et al. 1994	Sweden	To evaluate the risk of acute childhood leukaemia in areas of Sweden contaminated after the Chernobyl reactor accident in April 1986	• All Swedish children aged 0-15 years were marked on a digitised map and were narrowed down to place of household from 1982-1988. • A background of 1.6 million children was distributed among 1 million data points. • A number of 888 cases of ACL were identified and diagnosed between 1980-1992 and marked in the same	• Children diagnosed between June 1986 and December 1992, after the accident in the highly contaminated areas were compared with children diagnosed in the same areas from January 1980 to May 1986, before the accident.	• The Swedish Geological Company measured the radiation exposure between May and October 1986 using an airborne spectrometer in order to register nuclide radiation	• Geographical information system, ARC/INFO	British Medical Journal

			way on the map				
Infante-Rivard et al. 2002	Quebec Canada	To evaluate the relation between childhood ALL and parental alcohol consumption in the month before conception, as well as during pregnancy and the nursing period. The study was divided into a case-control study and into a case-only study	Case-control study: • Selected from tertiary care centres • Diagnosed with ALL at the age of 0-9 years between 1980 and 1993 • A total number of 491 cases Case-only study: • Employed a number of 186 cases that were identified at the largest paediatric centre in	Case-control study: • Selected from family allowance files • Matched on age, sex and region of residence at the time of case diagnosis • A total number of 491 controls Case-only study: • No controls employed for this part of the study	Case-control study: • Telephone interviews with parents of case-control sets by using a structured questionnaire • Mothers and fathers interviewed separately Case-only study: • Genomic DNA was extracted from cells derived either from mouth epithelium, peripheral blood or	Case-control study: • Conditional Logistic Regression model Case-only study: • Unconditional Logistic Regression Model	Epidemiology

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			the providence		bone marrow		
Li et al. 1998	Taiwan	To examine the risk of leukaemia in children living near High-Voltage Transmission Lines (HVTL) in Taiwan	• Between 1987 and 1992 in three districts of northern Taiwan • 28 new cases of childhood leukaemia were diagnosed and reported to the National Cancer Registration Centre of Taiwan	• Compared to all the children in Taiwan	The households in the three districts were categorized using utility route maps and were split into two categories: • Households within (considered as exposed) and; • Households outside 100m on each side of HVTL	Expected (EXP) number of cases of childhood leukaemia among exposed children was calculated and multiplied. SIRs were estimated by dividing the observed number of leukaemia cases (OBS) by the expected (EXP)	Journal of Occupational & Environmental Medicine
London et al. 1991	Los Angeles USA	To address the hypothesis that childhood leukaemia	• Cases and controls included from a previous study (Lowenga	• Selected by random digit dialling procedure • Matched on sex, age	• Telephone interviews with both parents of cases and controls • Based on	• Spearman rank • Conditional Logistic Regres	American Journal of Epidemiolo

		is related to increased exposure to electric and magnetic fields in Los Angeles	rt et al., 1987) were 123 between 1980-1984 • Cases added were children newly diagnosed with leukaemia a between 1980 and 1987 at the age of 0-10 years and also had to be residents in Los Angeles County, California • Identified from the Los Angeles CCSP The total number of cases 232	and ethnicity (black, white, Hispanic and Asian) • The total number of controls was 232	a questionnaire	sion model • Denver Werthe imer-Leiper wiring configuration • Kaune wiring configuration • Wye/Delta wiring configuration	gy
Lowengart et al. 1987	Los Angeles USA	To investigate the possible etiologic factors for childhood leukaemia related to	• Identified from the Los Angeles CCSP • Children with acute leukaemia 10 years or less at	• Selected from friends of cases whenever possible or by random digit dialling • Matched on age,	• Telephone interview between the years 1983-1985 • Using structured questionnaires	• Conditional Logistic Regression model	Journal of the National Cancer Institute

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		parents occupational and home exposures.	the time of diagnosis between the years of 1980 to 1984 • The biological mother to be available for interview • 123 cases	sex, race and Hispanic race for white • Controls also met specific age-matching criteria and race with a result to match on socio-economic status too.			
McBride et al. 1999	Canada	To show if there is an association between exposure to power-frequency EMF and the development of childhood leukaemia.	• Identified through paediatric oncology treatment centres • Children with leukaemia at age 0-14 years between January 1990 and December 1994 (June 1995 for British Columbia and Quebec) • Residents in census tracks within 100 Km of the principal cities of British Columbia, Alberta, Saskatchewan,	• Selected randomly from provincially based government health insurance rolls • Matched on age, area and sex • A total number of 526 controls	• Interviews by using a standardised questionnaire • EMF exposure consisted of personal 48-hour measurement using a position EMF meter worn in a small backpack and a 48-hour EMF measurement of the child's bedroom	• Used a positron meter for exposure measurement • Conditional Logistic Regression model on strata	American Journal of Epidemiology

			Manitoba and Quebec • A total number of 445 cases				
McKinney et al. 1998	Scotland	To test the postulation of a link between neonatal intramuscular vitamin K and childhood leukaemia and other cancers in the population of Scotland.	• Cross checked with the Scottish Cancer Registration Scheme and the National Register of Childhood Tumours in Britain • Children from (0-14) years diagnosed with leukaemia and cancer between 1991-1994 while residents in Scotland • Total number of cases selected was 417	• Selected by random from all eligible children registered for primary care within each health board • Matched on age, sex and health board of residence • The total number of selected controls was 777	• Interviews with the mothers of subjects • Abstraction of medical notes	• STATA • Conditional Logistic Regression model	British Medical Journal
Meinert et al.	German	To investigate	NW part: • Identified	• Selected from complete	• Structured questionn	• Conditional Logisti	American

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1999	y	the associations between sources of exposure to ionising radiation and childhood cancer in Germany. Two parts of the study: NW (nationwide) and the NI part (restricted to geographical areas around nuclear installations and selected control regions).	from the GCCR • Children with acute leukaemia, NHL and a group of solid tumours under the age of 15 years between October 1992 and September 1994 and lived in West Germany on the date of diagnosis NI part: • Children with acute leukaemia or NHL diagnosed between January 1980 and September 1994 age less than 15 years born after July 1975 and living in a nuclear installation area Total number of cases were 1184 leukaemia	files of local offices for the registration of residents • Randomly selected one control per case individually matched for sex, date of birth within 1 year and district of residence Same criteria for controls for both parts of the study existed Total number of controls were 2588	aires and followed up telephone interviews	c Regression model using the PHREG procedure for SAS 6.12 • SAS procedure PROC PHREG	Journal of Epidemiology

			cases, 234 NHL and 940 solid tumours				
Meinert et al. 2000	Germany	To examine the possible link between exposure to pesticides and diagnosis of different types of leukaemia in Germany	• Same as above	• Same as above	• Structure questionnaires (developed by the USA CCG) were mailed to parents of subjects • Followed up telephone interviews	• Conditional Logistic Regression model using PHREG procedure for SAS 6.12 • In case of sparse data the LogXact software program	Cancer Epidemiology, Biomarkers & Prevention.
Michaelis et al. 1997	Germany	To explore the potential health hazards and possible causes of childhood leukaemia due to the electromagnetic fields in	• Identified from the GCCR • All newly diagnosed children with leukaemia under the age of 15 years between July 1988 and June 1993 and residents	• Selected randomly from the files of government offices for registration of residents • Matched on gender and date of birth • Two sets of controls divided into 305 local	• Questionnaires mailed to participants • Telephone interview to for completion of information Exposure assessment	• Conditional Logistic Regression model (SAS 6.08, PROC PHREG)	Cancer Causes & Control

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		Germany	of Lower Saxony • A total number of 219 cases	controls and 308 state controls • A total number of 613 controls	estimated by: • Measurement of magnetic field over a 24-hour • Indoor spot measurements		
Naumburg et al. 2002	Sweden	To assess the risk for childhood leukaemia following perinatal exposure to infection during the entire pregnancy of the mother and infections during the first two weeks of neonatal life	• Identified from the Swedish birth Register and NCR • Included all live born infants from 1973 to 1989 • All cases identified were 652 with childhood leukaemia (578 cases of Lymphatic leukaemia and 74 cases with myeloid)	• Randomly chosen from the computerised Swedish Birth Register • Matched on sex and same year and month of birth. • Total number of controls were 652	• Antenatal, obstetric and other standardise medical records were retrieved	• Conditional Logistic Regression model • Statistical software STATA	Medical & Pediatric Oncology
Passmore et al. 1998	England and Wales	To investigate whether there was a possible link between neonatal	• Children with cancer born in selected hospitals, from 1968 to 1985 and	• Identified from hospital birth registers. Randomisation took place • Matched on	• Obtaining medical records from selected hospitals	• Standard Conditional Logistic Regression model	British Medical Journal

		vitamin K administration and childhood cancer in England and Wales	were diagnosed from 1969 to 1986 • Total number of cases 523	sex, month of birth and hospital of birth • Total number of controls 523			
Petridou et al. 2000	Greece	To explore the role of sociodemographic, medical and environmental risk factors, as well as of the IGF-1 and IGFBP-3 in the aetiology of childhood leukaemia.	• 118 children with acute leukaemia, between 0-14 years of life	• Selected from 5 teaching children hospitals in Athens • Children with mild acute conditions that required short hospitalisation (minor ear, nose, throat or eye conditions) • Matched on gender, age and residence • Total number of controls was 118	• A pre-coded questionnaire • A blood sample was drawn in combination with hospital routine procedures. • Coded, frozen blood samples were shipped from Athens to Beth Israel Hospital where the IGF-1 and IGF-2 were determined.	• IGF-1 concentrations measured with immunoradio-metric assay kit • IGF-2 measured with a new developed radioimmuno-assay kit • Multiple logistic regression model	Cancer Causes & Control
Pobel and Viel 1997	France	To investigate the association between childhood leukaemia	• Identified from local and regional hospitals and pathology laboratori	• Selected from general practitioners • Matched on sex, age, place	• Face to face interviews with the parents of selected subjects by using a	• Exact Conditional Logistic Regression modul	British Medical Journal

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		and established risk factors or other factors related to La Hague nuclear waste reprocessing plant, in France	es • Children with leukaemia diagnosed between January 1978 and December 1993, under the age of 25 years • Residents in the study area (within a 35Km radius of the nuclear plant) • The total number was 27 cases	of birth and place of residence • A total number of 192 controls	detailed structured questionnaire • Obtained permission from parents to access their occupational records	e of the LogXact computer package	
Shu et al. 1988	Shanghai China	To explore suspected risk factors for childhood leukaemia in relation to specific cell types in the Shanghai urban area during 1985 to 1986 in China	• Identified from the population-based tumour registry of the Shanghai Cancer Institute • All the children diagnosed with childhood leukaemia younger than 15 years and diagnosed between	• Randomly selected from the general population of Shanghai and matched in a 2:1 ratio to cases on sex, and birth calendar year • Total number of controls were 618	• In person interviews	• Unconditional Logistic Regression techniques	Cancer Epidemiology, Biomarkers & Prevention.

			July 1974 and June 1986 in the Shanghai urban area • Total number of cases were 309				
Shu et al. 1999	Minnesota USA	To conduct an in-depth evaluation of association between parental occupational exposure and the risk of childhood leukaemia in their offspring Used a recently completed study by the Children's Cancer Group	• Identified by a CCG institutions • All children with ALL under the age of 15 years between January 1989 and June 1993 • A telephone in the case's residence should exist • The biological mother had to speak English and be available for an interview • Total number of cases were	• Randomly selected by using a random digit dialling procedure • Matched on age, race and telephone area code and exchange • A telephone in the case's residence should exist • The biological mother had to speak English and be available for an interview • A total number of 1986 controls	• An independent telephone interview with the parents of cases and controls using a structured questionnaire, which was already sent to the families prior to interview	• Conditional Logistic Regression model • Unconditional Logistic Regression techniques	Cancer Epidemiology, Biomarkers & Prevention.

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			1842				
Shu et al. 2002	USA	To evaluate the association between in uterus diagnostic X-Rays and childhood acute lymphoblastic leukaemia and the well-studied relationship of this malignancy to preconception and postnatal diagnostic X-Rays or foetal ultrasound exposure	• Identified by a CCG institutions • Newly diagnosed between January 1989 and June 1993 • Younger than 15years at the date of diagnosis • To live in a home with a telephone • An English-speaking biological mother to be available for interview • A total number of 1842 cases	• Randomly selected by using a random digit dialling procedure • Matched on age, race and telephone area code and exchange • A telephone in the case's residence should exist • The biological mother had to speak English and be available for an interview • A total number of 1842 controls	• Telephone interview with the parents of cases and controls using a structured questionnaire	• Conditional Logistic Regression model • Unconditional Logistic Regression techniques	Cancer Epidemiology, Biomarkers & Prevention.
Soderberg et al. 2002	Sweden	To determine whether exposure to magnetic fields in infant	• Identified from the MBR and NCR • The study included all children with leukaemia	• Selected randomly from the study base • Matched on sex, birth year and month • A total number of	• Information about pre- and neonatal conditions, treatments and incubator treatment	• Conditional Logistic Regression model using the SAS	Epidemiology

		incubators was related to any risk towards childhood leukaemia	born in Sweden between 1973 and 1989 • Traced from the date of birth until diagnosis death or December 1989 • Information on date of death obtained from CDR • Total number of cases were 726	647 complete case-control sets	obtained from medical records at each hospital • Measurements of the magnetic field were made inside the incubator for each incubator model owned by the hospitals in Sweden • The number of the different incubator models was 29, and children included in the study were treated in 17 of the models. • Exposure assessment based on measurements of magnetic fields inside the incubator • Interviews with hospital staff	program PHREG	

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Thomas et al. 1999	USA	To predict long-term magnetic field exposure using the wiring configuration model. Reanalysed the Los Angeles case-control study conducted by London et al. (1991)	London et al. (1991) study: • Identified from the Cancer Surveillance Project children from 0-9 years old from 1980 to 1987 • Number of cases 232	London et al. (1991) study: • Drawn from friends • Number of controls 232	• Information on wiring configuration was sought for each house where the same case-control sets reported of living	• Geometric mean of the EMF magnitudes for over 24-hours • Used a new wiring configuration model that is more precise than the WL wiring configuration model	Bioelectroma-gnetics

ABREVIATIONS
ACL=ACUTE CHILDHOOD LEUKAEMIA
ALL=ACUTE LYMPHOBLASTIC LEYKAEMIA
AML=ACUTE MYELOID LEUKAEMIA
CCG= CHILDRENS CANCER GROUP
CCR= CHILDRENS CANCER REGISTRY
CCSP= COUNTY CANCER SURVEILLANCE PROGRAM
CDR= CAUSE OF DEATH REGISTRY
EMF= ELECTROMAGNETIC FIELDS
GCCR= GERMAN CHILDHOOD CANCER REGISTRY
HVTL= HIGH VOLTAGE TRANSMISSION LINES
MBR= MEDICAL BIRTH REGISTRY
MCR= MASSACHUSSETS CANCER REGISTRY
NCR= NATIONAL CANCER REGISTRY
NRCT= NATIONAL REGISTRY OF CHILDHOOD TUMOURS
NRRW= NATIONAL REGISTRY FOR RADIATION WORKERS
OPCS=OFFICE OF POPULATION CENSUSES AND SURVEYS
OSCT=OXFORD SURVEY OF CHILDHOOD TUMOURS
SCR=SWEDISH CANCER REGISTRY
WPSR=WOBURN PUBLIC SCHOOL RECO