Cancer Investigation, 1:60–75, 2005

ISSN: 0735-7907 print / 1532-4192 online
DOI: 10.1081/CNV-200046402

Taylor & Francis
Taylor & Francis Group

ENVIRONMENTAL CARCINOGENESIS

Environmental and Genetic Risk Factors for Childhood Leukemia: Appraising the Evidence

Patricia A. Buffler and Marilyn L. Kwan
School of Public Health, University of California, Berkeley, California, USA

Peggy Reynolds and Kevin Y. Urayama
California Department of Health Services, Environmental Health Investigations Branch, Oakland, California, USA

Childhood leukemia 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. Confirmed clinical and epidemiologic associations explain less than 10% of disease incidence, leaving 90% of cases with an unclear etiology. To effectively study leukemia in children, one must recognize that this disease has a multifactorial causal mechanism and a heterogeneous biological composition. In addition, the timing of environmental exposures and genetic changes related to disease risk must be considered. This review of both environmental and genetic risk factors for childhood leukemia evaluates the current published literature and synthesizes the available knowledge. Furthermore, attention is directed to expected sources of new advances and the compelling current issues that need to be addressed before further progress can be made. We discuss parental occupational exposures, air pollution, other chemical exposures such as household solvents and pesticides, radiation, dietary factors, immunological factors, socioeconomic status, and genetic susceptibility. We hope to provide the reader with an understanding of the challenge and promise that characterizes the current and future directions in childhood leukemia research.

Keywords Childhood Leukemia; Environmental Exposures; Epidemiology; Genetic Susceptibility; Review

INTRODUCTION

Leukemia is the most common cause of childhood malignancy under the age of 15. With an annual incidence rate of 43 cases per million, leukemia represents 31% of all cancer cases occurring among children younger than 15 years of age.[1,2] About 2,200 cases of childhood leukemia (ages 0–14 years) are diagnosed annually in the United States; 79% of these cases are acute lymphoblastic leukemia (ALL), followed by acute myeloblastic leukemia (AML), chronic myeloid leukemia (CML), and other types.[1,2] Recent molecular studies have demonstrated that leukemia is more heterogeneous than suggested by these groupings. Incidence has shown a modest increase, less than 1% annually, over the past 20 years in the United States, but the rates have plateaued and slightly decreased since 1989.[1,3]

Confirmed clinical and epidemiologic associations explain less than 10% of childhood leukemia incidence, leaving at least 90% of cases with an unresolved etiologic mechanism.[4] The difficulty arises from the fact that pediatric leukemias, like most cancers, have multifactorial etiologies involving the interaction between various aspects originating from the environment as well as human genetics. Established evidence for increased risk of ALL includes sex, age, race, prenatal exposure to x-rays, therapeutic radiation, and specific genetic syndromes while the evidence for increased risk of AML includes race, exposure to specific chemotherapy agents, prenatal exposure to x-rays, and genetic syndromes.[1]

Current evidence suggests that leukemia results from chromosomal alterations and mutations that disrupt the normal process by which lymphoid or myeloid progenitor cells differentiate and senesce.[5–7] The underlying triggers for molecular damage may be inherited during pregnancy and may develop during infancy and childhood. These translocations are a ''hallmark'' genetic event in leukemia. Many leukemia patients have a chromosomal translocation that is often the only observable cytogenetic aberration. These abnormalities help categorize leukemia for treatment strategy and prognosis and may also delineate specific causal pathways to malignancy. Recently, genetic backtracking analyses, using archived newborn blood specimens and pretreatment bone marrow or peripheral blood specimens obtained at the time of diagnosis, have been applied to study the timing of various translocations. To date, a prenatal origin has been established for several chromosomal abnormalities, including t(12;21) *TEL-AML1*, 11q23 *MLL-AF4*, t(8;21) *AML1-ETO*, t(15;17) *PML-RARA*, and inv(16) *CPFB-MYH11*.[8–12] Hyperdiploidy, the most

Address correspondence to Patricia A. Buffler, School of Public Health, University of California, Berkeley, CA 94720-7360, USA; E-mail: pab@berkeley.edu

common chromosomal abnormality, has also been shown to be an in utero event in leukemogenesis.[13,14] The biology of childhood leukemia makes it clear that this cancer is a group of heterogeneous diseases rather than a homogeneous entity.

In addition, the investigation of childhood leukemia requires cognizance of the timing of exposure, regardless of its environmental and molecular origin. Biologic and epidemiological evidence supports the importance of timing when studying childhood cancers.[15] Various animal models have demonstrated preconceptional, in utero, and perinatal carcinogenesis for a variety of types of radiation and chemicals. In contrast, data from human studies have not been as definitive. Nonetheless, the list of suggested human in utero and preconceptional factors continues to grow, including exposure to infectious agents and pesticides. Therefore, emphasis needs to be placed on addressing not only the relevant exposure but also the timing of the exposure during fetal and childhood development.

This review of both environmental and genetic risk factors of childhood leukemia evaluates the current published literature and synthesizes the knowledge gained thus far. Furthermore, comments are made on where new advances will emerge and what issues need to be addressed before further progress can be made. We attempt to delineate between environmental agents and their sources, realizing that these two mechanisms are inextricably intertwined. As for genetic factors, we provide a careful overview of genetic polymorphisms and their associated risks. This review is not meant to be exhaustive. Instead, we have selected papers that we believe are timely and germane to this review. At the conclusion of the paper, we hope to have provided the reader with an understanding of the breadth and excitement that characterizes the current and future directions in childhood leukemia research.

PARENTAL OCCUPATIONAL EXPOSURES

After three decades of research, the role of parental occupational exposures in the development of childhood leukemia remains unclear. Chemical exposures from parental occupations, specifically paternal, were early suspects in the search for causes of childhood leukemia. To date, most studies addressing parental occupational exposures have focused mainly on father's exposure and much less on mother's exposure since mother's occupation was often not available in record-based studies. In addition, some studies that collected data on maternal occupation did not present results for mothers due to the small number of mothers in exposed occupations.[16]

In 1974, the first published study on this topic suggested that mortality from childhood leukemia was elevated in children born to fathers with hydrocarbon-related jobs.[17] Subsequent studies that have investigated these kinds of job exposures have reported mixed results.[18–23] Several investigations have also suggested that parental occupational exposure to solvents, pesticides, metals, paints, or plastics may increase risk, but these findings are not consistent across studies due to specific methodological issues.[24–26] For example, one study found that parental occupational exposures to herbicides, insecticides, and fungicides were related to childhood leukemia regardless of the time period of exposure but attributed these results to the possible differential recall of past exposures by the parents of cases and controls.[27] A more recent study by Schuz and colleagues examined the impact of recall bias in a German population-based case-control study on parental occupational exposures and childhood cancer.[28] They found that fathers reported more occupational exposures during the child's prenatal period as compared to the postnatal period, especially when the time between the exposure and interview was short, and that the subsequent risk estimates could be inflated. Schuz and colleagues also reported that job titles were not a satisfactory substitute for information on specific occupational exposures. Finally, a review of 48 studies by Colt and Blair (1998) on parental occupational exposures and cancer risk in children highlighted several study limitations, including quality of exposure assessment, small numbers of exposed cases, and multiple comparisons, which might explain some of the inconsistencies across studies.[25] The review also emphasized the importance of addressing the relationship between parental occupational exposures and risk of childhood leukemia in a large study with an enhanced protocol for exposure assessment, such as job-specific occupational questionnaires (i.e. job modules).[16,29–32]

Job modules were first suggested by Gerin and Siemiatycki[29] in order to increase the validity of community-based occupational studies. They proposed the following: use in-person interviews to allow more probing about occupational tasks; precede questions about specific exposures with questions about general occupational history; develop specific questionnaires that use indirect questions when exposure is to chemicals rather than common materials; and have industrial hygienists or chemists take a leading role in developing and interpreting the questionnaires. Subsequently, Stewart and Stewart[31,32] at the National Cancer Institute (NCI) suggested modifications to the approach by Gerin and Siemiatycki in a study of adult brain tumors. They developed an interview to obtain a generic work history first, then for particular jobs of interest, the interview branched to job-specific questions to obtain detailed task and exposure information about those jobs. These generic history and branching questions were called modules. Currently, the Northern California Childhood Leukemia Study (NCCLS) has adapted the approaches of Gerin and Siemiatycki and Stewart and Stewart to create a series of job-specific interviews to obtain detailed occupational exposure information in the study of chemical exposures and childhood leukemia.[16,33] With these recent improvements of occupational exposure assessment in relation to cancer risk, more precise estimates of exposure can be anticipated.[16]

AIR POLLUTION

Tobacco Smoke

The passive smoking literature is inconsistent regarding an association of maternal or paternal smoking on the risk of childhood leukemia. Five case-control studies[34–38] reported that parental smoking, either maternal, paternal, or both, had a significant effect on childhood acute leukemia, while a number of case-control studies[39–51] found no association between parental smoking and childhood leukemia. Two large cohort studies reported no significant association between maternal smoking during pregnancy (reported as either yes/no or number of cigarettes) and risk of childhood leukemia.[52,53] Furthermore, a meta-analysis for maternal smoking during pregnancy indicated no statistically significant associations for all leukemia, acute leukemia, or ALL.[54] Possible reasons for these conflicting results stem from two methodological issues, misclassification and bias. Underreporting or over-reporting of smoking during pregnancy by both case mothers and control mothers[55,56] and lack of time- and dose-specific exposure assessment can lead to either differential or non-differential misclassification. Furthermore, failure to adjust for possible confounders such as diet and race and use of random digit dial controls (RDD)[36,48] and/or hospital controls[35,40] can generate biased risk estimates. Future studies addressing parental smoking need to take these limitations as well as inclusion of tumor genetic subgroups of leukemia into consideration during both the design and analysis phase.

Benzene

Benzene is one of a short list of agents that is now considered an established risk factor for leukemia in adults, primarily AML. It has been postulated to play a significant etiologic role in children as well since AML makes up 16% of all childhood leukemias.[1] Although the genotoxic potential of benzene on bone marrow was first proposed a century ago, it was not until the early 1980's that a scientific consensus concluded benzene to be an etiologically relevant agent to the development of AML in adults. Since then, numerous studies have consistently reported positive associations between occupational exposure to benzene and adult leukemia.[57–66] A recent collaborative effort between the Chinese Academy of Preventive Medicine and the NCI investigating cancer risk among workers exposed to benzene in China reported statistically significant excess mortality rates and a two- to three-fold increase risk of leukemia in exposed workers.[60]

Exposures to benzene are not confined to occupational settings only but also can be found in the general environment as vehicle and industrial emissions, active and passive cigarette smoke, and food. Knox, in a cluster investigation conducted in the United Kingdom, reported that childhood leukemia cases were distributed non-randomly and occurred closer to industrial sites, pointing to an association with fossil fuels, especially petroleum.[67] More recently, Knox and colleagues conducted a study in a group of 22,458 children who died from cancer in England, Wales, and Scotland between 1953 and 1980 to examine the relationship between the birth and death addresses of these children and sites of potential environmental hazards.[68] Childhood cancers were found to be geographically associated with industrial atmospheric effluents, namely petroleum-derived volatiles, kiln and furnace smoke and gases, and emissions from internal combustion engines. Similarly, a case-control study conducted in France reported an association between acute childhood leukemia and dwellings neighboring auto repair garages and petrol stations.[69] These findings support the hypothesis of a benzene-related etiology and are consistent with studies reporting an increased risk of childhood leukemia associated with parental occupational exposure to solvents containing benzene.[70–74]

Other Air Contaminants

Outdoor air pollution in urban areas is often dominated by a mixture of chemical compounds that originate from motor vehicle emissions. Many of these compounds such as benzene, butadiene, and nitrogen dioxide fall under the classification of hazardous air pollutants (HAPs), which are compounds that have been shown to cause cancer or other adverse health effects in laboratory animals or in occupational health studies. Interest in addressing the question of whether these air pollutants affect risk of childhood leukemia partly comes from the compelling evidence in support of the causal relationship between benzene and AML in adults. Although still fairly limited, previous studies on this topic have provided mixed results, and the relationship remains controversial. Several studies have reported associations between childhood cancers and surrogate measures of exposure to motor vehicle exhausts including traffic density, vehicle density, and estimated concentrations of nitrogen dioxide and benzene.[68,75–81]

For example, in 1989, a study in Denver, Colorado that assigned traffic density measures to street addresses of cases and controls reported a nearly five-fold increase in risk of leukemia among children who resided on streets with the highest traffic density scores compared to those residing in the lowest.[76] A recent re-analysis of this same data after refining the exposure measurements with geographic information system (GIS) techniques yielded an even larger risk estimate associated with childhood leukemia for the highest traffic density category.[80] A Swedish study estimated nitrogen dioxide concentrations in outdoor air around the homes of cases and controls and found a positive association between the highest exposure category and childhood cancer.[78] Estimated mean concentration of benzene outside the home was also associated with leukemia according to a report from an Italian case-control study.[81] Finally, studies conducted in the United Kingdom used proximity to main roads, gasoline stations, or railways to indicate air pollutant exposure and reported results that were suggestive of an increased risk of

childhood leukemia.[79,82] Recently, modeled HAPs data at the census tract level provided by the U.S. Environmental Protection Agency along with cancer potency factors were used to estimate exposure scores for 25 potentially carcinogenic HAPs in California.[83] An elevated rate ratio was found for childhood leukemia in the tracts ranked highest for exposure to the combined group of 25 HAPs and in tracts ranked highest for exposure to HAPs emitted primarily from point sources.

In contrast, recent studies conducted in California and Denmark that used similar proxy measurements of exposure to vehicle exhaust as those used in other studies did not find an increased risk of childhood leukemia.[84–87] Both the San Diego and Los Angeles studies assessed traffic density with methods used in the Denver study, but neither was able to confirm the association. Similarly, two other California studies, one ecologic and the other case-control in design, found no significant association between traffic exposure patterns (vehicle density, road density, and traffic density) and childhood cancer.[85,87] Furthermore, an elevated risk was not found in a well-designed Danish study that utilized a large sample population, minimized recall and participation bias by relying on registry-based information sources, and used a detailed exposure assessment protocol.[84] The large inconsistencies observed in the air pollution and childhood leukemia literature may be due, in part, to relative differences in modeling techniques and exposure assessment protocols and variations in individual genetic susceptibilities of the at risk populations sampled between studies.

OTHER CHEMICAL EXPOSURES

Household Solvents

Few studies have examined the risks of childhood leukemia associated with exposures to solvents in the home other than pesticides. Common household exposures may occur as a consequence of a child's or their parents' hobbies such as painting, model building, or home maintenance activities. A review of studies addressing environmental agents and childhood cancer by McBride found suggestive associations with exposures to paints, petroleum products, solvents, pesticides, and metals.[88] More recently, the risk of childhood ALL was linked to frequent exposure to artwork using solvents and also among children whose mothers lived in homes painted extensively in the year before the children's birth.[89] The association between solvents and household chemicals and childhood leukemia remains an important but inadequately addressed question.

Pesticides

Pesticide is a term used to refer to any one of a number of chemical agents designed to kill insects, weeds, fungi, rodents, and other unwanted animals and plant life. The pathways by which children may be exposed to, or suffer the effects of, pesticides include prenatal parental occupational exposure, parental occupational ''take home'' exposure, direct inhalation of ambient air around agricultural settings, use of pesticides in the home, ingestion of contaminated household dust, and pesticide-treated foods. There is growing evidence in support of the association between pesticide exposure and childhood leukemia. Most of the studies evaluating exposure to household pesticides and risk of childhood leukemia suggest that an increased risk is associated with in utero and postnatal pesticide exposures, although the subtype of leukemia, definition of exposure, and exposure period of interest differed in these studies.[27,72,90–96]

Elevated risks have been consistently associated with no-pest strips and home use of pesticides,[72,90,93,95,96] but associations with professional extermination and garden pesticide use have been mixed.[27,90,91,93–96] Few studies have examined specific subtypes of leukemia risk associated with pesticide exposure. The Children's Cancer Group (CCG) reported an increased risk of acute non-lymphocytic leukemia associated with a child's direct exposure to household pesticides.[72] A few years later, the CCG reported a significant association between both child and parental exposures to insecticides and common ALL, but not for other major subtypes of ALL,[92] suggesting possible etiologic differences among these subclassifications. Two other studies examining childhood ALL also reported elevated risks associated with insecticide exposure, but were inconsistent regarding the risk related to herbicides and outdoor pesticide use.[95,96] The NCCLS demonstrated the importance of timing and location of exposure by showing differential risk estimates between various prenatal and postnatal time periods and between indoor and outdoor pesticide uses.[96] The highest risk was observed for insecticide exposures during pregnancy and gradually decreased for exposures occurring in the subsequent years, becoming non-significant by the third year of life. Furthermore, this same trend was observed for exposures to indoor pesticides but not for outdoor pesticides.

Studies examining the degree to which agricultural pesticide use contributes to a child's overall exposure to pesticides are limited. A recent ecologic study in California found little evidence of an association between agricultural pesticide use density and childhood cancer incidence rates.[97] Likewise, a statewide case-control study of early childhood leukemia found little evidence of risk differences among children living near areas of intensive agricultural pesticide use.[98] Although the findings from these studies are in contrast with the associations observed with household exposures to pesticides, the authors note that it does not discredit the possibility of a real association with pesticides in general since little is known about the role of timing of exposure, and the specific pesticides examined in these studies are different from those used around the home. Studies to date provide evidence of some involvement of pesticides in the

etiology of childhood leukemia. However, issues of timing, type of agent, and pathway of exposure require further investigation using studies with larger sample sizes and refined exposure assessment.

RADIATION

Ionizing Radiation

In 1956, Stewart and colleagues in the United Kingdom released the first report of an association between in utero exposure to low-dose ionizing radiation from diagnostic radiography and childhood cancer.[99] Although initially received with skepticism, subsequent studies, most of which were case-control in design, have reported consistently a 40% increased risk of childhood leukemia and other cancers after in utero exposure to ionizing radiation.[100–103]

The causal relationship has been the subject of controversy for the past forty years with the argument that case-control studies are highly prone to the effects of recall bias, studies evaluating the effects of the atomic bomb in Japan do not support the association, and experimental studies have not substantiated a clear link.[103,104] Furthermore, earlier cohort studies conducted in the United Kingdom and the United States did not find evidence of an association between maternal pelvimetry during pregnancy and childhood leukemia.[105,106] However, Doll and Wakeford, in a recent review on the topic of fetal irradiation and childhood cancer, concluded that recall bias or confounding with obstetric conditions cannot plausibly explain the associations reported, and the evidence in support of an increased risk of childhood cancer after exposure to ionizing radiation, particularly in the third trimester, is strong.[103] The issue of recall bias had been addressed with the publication of studies showing positive associations that used medical records to assess ionizing radiation exposure instead of relying on the recall of the mothers.[107-109] A dose response effect has also been reported where the risk of childhood cancer was found to increase with the number of x-ray films.[110]

Earlier studies of radiation-induced mutations indicated that essentially no mutations were observed in immature resting oocytes.[111] However, recent studies in mice revealed that significant genetic damage can result from the irradiation of these female reproductive cells.[112] In addition, point mutations and structural rearrangements appear to occur de novo far more frequently in males than females and arise in the preconception period.[111] Currently, in utero low-dose ionizing radiation exposure is recognized as an established risk factor for childhood cancers under the assumption that the fetus may be more susceptible to the leukemogenic effects of radiation than the child. Recent molecular studies support this assumption where chromosomal abnormalities common to pediatric leukemia have been tracked to a prenatal origin and are considered key events in the leukemogenic process.[8–12] The medical community has responded accordingly by replacing, to a great extent, pelvimetric x-rays with ultrasound procedures.

Results from studies evaluating the effect of postnatal diagnostic irradiation exposure on risk of childhood leukemia have been inconsistent.[71,101,113–116] A Canadian study recently reported statistically significant elevated risks of leukemia in children having two or more postnatal diagnostic x-rays.[116] Their results also suggest that the effect of postnatal diagnostic irradiation on childhood leukemia may be modified by variants in DNA repair genes, including *XRCCI*, *hMLH1*, *hMSH3*, and *APE*. Previous to this report, large-scale studies conducted in China and Germany did not find statistically significant associations between postnatal diagnostic irradiation and childhood leukemia, even in those children receiving four or more x-rays.[115,117] Some authors have noted a likely involvement of confounding and information biases in their studies and recommend that future studies address these issues. Therefore, the relationship between postnatal diagnostic irradiation exposure and childhood leukemia is inconclusive given that the literature on this topic is still fairly limited.

The long-standing interest in potential risks from exposure to ionizing radiation has also carried over into community concerns about proximity to nuclear installations. This was accentuated in the late 1980's in response to a provocative series of investigations of excess incidence of leukemia and lymphoma among children and young adults living near the Sellafield nuclear fuels processing plant in England. Gardner and colleagues reported that the community excess incidence was associated with residential proximity to the Sellafield plant, with having a father employed at the plant, and with higher levels of measured radiation dosimetry among those fathers.[118] Follow-up studies, however, failed to find a clear pattern of such geographic excesses near other nuclear installations in Britain,[119-121] nor similar relationships in areas outside of Britain.[122-124] A number of more likely explanations have been offered for the observed excess of cases near Sellafield ranging from that of expected statistical variations in small area analyses[125] to support for the hypothesis of population-mixing advanced by Kinlen.[126-128]

Non-ionizing Radiation

Since the first study of childhood cancers and wire codes by Wertheimer and Leeper in 1979,[75] numerous epidemiologic studies have examined the potential association between various measures of extremely low frequency magnetic fields (ELF-MF) exposure and development of childhood leukemia and other childhood cancers. All recent expert evaluations concluded that there might be an association between childhood leukemia development and exposure to ELF-MF. The National Institute of Environmental Health Sciences (NIEHS) Working Group reported that there is limited evidence that residential exposure to ELF-MF is carcinogenic in

children.[129] The National Radiological Protection Board (NRPB) in the United Kingdom stated that relatively high average exposure to ELF-MF (0.4 μT or more) is associated with a doubling of the risk of childhood leukemia.[130] The International Agency for Research on Cancer (IARC) classified ELF-MF as a possible carcinogen in June 2001.[131] The International Commission for Non-Ionizing Radiation Protection (ICNIRP) Standing Committee on Epidemiology concluded that among all the health outcomes evaluated in epidemiologic studies of ELF-MF, the strongest evidence for an association exists between childhood leukemia and postnatal exposure to magnetic fields above 0.4 μT.[132]

Expert reviews completed after 2000 were strongly influenced by the results of two pooled analyses of epidemiologic studies of magnetic fields and childhood leukemia.[133,134] One of the pooled analyses, by Greenland and colleagues,[134] included original data from 15 epidemiologic studies of magnetic fields and childhood leukemia. Twelve of the included studies had data on measured or calculated magnetic fields. Based on these 12 studies, there was no association between childhood leukemia and magnetic fields below 0.3 μT. However, the summary odds ratio for magnetic field exposure above 0.3 μT as compared to exposure below 0.1 μT was 1.7 with 95% confidence intervals at 1.2 and 2.3. Results from the individual studies were consistent with the pooled results.

In the other study, Ahlbom and colleagues[133] conducted a pooled analysis of 9 epidemiologic studies of magnetic fields and childhood leukemia. Studies with calculated magnetic fields (4 studies) and 24 or 48-hour measured fields (5 studies) were included. There was no apparent association between magnetic fields and childhood leukemia below magnetic field exposure levels of 0.4 μT. However, the summary odds ratio for exposure above 0.4 μT as compared to exposure below 0.1 μT was 2.1, with 95% confidence interval at 1.3 and 3.3. In both pooled analyses,[133,134] the most influential study with the largest number of cases in the highest analyzed magnetic field exposure category was the study conducted by the NCI in the United States.[135]

In spite of the consistent epidemiologic findings, it remains unclear as to whether or not this association is causal in nature. A potential causal relationship between particular physical characteristics of ELF-MF exposure and childhood leukemia is one of the possible explanations for the consistently found association between ELF-MF and childhood leukemia in epidemiologic studies.[136] However, the lack of convincing experimental evidence in either cellular or animal studies designed to examine the biological effects of environmental ELF-MF exposure on cancer development has been frequently cited as a major argument against a causal explanation.[129,137]

Among potential alternative explanations, the role of confounding has been examined extensively.[129,138,139] In spite of this research, no single confounder or set of confounders has been identified so far which could fully explain the observed epidemiologic association. Although the lack of an identified confounder should not strengthen one's belief in causality, it has been repeatedly used as an argument for a causal relationship between ELF-MF and childhood leukemia.

Measurement error and misclassification are also considered among the potential major sources of error in the ELF-MF—childhood leukemia epidemiologic studies. It is mostly agreed, however, that exposure misclassification is likely to be non-differential. Although the possibility of differential misclassification in selected studies has also been raised, the direction and magnitude of these types of errors remain speculative.[140,141]

Selection bias has been repeatedly discussed by expert review panels (ICNIRP, IARC, NRPB) as the most likely candidate for providing a non-causal explanation for the apparent association between EMF and childhood leukemia. In its recent recommendation, the European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment also suggested that assessing the role of selection bias in the ELF-MF—childhood leukemia association should be a high priority research area.

A limited number of studies have addressed directly the issue of selection bias and have attempted to identify and quantify the direction and magnitude of bias.[138,142–146] Gurney and colleagues assessed the relationship between family income and wire codes and found that lower family income tended to be associated with higher wire codes.[144] They estimated that differential participation of cases and controls by their income status could result in an upward bias of the high wire code and childhood leukemia association in a case-control study; the odds ratio would be inflated by 1.03 to 1.24-fold. Jones and colleagues reported that people who changed addresses more frequently (high residential mobility) were more likely to live at an address with higher wire codes.[143] They argue that studies with differential case-control participation based on mobility may show a spurious association between wire codes and disease status. Spinelli and colleagues further analyzed data from the 1999 Canadian study of EMF and childhood leukemia by McBride and colleagues and found that participating controls tended to live in census tracts with higher average income than did non-participant controls.[146]

The most comprehensive evaluation of the possible role of selection bias was published by Hatch and colleagues analyzing data from the 1997 study by Linet and colleagues.[138] The authors observed that, compared to partial participants, full participants tended to have higher socioeconomic status (higher education, higher income, and more likely to own residence) but were less likely to live in homes with very high wire codes (VHCC) or high measured fields (measurements at front door above 0.2 μT). Most importantly, while the analysis of full participants only showed a slight association between living in a VHCC home and developing childhood leukemia (odds ratio 1.2), the analysis including

all subjects (partial and full participants) showed no association between wire code and childhood leukemia (odds ratio 1.0). Unfortunately, the study had no information on non-participants.

The results of these studies support the argument that selection bias may now be the most critical issue to explore in order to disentangle the likelihood of causal versus artifactual relationships between EMF and childhood leukemia. This bias is likely to result in bias away from the null, resulting in an overestimation of the potential effect of ELF-MF on childhood leukemia incidence. The answer to the question whether selection bias can be regarded as a full explanation for the childhood leukemia-EMF association, however, remains inconclusive.

DIETARY FACTORS

Maternal Diet

There has been little systematic research on maternal dietary factors in childhood leukemia, and the results from this body of research have been limited by incomplete exposure assessment. Most studies of maternal diet have focused on specific food groups such as cured meats,[147–149] supplementation with folate[150] or vitamins A and D,[71] or foods containing topoisomerase II inhibitors[151] and their relationship to childhood leukemia.

Cured meats, which contain *N*-nitroso precursors that can be converted to carcinogenic *N*-nitroso compounds in an acidic environment, have been hypothesized to increase the risk of childhood leukemia either through maternal consumption during pregnancy or child consumption early in life.[149] Sarasua and colleagues and Peters and colleagues examined the impact of maternal consumption of cured meats and risk of childhood leukemia and found no significant association.[147,148] Recently, Jensen and colleagues were the first to produce a comprehensive assessment of maternal diet and childhood leukemia risk.[152] They examined maternal dietary intake of 76 food items as well as questions on vitamin supplements during the year before pregnancy. Among food groups, it was reported that consumption of vegetables, protein sources, and fruits were inversely associated with risk of ALL. As for nutrients, it was found that consumption of provitamin A carotenoids and the antioxidant glutathione were associated with a reduced risk of ALL. No association was apparent for consumption of cured meats and disease risk.

Another intriguing dietary topic is the role of inhibitors of DNA topoisomerase II, an enzyme necessary for gene transcription, DNA recombination, and replication, in maternal diet. Ross investigated maternal exposure to potential DNA topoisomerase II inhibitors and risk of infant leukemia in foods such as beans, fresh vegetables, canned vegetables, fruit, soy, regular coffee, black tea, green tea, cocoa, and wine.[151] She reported a statistically significant positive association with increasing consumption of DNA topoisomerase II inhibitor-containing foods for risk of AML.[151] However, this study was based on an extremely small number of exposed cases ($n = 25$ for medium and high exposures combined) and referent cases ($n = 4$ for low exposure).

Child's Diet

For child's diet, the current literature has mainly examined the effect of cured meats such as hotdogs, ham, bacon, and sausage on risk of childhood brain cancer and childhood leukemia. Most studies[147,153–157] reported no association with consumption of cured meats and risk of either of these two childhood cancers. In contrast, one study[148] described an increased risk of childhood leukemia if the child consumed 12 or more hotdogs per month up to the reference period. The authors were cautious in noting that the positive association could be due to use of RDD controls and/or existence of recall bias by the parents of the cases.

In a more comprehensive study of child's diet and childhood leukemia, Kwan and colleagues found a protective association between regular consumption of both oranges/bananas and orange juice during the first two years of life and risk of childhood leukemia.[157] A strength of this study was the use of a more comprehensive dietary questionnaire asking about the frequency of consumption of nine foods/food groups and vitamin supplements during early childhood. Another study by Fear and colleagues investigated neonatal vitamin K administration and risk of childhood leukemia.[158] They reported no association between vitamin K given by the intramuscular or oral route and risk of disease. Overall, future dietary studies of maternal and especially child's diet need to focus on a broader spectrum of foods using a systematic dietary assessment method, such as a food frequency questionnaire. In addition, because of the importance of timing of exposures during critical developmental periods, both the maternal and child's diet need to be considered together in the causal diagram and statistical model.

IMMUNOLOGICAL FACTORS

Infection and Allergy

An infectious origin of childhood leukemia has been hypothesized for over 65 years.[159] The first documented study on a leukemia cluster was investigated by the Communicable Disease Center (now the Centers for Disease Control—CDC).[160] This cluster consisted of eight cases of childhood leukemia, all living in the same residential neighborhood in a Chicago suburb. This report suggested that leukemia was the manifestation of an infectious process. Thirty years later, Kinlen postulated that childhood leukemia occurs as a rare response to a specific, although unidentified infection(s), commonly seen with the influx of infected persons into a previously sparsely populated area.[126,161,162] On the contrary, Greaves proposed that childhood ALL, and particularly common pre-B cell ALL (a type of leukemia that

usually occurs among children age 2–5 years), is the result of a rare, abnormal response to non-specific common infections.[6,163] Furthermore, two other hypotheses have been suggested regarding the role of immune function in the etiology of hematopoietic cancers. Under the immune-surveillance hypothesis, allergic disorders are protective because of an enhanced ability of the immune system to identify and destroy cells undergoing malignant mutations.[164] In contrast, the antigenic-stimulation hypothesis suggests that conditions which stimulate the immune system, such as infectious diseases and allergies, would be associated with increased risks of lymphoblastic malignancies due to a higher probability for mutations in actively dividing cells.[165]

However, most of the attention in subsequent research has focused on the hypotheses of Kinlen and Greaves. A few recent studies have attempted to test these hypotheses. Population mixing was suggested by an expert panel as a possible explanation for the widely publicized cluster of childhood leukemia cases in Fallon, Nevada,[162] but this continues to be debated.[166] A rather comprehensive analysis of the hypothesis that rapid population movement into rural areas is associated with increased risk of childhood leukemia was conducted by Wartenberg[167] using the Survey, Epidemiologic, and End Results (SEER) data from the United States. Data from this investigation were consistent with Kinlen's population mixing hypothesis.

A large German study examining the association between various markers of infection during early childhood and risk of leukemia reported findings which were weakly supportive of the Greaves hypothesis.[49] Among several characteristics related to the child's immune system and exposure to infectious agents, a significant positive association between fewer routine immunizations and childhood leukemia was the major finding, but the association was noted as being partially explained by reporting bias. In contrast, one study found that extensive contact with other children in a daycare setting was associated with a reduced risk of ALL.[168] A similar protective association with early day care attendance was noted in a large case-control study conducted in France.[169] Similarly, the study by Perrillat and colleagues[170] reported an inverse association between childhood leukemia and daycare attendance, repeated early common infections, and prolonged breastfeeding. Finally, serologic markers of infection were used in a study conducted in Greece which reported an increased risk of ALL in children five years or older who had low herd immunity for several infectious agents.[171]

Other immunologic factors such as allergies and vaccinations may also play a role in the etiology of childhood leukemia.[172,173] One study[173] reported evidence of a protective association between allergic disorders and ALL. The investigators found that children with a history of allergic disorders including asthma, hay fever, food or drug allergies, and eczema have a significantly reduced risk of ALL. In addition, allergic disorders among siblings of the study subjects showed a significant inverse association with ALL, thus suggesting the possibility of an underlying familial or genetic influence. In contrast to these studies, Spector and colleagues collected data on allergic conditions from medical records and found an increased risk associated with atopy or hives and asthma.[174] As a major strength of the study, they had access to dates of allergy diagnosis, which allowed them to ensure that the allergies preceded the diagnosis of ALL and to account for the latent period.

Importantly, the role of maternal infection with cytomegalovirus, Epstein-Barr virus (EBV), and human herpes virus 6 has also been examined in a large case-control study of leukemia among offspring nested within national maternity cohorts in Finland and Iceland.[175] Only EBV immunoglobulin M positivity in EBV-immunoglobulin-G-positive mothers was associated with a significantly increased risk of ALL, suggesting that the reactivation of maternal EBV infection may be associated with childhood leukemia.

Human Leukocyte Antigen

Recently, studies investigating the role of polymorphic alleles of the human leukocyte antigen (HLA) class II genes have reported evidence of an association with childhood ALL.[176–178] The HLA class II genes encode highly polymorphic cell surface glycoproteins that play an important role in adaptive immune response to infections. The most recent study revealed that childhood ALL cases were reportedly more likely to have *HLA-DPB1* alleles coding specific polymorphic amino acids than normal infants or cases with solid tumors.[179] This suggests that susceptibility to childhood ALL may involve the presentation of specific antigenic peptides derived from infectious agents. As a result, activation of helper T cells occurs, which mediates proliferative stress on preleukemic cells.

SOCIOECONOMIC STATUS

In the vast majority of the epidemiologic literature focusing on childhood leukemia, the role of socioeconomic status (SES) in the causal pathway is controversial. Early ecologic and descriptive studies from the United States suggested that higher SES was a possible risk factor for childhood leukemia while early United Kingdom studies reported mixed results.[16] In contrast, case-control studies conducted in the United States and United Kingdom have rarely reported higher SES in cases compared to controls.[16] Further complicating the issue is the fact that SES is often correlated with and may even be a surrogate for certain environmental exposures. Indeed, it has been shown in childhood leukemia studies to be associated with environmental factors such as pesticide use[180] and traffic density[85] and dietary factors such as maternal diet[152] and child's diet.[157] Yet, most investigators choose to adjust for some marker of SES in their statistical models since they almost automatically consider SES as a potential confounder in their analysis. As a result, this process may minimize any main effects of the exposure of

interest in the exposure-outcome causal pathway. Therefore, an important question arises: how should investigators regard and treat SES in the analysis of environmental exposures and childhood leukemia?

To answer this question, SES needs to be thoroughly examined in the causal diagram as a potential confounder in every exposure-outcome relationship under study. It is suggested that the investigator should evaluate confounding by SES using three non-mutually exclusive considerations.[181,182] First, the causal structure of the variables under study must be understood based on prior subject-matter knowledge. Second, the rigorous definition of a confounder must be satisfied (i.e. a confounder is associated with both the exposure and the outcome and does not lie on the causal pathway between the two). Third and finally, the adjusted and unadjusted point estimates in a multivariable analysis must be compared, and if the change in the estimate after adjustment for SES is above a certain value (suggested to be 10%), then SES should be treated as a confounder and adjusted for in the statistical analysis. Therefore, if the second and/or the third consideration(s) are not satisfied, then SES should not be adjusted for in the analysis.

GENETIC SUSCEPTIBILITY

Progress in understanding the role of endogenous and exogenous xenobiotics in the pathway leading to carcinogenesis, together with the rapid advances in human genomics and molecular techniques, has enabled researchers to consider more realistically, the influence of inherited genetic traits in cancer etiology. Genetic factors ranging from predisposing highly penetrant mutations to low penetrant genetic polymorphisms have been shown to significantly influence the interindividual variation in cancer incidence.[183]

Xenobiotic Metabolism and Transport

Genetic susceptibility studies of genes that encode enzymes with critical roles in xenobiotic metabolism and membrane transport have shown associations with an increased risk of childhood leukemia.[50,95,184–194] The complete metabolism of xenobiotic compounds is divided into two phases, each utilizing different sets of metabolic enzymes. The metabolic activation of the xenobiotic performed by the phase I enzymes are usually necessary in order for the phase II enzymes to convert this activated intermediate into a detoxified water-soluble compound that can be easily eliminated from the cell.[195] Genetic polymorphisms that disrupt the equilibrium between these two phases compromise the hosts' ability to respond appropriately to xenobiotics and may potentially increase the hosts' susceptibility to developing cancer.

The cytochrome P450 (*CYP*) superfamily of genes comprises most of the phase I enzyme system, of which *CYP1* and *CYP2* have been particularly considered in the area of cancer susceptibility. Studies have shown that *CYP1A1m1*, *CYP1A1m2*, and polymorphisms of *CYP2E1* increase a child's susceptibility to leukemia.[50,95,185,191] An evaluation of the gene-environment interaction between a child's genotype and pesticide exposure in the risk of childhood leukemia revealed significant odds ratios of interaction among carriers of the *CYP1A1m1* and *CYP1A1m2* polymorphisms.[95]

Polymorphisms in the genes encoding NAD(P)H quinone oxidoreductase 1 (*NQO1*) and myeloperoxidase (*MPO*) of phase I have also recently been associated with childhood leukemia.[186,191,192] A study conducted in the United Kingdom tested a specific hypothesis involving the low function *NQO1* genotype and *MLL* gene rearranged infant leukemias and found a significantly increased risk.[186] These findings were later confirmed in a United States population supporting the idea of a specific causal mechanism in infant leukemias that involves genotoxic exposures in utero.[192] In another study, the *MPO* allele alone was not found to be associated with ALL.[191] However, when considered together with the *CYP2E1* and *NQO1* polymorphisms, the risks conferred by the three polymorphisms were elevated compared to any of them alone suggesting the presence of interaction between multiple loci.

Of the genes that express phase II enzymes, recent studies have been focusing on the glutathione S-transferase (*GST*) and N-acetyltransferase 1 (*NAT1*) and 2 (*NAT2*) polymorphisms as potential risk modifiers of childhood leukemia. The null genotypes of *GSTM1* and *GSTT1*, low function *GSTP1* genotypes, and slow *NAT2* acetylation genotypes were shown to be associated with an increased risk of childhood ALL.[184,185,187,188,190] In addition, the polymorphic *NAT2* genotype, together with the other risk-elevating genotypes of the *GSTM1* and *CYP1A1* polymorphisms had the effect of further increasing the risk of childhood ALL.[187] The same group also found that *GSTP1* variants, alone or combined with other *GSTs*, represent significant genetic determinants of childhood ALL.[190] There have been several reports on the interaction of multiple genes, which include one showing an elevated risk when a child carried both a metabolic and DNA repair polymorphism.[193,196] Overall, there is evidence that genetic susceptibility to childhood leukemia may lie partly in the genes that determine how cells respond to xenobiotic exposures.

Polymorphisms of the multidrug resistance (*MDR1*) gene have recently been implicated in the literature to play a role in the genetic susceptibility to cancers, including childhood leukemia.[194,197] *MDR1* encodes a membrane efflux transport protein that plays a critical role in regulating intracellular concentrations of various lipophilic substrates including metabolites of phase I and phase II processes, naturally occurring xenobiotics, and genotoxic hydrocarbons.[198] The biology of this gene is well documented and there is a wide interest in studying the effects of its functional polymorphisms on clinical outcome of cancer patients, especially those with leukemia. However, studies evaluating its impact on genetic

susceptibility to childhood leukemia are limited.[194,199] One study recently reported a significantly increased risk of ALL in children who carried the homozygous variant genotype of the C3435T polymorphism.[194] There is a need for more studies to evaluate the influence of this gene on childhood leukemia risk.

Folate Metabolism

Low dietary folate intake and alterations in folate metabolism as a result of polymorphisms in the gene encoding methylenetetrahydrofolate reductase (*MTHFR*) have been associated with a variety of diseases, including ALL in both adults and children.[189,200–203] In addition, the recent reported finding of a protective effect of folate supplementation in pregnancy against the risk of childhood ALL further highlights the potential importance of studying genes related to folate metabolism.[150] Low function variants of *MTHFR* result in enhanced thymidine pools and more efficient DNA synthesis and repair capabilities afforded by the increased availability of the *MTHFR* substrate, 5,10-methylenetetrahydrofolate. This may effectively reduce the potential for double strand breaks, which are the precursors to chromosomal translocations and deletions, a molecular phenomenon common in pediatric leukemias. In studies of childhood ALL, the *C677T* and A1298C variants of *MTHFR* was associated with decreased risk suggesting that features of *MTHFR* influence the leukemogenesis process.[189,204] An analysis stratified by year of birth showed that the protective effect is accentuated and present only in children born before 1996, the year Health Canada recommended folic acid supplementation.[204] Another study showed evidence of differential effects of *MTHFR* variants on risk of childhood acute leukemias between molecularly defined subtypes.[203] In a stratified analysis by molecular cytogenetic subgroups, a significant protective association for carriers of the *C677T* variant was demonstrated for leukemias with *MLL* translocations and hyperdiploidy. The *A1298C* variant of *MTHFR* was associated with hyperdiploid leukemias, while *TEL-AML1* leukemias showed no associations with either of the variants. Although these studies yielded interesting findings, the lack of statistical precision remains a challenge that needs to be addressed with larger studies.

Gene-Environment Interaction

Evaluation of gene-environment interactions with a sufficiently large sample size is the next critical step to understanding and assessing the degree to which genetics, together with the environment, influence the development of childhood leukemia. For example, Infante-Rivard and colleagues assessed the roles of variant *CYP1A1* alleles in a group of 158 ALL cases and reported odds ratios of interaction that were increased for the *CYP1A1*4* allele at high levels of maternal smoking in the last trimester of pregnancy and decreased at low levels of paternal postnatal smoking.[50] However, interaction odds ratios for the *CYPA1*2B* allele were generally decreased throughout all levels of parental smoking. These results lacked precision but indicated that the effect of parental smoking could be modified by variant alleles in the *CYP1A1* gene. In another study, they found that the *CYP1A1m1* and *m2* alleles modified the association between pesticide exposure and childhood ALL.[95]

CONCLUSIONS

It is evident from decades of basic science, clinical, and epidemiological research that childhood leukemia is a biologically heterogeneous group of malignancies that has complex etiologies involving the interaction between the environment, genetic susceptibility loci, and chance. Equipped with this general understanding, a logical and essential next step, as it pertains to cancer epidemiology, is to examine these factors simultaneously in an attempt to further unravel the existing causal relationships for childhood leukemia. In order to proceed, investigators in the field will need to address relevant methodological and analytical issues during both the study design and data analysis phases of the epidemiologic investigation. Such important issues include ensuring adequate statistical power to detect even modest associations in a valid manner, utilizing the most effective and comprehensive methods when assessing exposure, minimizing selection bias by avoiding the selection of controls by RDD, reducing recall bias by using detailed questionnaire instruments and memory aids during the interview, and giving appropriate attention to confounding factors and effect modifiers while designing studies and conducting data analyses.

First and foremost, future studies of childhood leukemia will require more large-scale population-based studies that have the capability of distinguishing molecular subtypes of pediatric leukemia in the analysis while providing sufficient power to detect even modest associations with precision. This issue is particularly important when evaluating gene-environment interactions. For example, in case-control studies, assessing interaction would require stratifying the population by the effect modifier and comparing the magnitude of the odds ratios that relates the exposure to the disease. Statistical power depends on the numbers of cases and controls in the each of the strata rather than the case and control population as a whole. The lack of adequate statistical power could introduce random error and an inability to interpret the results in a valid manner. Given the rarity of most neoplasms, large multicenter collaborative efforts may be a solution. The initial design of such studies should be conducted in close collaboration with the appropriate clinical working groups (i.e. as active participants in the study).[206]

Second, as a malignancy with an onset during childhood, issues of timing (i.e. during the preconceptional, gestational, or postnatal periods) of exposure are important considerations in understanding the temporal nature of childhood leukemia, as well as making informed decisions regarding preventive

guidelines and policy. Therefore, exposure assessment should focus on specific periods during childhood. Furthermore, as a complement to the data obtained from environmental monitoring devices, study questionnaires, and interviews, the measurement of biological markers of exposure and outcome can be used in effective ways to refine exposure measures. Using these markers may also resolve some issues related to the impact of recall bias on the interpretability of the findings.

Third, control selection should be carefully thought out before initiating a case-control study. Ideally, population-based controls should be utilized since these controls represent the case base from which the cases arose. Ma and colleagues evaluated the representativeness of controls in a case-control study by comparing data on parental age, parental education, mother's reproductive history, and birth weight among birth certificate and friend controls to that of ''ideal'' population-based controls randomly chosen from birth records for the study area.[205] For all variables except birth weight, the differences between participating birth certificate controls and ''ideal'' controls were smaller and non-significant as compared to those between participating friend controls and ''ideal'' controls. These results indicate that birth certificate controls appear to provide a representative sample of children. In contrast, use of controls selected by RDD should be avoided due to the inability to adequately define the study population, in addition to the field operation difficulties stemming from current telephone technology (i.e. answering machines, call waiting, and multiple phone lines per household). Most importantly, RDD controls can be systematically different from the cases, thus leading to selection bias, an issue that is particularly relevant to studies of non-ionizing radiation.

Fourth, recall bias and general recall issues remain an issue of all case-control studies. One can minimize recall bias by designing detailed questionnaires that ask for specific time periods of exposure and doses of exposure. For general recall issues, memory aids can be used both before and during the interview. Before the interview, study staff can send out a reminder list of specific exposures that will be asked about in the interview while during the interview, show cards displaying certain exposures can be utilized that accompany relevant questions. Most importantly, both case and control interviews should be conducted concurrently and as soon as possible after the date of diagnosis.

Finally, before any investigator can embark on studying an environmental or genetic exposure and its relation to childhood leukemia, a diagram of known and proposed causal relationships should be constructed so that all potential confounders and effect modifiers are fully accounted for and understood mechanistically for study design and data analysis purposes. Particularly relevant to this causal diagram of childhood leukemia is the role of SES and whether or not it is a true confounder in the exposure-disease pathway.

Overall, the current literature on the causes of childhood leukemia indicates tremendous progress over the years. Researchers in epidemiology and genetics are now at a critical point where they are collaborating productively. As a result, the role of environmental exposures in conjunction with genetics in the etiology of childhood leukemia can be elucidated in a more refined fashion.

ACKNOWLEDGMENTS

This commentary was made possible by three research grants from the National Institute of Environmental Health Sciences (PS42 ES04705, R01 ES09137, and R01 CA0092674). We thank Dr. Joseph Wiemels and Ms. Julie Von Behren for their valuable comments and suggestions.

REFERENCES

1. Smith, M.; Ries, L.; Gurney, J.; Ross, J. Leukemia. In *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995, (Pub. No. 99-4649)*; Ries, L., Smith, M., Gurney, J., Linet, M., Tamra, T., Young, J., Eds.; National Cancer Institute, SEER Program: Bethesda, MD, 1999; 17–34.
2. U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 2000 Incidence*; Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute: Atlanta, GA, 2003.
3. Linet, M.S.; Ries, L.A.; Smith, M.A.; Tarone, R.E.; Devesa, S.S. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J. Natl. Cancer Inst. **1999**, *91* (12), 1051–1058.
4. Greaves, M.F.; Alexander, F. An infectious etiology for common acute lymphoblastic leukemia in childhood? Leukemia **1993**, *7*, 349–360.
5. Pui, C.H. Childhood leukemias. N. Engl. J. Med. **1995**, *332* (24), 1618–1630.
6. Greaves, M. Molecular genetics, natural history and the demise of childhood leukaemia. Eur. J. Cancer **1999**, *35* (2), 173–185.
7. Rowley, J.D. Molecular genetics in acute leukemia. Leukemia **2000**, *14* (3), 513–517.
8. Gale, K.B.; Ford, A.M.; Repp, R.; Borkhardt, A.; Keller, C.; Eden, O.B.; Greaves, M.F. Backtracking leukemia to birth: identification of clonotypic gene fusion sequences in neonatal blood spots. Proc. Natl. Acad. Sci. **1997**, *94*, 13950–13954.
9. Wiemels, J.L.; Cazzaniga, G.; Daniotti, M.; Eden, O.B.; Addison, G.M.; Masera, G.; Saha, V.; Biondi, A.; Greaves, M.F. Prenatal origin of acute lymphoblastic leukaemia in children. Lancet **1999**, *354*, 1499–1503.
10. Wiemels, J.L.; Xiao, Z.; Buffler, P.A.; Maia, A.T.; Ma, X.; Dicks, B.M.; Smith, M.T.; Zhang, L.; Feusner, J.; Wiencke, J.; Pritchard-Jones, K.; Kempski, H.; Greaves, M. In utero origin of t(8;21) AML1-ETO translocations in childhood acute myeloid leukemia. Blood **2002**, *99* (10), 3801–3805.
11. McHale, C.M.; Wiemels, J.L.; Zhang, L.; Ma, X.; Buffler, P.A.; Feusner, J.; Matthay, K.; Dahl, G.; Smith, M.T. Prenatal origin of childhood acute myeloid leukemias harboring chromosomal rearrangements t(15;17) and inv(16). Blood **2003**, *101* (11), 4640–4641.
12. McHale, C.M.; Wiemels, J.L.; Zhang, L.; Ma, X.; Buffler, P.A.; Guo, W.; Loh, M.L.; Smith, M.T. Prenatal origin of TEL-AML1-positive acute lymphoblastic leukemia in children born in California. Genes Chromosomes Cancer **2003**, *37* (1), 36–43.
13. Panzer-Grumayer, E.R.; Fasching, K.; Panzer, S.; Hettinger, K.; Schmitt, K.; Stockler-Ipsiroglu, S.; Haas, O.A. Nondisjunction of chromosomes leading to hyperdiploid childhood B-cell precursor acute lymphoblastic leukemia is an early event during leukemogenesis. Blood **2002**, *100* (1), 347–349.
14. Taub, J.W.; Konrad, M.A.; Ge, Y.; Naber, J.M.; Scott, J.S.; Matherly, L.H.; Ravindranath, Y. High frequency of leukemic clones in newborn

screening blood samples of children with B-precursor acute lymphoblastic leukemia. Blood **2002**, *99* (8), 2992–2996.
15. Anderson, L.M.; Diwan, B.A.; Fear, N.T.; Roman, E. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ. Health Perspect. **2000**, *108* (Suppl. 3), 573–594.
16. Reinier, K.S. *Methodological Issues in Epidemiologic Studies of Childhood Leukemia: Control Selection and Exposure Assessment (Ph.D Dissertation)*; Division of Epidemiology, University of California: Berkeley, 2002.
17. Fabia, J.; Thuy, T.D. Occupation of father at time of birth of children dying of malignant diseases. Br. J. Prev. Soc. Med. **1974**, *28*, 98–100.
18. Hakulinen, T.; Salonen, T.; Teppo, L. Cancer in the offspring of fathers in hydrocarbon-related occupations. Br. J. Prev. Soc. Med. **1976**, *30* (2), 138–140.
19. Zack, M.; Cannon, S.; Loyd, D.; Heath, C.W., Jr.; Falletta, J.M.; Jones, B.; Housworth, J.; Crowley, S. Cancer in children of parents exposed to hydrocarbon-related industries and occupations. Am. J. Epidemiol. **1980**, *111* (3), 329–336.
20. Shu, X.O.; Stewart, P.; Wen, W.-Q.; Han, D.; Poter, J.D.; Buckley, J.D.; Heineman, E.; Robison, L.L. Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. Cancer Epidemiol. Biomark. Prev. **1999**, *8*, 783–791.
21. Schuz, J.; Kaletsch, U.; Meinert, R.; Kaatsch, P.; Michaelis, J. Risk of childhood leukemia and parental self-reported occupational exposure to chemicals, dusts, and fumes: results from pooled analyses of German population-based case-control studies. Cancer Epidemiol. Biomark. Prev. **2000**, *9*, 835–838.
22. Feychting, M.; Plato, N.; Nise, G.; Ahlbom, A. Paternal occupational exposures and childhood cancer. Environ. Health Perspect. **2001**, *109* (2), 193–196.
23. McKinney, P.A.; Fear, N.T.; Stockton, D. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. Occup. Environ. Med. **2003**, *60* (12), 901–909.
24. Savitz, D.A.; Chen, J.H. Parental occupation and childhood cancer: review of epidemiologic studies. Environ. Health Perspect. **1990**, *88*, 325–337.
25. Colt, J.S.; Blair, A. Parental occupational exposures and risk of childhood cancer. Environ. Health Perspect. **1998**, *106* (Suppl. 3), 909–925.
26. Zahm, S.H.; Ward, M.H. Pesticides and childhood cancer. Environ. Health. Perspect. **1998**, *106* (Suppl. 3), 893–908.
27. Meinert, R.; Schuz, J.; Kaletsch, U.; Kaatsch, P.; Michaelis, J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. Am. J. Epidemiol. **2000**, *151* (7), 639–646.
28. Schuz, J.; Spector, L.G.; Ross, J.A. Bias in studies of parental self-reported occupational exposure and childhood cancer. Am. J. Epidemiol. **2003**, *158* (7), 710–716.
29. Gerin, M.; Siemiatycki, J. The occupational questionnaire in retrospective epidemiologic studies: recent approaches in community-based studies. Appl. Occup. Environ. Hyg. **1991**, *6* (6), 495–499.
30. Stewart, P.A.; Herrick, R.F. Issues in performing retrospective exposure assessment. Appl. Occup. Environ. Hyg. **1991**, *6* (6), 421–427.
31. Stewart, W.; Stewart, P. Occupational case-control studies: I. Collecting information on work histories and work-related exposures. Am. J. Ind. Med. **1994a**, *26*, 297–312.
32. Stewart, P.; Stewart, W. Occupational case-control studies: II. Recommendations for exposure assessment. Am. J. Ind. Med. **1994b**, *26*, 313–326.
33. Reinier, K.; Hammond, S.K.; Buffler, P.A.; Gunier, R.B.; Lea, C.S.; Quinlan, P.; Kirsch, J. Development and evaluation of parental occupational exposure questionnaires for a childhood leukemia study. Scand. J. Work. Health **2004**, *30* (6), 450–458.
34. Stewart, A.; Webb, J.; Hewitt, D. A survey of childhood malignancy. Br. Med. J. **1958**, *i*, 1495–1508.
35. Stjernfeldt, M.; Berglund, K.; Lindsten, J.; Ludvigsson, J. Maternal smoking during pregnancy and risk of childhood cancer. The Lancet **1986**, *8494*, 1350–1352.
36. John, E.; Savitz, D.; Sandler, D. Prenatal exposure to parent's smoking and childhood cancer. Am. J. Epidemiol. **1991**, *133*, 123–132.
37. Shu, X.-O.; Ross, J.; Pendergrass, T.; Reaman, G.; Lampkin, B.; Robison, L. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a childrens cancer group study. J. Natl. Cancer Inst. **1996**, *88* (1), 24–31.
38. Ji, B.-T.; Shu, X.-O.; Linet, M.S.; Zheng, W.; Wacholder, S.; Gao, Y.-T.; Ying, D.-M.; Jin, F. Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. J. Natl. Cancer Inst. **1997**, *89* (3), 238–244.
39. Buckley, J.D.; Hobbie, W.L.; Ruccione, K.; Sather, H.N.; Woods, W.G.; Hammond, G.D. Maternal smoking during pregnancy and the risk of childhood cancer. The Lancet **1986**, *8505*, 519–520.
40. McKinney, P.A.; Stiller, C.A. Maternal smoking during pregnancy and the risk of childhood cancer. The Lancet **1986**, *8505*, 519.
41. Severson, R.K.; Buckley, J.D.; Woods, W.G.; Benjamin, D.; Robison, L.L. Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia: an analysis within morphological subgroups–a report from the Childrens Cancer Group. Cancer Epidemiol. Biomark. Prev. **1993**, *2* (5), 433–439.
42. Cnattingius, S.; Zack, M.; Ekbom, A.; Gunnarskog, J.; Linet, M.; Adami, H.O. Prenatal and neonatal risk factors for childhood myeloid leukemia. Cancer Epidemiol. Biomark. Prev. **1995**, *4* (5), 441–445.
43. Cnattingius, S.; Zack, M.M.; Ekbom, A.; Gunnarskog, J.; Kreuger, A.; Linet, M.; Adami, H.O. Prenatal and neonatal risk factors for childhood lymphatic leukemia. J. Natl. Cancer Inst. **1995**, *87* (12), 908–914.
44. Sorahan, T.; Lancashire, R.; Prior, P.; Peck, I.; Stewart, A. Childhood cancer and parental use of alcohol and tobacco. Ann. Epidemiol. **1995**, *5* (5), 354–359.
45. Petridou, E.; Trichopoulos, D.; Kalapothaki, V.; Pourtsidis, A.; Kogevinas, M.; Kalmanti, M.; Koliouskas, D.; Kosmidis, H.; Panagiotou, J.P.; Piperopoulou, F.; Tzortzatou, F. The risk profile of childhood leukaemia in Greece: a nationwide case-control study. Br. J. Cancer **1997**, *76* (9), 1241–1247.
46. Sorahan, T.; Lancashire, R.J.; Hulten, M.A.; Peck, I.; Stewart, A.M. Childhood cancer and parental use of tobacco: deaths from 1953 to 1955. Br. J. Cancer **1997**, *75* (1), 134–138.
47. Sorahan, T.; Prior, P.; Lancashire, R.J.; Faux, S.P.; Hulten, M.A.; Peck, I.M.; Stewart, A.M. Childhood cancer and parental use of tobacco: deaths from 1971 to 1976. Br. J. Cancer **1997**, *76* (11), 1525–1531.
48. Brondum, J.; Shu, X.O.; Steinbuch, M.; Severson, R.; Potter, J.D.; Robison, L.L. Parental cigarette smoking and the risk of acute leukemia in children. Cancer **1999**, *85*, 1380–1388.
49. Schüz, J.; Kaatsch, P.; Kaletsch, U.; Meinert, R.; Michaelis, J. Association of childhood cancer with factors related to pregnancy and birth. Int. J. Epidemiol. **1999**, *28* (4), 631–639.
50. Infante-Rivard, C.; Krajinovic, M.; Labuda, D.; Sinnett, D. Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Quebec, Canada). Cancer Causes Control **2000**, *11* (6), 547–553.
51. Pang, D.; McNally, R.; Birch, J.M. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. Br. J. Cancer **2003**, *88* (3), 373–381.
52. Pershagen, G.; Ericson, A.; Otterblad-Olausson, P. Maternal smoking in pregnancy: does it increase the risk of childhood cancer? Int. J. Epidemiol. **1992**, *21* (1), 1–5.
53. Klebanoff, M.A.; Clemens, J.D.; Read, J.S. Maternal smoking during pregnancy and childhood cancer. Am. J. Epidemiol. **1996**, *144* (11), 1028–1033.
54. Boffetta, P.; Trédaniel, J.; Greco, A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environ. Health Perspect. **2000**, *108* (1), 73–82.
55. Feldman, Y.; Koren, G.; Mattice, K.; Shear, H.; Pellegrini, E.; MacLeod,

S.M. Determinants of recall and recall bias in studying drug and chemical exposure in pregnancy. Teratology **1989**, *40* (1), 37–45.
56. Dietz, P.M.; Adams, M.M.; Rochat, R.W.; Mathis, M.P. Prenatal smoking in two consecutive pregnancies: Georgia, 1989–1992. Matern. Child Health J. **1997**, *1* (1), 43–51.
57. Aksoy, M. Benzene as a leukemogenic and carcinogenic agent. Am. J. Ind. Med. **1985**, *8* (1), 9–20.
58. McCraw, D.S.; Joyner, R.E.; Cole, P. Excess leukemia in a refinery population. J. Occup. Med. **1985**, *27* (3), 220–222.
59. Bond, G.G.; McLaren, E.A.; Baldwin, C.L.; Cook, R.R. An update of mortality among chemical workers exposed to benzene. Br. J. Ind. Med. **1986**, *43* (10), 685–691.
60. Yin, S.N.; Hayes, R.B.; Linet, M.S.; Li, G.L.; Dosemeci, M.; Travis, L.B.; Li, C.Y.; Zhang, Z.N.; Li, D.G.; Chow, W.H.; Wacholder, S.; Wang, Y.Z.; Jiang, Z.L.; Dai, T.R.; Zhang, W.Y.; Chao, X.J.; Ye, P.Z.; Kou, Q.R.; Zhang, X.C.; Lin, X.F.; Meng, J.F.; Ding, C.Y.; Zho, J.S.; Blot, W.J. A cohort study of cancer among benzene-exposed workers in China: overall results. Am. J. Ind. Med. **1996**, *29* (3), 227–235.
61. Wong, O.; Morgan, R.W.; Bailey, W.J.; Swencicki, R.E.; Claxton, K.; Kheifets, L. An epidemiological study of petroleum refinery employees. Br. J. Ind. Med. **1986**, *43* (1), 6–17.
62. Wong, O. An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses. Br. J. Ind. Med. **1987**, *44* (6), 382–395.
63. Rinsky, R.A.; Smith, A.B.; Hornung, R.; Filloon, T.G.; Young, R.J.; Okun, A.H.; Landrigan, P.J. Benzene and leukemia. An epidemiologic risk assessment. N. Engl. J. Med. **1987**, *316* (17), 1044–1050.
64. Wong, O. An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. Br. J. Ind. Med. **1987**, *44* (6), 365–381.
65. Hayes, R.B.; Yin, S.N.; Dosemeci, M.; Li, G.L.; Wacholder, S.; Travis, L.B.; Li, C.Y.; Rothman, N.; Hoover, R.N.; Linet, M.S. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group. J. Natl. Cancer Inst. **1997**, *89* (14), 1065–1071.
66. Rushton, L.; Romaniuk, H. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Occup. Environ. Med. **1997**, *54* (3), 152–166.
67. Knox, E.G. Leukaemia clusters in childhood: geographical analysis in Britain. J. Epidemiol. Community Health **1994**, *48* (4), 369–376.
68. Knox, E.G.; Gilman, E.A. Hazard proximities of childhood cancers in Great Britain from 1953–80. J. Epidemiol. Community Health **1997**, *51* (2), 151–159.
69. Steffen, C.; Auclerc, M.F.; Auvrignon, A.; Baruchel, A.; Kebaili, K.; Lambilliotte, A.; Leverger, G.; Sommelet, D.; Vilmer, E.; Hemon, D.; Clavel, J. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup. Environ. Med. **2004**, *61* (9), 773–778.
70. Van Steensel-Moll, H.A.; Valkenburg, H.A.; Van Zanen, G.E. Childhood leukemia and parental occupation: a register-based case-control study. Am. J. Epidemiol. **1985**, *121* (2), 216–224.
71. Shu, X.O.; Gao, Y.T.; Brinton, L.A.; Linet, M.L.; Tu, J.T.; Zheng, W.; Joseph, F.; Fraumeni, J. A population-based case-control study of childhood leukemia in Shanghai. Cancer **1988**, *62* (3), 635–644.
72. Buckley, J.D.; Robison, L.L.; Swotinsky, R.; Garabrant, D.H.; LeBeau, M.; Manchester, P.; Nesbit, M.E.; Odom, L.; Peters, J.M.; Woods, W.G.; et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res. **1989**, *49* (14), 4030–4037.
73. McKinney, P.A.; Alexander, F.E.; Cartwright, R.A.; Parker, L. Parental occupations of children with leukaemia in west Cumbria, north Humberside, and Gateshead. Br. Med. J. **1991**, *302* (6778), 681–687.
74. Kishi, R.; Katakura, Y.; Yuasa, J.; Miyake, H. [Association of parents' occupational exposure to cancer in children. A case-control study of acute lymphoblastic leukemia]. Sangyo Igaku **1993**, *35* (6), 515–529.
75. Wertheimer, N.; Leeper, E. Electrical wiring configurations and childhood cancer. Am. J. Epidemiol. **1979**, *109* (3), 273–284.
76. Savitz, D.A.; Feingold, L. Association of childhood cancer with residential traffic density. Scand. J. Work Environ. Health **1989**, *15* (5), 360–363.
77. Nordlinder, R.; Jarvholm, B. Environmental exposure to gasoline and leukemia in children and young adults–an ecology study. Int. Arch. Occup. Environ. Health **1997**, *70* (1), 57–60.
78. Feychting, M.; Svensson, D.; Ahlbom, A. Exposure to motor vehicle exhaust and childhood cancer. Scand. J. Work, Environ. Health **1998**, *24* (1), 8–11.
79. Harrison, R.M.; Leung, P.L.; Somervaille, L.; Smith, R.; Gilman, E. Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations. Occup. Environ. Med. **1999**, *56* (11), 774–780.
80. Pearson, R.L.; Wachtel, H.; Ebi, K.L. Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. J. Air Waste Manage. Assoc. **2000**, *50* (2), 175–180.
81. Crosignani, P.; Tittarelli, A.; Borgini, A.; Codazzi, T.; Rovelli, A.; Porro, E.; Contiero, P.; Bianchi, N.; Tagliabue, G.; Fissi, R.; Rossitto, F.; Berrino, F. Childhood leukemia and road traffic: a population-based case-control study. Int. J. Cancer **2004**, *108* (4), 596–599.
82. Dickinson, H.O.; Hammal, D.M.; Dummer, T.J.; Parker, L.; Bithell, J.F. Childhood leukaemia and non-Hodgkin's lymphoma in relation to proximity to railways. Br. J. Cancer **2003**, *88* (5), 695–698.
83. Reynolds, P.; Von Behren, J.; Gunier, R.B.; Goldberg, D.E.; Hertz, A.; Smith, D.F. Childhood cancer incidence rates and hazardous air pollutants in california: an exploratory analysis. Environ. Health Perspect. **2003**, *111* (4), 663–668.
84. Raaschou-Nielsen, O.; Hertel, O.; Thomsen, B.L.; Olsen, J.H. Air pollution from traffic at the residence of children with cancer. Am. J. Epidemiol. **2001**, *153* (5), 433–443.
85. Reynolds, P.; Von Behren, J.; Gunier, R.; Goldberg, D.; Hertz, A.; Smith, D. Traffic patterns and childhood cancer incidence rates in California, United States. Cancer Causes Control **2002**, *13*, 665–673.
86. Langholz, B.; Ebi, K.L.; Thomas, D.C.; Peters, J.M.; London, S.J. Traffic density and the risk of childhood leukemia in a Los Angeles case-control study. Ann. Epidemiol. **2002**, *12* (7), 482–487.
87. Reynolds, P.; Von Behren, J.; Gunier, R.B.; Goldberg, D.E.; Hertz, A. Residential exposure to traffic in California and childhood cancer. Epidemiology **2004**, *15* (1), 6–12.
88. McBride, M.L. Childhood cancer and environmental contaminants. Can. J. Public Health **1998**, *89* (Supplement 1), S53–S62.
89. Freedman, D.M.; Stewart, P.; Kleinerman, R.A.; Wacholder, S.; Hatch, E.E.; Tarone, R.E.; Robison, L.L.; Linet, M.S. Household solvent exposures and childhood acute lymphoblastic leukemia. Am. J. Public Health **2001**, *91* (4), 564–567.
90. Lowengart, R.A.; Peters, J.M.; Cicioni, C.; Buckley, J.; Bernstein, L.; Preston-Martin, S.; Rappaport, E. Childhood leukemia and parents' occupational and home exposures. J. Natl. Cancer Inst. **1987**, *79* (1), 39–45.
91. Schwartzbaum, J.A.; George, S.L.; Pratt, C.B.; Davis, B. An exploratory study of environmental and medical factors potentially related to childhood cancer. Med. Pediatr. Oncol. **1991**, *19*, 115–121.
92. Buckley, J.; Buckley, C.; Ruccione, K.; Sather, H.; Waskerwitz, M.; Woods, W.; Robison, L. Epidemiological characteristics of childhood acute lymphocytic leukemia. Analysis by immunophenotype. Leukemia **1994**, *8* (5), 856–864.
93. Leiss, J.K.; Savitz, D.A. Home pesticide use and childhood cancer: a case-control study. Am. J. Public Health **1995**, *85* (2), 249–252.

94. Meinert, R.; Kaatsch, P.; Kaletsch, U.; Krummenauer, F.; Miesner, A.; Michaelis, J. Childhood leukaemia and exposure to pesticides: results of a case-control study in Northern Germany. Eur. J. Cancer **1996**, *32A* (11), 1943–1948.
95. Infante-Rivard, C.; Labuda, D.; Krajinovic, M.; Sinnett, D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology **1999**, *10* (5), 481–487.
96. Ma, X.; Buffler, P.A.; Gunier, R.B.; Dahl, G.; Smith, M.T.; Reinier, K.; Reynolds, P. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ. Health Perspect. **2002**, *110* (9), 955–960.
97. Reynolds, P.; Von Behren, J.; Gunier, R.B.; Goldberg, D.E.; Hertz, A.; Harnly, M.E. Childhood cancer and agricultural pesticide use: an ecologic study in California. Environ. Health Perspect. **2002**, *110* (3), 319–324.
98. Reynolds, P.; Von Behren, J.; Gunier, R.B.; Goldberg, D.E.; Harnly, M.; Hertz, A. A case-control study of childhood cancer and agricultural pesticide use in California. Epidemiology **2005**, *16* (1), 93–100.
99. Stewart, A.; Webb, J.; Giles, D.; Hewitt, D. Malignant disease in childhood and diagnostic irradiation in utero. Lancet **1956**, *2*, 447.
100. MacMahon, B.; Hutchison, G.B. Prenatal x-ray and childhood cancer: a review. Acta Union Int. Contre Le Cancer **1964**, *20*, 1172–1174.
101. Graham, S.; Levin, M.L.; Lilienfeld, A.M.; Schuman, L.M.; Gibson, R.; Dowd, J.E.; Hempelmann, L. Preconception, intrauterine, and postnatal irradiation as related to leukemia. Natl. Cancer Inst. Monogr. **1966**, *19*, 347–371.
102. Mole, R.H. Childhood cancer after prenatal exposure to diagnostic x-ray examinations in Britain. Br. J. Cancer **1990**, *62* (1), 152–168.
103. Doll, R.; Wakeford, R. Risk of childhood cancer from fetal irradiation. Br. J. Radiol. **1997**, *70*, 130–139.
104. Boice, J.D., Jr.; Miller, R.W. Childhood and adult cancer after intrauterine exposure to ionizing radiation. Teratology **1999**, *59* (4), 227–233.
105. Court-Brown, W.M.; Doll, R.; Hill, A.B. Incidence of leukemia after exposure to diagnostic radiation in utero. Br. Med. J. **1960**, *2*, 1539–1545.
106. Diamond, E.L.; Schmerler, H.; Lilienfeld, A.M. The relationship of intra-uterine radiation to subsequent mortality and development of leukemia in children. A prospective study. Am. J. Epidemiol. **1973**, *97* (5), 283–313.
107. MacMahon, B. Prenatal x-ray exposure and childhood cancer. J. Natl. Cancer Inst. **1962**, *28*, 1173–1191.
108. Hewitt, D.; Sanders, B.; Stewart, A. Oxford Survey of Childhood Cancers: progress report. IV. Reliability of data reported by case and control mothers. Mon. Bull. Minist. Health Public Health Lab. Serv. **1966**, *25*, 80–85.
109. Knox, E.G.; Stewart, A.; Kneale, G.W.; Gilman, E. Prenatal irradiation and childhood cancer. J. Soc. Radiol. Prot. **1987**, *7*, 177–189.
110. Bithell, J.F.; Stewart, A.M. Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey. Br. J. Cancer **1975**, *31* (3), 271–287.
111. Little, J. *Epidemiology of Childhood Cancer.* IARC Scientific Publications; Oxford University Press: Oxford, 1999.
112. Chandley, A.C. On the parental origin of de novo mutation in man. J. Med. Genet. **1991**, *28* (4), 217–223.
113. Magnani, C.; Pastore, G.; Luzzatto, L.; Terracini, B. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case-control study. Tumori **1990**, *76* (5), 413–419.
114. Shu, X.O.; Jin, F.; Linet, M.S.; Zheng, W.; Clemens, J.; Mills, J.; Gao, Y.T. Diagnostic x-ray and ultrasound exposure and risk of childhood cancer. Br. J. Cancer **1994**, *70* (3), 531–536.
115. Meinert, R.; Kaletsch, U.; Kaatsch, P.; Schuz, J.; Michaelis, J. Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. Cancer Epidemiol. Biomark. Prev. **1999**, *8* (9), 793–799.
116. Infante-Rivard, C. Diagnostic x-rays, DNA repair genes and childhood acute lymphoblastic leukemia. Health Phys. **2003**, *85* (1), 60–64.
117. Shu, X.O.; Gao, Y.T.; Brinton, L.A.; Linet, M.S.; Tu, J.T.; Zheng, W.; Fraumeni, J.F., Jr. A population-based case-control study of childhood leukemia in Shanghai. Cancer **1988**, *62* (3), 635–644.
118. Gardner, M.J.; Snee, M.P.; Hall, A.J.; Powell, C.A.; Downes, S.; Terrell, J.D. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. Br. Med. J. **1990**, *300* (6722), 423–429.
119. Gardner, M.J. Review of reported increases of childhood cancer rates in the vicinity of nuclear installations in the UK. J. R. Stat. Soc. **1989**, *152*, 307–325.
120. Wheldon, T.E. The assessment of risk of radiation-induced childhood leukemia in the vicinity of nuclear installations. J. R. Stat. Soc. **1989**, *152*, 327–339.
121. Black, R.J.; Sharp, L.; Harkness, E.F.; McKinney, P.A. Leukaemia and non-Hodgkin's lymphoma: incidence in children and young adults resident in the Dounreay area of Caithness, Scotland in 1968–91. J. Epidemiol. Community Health **1994**, *48* (3), 232–236.
122. McLaughlin, J.R.; King, W.D.; Anderson, T.W.; Clarke, E.A.; Ashmore, J.P. Paternal radiation exposure and leukaemia in offspring: the Ontario case-control study. Br. Med. J. **1993**, *307* (6910), 959–966.
123. Viel, J.F.; Richardson, S.; Danel, P.; Boutard, P.; Malet, M.; Barrelier, P.; Reman, O.; Carre, A. Childhood leukemia incidence in the vicinity of La Hague nuclear-waste reprocessing facility (France). Cancer Causes Control **1993**, *4* (4), 341–343.
124. Boice, J.D., Jr.; Bigbee, W.L.; Mumma, M.T.; Blot, W.J. Cancer mortality in counties near two former nuclear materials processing facilities in Pennsylvania, 1950–1995. Health Phys. **2003**, *85* (6), 691–700.
125. Beral, V. Childhood leukemia near nuclear plants in the United Kingdom: the evolution of a systematic approach to studying rare disease in small geographic areas. Am. J. Epidemiol. **1990**, *132* (1 Suppl.), S63–S68.
126. Kinlen, L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. Lancet **1988**, *2* (8624), 1323–1327.
127. Kinlen, L.J.; Stiller, C. Population mixing and excess of childhood leukemia. Br. Med. J. **1993**, *306* (6882), 930.
128. Doll, R. The Seascale cluster: a probable explanation. Br. J. Cancer **1999**, *81* (1), 3–5.
129. Portier, C.J.; Wolfe, M.S. Assessment of health effects from exposure to power-line frequency electric and magnetic fields. In *NIEHS Working Group Report, NIH Publication No. 98-3981*; NIH: Research Triangle Park, 1998.
130. National Radiologic Protection Board. *ELF Electromagnetic Fields and the Risk of Cancer: Report of an Advisory Group on Non-ionising Radiation*; National Radiological Protection Board, 2001.
131. International Agency of Research on Cancer. Non-ionizing radiation, part I: static and extremely low frequency electric and magnetic fields. In *Monographs on the Evaluation of Carcinogenic Risks to Humans*; IARC Press: Geneva, 2002; Vol. 80.
132. Ahlbom, I.C.; Cardis, E.; Green, A.; Linet, M.; Savitz, D.; Swerdlow, A. Review of the epidemiologic literature on EMF and Health. Environ. Health Perspect. **2001**, *109* (Suppl. 6), 911–933.
133. Ahlbom, A.; Day, N.; Feychting, M.; Roman, E.; Skinner, J.; Dockerty, J.; Linet, M.; McBride, M.; Michaelis, J.; Olsen, J.H.; Tynes, T.; Verkasalo, P.K. A pooled analysis of magnetic fields and childhood leukaemia. Br. J. Cancer **2000**, *83* (5), 692–698.
134. Greenland, S.; Sheppard, A.R.; Kaune, W.T.; Poole, C.; Kelsh, M.A. A

pooled analysis of magnetic fields, wire codes, and childhood leukemia. Epidemiology **2000**, *11* (6), 624–634.
135. Linet, M.S.; Hatch, E.E.; Kleinerman, R.A.; Robison, L.L.; Kaune, W.T.; Friedman, D.R.; Severson, R.K.; Haines, C.M.; Hartsock, C.T.; Niwa, S.; Wacholder, S.; Tarone, R.E. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. N. Engl. J. Med. **1997**, *337* (1), 1–7.
136. Brain, J.D.; Kavet, R.; McCormick, D.L.; Poole, C.; Silverman, L.B.; Smith, T.J.; Valberg, P.A.; Van Etten, R.A.; Weaver, J.C. Childhood leukemia: electric and magnetic fields as possible risk factors. Environ. Health Perspect. **2003**, *111* (7), 962–970.
137. Hone, P.; Edwards, A.; Halls, J.; Cox, R.; Lloyd, D. Possible associations between ELF electromagnetic fields, DNA damage response processes and childhood leukaemia. Br. J. Cancer **2003**, *88* (12), 1939–1941.
138. Auvinen, A.; Baris, D.; Robison, L.L.; Wacholder, S. Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of electromagnetic fields studies. Epidemiology **2000**, *11* (2), 189–198.
139. Langholz, B. Factors that explain the power line configuration wiring code-childhood leukemia association: what would they look like? Bioelectromagnetics **2001**, *Suppl 5*, S19–S31.
140. Jaffa, K.C.; Kim, H.; Aldrich, T.E. The relative merits of contemporary measurements and historical calculated fields in the Swedish childhood cancer study. Epidemiology **2000**, *11* (3), 353–356.
141. Mezei, G.; Kheifets, L. Is there any evidence for differential misclassification or for bias away from the null in the Swedish childhood cancer study? Epidemiology **2001**, *12* (6), 750–752.
142. Savitz, D.A.; Wachtel, H.; Barnes, F.A.; John, E.M.; Tvrdik, J.G. Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. Am. J. Epidemiol. **1988**, *128* (1), 21–38.
143. Jones, T.L.; Shih, C.H.; Thurston, D.H.; Ware, B.J.; Cole, P. Selection bias from differential residential mobility as an explanation for associations of wire codes with childhood cancer. J. Clin. Epidemiol. **1993**, *46* (6), 545–548.
144. Gurney, J.G.; Davis, S.; Schwartz, S.M.; Mueller, B.A.; Kaune, W.T.; Stevens, R.G. Childhood cancer occurrence in relation to power line configurations: a study of potential selection bias in case-control studies. Epidemiology **1995**, *6* (1), 31–35.
145. Ebi, K.L.; Kheifets, L.I.; Pearson, R.L.; Wachtel, H. Description of a new computer wire coding method and its application to evaluate potential control selection bias in the Savitz et al. childhood cancer study. Bioelectromagnetics **2000**, *21* (5), 346–353.
146. Spinelli, J.J.; McBride, M.; Abanto, Z.U.; Tamaro, S.; Bajdik, C.D.; Gallagher, R.P. Assessing response bias as an explanation for the observation of low socioeconomic status (SES) as a risk factor for childhood leukemia. Am. J. Epidemiol. **2001**, *153*, S254 (Abstract 948).
147. Sarasua, S.; Savitz, D.A. Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States) [see comments]. Cancer Causes Control **1994**, *5* (2), 141–148.
148. Peters, J.; Preston-Martin, S.; London, S.J.; Bowman, J.D.; Buckley, J.D.; Thomas, D.C. Processed meats and risk of childhood leukemia: California, USA. Cancer Causes Control **1994**, *5*, 195–202.
149. Blot, W.J.; Henderson, B.E.; Boice, J.D., Jr. Childhood cancer in relation to cured meat intake: review of the epidemiological evidence. Nutr. Cancer **1999**, *34* (1), 111–118.
150. Thompson, J.R.; Gerald, P.F.; Willoughby, M.L.; Armstrong, B.K. Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukaemia in childhood: a case-control study. Lancet **2001**, *358* (9297), 1935–1940.
151. Ross, J.; Potter, J.; Robison, L.; Reaman, G.; Pendergrass, T. Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Childrens Cancer Group. Cancer Causes Control **1996**, *7* (6), 581–590.
152. Jensen, C.D.; Block, G.; Buffler, P.; Ma, X.; Selvin, S.; Month, S. Maternal dietary risk factors in childhood acute lymphoblastic leukemia (United States). Cancer Causes Control **2004**, *15* (6), 559–570.
153. Grufferman, S.; Wang, H.H.; DeLong, E.R.; Kimm, S.Y.; Delzell, E.S.; Falletta, J.M. Environmental factors in the etiology of rhabdomyosarcoma in childhood. J. Natl. Cancer Inst. **1982**, *68* (1), 107–113.
154. Howe, G.R.; Burch, J.D.; Chiarelli, A.M.; Risch, H.A.; Choi, B.C. An exploratory case-control study of brain tumors in children. Cancer Res. **1989**, *49* (15), 4349–4352.
155. Cordier, S.; Iglesias, M.J.; Le Goaster, C.; Guyot, M.M.; Mandereau, L.; Hemon, D. Incidence and risk factors for childhood brain tumors in the Ile de France. Int. J. Cancer **1994**, *59* (6), 776–782.
156. McCredie, M.; Maisonneuve, P.; Boyle, P. Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. Int. J. Cancer **1994**, *56* (1), 11–15.
157. Kwan, M.L.; Block, G.; Selvin, S.; Month, S.; Buffler, P.A. Food consumption by children and the risk of childhood acute leukemia. Am. J. Epidemiol. **2004**, *160* (11), 1098–1107.
158. Fear, N.T.; Roman, E.; Ansell, P.; Simpson, J.; Day, N.; Eden, O.B. Vitamin K and childhood cancer: a report from the United Kingdom Childhood Cancer Study. Br. J. Cancer **2003**, *89* (7), 1228–1231.
159. Kellett, C.E. Acute leukaemia in one of identical twins. Arch. Dis. Child. **1937**, *12*, 239–252.
160. Heath, C.W., Jr.; Hasterlik, R.J. Leukemia among children in a suburban community. Am. J. Med. **1963**, *34*, 796–812.
161. Kinlen, L.J. Infection and childhood leukemia. Cancer Causes Control **1998**, *9*, 237–239.
162. Kinlen, L.J. Re: ''Childhood cancer and population mixing.'' Am. J. Epidemiol. **2004**, *159* (7), 716; author reply 717.
163. Greaves, M.F. Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia **1988**, *2* (2), 120–125.
164. Severson, R.K.; Davis, S.; Thomas, D.B.; Stevens, R.G.; Heuser, L.; Sever, L.E. Acute myelocytic leukemia and prior allergies. J. Clin. Epidemiol. **1989**, *42* (10), 995–1001.
165. Doody, M.M.; Linet, M.S.; Glass, A.G.; Friedman, G.D.; Pottern, L.M.; Boice, J.D., Jr.; Fraumeni, J.F., Jr. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. Cancer Causes Control **1992**, *3* (5), 449–456.
166. Law, G.R.; Parslow, R.C.; Roman, E. Childhood cancer and population mixing. Am. J. Epidemiol. **2003**, *158* (4), 328–336.
167. Wartenberg, D.; Schneider, D.; Brown, S. Childhood leukaemia incidence and the population mixing hypothesis in US SEER data. Br. J. Cancer **2004**, *90* (9), 1771–1776.
168. Ma, X.; Buffler, P.A.; Selvin, S.; Matthay, K.K.; Wiencke, J.K.; Wiemels, J.L.; Reynolds, P. Daycare attendance and risk of childhood acute lymphoblastic leukaemia. Br. J. Cancer **2002**, *86* (9), 1419–1424.
169. Jourdan-Da Silva, N.; Perel, Y.; Mechinaud, F.; Plouvier, E.; Gandemer, V.; Lutz, P.; Vannier, J.P.; Lamagnere, J.L.; Margueritte, G.; Boutard, P.; Robert, A.; Armari, C.; Munzer, M.; Millot, F.; De Lumley, L.; Berthou, C.; Rialland, X.; Pautard, B.; Hemon, D.; Clavel, J. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. Br. J. Cancer **2004**, *90* (1), 139–145.
170. Perrillat, F.; Clavel, J.; Auclerc, M.F.; Baruchel, A.; Leverger, G.; Nelken, B.; Philippe, N.; Schaison, G.; Sommelet, D.; Vilmer, E.; Hemon, D. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. Br. J. Cancer **2002**, *86* (7), 1064–1069.
171. Petridou, E.; Dalamaga, M.; Mentis, A.; Skalkidou, A.; Moustaki, M.; Karpathios, T.; Trichopoulos, D. Evidence on the infectious etiology of childhood leukemia: the role of low herd immunity (Greece). Cancer Causes Control **2001**, *12* (7), 645–652.
172. Schuz, J.; Kaletsch, U.; Meinert, R.; Kaatsch, P.; Michaelis, J. Association of childhood leukaemia with factors related to the immune system. Br. J. Cancer **1999**, *80* (3–4), 585–590.
173. Wen, W.; Shu, X.O.; Linet, M.S.; Neglia, J.P.; Potter, J.D.; Trigg, M.E.;

Robison, L.L. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). Cancer Causes Control **2000**, *11* (4), 303–307.

174. Spector, L.; Groves, F.; DeStefano, F.; Liff, J.; Klein, M.; Mullooly, J.; Black, S.; Shinefield, H.; Ward, J.; Marcy, M. Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. Eur. J. Cancer **2004**, *40* (4), 579–584.
175. Lehtinen, M.; Koskela, P.; Ogmundsdottir, H.M.; Bloigu, A.; Dillner, J.; Gudnadottir, M.; Hakulinen, T.; Kjartansdottir, A.; Kvarnung, M.; Pukkala, E.; Tulinius, H.; Lehtinen, T. Maternal herpesvirus infections and risk of acute lymphoblastic leukemia in the offspring. Am. J. Epidemiol. **2003**, *158* (3), 207–213.
176. Dearden, S.; Taylor, G.; Gokhale, D.; Robinson, M.; Thompson, W.; Ollier, W.; Binchy, A.; Birch, J.; Stevens, R.; Carr, T.; Bardsley, W. Molecular analysis of HLA-DQB1 alleles in childhood common acute lymphoblastic leukaemia. Br. J. Cancer **1995**, *73* (5), 603–609.
177. Taylor, G.; Robinson, M.; Binchy, A.; Birch, J.; Stevens, R.; Jones, P.; Carr, T.; Dearden, S.; Gokhale, D. Preliminary evidence of an association between HLA-DPB1*0201 and childhood common acute lymphoblastic leukaemia supports an infectious aetiology. Leukemia **1995**, *9*, 440–443.
178. Taylor, G.; Dearden, S.; Payne, N.; Ayres, M.; Gokhale, D.; Birch, J.; Blair, V.; Stevens, R.; Will, A.; Eden, O. Evidence that an HLA-DQA1-DQB1 haplotype influences susceptibility to childhood common acute lymphoblastic leukaemia in boys provides further support for an infection-related aetiology. Br. J. Cancer **1998**, *78* (5), 561–565.
179. Taylor, G.M.; Dearden, S.; Ravetto, P.; Ayres, M.; Watson, P.; Hussain, A.; Greaves, M.; Alexander, F.; Eden, O.B. Genetic susceptibility to childhood common acute lymphoblastic leukaemia is associated with polymorphic peptide-binding pocket profiles in HLA-DPB1*0201. Hum. Mol. Genet. **2002**, *11* (14), 1585–1597.
180. Gunier, R.B.; Harnly, M.E.; Reynolds, P.; Hertz, A.; Von Behren, J. Agricultural pesticide use in California: pesticide prioritization, use densities, and population distributions for a childhood cancer study. Environ. Health Perspect. **2001**, *109* (10), 1071–1078.
181. Hernan, M.A.; Hernandez-Diaz, S.; Werler, M.M.; Mitchell, A.A. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am. J. Epidemiol. **2002**, *155* (2), 176–184.
182. Kwan, M.L. *Postnatal Nutritional Factors in the Etiology of Childhood Leukemia (Ph.D dissertation)*; Division of Epidemiology, University of California: Berkeley, 2004.
183. Shields, P.G.; Harris, C.C. Cancer risk and low-penetrance susceptibility genes in gene-environment interactions. J. Clin. Oncol. **2000**, *18* (11), 2309–2315.
184. Chen, C.L.; Liu, Q.; Pui, C.H.; Rivera, G.K.; Sandlund, J.T.; Ribeiro, R.; Evans, W.E.; Relling, M.V. Higher frequency of glutathione S-transferase deletions in black children with acute lymphoblastic leukemia. Blood **1997**, *89* (5), 1701–1707.
185. Krajinovic, M.; Labuda, D.; Richer, C.; Karimi, S.; Sinnett, D. Susceptibility to childhood acute lymphoblastic leukemia: influence of CYP1A1, CYP2D6, GSTM1, and GSTT1 genetic polymorphisms. Blood **1999**, *93* (5), 1496–1501.
186. Wiemels, J.L.; Pagnamenta, A.; Taylor, G.M.; Eden, O.B.; Alexander, F.E.; Greaves, M.F. A lack of a functional NAD(P)H: quinone oxidoreductase allele is selectively associated with pediatric leukemias that have MLL fusions. Cancer Res. **1999**, *59*, 4095–4099.
187. Krajinovic, M.; Richer, C.; Sinnett, H.; Labuda, D.; Sinnett, D. Genetic polymorphisms of N-acetyltransferases 1 and 2 and gene-gene interaction in the susceptibility to childhood acute lymphoblastic leukemia. Cancer Epidemiol. Biomark. Prev. **2000**, *9* (6), 557–562.
188. Saadat, I.; Saadat, M. The glutathione S-transferase mu polymorphism and susceptibility to acute lymphocytic leukemia. Cancer Lett. **2000**, *158* (1), 43–45.
189. Franco, R.F.; Simoes, B.P.; Tone, L.G.; Gabellini, S.M.; Zago, M.A.; Falcao, R.P. The methylenetetrahydrofolate reductase C677T gene polymorphism decreases the risk of childhood acute lymphocytic leukaemia. Br. J. Haematol. **2001**, *115* (3), 616–618.
190. Krajinovic, M.; Labuda, D.; Sinnett, D. Glutathione S-transferase P1 genetic polymorphisms and susceptibility to childhood acute lymphoblastic leukaemia. Pharmacogenetics **2002**, *12* (8), 655–658.
191. Krajinovic, M.; Sinnett, H.; Richer, C.; Labuda, D.; Sinnett, D. Role of NQO1, MPO and CYP2E1 genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. Int. J. Cancer **2002**, *97* (2), 230–236.
192. Smith, M.T.; Wang, Y.; Skibola, C.F.; Slater, D.J.; Lo Nigro, L.; Nowell, P.C.; Lange, B.J.; Felix, C.A. Low NAD(P)H:quinone oxidoreductase activity is associated with increased risk of leukemia with MLL translocations in infants and children. Blood **2002**, *100* (13), 4590–4593.
193. Canalle, R.; Burim, R.V.; Tone, L.G.; Takahashi, C.S. Genetic polymorphisms and susceptibility to childhood acute lymphoblastic leukemia. Environ. Mol. Mutagen. **2004**, *43* (2), 100–109.
194. Jamroziak, K.; Mlynarski, W.; Balcerczak, E.; Mistygacz, M.; Trelinska, J.; Mirowski, M.; Bodalski, J.; Robak, T. Functional C3435T polymorphism of MDR1 gene: an impact on genetic susceptibility and clinical outcome of childhood acute lymphoblastic leukemia. Eur. J. Haematol. **2004**, *72* (5), 314–321.
195. Lang, M.; Pelkonen, O. Metabolism of xenobiotics and chemical carcinogenesis. IARC Sci. Publ. **1999** (148), 13–22.
196. Mathonnet, G.; Krajinovic, M.; Labuda, D.; Sinnett, D. Role of DNA mismatch repair genetic polymorphisms in the risk of childhood acute lymphoblastic leukaemia. Br. J. Haematol. **2003**, *123* (1), 45–48.
197. Brockmoller, J.; Cascorbi, I.; Henning, S.; Meisel, C.; Roots, I. Molecular genetics of cancer susceptibility. Pharmacology **2000**, *61* (3), 212–227.
198. Ambudkar, S.V.; Dey, S.; Hrycyna, C.A.; Ramachandra, M.; Pastan, I.; Gottesman, M.M. Biochemical, cellular, and pharmacological aspects of the multidrug transporter. Annu. Rev. Pharmacol. Toxicol. **1999**, *39*, 361–398.
199. Urayama, K.; Wiencke, J.; Buffler, P.; Wiemels, J.L. The role of MDR1 polymorphisms in the genetic susceptibility to childhood leukemia. In *The American College of Epidemiology Annual Scientific Sessions, American College of Epidemiology Annual Meeting, Albuquerque, NM, October 2002*; Rothenberg, R., Ed.; Elsevier Science Inc., 2002.
200. Nutr Rev. Folate supplements prevent recurrence of neural tube defects. Nutr. Rev. **1992**, *50* (1), 22–24.
201. Frosst, P.; Blom, H.J.; Milos, R.; Goyette, P.; Sheppard, C.A.; Matthews, R.G.; Boers, G.J.; den Heijer, M.; Kluijtmans, L.A.; van den Heuvel, L.P. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat. Genet. **1995**, *10* (1), 111–113.
202. Duthie, S.J. Folic acid deficiency and cancer: mechanisms of DNA instability. Br. Med. Bull. **1999**, *55* (3), 578–592.
203. Wiemels, J.L.; Smith, R.N.; Taylor, G.M.; Eden, O.B.; Alexander, F.E.; Greaves, M.F.; Investigators, U.K.C.C.S. Methylenetetrahydrofolate reductase (MTHFR) polymorphisms and risk of molecularly defined subtypes of childhood acute leukemia. Proc. Natl. Acad. Sci. **2001**, *98*, 4004–4009.
204. Krajinovic, M.; Lamothe, S.; Labuda, D.; Lemieux-Blanchard, E.; Theoret, Y.; Moghrabi, A.; Sinnett, D. Role of MTHFR genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. Blood **2004**, *103* (1), 252–257.
205. Ma, X.; Buffler, P.A.; Layefsky, M.; Does, M.B.; Reynolds, P. Control selection strategies in case-control studies of childhood diseases. Am. J. Epidemiol. **2004**, *159* (10), 915–921.
206. International Agency of Research on Cancer. *Mechanisms of Carcinogenesis: Contributions of Molecular Epidemiology*; Buffer, P., Rice, I., Baan, R., Bird, M., Boffetta, P., Eds; IARC Press: Lyon, France, 2004; Vol. 157.