

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: www.tandfonline.com/journals/ilal20

Case-only study of interactions between DNA repair genes (*hMLH1*, *APEX1*, *MGMT*, *XRCC1* and *XPD*) and low-frequency electromagnetic fields in childhood acute leukemia

You Yang, Xingming Jin, Chonghuai Yan, Ying Tian, Jingyan Tang & Xiaoming Shen

To cite this article: You Yang, Xingming Jin, Chonghuai Yan, Ying Tian, Jingyan Tang & Xiaoming Shen (2008) Case-only study of interactions between DNA repair genes (*hMLH1*, *APEX1*, *MGMT*, *XRCC1* and *XPD*) and low-frequency electromagnetic fields in childhood acute leukemia, Leukemia & Lymphoma, 49:12, 2344-2350, DOI: 10.1080/10428190802441347

To link to this article: https://doi.org/10.1080/10428190802441347

Published online: 01 Jul 2009.

Submit your article to this journal

Article views: 276

View related articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ilal20

Leukemia & Lymphoma, December 2008; 49(12): 2344–2350

informa
healthcare

ORIGINAL ARTICLE: RESEARCH

Case-only study of interactions between DNA repair genes (*hMLH1*, *APEX1*, *MGMT*, *XRCC1* and *XPD*) and low-frequency electromagnetic fields in childhood acute leukemia

YOU YANG[1], XINGMING JIN[2], CHONGHUAI YAN[1], YING TIAN[1,3], JINGYAN TANG[2], & XIAOMING SHEN[1]

[1]*Shanghai XinHua Hospital of Shanghai Jiao Tong University School of Medicine, Shanghai Institute for Pediatric Research, Shanghai Key Laboratory of Children's Environmental Health, Shanghai, China,* [2]*Shanghai Children's Medical Center of Shanghai Jiao Tong University School of Medicine, Shanghai, China, and* [3]*Department of Environmental Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

(Received 20 May 2008; revised 24 August 2008; accepted 26 August 2008)

Abstract
A case-only study was conducted in 123 patients with sporadic acute leukemia (AL). The locations of electric transformers and power lines were noted in each area, and their distances from the houses of the study patients were measured. The intensities of magnetic fields (*B*) were measured in 66 cases. Unconditional logistic regression analysis was performed adjusting for age, gender, parental education and occupation, indoor and outdoor pesticides use, presence of television sets, refrigerators and microwave ovens in children's rooms and the presence of chemical factories or telecommunication transmitters within 500 m of the houses. The results of the gene–environment analyses revealed that an interaction existed between the *XRCC1* Ex9 + 16 A allele and the presence of electric transformers and power lines within 100 m (Mean $B = 0.14$ μTeslas, μT) of the houses (interaction odds ratio, COR = 4.31, 95%CI: 1.54–12.08). The COR for the interaction of *XRCC1* Ex9 + 16A and the presence of these installations within 50 m (Mean $B = 0.18$ μT) of the houses was 4.39 (95%CI: 1.42–13.54). Our results suggest a possible association between electric transformers and power lines and the *XRCC1* Ex9 + 16A allele in patients with childhood AL.

Keywords: *Electromagnetic fields, gene–environment interactions, DNA damage, single nucleotide polymorphisms, cancer*

Introduction

Leukemias account for 25–35% of all childhood cancers [1,2]. The mechanism by which leukemia arises is likely to involve gene–environment interactions, with the environmental exposure including both endogenous and exogenous factors [3]. Exposure to residential power-frequency magnetic fields has been suspected to increase the risk of childhood leukemia, though the risk suggested by the first report [4] has not consistently been supported by the following ones [5–12]. Laboratory-based experiments and recent studies have suggested that low frequency electromagnetic fields (EMF) can influence cell proliferation and DNA damage in both normal and tumour cells through the action of free radicals [13–15]. Many of the enzymatic genes involved in DNA repair are polymorphic and can affect the capacity for DNA repair [16,17], possibly accounting for differential susceptibilities to childhood leukemia.

Genetic variation in the coding regions of the mismatch repair gene *hMLH1* (Ile-219Val) could contribute to an individual's susceptibility to leukemogenesis [18,19], though the involvement of the repair system in the pathogenesis of plasma cell dyscrasias has not yet been fully elucidated [20]. A single base A to G transition in exon 8 at position 23

Correspondence: Xiaoming Shen, Shanghai XinHua Hospital of Shanghai Jiaotong University School of Medicine, Shanghai Institute for Pediatric Research, Shanghai Key Laboratory of Children's Environmental Health, 1665 Kong Jiang Road, Shanghai 200092, China. Fax: +86 021 65791316.
E-mail: xminshen@gmail.com

ISSN 1042-8194 print/ISSN 1029-2403 online © 2008 Informa Healthcare USA, Inc.
DOI: 10.1080/10428190802441347

upstream was identified as a polymorphism of the *hMLH1* gene, and the AA genotype may be associated with decreased activity of the encoded enzyme. Genetic variations in base excision repair genes are associated with bladder cancer risk through gene–gene and gene–environment interactions. The Asp148Glu amino acid substitution is due to a single T to G base pair change in exon 5 at position 5 downstream in the *APEX1* gene which has been well studied [21]. Silencing of the *MGMT* gene, a key gene for DNA repair, is involved in carcinogenesis. However, the effects of these polymorphisms on the levels and types of genetic damage induced by specific environmental carcinogens remains to be fully determined. Evidence suggests that the 143 Val c single nucleotide polymorphism (SNPs) (*MGMT* Ex7 + 13 G allele) may alter the functional characteristics of the *MGMT* protein, resulting in suboptimal repair of genetic damage [22]. The *XRCC1* 280His (*XRCC1* Ex9 + 16 A) alleles affect individual chromosomal aberration levels, most probably by influencing the DNA repair phenotype [17]. The Asp312Asn and Lys751Gln polymorphisms in the *XPD* gene may also alter DNA repair capacity. The hypothesis that these two *XPD* polymorphisms were associated with lung cancer risk was confirmed in a large hospital-based, case–control study among Chinese patients [23].

EMF and the aforementioned genetic polymorphisms may be associated with childhood acute leukemia (AL), in light of the fact that there is an unexplained association between exposure to the magnetic fields arising from the supply and use of electricity, and an increase in risk of childhood leukemia [24]. The present study was conducted to explore the role of interactions between EMF and DNA repair enzymes in childhood leukemia, using a case-only study in a Chinese Han population of children.

Methods

Study population and data collection

Participants in the study were all inpatients admitted to the hematological department of the Children's Medical Centre affiliated to Shanghai Jiao Tong University School of Medicine in Shanghai, China. All subjects were ethnic Han Chinese and residents of Shanghai and Zhejiang and Jiangsu province, who resided within 500 km of Shanghai. We recruited 123 patients who had been diagnosed with AL at ages < 15 between May 2006 and August 2007. Children with AL were diagnosed according to the French–American–British classification by bone marrow biopsy [25]. A combination of morphologic, immunophenotypic and cytogenetic studies is used to establish the diagnosis of acute myeloid leukemia (AML) [26,27]. After informed consent from the parents of each participant, 0.5 mL of blood was collected before chemotherapy and stored at -80°C. The study was approved by the ethics and research committee of the Shanghai Children's Medical Centre, which is affiliated with the Shanghai Jiaotong University School of Medicine.

The mothers of the patients were interviewed at the hospital by specifically trained medical doctors using a questionnaire. Visits to the present (or previous) residential areas of 66 cases were arranged, and the actual values of magnetic field intensities were measured using an EMF detector (TriField Meter, AlphaLab, USA). Questionnaires covered information about the parents' sociodemographic characteristics, the children's pre and postnatal characteristics and the familial history of cancer and autoimmune diseases. The questions related to environmental exposure covered pregnancy and the period from birth to diagnosis and detailed information including: Was there a television set/refrigerator/microwave oven in the children's rooms? Did you regularly use insecticides at home? Did you use gardening chemicals such as, fertilisers, herbicides, insecticides, fungicides, others? Were there chemical factories/telecommunication transmitters/electric transformers/power lines around your house? Electric transformers were taken to mean those typically located within a city area to serve city districts or the main power transformation stations (10, 35, 110 kV). Distances between such installations and the houses were noted. The questionnaire also addressed the parents' occupations during pregnancy and during the study subjects' childhoods.

SNP detection using the MassARRAY system

The MassARRAY technology platform (Sequenom, San Diego, California, USA) was used to detect the SNPs in *hMLH1* Ex8–23A > G (rs1799977), *APEX1* Ex5 + 5T > G (rs1130409), *MGMT*Ex7 + 13A > G (rs2308321), *XRCC1* Ex9 + 16G > A (rs25489), *XPD* Ex10–16G > A (rs1799793) and *XPD* Ex23 + 61 T > G (rs13181) [28]. The test was based on the principle of allele-specific primer extension reaction, whereas the read-out of the result was realised using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF-MS). Polymerase chain reaction (PCR) primers and extension primers were designed by MassARRAY Assay Design 2.0 software. To provide a significant improvement in overall performance, 10-mer tag (5′-ACGTTGGATG-3′) was added to the 5′ ends of each PCR primer (Table I). To start

the experiment, the polymorphic loci were amplified by PCR on a 384-well plate in a volume of 5 μL reaction mixture with 0.1 U HotStarTaq DNA polymerase (QIAGEN GmbH, Hilden, Germany). PCR thermocycles were performed as follows: a denaturation at 95°C for 15 min, 45 cycles consisting of 20 s at 95°C, 30 s at 56°C and 60 s at 72°C, followed by a final elongation step at 72°C for 3 min. The PCR products were then purified with shrimp alkaline phosphatase. In the second step, 2 μL primer extension mixture, including approximately 9 μM extension primer (Table I), 0.018 μL Thermosequenase and 0.2 μL 10 × Termination Mix of ddATP, ddCTP, ddTTP and ddGTP (suitable for the each SNP) (Amersham Biosciences, Uppsala, Sweden) were added to the PCR products. The mixture was thermocycled to process the reaction protocol as follows: 94°C for 2 min; 55 cycles each of 94°C for 5 s, then 52°C for 5 s and 72°C for 5 s. After desalting, the reaction products were transferred onto a 384-well SpectroCHIP and analysed by using the MassARRAY Analyser (Sequenom).

Statistical analysis

The χ^2-goodness-of-fit test was used to test the Hardy-Weinberg equilibrium. For polymorphisms with a low variant allele frequency, the homozygote for the variant allele was combined with the heterozygote, including *hMLH1* Ex8–23A > G, *APEX1* Ex5 + 5T > G, *XRCC1* Ex9 + 16G > A and *XPD* Ex23 + 61 T > G. The low risk genotypes (in *hMLH1* genotypes, A/A allele; in *APEX1* genotypes, T/T allele; in *MGMT* genotypes, A/A allele; in *XRCC1* genotypes, the G/G allele; in *XPD* Ex23 + 61T > G genotypes, T/T allele; in *XPD* Ex10-16G > A, G/G allele) were designated as the referent category to evaluate potential effect modification. For *XRCC1*, genotypes were also combined based on a known phenotype–genotype relationship. The combination of *XRCC1* Ex9 + 16 A/G and A/A genotypes was defined as a 'poor metaboliser', whereas the G/G genotype of *XRCC1* Ex9 + 16 was termed as an 'extensive metaboliser' [16,17,29].

To estimate gene–environment interactions, a case-only design was applied. The case-only design is an efficient way of estimating gene–environment interactions, but it cannot evaluate the main effect of either [30–32]. Such interactions may be obtained in a case-only design if independence between genotypes and environment exposure is assumed. In this study, we validated this independence assumption through the analysis of a relatively large number of healthy subjects ($n = 135$, median age 5.0 years, range 0.5–15 years) randomly selected from the same population. Generally, when E is categorical or continuous, we can assess the independence assumption by fitting the following logistic regression model to the control data:

$$\log \text{ it } P\,(G = 1) = \eta_0 + \eta_1 E \qquad (1)$$

where a test of whether $\eta_1 = 0$ is a test of the independence assumption. We assume that the genetic mutation and environmental exposure are binary variables. G and E indicate presence of the genetic mutation or polymorphism, and environmental exposure, respectively. We perform a case-only analysis if the test is nonsignificant at the 0.05 significance level or otherwise a case–control analysis

Table I. Oligonucleotide primers for polymerase chain reaction.

Genes	Primers (5′–3′; F, forward; R, reverse; E, extension)	Fragment length (bp)
hMLH1 Ex8-23A > G	F: ACGTTGGATGCTGATGTTAGGACACTACCC R: ACGTTGGATGTCGACATACCGACTAACAGC E: GACTAACAGCATTTCCAAAGA	102
APEX1 Ex5 + 5T > G	F: ACGTTGGATGCACCTCTTGATTGCTTTCCC R: ACGTTGGATGACAATCACCCGGCCTTCCTG E: CCTCCTGATCATGCTCCTC	120
MGMT Ex7 + 13A > G	F: ACGTTGGATGCTGCTGCAGACCACTCTGT R: ACGTTGGATGAGATCCCTGACTGACAGTGG E: ACCTGTCTTCCAGGTCCCCATCCTC	100
XRCC1 Ex9 + 16G > A	F: ACGTTGGATGTTTGCCTGTCACTGCCCCCT R: ACGTTGGATGTTTGTCTTCTCCAGTGCCAG E: TGTCGTCTCCAGTGCCAGCTCCAACTC	105
XPD Ex10-16G > A	F: ACGTTGGATGACGGACGCCCACCTGGCCAA R: ACGTTGGATGAGGCGGGAAAGGGACTGGG E: CTGCGCACCCTGCAGCACTTCGT	112
XPD Ex23 + 61 T > G	F: ACGTTGGATGAGCAGCTAGAATCAGAGGAG R: ACGTTGGATGCACCAGGAACCGTTTATGGC E: GCAATCTGCTCTATCCTCT	113

is used. When the log-odds ratio (η_1) assessing independence is zero, the case-only design is unbiased and very efficient. In our study, the odds ratio assessing independence between electric transformers and power lines and *XRCC1* was closer to 1 (estimate 1.37, $P = 0.656$).

Case-only odds ratios for the relevant interactions and 95% confidence intervals (95%CI) were estimated using unconditional logistic regression. Possible confounding variables included for age, gender, parental education and occupation, indoor and outdoor pesticides use, television sets, refrigerators and microwave ovens in children's rooms and chemical factories or telecommunication transmitters within 500 m of the houses. Participants with missing values for any of the variables in the regression model were omitted from the analysis. The Mann–Whitney test was used for comparison between magnetic field intensities at residences for 66 cases in terms of distances from residences to the electric transformers.

All *P*-values are two-sided, and all analyses were carried out using SPSS software packages (version 11, SPSS, USA).

Results

Characteristics of children with AL

The characteristics of children with AL are shown in Table II. Of the participants, 66.67% were boys and 33.33% were girls; 56.10% of the cases were 2–7 years old, with the median age 5.0 years (range 0.5–14 years). Ninety-nine of the patients had acute lymphoid leukemia (ALL), and 24 had AML. All those exposed to electric transformers were also exposed to the power lines (Table III) and two cases exposed only to power lines are not included in the table. Mean peak values for magnetic field intensities were 0.13 μT ($n = 19$), 0.14 μT ($n = 13$) and 0.18 μT ($n = 9$) for houses within 500, 100 and 50 m of electric transformers and power lines, respectively. There were significant changes in magnetic field intensity with different distances (500 m, 100 m, 50 m) between the houses and the electric transformers or power lines in 66 cases (Table IV).

Table II. Characteristics of study patients with childhood AL.

Variables	Cases no. (%)
Sex	
Boys	82 (66.67)
Girls	41 (33.33)
Age (years)	
<2	14 (11.38)
2–7	69 (56.10)
8–14	40 (32.52)
Maternal education	
≤High school	70 (56.91)
>High school	53 (43.09)
Paternal education	
≤High school	78 (63.41)
>High school	45 (36.59)
Socioprofessional categories*	
Professional, technical workers, administrators and managers	23 (18.70)
Clerical, sales and services workers	55 (44.72)
Factory and agricultural workers	45 (36.58)
Television set in children's rooms	
No	27 (21.95)
Yes	96 (78.05)
Refrigerator in children's rooms	
No	120 (97.56)
Yes	3 (2.44)
Microwave oven in children's rooms	
No	122 (99.19)
Yes	1 (0.81)
Home insecticide use	
Never	61 (49.59)
Ever	62 (50.41)
Garden pesticide use	
Never	120 (97.56)
Ever	3 (2.44)

*Socioprofessional categories: best occupational activity of child's mother or father.

Table III. Distances between installations and the houses.

Installations around the houses	Cases no. (%)		
Electric transformers and power lines	Within 500 m	Within 100 m	Within 50 m
No	84 (68.29)	92 (74.80)	103 (83.74)
Yes	39 (31.71)	31 (25.20)	20 (16.26)
Telecom transmitter	Within 500 m	Within 100 m	Within 50 m
No	103 (83.74)	116 (94.31)	121 (98.37)
Yes	20 (16.26)	7 (5.69)	2 (1.63)
Chemical factory	Within 500 m	Within 100 m	Within 50 m
No	109 (88.62)	114 (92.68)	119 (96.75)
Yes	14 (11.38)	9 (7.32)	4 (3.25)

Table IV. Peak values of magnetic field intensity with different distances from the houses to electric transformers and power lines for 66 cases, median (range) μT.

Cut-offs of the distances	Houses within distance ≤cut-offs	Houses within distance > cut-offs	*P*-value*
500 m	0.02 (0.02–0.8)	0.02 (0.01–0.2)	0.005
100 m	0.02 (0.02–0.8)	0.02 (0.01–0.3)	0.006
50 m	0.02 (0.02–0.8)	0.02 (0.01–0.3)	0.014

*Comparisons of magnetic field intensity for houses within distance ≤cut-offs and houses within distance > cut-offs from electric transformers and power lines; by Mann–Whitney test.

The effect of gene–environment interactions on childhood acute lymphoma

COR for gene–environment interactions between DNA repair enzyme genotypes and electric transformers and power lines is shown in Table V. Case-only analyses revealed that an interaction existed between electric transformers and power lines situated within 100 m of the houses and the presence of the *XRCC1* Ex9 + 16A allele in childhood AL (COR = 4.31, 95%CI: 1.54–12.08), while the COR for the interaction between *XRCC1* Ex9 + 16A and their occurrence within 50 m of the houses was increased further (COR = 4.39, 95%CI: 1.42–13.54). No significant interactions between the proximity of the electric transformers and power lines and other genotypes were observed. No significant interactions were observed between genotypes and the presence of television sets, refrigerators or microwave ovens in children's rooms, pesticides use or the presence of chemical factories or telecommunication transmitter within 500 m of the houses.

Discussion

Epidemiological studies have suggested that gene–environment interactions were associated with cancer susceptibility [33–35]. Therefore, investigation of the role of gene–environment interactions involving low penetrance genes may help to elucidate the cause of common sporadic cancers. In the present study, we examined gene–environment interactions for six polymorphisms of DNA repair genes and generators of EMF using a case-only design.

Our gene and environment combined analyses suggest that a significant interaction, which could potentially increase the risk of childhood AL, exists between the *XRCC1* Ex9 + 16A and the proximity of electric transformers and power lines. No previous reports have described an association between this gene–environment interaction and childhood leukemia risk to date. However, a gene–environment interaction in childhood AL has been reported between the *CYP1A1**2A variant allele, *GSTM1* deletion and maternal smoking during pregnancy, *NQO1* polymorphism and coffee drinking [36], DNA repair genes and X-rays [37] and *CYP1A1*m1 and *CYP1A1*m2 mutations and insecticides [38]. Previous studies have also suggested an association between leukemogenesis in children and DNA repair, and thus pointing to an the effect of environmental exposure [18,39]. Moreover, it was indicated that modification of genetic susceptibility in vulnerable subjects may be involved in the effect of extremely low frequency magnetic fields [40]. Although studies have been carried out on various biological aspects of childhood AL, very little has been done with regard to the role of genetic polymorphisms in the DNA repair gene *XRCC1,* and other members of the various DNA repair pathways, in susceptibility to the disease. It was reported that individuals with the XRCC1 399Gln allele were associated with increased risk for this disease [41–43]. Risk of ALL among children with XRCC1 codon 194 variant genotypes were disputable [42,43]. Molecular epidemiologic research provides compelling evidence that environmental factors are major contributors to human carcinogenesis and that the risk of developing cancer is strongly influenced by genetically determined differences [44,45]. Our results indicated that carriers of *XRCC1* Ex9 + 16A allele were at increased risk from electric transformers and power lines. No study has been published regarding the combination of *XRCC1* and electric transformers and power lines in association with childhood leukemia risk. It has been reported that EMF contributes to DNA damage through the action of free radical species [13–15]. Functional studies using lymphocytes suggested that the 280His polymorphism reduced genomic stability [16,17]. DNA damage and chromosome breaks which are inadequately repaired, ultimately lead to the initiation and progression of disease [3]. Carriers of the *XRCC1* Ex9 + 16A allele exposed to electric transformers may experience a similar process. The risk of leukemia was further increased with shorter distance between the houses and the electric

Table V. Gene–environment interactions for combination of *XRCC1* Ex9 + 16G > A and electric transformers and power lines in childhood AL.

Electric transformers and power lines	*XRCC1* Ex9 + 16G > A		OR (95%CI)*
	G/G	A/G+A/A	
Within 500 m from houses			
No	66	16	1.00 (Ref)
Yes	25	16	2.37 (0.94–5.97)
Within 100 m from houses			
No	75	17	1.00 (Ref)
Yes	16	15	4.31 (1.54–12.08)#
Within 50 m from houses			
No	82	21	1.00 (Ref)
Yes	9	11	4.39 (1.42–13.54)#

*Unconditional logistic regression adjusted for age, gender, parental education and occupation, indoor and outdoor pesticides use, television set, refrigerator and microwave oven in children's room, the chemical factory, telecom transmitter around the houses in 500 meters.
#$P < 0.01$.

transformers and power lines. However, our current knowledge of the role of these enzymes in the DNA repair process is based primarily on *in vitro* models, which might not reflect the complex biological situation, and the biological interpretation remains to be understood. Larger studies are needed to explore the interactions between the susceptibility genes and electric transformers, and to identify the underlying mechanisms of childhood leukemia.

One of the limitations of the case-only design is that, in order to identify gene–environment interactions, independence between genotypes and environmental exposure must be assumed. However, relying on tests of independence in the controls is not effective because of their generally low power to detect meaningful departures from independence [46]. Another limitation of the current study was the potential for biased recall by patients' parents. Though the mothers of the cases were interviewed in hospital, face-to-face, by specifically trained medical doctors using a questionnaire, we did not visit the residential areas of all cases and actual values for magnetic field intensities were measured only for those cases visited, because of limited time and loss of contact in some cases. The possibility of some recall bias in our findings cannot, therefore, be ruled out.

Although our studies were limited by EMF exposure information, the small number of exposed subjects and an independence assumption, it is still noteworthy that children with the *XRCC1* Ex9 + 16A polymorphism could be particularly sensitive to the carcinogenic effects of EMF. Future research should include improved exposure assessments, evaluation of risk in relation to age at exposure and an investigation of genetic-environmental interactions using a case–control design. There is the potential to prevent some childhood leukemias by reducing or eliminating EMF exposure for children with *XRCC1* Ex9 + 16A.

In summary, our results demonstrated a possible association between electric transformers and power lines and the XRCC1 Ex9 + 16A allele in patients with childhood AL. Residence near electric transformers and power lines, at distances $\leq$100 m, and magnetic fields >0.14 μT, may be considered a risk factor for the development of AL in children with *XRCC1* Ex9 + 16A genotypes. These preliminary exploratory results need to be confirmed by further, larger studies.

Acknowledgments

This work was funded by the Science and Technology Commission of Shanghai Municipality (07dz22013), Shanghai Key Laboratory of Children's Environmental Health (06DZ22024), the Key Discipline in Pediatrics of Shanghai Municipal Education Commission (T0204), Shanghai Municipal Education Commission (08YZ41) and the Key Project in Medicine of Shanghai Municipal Bureau of Health (05III002), China. We are grateful to Jingyi Shi at Shanghai Institute of Hematology, Shanghai Jiao Tong University, for her excellent technical assistance.

References

1. Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. Int J Cancer 1988;42:511–520.
2. Sriamporn S, Vatanasapt V, Martin N, Sriplung H, Chindavijak K, Sontipong S, et al. Incidence of childhood cancer in Thailand 1988–1991. Paediatr Perinat Epidemiol 1996;10:73–85.
3. Lightfoot T. Aetiology of childhood leukemia. Bioelectromagnetics 2005; 13 (Suppl 7):S5–S11.
4. Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. Am J Epidemiol 1979;109:273–284.
5. Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, et al. A pooled analysis of magnetic fields and childhood leukaemia. Br J Cancer 2000;83:692–698.
6. Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Childhood Leukemia-EMF Study Group. Epidemiology 2000;11:624–634.
7. Mizoue T, Onoe Y, Moritake H, Okamura J, Sokejima S, Nitta H. Residential proximity to high-voltage power lines and risk of childhood hematological malignancies. J Epidemiol 2004;14:118–123.
8. Draper G, Vincent T, Kroll ME, Swanson J. Childhood cancer in relation to distance from high voltage power lines in England and Wales: a case-control study. BMJ 2005;330:1290.
9. Kabuto M, Nitta H, Yamamoto S, Yamaguchi N, Akiba S, Honda Y, et al. Childhood leukemia and magnetic fields in Japan: a case–control study of childhood leukemia and residential power-frequency magnetic fields in Japan. Int J Cancer 2006;119:643–650.
10. Mejia-Arangure JM, Fajardo-Gutierrez A, Perez-Saldivar ML, Gorodezky C, Martinez-Avalos A, Romero-Guzman L, et al. Magnetic fields and acute leukemia in children with Down syndrome. Epidemiology 2007;18:158–161.
11. Schuz J. Implications from epidemiologic studies on magnetic fields and the risk of childhood leukemia on protection guidelines. Health Phys 2007;92:642–648.
12. O'Carroll MJ, Henshaw DL. Aggregating disparate epidemiological evidence: comparing two seminal EMF reviews. Risk Anal 2008;28:225–234.
13. Crumpton MJ, Collins AR. Are environmental electromagnetic fields genotoxic? DNA Repair (Amst) 2004;3:1385–1387.
14. Ivancsits S, Diem E, Pilger A, Rudiger HW, Jahn O. Induction of DNA strand breaks by intermittent exposure to extremely-low-frequency electromagnetic fields in human diploid fibroblasts. Mutat Res 2002;519:1–13.
15. Wolf FI, Torsello A, Tedesco B, Fasanella S, Boninsegna A, D'Ascenzo M, et al. 50-Hz extremely low frequency electromagnetic fields enhance cell proliferation and DNA damage: possible involvement of a redox mechanism. Biochim Biophys Acta 2005;1743:120–129.

16. Tuimala J, Szekely G, Gundy S, Hirvonen A, Norppa H. Genetic polymorphisms of DNA repair and xenobiotic-metabolizing enzymes: role in mutagen sensitivity. Carcinogenesis 2002;23:1003–1008.
17. Kiuru A, Lindholm C, Heilimo I, Ceppi M, Koivistoinen A, Ilus T, et al. Influence of DNA repair gene polymorphisms on the yield of chromosomal aberrations. Environ Mol Mutagen 2005;46:198–205.
18. 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;123:45–48.
19. Krajinovic M, Labuda D, Mathonnet G, Labuda M, Moghrabi A, Champagne J, et al. Polymorphisms in genes encoding drugs and xenobiotic metabolizing enzymes, DNA repair enzymes, and response to treatment of childhood acute lymphoblastic leukemia. Clin Cancer Res 2002;8:802–810.
20. Martin P, Santon A, Garcia-Cosio M, Bellas C. hMLH1 and MGMT inactivation as a mechanism of tumorigenesis in monoclonal gammopathies. Mod Pathol 2006;19:914–921.
21. Huang M, Dinney CP, Lin X, Lin J, Grossman HB, Wu X. High-order interactions among genetic variants in DNA base excision repair pathway genes and smoking in bladder cancer susceptibility. Cancer Epidemiol Biomarkers Prev 2007;16: 84–91.
22. Hill CE, Wickliffe JK, Wolfe KJ, Kinslow CJ, Lopez MS, Abdel-Rahman SZ. The L84F and the I143V polymorphisms in the O6-methylguanine-DNA-methyltransferase (MGMT) gene increase human sensitivity to the genotoxic effects of the tobacco-specific nitrosamine carcinogen NNK. Pharmacogenet Genomics 2005;15:571–578.
23. Liang G, Xing D, Miao X, Tan W, Yu C, Lu W, et al. Sequence variations in the DNA repair gene XPD and risk of lung cancer in a Chinese population. Int J Cancer 2003;105: 669–673.
24. Maslanyj MP, Mee TJ, Renew DC, Simpson J, Ansell P, Allen SG, et al. Investigation of the sources of residential power frequency magnetic field exposure in the UK Childhood Cancer Study. J Radiol Prot 2007;27:41–58.
25. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) cooperative group. Br J Haematol 1976;33:451–458.
26. Jaffe E, Harris N, Stein H, Vardiman J, editors. World Health Organization Classification of Tumors: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001.
27. Ross ME, Mahfouz R, Onciu M, Liu HC, Zhou X, Song G, et al. Gene expression profiling of pediatric acute myelogenous leukemia. Blood 2004;104:3679–3687.
28. Rodi CP, Darnhofer-Patel B, Stanssens P, Zabeau M, van den Boom D. A strategy for the rapid discovery of disease markers using the MassARRAY system. Biotechniques 2002; Suppl: 62–6, 68–69.
29. Pachkowski BF, Winkel S, Kubota Y, Swenberg JA, Millikan RC, Nakamura J. XRCC1 genotype and breast cancer: functional studies and epidemiologic data show interactions between XRCC1 codon 280 His and smoking. Cancer Res 2006;66:2860–2868.
30. Piegorsch WW, Weinberg CR, Taylor JA. Non-hierarchical logistic models and case-only designs for assessing susceptibility in population-based case-control studies. Stat Med 1994;13:153–162.
31. Yang Q, Khoury MJ, Sun F, Flanders WD. Case-only design to measure gene-gene interaction. Epidemiology 1999; 10:167–170.
32. Hamajima N, Yuasa H, Matsuo K, Kurobe Y. Detection of gene-environment interaction by case-only studies. Jpn J Clin Oncol 1999;29:490–493.
33. Giarelli E, Jacobs LA. Modifying cancer risk factors: the gene-environment interaction. Semin Oncol Nurs 2005;21:271–277.
34. Kotnis A, Sarin R, Mulherkar R. Genotype, phenotype and cancer: role of low penetrance genes and environment in tumour susceptibility. J Biosci 2005;30:93–102.
35. Mucci LA, Wedren S, Tamimi RM, Trichopoulos D, Adami HO. The role of gene-environment interaction in the aetiology of human cancer: examples from cancers of the large bowel, lung and breast. J Intern Med 2001;249:477–493.
36. Clavel J, Bellec S, Rebouissou S, Menegaux F, Feunteun J, Bonaiti-Pellie C, et al. Childhood leukaemia, polymorphisms of metabolism enzyme genes, and interactions with maternal tobacco, coffee and alcohol consumption during pregnancy. Eur J Cancer Prev 2005;14:531–540.
37. Infante-Rivard C, Mathonnet G, Sinnett D. Risk of childhood leukemia associated with diagnostic irradiation and polymorphisms in DNA repair genes. Environ Health Perspect 2000;108:495–498.
38. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology 1999;10:481–487.
39. Bolufer P, Barragan E, Collado M, Cervera J, Lopez JA, Sanz MA. Influence of genetic polymorphisms on the risk of developing leukemia and on disease progression. Leuk Res 2006;30:1471–1491.
40. Hakansson N, Gustavsson P, Sastre A, Floderus B. Occupational exposure to extremely low frequency magnetic fields and mortality from cardiovascular disease. Am J Epidemiol 2003;158:534–542.
41. Zhu R, Lu FJ, Zhang ZB, Zhai XW, Liu J, Lu G, et al. Association of genetic polymorphism of XRCC1 with susceptibility to acute childhood leukemia. Wei Sheng Yan Jiu 2005;34:300–302.
42. Joseph T, Kusumakumary P, Chacko P, Abraham A, Pillai MR. DNA repair gene XRCC1 polymorphisms in childhood acute lymphoblastic leukemia. Cancer Lett 2005;217:17–24.
43. Pakakasama S, Sirirat T, Kanchanachumpol S, Udomsubpayakul U, Mahasirimongkol S, Kitpoka P, et al. Genetic polymorphisms and haplotypes of DNA repair genes in childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2007;48:16–20.
44. Nebert DW, McKinnon RA, Puga A. Human drug-metabolizing enzyme polymorphisms: effects on risk of toxicity and cancer. DNA Cell Biol 1996;15:273–280.
45. Perera FP, Weinstein IB. Molecular epidemiology: recent advances and future directions. Carcinogenesis 2000;21:517–524.
46. Albert PS, Ratnasinghe D, Tangrea J, Wacholder S. Limitations of the case-only design for identifying gene-environment interactions. Am J Epidemiol 2001;154:687–693.